DOI: 10.1002/ejic.201100162

Polymers for Green C–C Couplings

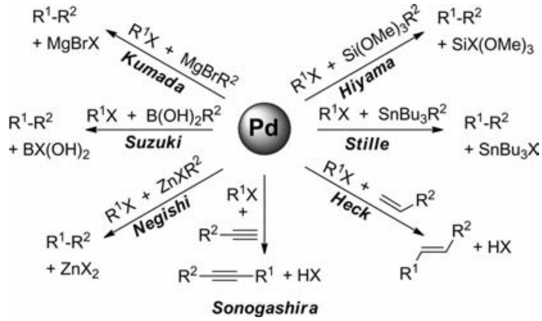
Ana C. Albéniz*[a] and Nora Carrera[a]

Keywords: Polymers / Cross-coupling / Supported catalysts / Stille reaction / Stannanes / Palladium

Cleaner and environmentally more friendly cross-coupling reactions can be carried out by the use of polymers as supports. A lot of work has been devoted to attach palladium catalysts on polymers, so they can be easily separated from the reaction mixture and reused. An overview of the methods used for this purpose is given; they include the encapsulation of palladium complexes or palladium nanoparticles by polymers and the synthesis of polymeric ligands that coordinate to palladium. Polymer-supported reagents are also important in making cross-coupling reactions easier to work up and more sustainable. The use of polymer-supported stannanes in the Stille reaction has a special advantage, because organotin derivatives that are used as reagents are toxic. When polymeric tin reagents are used, the separation of the byproducts from the target product is good and the tin-containing byproducts can be recycled, thus tin waste is avoided. Examples of this application will also be discussed.

1. Introduction

Since their discovery in the 1970s, palladium-catalyzed cross-coupling reactions have proved their synthetic utility by far. They have become bench tools in any synthetic laboratory, and their use has extended to materials chemistry as well as the fine chemicals industry. The Heck,[1] Stille,[2] Suzuki,[3] Negishi,[4] Hiyama,[5] Kumada,[6] or Sonogashira[7] reactions (Scheme 1) allow the formation of new C–C bonds and thereby the construction of organic molecules under mild conditions. These transformations have developed to a point where bonds can be formed not only between sp^2 carbon atoms, as in the early versions of most of the couplings, but also between all possible combinations of sp, sp^2, and sp^3 carbon atoms.[8] The importance of these transformations and their impact on synthetic chemistry has been recently recognized by the 2010 Nobel Prize for Chemistry to R. F. Heck, E. Negishi, and A. Suzuki.[9]



Scheme 1. Palladium-catalyzed cross-coupling reactions.

---

[a] IU CINQUIMA/Química Inorgánica, Universidad de Valladolid,
47071 Valladolid. Spain
Fax: +34-983423013
E-mail: albeniz@qi.uva.es

Ana C. Albéniz is a Full Professor of Inorganic Chemistry at the University of Valladolid. She obtained her Ph. D. at the University of Valladolid and worked as a postdoctoral Fulbright fellow in Prof. Crabtree's group at Yale University. In 1991 she returned to Valladolid as an Associate Professor. Since 2007 she is a Full Professor working in the Centre for Innovation in Chemistry and Advanced Materials (CINQUIMA) at the University of Valladolid. Her research interests include the development and mechanistic study of new metal-catalyzed reactions applied to organic synthesis, the synthesis of new polymers, and their application in catalysis as recyclable supports for catalysts and reagents.

Nora Carrera just finished her Ph. D. at the University of Valladolid and obtained a European Doctorate in Chemistry. Her work has dealt with the development of stannylated polymers and their application as recyclable reagents in the Stille reaction.

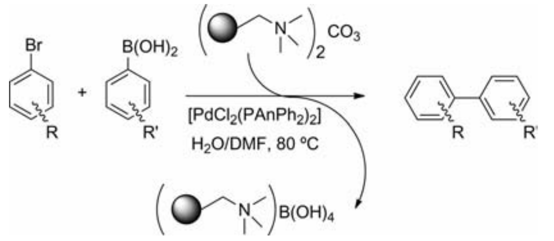
It would be desirable to have methods to carry out these important and widely applicable synthetic transformations in more simple, atom-economical, and clean ways. Thus, efforts are being made to transform metal-catalyzed cross-coupling reactions into greener processes without losing any of their advantages. A typical cross-coupling reaction employs an organic electrophile (R^1X), a second reagent acting as or carrying a nucleophile (R^2), and a transition-metal catalyst, palladium being by far the most frequently used (Scheme 1). Additives are also needed in some of the reactions. In principle, each of these components can be modified, so the overall process can be made more efficient in terms of protection-derivatization of reagents, purification of the final products, generation of less waste, and reuse of some of the components of the reaction. Polymers have been used as tools to achieve these goals. Their special properties, as far as solubility is concerned, make them good supports for reagents or catalysts, as will be addressed below.

The electrophilic reagent is generally an organic halide or sulfonate, although other derivatives such as diazonium salts are sometimes used. In any case, it is necessary to introduce the proper functionalization (X) in the fragment to be coupled, and X will be part of the byproducts at the end of the reaction. Most efforts to avoid this previous functionalization have concentrated on the direct activation of C–H bonds by the catalyst (X = H), which would extend the scope of the coupling reactions to substrates onto which it is not easy to introduce an X group. This has been an important achievement, and it has been applied to many substrates.[10] Since the C–H bond is activated by Pd^{II}, the presence of an oxidant to effect a Pd^0/Pd^{II} oxidation is required in the catalytic cycle. This is a drawback as far as atom economy is concerned, but the use of oxygen as oxidant would overcome it. Although there still remains a long way to go, coupling reactions by C–H activation is an interesting and thriving field.

As for the electrophilic partner, the introduction of an R^2 group by direct activation of C–H bonds is possible for some substrates.[11] However, in most couplings, the nucleophile (R^2) is a substituent in an organometallic compound of boron (Suzuki), tin (Stille), silicon (Hiyama), zinc (Negishi), or magnesium (Kumada). Once the reaction has been completed, the main group byproduct has to be separated from the coupling product, and this may not be a straightforward process. This is especially important in the Stille reaction, since the tin derivatives commonly used are toxic.[12] Even if toxicity is not an issue for other couplings, a good and easy separation of the byproducts from the target derivative is also desirable, avoiding time-consuming purifications (usually chromatography-based) and the waste of extra solvent and reagents.

The Suzuki and Hiyama reactions require the use of bases or fluoride salts, which reduce the atom economy of the process. Although some reports have communicated the feasibility of base-free Suzuki couplings by using boron derivatives different from boronic acids,[13] most Suzuki and Hiyama reactions still depend on the use of these additives. The Heck and the Sonogashira reactions use the alkene and the alkyne as reagents, respectively, instead of the stoichiometric amount of an organometallic derivative, so they can be considered cleaner processes; however, the presence of a base is needed in both cases. In some versions of the Sonogashira coupling, a copper(I) compound is also used.

Polymeric reagents have been introduced in coupling reactions to aid in the separation of the main group organometallic byproduct from the coupling product. A nice example of the use of polymers for this purpose has been reported by Parlow et al., who used a polymeric base, a polystyrene-supported tetraalkylammonium carbonate, in Suzuki couplings. In this case the additive, the base, is polymeric, and the polymeric tetraalkylammonium borate byproduct formed after the coupling reaction can easily be separated by filtration (Scheme 2).[14]



Scheme 2. Suzuki coupling in the presence of a polymeric base.

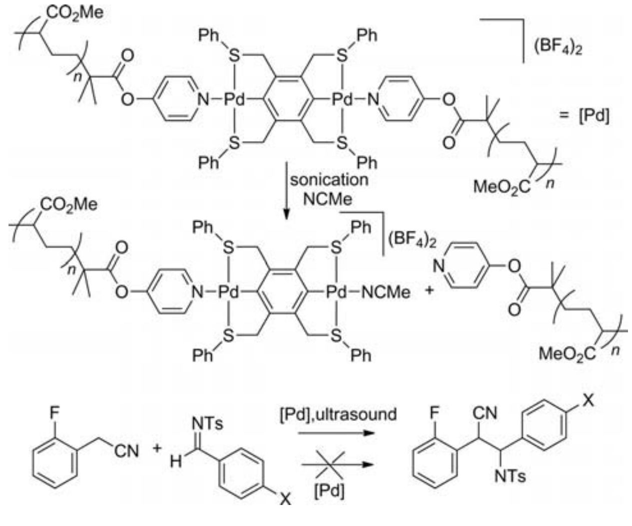
Polymers have been used as support for either the organic electrophile or the main group organometallic derivative in solid-phase synthesis. In this case, insoluble polymers are used, usually commercial polystyrene resins. One of the reagents is attached to the polymer support, and the other one is usually in solution, allowing the synthesis of libraries of coupling products that, at a later stage, will be liberated from the support by a chemical transformation. This has been used in combinatorial chemistry, and, although it is easier to purify coupling products attached to a polymer, as the main goal of the technique is not to make the reaction cleaner, this type of polymer use in C–C coupling reactions will not be included here. Several reviews have been published on the topic,[15] and polymer-supported boronic acids have been synthesized for this purpose.[16]

Since the recovery of polymer-supported compounds is generally good, their main advantage is the feasibility of reuse. This is especially important when applied to the reaction catalysts, highly valuable palladium compounds that, ideally, should be long-lived. Also, the contamination of the target products with Pd should be prevented, as palladium derivatives are potentially toxic.[17] The recycling of the tin byproducts in the Stille reaction is also important, and an efficient way of doing this would make this process environmentally friendly. This microreview will concentrate on these two aspects, giving an overview of the methods used to immobilize palladium catalysts on polymers that have been employed in C–C coupling reactions and analyzing in more detail the Stille reaction and the advantages of the use of polymer-supported reagents in it.

2. Polymer-Supported Catalysts in C–C Coupling Reactions

A lot of work has been done on the immobilization of catalysts on polymer supports, their recovery, and reuse. The subject has been extensively reviewed in the last decade from different points of view, including applications to cross-coupling reactions, and relevant references are given below. Polymers are a large family of compounds that provide a variety of compositions and properties that can be useful in catalysis. Insoluble polymers offer suitable substrates for the heterogenization of homogeneous catalysis,[18] but even the attachment of catalysts to soluble polymers have advantages, since, being macromolecules, these polymers can easily be separated from the reaction mixture by the addition of a co-solvent or by ultrafiltration.[19,20] Immobilized catalysts on insoluble polymer supports can also be used in continuous flow reactions employing the microreactor technology.[21] Water-soluble polymers serve as catalyst carriers to perform reactions in aqueous media.[22]

With a different but very interesting purpose, polymers have been applied to trigger the activation of a catalyst by a mechanical stimulus, such as sonication. Recently, Bielawski et al. have developed a pyridine-functionalized poly(methyl methacrylate), which is coordinated to a palladacycle (Scheme 3). Upon application of ultrasound, a mechanical response takes place, and one pyridine group decoordinates, creating a vacant coordination site so that the complex can catalyze a transformation. This method has been tested in a the C–C forming reaction of benzylcyanide and *N*-tosylimines.[23]



Scheme 3. Activation of a polymer-supported Pd catalyst by ultrasound.

A large number of polymer-supported palladium catalysts for C–C coupling reactions have been developed in order to achieve reuse of catalysts and to prevent contamination of the products. Nonetheless, these goals have also been pursued by other strategies, and palladium catalysts have been attached to a variety of supports other than polymers when used in cross-coupling reactions. Silica, metal oxides, molecular sieves, other aluminosilicates, or carbon surfaces have been used for this purpose, and the subject has been reviewed.[24] Dendrimers have also been used.[25] Phase separation of the catalysts and the products after reaction has been achieved by adding suitable substituents (tags) to the catalyst,[26] or by using ionic liquids.[27]

Palladium has been attached to different types of polymers either as a complex or as Pd^0 nanoparticles or colloids, by following different procedures. The field is vast, and, in this microreview, selected relevant examples of synthesized precatalyst for cross-coupling reactions will be organized according to the type of polymeric support used and the nature of palladium attached to it. The first of the following two sections illustrates the encapsulation of palladium nanoparticles in polymers and the second one collects examples of precatalysts synthesized by using polymer-attached ligands that have proved useful in homogeneous catalysis. It is important to state that, regardless of the precatalyst used, the mechanisms of the reactions with supported palladium are often difficult to ascertain. For immobilized catalysts, the actual catalytic reaction can occur on the support, but often palladium is leached either as homogeneous complexes or as nanoparticles. In these cases, even for very low leaching, the actual catalysis can be homogeneous, and the support acts as a reservoir of palladium. A variety of experiments can be conducted to determine whether the actual catalysis is hetero- (on the supported catalyst) or homogeneous (by leached species); they comprise kinetic studies to determine possible induction times, catalytic activity of the filtrate at small conversions (split or filtration tests), additional immobilization of one of the reagents (three-phase tests), addition of suitable poisons, measurement of residual Pd content in the products, and other experiments. The subject has been discussed,[22,28] and systems have been found that are active either by leaching of homogeneous species or by catalysis on the support. Thus, mechanistic proposals for a new supported precatalyst or for application of a known one under a new set of conditions should be carefully checked. Most reports of supported palladium catalyst often concentrate on discussing the activity and recyclability of the catalysts but do not include sufficient experimental information to determine the nature of the actual active catalytic species. It has been found that, even some supported precatalysts that perform catalysis through leaching by a homogeneous mechanism could be useful and greener than the conventional homogeneous catalysts. In many cases, the dissolved Pd is reprecipitated on the support at the end of the reaction; thus, very little contamination is present in the coupling products and the catalyst can be recycled. Even if this is a problem for mechanistic studies, since some experiments can be misleading and conceal the actual mechanism (i.e. loss of catalytic activity of the filtrate after reaction or when lowering the reaction temperature to perform the filtration), the systems are useful for synthetic purposes.

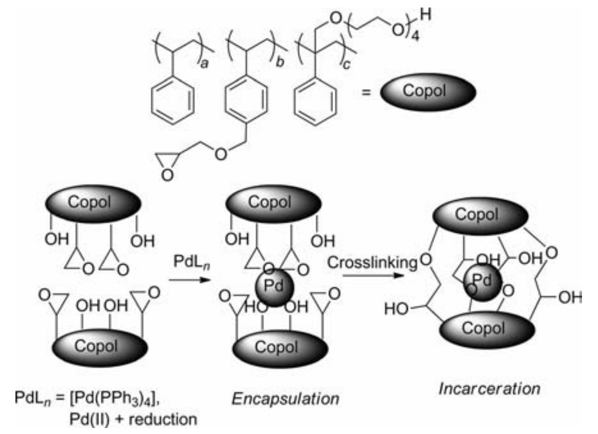
2.1 Pd^0 Encapsulated or Embedded into Polymers

Palladium(0) in different forms has been attached to polymers and used as catalyst in cross-coupling reactions. The metal can be introduced by using a Pd^0 complex but it is more common to use a Pd^{II} precursor followed by reduction. Depending on the support, precursor, and reduction conditions palladium nanoparticles or colloids are deposited.

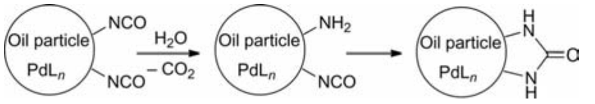
For low-functionalized supports, the metal can be physically enveloped in the polymer structure, linked by weak interactions, and this has been called microencapsulation. Kobayashi et al. have developed this method with polystyrene supports where the metal can interact with the aromatic rings of the polymer through weak π interactions.[29] The supported catalyst can be prepared by mixing a solution of polystyrene with $[Pd(PPh_3)_4]$ and precipitating the resulting polymer by addition of hexane. It has been shown that three phosphane ligands dissociate and palladium is microencapsulated in the polymer with the remaining PPh_3 ligand coordinated to it. This catalyst is air-stable and has been used in Suzuki couplings of aryl bromides with arylboronic acids in the presence of $P(o\text{-Tol})_3$.[30]

A better attachment of the metal to the support is obtained by the so-called polymer incarceration method. After microencapsulation of palladium, as described above, the polymer undergoes a crosslinking process, and the catalyst is trapped inside the formed receptacles, leading to a more robust and less soluble material. This has been achieved by using copolymers of styrene with properly functionalized monomers, such as 4-vinylbenzyl glycidyl ether, and another monomer with an alcohol group as shown in Scheme 4. After mixing the copolymer with $[Pd(PPh_3)_4]$, crosslinking by reaction of the alkoxy and epoxide groups occurs. The process leads to the loss of the four PPh_3 ligands from the precursor palladium complex.[31] This type of catalyst has been used in Suzuki couplings of aryl bromides with good results in the presence of one equivalent of a phosphane. Using a mixture of toluene/water (4:1) as solvent, good recyclability and very low contamination of the products were attained.[32] The supported catalysts can be recovered by simple filtration and reused five times with no decrease in yield of the coupling product. The addition of phosphane can be avoided by using a PR_3-functionalized polystyrene as support.[33] An alternative route for the preparation of these polymer-incarcerated catalysts involves the use of a more accessible Pd^{II} compound, such as palladium acetate or nitrate, that gets incorporated into the support and is then reduced to Pd^0 (Scheme 4). Catalysts prepared in this way have been used in the Suzuki and Heck reactions and can easily be recycled.[34]

An interesting system for microencapsulation of palladium is the now commercial Pd-EnCat developed by Ley et al. The catalyst is entrapped in polyurea microcapsules formed by in situ interfacial polymerization in a water/oil emulsion. The emulsion is formed by: (a) polymethylene polyphenylene diisocyanate and the palladium species to be encapsulated and (b) water containing emulsifiers and colloid stabilizers. Polyurea is formed in the water–oil interface in a wall-forming process that produces microcapsules in which palladium is trapped (Scheme 5).[35] $Pd(OAc)_2$ has been microenpsulated in this way and used in the Suzuki, Heck, and Stille couplings with good yields and easy recyclability just by filtering the microcapsules off, washing and reusing them.[35,36] Very low leaching was found in the crude reaction mixture. Preformed palladium nanoparticles have also been trapped in these polyurea microcapsules and used as catalysts.[35] Continuous-flow Suzuki couplings with Pd-EnCat packed reactors under standard conditions,[37] or under microwave irradiation,[38] have also been carried out.



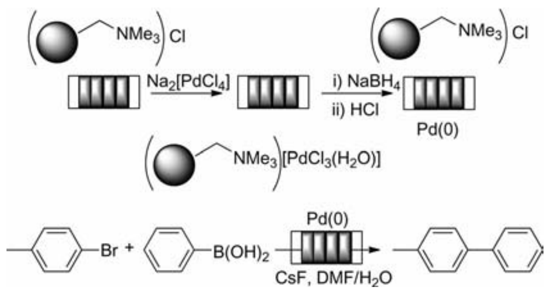
Scheme 4. Polymer-incarcerated Pd catalysts.



Scheme 5. Formation of polyurea microcapsules Pd-EnCat.

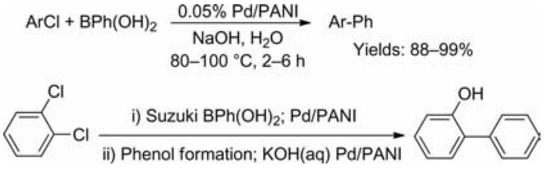
A palladium(II) ionic complex can be attached as counterion to polymers bearing an ionic functionalization; the Pd^{II} is subsequently reduced to Pd^0. Mennecke and Kirschning have described a polystyrene material synthesized by copolymerization of styrene, divinylbenzene, and vinylbenzyl chloride that can be deposited on glass supports such as Raschig rings aligned in a rodlike device. NMe_3 is pumped through the polymer and reacts with the chlorobenzyl groups to form a polymer-bound alkylammonium chloride. Palladium is attached to the polymer by ionic exchange, by using $Na_2[PdCl_4]$, and then reduced to form Pd nanoparticles (Scheme 6). Suzuki and Heck reactions have been performed with this catalyst device under flow conditions in a cyclic mode. The catalyst shows excellent stability, without loss of activity after ten runs, and low Pd leaching (about 0.7 ppm).[39] Polymeric ionic liquids have also been used to stabilize palladium nanoparticles and perform Suzuki, Heck, and Stille couplings.[40]

Supports made by polymerization of other monomers intrinsically more functionalized than styrene may increase the interactions of palladium with the polymer and the stability of the system. Thus, poly(methyl acrylate) beads have been used to support palladium(0) by treatment with



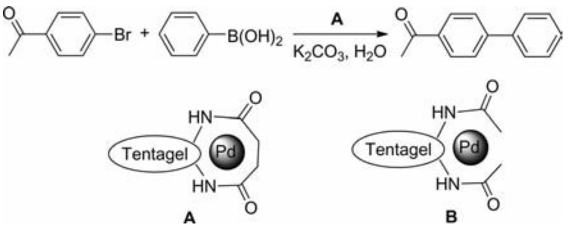
Scheme 6. Suzuki coupling catalyzed by polystyrene-supported Pd in a flow system.

$H_2[PdCl_4]$ followed by reduction with formaldehyde. The palladium-containing beads were used in Suzuki and Heck reactions and recycled four times with good results and low leaching (up to 7.8 ppm). A hot filtration test in the Heck reaction indicates that catalytic activity occurs mainly on the support.[41] Polyaniline fibers (PANI) offer a high surface and porous support for palladium nanoparticles. In this case, the support serves also as reducing agent and Pd^0 is formed just by treating the PANI fibers with palladium nitrate. This catalyst system is very active and capable of performing the Suzuki coupling of aryl chlorides with aryl boronic acids in water, as well as the tandem Suzuki coupling-phenol formation of aryl dichlorides (Scheme 7). It can be easily recovered and was reused ten times with leaching levels in the order of ppm.[42] Polyvinylpyrrolidone attached to silica has also been used as palladium support for Suzuki and Heck reactions. The catalyst is recyclable by filtration and some mechanistic tests (hot filtration) seem to indicate that leached species are not responsible for the activity observed.[43]



Scheme 7. Reactions catalyzed by Pd supported on polyaniline (PANI).

The use of water as a solvent is a great asset for the sustainability of cross-coupling processes. For this purpose, palladium has been supported on polymers that are either soluble or compatible with aqueous conditions, so they show good activity in water. Polyethylene glycol supports are one of the most popular polymers for this purpose. An interesting example uses aminomethylated commercial polystyrene–polyethylene glycol copolymer (Tentagel), which is treated with $Pd(OAc)_2$, and the metal is reduced with hydrazine to give trapped palladium nanoparticles. The polymer is then crosslinked by using succinyl chloride to fix the captured palladium (**A**, Scheme 8). This material effectively catalyzes the Suzuki coupling of aryl bromides in water and can be recycled by simple filtration and washing without loss of activity. Several mechanistic experiments show that leached palladium is not responsible for the catalytic activity observed, in contrast to palladium nanoparticles supported on a noncrosslinked analogous polymer (**B**, Scheme 8).[44] Chitosan, a linear polysaccharide of natural origin, has also been used to stabilize palladium nanoparticles by itself,[45] or as a chitosan-PEG-functionalized copolymer.[46] These catalysts have been applied to Suzuki couplings of aryl bromides in water.



Scheme 8. Suzuki coupling in water catalyzed by Tentagel-supported Pd.

Polymers with composite architectures have also served as supports. As an example, microspheres of poly(styrene-*co*-4-vinyl-pyridine) containing a core of polystyrene and an outer shell of poly(4-vinylpyridine) have been synthesized by a one-stage, soap-free emulsion polymerization in water. Palladium nanoparticles were embedded on the microspheres and used as catalyst in the Suzuki reaction in water. Very low leaching was found, and the material can be separated by filtration and reused without loss of activity.[47]

2.2 Pd Coordinated to Polymer-Bound Ligands

Most polymer-supported catalysts employed in cross-coupling reactions involve the use of ligand-functionalized polymers. Through complexation, a stronger interaction with the metal and a more robust attachment is anticipated. In many cases, the precatalyst used is formed by previous coordination of palladium(II) to the support to give well-characterized polymeric complexes. However, sometimes the nature of the palladium species is not so clear, as the catalytic systems are formed in situ by mixing reactants, a palladium precursor, and the polymeric ligand, or, even if palladium is previously mixed with the ligand, the exact coordination sphere of the metal is not known. In other cases, the polymeric ligand is mainly used to fix palladium to the polymeric matrix more strongly in an encapsulation-type procedure that may involve the reduction of the attached palladium to form entrapped nanoparticles. Precatalyst systems formed by every procedure mentioned above have been used in C–C couplings, mostly in the Suzuki and Heck reactions, which have become the paradigmatic tests for supported catalysts. Many types of polymeric supports have been used; what follows collects several examples of different polymer types and the ligands that can be attached. They are organized by the separation strategies used for the catalytic system or other interesting reactivity features that account for their special advantages when compared with conventional homogeneous systems. Thus, examples of insoluble supported catalysts that can easily be separated by filtration are collected first. Biphasic separation is also advantageous for recovery and recycling of supported catalysts, although it shows more limitations as far as the combination of suitable solvents that can be used. Finally, some examples of the use and recycling of supported catalysts in water, the greenest solvent of all, will be discussed.

2.2.1 Polystyrene-Supported Ligands for Filtration Recovery

Polystyrene is the most popular polymeric support used to attach ligands. There are many types of polystyrene resins with different degrees of functionalization that are commercially available, so they can be used as convenient scaffolds to introduce the desired donor moiety.[15c] Most of the polystyrenes used for this purpose are insoluble in common solvents, and, after the reaction, the catalyst can be recovered by filtration. It should be noted that derivatization of the polystyrene support and/or introduction of palladium is often incomplete, and this may lead to low loadings of the active species. Copolymerization of styrene and a ligand-functionalized styrene has also been used, and this allows better control of the amount of ligand incorporated. A large variety of ligands have been attached to polystyrene,[48,49] and some examples are depicted in Figures 1 and 2.

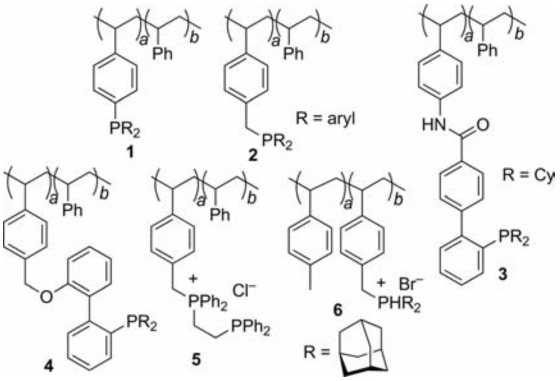


Figure 1. Polystyrene-supported phosphane ligands.

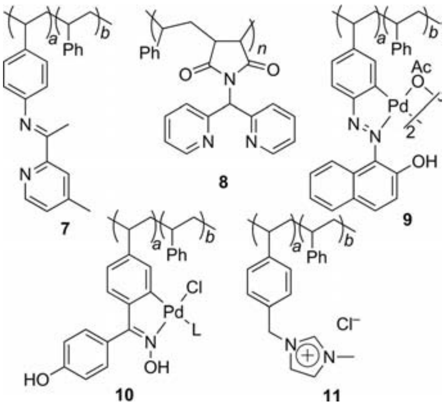


Figure 2. Other polystyrene-supported ligands.

Triarylphosphane-functionalized polystyrenes have been used in Suzuki couplings. The phosphane is usually attached to the polymer by one of its aryl substituents, which can be the styrene phenyl (**1**, Figure 1) or a tethered aryl (**2**, Figure 1) group. Early work used polystyrene ligand **2**, in which palladium was incorporated by reaction with $PdCl_2$ and subsequent reduction with hydrazine,[50] or by reaction with either $[PdCl_2(NCR)_2]$ or a Pd^0 precursor such as Pd_2dba_3 or $Pd(PPh_3)_4$.[51] The catalysts thus prepared and not further characterized, were active in Suzuki couplings of iodo- and bromoaryls as well as aryl triflates and alkenylbromides. Phosphanes **1** (R = Ph, Figure 1) have been used to encapsulate $Pd(OAc)_2$ and perform Suzuki reactions with ArI.[52] The same systems (**1**, R = Ar) react with $Pd(PPh_3)_4$, whereupon the four PPh_3 ligands are eliminated; the system has been used in Suzuki, Sonogashira, and Heck couplings, and it is recyclable at least four times.[53]

As their homogeneous analogues, the use of polystyrene-supported phosphanes with bulky substituents lead to catalytic systems that are active in the Suzuki coupling of the reluctant aryl chlorides; an example is ligand **3** (R = Cy, Figure 1).[54] Buchwald et al. prepared supported phosphane **4** (R = Cy, Figure 1), and upon reaction with $Pd(OAc)_2$ or Pd_2dba_3, obtained a colored polymer that is active in the coupling of ArCl (as well as ArBr) and aryl boronic acids. The catalyst can be recycled by filtration up to four times, although longer reaction times are needed.[55] The reaction of ligand **1** (R = *t*Bu, tolyl, naphthyl, Figure 1) with $Pd(PPh_3)_4$ incorporates PPh_3-free palladium into the support, and this is also a useful catalyst in the Suzuki coupling of ArCl and arylboronic acids.[56]

Phosphanes have been attached to polystyrene supports by reaction of a phosphane with a halo-functionalized polymer to give a phosphonium salt. These salts have been used in different reactions including Suzuki and Sonogashira couplings, where, considering the basic reaction conditions, the phosphane is presumably formed and acts as a ligand. Dppe has been linked in this way (**5**, Figure 1), and the polymer was treated with $PdCl_2(PhCN)_2$ and then subjected to reduction to Pd^0. This procedure yielded a recyclable catalyst system that was used in Cu-free Sonogashira couplings.[57] A diadamantyl phosphonium salt was formed by reaction of a partially brominated soluble polystyrene with diadamantylphosphane. This afforded a polymeric air-stable ligand precursor (**6**, Figure 1), which was used, in the presence of a palladium complex such as $PdCl_2(PhCN)_2$, to catalyze Suzuki and Sonogashira reactions. Since, in this case, the polystyrene used is soluble in the reaction medium, ultrafiltration through a poly(dimethylsiloxane) membrane was performed to separate the polymeric species. The residue was recycled and reused; no further addition of Pd complex, or Cu in the case of the Sonogashira reaction, was needed. The results were very good, especially for Suzuki couplings (ten cycles with no activity loss), but a small decrease in the yields was observed in the Sonogashira reaction upon recycling. The system cannot be efficiently reused for Heck couplings, and the authors attribute this effect to the highly polar solvents used in this reaction (NMP for example) that are detrimental to the integrity of the membrane.[58]

Ligands different from phosphanes have been supported onto polystyrene (or polystyrene copolymers in some cases) to give insoluble polymers that have been coordinated to palladium(II). Some recent examples are shown in Figure 2. Separation of the polymer by filtration and reuse of the catalysts have been achieved for iminopyridine (**7**)[59] and -dipyridine (**8**) ligands,[60] aryldiazo- (**9**)[61] or oxime-derived palladacycles (**10**) (Figure 2).[62]

N-heterocyclic carbenes have become very popular and useful ligands in catalysis including cross-coupling reactions. Thus, supported versions of the precursor imidazolium salts (**11**, Figure 2) have been generally synthesized by reaction of imidazole derivatives with halosusbstituted polystyrenes.[63,64] Suspension copolymerization of styrylimidazolium salts with styrene and divinylbenzene in water has also been used; it leads to a polymer with the imidazolium groups on the surface of the resin.[65] Complexation of palladium to the support is generally achieved in the same way as the discrete complexes are formed, that is, reaction of the imidazolium polymer with a palladium derivative in the presence of base that generates the free carbene, which coordinates to the metal. Alternatively, reaction with $Pd(OAc)_2$, in which the acetate acts as a base, is usually a viable route. Recyclable catalysts have been prepared in this way for Suzuki couplings[65,63] and also for the Heck reaction.[64] In the latter study, Verdugo, Luis et al. demonstrate that soluble palladium species, which are responsible for the catalysis, are formed in the Heck reaction with their system. Nonetheless if the reaction is carried out at 130 °C, recyclability is possible since the soluble species are trapped back into the support under these conditions and there is no metal residue in the products or activity loss of the catalyst.

2.2.2 Other Polymer-Supported Ligands for Filtration Recovery

Although less widely used than polystyrene, many other polymer types are useful for attaching ligands. Phosphane ligands have been supported on materials derived from the copolymerization of simple α-olefins such as polyethylene or polypropylene and functional monomers. Pd^{II} and Pd^0 complexes of the general formula $[PdX_2(PolPR_2)L]$ or $[Pd(PolPR_2)L]$ are commercialized by Johnson Matthey as FibreCat®. The polymers are fibers instead of beads, which may facilitate the contact of the catalyst and the reagents without the swelling required for some of the polystyrene materials. They have been used in Suzuki and Heck couplings, and their reactivity can be tuned by choosing the appropriate supported or auxiliary ligands (L), so they can also be applied for Suzuki couplings of aryl chlorides.[66] Low leaching is generally observed. Their recyclability is very dependent on the substrates and reaction conditions, but good results have been obtained for some Suzuki reactions.[66,67]

Polynorbornenes synthesized by ROMP of ligand-functionalized norbornenes have also been developed to support palladium catalysts in coupling reactions. In contrast with most of the polymeric supports commonly used, in this case the backbone is unsaturated and potentially more reactive and unstable under the conditions used in catalysis. Nonetheless, several polynorbornene-supported catalysts of this type have proved useful and robust enough. A functionalized norbornene with pendant triarylphosphanes was polymerized using Grubbs-type catalyst to give polymer **12** (Figure 3). The catalyst systems formed in situ with the ligand and $Pd(OAc)_2$ can be used in Heck reactions. The polymer is soluble at high temperatures in DMF, used as reaction solvent, but insoluble when the temperature is lowered, so the solid fraction after reaction can be recovered. It was reused five times with only a very small decrease in yield. Sonogashira and Negishi couplings were also catalyzed by the mixture **12**/$Pd_2(dba)_3$; whereas it can be reused for the former reaction, it could not be recycled for further Negishi couplings.[68] Living polymerization of a norbornene-functionalized dipyridine followed by crosslinking with 1,4,4a,5,8,8a-hexahydro-1,4,5,8-*exo*-*endo*-dimethanonaphthalene (DMNH6) leads to a material in which the crosslinked core has pendant polynorbornene ligands (**13**, Figure 3). The ligand was treated with $H_2[PdCl_4]$ to give $[Pd(Pol\text{-}py_2)Cl_2]$, which was used in the Heck reaction of ArX (X = Cl, Br, I) with styrene and ethyl acrylate. The reaction was rerun with the same catalytic system and observed to keep its activity.[69] N-heterocyclic carbenes have also been supported on polynorbornene. Sommer and Weck reported a polymeric palladium complex (**14**, Figure 3) by ROM copolymerization of a norbornene ester and a preformed monomeric palladium carbene with a norbornene unit. The complex is active in Suzuki couplings of aryl chlorides as well as Sonogashira reactions, the nature of the active species (supported palladium or leached species) being very dependent on the actual palladium complex used. The catalyst could not be recycled without a serious decrease in the conversions observed.[70] Buchmeiser reported a polynorbornene with a pendant CO_2-stabilized carbene (**15**, Figure 3). The reaction of this zwitterionic species with $PdCl_2$ afforded a catalyst that was used in the Heck reaction with good activity and recyclability without contamination of the products (< 0.1 ppm of Pd).[71]

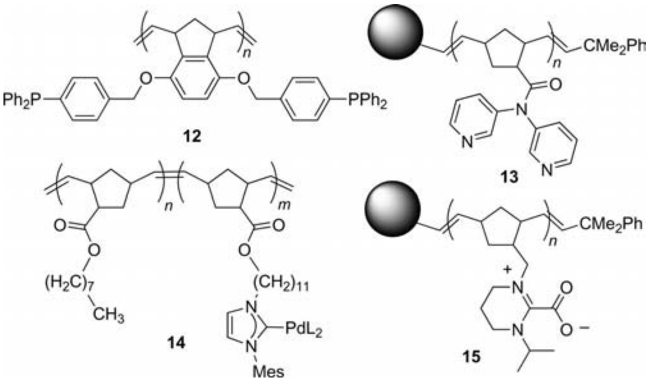
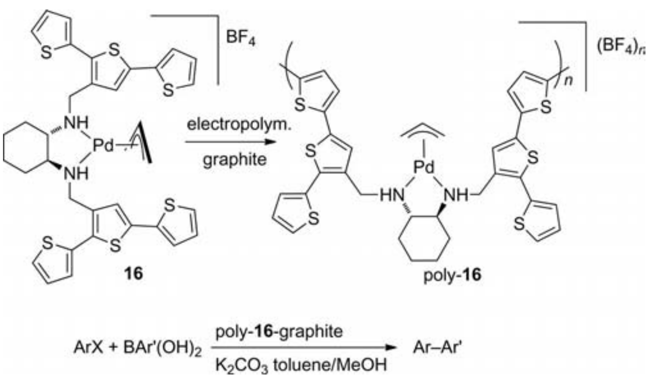


Figure 3. ROMP of polynorbornene-supported ligands.

Palladium complexes with diaminocyclohexane ligands functionalized with pendant thiophenes (Scheme 9) have been electropolymerized on graphite electrodes and used in the Suzuki coupling of aryl bromides and boronic acids. These couplings require longer reaction times than those with an analogous homogeneous catalyst. The catalyst deposited on the electrode can be easily recovered and recycled at least six times.[72]



Scheme 9. Polythiophene-supported catalyst.

2.2.3 Polymer-Supported Ligands for Phase Separation Recovery

The separation of the catalyst by using biphasic systems is also a convenient method for laboratory or industrial use. To do so, polymeric metal complexes as catalysts have been used. Making a suitable choice of polymer support, it is possible to obtain soluble catalysts that still show enough difference in solubility relative to the coupling products.

Poly(*N*-isopropylacrylamide) (PNIPAM) has been used to synthesize thermomorphic systems in which, with use of two immiscible solvents and the polymer, phase separation can be controlled by changing the temperature. The PNIPAM-supported palladacycle in Figure 4 has been well characterized and it has been used as catalyst in Suzuki and Heck reactions in a mixture DMF/heptane (90:10). The mixture is miscible at the reaction temperature (95 °C). After the reaction is complete the temperature is lowered, and phase separation occurs, the polymer being quantitatively recovered in the DMF phase and the products in the heptane phase. The DMF phase can be reused several times for the same procedure.[73] Phosphane ligands attached to the same type of polymers and used in Sonogashira couplings have also been reported.[74]

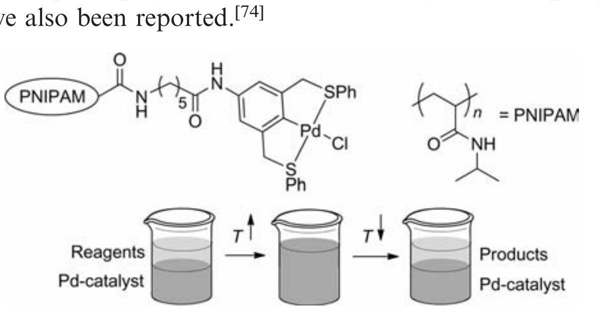


Figure 4. PNIPAM-supported Pd catalyst in biphasic conditions.

Ligands supported on polyethylene glycol (PEG) also lead to thermomorphic systems. For example, a phosphane ligand analogous to **1** (R = Ph, Figure 1) or phosphonium salt **6** (Figure 1) has been attached to soluble polyethylene glycol instead of polystyrene. These PEG ligands were mixed with $[PdCl_2(NCR)_2]$ or $Na_2[PdCl_4]$ and used in Sonogashira reactions under biphasic conditions. Once the reaction is finished, phase separation of the catalyst (in NCMe or DMSO) and the products (in heptane) occurs upon lowering the temperature. The catalyst phase was reused up to five times in this work.[75]

Polyisobutylene-bound N-heterocyclic carbenes have also been used to synthesize the corresponding palladium complexes active as catalyst in the Heck reaction (Figure 5). By using a DMF/heptane mixture as solvent in the reaction, phase separation on changing the temperature was also possible. The catalyst was recovered in the heptane phase in this case and recycled at least ten times.[76] In this and in most systems working under biphasic conditions, it has been shown that the products can be partially extracted in the catalyst phase (heptane in this case). However, this is not a problem because it only reduces the yield of the first cycle. Once the catalyst phase becomes saturated in the product, and this occurs easily with a suitable choice of solvents, the yield in subsequent cycles for recyclable systems becomes high and constant.

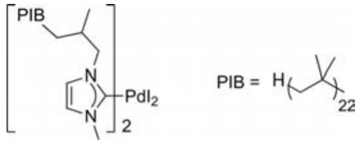


Figure 5. Polyisobutylene-supported complex.

2.2.4 Polymer-Supported Ligands for Reactions in Water

As it was mentioned in section 2.1, the interest in developing supported palladium catalysts to perform cross-coupling reactions in water is strong. Thus, ligands bound to polymers that are compatible with aqueous conditions and enable improved substrate–catalyst contact in this solvent have been synthesized. PEG and PEG-polystyrene copolymers (PS-PEG) are the most common polymers used, since the polyether backbone of these supports favors their solubility or their swelling volumes in water. There is also a large variety of PEG polymers and copolymers with different monomer ratios and molecular weights, and this makes it easy to find a material with the right properties for each application. Most of the ligand types bound to polystyrene (see Figures 1 and 2) have also been linked to PEG or PS-PEG. A dipyridinemethoxy group bound to PEG has been described and this ligand (**17**, Figure 6), when reacted with $Pd(OAc)_2$, catalyzes Suzuki couplings in water and polyethylene glycol as solvent, and it is recyclable as well.[77] Palladacycles derived from acetophenone oxime (**18**, Figure 6) have been used in Suzuki, Sonogashira, and Heck couplings, although, as in the former example, the reactions work better in polyethylene glycol as solvent than in water.[78]

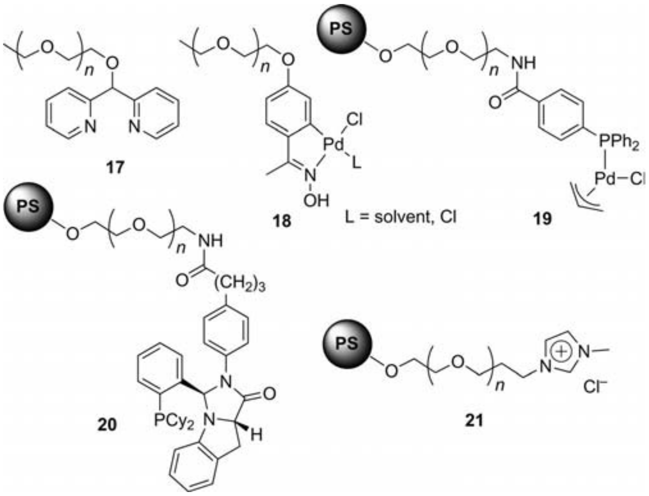


Figure 6. PEG or PS-PEG-supported ligands and catalysts.

Most examples of PEG-supported phosphane ligands use PS-PEG copolymers. Uozumi et al. used palladium complex **19** (Figure 6) as catalyst for Suzuki coupling in water.[79] The catalyst is not soluble in water, but conversions are very good and the catalyst can be recovered by filtration and recycled. The same system has been applied to the selective monoarylation of dibromoaryls by Suzuki coupling[80] and also to the Cu-free Sonogashira reaction.[81] The asymmetric Suzuki coupling in water to afford binaphthyls and other arylnaphthyls enantioselectively was carried out with chiral PS-PEG phosphane **20** (Figure 6) mixed in situ with Pd(OAc)$_2$;[82] this catalyst system can be recycled. The Suzuki coupling of aryl chlorides with a PS-PEG-supported analogue of ligand **3** (R = Cy, Figure 1) in a toluene/EtOH/H$_2$O solvent mixture has been reported.[54]

PS-PEG copolymers functionalized with an imidazolium salt (**21**, Figure 6) have been used as precursors of supported palladium carbenes by reaction with Pd(OAc)$_2$ in the presence of KO*t*Bu. They catalyze the Suzuki coupling of a variety of aryl bromides and iodides with phenylboronic acid by using water as solvent. The catalyst swells in water but can be recovered by filtration and recycles at least five times.[83]

Acrylic polymers have proved useful as catalyst supports for reactions in water. A copolymer synthesized from *N*-isopropylacrylamide and *para*-diphenylphosphanylstyrene coordinates to palladium to give a polymeric complex in which the metal produces a crosslinked and insoluble material by coordination to two polymeric phosphane ligands as shown in Figure 7. This catalysts is very active in the Suzuki reaction of a large variety of arylboronic acids, aryl bromides, and aryl iodides in water. The catalyst has been reused ten times without loss of activity.[84]

Palladium has been supported on polymers that are functionalized in a way that they change their properties when the pH of the aqueous solution changes. Zhang et al. reported a pH-responsive material consisting of microspheres formed by a core of polystyrene and a shell of poly(methacrylic acid) that has been functionalized on the surface with iminodiacetic acid [NH(COOH)$_2$]. The microspheres are reacted with PdCl$_2$, and coordination of the metal to some of the iminoacetate groups on the shell occurs. This Pd-loaded polymer is highly dispersed in water at pH > 10, in which the carboxylic groups are deprotonated, and it has been used for Suzuki and Heck reactions in water, which are carried out under basic conditions. After the coupling reaction has been completed, the products are extracted in an organic solvent, and the catalyst is precipitated by lowering the pH of the aqueous phase to 5. It can be recovered by filtration and recycled. Low leaching has been detected (about 2.8% of the palladium contained in the catalyst), but this may be the reason for a slight decrease in the yields obtained upon recycling.[85]

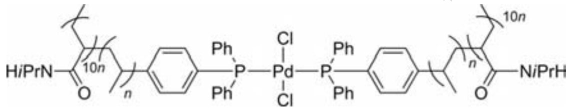


Figure 7. Pd-crosslinked polyacrylamide catalyst.

The same group reported a polymer, which behaves as a hydrogel and it is pH- and thermoresponsive. In this case the material is a copolymer of *N*-isopropylacrylamide and a functionalized methacrylate: poly(*N*-isopropylacrylamide)-*co*-poly{2-methacrylic acid 3-[bis(carboxymethyl)amino]-2-hydroxypropyl ester}. The reaction with an appropriate palladium precursor leads to the immobilization of the metal by coordination to the carboxymethylamino groups, as proposed by the authors. This palladium-supported catalyst was used in Suzuki and Heck couplings by the following procedure. The hydrogel swells in water at low temperature and pH below 10. Under these conditions, the reagents are mixed and they can be absorbed by the hydrogel. Upon heating and increasing the pH, the material undergoes a transition from a hydrophilic structure to a partially hydrophobic one, which leads to a deswelling, and water is expelled from the structure. The reagents are trapped in the deswelled gel, and the reaction proceeds under a higher concentration, so it is accelerated. After the reaction, the temperature and pH are adjusted, the products are extracted into an organic solvent, and the hydrogel is reused (Figure 8).[86]

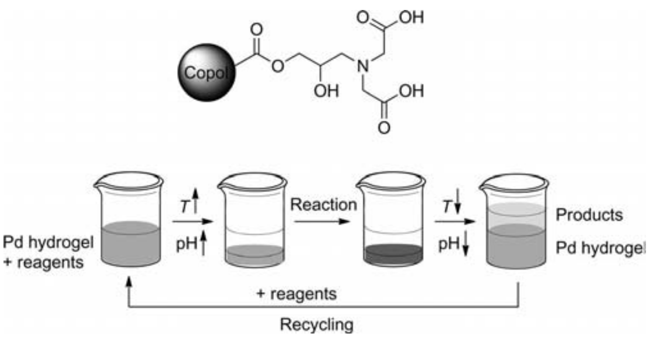


Figure 8. Use of a polymeric Pd hydrogel as catalyst.

Amphiphillic polymers that may form micelles in water have been also functionalized to form ligands that can coordinate to palladium. A polyoxazoline material was formed by copolymerization of 2-methyloxazoline and 2-alkyl oxazolines, some of the latter with pendant palladium N-heterocyclic carbene complexes (Figure 9). Heck reactions were catalyzed with this polymer under conditions where it forms micelles in water. After the reaction, the product was extracted in an organic solvent, and the aqueous layer containing the catalyst was reused three times; no loss of activity was observed.[87]

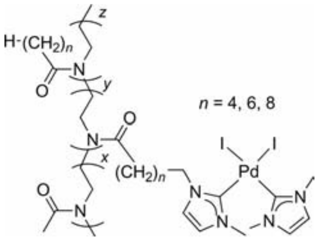


Figure 9. Polyoxazoline Pd-NHC catalyst.

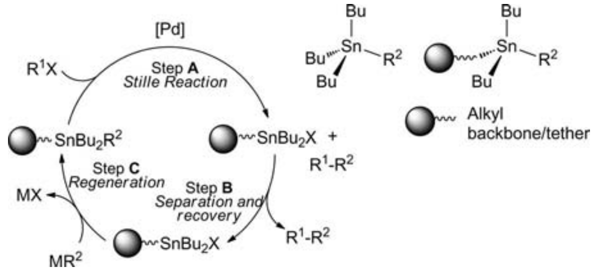
3. Polymer-Supported Reagents: The Stille Reaction

The Pd-catalyzed coupling of organostannanes with organic electrophiles was first reported by the groups of Eaborn and Kosugi,[88] but the synthetic and mechanistic work of Stille in the late nineteen seventies[89] made of this process one of the most useful cross-coupling reactions (Scheme 1).[2,90–91] Organotin derivatives have many advantages when compared to other organometallic derivatives. Many organostannanes are available or can be readily synthesized and they are water- and air-stable so they can be easily stored. Since they are tolerant to most functional groups, protection-deprotection procedures are not necessary. Their intermediate reactivity allows to perform the coupling reaction in the presence of other sensitive functional groups in the substrate molecules. Moreover, the addition of other reagents such as bases, as it is the case for other coupling reactions, is not required. Because of all these advantages, the Stille reaction has been extensively used in the synthesis of natural products, especially in the construction of cycles in the presence of other functional groups.[92–95] One beautiful example is the last step of the synthesis of rapamycin reported by Nicolaou et al., which is a double Stille coupling with bis(tributyltin)ethene.[96]

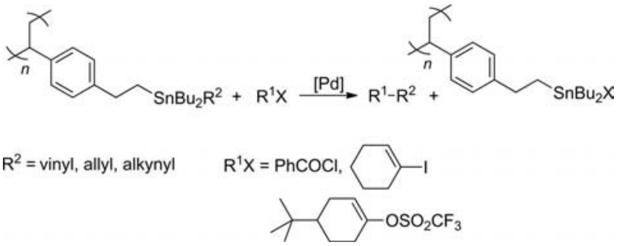
The drawback of the Stille reaction is the toxicity of the organotin derivatives employed.[12,97,98] The toxicity of the members of the family SnR_3X becomes lower as the alkyl group gets larger (i.e. SnR_3X is less toxic with R = Bu than that with R = Et), and $SnBu_3X$, the most common byproduct in Stille couplings, is moderately toxic.[99] However, the use of this coupling reaction in the synthesis of products that may have a pharmaceutical application needs the complete separation of the tin byproduct from the target coupling product. This is not a simple a procedure, and many efforts have been made to devise separation techniques and suitable reagents to ensure the total absence of tin byproducts in the desired products. The most common workup of a Stille reaction, and many reactions that employ tin compounds for that matter, involves the treatment of the reaction mixture with an aqueous solution of KF to form insoluble $SnBu_3F$, which is then filtered off.[100] This procedure is cumbersome, since the separation is often biphasic and not very efficient, and the tin fluoride tends to form suspensions that are difficult to filter. This separation usually leaves behind about 4–5% (by weight) of tin in the coupling product. New strategies for a better separation include the modification of the tin reagent to introduce appropriate tags such as fluorinated groups,[101] polyaromatic groups,[102] and others,[103,104] or the use of special chromatography techniques.[105] Some efforts have also been made to use less toxic $SnCl_3R$ derivatives[106] or to use a substoichiometric amount of tin reagents.[107] All these approaches do not achieve the recycling of the tin byproducts, so their accumulation and post-handling is still a problem.

A major improvement in this reaction can be achieved by the use of polymer-supported tin reagents. Separation of a polymeric tin byproduct from a discrete molecular product should be easier and, if a good recovery and recycling of the polymeric tin reagent is possible, the tin waste in the reaction is eliminated (Scheme 10). This would leave the Stille reaction as the cleanest member of the cross-coupling reaction family, as no additives are required and mild conditions usually operate. The Sn–polymer bond should be nonreactive to avoid leaching and ensure a reactivity centered on the R group that will be coupled. The polymeric link should then mimic the butyl groups in the common Stille reaction, which are reluctant to transmetalate to palladium and guarantee selective transmetalation of the R group (Scheme 10). Thus, a polymer with an aliphatic skeleton would be an ideal support, and, if this is not the case, the support must provide at least an aliphatic link to tin. An additional advantage is that, using such a type of support, that is, a butyl group in $SnBu_3R$ substituted by a polymer, should reduce the toxicity of the tin compound, according to the trend described above. Other than polymers as supports, only the use of tin-functionalized ionic liquids makes it possible to carry out the Stille reaction and recycle the tin byproducts.[108] As for other coupling reactions, the use of polymers in the Stille reaction includes supporting the palladium catalyst by some of the strategies discussed above.[40,109,110]

The first use of polymers as reagents in the Stille reaction was reported by Kuhn and Neumann.[111] They used a polystyrene derived from hydrostannation of one double bond of divinylbenzene and subsequent radical polymerization of the resulting monomer.[112] This polymer was applied to the Stille coupling of alkynyl, allyl, and vinyl R^2 groups with moderate to good yields (Scheme 11). The authors checked the possibility of recovery and reuse of these reagents by repeating the coupling of benzoyl chloride and the polymer where R^2 = –C≡C–Ph, which could be carried out three times; however, no specific conversion data were given.

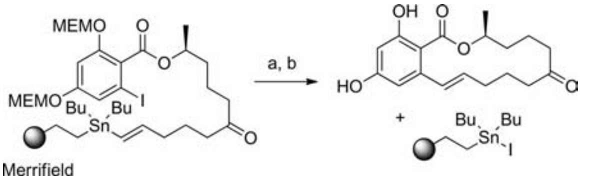


Scheme 10. Use of polymeric tin reagents in the Stille reaction.



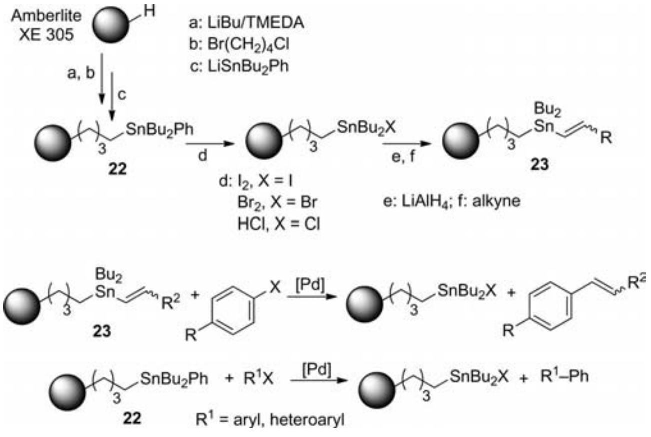
Scheme 11. Polystyrene tin reagents in the Stille reaction.

Nicolaou et al. used a polymer-supported tin reagent for the synthesis of macrocycles including the synthesis of *S*-zearalenone (Scheme 12).[113] They used a Merrifield resin with a pendant stannyl group bearing a properly functionalized vinyl moiety that undergoes a subsequent intramolecular Stille coupling. The authors established the proof of principle, but no recycling of the polymer was attempted in this work.



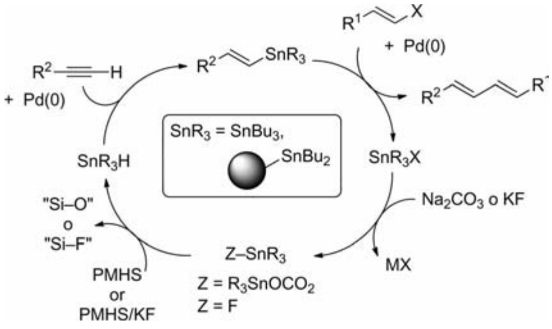
Scheme 12. Last steps of the synthesis of *S*-zearalenone: (a) Stille coupling; (b) deprotection.

Quintard et. al synthesized a tin-functionalized polystyrene derived from Amberlite XE305 by following the procedure shown in Scheme 13. They introduced vinyl groups in this polymer either by reaction with vinylmagnesium bromide or by hydrostannation of alkynes, after conversion of the Sn–I to the Sn–H derivative. These polymeric vinyl stannanes (**23**) can be used in Stille couplings with aryl halides as electrophiles, leading to a very low contamination of the coupling products (< 7 ppm). No recycling of the tin reagent was attempted.[114,115] They also used the polymer-supported phenyl stannane **22** (Scheme 13) to synthesize biaryls by the Stille coupling with aryl halides.[116] In this case the polymer was reused, although an important decrease in the yield of the coupling product was observed upon recycling. Treatment of the used polymer with 2,4,6-trimercapto-*s*-triazine before the next cycle is beneficial and allows a more efficient reuse of the polymer. The authors attribute this effect to the elimination of the residual palladium that is deposited in the polymer after the first reaction.



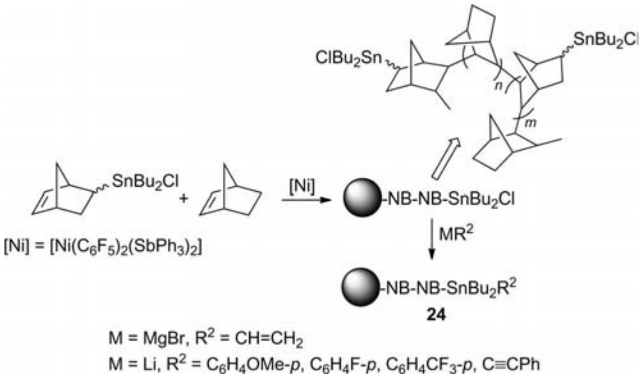
Scheme 13. Synthesis of supported stannanes **22** and **23** and their use in Stille couplings.

Polystyrene-supported stannanes have also been used in the Stille reaction catalytic in tin developed several years ago by Maleczka et al.[107,117] This reaction is a Stille coupling of organic electrophiles and vinyl tin derivatives that uses substoichiometric amounts of the tin derivative (5–10 %). The vinylstannane is generated in situ by hydrostannation of alkynes, and the required tin hydride is generated in the course of the reaction by reduction with a polysiloxane (Scheme 14). This is an interesting concept that helps to reduce the amount of tin used in these reactions; however, the reaction is limited to the coupling of vinyl fragments, since the generation of the tin compound relies on hydrostannation of an alkyne. Killburn et al. used polystyrene-supported tin compounds in this process (Scheme 14). Under these conditions, the amount of tin contamination in the products is low (5–60 ppm).[118]



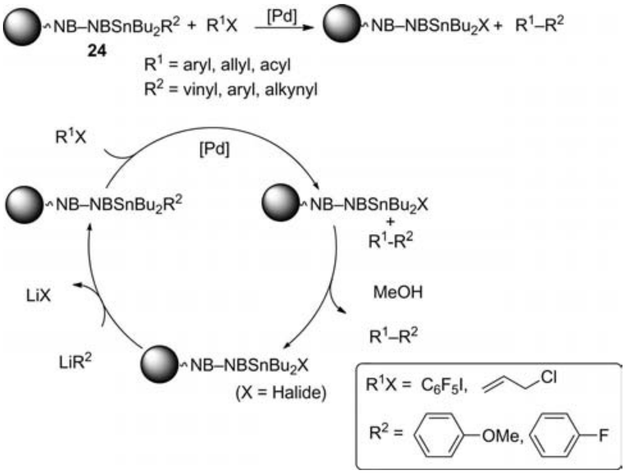
Scheme 14. Stille reaction catalytic in tin.

We have recently prepared a stannylated vinylic polynorbornene and used it in the Stille reaction.[119] This polymer is synthesized by copolymerization of norbornene and a stannylated norbornene derivative catalyzed by a Ni–pentafluorophenyl complex. The polymer backbone is completely aliphatic and unreactive, features that are ideal to obtain a selective transmetalation of R^2 (Scheme 15).



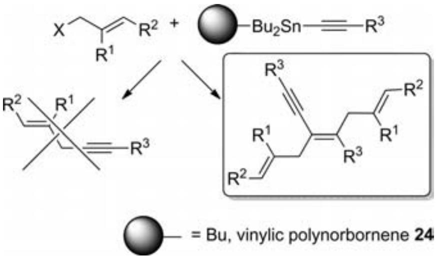
Scheme 15. Vinylic polynorbornene-supported tin reagents.

Polymers **24** are useful in Stille reactions. They can be recycled, as tested for several couplings and five cycles (Scheme 16). The polymeric reagent can be separated easily by precipitation in MeOH and filtration. The tin content of the products is low (0.07–0.02% Sn by weight), about two orders of magnitude lower than the values obtained with the traditional KF (aq.) workup.



Scheme 16. Stille reactions and recycling of stannanes supported on vinylic polynorbornene.

Polymers **24** bearing a Sn–alkynyl moiety have also been used in the recently developed tandem double Stille coupling of allyl halides and polymeric alkynyl stannanes to give trienynes (Scheme 17).[120] In this reaction, a double coupling occurs, and the use of the polymeric reagents allows a simple workup and affords clean coupling products.



Scheme 17. Tandem double Stille reaction of allyl halides and alkynyl stannanes supported on vinylic polynorbornene.

Conclusions

Polymers have largely contributed to make cleaner cross-coupling reactions by supporting catalysts or reagents that can be better separated and recycled. Much work has been carried out to support palladium catalysts on polymers. Palladium can be embedded into polymers by physical encapsulation and weak palladium–polymer interactions. However, coordination of the metal to polymer-supported ligands is the most common procedure. In either way, catalytic systems that can be easily separated and recycled are now available and have proved to be as useful as their homogeneous counterparts. The separation of the polymeric catalysts can be effected by filtration for insoluble polymeric supports, and systems that are amenable to biphasic separation have also been developed. Efficient supported palladium catalysts in water as solvent have also been synthesized. Most catalytic systems have been tested in Suzuki couplings and also with the Heck reaction. Some examples of the Sonogashira or Stille reactions have also been carried out with polymer-supported catalysts, but the other members of the cross-coupling family (Kumada, Negishi) have been little explored.

Polymer-supported reagents are especially important in the Stille reaction, since their good separation and reuse eliminates the problem of tin contamination and the handling of toxic tin byproducts. Some work has been done in this area with the development of reagents based on polystyrene and vinylic polynorbornene. These stannylated polymers have proved useful in the Stille coupling, can be recycled, and strongly reduce the tin content of the coupling products. The Stille reaction is synthetically very powerful, but tin toxicity makes this process rather underused. The use of supported organotin reagents would contribute to put it back among the synthetic chemist's bench tools.

Acknowledgments

Financial support from the Spanish Ministerio de Ciencia e Innovación (Grant CTQ2010-18901/BQU; Consolider Ingenio 2010, Grant INTECAT, CSD2006-0003; fellowship – FPU program – to N. C.) is gratefully acknowledged.

---

[1] R. F. Heck, *Org. React.* **1982**, *27*, 345–390.
[2] J. K. Stille, *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 508–524.
[3] N. Miyaura, A. Suzuki, *Chem. Rev.* **1995**, *95*, 2457–2483.
[4] E.-I. Negishi, *Acc. Chem. Res.* **1982**, *15*, 340–348.
[5] a) T. Hiyama, E. Shirakawa, *Top. Curr. Chem.* **2002**, *219*, 61–85; b) T. Hiyama, *J. Organomet. Chem.* **2002**, *653*, 58–61.
[6] M. Kumada, *Pure Appl. Chem.* **1980**, *52*, 669–679.
[7] K. Sonogashira in *Comprehensive Organic Synthesis* (Eds.: B. M. Trost, I. Fleming), Pergamon Press, Oxford, **1991**, vol. 3, pp. 521–549.
[8] a) A. Rudolph, M. Lautens, *Angew. Chem. Int. Ed.* **2009**, *48*, 2656–2670; b) J. Hassan, M. Sevignon, C. Gozzi, E. Schulz, M. Lemaire, *Chem. Rev.* **2002**, *102*, 1359–1469.

[9] a) Nobel Foundation: http://nobelprize.org/nobel_prizes/chemistry/laureates/2010/press.html; b) X.-F. Wu, P. Anbarasan, H. Neumann, M. Beller, *Angew. Chem. Int. Ed.* **2010**, *49*, 9047–9050.
[10] a) X. Chen, K. M. Engle, D.-H. Wang, J.-Q. Yu, *Angew. Chem. Int. Ed.* **2009**, *48*, 5094–5115; b) B. Karimi, H. Behzadnia, D. Elhamifar, P. F. Akhavan, F. K. Esfahani, A. Zamani, *Synthesis* **2010**, 1399–1427.
[11] a) D. Alberico, M. E. Scott, M. Lautens, *Chem. Rev.* **2007**, *107*, 174–238; b) G. P. Chiusoli, M. Catellani, M. Costa, E. Motti, N. Della Ca′, G. Maestri, *Coord. Chem. Rev.* **2010**, *254*, 456–469.
[12] Tin and Organotin Compounds – Environmental Health Criteria Series 15, International Programme on Chemical Safety, World Health Organization, Geneva, **1980**.
[13] J. Yan, M. Zhu, Z. Zhou, *Eur. J. Org. Chem.* **2006**, 2060–2062.
[14] P. Lan, D. Berta, J. A. Porco Jr., M. S. South, J. J. Parlow, *J. Org. Chem.* **2003**, *68*, 9678–9686.
[15] a) B. A. Lorsbach, M. J. Kurth, *Chem. Rev.* **1999**, *99*, 1549–1581; b) R. E. Sammelson, M. J. Kurth, *Chem. Rev.* **2001**, *101*, 137–202; c) S. Bräse, J. H. Kirchhoff, J. Köbberling, *Tetrahedron* **2003**, *59*, 885–939; d) A. Kirschning, H. Monenschein, R. Wittenberg, *Angew. Chem. Int. Ed.* **2001**, *40*, 650–679; e) P. J. H. Scott, P. G. Steel, *Eur. J. Org. Chem.* **2006**, 2251–2268.
[16] a) W. Li, K. Burgess, *Tetrahedron Lett.* **1999**, *40*, 6527–6530; b) C. Pourbaix, F. Carreaux, B. Carboni, *Org. Lett.* **2001**, *3*, 803–805; c) M. Gravel, K. A. Thompson, M. Zak, C. Bérubé, D. G. Hall, *J. Org. Chem.* **2002**, *67*, 3–15; d) P. Gros, A. Doudouh, Y. Fort, *Tetrahedron Lett.* **2004**, *45*, 6239–6241.
[17] a) Palladium – Environmental Health Criteria Series 226, International Programme on Chemical Safety, World Health Organization, Geneva, **2002**; b) T. Z. Liu, S. D. Lee, R. S. Bhatnagar, *Toxicol. Lett.* **1979**, *4*, 469–473.
[18] a) B. M. L. Dioos, I. F. J. Vankekecom, P. A. Jacobs, *Adv. Synth. Catal.* **2006**, *348*, 1413–1446; b) J. Lu, P. H. Toy, *Chem. Rev.* **2009**, *109*, 815–838.
[19] a) D. E. Bergbreiter, *Chem. Rev.* **2002**, *102*, 3345–3384; b) T. J. Dikerson, N. N. Reed, K. D. Janda, *Chem. Rev.* **2002**, *102*, 3325–3344; c) D. E. Bergbreiter, S. D. Sung, *Adv. Synth. Catal.* **2006**, *348*, 1352–1366; d) D. E. Bergbreiter, J. Tian, C. Hongfa, *Chem. Rev.* **2009**, *109*, 530–582.
[20] H. P. Dijkstra, G. P. M. Van Klink, G. Van Koten, *Acc. Chem. Res.* **2002**, *35*, 798–810.
[21] C. G. Frost, L. Mutton, *Green Chem.* **2010**, *12*, 1687–1703.
[22] M. Lamblin, L. Nassar-Hardy, J. C. Hierso, E. Fouquet, F. X. Felpin, *Adv. Synth. Catal.* **2010**, *352*, 33–79.
[23] A. G. Tennyson, K. M. Wiggins, C. W. Bielawski, *J. Am. Chem. Soc.* **2010**, *132*, 16631–16636.
[24] a) A. Biffis, M. Zecca, M. Basato, *J. Mol. Catal. A: Pol. Chem.* **2001**, *173*, 249–274; b) L. Yin, J. Liebscher, *Chem. Rev.* **2007**, *107*, 133–173; c) L. De Rogatis, M. Cargnello, V. Gombac, B. Lorenzut, T. Montini, P. Fornasiero, *ChemSusChem* **2010**, *3*, 24–42.
[25] a) R. van Herbeek, P. C. J. Kramer, P. W. N. M. van Leeuven, J. N. H. Reek, *Chem. Rev.* **2002**, *102*, 3717–3756; b) D. Astruc, E. Boisselier, C. Omelas, *Chem. Rev.* **2010**, *110*, 1857–1959.
[26] J.-I. Yoshida, K. Itami, *Chem. Rev.* **2002**, *102*, 3693–3716.
[27] V. I. Pârvulescu, C. Hardacre, *Chem. Rev.* **2007**, *107*, 2615–2665.
[28] See for example: a) S. P. Andrews, A. F. Stepan, H. Tanaka, S. V. Ley, M. D. Smith, *Adv. Synth. Catal.* **2005**, *347*, 647–654; b) N. T. S. Phan, M. Van Der Sluys, C. W. Jones, *Adv. Synth. Catal.* **2006**, *348*, 609–679; c) M. Weck, C. W. Jones, *Inorg. Chem.* **2007**, *46*, 1865–1875.
[29] R. Akiyama, S. Kobayashi, *Chem. Rev.* **2009**, *109*, 594–642.
[30] R. Akiyama, S. Kobayashi, *Angew. Chem. Int. Ed.* **2001**, *40*, 3469–3471.
[31] R. Akiyama, S. Kobayashi, *J. Am. Chem. Soc.* **2003**, *125*, 3412–3413.
[32] K. Okamoto, R. Akiyama, S. Kobayashi, *Org. Lett.* **2004**, *6*, 1987–1990.
[33] R. Nishio, M. Sugiura, S. Kobayashi, *Org. Lett.* **2005**, *7*, 4831–4834.
[34] H. Hagio, M. Sugiura, S. Kobayashi, *Org. Lett.* **2006**, *8*, 375–378.
[35] C. Ramarao, S. V. Ley, S. C. Smith, I. M. Shirley, N. DeAlmeida, *Chem. Commun.* **2002**, 1132–1133.
[36] S. V. Ley, C. Ramarao, R. S. Gordon, A. B. Holmes, A. J. Morrison, I. F. McConvey, I. M. Shirley, S. C. Smith, M. D. Smith, *Chem. Commun.* **2002**, 1134–1135.
[37] C. K. Y. Lee, A. B. Colmes, S. V. Ley, I. F. MacConvey, B. Al-Duri, G. A. Leeke, R. C.-D. Santos, J. P. K. Seville, *Chem. Commun.* **2005**, 2175–2177.
[38] I. R. Baxendale, C. M. Griffiths-Jones, S. V. Ley, G. K. Tranmer, *Chem. Eur. J.* **2006**, *12*, 4407–4416.
[39] K. Mennecke, A. Kirschning, *Beilstein J. Org. Chem.* **2009**, *5*, DOI: 10.3762/bjoc.5.21.
[40] X. Yang, Z. Fei, D. Zhao, W. H. Ang, Y. Li, P. J. Dyson, *Inorg. Chem.* **2008**, *47*, 3292–3297.
[41] D. Song, W.-B. Yi, *J. Mol. Catal. A* **2008**, *280*, 20–23.
[42] B. J. Gallon, R. W. Kojima, R. B. Kaner, P. L. Diaconescu, *Angew. Chem. Int. Ed.* **2007**, *46*, 7251–7254.
[43] B. Tamami, H. Allahyari, S. Ghasemi, F. Farjadian, *J. Organomet. Chem.* **2010**, *696*, 594–599.
[44] J. K. Cho, R. Najman, T. W. Dean, O. Ichihara, C. Muller, M. Bradley, *J. Am. Chem. Soc.* **2006**, *128*, 6276–6277.
[45] S.-S. Yi, D.-H. Lee, E. Sin, Y.-S. Lee, *Tetrahedron Lett.* **2007**, *48*, 6771–6775.
[46] E. Sin, S.-S. Yi, Y.-S. Lee, *J. Mol. Catal. A* **2010**, *315*, 99–104.
[47] F. Wen, W. Zhang, G. Wei, Y. Wang, J. Zhang, M. Zhang, L. Shi, *Chem. Mater.* **2008**, *20*, 2144–2150.
[48] N. E. Leadbeater, M. Marco, *Chem. Rev.* **2002**, *102*, 3217–3274.
[49] C. A. McNamara, M. J. Dixon, M. Bradley, *Chem. Rev.* **2002**, *102*, 3275–3300.
[50] S.-B. Jang, *Tetrahedron Lett.* **1997**, *38*, 1793–1796.
[51] I. Fenger, C. Le Drian, *Tetrahedron Lett.* **1998**, *39*, 4287–4290.
[52] H. S. He, J. J. Yan, R. Shen, S. Zhuo, P. H. Toy, *Synlett* **2006**, 563–566.
[53] S. Schweizer, J. M. Becht, C. Le Drian, *Adv. Synth. Catal.* **2007**, *349*, 1150–1158.
[54] K. Glegola, E. Framery, K. M. Pietrusiewicz, D. Sinou, *Adv. Synth. Catal.* **2006**, *348*, 1728–1733.
[55] C. A. Parrish, S. L. Buchwald, *J. Org. Chem.* **2001**, *66*, 3820–3827.
[56] S. Schweizer, J. M. Becht, C. Le Drian, *Tetrahedron* **2010**, *66*, 765–772.
[57] M. Bakherad, A. Keivanloo, B. Bahramian, S. Mihanparast, *Tetrahedron Lett.* **2009**, *50*, 6418–6420.
[58] A. Datta, K. Ebert, H. Plenio, *Organometallics* **2003**, *22*, 4685–4691.
[59] S. M. Islam, P. Mondal, K. Tuhina, A. S. Roy, S. Mondal, D. Hossain, *J. Inorg. Organomet. Polym.* **2010**, *20*, 264–277.
[60] J. Gil-Moltó, S. Karlström, C. Nájera, *Tetrahedron* **2005**, *61*, 12168–12176.
[61] S. M. Islam, P. Mondal, A. S. Roy, S. Mondal, D. Hossain, *Tetrahedron Lett.* **2010**, *51*, 2067–2070.
[62] E. Alacid, C. Nájera, *J. Organomet. Chem.* **2009**, *694*, 1658–1665.
[63] a) J.-W. Byun, Y.-S. Lee, *Tetrahedron Lett.* **2004**, *45*, 1838–1840; b) D.-H. Lee, J.-H. Kim, B.-H. Jun, H. Kang, J. Park, Y.-S. Lee, *Org. Lett.* **2008**, *10*, 1609–1612.
[64] M. I. Burguete, E. García-Verdugo, I. García-Villar, F. Gelat, P. Licence, S. V. Luis, V. Sans, *J. Catal.* **2010**, *269*, 150–160.
[65] J.-H. Kim, J.-W. Kim, M. Shokouhimehr, Y.-S. Lee, *J. Org. Chem.* **2005**, *70*, 6714–6720.
[66] T. J. Colacot, W. A. Carole, B. A. Neide, A. Harad, *Organometallics* **2008**, *27*, 5605–5611.
[67] T. J. Colacot, E. S. Gore, A. Kuber, *Organometallics* **2002**, *21*, 3301–3304.

[68] Y.-C. Yang, T.-Y. Luh, *J. Org. Chem.* **2003**, *68*, 9870–9873.

[69] M. R. Buchmeiser, K. Wurst, *J. Am. Chem. Soc.* **1999**, *121*, 11101–11107.

[70] W. J. Sommer, M. Weck, *Adv. Synth. Catal.* **2006**, *348*, 2101–2113.

[71] G. M. Pawar, M. R. Buchmeiser, *Adv. Synth. Catal.* **2010**, *352*, 917–928.

[72] M. Bandini, A. Pietrangelo, R. Sinisi, A. Umani-Ronchi, M. O. Wolf, *Eur. J. Org. Chem.* **2009**, 3554–3561.

[73] D. E. Bergbreiter, P. L. Osburn, A. Wilson, E. M. Sink, *J. Am. Chem. Soc.* **2000**, *122*, 9058–9064.

[74] D. E. Bergbreiter, Y.-S. Liu, *Tetrahedron Lett.* **1997**, *38*, 7843–7846.

[75] A. Köllhofer, H. Plenio, *Chem. Eur. J.* **2003**, *9*, 1416–1425.

[76] D. E. Bergbreiter, H.-L. Su, H. Koizumi, J. Tian, *J. Organomet. Chem.* **2011**, *696*, 1272–1279.

[77] W. Mai, L. Gao, *Synlett* **2006**, 2533–2558.

[78] A. Corma, H. García, A. Leyva, *J. Catal.* **2006**, *240*, 87–99.

[79] Y. Uozumi, H. Danjo, T. Hayashi, *J. Org. Chem.* **1999**, *64*, 3384–3388.

[80] Y. Uozumi, M. Kikuchi, *Synlett* **2005**, 1775–1778.

[81] T. Suzuka, Y. Okada, K. Ooshiro, Y. Uozumi, *Tetrahedron* **2010**, *66*, 1064–1069.

[82] Y. Uozumi, Y. Matsuura, T. Arakawa, Y. M. A. Yamada, *Angew. Chem. Int. Ed.* **2009**, *48*, 2708–2710.

[83] J.-W. Kim, J.-H. Kim, D.-H. Lee, Y.-S. Lee, *Tetrahedron Lett.* **2006**, *47*, 4745–4748.

[84] Y. M. A. Yamada, K. Takeda, H. Takahashi, S. Ikegami, *J. Org. Chem.* **2003**, *68*, 7733–7741.

[85] J. Zhang, W. Zhang, Y. Wang, M. Zhang, *Adv. Synth. Catal.* **2008**, *350*, 2065–2076.

[86] Y. Wang, J. Zhang, W. Zhang, M. Zhang, *J. Org. Chem.* **2009**, *74*, 1923–1931.

[87] D. Schönfelder, K. Fischer, M. Schmidt, O. Nuyken, R. Weberskirch, *Macromolecules* **2005**, *38*, 254–262.

[88] a) D. Azarian, S. S. Dua, C. Eaborn, D. R. M. Walton, *J. Organomet. Chem.* **1976**, *117*, C55–C75; b) M. Kosugi, K. Sasazawa, Y. Shimizu, T. Migita, *Chem. Lett.* **1977**, 301–302; c) M. Kosugi, Y. Shimizu, T. Migita, *Chem. Lett.* **1977**, 1423–1424.

[89] D. Milstein, J. K. Stille, *J. Am. Chem. Soc.* **1978**, *100*, 3636–3638.

[90] V. Farina, V. Krishanamurthy, W. J. Scott, *The Stille Reaction*, Wiley, New York, **1998**.

[91] P. Espinet, A. M. Echavarren, *Angew. Chem. Int. Ed.* **2004**, *43*, 4704–4734.

[92] The use of cross-coupling reaction in natural product syntheses has been reviewed: K. C. Nicolau, P. G. Bulger, D. Sarlah, *Angew. Chem. Int. Ed.* **2005**, *44*, 4442–4489.

[93] H. W. Lam, G. Pattenden, *Angew. Chem. Int. Ed.* **2002**, *41*, 508–511.

[94] K. C. Nicolaou, J. Xu, F. Murphy, S. Barluenga, O. Baudoin, H.-X. Wei, D. L. F. Gray, T. Ohshima, *Angew. Chem. Int. Ed.* **1999**, *38*, 2447–2451.

[95] M. D. Shair, T. Y. Yoon, K. K. Mosny, T. C. Chou, S. J. Danishefsky, *J. Am. Chem. Soc.* **1996**, *118*, 9509–9525.

[96] K. C. Nicolaou, T. K. Chakraborty, A. D. Piscopio, N. Minowa, P. Bertinato, *J. Am. Chem. Soc.* **1993**, *115*, 4419–4420.

[97] Young in *Tin Chemistry-Fundamentals, Frontiers and Applications* (Eds.: A. G. Davies, M. Gielen, K. H. Pannell, R. T. Tiekink), Wiley, Chichester, **2008**, ch. 5, pp. 653–665.

[98] B. Buck, A. Mascioni, L. Que Jr., G. Veglia, *J. Am. Chem. Soc.* **2003**, *125*, 13316–13317 and references cited therein .

[99] Y. Arakawa, O. Wada, T. H. Yu, *Toxicol. Appl. Pharmacol.* **1981**, *60*, 1–7.

[100] J. E. Leibner, J. Jacobus, *J. Org. Chem.* **1979**, *44*, 449–450.

[101] a) M. Hocino, P. Degenkolb, D. P. Curran, *J. Org. Chem.* **1997**, *62*, 8341–8349; b) D. P. Curran, M. Hoshino, *J. Org. Chem.* **1996**, *61*, 6480–6481.

[102] D. Stien, S. Gastaldi, *J. Org. Chem.* **2004**, *69*, 4464–4470.

[103] J.-C. Poupon, D. Marcoux, J.-M. Cloarec, A. B. Charette, *Org. Lett.* **2007**, *9*, 3591–3594.

[104] M. S. Jensen, C. Yang, Y. Hsiao, N. Rivera, K. M. Wells, J. Y. L. Chung, N. Yasuda, D. L. Hughes, P. J. Reider, *Org. Lett.* **2000**, *2*, 1081–1084.

[105] a) D. C. Harrowven, I. L. Guy, *Chem. Commun.* **2004**, 1968–1969; b) D. C. Harrowven, D. P. Curran, S. L. Kostiuk, I. L. Wallis-Gay, S. Whiting, K. J. Stenning, B. Tang, E. Packard, L. Nanson, *Chem. Commun.* **2010**, *46*, 6335–6337.

[106] a) A. I. Roshchin, N. A. Bumagin, I. P. Beletskaya, *Tetrahedron Lett.* **1995**, *36*, 125–128; b) E. Fouquet, M. Pereyre, A. Rodríguez, *J. Org. Chem.* **1997**, *62*, 5242–5243.

[107] R. E. Maleczka Jr., W. P. Gallagher, I. Terstiege, *J. Am. Chem. Soc.* **2000**, *122*, 384–385.

[108] a) J. Vitz, D.-H. Mac, S. Legoupy, *Green Chem.* **2007**, *9*, 431–433; b) P. D. Pham, J. Vitz, C. Chamignon, A. Martel, S. Legoupy, *Eur. J. Org. Chem.* **2009**, 3249–3257; c) N. Louaisil, P. D. Pham, F. Boeda, D. Faye, A.-S. Castanet, S. Legoupy, *Eur. J. Org. Chem.* **2011**, 143–149.

[109] J. K. Stille, H. Su, D. H. Hill, P. Schneider, M. Tanaka, D. L. Morrison, L. S. Hegedus, *Organometallics* **1991**, *10*, 1993–2000.

[110] K. C. Y. Lau, P. Chiu, *Tetrahedron Lett.* **2007**, *48*, 1813–1816.

[111] H. Kuhn, W. P. Neumann, *Synlett* **1994**, 123–124.

[112] U. Gerigk, M. Gerlach, W. P. Neumann, R. Vieler, V. Weintritt, *Synthesis* **1990**, 448–452.

[113] K. C. Nicolaou, N. Winssinger, J. Pastor, F. Murphy, *Angew. Chem. Int. Ed.* **1998**, *37*, 2534–2537.

[114] J.-M. Chrétien, A. Mallinger, F. Zammattio, E. Le Grognec, M. Paris, G. Montavon, J.-P. Quintard, *Tetrahedron Lett.* **2007**, *48*, 1781–1785.

[115] G. Kerric, E. Le Grognec, V. Fargeas, F. Zammattio, J.-P. Quintard, M. Biesemans, R. Willem, *J. Organomet. Chem.* **2010**, *695*, 1414–1424.

[116] G. Kerric, E. Le Grognec, F. Zammattio, M. Paris, J.-P. Quintard, *J. Organomet. Chem.* **2010**, *695*, 103–110.

[117] a) W. P. Gallagher, I. Terstiege, R. E. Maleczka Jr., *J. Am. Chem. Soc.* **2001**, *123*, 3194–3204; b) R. E. Maleczka Jr., W. P. Gallagher, *Org. Lett.* **2001**, *3*, 4173–4176; c) W. P. Gallagher, R. E. Maleczka Jr., *J. Org. Chem.* **2005**, *70*, 841–846.

[118] A. G. Hernán, V. Guillot, A. Kuvshinov, J. D. Kilburn, *Tetrahedron Lett.* **2003**, *44*, 8601–8603.

[119] N. Carrera, E. Gutiérrez, R. Benavente, M. M. Villavieja, A. C. Albéniz, P. Espinet, *Chem. Eur. J.* **2008**, *14*, 10141–10148.

[120] I. Meana, A. C. Albéniz, P. Espinet, *Adv. Synth. Catal.* **2010**, *352*, 2887–2891.

Received: February 18, 2011
Published Online: April 19, 2011