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7.4.2
Coupling Reactions

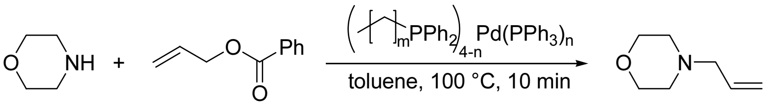
Stefan Mecking and Ulf Schlotterbeck

Coupling reactions, most prominently Heck and Suzuki couplings but also Sonogashira coupling and allylic substitution, are established catalytic transformations for the synthesis of fine chemicals. The recovery of catalytically active complexes from such coupling reactions, by the concept of covalent binding to soluble polymers, has been studied by various research groups. This research, addressed in the following section, has been carried out for the largest part only since the late 1990s. On a different level, since approximately the same time, coupling reactions with palladium colloids as catalysts have also attracted substantial interest. In addition to the synthetic utility and also catalyst re-use, the challenging question of the mechanistic function of colloids has been the focus of attention. The colloids employed are usually stabilized either by polymers or by low molecular weight surfactants. Coupling reactions with colloids are discussed in Sections 7.4.2.2 and 7.4.2.3.

7.4.2.1
Polymer-Bound Metal Complexes as Catalysts for C–C and C–N Coupling

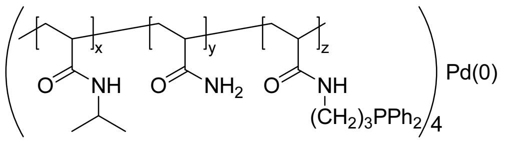
In an early report dating from 1989, Bergbreiter et al. reported on phosphine-terminated ethylene oligomers (M_n = 1400–2000 g mol^{-1}) as ligands for Pd(0) complexes, used as precursors for allylic substitution of allyl esters with secondary amines [Eq. (1)]. The reactions were carried out at elevated temperatures around 100 °C, at which the polymeric ligand is soluble (complete conversion in 10 min at

100 °C in toluene, 2 mol% palladium). Upon cooling to room temperature the complex was precipitated and could be separated by centrifugation. Repeated recycling over nine cycles was possible without an observed reduction in activity or loss of palladium (< 0.001%) [1].

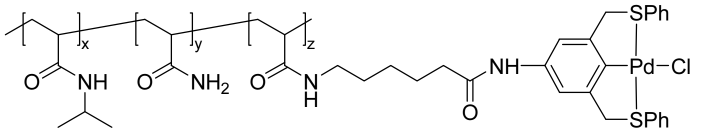


(1)

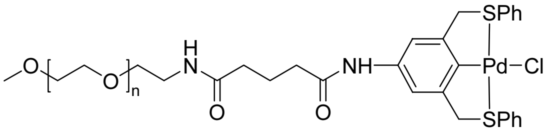
Allylic substitutions were also carried out with Pd(0) complexes as catalyst precursors with phosphine ligands bound covalently to polar polymers, namely random copolymers of acrylamide and *N*-isopropylacrylamide (PNIPAM) (**1a**, $M_v = 500\,000$, determined by viscometry). After the catalytic reaction, the polymer-bound catalysts were precipitated by adding the reaction mixture to an apolar solvent and could be re-used for further cycles (with an average of 93% conversion in ten consecutive reaction cycles, each 6 h at 50 °C in THF/H_2O 1 : 1, 1 mol% palladium) [2].



1a



1b

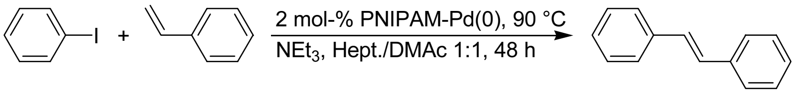


1c

After 15 consecutive reaction cycles, only a slight loss in productivity was observed, which was ascribed to a partial oxidation of the phosphine ligand. The fact that these polymers were no longer soluble in neat water above a certain temperature was used as an alternative for separating this catalyst; the polymers were precipitated upon heating and could be separated. However, this concept required the catalytic reaction to be performed at lower temperatures (10 °C), consequently resulting in longer reaction times [2].

A further possible way to separate the catalyst is to employ a biphasic system, in which the polymer-bound complex is soluble selectively only in one phase, while the substrates and products are soluble in the other phase. Fluorinated polymers are, for example, selectively soluble in fluorous solvents or in supercritical CO_2. By phase separation the catalyst can be recovered (cf. also Chapters 4 and 6). A variation of these permanently biphasic mixtures is, e.g., a polar and an apolar phase which are miscible at elevated temperatures to form a single phase. Such solvent combinations have been termed “thermomorphic”.

The aforementioned PNIPAM-bound palladium(0) complexes (**1a**) were employed as catalyst precursors for Heck and Suzuki couplings under “thermomorphic” conditions in heptane/DMAc or heptane/EtOH/water, respectively [Eqs. (2) and (3); DMAc = dimethylacetamide] [3]. After cooling to room temperature, the heptane-rich phase formed was separated from the polar phase containing the polymer-bound catalyst. New heptane solution of the substrate was added to the catalyst phase. In three consecutive cycles, no loss in activity was observed.



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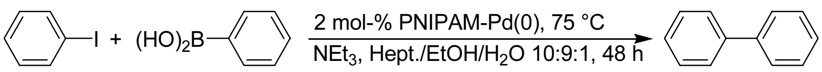


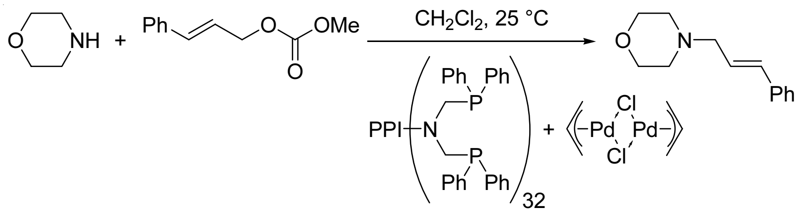
(3)

In allylic substitutions, a similar behavior was observed in “thermomorphic” solvent mixtures to that in the aforementioned reaction in toluene (100% conversion in five consecutive reaction cycles, each 11 h at 70 °C in heptane/EtOH/H_2O, 10 : 9 : 1) [4].

PNIPAM- and PEO-bound Pd(II) pincer complexes (**1b**: M_v = 870 000 g mol^{-1}; **1c**: M_n(PEG) = 5000 g mol^{-1}) were used for the same reactions (20 h at 95 °C, 0.2 mol% palladium, NEt_3) in heptane/DMAc/H_2O (20 : 9 : 1). In contrast to the Pd(0) phosphine complexes, these catalyst precursors are not sensitive to oxidation (to the phosphine oxides). Again, over five consecutive cycles under the reaction conditions chosen, no decrease in catalyst activity is evident [3].

Very recently, Plenio and co-workers investigated Sonogashira and Suzuki coupling in biphasic organic systems, such as DMSO/cyclohexane, with catalysts formed in situ from complexes [$(RCN)_2PdCl_2$] and polymers substituted with bulky electron-rich diadamantylphosphine moieties. Depending on the preference of the substrate for either of the two phases, the catalyst was made soluble in the other phase by choice of poly(ethylene glycol) or polymethylstyrene, respectively, as the soluble polymeric support. For example, in the Sonogashira coupling of bromoacetophenone with phenylacetylene, a very small reduction in catalyst activity from an average TO of 220 h^{-1} in the first cycle to 210 h^{-1} in the fifth cycle was observed. High yields were obtained for various substrates (cyclohexane/DMSO; 60 °C; 1 mol% catalyst; 5000 g mol^{-1} phosphine-substituted polymethylstyrene) [5]. Reactions were also run in a bubble-column type reactor in continuous mode with similar results [6]. Palladium losses were determined to be less than 0.005% with DMSO as the catalyst phase by means of total reflection X-ray fluorescence [7].

Continuous catalyst recovery by means of ultrafiltration in a membrane reactor was described by Kragl and Reetz for an allylic substitution reaction [Eq. (4)] [8].

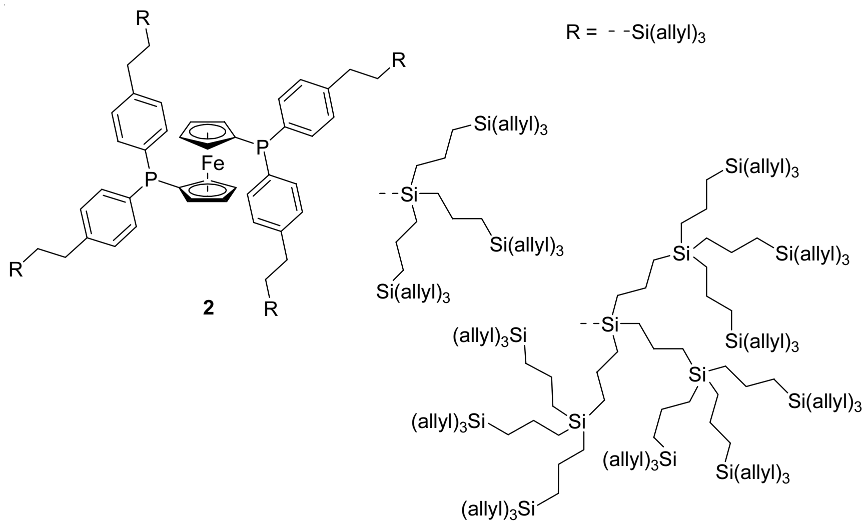


(4)

A second- or third-generation poly(propylene imine) dendrimer substituted with diphosphine end-groups was utilized as a polymeric ligand. The catalyst was prepared in situ with either the dimeric allylpalladium(II) chloride as a palladium source, or the well-defined complex PPI(G2)-[(diphosphine)$PdMe_2]_{16}$. For the former, solutions of the substrates methyl 3-phenylprop-2-enyl carbonate (30 mmol L^{-1}) and morpholine (60 mmol L^{-1}) in methylene chloride were pumped into the reactor continuously at a rate of 20 mL h^{-1}, with a catalyst concentration of 30 mmol L^{-1} palladium in the membrane reactor. Palladium losses of 0.07% to 0.14% per exchanged reactor volume were observed. The observed slight decrease in conversion from full conversion to 75% after 100 exchanged reactor volumes could not be ascribed to palladium losses by leaching alone. A part of the catalyst was apparently deactivated by other pathways. The TTN in the aforementioned experiment corresponded to 95. Nonetheless, the catalyst displayed a considerable stability under the reaction conditions.

The same catalyst precursor PPI(G2)-[(diphosphine)$PdMe_2]_{16}$ was employed by Reetz and co-workers for Heck reactions [9]. By addition of diethyl ether the polymer-bound catalyst could be precipitated and isolated by filtration. Upon its repeated use for catalysis, a slight decrease in activity was observed. By contrast to analogous low molecular-weight catalysts that were not polymer-bound, no formation of palladium black was observed with the dendrimer-bound catalyst.

In addition to the utilization of dendrimers as multifunctional polymeric supports for catalytically active complexes by means of their end-groups, core-functionalized dendrimers have also been investigated. By comparison, in the latter approach the molar mass per active site is rather high. However, selectivity induced by shielding of the metal center may be of interest. Van Leeuwen et al. prepared carbosilane dendrimers of various generations with a bidentate ferrocenylphosphine as the core unit (**2**). These ligands were employed in the palladium-catalyzed allylic alkylation of 3-phenylallyl acetate with sodium diethyl 2-sodio-2-methylmalonate [Eq. (5); complete conversion at room temperature within 24 h; 0.05 mol% palladium]. With increasing generation number, a slight change of the regioselectivity in favor of the branched product was observed [10]. A possible explanation is an increase in the steric demand of the ligand with increasing dendrimer generation, or also the increasingly apolar local environment of the active site.



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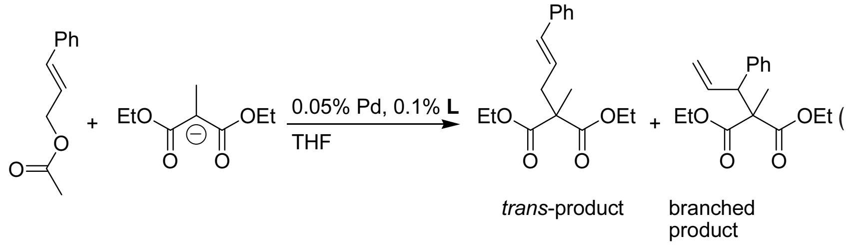


(5)

7.4.2.2
C–C Coupling by Palladium Colloids

C–C coupling is attained by “soluble” palladium colloids, i.e., palladium nanoparticles dipersed in a liquid phase, the particles being colloidally stabilized by polymers. As they do not differ fundamentally either in terms of selectivity and activity in catalysis or in physical properties, e.g., those relevant for catalyst recovery, palladium colloids stabilized by low molecular weight surfactants and ligands are also included.

There is evidence in some cases that C–C coupling by heterogeneous catalysts also occurs by soluble metal colloids (or smaller species) leached from solid supports, such as silica. In the 1970s, the catalytic activity of palladium black for C–C coupling was already being reported by Mizoroki et al. [11, 12]. Various examples of Heck reactions with “heterogeneous” catalysts have been reported since then [13]. Therefore, while heterogeneous catalysts are not the main focus of this section, they are addressed where appropriate.

C–C coupling by metal colloids has only received attention since about the mid-1990s. In 1996, Beller et al. reported on Heck coupling by palladium colloids [14].

The latter were prepared by reducing $PdCl_2$ with tetraalkylammonium triethylborohydride [15]. High activities were observed only with activated aryl bromides, in particular with 4-bromoacetophenone in coupling with butyl acrylate. Adding a freshly prepared colloid to the reaction mixture resulted in a temperature increase of 20 °C within 5 min at a low catalyst loading (97% conversion; 0.05 mol% palladium; DMAc as a solvent; 140 °C; activity, TO ca. 24 000 h^{-1}) (Table 1). Only with freshly prepared colloids were high conversions observed. Irreproducible results were obtained when the colloid was added prior to heating the reaction mixture to the reaction temperature; these were ascribed to a thermal instability of the colloids.

Reetz et al. reported on catalytically active solvent-stabilized colloids in propylene carbonate, which were prepared electrochemically or by thermal decomposition of $[Pd(OAc)_2]$ assisted by ultrasound. The colloidal particles had sizes of 8 to 10 nm, as determined by TEM. After addition of aryl bromide, styrene, and base to the colloid solution, satisfactory conversions were obtained within reaction times of 5–20 h. Isolation of the particles stabilized by propene carbonate was not possible, however [16]. The same authors also reported Suzuki and Heck reactions with electrochemically prepared Pd or Pd/Ni colloids stabilized by tetraalkylammonium, as well as polyvinylpyrrolidone (PVP)-stabilized palladium colloids prepared by hydrogen reduction (Table 1) [17]. It was assumed that the reaction occurs on the nanoparticle surfaces.

In 1997, Antonietti et al. reported on catalytically active palladium nanoparticles prepared by reduction of palladium(II) compounds in inverse block copolymer micelles, namely polystyrene-*b*-poly(4-vinylpyridine) (PS-*b*-P4VP). Activated aryl bromides were coupled reproducibly in Heck reactions, with apparent structural changes of the colloids during the reaction [18]. Small particle sizes were a prerequisite for high conversions, as indicated by qualitative TEM investigations. Very high total turnovers were reported (0.0012 mol% palladium, 68% conversion in five days, corresponding to 56 000 TO) (Table 1). Catalyst activity was found to be dependent on the structure of the block copolymer employed, which was attributed to a better accessibility of the metal particles in smaller micelles with a high surfacer area and thinner polystyrene layer.

Bradley et al. employed PVP-stabilized palladium colloids, which were "pretreated" with the base and the olefin at the reaction temperature prior to addition of the aryl halide (Table 1) [19]. The colloids were prepared by stirring $[Pd(dba)_2]$ in the presence of PVP at variable hydrogen pressures, affording particles of different average particle size (diameter 1.7 ± 0.5 nm × 3.7 ± 0.3 nm). The initial activities of Heck reactions catalyzed by these colloids of different average particle size were correlated with the number of low-coordinated atoms, i.e., corner and edge atoms in the palladium particles rather than all surface atoms. A general difficulty in such considerations is that the particles are not monodisperse, and also are not ideal cuboctahedra.

El-Sayed and co-workers more recently reported on the catalytic activity of PVP-stabilized aqueous palladium colloids in Suzuki reactions (substrates: 2-iodothiophene or phenyl iodide and 2-thiophene boronic acid or phenylboronic acid;

Table 1 Examples of C–C coupling reactions catalyzed by palladium colloids stabilized by polymers or surfactants.

Ref.	***Stabilizer***	***Solvent***	***Cat. [mol%]***	***d_{TEM} [nm]***	***Substrates***	***Base***	***T [°C]***	***Time [h]***	***Conv. [%]***	***Reaction type***
[14]	$Oct_4N^+Cl^-$/b	DMAc	0.05	n.d.	BrAc; BuA	NaOAc	140	0.08	97	HE
[16]	PC	PC	3.5	8–10	BrNi; S	NEt_3	130	21	96	HE
[17]	$Oct_4N^+Br^-$/b	DMAc	2[a)]	2–3	BrB; PhB	KOAc	120	2.5	100	SU
[17]	PVP	DMAc	0.5	n.d.	BrB; PhB	KOAc	100	3.5	100	SU
[17]	$Oct_4N^+Br^-$/e	DMF	1	3	IB; BuA	$NaHCO_3$[b)]	30	14	~100	HE
[18]	PS-*b*-P4VP	xylene	0.05	n.d.	BrAc; BuA	NBu_3	140	48	93	HE
[19]	PVP	DMAc	0.025	2–4	BrBA; BuA	NaOAc	140	1	> 95	HE
[20]	PVP	H_2O[c)]	0.3	3.6	IB; PhB	Na_3PO_4	R[d)]	12	95	SU
[29]	$Oct_4N^+HCO_2^-$	DMF	2[e)]	2	BrNi; PhB	K_2CO_3	110	2	100	SU
[22]	PAMAM-OH	EtOH	0.055	3.2	IB; TB	K_2CO_3	R[d)]	18	98	SU
[26]	star-PS-*b*-P2VP	xylene	0.5	2–3	BrNi; BuA	NBu_3	125	2	96	HE
[27]	polyacrylate microgel	DMAc	0.1	4.2	BrAc; BuA	NaOAc	120	1	89	HE

Stabilizer: $Oct_4N^+Cl^-$/b, colloid prepared by reduction with $[Oct_4N]^+[BEt_3H]^-$; PC, propylene carbonate; $Oct_4N^+Br^-$/e, prepared electrochemically; PS-*b*-P4VP, block copolymer polystyrene-*b*-poly(4-vinylpyridine); $Oct_4N^+HCO_2^-$, colloid prepared by reduction with $[Oct_4N]^+[HCO_2]^-$; PAMAM-OH, hydroxy-terminated PAMAM dendrimer; star-PS-*b*-P2VP, star polymer with cross-linked polystyrene core; acrylate microgel, cross-linked acrylate microgel partially substituted with amines.
Substrates: BrAc, 4-bromoacetophenone; BrB, bromobenzene; BrBA, 4-bromobenzaldehyde; BrNi, 4-bromonitrobenzene; BuA, butyl acrylate; IB, iodobenzene; PhB, phenylboronic acid; S, styrene; TB, 4-tolylboronic acid.
Reaction type: HE, Heck reaction; SU, Suzuki reaction.

a) Pd/Ni bimetallic colloid (1 : 3).
b) $NaHCO_3/Bu_4NBr$.
c) H_2O : EtOH 6 : 4 (v/v).
d) Reflux.
e) Pd/Cu bimetallic colloid (1 : 1).

0.3 mol% palladium; 12 h reflux) (Table 1) [20]. They did not find such a clear correlation of particle size and activity. In addition to PVP, hydroxy-terminated PAMAM dendrimers or polystyrene-*block*-poly(sodium acrylate) also stabilized colloids, which were catalytically active [21, 22]. Colloids stabilized by the G4 dendrimer were found to be more stable than those stabilized with the G3 dendrimer or the linear polymers, but they also possessed a lower activity. This was attributed to a more efficient shielding of the metal particles by the higher-generation dendrimer, findings similar to those on hydrogenations of various allyl alcohols [23]. Reasonable conversions were only observed with aryl iodides however.

Suzuki reactions of phenylboronic acid with phenyl iodide were investigated further, employing PVP-stabilized palladium particles of different average sizes from 3 to 7 nm [24]. TEM investigations reveal that particle sizes increase under reaction conditions. Beyond this, results concerning effects of particle sizes and colloid concentrations on reaction rates are not straightforward, and various explanations have been brought forward to account for experimental observations [24, 25].

Fréchet and Hawker prepared polystyrene-*block*-poly(2-vinylpyridine) (PS-*b*-P2VP) block copolymers with an alkoxyamine moiety on the P2VP block by alkoxyamine-controlled free-radical polymerization. In a second step, star polymers with ca. 40 to 50 arms and a cross-linked polystyrene core were prepared by terpolymerization of these block copolymers with styrene and divinylbenzene (1 : 4 : 10). The resulting polymers solubilized $[Pd(OAc)_2]$ and stabilized palladium colloids formed upon heating with ethanol as a reducing agent [26]. The colloids were active for the Heck reaction of activated aryl bromides with butyl acrylate (Table 1). No undesired formation of palladium black was observed, and the colloids retained an identical performance upon recycling by preciptiation with methanol over four repeated cycles.

Biffis et al. employed soluble microgels to stabilize colloidal palladium particles [27, 28]. These cross-linked polyacrylates, characterized by gel permeation chromatography, contained amino groups, which coordinate palladium ions. Reduction results in colloids with particle sizes of 3 to 9 nm. Particle sizes can be influenced by the degree of crosslinking of the microgel. Heck reactions of activated aryl bromides proceed with high activities (Table 1).

In 2002, Rothenberg et al. reported on Suzuki reactions catalyzed by surfactant-stabilized colloids of Cu, Pd, Pt, or Ru or bimetallic combinations of these metals [29]. The colloids were prepared of metal salt solutions in DMF with tetraoctylammonium formate, which served as a reducing agent as well as a stabilizer. Interestingly, ruthenium and even copper colloids were found to convert aryl iodides completely to the corresponding biphenyls, albeit more slowly than palladium colloids.

Gedanken et al. prepared palladium nanoparticles by decomposition of $[Pd_2(dba)_3]$ or $[Pd(OAc)_2]/Me_3(C_{14}H_{29})NBr$ by extended exposure to ultrasound. In the case of $[Pd_2(dba)_3]$, the colloidal metal particles were stabilized by amorphous carbon formed from dba. Activities of the soluble colloids in the Heck reaction were comparable to those of the “heterogeneous” catalyst palladium on charcoal (Table 2) [30, 31].

Table 2 Examples of C–C coupling reactions with colloids stabilized by other means than polymers or surfactants and Heck coupling with heterogeneous catalysts.

Ref.	*Stabilizer*	*Solvent*	*Cat. [mol%]*	*d_{TEM} [nm]*	*Substrates*	*Base*	*T [°C]*	*Time [h]*	*Conv. [%]*	*Reaction type*
[30]	$C_{amorphous}$	DMF	~1.6	~2	BrB; S	KOAc	125	20	30	HE
[32]	$[PW_{11}O_{39}]^{7-}$	$H_2O^{a)}$	0.01	$15^{b)}$	BrAc; PhB	$i\mathrm{Pr}_2NH$	85	12	92	SU
[32]	$[PW_{11}O_{39}]^{7-}$	H_2O^{a}	0.01	$15^{b)}$	TBr; S	$i\mathrm{Pr}_2NH$	85	16	95	HE
[34]	$(bbim)^+X^-$	$(bbim)^+X^-$	1	~2	IB; EtA	NaOAc	30	1.5	87	HE
[35]	$Bu_4N^+X^-$	$Bu_4N^+Br^-$	1.5	3.3	TBr; ZE	$Bu_4N^+OAc^-$	130	1	95	HE
[36]	PPI-F	FC-75/org$^{c)}$	3–5	2	IB; BuA	NEt_3	90	24	70	HE
[54]	Pd/C	NMP	0.005	3	BrB; S	NaOAc	140	2	90	HE
[52]	Pd/C	NMP	1.5	5	IB; MA	Na_2CO_3/NEt_3	160	0.5	100	HE

Stabilizer: $C_{amorphous}$, amorphous carbon; $[PW_{11}O_{39}]^{7-}$, Keggin ion; $(bbim)^+X^-$, dibutylimidazolium salt (ionic liquid); $Bu_4N^+X^-$, ionic liquid; PPI-F, perfluoroalkyl-substituted PPI dendrimer; Pd/C, palladium on charcoal.
Substrates: BrAc, 4-bromoacetophenone; BrB, bromobenzene; BuA, butyl acrlyate; EtA, ethyl crylate; IB, iodobenzene; MA, methyl acrylate; PhB, phenylboronic acid; S, styrene; TBr, 4-tolylbromide; ZE, *E*-ethyl cinnamate.
Reaction type: HE, Heck reaction; SU, Suzuki reaction.

a) $H_2O/EtOH$ (2 : 8) (v/v).
b) Incl. stabilizer.
c) Perfluoro-2-butyl-THF (FC-75)/heptane/benzene (2 : 1 : 1).

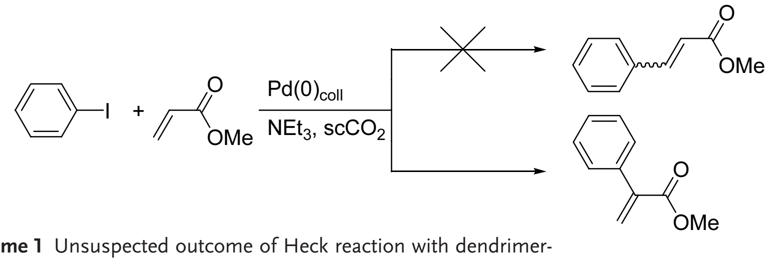
In addition to surfactants and polymers, other compounds have also been studied as stabilizers. Water-soluble polyoxometallate-stabilized nanoparticles display satisfactory activities in Suzuki, Heck and Stille reactions in aqueous solution (Table 2) [32]. Thiol-substituted cyclodextrins have been employed as stabilizers for palladium colloids, which were active in Suzuki reactions, although the stability was limited [33].

Examples of C–C coupling with palladium colloids in *biphasic* systems have also been reported. Heck-coupling and copper-free Sonogashira coupling with $[Pd(OAc)_2]$ in ionic liquids have been studied (Table 2) [34]. Under ultrasound irradiation, high conversions were obtained within 1.5 to 3 h. The product was isolated from the ionic liquid phase by extraction with organic solvents. A palladium—carbene complex formed under the reaction conditions of C–C coupling was assumed to be the source of colloidal palladium particles, as TEM investigations of a reaction mixture after a Heck reaction suggest. The catalytic system is active only toward aryl iodides (see also Section 2.4.4.4).

Another report on Heck reactions in ionic liquids also confirms that, in Bu_4NBr as an ionic liquid, $[Pd(OAc)_2]$ rapidly reacts to form catalytically active colloidal particles [35]. The authors point out that it is unclear whether the palladium particles are the actual active species or whether they are a precursor to the latter.

Polypropylene imine dendrimers with covalently attached perfluorinated poly(propylene oxide) end-groups have been employed for the stabilization of palladium colloids in Heck reactions in fluorous solvents by Crooks et al. [36] (Table 2). Relatively low activities were obtained, which were further reduced upon re-use of the fluorous phase in a second cycle. From the results of repeated Heck reactions without an added base, it can be assumed that the reduction in activity upon recycling is due to protonation of the dendrimer scaffold, serving as a base. No leaching of palladium from the fluorous phase was detected (< 0.01 ppm); however, this value was not related to the overall palladium loading (cf. also Section 4.2).

Employing the same dendrimer-stabilized palladium colloids for Heck reactions in supercritical carbon dioxide, after a 24 h reaction time and 55% conversion no further reaction was observed for reasons not clarified. Remarkably, methyl 2-phenylacrylate was formed exclusively instead of the expected methyl cinnamate (Scheme 1) [37].



Scheme 1 Unsuspected outcome of Heck reaction with dendrimer-stabilized Pd colloidal catalysts in $scCO_2$ [37].

7.4.2.3
Homogeneous or Heterogeneous Catalysis in C–C Coupling by Palladium Colloids?

The importance of colloids in C–C coupling reactions is generally accepted today. The open question remains whether colloidal particles themselves represent the true active species, or whether they are a precursor to smaller structures – ultimately mononuclear soluble metal complexes – as the active species. Along the same lines, for homogeneous catalysis with defined metal complexes as a precursor, it is debatable whether colloidal particles form as the true active species (Figure 1). The topic is attractive due to its relevance for the fundamental understanding of such catalytic reactions, as well as its practical importance. Ultimately answering the aforementioned questions is very difficult, as the actual active species can have very high activities of millions of turnovers per hour [13], making them hard to detect in the very low concentrations in which they are present.

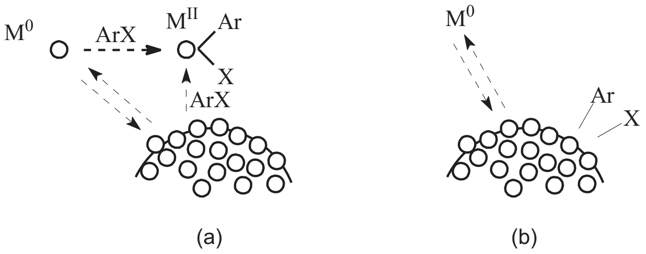


Figure 1 True active species (colloidal vs. smaller structures).

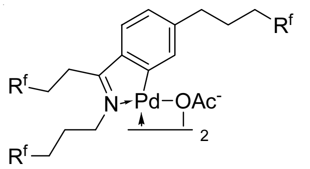
Mizoroki et al. demonstrated as early as 1971 that palladium black is active for the reaction of iodobenzene with styrene [11]. Beyond 2 mol% palladium black, no increase in activity was observed upon increasing the amount of catalyst [12]. The authors concluded that the reaction does not occur on the surface of palladium black in a heterogeneous fashion, but that the aryl halide reacts with palladium to form a soluble species. The low solubility of such compounds in the methanol solvent used was assumed to result in saturation by the soluble active species at low concentrations, accounting for the lack of effect of further increases in the amount of palladium black. At the same time, Julia et al. investigated the catalytic activity of palladium on charcoal for the Heck reactions, but focusing on the reactivity of aryl chlorides rather than mechanistic aspects [38, 39].

Reetz et al. addressed the function of palladium colloids in palladium-catalyzed C–C coupling reactions [40]. The homogeneous catalyst system $[PdCl_2(PhCN)_2]$/*N,N*-dimethylglycine (DMG) shows a clear induction period of ca. 1 h. Only after this time were colloidal 1.6 ± 0.3 nm palladium particles also detected by TEM of the reaction solutions. Nanoparticles are formed too in phosphine-free Heck reactions with addition of Bu_4NBr (Jeffrey conditions) as well as in Suzuki coupling utilizing only $[Pd(OAc)_2]$. On the other hand, with $[Pd(OAc)_2]/PPh_3$ or Herrmann's palladacycle [41] no nanoparticles were observed in the reaction solutions. Also, the tetraalkylammonium-stabilized colloids used in some investigations were found to react with aryl iodide to form soluble palladium(II) species (Ar–Pd–X_n), even with stoichiometic amounts [42].

In their investigations of Heck reactions of aryl bromides with very active "ligand-free" catalysts, based on [$Pd(OAc)_2$], de Vries et al. found that turnover frequencies increase strongly with decreasing catalyst concentration in the range 0.01–0.1 mol% palladium under a given set of conditions (135 °C; reaction of phenyl bromide with butyl acrylate) [43]. At a high concentration of 1 mol%, the reaction stops at an early stage and virtually no conversion is observed. These observations were ascribed to the active species being in equilibrium with (inactive) soluble palladium colloid particles, which can aggregate to palladium black. Thus, high catalyst concentrations would favor deactivation.

Extended X-ray absorption fine structure (EXAFS) has been employed recently for the investigation of the role of colloids in catalysis. For Heck reactions with Herrmann's palladacycle or with [$Pd(OAc)_2$]/P(*tert*-Bu)$_3$, no indication of formation of colloidal palladium was found [44]. By contrast, Koningsberger and co-workers found that in allylic amination with allylpalladium complexes with bidentate phosphine ligands, from the early stages of the reaction onward, deactivation occurs by formation of di- and trinuclear clusters, which aggregate to larger clusters and finally to palladium black [45].

A further well-documented example of the occurrence of metal colloids in homogeneous catalysts derived from defined transition metal complexes is provided by investigations by Gladysz et al. of Heck reactions with perfluro-substituted palladacycles (**3** and **4**) [46, 47]. The complexes are soluble in DMF at elevated temperatures, display high activities, and can be recovered by precipitation upon cooling. The course over time of the reaction, which has an induction period, the recycling behavior, and finally TEM images of the DMF solution after the Heck reaction suggest that colloidal palladium particles are the active species. As a stabilizer, $Et_3NH^+X^-$ formed in the Heck reaction was suggested.



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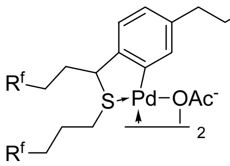

4

R^f: *n*-C_8F_{17}

Studies on C–C coupling reactions with heterogeneous palladium catalysts are also of interest in the context of the role of palladium colloids in such reactions. In early studies Augustine and O'Leary concluded that Heck reactions with supported palladium catalysts occurred in a heterogeneous fashion [48, 49]. By contrast, the occurrence of soluble palladium compounds also with heterogeneous palladium catalysts has been demonstrated in recent years by different research groups. In the examples investigated, the onset of the reaction was accompanied by significant "leaching" of palladium species into the liquid phase [50].

Biffis et al. concluded that, in C–C coupling reactions, heterogeneous catalysts are only a source of the actual soluble active species, which is formed under reaction conditions by interaction of the catalyst with one or more of the reagents [50]. They argued that the finding of a correlation of the number of corner and surface atoms with the catalyst activity of colloids in Heck reactions [19] and Suzuki reactions [24, 25] could also be explained by these atoms being particularly susceptible to dissolution as (mononuclear) complexes.

Arai et al. investigated Heck coupling of iodobenzene with methyl acrylate by heterogeneous palladium catalysts based on silica or charcoal as a support. Under reaction conditions a substantial portion of the palladium was already present in the liquid phase in the early stages of the reaction, and activities correlated with the palladium concentration in solution [51, 52]. The presence of only base or olefin did not result in detectable palladium concentrations. By comparison to silica, charcoal had a stronger propensity for readsorbing palladium from solution. Under appropriate conditions, a catalyst could be recycled without loss in activity [53].

In investigations of Heck reactions with different palladium-on-charcoal heterogeneous catalysts, Köhler and co-workers found that among other factors the palladium particle size had a strong effect [54]. A high degree of dispersion resulted in stronger leaching under reaction conditions, and consequently higher activities. Palladium concentrations in the liquid phase were highest in the early stages of the reaction. At the end of the reaction, the palladium was adsorbed onto the solid support, again nearly completely. Palladium particle sizes on the support were significantly increased after the reaction, as studied by TEM. Consequently, activities upon re-using these catalysts were significantly lowered by comparison to the first run.

In summary, palladium colloids are precursors to highly active catalysts for C–C coupling reactions. Whether the colloidal metal nanoparticles are the active species, or whether catalysis occurs by soluble metal complexes formed from the colloids under reaction conditions, cannot be answered unambiguously in a general sense to date.

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