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Polystyrene-supported diaminocarbene complexes of palladium(II): synthesis, characterization and application as a precatalyst in Sonogashira – Hagihara and Suzuki – Miyaura cross coupling

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One of the topical research areas dealing with Pd-catalyzed cross-coupling reactions is the development of regenerable catalytic systems through immobilization of highly active palladium complexes, clusters or nanoparticles onto an inert support. In the context of increased environmental requirements, highly active and multiply reusable heterogeneous catalytic systems have a number of practical advantages over homogeneous analogues. In this review, various approaches to immobilization on a polystyrene support of N-heterocyclic carbene and acyclic diaminocarbene palladium complexes have been considered for the first time; these complexes are a promising alternative to the widely used phosphine complexes. Special attention focuses on modern physicochemical methods used for investigation of corresponding heterogeneous systems. In addition, examples are given of using reusable heterogeneous catalysts for Sonogashira – Hagihara and Suzuki – Miyaura reactions, with emphasis on the true nature of the palladium catalytic species.
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I. Introduction

The study of catalytic cross-coupling reactions is a key area of modern organic chemistry, since such transformations make it possible to synthesize complex molecules in a highly selective way with atomic precision.[1] In particular, palladium-catalyzed Sonogashira – Hagihara and Suzuki – Miyaura cross coupling is used as a convenient and efficient tool in organic synthesis for preparing important substrates for pharmaceutical,[2 – 5] agrochemical and chemical industry.[6 – 8] In this context, the development of the chemistry of palladium-catalyzed cross-coupling reactions is currently undergoing an important stage, the main goal of which is the development of 'ideal' catalytic systems[9] capable of essentially increasing the efficiency of laboratory and industrial organic synthesis.

Current studies of Pd-catalyzed cross-coupling reactions pursue two separate goals:

1) synthesis of highly active homogeneous catalysts based on palladium clusters,[10 – 12] ligand-free palladium systems or stabilized palladium clusters,[13 – 15] capable of efficiently operating at low catalytic concentrations;

2) design of reusable catalysts[16] through immobilization of highly active homogeneous complexes and palladium clusters or nanoparticles on an appropriate support (inert under the reaction conditions used).

The latter approach aimed at developing catalysts that have high catalytic activity in combination with the possibility of regeneration and reuse is obviously advan-

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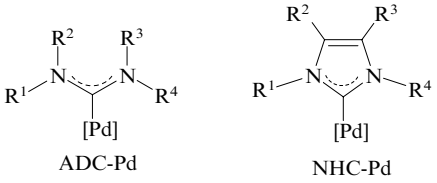
tageous for fine organic synthesis. However, it is worth noting that the application of heterogeneous precatalysts is basically limited to laboratory practice and they are not widely used commercially, which is mainly due to their low economic efficiency.[17] Thus, the development of new heterogeneous catalytic systems — active, with high turnover numbers (TON) and stable to irreversible leaching of palladium, and also convenient for production and use — is an important task of researchers working in this area.

Among catalytic systems for cross-coupling reactions, phosphine,[11,18,19] N-heterocyclic carbene (NHC-Pd)[20–24] and acyclic diaminocarbene (ADC-Pd)[25–28] complexes of palladium are of particular importance; some of them are commercially available compounds. As compared with phosphine complexes, diaminocarbene palladium complexes[27,29] exhibit high stability to air oxygen, which makes it possible to carry out reactions catalyzed by them under aerobic conditions. In addition, the noticeabled donor ability of the carbene ligand is responsible for the high strength of the metal–carbene bond and also promotes the key stage of oxidative addition involved in any catalytic cycle of cross-coupling reactions.

The history of the development of regenerable heterogeneous catalytic systems based on immobilized N-heterocyclic carbene complexes of palladium in cross-coupling reactions began in 2000 with the work of the German research team led by Wolfgang Herrmann, a noted scientist in the field of carbene coordination chemistry.[30] They successfully immobilized the NHC-Pd complex on a polystyrene support and demonstrated that the synthesized heterogeneous precatalyst exhibits high catalytic activity in the Heck reaction without appreciable loss of activity after 12 runs.

Currently, efficient heterogeneous catalytic systems based on N-heterocyclic carbene complexes of palladium immobilized on various supports have been developed.[31,32] Among the supports, functionalized polystyrene is one of the most frequently used and easily modified ones.[33] Low toxicity, high inertness with respect to a wide number of solvents and reagents in combination with the ease of separation from the reaction solution — it is precisely these features that contribute to the wide use of this support. It is noteworthy that the only commercially available heterogeneous precatalyst based on the N-heterocyclic carbene complex of palladium(II) [650927 ALDRICH — *N*-methylimidazolium palladium(II), polymer-bound] was obtained on the basis of polystyrene.

Carbene palladium complexes



To date, a number of reviews[16,31,34,35] have been published that include sections discussing the use of polystyrene-supported N-heterocyclic carbene palladium complexes as catalysts in cross-coupling reactions. However, in contrast to previous publications, this review addresses modern physicochemical methods of investigation used to study the surface of the corresponding heterogeneous systems (see Sections II, IV). Particular attention is paid to discussing the features of immobilization of carbene Pd complexes, including disadvantages and advantages of different approaches (see Section V). In the last Section VI, examples of reuse of heterogeneous precatalysts in the Sonogashira–Hagihara and Suzuki–Miyaura reactions are considered and data on the true nature of the catalytic species given in the original work are discussed. In analysis of the literature, the focus was on papers published in the period 2010–2016.

II. Methods of investigation of polystyrene supports functionalized with imidazolium salts

The most common solid phases for the synthesis of immobilized diaminocarbene palladium complexes are polystyrene (PS) supports functionalized with imidazolium salts (IS-functionalized). Before discussing modern approaches to the synthesis of such supports, one should dwell on the basic methods used to study the structure of their surfaces. Due to the possibilities of modern analytical chemistry, analysis of the solid phase becomes sufficiently informative, demonstrative and available, despite certain limitations in the choice of physicochemical methods for studying compounds immobilized on the resin surface.

Using IR spectroscopy, the presence of polymer-supported imidazolium salts can be confirmed by characteristic bands. In particular, the appearance of a strong band at 1653–1670 cm^{-1} due to C=N stretching vibrations[14,15] and a band at 1588 cm^{-1} arising from C=C stretching vibrations in the IR spectrum of modified polymers can be evidence of the existence of the corresponding structural fragment on the support surface.[36]

Another important optical method of analysis is Raman spectroscopy. This method enables qualitative and quantitative evaluation of the conversion of chloromethyl groups on the surface of the initial Merrifield resin† into imidazolium moieties (the degree of IS functionalization). Analysis is performed by monitoring the change in the intensity of the easily recognizable band at 1265 cm^{-1} in the spectrum of the unmodified sample.[37] This band corresponds to out-of-plane bending (wagging) vibrations of the CH_2 group bonded to the chlorine atom. From the change in the integral intensity of this band, it is possible to determine the degree of functionalization of the support and estimate the time required for complete conversion, which is especially useful for selecting optimal modification conditions. The change in the intensity of the C–Cl stretching vibration band at 678 cm^{-1} can also be a reliable indicator of the degree of IS functionalization of the Merrifield resin.[37] Moreover, Raman spectroscopy has special advantages for solving this problem since the

† Merrifield resin is a commercially available cross-linked polystyrene bearing benzyl chloride groups, which is mainly used for covalent binding of imidazolium salts to the support surface.

use of IR spectroscopy is limited by frequent overlapping of neighbouring bands in the observed spectral range.

As a rapid analysis for the presence of unreacted chloromethyl groups, there exists a so-called NBP test based on the qualitative reaction of 4-(4-nitrobenzyl)-pyridine with free chloromethyl groups.[38]

Scanning electron microscopy (SEM) assesses the presence or absence of destructive changes in the support in the course of the IS functionalization.[39, 40]

In the overwhelming majority of cases, the content of imidazolium salts on a modified support is quantified by elemental analysis.[36, 39 – 45]

The polarity of the microenvironment of the IS-functionalized polystyrene materials has a critical effect on their macroscopic properties, which, in turn, affects the catalytic activity of palladium precatalysts derived from them.[46] The polarity of the microenvironment on the surface of a functionalized support can be estimated from a change in the fluorescence spectrum of the adsorbed pyrene as a fluorescent probe. The polarity of the environment of the molecule can be judged by the change in the vibronic structure in the pyrene fluorescence spectrum consisting of five lines. The intensity of the first band ($\sim$370 nm) corresponding to the $S_1^{v=0} \rightarrow S_0^{v=0}$ transition depends on the polarity of the medium provided there is a vibronic coupling between states S_1 and S_2. The intensity of the third band ($\sim$382 nm) associated with the $S_1^{v=0} \rightarrow S_0^{v=2}$ transition is polarity independent. In particular, Luis and coworkers[46] have performed quantitative analysis of IS-functionalized resins with the use of pyrene as a fluorescent probe to study the polarity of a microenvironment. The original Merrifield resin, as expected, turned out to be less polar than the IS-functionalized resins with different counterions; the nature of the latter, in turn, affected the polarity of the modified resins.

III. Synthesis of polystyrene supports functionalized with imidazolium salts

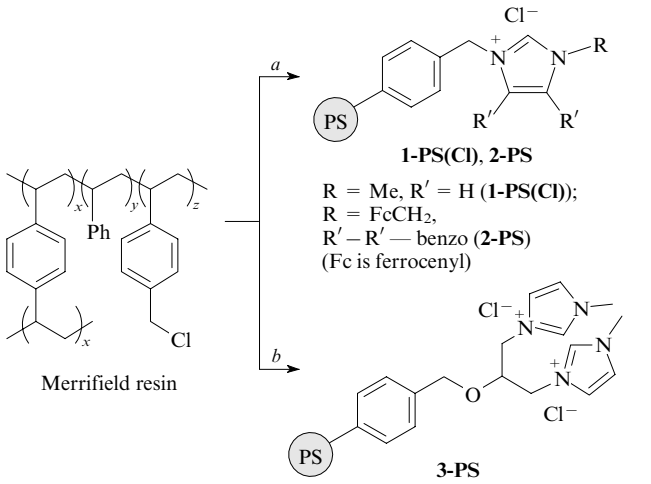
A general approach to the synthesis of N-heterocyclic carbene palladium complexes immobilized on a polymeric support is to treat the imidazolium salts covalently bound to the insoluble substrate, hereinafter referred to as IS functions, with a Pd precursor [$Pd(OAc)_2$, $PdCl_2$].

In the vast majority of cases, commercially available gel-type Merrifield resins, widely applied as solid-phase supports in the synthesis of peptides and also for the production of various modified resins, are used to prepare different IS-functionalized polystyrene supports. The Merrifield resin is a granulated cross-linked styrene – 4-(chloromethyl)styrene copolymer. Being a solid-phase functional analogue of benzyl chloride, the Merrifield resin is able to readily react with appropriate nucleophilic reagents, which leads to a targeted modification of the support surface. A major advantage of using cross-linked polymers as supports is the ease of handling (filtration, weighing, storage) and sufficient stability of spherical particles to the modification conditions, which is critical for most of subsequent applications. However, it should be taken into account that the grain size of a commercial support, the degree of cross-linking and the concentration of chloromethyl groups are of crucial importance in the synthesis of functionalized supports and directly affect their physicochemical properties.

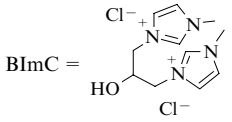
In solid-phase complexation and nucleophilic substitution reactions on the surface of polystyrene polymers, THF and DMF are most often used as solvents. This choice is due to the specificity of the reactions themselves and the good swellability of cross-linked polystyrene in these media (>4 ml g^{-1}), which facilitates rapid diffusion of the reagents into the macroporous structure of the support. It is optimal to carry out the functionalization of the polymer material at a temperature of $\leqslant$150 °C because of its possible destruction at higher temperatures.[47]

The IS-functionalized polystyrene supports discussed in this Section are referred to as ***n*-PS**, where *n* is the consecutive number; in some cases, a counterion is indicated in parentheses. The existing methods of synthesis of IS-functionalized polymer supports based on Merrifield resins can be divided into three general strategies. The most simple and often used classical strategy is a one-step synthesis. It can be carried out in two alternative ways. The first one involves the alkylation of *N*-alkylimidazole (benzimidazole) with benzyl chloride groups of the Merrifield resin. Samples **1-PS(Cl)** (Ref. 48) and **2-PS** (Ref. 39) have been synthesized by this method (Scheme 1 *a*). In this case, natural compounds can be used, for example, theophylline.[45, 49] In the second method, the nucleophilic displacement of the chlorine atom of the support is carried out using a pre-synthesized imidazolium salt with a hydroxyl-containing substituent as, for example, in the preparation of IS-functionalized polymer **3-PS** (Refs 40 and 50) (see Scheme 1 *b*). Functionalization of the surface by means

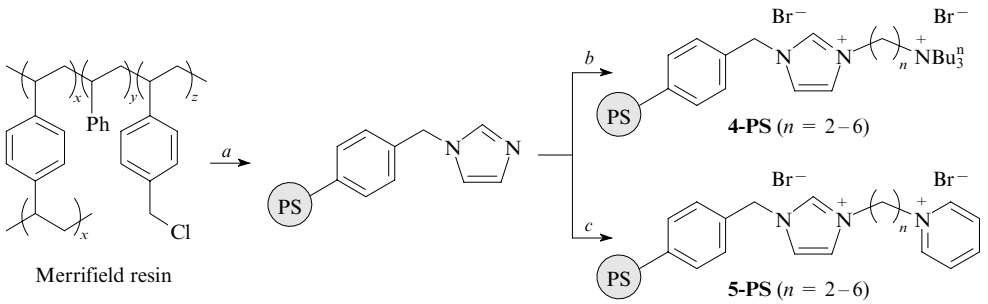
Scheme 1



(*a*) *N*-ferrocenylmethylbenzimidazole, DMF, 60 °C;[39] or *N*-methylimidazole, NMP, 80 °C, 12 h;[48] or *N*-methylimidazole, 90 °C;[41] (*b*) BImC, NaH, THF, rt, 48 h;[40] or BImC, Bu^n_3N, KI, DMF, rt, 4 days;[50] NMP is *N*-methyl-2-pyrrolidone



Scheme 2

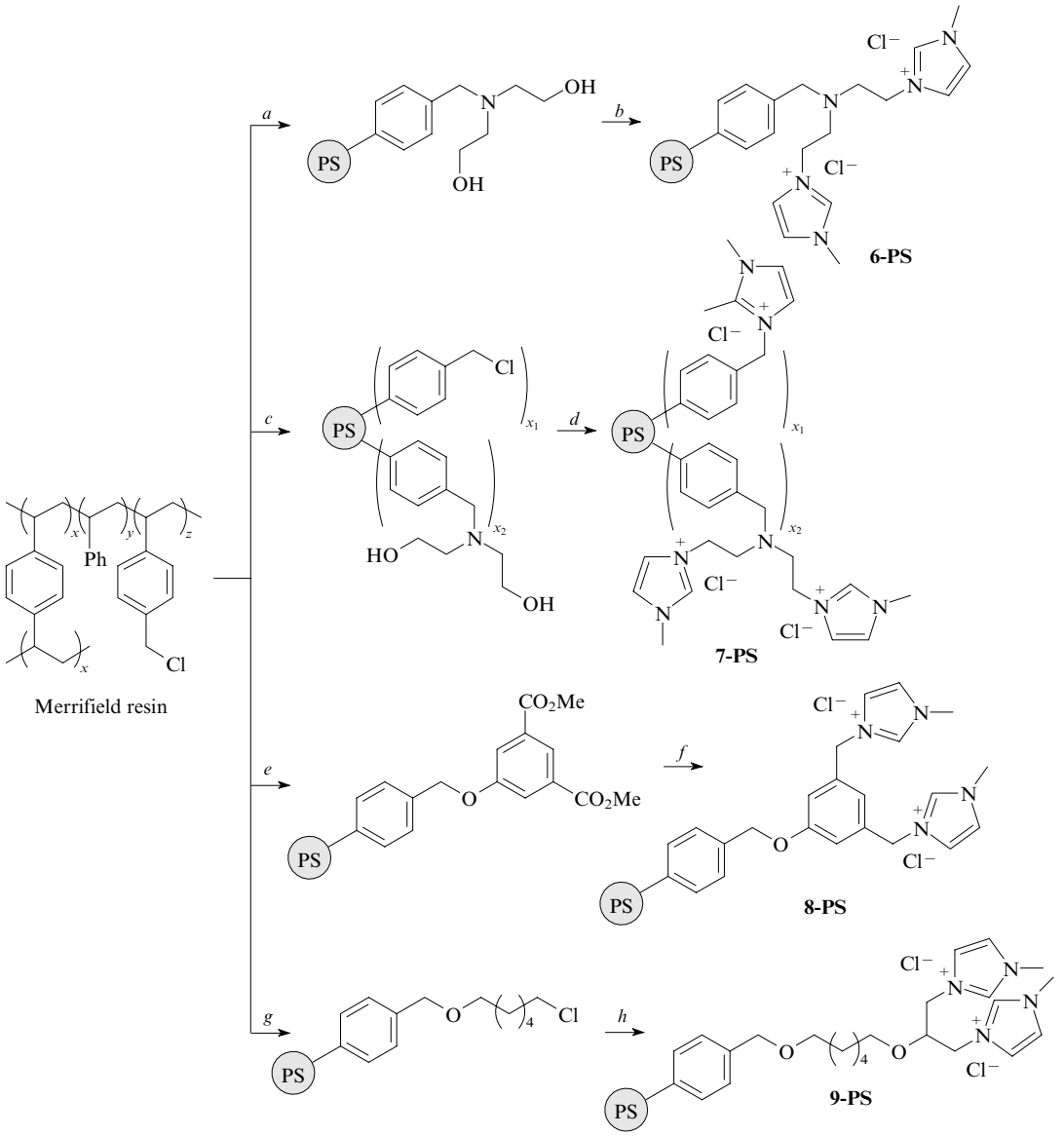


(*a*) Imidazole, DMF, refluxing, 4 h; (*b*) 1) 1,ω-dibromoalkane (ω = 2–6), refluxing, 4 h; 2) Bu^n_3N, 70 °C, 24 h; (*c*) 1) 1,ω-dibromoalkane (ω = 2–6), refluxing, 4 h; 2) pyridine, 80 °C, 12 h

of *N*-alkylimidazole derivatives is simplest in execution; however, for the introduction of a bis-IS-functionalized fragment, the first approach cannot be applied.

The second strategy involves at least two steps, namely: pretreatment of the Merrifield resin with N-unsubstituted imidazole and subsequent alkylation

Scheme 3



(*a*) Diethanolamine, DMF, 70 °C, 1 h;[36] (*b*) 1) $SOCl_2$, CH_2Cl_2, 50 °C, 4 h;[36] 2) *N*-methylimidazole, 80 °C, 2 h;[36] (*c*) diethanolamine, DMF, rt, 2 h;[36] (*d*) 1) 1,2-dimethylimidazole, DMF, 80 °C, 5 h;[36] 2) $SOCl_2$, CH_2Cl_2, 50 °C, 4 h;[36] 3) *N*-methylimidazole, 80 °C, 2 h;[36] (*e*) dimethyl-5-hydroxyisophthalate, acetone, 18-crown-6, K_2CO_3, refluxing, 12 h;[36] (*f*) 1) $LiBH_4$, $B(OMe)_3$ THF, N_2, refluxing, 24 h;[36] 2) $SOCl_2$, CH_2Cl_2, 50 °C, 4 h;[36] 3) *N*-methylimidazole, 80 °C, 2 h;[36] (*g*) 6-chlorohexanol, NaH, THF, rt, 48 h;[40] (*h*) BImC, NaH, THF, rt, 48 h (Ref. 40)

with alkyl bromides, which can be the final stage of synthesis or the preceding stage for further modification. This approach has been used to synthesize modified polystyrenes **4-PS** and **5-PS** (Scheme 2).[36]

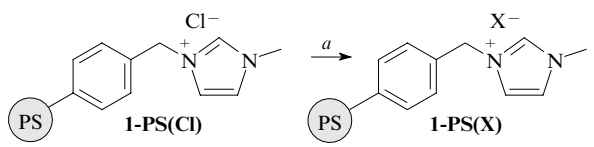
The third synthetic strategy consists of the preliminary modification of the support surface with a specific spacer followed by IS functionalization. In the synthesis of samples **6-PS**, **7-PS**, **8-PS** (Ref. 36) and **9-PS** (Ref. 40), this approach has been used to increase the distance between the IS function and the polymer backbone in order to reduce the steric effects of the latter (Scheme 3).

The measure of the efficiency of the synthesis method is the degree of modification of the active groups of the support, which is determined by both the physicochemical properties of the initial polymer material and the reaction conditions. It is evident that the degree of IS functionalization directly depends on the limiting concentration of chloride on the surface of the support. In particular, exposure of a suspension of Merrifield resins with different degree of cross-linking and chlorine content (1% DVB, 1.1 mmol Cl g^{-1} and 2% DVB, 4.3 mmol Cl g^{-1}; DVB is divinylbenzene) in pure *N*-methylimidazole at 90 °C led to IS-functionalized polymeric supports with a content of imidazolium fragments of 0.93 and 3.03 mmol IS g^{-1}, respectively.[43]

The degree of IS-functionalization has an effect on the degree of swelling of the material in polar (protogenic, aprotic) and nonpolar solvents. In particular, as the number of imidazolium fragments increased, the swellability of polymer **1-PS(Cl)** increased in polar protogenic solvents (H_2O, MeOH), did not change in DMF and decreased in nonpolar solvents (CH_2Cl_2, THF, toluene).[48]

It has been found that the properties of IS-functionalized polystyrenes also depend to a significant extent on the nature of the counterion. For example, polymer **1-PS(Cl)** was easily converted into the corresponding IS-functionalized supports containing other counterions[51] through anion exchange with $NaBF_4$, TfOH, $NaSbF_6$ and $LiNTf_2$ (Scheme 4). It has been demonstrated that the hygroscopicity of the samples decreases in the following series of counterions: $Cl^- > TfO^- > BF_4^- > SbF_6^- > NTf_2^-$. The polarity of the microenvironment of a polymeric material decreases in the series $Cl^- > TfO^- > NTf_2^- > BF_4^- > SbF_6^-$. In addition, the nature of the counterion also determines the ability of the modified support to swell in polar solvents (EtOH, H_2O). It is noteworthy that the original Merrifield resin, having a high swelling ability in DMF and a low swelling ability in an aqueous medium, after the modification, swells equally well in both DMF and H_2O. However, replacing the counterion by NTf_2^- leads to a change in the swellability to the level of the original Merrifield resin.

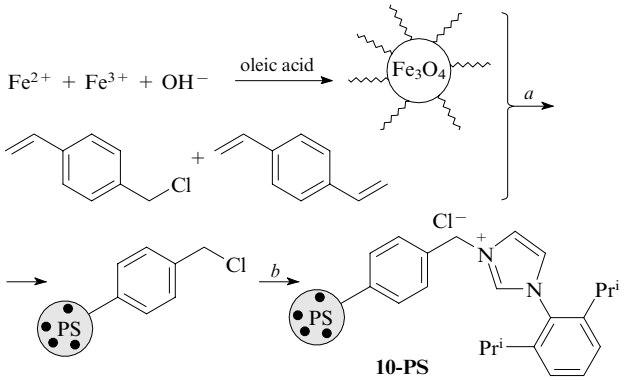
Scheme 4



(*a*) $NaBH_4$, or TfOH, or $NaSbF_6$, or $LiNTf_2$; MeOH – H_2O; X = TfO, BF_4, SbF_6, NTf_2 (Tf = CF_3SO_2)

In addition to works based on the commercially available Merrifield resin, examples of the synthesis of IS-functionalized supports with the preceding stage of polymerization of 4-(chloromethyl)styrene in the presence of divinylbenzene have been described. A principal feature of this approach is the possibility of obtaining supports that have a number of unique properties. In particular, miniemulsion polymerization was used to prepare magnetically active IS-functionalized supports **10-PS** (Ref. 44) and catalysts supported on them doped with superparamagnetic magnetite nanoparticles (Scheme 5). In addition, the relatively high dispersion of the material favourable for the diffusion of substrates and reagents is an extra advantage of such a support over the IS-functionalized supports synthesized from commercially available cross-linked polystyrene resins. The average diameter of the magnetically active particles of **10-PS** was 0.097 μm as compared with 75 – 150 μm (100 – 200 mesh) for the commercial Merrifield resin.

Scheme 5



(*a*) $K_2S_2O_8$, 80 °C, 24 h;[44] (*b*) *N*-(2,6-diisopropylphenyl)imidazole, PhMe, 90 °C, 24 h; ⁓ oleic acid molecules; ● magnetite particles

IV. Methods of investigation of polystyrene-supported N-heterocyclic carbene complexes of palladium

As in the case of IS-functionalized supports, the most common method for studying immobilized carbene complexes of palladium is IR spectroscopy. The formation of NHC-Pd complexes can be judged from the change in the intensities of absorption bands at 1157 – 1160 and 620 cm^{-1} [due to C(2) – H bond vibrations].[41, 52, 53] A decrease in intensity indicates the transformation of the C – H into the $C_{carbene}$ – Pd bond in the immobilized complex. Another criterion of the specific palladium immobilization is the increase in the intensity of the band at 1665 cm^{-1} (the C=C bond of an NHC ligand).[53] The formation of the NHC-Pd complex on support **2-PS** has been confirmed by the presence of another band characteristic of the NHC ligand at 1447 – 1476 cm^{-1} (N – $C_{carbene}$ – N moiety vibrations).[39, 45]

The use of solid-state ^{13}C NMR spectroscopy to prove the formation of an NHC-Pd complex by the

presence of characteristic signals of the carbene carbon atoms is limited due to the presence of signals of polystyrene carbon atoms in the spectrum and the relatively low resolution of the method.[54] The spectra of NHC-Pd-functionalized and unmodified samples show no difference.[53]

The Pd $3d_{5/2}$ and $3d_{3/2}$ electron binding energies measured by X-ray photoelectron spectroscopy (XPS) make it possible to not only confirm immobilization but also to assess the occurrence or absence of reduction side reactions in the course of applying palladium to the support,[40] as well as to study the oxidation state of palladium on the support surface after cross-coupling reactions.[44, 55]

Nearly in all cited papers, the palladium content on a support has been quantified by inductively coupled plasma atomic emission spectroscopy (ICP-AES) or mass spectrometry (ICP-MS). It should be noted that the development of mass spectral methods for the direct analysis of solid samples extends the analytical capabilities of this method as applied to the objects under consideration.[56] In some studies, the concentration of palladium on a support has been evaluated by energy-dispersive X-ray spectroscopy (EDX or EDS).[39]

The study of heterogeneous catalysts based on organic polymers by electron microscopy is difficult because of the low stability of organic compounds exposed to electron beam. This problem can be solved by using low-voltage microscopy and moderate electron beam currents.[57] In particular, scanning electron microscopy has been used to visually assess the presence or absence of destructive changes in the support in the course of immobilization of NHC-Pd complexes.[39, 40] In some cases, this method allows one to visualize the formation of palladium metal nanoparticles on the support in the course of immobilization.[41]

V. Synthesis of polystyrene-supported carbene complexes of palladium

Based on the analysis of the relevant literature, it can be concluded that the most popular method for the preparation of heterogeneous precatalysts based on carbene palladium complexes is the introduction of palladium into a support, pre-functionalized with imidazolium salts, by treatment with palladium(II) salts in the presence of a base or without it. The highest degree of NHC-Pd functionalization is achieved in the absence of an external base, when the imidazolium salt is deprotonated by the acetate anion in $Pd(OAc)_2$, which is probably due to differences in the carbene generation mechanisms.

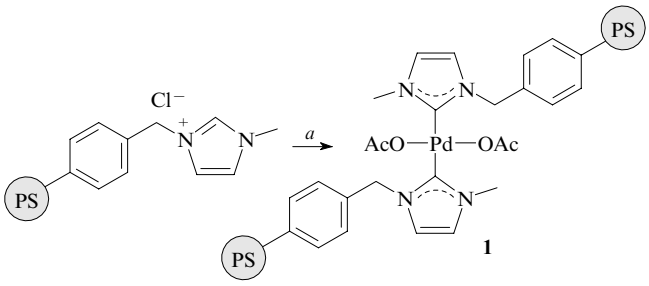
An alternative synthesis strategy involves the immobilization of a presynthesized homogeneous NHC-Pd complex or the polymerization of monomers containing an N-heterocyclic carbene palladium(II) complex. This approach makes it possible to directly prove the structure of the immobilized complex. However, when choosing the method for palladium immobilization in each specific case, it is necessary to take into account the physical and chemical properties of the substrates, and also to realistically assess the disadvantages and advantages of the methods in question, comparing them with the requirements to the desired heterogeneous precatalysts.

It should be noted that no reliable data on the structure of polystyrene-supported NHC-Pd complexes have been reported in some of the papers under discussion. Such NHC-Pd-containing systems are hereinafter referred to as **Pd-NHC-*n*-PS**, where ***n*-PS** is the corresponding IS-functionalized support. A similar designation was also used for complexes that, according to the authors of this review, have a contradictory description in the original work. For the other structures, standard digital numbering is used.

V.1. Metallation of the surface of modified polystyrene supports to give carbene complexes of palladium

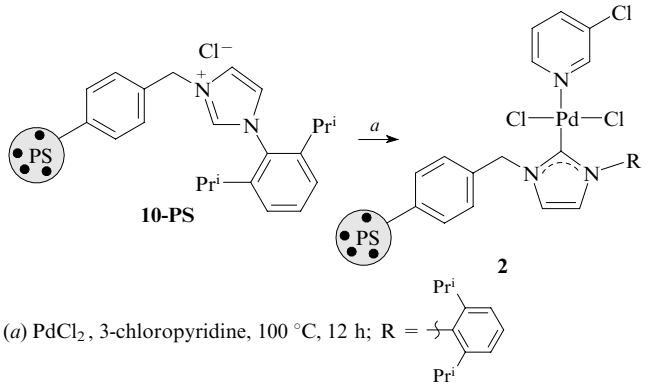
The conventional palladium immobilization strategy leading to an N-heterocyclic carbene complex on an IS-functionalized support involves the *in situ* generation of a carbene ligand (NHC ligand) by the reaction with a base [Na_2CO_3 (Scheme 6)[58–63] or Bu^tOK (Scheme 7)[36, 41, 43]] in an inert atmosphere with subsequent metallation of the activated ligand by means of treatment with palladium acetate [$Pd(OAc)_2$]. It is worth noting that, under these conditions, the concentration of immobilized palladium is always lower as compared to the total number of imidazolium moieties fixed on the support. This is especially the case for supports with a high degree of functionalization. The high concentration of imidazolium fragments in the bulk of the polymeric material is favourable for close spatial arrangement of base-generated NHC ligands, which increases the probability of the formation of the $(NHC)_2Pd$ structure

Scheme 6



(*a*) $Pd(OAc)_2$, Na_2CO_3, DMF–H_2O (1 : 1), 50 °C, 2 h

Scheme 7



(*a*) $PdCl_2$, 3-chloropyridine, 100 °C, 12 h; R =

(see Scheme 6, complex **1**). The presence of acetate anions in complex **1** have been demonstrated by the presence of signals at 14 ppm ($\underline{C}H_3COO$) and 187 ppm ($CH_3\underline{C}OO$) in solid state ^{13}C NMR spectra.[63] However, it is not clear from the data presented in this paper why the immobilized complex has been attributed to the $(NHC)_2Pd(OAc)_2$ structure rather than to a possible mixture of the $(NHC)_2Pd(OAc)_2$, $(NHC)_2Pd(OAc)Cl$ and $(NHC)_2PdCl_2$ structures. In the original paper[48] where the procedure used by Qureshi *et al.*[63] was described for the first time, the immobilized structure is denoted by the formula $(NHC)_2PdX_2$, which allows different combinations of ligands X.

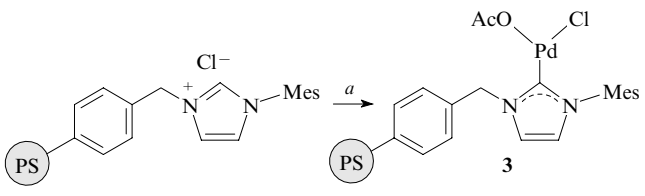
In addition, this method of immobilization often leads to the palladium concentration significantly lower than the NHC : Pd ratio (2 : 1), which indicates the presence of unreacted imidazolium fragments. This is assumed to be due to the diffusion limitations caused by the formation of the bis(carbene) structure $(NHC)_2PdX_2$ in the surfase layer of the polymer granule, which prevents the penetration of palladium into the support bulk and determines the preferential localization of the Pd complexes on the surface.[48] Given that the major contribution to the catalytic activity is made by the surface of polystyrene granules,[53, 64] the methods of immobilization of palladium with its predominantly superficial distribution can be considered acceptable and justified.

The approach involving the metallation of a modified support through the reaction with $Pd(OAc)_2$ in the presence of an external base (Bu^tOK) has also been used for palladium immobilization on supports.[36, 40] For example, precatalysts **Pd-NHC-*n*-PS** ($n = 4-8$) have been prepared on the basis of modified supports **4-PS** – **8-PS** (THF, 50 °C, 3 h) by this procedure.[36, 41, 43] However, their structures have not been described.

An interesting example of immobilization in the presence of an external base is the preparation of complex **2** (see Scheme 7),[44] which is structurally similar to the commercially available catalyst PEPPSI-IPr (CAS No. 905459-27-0). Under the reaction conditions, 3-chloropyridine acts as a base, a ligand and a solvent.

The immobilization of the NHC-Pd complex in the whole volume of a cross-linked polymer has been accomplished by Lee *et al.*[65] without the use of an external base and on a support with a relatively low concentration of the deposited imidazolium salt (0.32 mmol IS g^{-1}) (Scheme 8).

Scheme 8

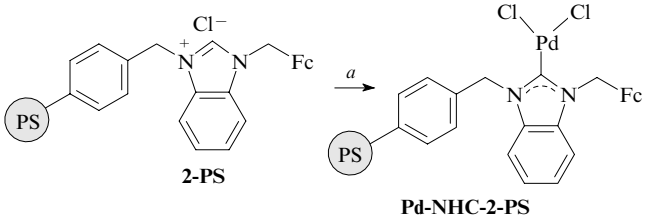


(*a*) $Pd(OAc)_2$, DMSO, 50 °C, 4 h → 100 °C, 0.5 h;
Mes = 2,4,6-$Me_3C_6H_2$

The presence of bulky substituents (Mes) at the nitrogen atom could also prevent the formation of a surface-localized bis(carbene) structure and favour the uniform distribution of monocarbene NHC-Pd complex **3** (0.33 mmol Pd g^{-1}) over the entire volume of the support.[65] A monocarbene structure has been attributed to the immobilized complex based on the experimental equimolar Pd : ligand ratio (0.33 mmol Pd g^{-1} and 0.32 mmol IS g^{-1}). The selectivity of the immobilization process without side occurring of metal reduction was proved by the XPS method based on binding energies of 336.5 and 337.7 eV corresponding to Pd^{II}. The absence of an external base is an important feature of this approach: under the conditions of heterogeneous complexation, the acetate anion in $Pd(OAc)_2$ acts as a deprotonating agent, which leads *in situ* to a uniform carbene generation and eliminates the need for an inert atmosphere, which is required when free carbene is generated by treatment with an external base.

The immobilized complex produced by refluxing a suspension of polymer **2-PS** and $Pd(OAc)_2$ in tetrahydrofuran in the absence of a base has been described by Gaikwad *et al.*[39] as the monocarbene complex $(NHC)PdCl_2$ (**Pd-NHC-2-PS**, Scheme 9). The high degree of IS functionalization of polymer **2-PS** (1.41 mmol IS g^{-1}) in this case did not prevent the nearly complete conversion of the imidazolium moieties into the corresponding palladium complexes (1 mmol Pd g^{-1}), which underlines the decisive effect of carbene generation conditions on uniform distribution of the immobilized complex.

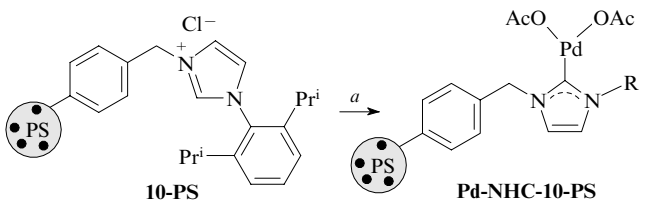
Scheme 9



(*a*) $Pd(OAc)_2$, THF, Δ, 48 h

At the same time, Wang *et al.*[44] have assigned the $(NHC)Pd(OAc)_2$ structure (**Pd-NHC-10-PS**, Scheme 10) to the immobilized complex formed under the conditions analogous to those described in Ref. 39. The structure of the monocarbene complex has been suggested on the basis of the experimentally determined equimolar Pd : ligand ratio (0.23 mmol Pd g^{-1} and 0.21 mmol IS g^{-1}). It is worth noting that the treatment of imidazolium salts with an equimolar amount of palladium acetate leads to the (NHC)Pd(OAc)X complexes;[65] if the imidazolium salt is taken in a twofold excess, the $(NHC)_2PdX_2$ complexes are formed (X is the counterion of the imidazolium salt).[53, 66] Given the

Scheme 10



(*a*) $Pd(OAc)_2$, DMSO, 50 °C, 12 h; R = 2,6-$Pr^i_2C_6H_3$

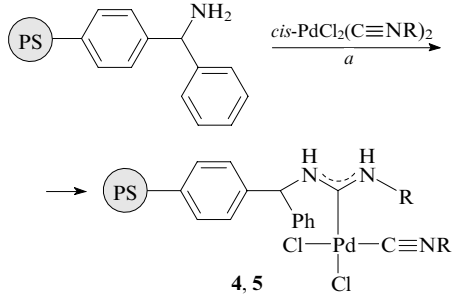
monocarbene character of the complexes described in Ref. 39 the adequacy of such an unambiguous interpretation of the immobilized structure is questionable.

To summarize, it is worth emphasizing that, because of known limitations when operating with such objects, it is not always a simple task to determine the immobilized structure.

It is essential that palladium immobilization through the metallation of the support with a high degree of IS functionalization can be accompanied by the side process of palladium reduction. For example, according to XPS data, there is a Pd^{II}/Pd^{0} mixture on the support in those cases when supports **1-PS(X)** with a high concentration of the applied imidazolium salt are used for immobilization.[41] The authors believe that the presence of Pd^{0} is associated with the affinity of the supports under consideration to polar solvents. Thus, Pd^{II} is partially reduced by a significant amount of methanol used in the synthesis and is adsorbed onto the polymer. Moreover, for polar supports **1-PS(Cl)** and **1-PS(TfO)**, the fraction of reduced palladium (Pd^{0}) was determined to be higher than for less polar support **1-PS(BF_4)**, which is extra evidence for the crucial role of the support microenvironment on the immobilization selectivity.

A radically different approach to the formation of diaminocarbene complexes on the polystyrene surface was described in 2016.[55] To simultaneously generate and immobilize acyclic diaminocarbene palladium(II) complexes (ADC-Pd) **4** and **5**, a simple metal-mediated reaction of nucleophilic addition of an NH_2 group of commercially available benzhydrylamine polystyrene resin to the isocyanide ligand of the palladium(II) complex was used (Scheme 11). The reaction proceeds under mild conditions with high regioselectivity (no ligand exchange products are observed). It is important that, under these conditions, immobilization is not accompanied by the side reduction of Pd^{II} to Pd^{0}, which often occurs under common conditions of NHC-Pd immobilization with the use of $Pd(OAc)_2$. The absence of reduction side processes makes it possible to determine with high accuracy the structure of the immobilized complex acting as a precatalyst in cross-coupling reactions. The immobilization has been proved by comparing the IR spectra of the immobilized complex and the non-immobilized complex pre-synthesized through the reaction with benzhydrylamine. The presence of only one CN stretching vibration band at 2225 cm^{-1} ($R = Bu^t$) in the spectrum of the immobilized complex (see Scheme 11), as distinct from the initial $PdCl_2(CNBu^t)_2$ complex for which the spectrum shows two bands of CN symmetric and antisymmetric stretching vibrations, has been used to confirm the formation of the mixed isocyanide-carbene complex on the polymer surface.

Scheme 11



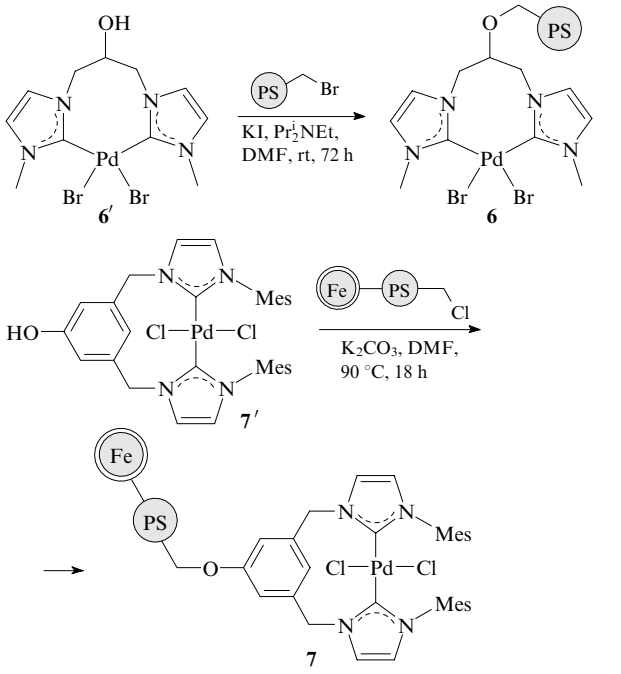
(*a*) $CHCl_3$, rt, 24 h; $R = Bu^t$ (**4**), Cy (**5**); Cy is cyclohexyl

This approach was also successfully used to synthesize acyclic diaminocarbene complexes of palladium(II) immobilized on a polymer support modified with chiral amino acid moieties.[67] Thus, the method enables the one-stage high-selectivity generation and immobilization of acyclic diaminocarbene complexes of palladium(II) with different structures by varying palladium isocyanide complexes and amino-functionalized supports.

V.2. Immobilization of pre-synthesized N-heterocyclic carbene complexes of palladium(II)

An alternative synthetic strategy involves direct immobilization of the pre-synthesized NHC-Pd complex **6′** containing a nucleophilic hydroxyl group to give complex **6** (Scheme 12).[42] Thus, the immobilized complex is bound to the support through a linker. Explaining the choice of this synthetic approach, the authors focused on the possibility of direct proof of the structure of the immobilized complex, pointing out the lack of an unambiguous description of the structure of such a complex obtained through the reaction of the IS-functionalized support with $Pd(OAc)_2$ in early works of Luo's team.[68–70]

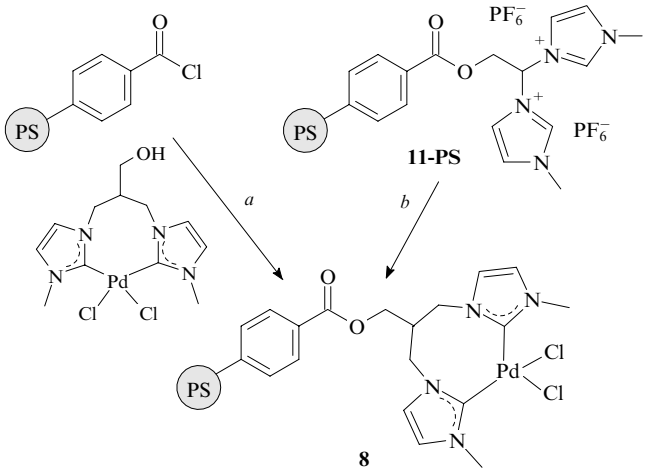
Scheme 12



The immobilization of the pre-synthesized NHC-Pd complex **7′** in the presence of a base on magnetically active nanoparticles with a chloromethylpolystyrene coating also led to complex **7** (see Scheme 12).[71]

Comparison of two alternative approaches (Scheme 13) to the synthesis of compound **8** revealed that the efficiency of the method used depends on the solubility of the preliminarily obtained complex under immobilization conditions.[54] If the complex is poorly soluble, the optimal strategy is to immobilize a target NHC-Pd complex through metallation of the corresponding IS-functionalized support **11-PS** (see Scheme 13, path *b*).

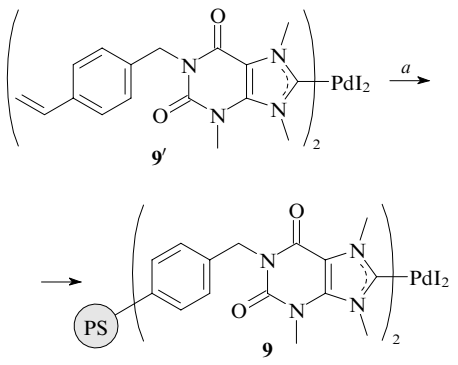
Scheme 13



(*a*) Pyridine, NMP, rt – 150 °C, 24 h;
(*b*) $PdCl_2$, NaOAc, DMSO, rt – 90 °C, 44 h

The synthesis of a supported NHC-Pd complex through the azobis(isobutyronitrile) (AIBN)-catalyzed copolymerization of the preliminarily synthesized *p*-vinylbenzyl-substituted diaminocarbene complex of palladium **9′** based on theobromine with a styrene excess has been described (Scheme 14).[52] Complex **9** grafted to a non-cross-linked polystyrene chain can act as a heterogeneous precatalyst in an aqueous medium. Owing to the good solubility of the polymeric support in organic solvents, the immobilized complex was studied by gel permeation chromatography (M_w = 13 780) and ^{1}H NMR (DMSO-d_6). Comparison with the spectrum of the monomer made it possible to assume that the initial structure of the complex was retained after polymerization.

Scheme 14



(*a*) Styrene, AIBN, DMF, 150 °C, 48 h

VI. Application of polystyrene-supported carbene complexes of palladium in catalysis of Sonogashira – Hagihara and Suzuki – Miyaura cross coupling

In the discussion of the use of heterogeneous precatalysts, a particular issue is the nature of the real catalytic palladium species. Alternative possibilities are considered for the reaction to occur both on the support surface and in the solution in which, after leaching from the support, catalytically active molecular complexes of palladium and/or colloidal palladium particles (clusters, nanoparticles and submicron particles) can be present.[72 – 74] The dynamic character of the distribution of catalytic palladium species between phases in cross-coupling reactions is increasingly frequently considered in modern research;[75 – 77] this feature enables the reuse of heterogeneous precatalysts when palladium is leached into a solution and then physi- or chemisorbed onto the support after the end of the catalytic reaction and the complete conversion of the substrate. Such heterogeneous catalytic systems are often referred to as 'release and catch' or 'boomerang' systems.[75, 78, 79]

In most of the papers discussed in this review, the heterogeneous nature of catalysis is attributed to the catalytic systems based on polystyrene-supported diaminocarbene palladium complexes for the Suzuki – Miyaura reaction. In favour of the heterogeneous nature of catalysis, the authors give negative results of the 'hot filtration test', the absence of substantial leaching of palladium into the solution after the reaction (according to the analysis of the reaction solution or support by various spectral methods), and insignificant changes in the catalytic activity of the precatalyst after multiple reuse. However, it is worth noting that in order to reliably establish the true nature of the catalytic species, a wide range of complementary methods should be applied.[72, 80, 81]

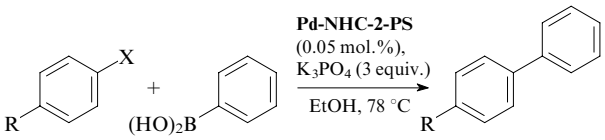
For the Sonogashira – Hagihara reaction catalyzed with multiply reused immobilized diaminocarbene complexes of palladium, catalysis is of homogeneous nature (boomerang system) owing to reversible leaching of catalytically active palladium species from the support. The observed difference can be caused both by the possibility that the Suzuki reaction is catalyzed by homeopathic amounts of the leached palladium and by different reaction mechanisms involved when heterogeneous precatalysts are used, which requires an additional comprehensive study.

VI.1. Suzuki – Miyaura reaction catalyzed by immobilized N-heterocyclic carbene complexes of palladium(II)

Rashinkar and co-workers[39] have demonstrated that immobilized complex **Pd-NHC-2-PS** (see Scheme 9) taken in a concentration of 0.05 mol.% is a highly active precatalyst in the Suzuki – Miyaura coupling, exhibiting high catalytic activity in EtOH. Ethanol, acetone, DMF, MeCN, THF and toluene were studied as solvents, and K_3PO_4, K_2CO_3 and KOH were used as bases. Refluxing in ethanol with the use of K_3PO_4 as a base was selected as the optimal conditions for the coupling of phenylboronic acid with different aryl iodides, aryl bromides and aryl chlorides (Scheme 15).

Under optimized conditions, the precatalyst in the reaction of iodobenzene with phenylboronic acid showed the ability to regenerate without significant loss of catalytic activity in the five catalytic runs. Scanning electron microscopy has demonstrated that the reaction conditions do not lead to destructive changes in the spherical morphology of the granular heterogeneous precatalyst **Pd-NHC-2-PS**. The reaction of aryl iodides proceeded in short times (~20 min) to give the target product in high yields (79%–82%). Under the same conditions, aryl chlorides reacted in 60–139 min to give the products in moderate yields (49%–69%). To determine the nature of the catalysis, a 'hot filtration test' was used, which showed that there was no further increase in the reaction product concentration after the separation of **Pd-NHC-2-PS**. In experiments on reuse, this heterogeneous precatalyst exhibited high stability in the course of, at least, six runs and did not lose its activity after two weeks of storage in air at room temperature. Relying on these data, the authors have concluded that heterogeneous catalysis is realized when the precatalyst **Pd-NHC-2-PS** they developed is used.

Scheme 15

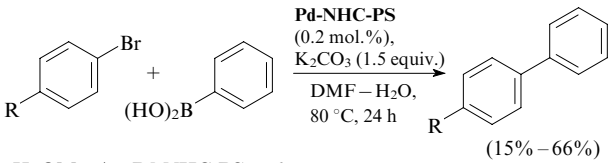


R = H, Ac, CHO, OH, Me, CF_3, NO_2, NH_2

X	Time /min	Yield (%)
I	18–21	79–82
Br	30–42	68–80
Cl	60–139	51–69

Heterogeneous catalyst **6** (see Scheme 12), containing an immobilized NHC-Pd chelate, was reported[42] to catalyze, with moderate activity, the coupling of phenylboronic acid with bromobenzene as well as with activated and deactivated aryl bromides: after 24 h at 80 °C, the yield of the products was no more than 66% (Scheme 16). In addition, for all substrates, the catalytic activity of complex **6′** was compared with that of immobilized complex **6**. It was shown that on going from the homogeneous catalytic system to the heterogeneous one, the decrease in the yield of the products was no more than 8%. Based on analysis of the liquid phase, the authors stated that the diaminocarbene complex was retained immobilized. However, no data were given on the method by which the reaction solution was studied for palladium content.

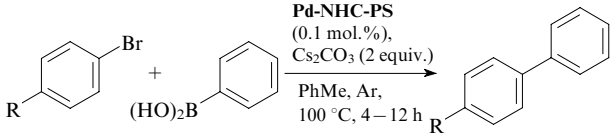
Scheme 16



R = H, OMe, Ac; **Pd-NHC-PS** = **6**

Later, Herrmann and co-workers[54] have studied the Suzuki–Miyaura reaction catalyzed by immobilized NHC palladium(II) chelate **8** (see Scheme 13). In the reactions of aryl bromides with phenylboronic acid under optimized conditions (Cs_2CO_3 as a base, toluene), precatalyst **8** (0.25 mol.%) could be used without significant loss in activity during four runs (Scheme 17). The lack of palladium leaching from the support surface was proved by the hot filtration test, which allowed the authors to state the heterogeneous nature of catalysis.

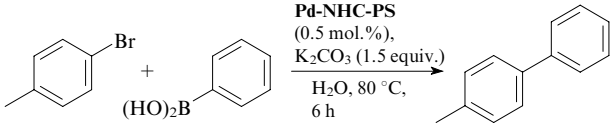
Scheme 17



R = OMe, Ac, CHO; **Pd-NHC-PS** = **8**

An interesting example of using N-heterocyclic carbene palladium(II) complex **9** immobilized on a linear polymer (see Scheme 14) in the Suzuki–Miyaura reaction in an aqueous medium has been described.[52] K_2CO_3 or Bu^tONa has been used as a base. The nature of this precatalyst is essentially different from that of most of the catalysts presented in this review, synthesized on the basis of insoluble cross-linked functionalized polystyrenes. Being highly soluble in most of organic solvents, the complex immobilized on a polymeric support is not dissolved in an aqueous medium and acts as a heterogeneous precatalyst in the reaction of 4-bromotoluene with phenylboronic acid (Scheme 18). After reuse for three times, precatalyst **9** (0.5 mol.%) showed insignificant loss of catalytic activity at 80 °C (yield of 67%, 65% and 61% for the first, second and third runs, respectively). Thus, the cross-linked nature of the support is not a prerequisite for the successful regeneration of the immobilized NHC-Pd complex. However, it should be noted that the results of the hot filtration test or the quantitative determination of the palladium leaching into a solution during the reaction have not been reported in this paper. Moreover, comparison of the catalytic activity of heterogeneous and structurally similar homogeneous (monomer **9′**) catalytic systems has not revealed differences.

Scheme 18

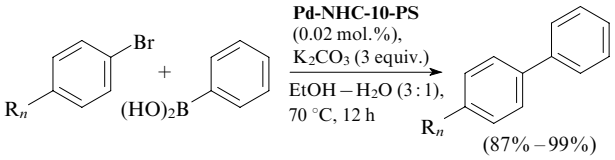


Pd-NHC-PS = **9**

An interesting and promising approach for enhancing recyclability of the catalytic systems is to metallize, with $Pd(OAc)_2$ or $PdCl_2$, a specially synthesized IS-functionalized polystyrene support doped with magnetite nanoparticles.[44] Precatalysts **Pd-NHC-10-PS** and **2** thus synthesized (see Schemes 7, 10) exhibited high catalytic activity in the Suzuki–Miyaura reaction. As solvents,

EtOH – H_2O (3 : 1 and 1 : 1), dioxane – H_2O (1 : 1), THF – H_2O (1 : 1), DMF – H_2O (2 : 1 and 1 : 1) and toluene – H_2O (1 : 1) mixtures have been studied, and M_2CO_3 (M = Na, K, Cs), K_3PO_4, MOH (M = Na, K) and Et_3N have been used as bases. An obvious advantage of this catalytic system was the possibility to separate the precatalyst using simple magnetic decantation. Precatalyst **Pd-NHC-10-PS** (0.02 mol.%) efficiently catalyzed the reaction of different aryl bromides with phenylboronic acid in an EtOH – H_2O (3 : 1) mixture in the presence of K_2CO_3 (3 equiv.) in 12 h to give target products in high yields (Scheme 19). A practically important result of this study is that the catalyst **Pd-NHC-10-PS** (1 mol.%) demonstrated the possibility of multiple regeneration (21 run) without loss of catalytic activity in the model reaction of *p*-bromophenone with phenylboronic acid. The heterogeneous nature of catalysis was confirmed by the negative hot filtration test. In addition, the ICP-AES method has shown that 99.8% of palladium remain on the support after the 21st run, which demonstrates the lack of palladium leaching in the course of reaction. X-ray powder diffraction has also shown that, after the reaction, no palladium nanoparticles are formed on the support surface. The absence of agglomeration of palladium into nanoparticles after the reaction is evidence in favour of the heterogeneous nature of catalysis. The authors explain the stability of the complex on the surface by the nature of the ligand, which is a bulky N-heterocyclic carbene strongly bound to the metal centre.

Scheme 19

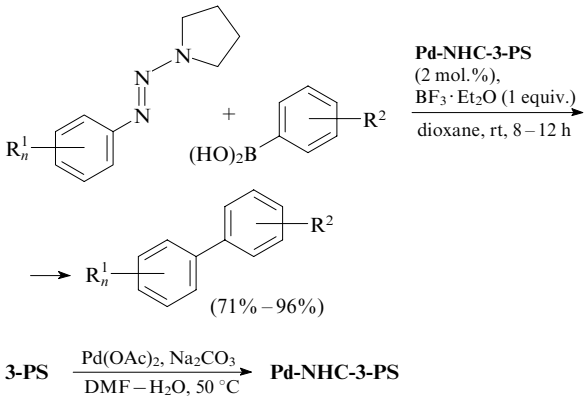


R_n = 4-Ac, 4-CHO, 4-OMe, 4-CO_2H, 4-Me, 4-CN, 2-Me, 4-NO_2, 2,3-benzo

When aryl chlorides were used as substrates, a reaction had to be carried out at higher temperature (100 °C). However, in this case, when catalyst **Pd-NHC-10-PS** was used, there was a noticeable leaching of palladium (2% – 5%) into the reaction solution. Going from precatalyst **Pd-NHC-10-PS** to immobilized complex **2**, containing 3-chloropyridine as a stabilizing ligand, made it possible to significantly enhance the stability of the catalytic system while it retained its high activity. The authors point out the heterogeneous nature of catalysis in the presence of the catalytic systems under study.

There are examples of the use of precatalysts based on polystyrene-immobilized N-heterocyclic carbene complexes of palladium, when aryltriazenes are used as substrates in the Suzuki – Miyaura reaction instead of aryl halides, which makes it possible to carry out the reaction under mild conditions with high chemoselectivity. Luo and co-workers [50] carried out the reaction of 1-aryltriazenes with arylboronic acids with the use of 2 mol.% of the precatalyst **Pd-NHC-3-PS** (Scheme 20, the positions of the substituents are specified in the initial compounds). Dioxane, dimethoxyethane (DME), THF, MeCN, DMF and DMSO have been studied as solvents. Optimal conditions were reached when the reaction was carried out in dioxane in the presence of an equivalent amount of Lewis acid ($BF_3 \cdot Et_2O$) at room temperature for 8 – 12 h to give the target products in high yields. It was found that the precatalyst could be reused in eight runs without significant loss of catalytic activity: the difference between the product yields in the first and eighth runs did not exceed 14% (92% and 78%). To confirm the heterogeneous nature of catalysis with the participation of **Pd-NHC-3-PS**, a hot filtration test was performed, which gave a negative result.

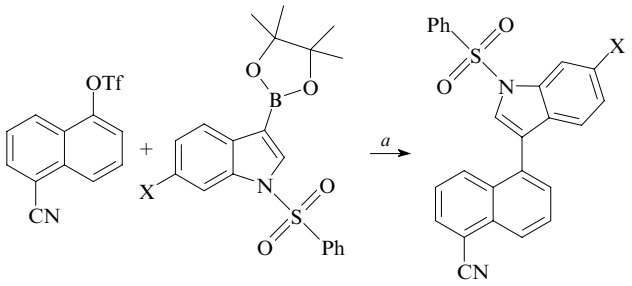
Scheme 20



R^1_n = H, 4-I, 4-Br, 4-Me, 4-OMe, 2-NO_2, 3-NO_2, 4-NO_2, 2-Me-4-NO_2;
R^2 = H, 4-CHO, 4-Me, 4-OMe, 3-NO_2

Heterogeneous precatalyst **Pd-NHC-3-PS**, previously developed by Luo an co-workers,[50, 68 – 70] has been used by Reddy's team [82] in the multistage synthesis of oxazole derivatives with potential antibacterial, antifungal, antituberculosis and anti-inflammatory activity. The multistage synthesis was based on the Suzuki – Miyaura reaction of 5-cyano-1-naphthyl trifluoromethanesulfonate with indolylboronate. The reaction was carried out in dimethoxyethane with the use of Na_2CO_3 as a base (Scheme 21). The heterogeneous precatalyst retained the high activity in the course of at least six runs.

Scheme 21

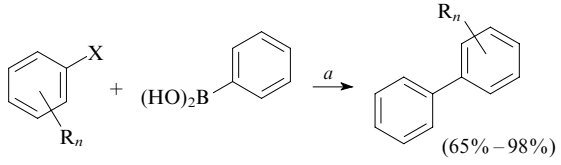


(*a*) **Pd-NHC-3-PS** (2 mol.%), Na_2CO_3, DME, 80 °C, 12 h; X = F, Cl

Catalytic systems based on polystyrene-immobilized acyclic diaminocarbene complexes of palladium were used in the Suzuki – Miyaura cross coupling of a wide range of aryl iodides and bromides with phenylboronic acid (Scheme 22).[55] The optimal reaction conditions for precatalysts **4** and **5** were as follows: DMF in the

presence of 5 vol.%–10 vol.% of water and K_2CO_3 as a base. The demonstrated ability of repeated reuse of catalysts **4** and **5** without significant loss in catalytic activity combined with the ease of obtaining makes these systems promising for synthetic application. It is noteworthy that the XPS study of the support before and after the reaction showed no change in the oxidation state of palladium(II), which can be indirect evidence that the immobilized complex was retained during the reaction. A detailed study of the nature of catalysis was not carried out in this work.

Scheme 22

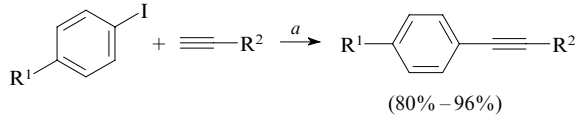


(*a*) **Pd-ADC-PS** (5 mol.%), Et_3N or K_2CO_3 (4 equiv.), DMF–H_2O, 70 °C, 50–150 min; **Pd-ADC-PS** = **4**, **5**; X = I, Br; R_n = 4-OMe, 4-NO_2, 4-CN, 2-Me-4-NO_2

VI.2. Sonogashira–Hagihara reaction catalyzed by immobilized N-heterocyclic carbene complexes of palladium(II)

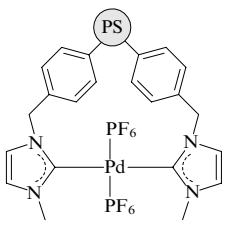
The use of a polystyrene-supported N-heterocyclic carbene palladium(II) complex as the precatalyst in the Sonogashira–Hagihara reaction was mentioned for the first time by Lee and co-workers.[83] When catalyzed by precatalyst **10** (1 mol.%), the cross-coupling of aryl iodides with terminal acetylenes in the presence of Cs_2CO_3 as a base proceeded at 60 °C for 1–4 h under copper-free conditions in ambient atmosphere to form the corresponding unsymmetrical alkynes in high yields (Scheme 23). The reaction was studied in DMF–H_2O (3 : 1), MeCN–H_2O (3 : 1), THF–H_2O (3 : 1) and dioxane–H_2O (3 : 1) mixtures in the presence of Cs_2CO_3, NaOH, pyridine, piperidine and 4-dimethylaminopyridine as bases. The use of piperidine as a base for some substrates (aryl bromides and 4-iodoanisole) was more preferable. However, under given conditions, the reaction exhibited critical dependence on the amount of the base: an increase in the piperidine amount was accompanied by a decrease in the yield of the product in the reaction of 4-iodoanisole with phenylacetylene in a DMF–H_2O (3 : 1) mixture at 80 °C. The increase in the base amount to 7 equiv. completely suppressed the catalytic system. According to the authors, this behaviour is associated with the difficulty of coordination of the alkyne to the Pd centre at a large excess of piperidine, which can act as a ligand.

Scheme 23



(*a*) **10** (1 mol.%), Cs_2CO_3 (1.6 equiv.), DMF–H_2O (3 : 1), 60 °C, 1–8 h; R^1 = H, Ac, OMe, NO_2, Cl, CF_3, Me; R^2 = Ph, 4-MeC_6H_4 4-$Bu^tC_6H_4$, 4-$MeOC_6H_4$, 4-NCC_6H_4, n-C_6H_{13};

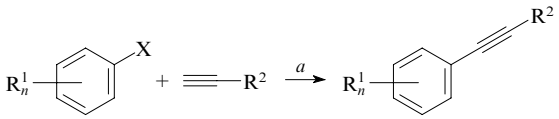
10 =



It is also important to note that this catalytic system could be used in four runs of the reaction of 4-iodoacetophenone with phenylacetylene under optimized conditions without loss of catalytic activity. Each reaction run was carried out for 1 h, and the yield of the product from the first to the fourth run was retained at 94%. Although the nature of catalysis was not discussed in the paper, the absence of Pd leaching into the solution from the support during the reaction was revealed by the ICP-AES method (the support was analyzed).

Salunkhe and co-workers[40] have studied the effect of the presence and absence of a spacer tethering the complex to the support surface in immobilized complexes **Pd-NHC-9-PS** and **Pd-NHC-3-PS** on their catalytic activity towards the Sonogashira–Hagihara cross-coupling reaction. It has been found that catalyst **Pd-NHC-9-PS** with a spacer is somewhat more active than precatalyst **Pd-NHC-3-PS**, due to the greater accessibility of active catalytic sites. The high activity of precatalyst **Pd-NHC-9-PS** (1 mol.%) has been demonstrated in the reactions of different aryl bromides with arylalkynes containing both electron-withdrawing and electron-releasing substituents. It is worth noting that all the reactions proceed under solvent-free conditions for 1.5–8 h to give target products in high yield (Scheme 24). As bases, Et_3N, pyridine, piperidine and pyrrolidine have been studied. At the same time, in the reaction of aryl chlorides with phenylacetylene, the yield of the target product after 12 h was no higher than 30%.

Scheme 24



(*a*) **Pd-NHC-*n*-PS** (1 mol.%), Et_3N (2 equiv.), 90 °C, 1.5–8 h (X = Br, 70%–95% yield) or 12 h (X = Cl, 20%–30%); R^1_n = H, 4-NO_2, 4-OMe, 4-Me, 4-CHO, 4-Ac, 4-NH_2, 4-CN, 2,4,6-Me_3, 4-Bz; R^2 = Ph, 4-MeC_6H_4

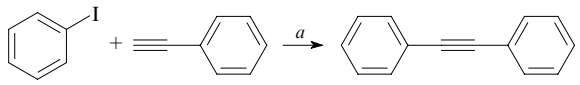
***n*-PS** $\xrightarrow[60\ ^\circ C,\ 8\ h]{Pd(OAc)_2,\ THF}$ **Pd-NHC-*n*-PS**

n = **3**, **9**

It is important that both precatalysts in the reaction of 1-iodo-4-nitrobenzene with phenylacetylene can be used within of five runs. The precatalyst **Pd-NHC-9-PS**, including experiments with repeated reuse, has exhibited higher relative efficiency. The decrease in the activity of **Pd-NHC-9-PS**, observed as a decrease in the yield of the product from the first to the sixth run was no higher than 20% (95% and 75%, respectively). However, it should be noted that the authors[40] have reported no data on the hot filtration test or quantitative determination of the palladium leaching into the solution from the support during the reaction.

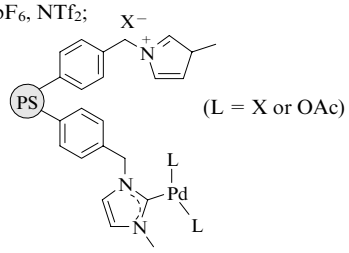
It has been previously noted that the simplest way to synthesize the polystyrene-supported N-heterocyclic carbene complexes of palladium(II) is through the direct metallation of supports pre-functionalized with imidazolium salts by means of $Pd(OAc)_2$. The nature of the counterion in the immobilized imidazolium salt can be varied over a wide range through anion exchange with the imidazolyl chloride-functionalized resin [**1-PS(Cl)**]. Luis team has studied the effect of the degree of IS functionalization, the nature of the base used and the counterion in immobilized N-heterocyclic carbene palladium(II) complexes on their catalytic activity and stability for the copper- and phosphine-free Sonogashira – Hagihara reaction.[43] Tetra-n-butylammonium acetate and benzoate, piperidine and Et_3N were used as bases. The effect of the anion was studied for the model reaction of iodobenzene with phenylacetylene in DMF at 70 °C catalyzed by 0.1 mol.% of the precatalyst in the presence of tetra-n-butylammonium benzoate (TBAB) as a base (Scheme 25).

Scheme 25



(*a*) **Pd-NHC-1-PS(X)** (0.1mol.%), TBAB (2 equiv.), DMF, 70 °C; X = Cl, TfO, BF_4, SbF_6, NTf_2;

Pd-NHC-1-PS(X) =

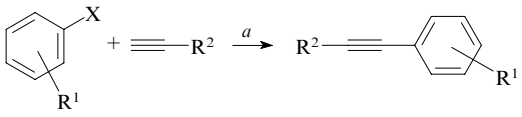


(L = X or OAc)

When precatalyst **Pd-NHC-1-PS(Cl)** was used, an induction period of > 10 h was observed. However, the reaction was completed in 24 h to form the target product in 90% yield. At the same time, precatalyst **Pd-NHC-1-PS(TfO)** exhibited considerably lower catalytic activity under the same conditions: the yield of the product after 24 h of the reaction was no more than 3%. The highest reaction rate and the shortest induction period (< 50 min) were observed in the presence of catalytic system **Pd-NHC-1-PS(SbF_6)**. The other counterions are arranged in the following order by their activity: $SbF_6^- > BF_4^- > NTf_2^-$. On the basis of the obtained kinetic data and the observed sigmoidal kinetic profiles, it has been assumed that the rate-limiting step is the formation of catalytically active palladium nanoclusters as a result of palladium leaching from the support surface into the solution. The catalytic activity of dissolved palladium species was confirmed by the hot filtration test. The influence of the nature of the anions on the induction period of the reaction is attributed to their coordination ability with respect to palladium: the higher the coordination ability, the less active the dissolved palladium species. The authors note that the nature of the base has a significant effect on the formation and stabilization of dissolved Pd species as well as on the deprotonation of alkynes in the copper-free Sonogashira reaction. It has been found that when tetra-n-butylammonium benzoate or acetate are used as bases, the catalytic activity is significantly higher as compared with the reactions in the presence of amines (Et_3N, piperidine). An important conclusion of this paper is that the support can play an active role not only in generating the active catalytic species but also in their capture and stabilization, acting as a reagent and precatalyst in catalytic processes.

To date, a small number of examples of the use of precatalysts based on immobilized acyclic diaminocarbene complexes of palladium(II) have been reported; nevertheless, the available data allow one to assess the high potential of such catalytic systems. In particular, precatalysts **4** and **5,** in which 13% of the amino groups of the support (benzhydrylamine polystyrene resin) are modified by diaminocarbene Pd complexes, exhibit the high and stable catalytic activity in the Sonogashira – Hagihara reaction (Scheme 26) for a wide range of substrates and can be reused (up to eight times).[46] Studying heterogeneous catalysts **4** and **5** by the XPS method has demonstrated that, as distinct from the Suzuki – Miyaura reaction, the Sonogashira – Hagihara cross coupling leads to the change in the oxidation state of palladium on the support from +2 to 0. This fact can be indirect evidence for the homogeneous nature of catalysis and for a boomerang system with a high capacity for adsorption of dissolved palladium species, given the low degree of their leaching after catalytic runs.

Scheme 26



(*a*) **Pd-ADC-PS** (0.5 mol.% – 10 mol.%), CuI (10 mol.%), Et_3N (4 equiv.), DMF, 40 – 70 °C; **Pd-ADC-PS** = **4**, **5**; X = I, Br; R^1 = 4-OMe, 4-NO_2, 4-CN, 4-NH_2, 4-CHO, 4-NMe_2, 2-NO_2, H; R^2 = CMe_2OH, n-C_5H_{11}, $SiMe_3$

* * *

Heterogeneous precatalysts based on polystyrene-supported carbene palladium complexes exhibit high efficiency in catalysis of the Suzuki – Miyaura and Sonogashira – Hagihara cross coupling, including copper-free reactions. These systems can be reused without significant loss of catalytic activity, regardless of the heterogeneous or homogeneous nature of catalysis. In the latter case, regeneration and stable efficiency of the immobilized catalyst in a series of catalytic runs are associated with the high capacity of the support to adsorb and retain the dissolved catalytically active palladium species. However, the immobilization of palladium in the form of N-heterocyclic carbene complexes on the surface of polystyrene functionalized with ionic liquids is often characterized by a low degree of limiting functionalization of the support. Using, as an alternative, immobilized diaminocarbene acyclic complexes, which retain the advantages of catalytic systems based on diaminocarbene palladium complexes, makes it possible to simplify the procedure of their preparation and

variation of the structure as well as to enhance the degree and selectivity of surface functionalization.

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