1

Metal-Catalyzed Cross-Couplings of Aryl Halides to Form C–C Bonds in Aqueous Media

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1.1

Introduction

Metal-catalyzed cross-coupling reactions have developed into a standard component of the synthetic chemist's toolbox [1–4]. These reactions date to the work of Ullmann and Goldberg in the early 1900s on copper-promoted C–C and C–heteroatom bond formations. Copper remained the catalyst of choice for these reactions until the pioneering work of Heck, Suzuki, Stille, Negishi, and others on palladium-catalyzed cross-coupling reactions. Palladium-catalyzed reactions, which can be generally carried out under milder conditions and with a wider range of substrates than reactions catalyzed by copper or other metals, have become standard methods for formation of carbon–carbon and carbon–heteroatom bonds.

Cross-coupling reactions are characterized by the metal-catalyzed coupling of an organic electrophile, typically an organic halide, with an organic nucleophile (Scheme 1.1). The organic halide can be an sp-, sp^2-, or sp^3-hybridized carbon with any halogen or pseudohalogen leaving group. The majority of research has focused on sp^2 carbon–halogen bonds. A variety of name reactions have been developed using organometallic carbon nucleophiles. Examples with nearly every metal in the periodic table have been demonstrated, but the most common organometallic species used include organotin (Stille), organoboron (Suzuki), Grignard reagents (Kumada), organosilicon (Hiyama), organozinc (Negishi), and *in situ* generated acetylide anions (Sonogashira). Key steps in these cross-coupling reactions include oxidative addition of the organic halide, transmetalation of the nucleophilic carbon, and reductive elimination to form the product. The Heck coupling of aryl halides and alkenes also falls into this class of reactions, although it involves a migratory insertion/β-hydride elimination sequence in the key bond-forming step rather than reductive elimination.

Organic synthetic methodology has largely developed using organic solvents. Homogeneous-metal-catalyzed reactions have similarly largely relied on the use of traditional organic solvents. Organic solvents have a number of advantages: they are good solvents for organic compounds, there are a range of properties (polarity, protic/aprotic, boiling point, viscosity) that can be chosen, and certain

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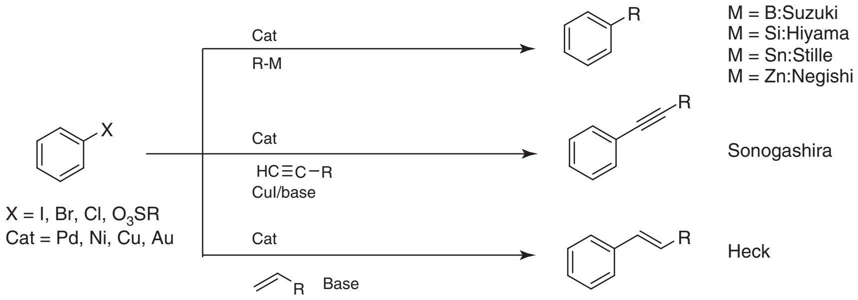


Scheme 1.1 Major classes of metal-catalyzed cross-coupling reactions.

organic solvents are inert toward highly reactive reagents. Disadvantages of organic solvents include flammability, toxicity, and lack of sustainability. Because of these latter issues, there has been an interest in moving away from organic solvents to safer and more renewable solvent systems. Water is a particularly attractive alternative solvent [5–9]. Water is a renewable, although limited, resource that is nontoxic, nonflammable, and relatively inexpensive. The unusual properties of water, such as its strong hydrogen bonding ability, can lead to unusual reactivity that is not seen in traditional organic solvents. Although water is an attractive solvent, it presents a number of challenges in synthetic organic chemistry. Water is a poor solvent for most organic compounds. Although this can limit the use of water as a reaction medium, it also provides opportunities for alternative reactivity and simplified product isolation compared to organic solvents. Water is also highly reactive with many useful reagents, particularly many organometallic reagents. This can limit the types of reactions that can be performed in water. Late transition metal–carbon bonds as well as many of the common organometallic reagents used in cross-coupling reactions, such as organotin, organoboron, and organosilicon compounds, are tolerant of water, however.

The primary motivations to carry out cross-coupling reactions in aqueous solvents have been economic and environmental. For the reasons described above, water is potentially safer than organic solvents. Although water is often considered an environmentally benign solvent, water contaminated with organic materials must still be treated as hazardous waste. Recycling of water and decreased solvent demand in purification may still make water a better choice economically and environmentally. Another motivation to use water is to allow for simple separation of the catalyst from the product stream. The simplified separation can significantly decrease cost and waste output for a given process. The palladium catalysts most commonly used in these reactions are expensive. The ability to recover and reuse the palladium catalyst is critical for the application of these methodologies in large-scale fine chemical synthesis. Because the catalysts are often homogeneous, separation of the metal from the product stream can also be quite challenging, particularly to the low levels required in pharmaceutical synthesis [10]. The use of a water-soluble catalyst in an aqueous–organic biphasic system helps in potentially constraining the catalyst to the aqueous phase, allowing for simple separation of the catalyst from the organic product stream. Recently, a number of researchers have shown that water can have promoting effects on cross-coupling reactions of hydrophobic substrates [11, 12].

In this chapter, the use of water as a reaction medium for metal-catalyzed coupling of organic halides and carbon nucleophiles is reviewed. Reactions catalyzed by hydrophilic catalysts, hydrophobic catalysts, and heterogeneous catalysts are discussed. A number of previous reviews have been published in this area, including reviews specifically on aqueous-phase Suzuki couplings [13–17] and more general reviews of aqueous-phase cross-coupling reactions [18–23].

1.2
Aqueous-Phase Cross-Coupling Using Hydrophilic Catalysts

One of the important motivations for the use of water as a reaction medium in catalysis is that it provides a way to simplify the separation of homogeneous transition metal catalysts from the organic product stream. By using a hydrophilic catalyst in an aqueous/organic biphasic solvent system, it is possible to constrain the hydrophilic catalyst in the aqueous phase. The hydrophobic product can then be separated by simple decantation. This approach was first demonstrated effectively in the Rhône–Poulenc process for the hydroformylation of propene using a Rh/TTPTS (trisodium tri(3-sulfonatophenyl)phosphine) catalyst system [24]. This novel approach to heterogeneous catalysis received limited attention initially, but over the past two decades there has been an extensive effort devoted to the synthesis and catalytic application of water-soluble ligands and catalysts [22].

1.2.1
Hydrophilic Triarylphosphines and Diarylalkylphospines

Hydrophilic triarylphosphines were the first class of ligands to be applied to aqueous-phase cross-coupling reactions. Sulfonated triphenylphosphines (i.e., *m*-TPPTS, Figure 1.1) have been the most widely used ligand. Sulfonated arylphosphines are attractive ligands because they can be readily prepared by sulfonating the parent phosphine in fuming sulfuric acid. Other ionic triphenylphosphine derivatives have been prepared with carboxylate, phosphonate, and guanidinium functional groups. These ligands typically require more involved syntheses, which has resulted in their use being limited.

The sulfonated triphenylphosphines were the first water-soluble ligands explored in aqueous-phase catalysis. Water-soluble phosphines, such as *m*-TPPTS, had been known since the 1970s, but it was not until 1990 that Casalnuovo first reported the application of a water-soluble ligand for Pd-catalyzed cross-coupling [25]. Casalnuovo prepared Pd(*m*-TPPMS)$_3$(m-TPPMS = sodium diphenyl(3-sulfonatophenyl)phosphine and applied it to the Suzuki, Sonogashira, and Heck coupling of aryl iodides and bromides in water/acetonitrile solvent systems (Equation 1.1). Good yields were obtained, although high catalyst loadings were required (10–15%). Both hydrophobic and hydrophilic substrates could be

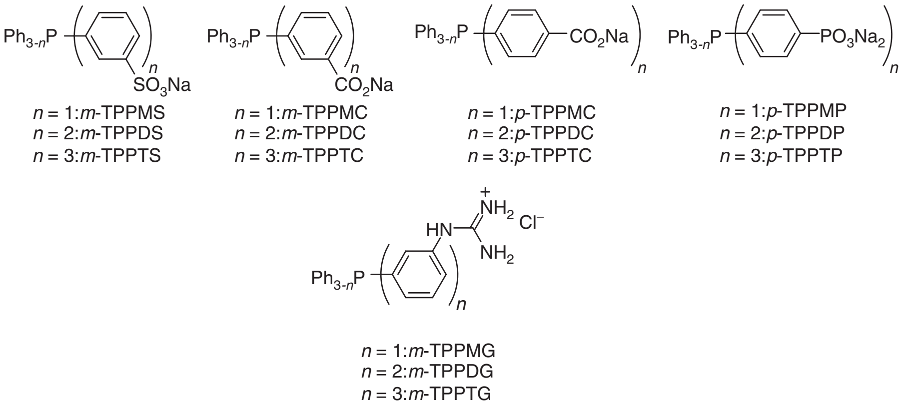
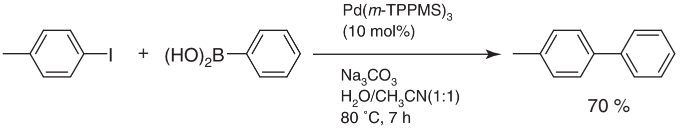


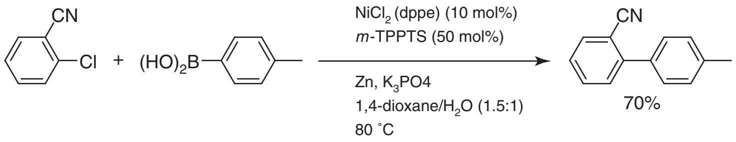
Figure 1.1 Triphenylphosphine derivatives with ionic substituents.

used, including unprotected nucleosides, nucleotides, and amino acid derivatives. Reuse of the aqueous solution for a subsequent reaction was reported, although visual inspection suggested leaching of palladium into the organic phase.



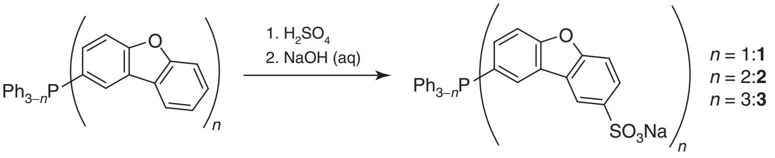
(1.1)

Genêt and coworkers first applied the more water-soluble *m*-TPPTS for Pd-catalyzed cross-coupling reactions. The $Pd(OAc)_2$/*m*-TPPTS system (2.5 mol%) gave good yields of coupled products in Heck, Sonogashira, Suzuki, and Trost–Tsuji reactions of aryl and alkenyl iodides in a 1 : 1 water/acetonitrile solvent system [26, 27]. Aryl bromides could be coupled at 80 °C with the $Pd(OAc)_2$/*m*-TPPTS system [28]. The aqueous catalyst solution could be reused for four cycles in the Suzuki coupling of an aryl bromide with good yields, although increasing reaction times were needed with each cycle. The Pd/*m*-TPPTS catalyst systems are generally not effective for coupling of aryl chlorides, however. A catalyst formed *in situ* from $NiCl_2$(dppe) and 5 equiv of *m*-TPPTS in the presence of zinc catalyzes the Suzuki coupling of aryl chlorides in water/dioxane, however [29]. A high catalyst loading (10 mol% Ni) was required and the reaction was limited to activated aryl chlorides. The Ni/*m*-TPPTS system was applied to the synthesis of 2-cyano-4′-methylbiphenyl, an important precursor to the sartan class of angiotensin II receptor antagonists (Equation 1.2).



(1.2)

A drawback to the synthesis of *m*-TPPTS is the harsh conditions required for the sulfonation reaction because the protonated phosphonium group acts as a deactivating group. Hiemstra and coworkers reported the synthesis of 2-benzofuranylphosphines and their sulfonation to ligands **1**–**3** (Equation 1.3) [30]. The furanyl oxygen activates the aromatic ring toward electrophilic aromatic substitution, allowing the sulfonation reaction to be carried out in sulfuric acid rather than in fuming sulfuric acid. As a result, no oxidation of the phosphorus center was observed. In addition, the benzofuran ring could be selectively sulfonated in the presence of phenyl groups, which allows for easy access to mono- and disulfonated ligands (**1** and **2**). Catalysts derived from ligand **3** gave comparable or lower activity in Heck and Suzuki couplings of aryl iodides to *m*-TPPTS-derived catalysts. The aryl rings can be similarly activated by inclusion of methyl or methoxy substituents. Tri(2,4-dimethyl-5-sulfonatophenyl)phosphine (TXPTS) was prepared as a more sterically demanding analog of *m*-TPPTS. Catalysts derived from TXPTS gave superior activity compared to *m*-TPPTS-derived catalysts for Heck and Suzuki couplings of aryl bromides in water/acetonitrile (Equation 1.4) [31, 32].



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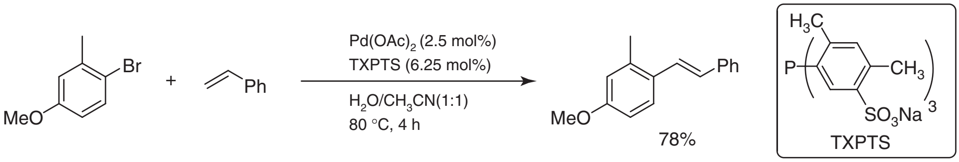
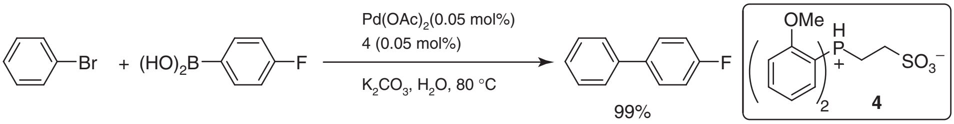


(1.4)

An alternate approach to appending the sulfonate group to the phosphine is through an alkyl linkage. Diarylphosphinoalkyl sulfonates can be prepared by reaction of diarylphosphides with ω-bromoalkylsulfonates [33]. Ligand **4** in combination with Pd(OAc)$_2$ (0.05 mol%) gave an effective catalyst for the Suzuki coupling of aryl bromides in water at 80 °C (Equation 1.5). Moderate yields were obtained in Suzuki couplings of aryl chlorides at 150 °C with microwave heating using this system.

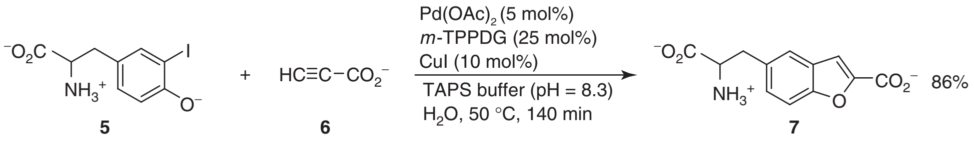


(1.5)

While sulfonated triarylphosphines have been most widely studied owing to their ease of synthesis, a range of other anionic, cationic, or neutral hydrophilic substituents have also been used to generate water-soluble ligands. Phosphonate-substituted ligands are more water-soluble than their sulfonate-substituted counterparts [34]. The catalyst derived from *p*-TPPMP (disodium 4-(diphenylphosphino)phenylphosphonate (Figure 1.1) and Pd(OAc)$_2$

gave higher yields than the catalyst derived from *m*-TPPDS(disodium phenyldi(3sulfonatophenyl)phosphine for Heck couplings of aryl iodides in water under microwave irradiation [35]. The carboxylate-substituted *m*-TPPTC(trisodium tri(3-carboxyphenyl)phosphine ligand provides higher activity in Heck couplings of aryl iodides than *p*-TPPTC ((trisodium tri(4-carboxyphenyl)phosphine) or *m*-TPPTG (tri(3-guanidinophenyl)phosphine trichloride) [36]. The *m*-TPPTC-derived catalyst is slightly more active than *m*-TPPTS. The *m*-TPPTC/Pd catalyst is also effective in the Sonogashira coupling of aryl iodides [37]. The catalyst system could be recycled four times, although increased reaction times were required to achieve high yields. The improved activity of catalysts derived from *m*-TPPTC can be attributed in part to the increased electron-donating ability of *m*-TPPTC compared to that of *m*-TPPTS.

Cationic ammonium or guanidinium moieties have also been applied to water-soluble triarylphosphine ligands. Guanidinium-substituted phosphines (*m*-TPPDG (di(3-guanidinophenyl)phenylphosphine dichloride), *m*-TPPTG, Figure 1.1) were shown to give effective catalysts for the Sonogashira coupling of anionic substrates **5** and **6** in water under biocompatible conditions to give amino acid **7** (Equation 1.6) [38, 39]. The *m*-TPPDG ligand gave higher activity than *m*-TPPTG or *m*-TPPTS. The higher activity of the *m*-TPPDG-derived catalyst compared to *m*-TPPTS was proposed to be due to favorable charge attraction between the cationic ligands and the anionic substrates. To demonstrate the biocompatibility of the coupling conditions, the reaction was performed in the presence of RNAase enzyme. The enzyme remained intact and did not lose catalytic activity.



(1.6)

Neutral water-soluble substituents such as poly(ethylene glycol) (PEG) or polyols are an attractive alternative to ionic substituents. Ligands with nonionic hydrophilic groups typically retain solubility in polar organic solvents, which can simplify their synthesis and purification. In addition, PEG and polyols often demonstrate thermoreversible solvation. Beller and coworkers reported the first example of a carbohydrate-modified triphenylphosphine analog (**8**–**10**, Figure 1.2) [40]. The carbohydrates were attached to diphenyl(4-hydroxyphenyl)phosphine by a glycosidic linkage to the anomeric carbons of glucose (**8**), galactose (**9**), and glucosamine (**10**). Both galactose-phosphine **9** and glucosamine-phosphine **10** gave higher activity catalysts than *m*-TPPTS for the Suzuki and Heck coupling of aryl bromides. A drawback of Beller's ligands is the hydrolytically sensitive glycosidic linkage between the phosphine and the carbohydrate. Miyaura prepared a carbohydrate-modified phosphine (**11**) with an amide linkage by ring opening of D-glucono-1,5-lactone with an amine-functionalized triarylphosphine [41]. Palladium complexes derived from **11** gave superior yields to catalysts derived from *m*-TPPTS in the Suzuki coupling of aryl bromides. An alternative approach to an amide-linked carbohydrate-modified

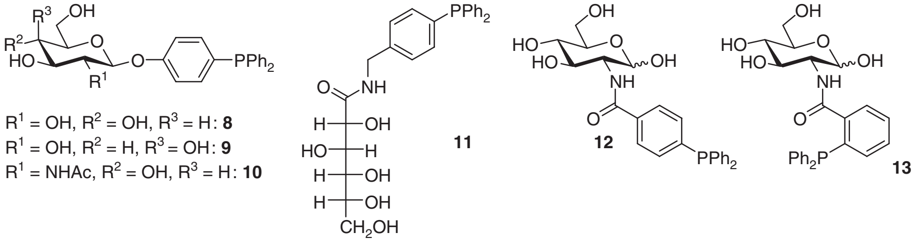


Figure 1.2 Carbohydrate-modified phosphines.

phosphine involved condensation of glucosamine to *o*- or *p*-TPPMC to give ligands **12** and **13** [42, 43]. The *para*-substituted ligand **12** gave a more active catalyst for the Suzuki coupling of aryl iodides than **13**. Up to 97 000 turnovers were achieved in the Suzuki coupling of highly activated 4-iodonitrobenzene.

1.2.2
Sterically Demanding, Hydrophilic Trialkyl and Dialkylbiarylphosphines

A wide range of hydrophilic triarylphosphines have been applied to palladium-catalyzed cross-coupling, but catalysts derived from these ligands are generally limited to aryl iodides and in some cases aryl bromides. Nonactivated aryl bromide substrates typically require high temperatures (80–150 °C). This level of reactivity mirrors that of triphenylphosphine in organic-phase coupling reactions. Beginning in the mid-1990s, research showed that sterically demanding and strongly electron-donating ligands provided optimal activity for Pd-catalyzed cross-couplings. Widely applicable ligand classes include trialkylphosphines with sterically demanding substituents, such as *tert*-butyl or adamantyl, and 2-dialkylphosphinobiaryl phosphines. These ligands generally provide catalysts that promote cross-coupling of aryl bromides at room temperature and aryl chlorides under mild conditions (<100 °C). On the basis of these developments, there have been efforts to prepare water-soluble phosphines with similar steric and electronic properties to these privileged ligand classes.

Our group has focused on the synthesis of water-soluble, sterically demanding trialkylphosphine ligands (Figure 1.3). Ammonium-substituted ligands, *t*-Bu-Amphos and *t*-Bu-Pip-phos, were shown to provide highly active catalysts for Suzuki coupling of aryl bromides at ambient temperature in water/acetonitrile [44]. Up to 10 000 turnovers could be achieved at room temperature over 24 h and over 700 000 turnovers at 80 °C for the coupling of 4-bromotoluene and phenylboronic acid. Analysis of crude organic products recovered from these reactions showed <1 ppm of residual Pd. The aqueous catalyst solution could be reused for two additional reaction cycles before loss of activity begins to occur. Using a hydrophilic palladacycle precatalyst allowed more than 10 reaction cycles on a single catalyst charge [45]. The Pd/*t*-Bu-Amphos system has been applied to the arylation of 7-iodocyclopenta[*d*]-[1,2]oxazine (**14**) to provide 7-arylcyclopenta[*d*][1,2]oxazines (**15**, Equation (1.7)) [46]. The Pd/*t*-Bu-Amphos catalyst is also effective for the

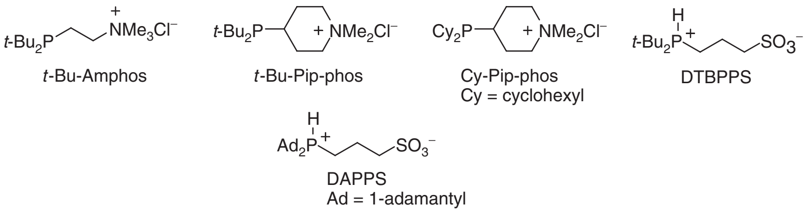
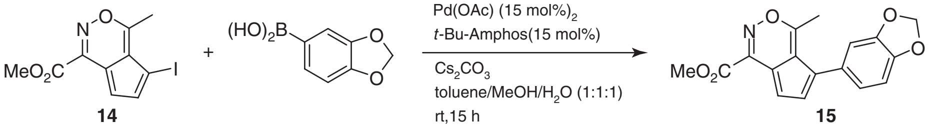


Figure 1.3 Ammonium- and sulfonate-modified trialkylphosphines.

Sonogashira and Heck coupling of aryl bromides at higher temperatures [47]. The *t*-Bu-Amphos ligand did not provide effective catalysts for coupling of aryl chlorides, however.

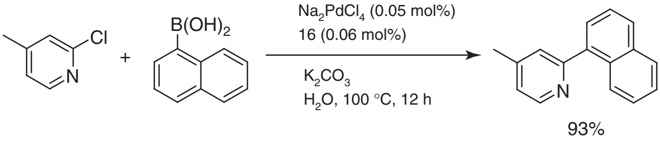


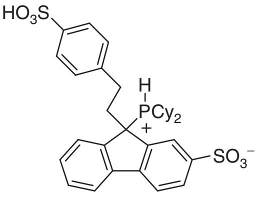
(1.7)

Calculated steric parameters showed a good correlation between ligand steric demand and activity for Suzuki coupling of aryl bromides [48]. The *t*-Bu-Amphos ligand was the largest of those studied and had the highest activity catalyst. In couplings of aryl chlorides, the more electron-donating *t*-Bu-Pip-phos gave a more effective catalyst than *t*-Bu-Amphos. The cationic ammonium substituent decreased the electron-donating ability of the phosphine compared to that of the neutral phosphines, such as tri-(*tert*-butyl)phosphine, presumably through an inductive or field effect. To provide more electron-rich ligands, the DTBPPS(3-(di-tert-butylphosphonium)propane sulfonate) and DAPPS(3-(di-1-adamantylphosphonium)propane sulfonate) ligands with anionic water-solubilizing groups were prepared (Figure 1.3) [49]. Catalysts derived from DTBPPS promoted Sonogashira coupling of aryl bromides at lower temperature compared to the Pd/*t*-Bu-Amphos catalyst and were also effective in aryl chloride coupling. On the basis of the calculated ionization potential (IP) values for the Pd–L complexes derived from these ligands, the sulfonate substituent significantly increases the electron-donating ability of DTBPPS compared to *t*-Bu-Amphos.

The Plenio group has developed a family of highly effective ligands based on 9-(dicyclohexylphosphino)fluorene (CataCXium F sulf®, **16**). Ligand **16** provides effective catalysts in the Suzuki coupling of aryl bromides and chlorides [50]. Nonactivated aryl chlorides can be coupled at ambient temperature, although longer reaction times (one day) are required. The catalyst derived from ligand **16** is also highly effective in the Suzuki coupling of heteroaryl substrates (Equation 1.8), which are often much more challenging than simple aryl halides [51–53]. A challenge with heterocycles, particularly pyridine and pyrrole derivatives, is the competitive binding of the heteroatom to the palladium catalyst. Plenio proposes that water binds with these coordination sites through hydrogen bonding, which allows for higher activity in water than can be achieved in organic solvents [53].

Ligand **16** also provides an effective catalyst for Sonogashira coupling of aryl bromides and activated heteroaryl chlorides [50, 54].

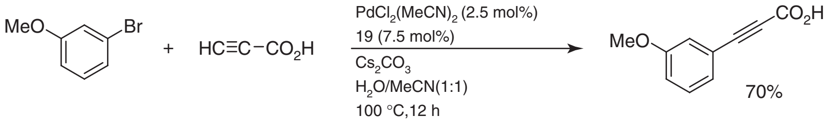




CataCXium F
16

(1.8)

The 2-biphenylphosphines developed by Buchwald are another privileged ligand class for cross-coupling of aryl bromide and chlorides [55]. Miyaura and coworkers synthesized a gluconic acid-modified 2-(dicyclohexylphosphino)biphenyl ligand (**17**, Figure 1.4) that provided catalysts with improved activity for the Suzuki coupling of aryl bromides than triphenylphosphine-based ligands, such as *m*-TPPTS or **11** [56]. Modest activity for Suzuki coupling of 4-chlorobenzoic acid was observed. The Sinou group reported a similar ligand with a glucosamine moiety (**18**) as the water-solubilizing group [57]. Good yields were obtained in Suzuki coupling of activated aryl chlorides, but unactivated aryl chlorides did not undergo conversion to biaryl products. The low activity of these ligands can be attributed in part to the fact that they are based on the simple 2-biphenylphosphine structure without *ortho*-substituents on the lower ring. Electron-donating substituents on the lower ring, such as in S-phos (2-(dicyclohexylphosphino)-2′, 6′-dimethoxylbiphenyl), provide more active catalysts [58]. The high electron density of the dimethoxy-substituted ring allows for easy sulfonation of S-phos to give **19** [59]. Ligand **19** also provides an effective catalyst for the Suzuki coupling of aryl chlorides at room temperature using 2 mol% palladium. At 100 °C, catalyst loadings as low as 0.1 mol% could be used. Ligand **18** also provides an effective catalyst for Sonogashira couplings of aryl bromides. Notably, the challenging propiolic acid substrate could be arylated with high yield (Equation 1.9).



(1.9)

Di-(*tert*-butyl)phosphinous acid is a water-soluble ligand under basic conditions. Complex **20** is an effective precatalyst for the aqueous-phase Stille [60] and Sonogashira coupling (Equation 1.10) [61] of aryl halides, whereas complex **21** is a more effective catalyst for the Hiyama coupling (Equation 1.11) [62, 63] than **20**. High temperatures (130–150 °C) were required to achieve these couplings, however. Microwave heating was used in many cases to accelerate the reactions.

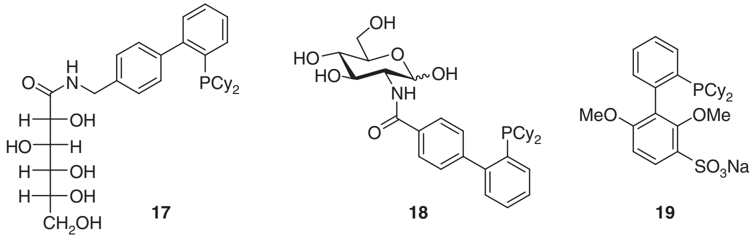
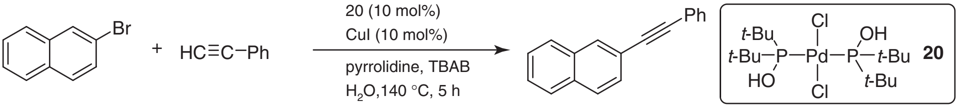


Figure 1.4 Water-soluble 2-biphenyldicyclohexylphosphine ligands.

Aryl bromides and chlorides could be coupled using this catalyst system. Recycling of the catalyst was demonstrated in the Stille coupling of 3-bromopyridine and phenyltrimethylstannane [60]. Over the course of four reaction cycles, the yield of product decreased from 96 to 84%.



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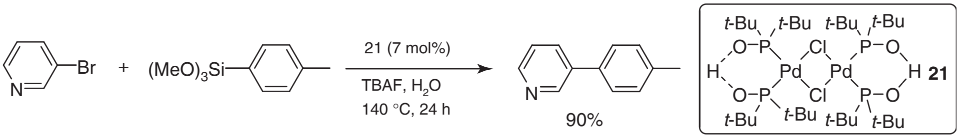

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1.2.3
NHC Ligands

The imidazol-2-ylidine and imidazolin-2-ylidine family of stable carbenes [64], commonly referred to as *N*-heterocyclic carbenes (NHCs), are another class of highly effective ligands for cross-coupling reactions [65]. NHC ligands are strong electron donors and with proper substituents can be highly sterically demanding. Only recently has their use in aqueous media received attention. The carbene carbon of an NHC is strongly basic (pK_a about 20 [66]), which precludes their use as free ligands in aqueous media. Metal–NHC complexes typically have strong M–L bonds, however. Metal complexes of NHCs are often water stable. Therefore, preformed metal–NHC complexes or complexes generated *in situ* from water-stable imidazolium preligands can be used in aqueous media.

The Plenio group reported the synthesis of a family of sulfonated 1,3-diarylimidazolium (**22** and **23**) and imidazolinium salts (**24**) that are structurally similar to the commonly used IMes and IPr ligands (Figure 1.5) [67]. The zwitterionic imidazolium salts formed active catalysts for the Suzuki coupling of aryl chlorides in the presence of Na_2PdCl_4. These ligands were also applied

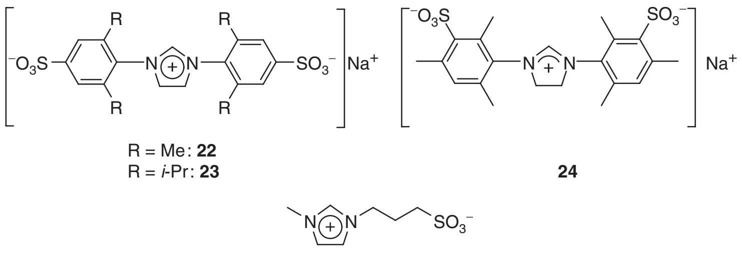


Figure 1.5 Zwitterionic imidazolium and imidazolinium ligand precursors.

in the Sonogashira coupling of aryl bromides and activated heteroaryl chlorides in an aqueous solvent mixture [68]. Zwitterionic alkylsulfonate-functionalized imidazolium salt **25** can be easily prepared by the reaction of 1-methylimidazole with 1,3-propane sultone [69, 70]. Palladium complexes derived from monodentate and tridentate alkylsulfonate-functionalized NHCs provide effective catalysts for the Suzuki coupling of aryl bromides and activated aryl chlorides at 110 °C. The smaller steric demand of these ligands likely accounts for the lower activity of catalysts derived from them compared to the ligands reported by Plenio.

A palladium complex derived from carboxylate-functionalized bis(NHC) ligand **26** was applied to the aqueous-phase Suzuki coupling of aryl bromides (Figure 1.6) [71]. The catalyst is soluble in basic water, but can be recovered intact by lowering the pH to 4. The recovered solid catalyst can be used for four cycles with only a small loss in activity. Somewhat improved performance was achieved by reusing the catalyst-containing aqueous solution. TEM analysis of the aqueous solution showed that palladium nanoparticles formed under the reaction conditions. The authors suggest that the ligand stabilizes the nanoparticles and prevents their aggregation into larger catalytically inactive particles. Pincer NHC complexes based on isonicotinic acid (**27** and **28**) have been synthesized and applied to Suzuki [72, 73] and Heck couplings [74]. Low catalyst loadings (8 ppb to 50 ppm) could be used, although high temperatures (> 100 °C) were required, even for Suzuki coupling of aryl bromides. Both catalyst systems could be effectively recycled by removing the organic product and adding new substrates to the catalyst-containing aqueous phase. The active catalyst derived from imidazolium-based pincer complex **27** appears to be

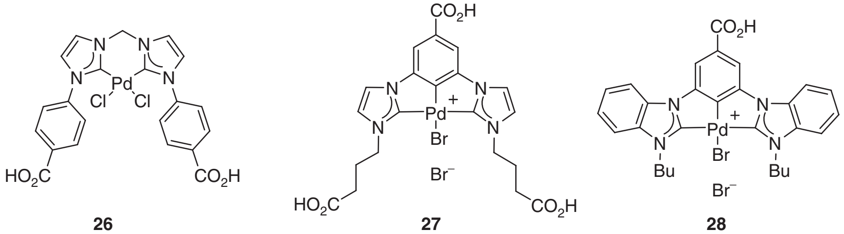
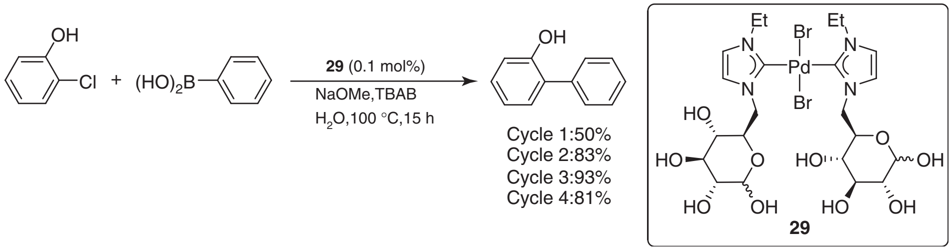


Figure 1.6 Hydrophilic palladium NHC complexes.

palladium nanoparticles [72]. In contrast, mercury and poly(vinylpyrrolidine) did not inhibit reactions catalyzed by benzimidazolium complex **28**, which suggests that it acts as a molecular catalyst [73].

Hydrophilic NHC ligands with nonionic substituents have also been applied to Pd-catalyzed cross-coupling. Glucose-modified palladium NHC complex **29** gave an active catalyst for the Suzuki coupling of aryl bromides and chlorides at 100 °C in water (Equation 1.12) [75]. The catalyst system could be effectively used for four reaction cycles without significant loss of activity. Metallocrown NHC complex **30** was applied to the Suzuki coupling of aryl bromides in water at 100 °C at low catalyst loading (0.001–0.005 mol%, Equation 1.13) [76].



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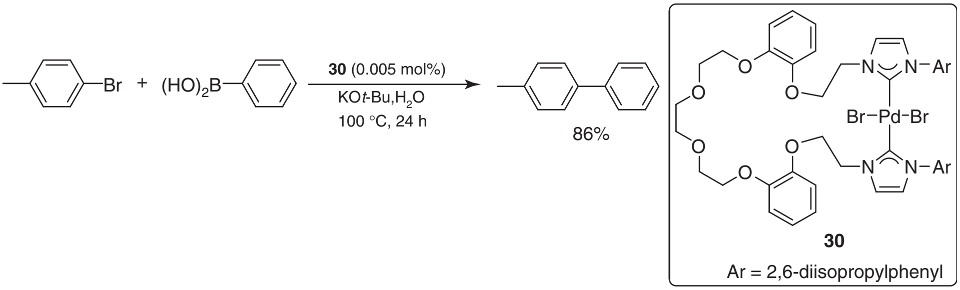
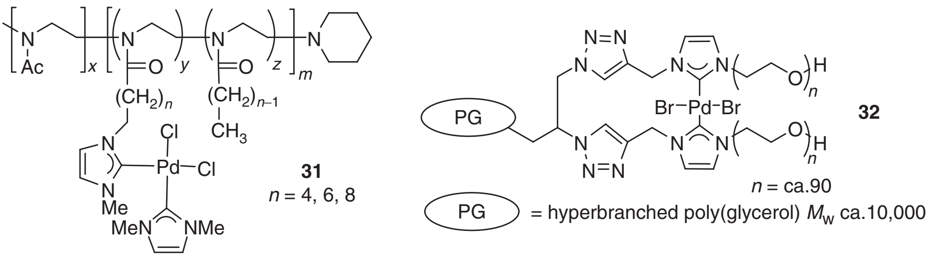


(1.13)

NHC ligands supported on water-soluble polymers have also been explored in palladium-catalyzed cross-coupling reactions. An imidazolium-functionalized amphiphilic poly(2-oxazoline) block copolymer (**31**, Figure 1.7) was used to support the palladium catalyst in the hydrophobic block [77]. The amphiphilic polymer was designed to promote a micellar phase to enhance interaction between the catalyst and the hydrophobic substrate. The water-soluble polymeric catalyst was applied to the Suzuki and Heck coupling of aryl iodides and bromides in water. A hyperbranched polyglycerol-supported NHC–Pd complex (**32**) was applied to the Suzuki coupling of aryl bromides in water at 80 °C [78]. In the coupling of 2-tolylboronic acid, the yields were similar to those obtained with a PEG-modified bis(NHC) ligand. In contrast, significantly higher activity was seen with the hyperbranched polymer-supported ligand for the Suzuki coupling of 4-pyridylboronic acid.



31 $n = 4, 6, 8$

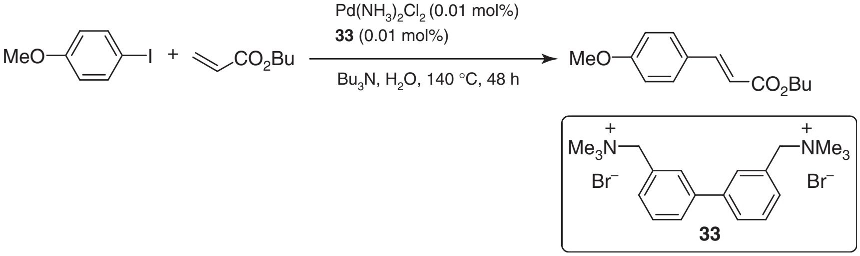
32

Figure 1.7 Hydrophilic, polymer-supported palladium NHC complexes.

1.2.4
Nitrogen Ligands

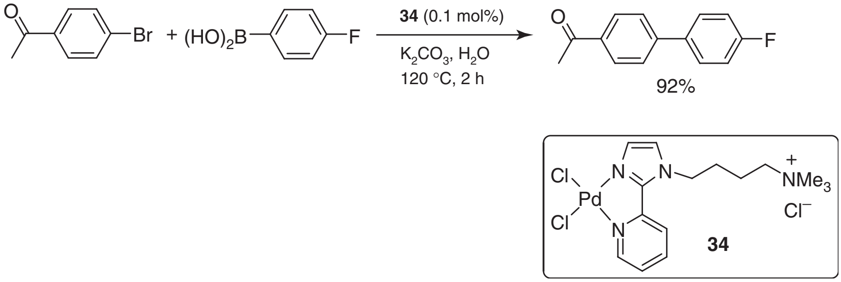
Nitrogen ligands have received significantly less attention in Pd-catalyzed cross-coupling compared to phosphine ligands. Amines tend to coordinate weakly to palladium resulting in low stability complexes. Bipyridine ligands provide stable complexes, but are much less electron donating than phosphines. Given the lower cost and toxicity of nitrogen-based ligands, there has been renewed interest in using these types of ligands, however.

4,4′-Bis(trimethylammoniummethyl)-2,2′-bipyridine (**33**, Equation 1.14) has been shown to be an effective ligand for a variety of cross-coupling reactions. This ligand provides active catalysts for the Suzuki coupling of aryl bromides at low catalyst loading (0.001–0.1 mol% Pd) [79]. The catalyst solution could be recycled five times to give the product in high yield, although the reaction time had to be increased from 30 min to 6 h from the first to fifth cycle. Activated aryl chlorides could be coupled at a higher temperature (140 °C) and catalyst loading (0.1–1 mol%). Similar results were obtained in the Hiyama coupling using this ligand [80]. The catalyst derived from ligand **33** could be used for the Heck coupling of aryl iodides, but unactivated aryl bromides showed no activity [81]. Good recyclability was obtained using 0.01 mol% Pd/**33** in the Heck coupling of 4-iodoacetophenone.



(1.14)

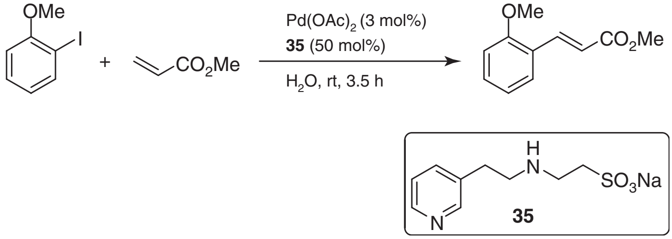
Palladium complex **34** derived from an ammonium-substituted 2-(2-imidazolyl)pyridine ligand was applied to the aqueous-phase Suzuki coupling of aryl bromides at 120 °C (Equation 1.15) [82]. Activated aryl chlorides could also be coupled with this catalyst system when tetrabutylammonium bromide (TBAB) was used. TEM analysis showed that palladium nanoparticles were formed during the reaction. The ligand is considered to stabilize the palladium nanoparticles. The palladium complex of 8-hydroxyquinoline-5-sulfonic acid is moderately active for the Suzuki coupling of aryl bromides in water [83]. Only electron-deficient aryl bromides gave good yields.



34

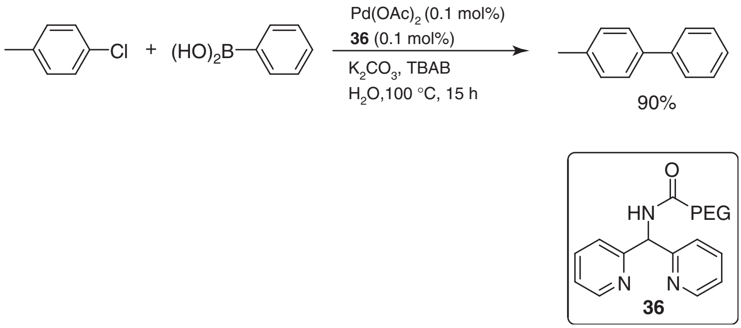
(1.15)

Simple monodentate pyridine ligands have also been shown to be effective ligands for cross-coupling reactions. Alkylsulfonate-modified pyridine ligand **35** in combination with Pd(OAc)$_2$ catalyzed the Heck coupling of aryl iodides and ethyl acrylate at room temperature in good yield (Equation 1.16) [84]. A 17 : 1 ligand/Pd ratio was used. Use of water as the solvent gave higher yields than use of polar aprotic solvents, such as a DMF or NMP, or mixed water/DMF solvent systems. 2-Amino-4,6-dihydroxypyrimidine is an inexpensive ligand for the aqueous-phase Suzuki coupling [85]. The palladium complex of this ligand was applied to the Suzuki coupling of iodide-functionalized amino acids and peptides under physiological conditions (37 °C, buffered solution) to give arylated products in good yield. Di-2-pyridylmethane ligand **36** supported on PEG has been applied to the Suzuki coupling of aryl bromides and chlorides (Equation 1.17) [86, 87]. Good yields were achieved with aryl chlorides using 0.1 mol% Pd/**36**.



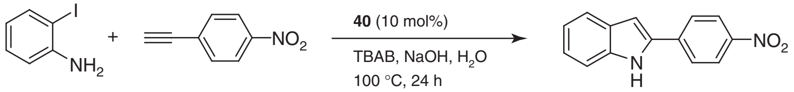
35

(1.16)



(1.17)

Sulfonated diimine complex **37** was applied to the Suzuki coupling of aryl bromides in water (Figure 1.8) [88]. Only activated aryl chlorides could be coupled with this system, however. Using 0.1 mol% catalyst **37**, the catalyst could be recycled for one use before the yield dropped significantly. Similar results were obtained using sulfonated β-diketimine ligand **38** [89]. Palladium–salen complex **39** was an effective catalyst for the Sonogashira coupling of aryl iodides in water in the presence of sodium lauryl sulfate (SLS) [90]. A Cu-catalyzed Sonogashira coupling in water was performed using sulfonated Cu–salen complex **40** (10 mol%) [91]. The reaction required TBAB as a phase-transfer catalyst (PTC) and was limited to aryl iodides. The catalyst was applied to the cascade coupling of 2-iodoaniline with phenylacetylene derivatives to give 2-arylindoles in excellent yield in water (Equation 1.18).



(1.18)

Ethylenediamine tetracetic acid (EDTA) is a commonly used water-soluble ligand for metals. Good yields were obtained using Pd(EDTA)Cl_2 as a precatalyst for the Suzuki coupling of aryl iodides and bromides [92]. *N,N,N′,N′*-Tetra(2-hydroxyethyl)ethylene diamine has also been used as a ligand for palladium-catalyzed Suzuki coupling of aryl bromides in water [93]. Low catalyst loadings (0.001–0.1 mol%) were used, although higher catalyst loadings were required with nonactivated aryl bromides.

1.2.5
Palladacyclic Complexes

Palladacyclic complexes formed by C–H activation near a coordination site in the ligand often provide stable precursors to effective catalyst systems [94, 95]. The palladacycles can be used alone or in some cases with additional supporting ligands. There has been much debate about the nature of the active species derived from

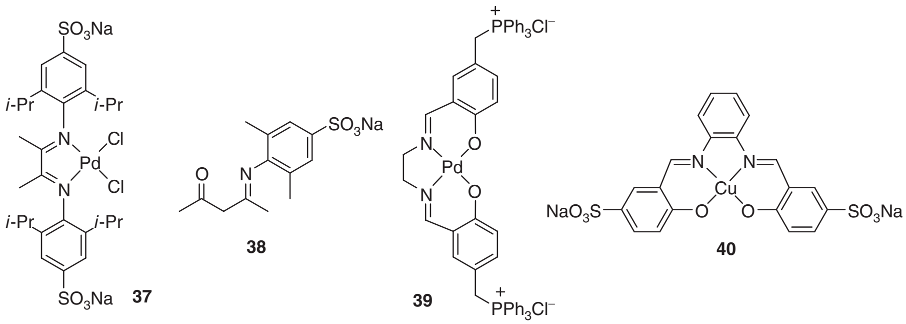
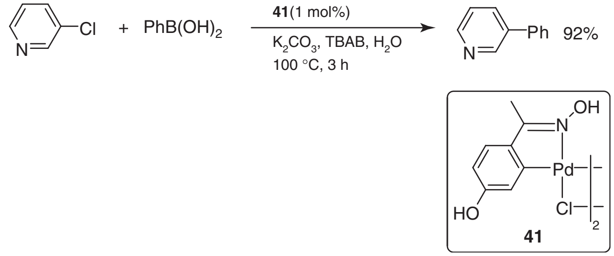


Figure 1.8 Water-soluble imine ligands and complexes.

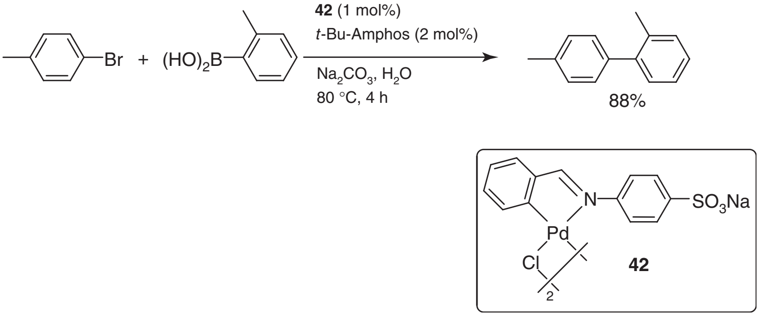
these precatalysts, but in most cases it has been shown that the palladacycle is either converted to a Pd(0) active species or decomposes to palladium nanoparticles.

Oxime-derived palladacycles have been shown to be effective precatalysts for a variety of reactions [96]. Oxime-derived palladacycle **41** was the first catalyst system to effectively promote Suzuki couplings of aryl chlorides in water (Equation 1.19) [97, 98]. The PTC TBAB was required, particularly with less reactive aryl chlorides. Palladacycle **41** has also been used in the Suzuki coupling of aryl chlorides and aryl or alkenyl trifluoroborates [99, 100]. Complex **41** is also an effective precatalyst for the Hiyama coupling of aryl halides and vinylsiloxanes [101]. The palladacycle catalyst gives slightly higher yields and improved recyclability compared to $Pd(OAc)_2$. Palladium leaching averaged 21 ppm over three reaction cycles for palladacycle **41**, while it averaged 25 ppm for $Pd(OAc)_2$. The similar result for the palladacycle and Pd(OAc)2 suggests that the palladacycle decomposes to palladium nanoparticles, which are the catalytically active species. Complex **41** also catalyzes the Heck coupling of aryl iodides [102, 103].



(1.19)

Imine palladacycle **42** provides an active catalyst for the Suzuki coupling of aryl bromides in the presence of *t*-Bu-Amphos (Equation 1.20) [45]. Good yields could be obtained at catalyst loadings as low as 0.01 mol% Pd. The catalyst derived from **42**/*t*-Bu-Amphos gave a quantitative yield of 4-methylbiphenyl for 11 reaction cycles using the same loading of catalyst and ligand without increasing the reaction time (1 h/cycle). The palladacycle derived from sulfonated 2-arylnaphthoxazole **43** is an effective catalyst for the Suzuki coupling of aryl bromides at 100 °C in water (Equation 1.21) [104].



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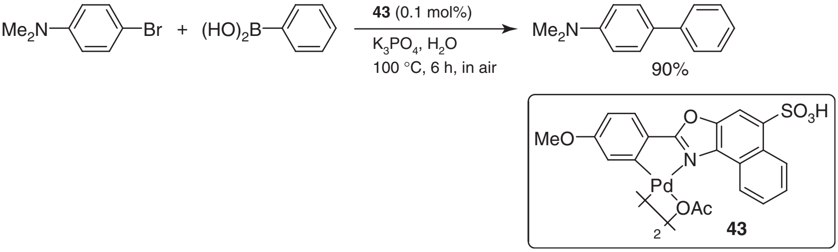


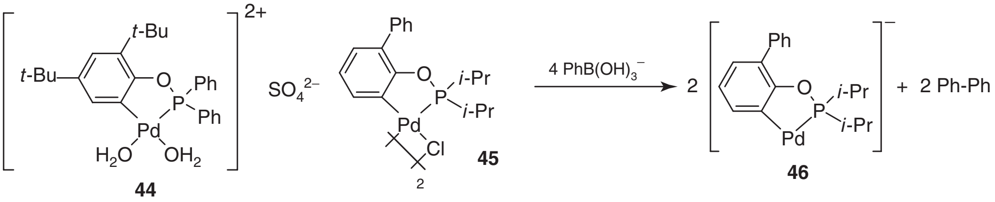
(1.21)

1.3
Cross-Coupling in Aqueous Media Using Hydrophobic Ligands

The initial motivation to use water in metal-catalyzed cross-coupling reactions was to allow for catalyst recovery and recycling while decreasing the environmental impact of the reaction. A number of authors have shown that water can be used as the reaction medium even when using hydrophobic catalysts and substrates. In some cases, reactions carried out in this manner give superior results to traditional homogeneous organic-phase reactions. In recent years, ‘‘on-water’’ reactions of this sort have received significant attention [11, 12]. Reactions of hydrophobic substrates and catalysts can be promoted by using surfactants or PTCs.

1.3.1
Surfactant-Free Reactions

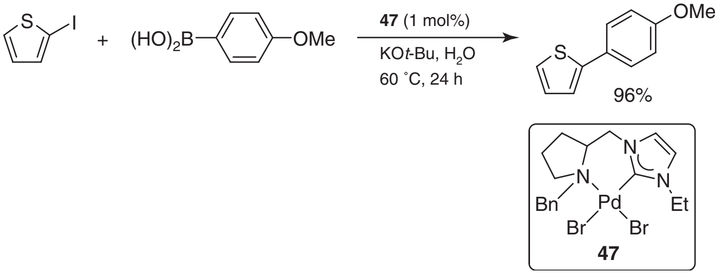
An early example of the use of a palladium complex for the on-water Suzuki coupling was reported by Hor *et al.* [105]. Using a palladium diimine complex, Suzuki coupling of aryl bromides were performed at 80 °C using 1 mol% catalyst. The water- and ether-insoluble catalyst could be recovered as a solid after extraction of the organic products with ether. The aqueous suspension of catalyst could be used for six cycles with a slight decrease in yield in the last two cycles.



Scheme 1.2 Conversion of phosphinite palladacycles to the active catalyst.

Eppinger reported hydrophobic phosphinite palladacycle catalysts (**44** and **45**, Scheme 1.2) that promoted the Suzuki coupling of aryl bromides at 30 °C with low catalyst loading (0.02 mol%) [106, 107]. When **45** is used as the precatalyst, the water-insoluble product can be filtered off leaving a solution that retains full catalytic activity. Thus, the catalytic species remains in the aqueous phase despite the fact that precatalyst **45** is water insoluble. The authors proposed that the active species is formed by reduction of the Pd(II) palladacycle without dissociation of the anionic ligand to give **46**, which may be water soluble.

The Suzuki coupling of aryl bromides in water was studied with a range of ligand-free and ligand-supported palladium catalysts [108]. Ligand-free catalysts, such as Pd/C or $Pd(OAc)_2$ gave low conversion. Of the phosphine-supported catalysts, $Pd(DPPF)Cl_2$ (1,1′-bis(diphenylphosphino)ferrocene) provided the highest yields of coupled products. Good yields were obtained with a range of aryl bromides at 80 °C using 0.1 mol% $Pd(DPPF)Cl_2$. The palladium complex of an amino-NHC ligand (**47**, Equation 1.22) was active for the Suzuki coupling of aryl bromides at room temperature in water [109]. Typical catalyst loadings were 1 mol%, but an 89% yield was obtained using 0.2 mol% of the complex in the coupling of 4-bromoanisole and 4-tolylboronic acid. P_2N_2 ligand **48** in combination with palladium was a highly effective catalyst for Suzuki coupling of aryl bromides [110]. Over 700 000 turnovers were obtained in the coupling of 4-bromoacetophenone and phenylboronic acid at 100 °C. An 82% yield of product was obtained with 0.4 mol% of the $Pd(OAc)_2$/**48** system in the coupling of 4-chlorobenzonitrile and phenylboronic acid (Equation 1.23).



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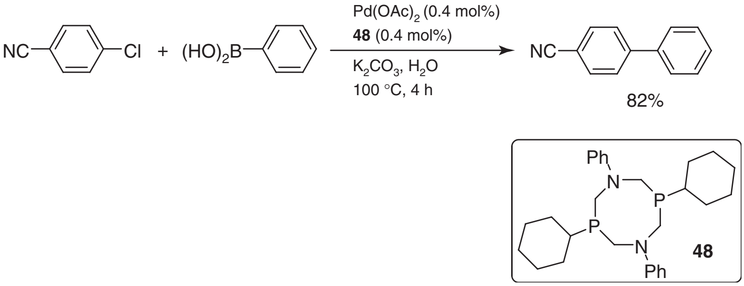
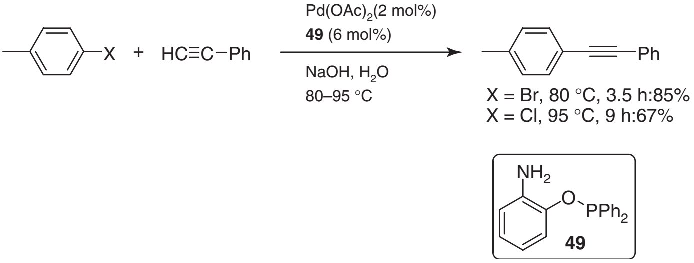


(1.23)

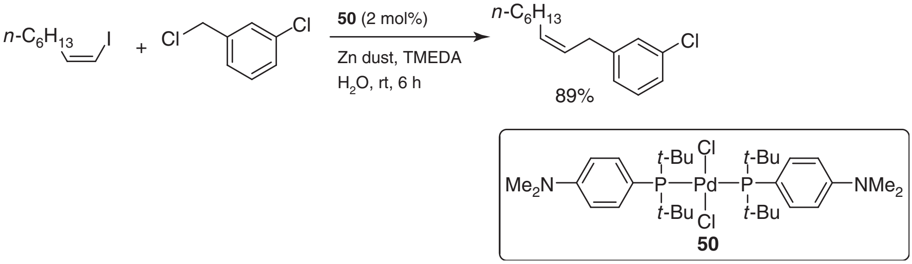
Sonogashira coupling catalyzed by palladium/triphenylphosphine complexes in water has been reported by a number of authors. Coupling of aryl iodides and bromides catalyzed by $Pd(PPh_3)_4$ (0.5 mol%) and CuI (1 mol%) with diisopropylethylamine occurred in good yield [111, 112]. The reaction occurred in two phases. Addition of DMF significantly reduced the reaction rate and resulted in increased side product formation. This system has been successfully applied to Sonogashira coupling of halopyridines [113]. Good yields were obtained with iodo- and bromopyridines, but no conversion occurred with 2-chloropyridine. By increasing the reaction temperature to 120 °C, the Sonogashira coupling could be accomplished with $Pd(PPh_3)_2Cl_2$ (2 mol%) [114]. Phosphinite-derived palladacycle **45** catalyzes the copper-free Sonogashira coupling of aryl iodides at 40 °C in water [115]. Aryl bromides gave low yields, however. The palladium-free Sonogashira reaction using CuI/PPh_3 as the catalyst can be accomplished in water in a sealed tube at 140 °C, but only aryl iodides can be used as substrates [116].

2-Aminophenyl diphenylphosphinite **49** in combination with $Pd(OAc)_2$ is a recyclable catalyst for the Sonogashira coupling of aryl iodides, bromides, and chlorides in water at 80–95 °C (Equation 1.24) [117]. The insoluble catalyst could be recovered by centrifugation and reused five additional times with no significant change in yield while keeping the reaction time constant (1 h). High melting substrates required the use of TBAB as a phase-transfer catalyst. Using TBAB also allowed the reactions of aryl iodides to occur at room temperature. The Pd/**49** catalyst system is also effective for the Heck coupling of aryl iodides and bromides [118]. Good yields with aryl chlorides were achieved at 130 °C in a sealed tube. Again, the insoluble catalyst could be filtered off and used for five additional cycles with no decrease in activity.



(1.24)

A limitation of the use of aqueous media is the reactivity of many main group organometallic species with water. Thus, cross-coupling reactions based on Grignard reagents (Kumada) or organozinc reagents (Negishi) are generally not possible. Zinc-mediated reactions are possible in water under Barbier-type conditions, however [8]. The Lipshutz group has developed a method for the on-water coupling of aryl and vinyl halides with benzyl chlorides using catalyst **50** and stoichiometric zinc (Equation 1.25) [119–121]. The zinc and palladium reagents react chemoselectively with the benzyl and aryl/vinyl halide substrates, respectively, and then cleanly form the cross-coupled product. This methodology was extended to the arylation of protected iodoalanine derivative **51** to prepare phenylalanine derivatives (e.g., **52**, Equation 1.26) [122]. The TMEDA-supported alkylzinc intermediate derived from **51** was observed by ESI-MS and infrared multiphoton dissociation spectroscopy, which was supported by DFT calculations.



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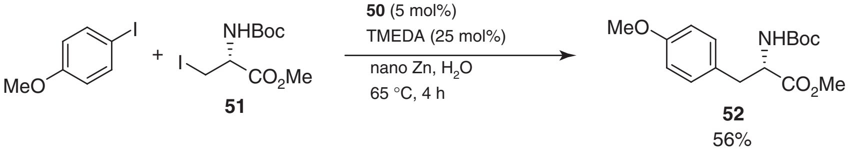


(1.26)

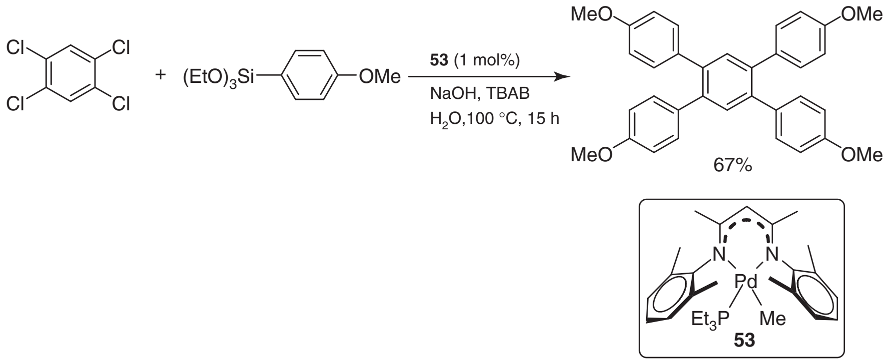
1.3.2
Surfactant-Promoted Reactions

Because of the low solubility of typical organic substrates in water, reaction rates are often suppressed when an organic cosolvent is not used. One approach to overcoming this limitation is through the use of surfactants or phase-transfer catalysts to enhance the solubility of water-insoluble reactants in the aqueous phase. A wide variety of surfactant and phase-transfer catalysts have been employed, including tetraalkylammonium salts, anionic surfactants, and nonionic surfactants. Surfactants and PTCs have been shown to promote cross-coupling reactions using water-soluble catalysts, hydrophobic catalysts, and heterogeneous catalysts.

1.3.2.1 Cationic Surfactants

The role of tetraalkylammonium salts in accelerating palladium-catalyzed cross-coupling reactions carried out in water was first demonstrated by Jeffery [123]. Low yields were obtained in the Heck coupling of phenyl iodide and methyl acrylate catalyzed by $Pd(PPh_3)_4$ in water at 50 °C. When 1 equiv of tetrabutylammonium chloride (TBAC) was added, the yield increased from 5 to 98% under otherwise identical conditions. Nearly identical yields were obtained with TBAB and hydrogensulfate salts. In contrast, LiCl and KCl did not improve reaction yields significantly. Jeffery concluded that the tetrabutylammonium ion promoted the reaction by acting as a PTC. TBAB is the most commonly used PTC for promoting cross-coupling reactions in aqueous media.

The Suzuki coupling of aryl bromides catalyzed by $Pd(PPh_3)_2Cl_2$ was carried out in water using TBAB as a promoter under microwave heating [124]. High yields were obtained with reactions times of 10 min. Hydrophobic β-diketiminate palladium complex **53** gave good yields in the Hiyama coupling of aryl chlorides and aryltriethoxysilanes in water/TBAB [125]. Higher catalyst loading, higher temperature, and a longer reaction time were required in the absence of TBAB. This system was applied to the diarylation of *o*-dichloroarenes to give *ortho*-terphenyls in excellent yields. Tetraarylation of 1,2,4,5-tetrachlorobenzene was accomplished in good yield with **53** (Equation 1.27).

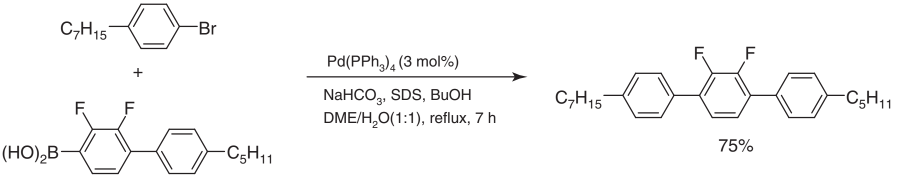


(1.27)

In the Sonogashira coupling of aryl iodides and bromides with a dipyridylmethane ligand, the use of TBAB gave higher reaction rates, slightly higher yields, and decreased formation of alkyne homodimerization products compared to reactions run in water alone [126]. Copper-catalyzed Sonogashira-type reactions are also promoted by TBAB [127, 128]. The copper catalysts were limited to aryl iodides and required high reaction temperatures. Microwave heating allowed the reactions to be completed with short reaction times. Using TBAB as the promoter gave higher yields than when the anionic surfactant sodium dodecyl sulfate (SDS) was used.

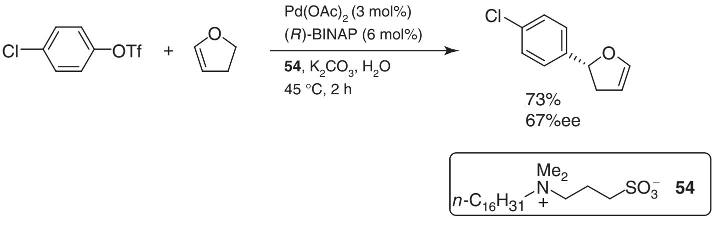
1.3.2.2 **Anionic Surfactants**

Anionic surfactants such as SDS or SLS are inexpensive commodity chemicals that can be used to generate microemulsions from water organic biphasic media. The high interfacial surface area of the microemulsion promotes reactions taking place at the water/organic interface. In the synthesis of liquid crystalline compounds by $Pd(PPh_3)_4$-catalyzed Suzuki coupling, SDS was shown to significantly improve product yields (Equation 1.28) [129]. Water/toluene/*n*-BuOH (1 : 1 : 0.14) was used as the solvent system. Butanol was added as a cosurfactant in the reaction mixture. The anionic surfactant was chosen because of the basic conditions required by the Suzuki coupling. The Sonogashira coupling of aryl iodides using a $Ni(PPh_3)_2Cl_2$ (1 mol%)/CuI (2 mol%) catalyst system gave good yields when SLS was used as the surfactant [130]. Optimal yields were obtained using 7 mol% surfactant (0.014 M), whereas higher and lower concentrations gave lower product yields.



(1.28)

A range of surfactants were tested in the asymmetric Heck coupling of 4-chlorophenyltriflate and 2,3-dihydrofuran using a palladium/(*R*)-BINAP catalyst (Equation 1.29) [131]. With no surfactant, a 33% yield was obtained and 60% ee. Cationic surfactants, such as cetyltrimethylammonium bromide (CTAB) gave little product. Modest yields and enantioselectivities were obtained with anionic surfactants, such as SDS or SLS. Using the zwitterionic surfactant *N*-hexadecyl-*N,N*-dimethyl-3-ammonio-1-propanesulfonate (**54**) the product was formed in 73% yield and 67% ee.



(1.29)

1.3.2.3 **Nonionic Surfactants**

PEG is a cheap, nontoxic surfactant that is commonly used to enhance solubility of hydrophobic compounds in water. When heterogeneous catalysts are used

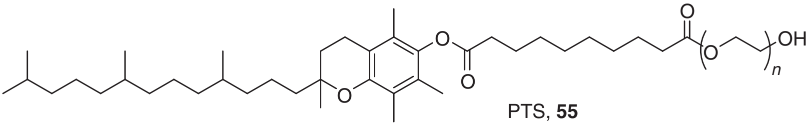
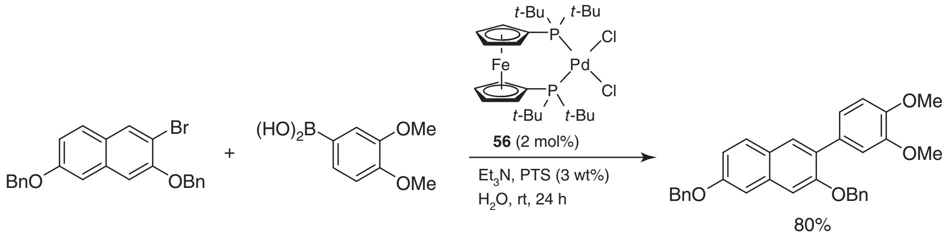

PTS, **55**

Figure 1.9 Polyoxyethanyl α-tocopheryl sebacate (PTS).

in aqueous media, they often cannot be recycled because they cannot be easily separated from the organic product. The Pd(DPPF)Cl_2-catalyzed Suzuki coupling of aryl bromides could be carried out in water with good yield, but the catalyst could not be recycled [108]. Using a 20% PEG 2000 aqueous solution, the catalyst could be retained in the aqueous/PEG phase, while the biaryl product was extracted with pentane. The aqueous catalyst solution was used for three reaction cycles with the yield decreasing from 91% in the first cycle to 80% in the third. PEG-400 was used in the Pd/DABCO-catalyzed Suzuki, Stille, Sonogashira, and Heck coupling of aryl bromides and iodides [132]. In the Suzuki coupling of 4-bromoanisole, a quantitative yield was obtained with PEG-400 compared to 87% without a surfactant. Other surfactants such as TBAB and 18-crown-6 did not significantly improve the yield compared to the reaction without surfactant. The use of PEG gave higher yields in the copper-catalyzed Sonogashira coupling of aryl iodides than were obtained in water alone or water in combination with water-miscible organic cosolvents, such as DMF or ethanol [133].

The Lipshutz group has pioneered the use of the nonionic polyoxyethanyl β-tocopheryl sebacate (PTS, **55**, Figure 1.9) surfactant. The PTS amphiphile is commercially available and forms nanoscale micelles in water that can accommodate hydrophobic compounds within the micelle interior. The Lipshutz group has applied the PTS surfactant to a wide range of palladium-catalyzed cross-coupling reactions, including those that normally do not proceed in aqueous solvents. The catalysts used in these reactions are based on hydrophobic phosphines that have been successfully applied in organic-phase reactions. The hydrophobic catalyst is believed to partition into the hydrophobic core of the micelle. Hydrophobic substrates can also partition into the micelle allowing the reactions to occur at very high local concentration.

The PTS/water solvent system allows Suzuki coupling of aryl and heteroaryl halides catalyzed by Pd(D*t*BPPF)Cl_2 (**56**) to be carried out under mild conditions even with highly hydrophobic substrates (Equation 1.30) [134, 135]. Sonogashira coupling of aryl bromides is efficiently catalyzed in water with 3% PTS by $PdCl_2(CH_3CN)_2$/X-Phos [136]. The Negishi coupling catalyzed by **50** is a particularly interesting example of Pd-catalyzed C–C bond formation, given the water-sensitivity of organozinc reagents (Equation 1.31) [137–139]. The aryl zinc species is formed *in situ* by the reaction of an alkyl iodide with zinc in the presence of TMEDA [138]. The highly hydrophobic nature of the alkyl iodides, used along with the stabilizing effect of the TMEDA on the organozinc species, allows it sufficient time to partition into the micelle and be coupled with the aryl halide before reacting with water.



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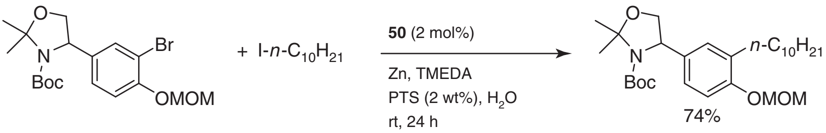
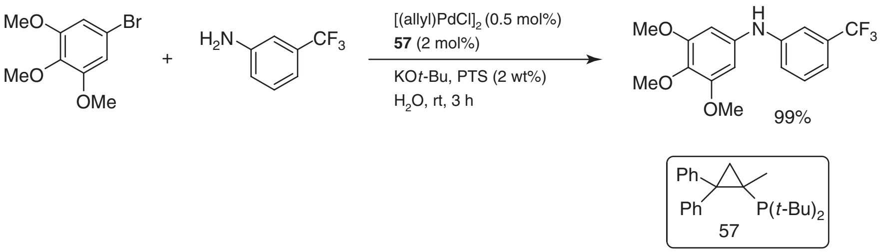


(1.31)

Examples of the powerful Buchwald–Hartwig C–N bond-forming reaction in aqueous solvents are rare [140, 141]. Using the PTS/water solvent system, $[Pd(allyl)Cl]_2$ in combination with the cBRIDP ligand **57** effectively catalyzes the coupling of aryl bromides with aniline derivatives (Equation 1.32) [142]. Miyaura borylation of aryl bromides catalyzed by $Pd(P(t\text{-}Bu)_3)_2$ is promoted by TPGS-750-M (**58**), which is a derivative of PTS in which the sebacate diester is replaced with a succinate diester (Equation 1.33) [143].



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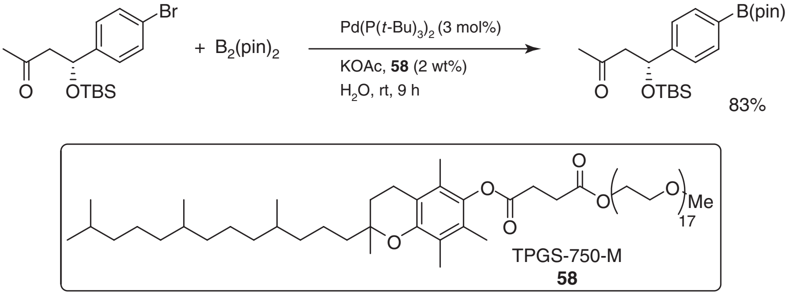

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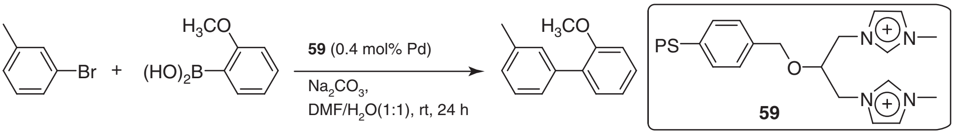
1.4
Heterogeneous Catalysts in Aqueous Media

1.4.1
Supported Palladium–Ligand Complexes

Biphasic catalysis using a water-soluble catalyst allows the catalyst to be easily separated from the organic product. A disadvantage of this methodology is that it is often difficult to separate the catalyst from the inorganic salt by-products formed in these reactions. Although these salts often do not hinder catalyst activity initially, they eventually begin to precipitate from the aqueous catalyst solution, which can hinder catalyst recovery. To address this issue, there has been significant interest in attaching metal–ligand complexes to insoluble supports and using these in aqueous-phase catalysis. In this way, the insoluble catalyst can be recovered and reused.

1.4.1.1 Polymer-Supported Palladium Complexes

Cross-linked polystyrene is commonly used to support metal–ligand complexes. Palladium coordinated to PS-CH_2PPh_2 (PS = cross-linked polystyrene) was applied to the Suzuki coupling of aryl bromides and tetraphenylborate in water/TBAB at 120 °C under microwave heating [144]. Using toluene or benzene as organic cosolvents lowered the yield of coupled product. The catalyst could be recovered by filtration and was used for 10 reaction cycles in the coupling of 2-bromonaphthalene and tetraphenylborate with no decrease in yield. Merrifield resin-supported chelating bis(NHC) ligand **59** was used to prepare a supported palladium complex (Equation 1.34) [145]. Owing to the poor swelling properties of the resin in water, DMF was required as a cosolvent to give high yields in the Suzuki coupling of aryl bromides. The catalyst could be used for five reaction cycles at room temperature with no loss in product yield.



(1.34)

Good yields for the Suzuki coupling of aryl bromides were obtained with a PS-supported palladium salen complex **60** (Figure 1.10) [146]. Unlike reactions catalyzed by supported phosphines [144], a small amount of toluene (30 : 1 H_2O/toluene) was required for optimal yields. The product yield decreased from 98 to 74% over five uses of the same catalyst in the coupling of 4-bromoanisole and phenylboronic acid at 90 °C. A similar PS-supported palladium salen complex (**61**) gave good yields in the Sonogashira coupling of aryl iodides and activated aryl bromides [147]. The catalyst was used for five reaction cycles in the coupling of phenyl iodide and phenyl acetylene with yields ranging from 99 to 85%. Analysis of the supported catalyst after the fifth cycle showed less than 0.3% palladium loss.

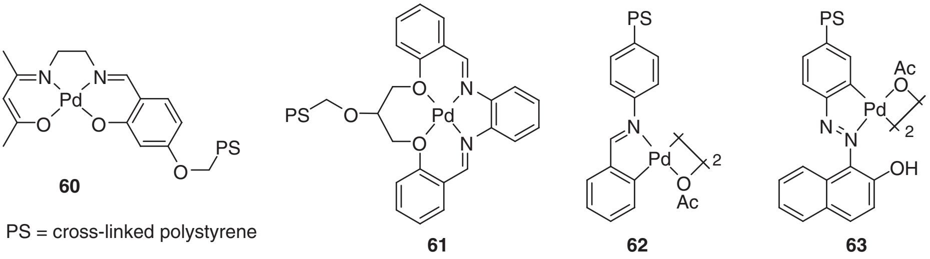
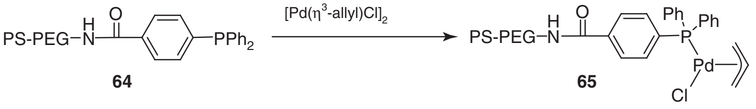


Figure 1.10 Cross-linked polystyrene-supported palladium complexes.

Polystyrene-supported palladacycle catalysts based on Schiff base (**62**) [148] and a diazo ligand (**63**) [149] were applied to the Suzuki and Sonogashira coupling of aryl iodides and bromides in aqueous DMF. Similar results were obtained with a Schiff-base palladacycle attached to poly(vinylcarbazole) in Suzuki and Sonogashira couplings [150].

Cross-linked polystyrene is a convenient support due to the range of commercially available functionalized resins such as Merrifield resin. Its application in aqueous-phase reactions is limited by the poor swelling characteristics of polystyrene in water, though. Grafted PEG–PS resin is more water compatible because of the ability of the PEG region to be swollen by water. The Uozumi group prepared PS–PEG-supported triphenylphosphine **64**. After complexation with $[Pd(allyl)Cl]_2$, the resin (**65**, Equation (1.35)) could be applied for the Suzuki [151, 152], Sonogashira [153, 154], and Heck couplings [155] in water. The PS–PEG-supported catalysts were more active than PS-supported catalysts allowing the reactions to be carried out at lower temperature. A bulky trialkylphosphine supported on the PS–PEG resin (**66**) provided an active catalyst for the Buchwald–Hartwig amination of aryl halides (Equation 1.36) [156–158]. This catalyst system represents one of the few examples of aqueous-phase Buchwald–Hartwig reactions. A PS–PEG-supported NHC ligand coordinated to $[Pd(allyl)Cl]_2$ gave good activity in the Suzuki coupling of aryl iodides and bromides at 50 °C in water [159]. The catalyst was used for five reaction cycles with a slow decrease in yield from 91 to 82%.



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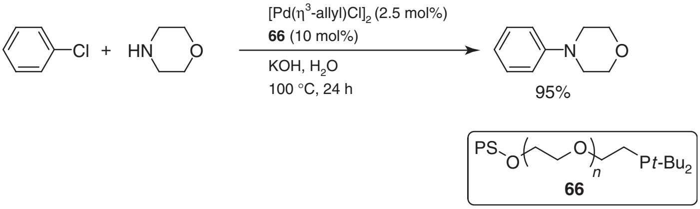

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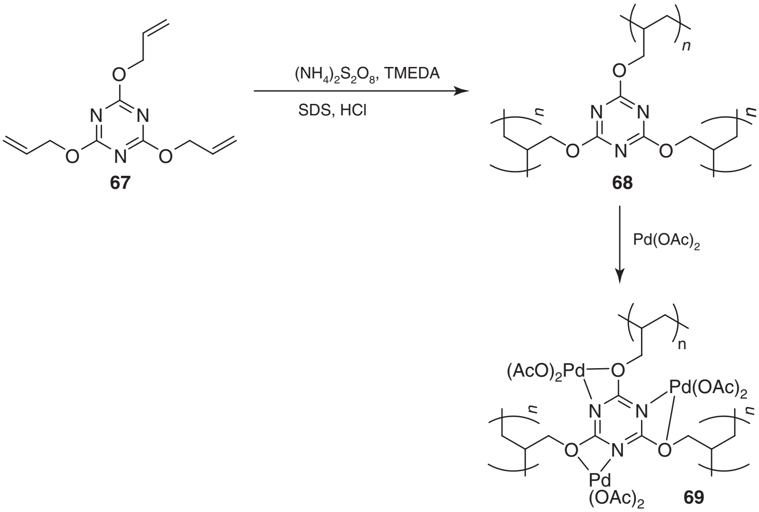

Scheme 1.3 Synthesis of a cross-linked polymeric support for palladium.

A novel network polymer containing coordination sites was prepared by the free radical polymerization of 2,4,6-triallyloxy-1,3,5-triazine (**67**, Scheme 1.3) [160]. The resulting polymer (**68**) was coordinated to $Pd(OAc)_2$ to give a material (**69**) that was active for the Heck coupling of aryl iodides and bromides in 50% aqueous ethanol at 100–140 °C. The catalyst could also be used for the Sonogashira and Heck coupling of aryl iodides at 85 °C. The catalyst could be reused, although a gradual decrease in product yield was observed in each cycle. The catalyst appears to remain bound to the polymeric support. Little catalyst activity was observed after removal of the polymeric catalyst by hot filtration. In addition, 3-mercaptopropyl-functionalized silica, which would be expected to inhibit a soluble catalyst species, did not inhibit the catalyst activity.

1.4.1.2 **Palladium Complexes Supported on Inorganic Materials**

The use of inorganic materials as supports for metal catalysts has a long history in heterogeneous catalysis. Cross-linked polymer supports have the advantage of highly flexible attachment chemistry. Their mechanical stability, particularly when swollen with solvent, is often limited, though. Inorganic materials, such as silica or alumina, are often mechanically stronger. While the range of attachment chemistry is limited with inorganic materials, a wide variety of organic ligands can be attached to metal oxides through the siloxane linker group. In addition, composite inorganic/polymer materials can provide more flexible attachment chemistry.

Polymer- and inorganic-supported oxime palladacycles were prepared and tested as catalysts for the Suzuki coupling of 4-chloroacetophenone [161]. Catalysts supported on silica and MCM-41 inorganic supports (**70**) gave >90% yields after 2 h at 100 °C in water (Equation 1.37). The same catalyst supported on cross-linked

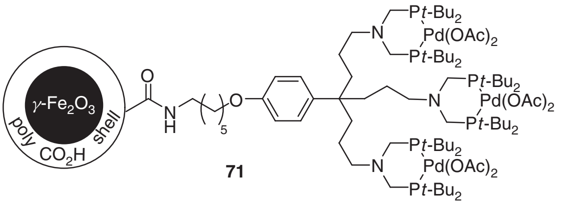

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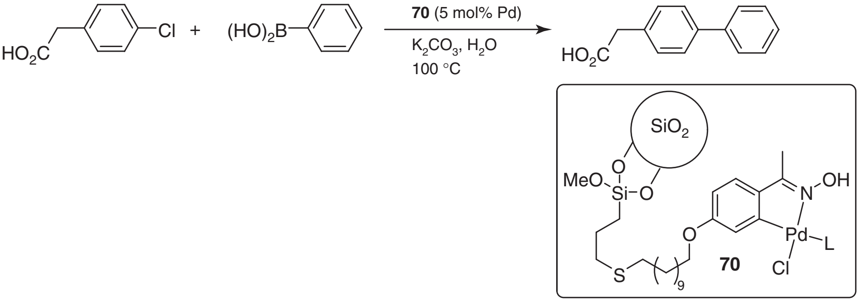
Figure 1.11 Magnetic particle-supported palladium complex.

polystyrene or poly(ethylene glycol bis(methacrylate)) gave yields below 40% under the same conditions. Leaching studies indicated that the palladium remained coordinated to the solid support and that the reaction was truly heterogeneous. Palladium loss was <1% per cycle. Magnetic nanoparticles are attractive catalyst supports because they can be separated from the reaction mixture using magnets. Core–shell γ-Fe_2O_3/polymer-supported dendritic diphosphine palladium complex **71** was prepared and applied to the Sonogashira reaction (Figure 1.11) [162]. Good yields were obtained with aryl bromides using water as the solvent with Triton X-405 as surfactant. The catalyst was highly recyclable with yields slowly decreasing from quantitative to 80% over 10 reaction cycles. Using methanol as a solvent gave higher yields, but the catalyst lost activity after five reaction cycles.



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It is not necessary to physically attach the catalyst to the solid support. Instead, the catalyst can be dissolved in hydrophobic or hydrophilic phases attached to inorganic supports [163]. Glass beads derivatized with a hydrophobic surface adsorb $Pd(PPh_3)_4$ to give a supported catalyst [164]. The resulting beads were effective for the Suzuki coupling of aryl iodides and bromides in water. Because the catalyst was not covalently attached to the support, palladium leaching was higher (2–4%/cycle) than that seen in covalently attached systems. A palladium–NHC complex dissolved in a magnetite (Fe_3O_4)-supported ionic liquid phase catalyzed the Suzuki coupling of aryl bromides in water [165]. The magnetic particles could be magnetically recovered and recycled. Nearly identical yields were obtained over five cycles. The water-insoluble catalyst remained in the hydrophobic IL phase. Palladium leaching into the aqueous phase was 10 ppm in the first reaction cycle (9% of total palladium lost), but then dropped to 1–2 ppm over the next four cycles.

In supported aqueous-phase catalysis (SAPC), a thin water layer is supported on a hydrophilic inorganic support, such as silica or porous glass beads. Water-soluble catalysts, such as Pd/*m*-TPPTS, can be dissolved in the supported aqueous phase. The resulting catalyst can then be used for cross-coupling reactions in hydrophobic solvents [166–169]. The SAPC systems typically require careful optimization of water and catalyst loading. Too much water will allow the catalyst solution to disperse into the organic reaction solvent. Too little water will limit the mobility of the catalyst resulting in low activity.

1.4.2
Nanoparticle-Catalyzed Coupling

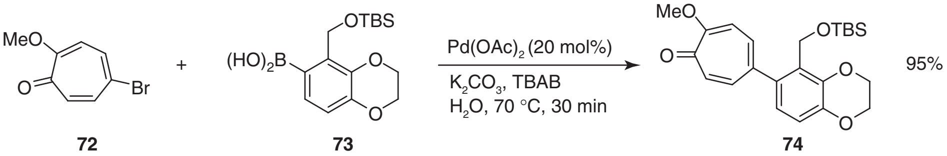
Palladium nanoparticles are readily formed under typical cross-coupling conditions, particularly in reactions performed at high temperatures. It is often unclear whether a particular Pd/ligand complex catalyzes a reaction as molecular species or through the formation of nanoparticles [170–172]. Examples of Pd/ligand catalyst systems in which nanoparticles are believed to be the true active species were discussed in previous sections. In some cases, the ligand may play a role in stabilizing the nanoparticles from agglomeration into larger catalytically inactive particles. In this section, palladium catalysts without strong supporting ligands, where nanoparticle formation is expected, and preformed palladium nanoparticle catalysts are discussed.

1.4.2.1 Unsupported Palladium Nanoparticle Catalysts

The use of phosphine or other strong ligands increases the cost of the catalyst system and can potentially complicate the product isolation. Early studies by Novak showed that triphenylphosphine can inhibit catalytic activity in the Suzuki coupling of highly activated aryl iodides in water/acetone [173]. Palladium acetate is an effective catalyst for the Suzuki coupling of water-soluble aryl iodides and bromides in water without supporting ligands or surfactants [174]. In the absence of ligands, the palladium nanoparticles aggregate into larger particles that precipitate from the solution as palladium black. To avoid precipitation, the substrate must react rapidly with the nanoparticles. Thus, these systems are often limited to highly reactive and water-soluble aryl iodides. Adding the base last to the reaction mixture resulted in improved catalyst performance with less reactive aryl iodides [175]. By adding the base last, nanoparticle formation occurs in the presence of the aryl iodide substrate and the catalytically active nanoparticle can enter the catalytic cycle before agglomeration occurs.

The ligand-free reactions in water show limited activity with hydrophobic substrates. Improved reaction rates can be achieved using water-miscible organic cosolvents or surfactants. Excellent yields were obtained with hydrophobic aryl bromides by using a water/acetone-mixed solvent system [176]. The anionic SDS surfactant has been used to promote palladium nanoparticle-catalyzed Suzuki [177], Sonogashira [178], and Heck [179] couplings in water. The cationic CTAB surfactant was shown to give higher yields in Heck coupling of aryl iodides in water catalyzed by $Pd(OAc)_2$ than SDS, Brij 56, or TBAB [180].

Tetraalkylammonium salts are commonly used in ligand-free systems to improve the catalyst activity and stability of the palladium nanoparticles. Badone showed that TBAB significantly increased the yield in ligand-free palladium-catalyzed Suzuki coupling of aryl bromides in water [181]. A 35% yield was obtained in water alone, whereas the yield was 95% with 1 equiv of TBAB. An 80% yield was obtained under homogeneous conditions in DMF. This methodology was used in the synthesis of colchinoids to overcome isolation problems encountered with triphenylphosphine, which was used as a ligand [182]. Coupling of tropolone **70** with boronic acid **73** gave colchinoid precursor **74** (Equation 1.38). Using aryl trihydroxyborates rather than arylboronic acids allows $Pd(OAc)_2$-catalyzed Suzuki coupling of aryl bromides and iodides to be carried out at room temperature in water/TBAB [183]. Activated aryl chlorides could be coupled at 100 °C. Using microwave heating, coupling of aryl bromides could be accomplished in 5 min at 150 °C in water/TBAB [184, 185].



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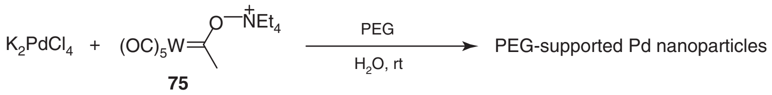
1.4.2.2 Polymer-Supported Nanoparticles

Although solubilized palladium nanoparticles can show good activity, they often have limited stability. Unless stabilized, they agglomerate to form larger, insoluble, and catalytically inactive particles. Polymers can be used to stabilize nanoparticles by preventing interaction between individual nanoparticles leading to agglomeration.

Water/PEG systems promote Suzuki coupling reactions catalyzed by palladium nanoparticles generated *in situ* from palladium salts in the absence of strongly coordinating ligands [186–189]. The PEG/water combination gave optimal results compared to water alone, PEG alone, or PEG in combination with organic co-solvents. Pluronic F86, a PEG–polypropylene oxide–PEG triblock copolymer, was also used to stabilize palladium nanoparticles [190]. Reaction of Na_2PdCl_4 with Pluronic F86 gave 5.4 nm nanoparticles that were active for the Suzuki coupling of water-soluble aryl iodides and bromides at room temperature.

The size of palladium nanoparticles generated by reduction with a tungsten Fischer carbene (**75**) complex could be controlled by the Pd/PEG ratio (Equation 1.39) [191]. With a 1 : 1 Pd/PEG ratio, the resulting nanoparticles had an average diameter of 9.75 nm, whereas nanoparticles generated with a 1 : 5 Pd/PEG ratio were 7.25 nm in diameter. Nanoparticles formed in this way were applied to Suzuki, Sonogashira, and Heck couplings of aryl iodides and a few bromides. In the Hiyama coupling, lower yields were obtained with increasing PEG:Pd ratio, although it is not clear if this is due to the higher PEG concentration or smaller nanoparticle size [192]. The $Pd(OAc)_2$/PEG system was applied to the cascade

Hiyama/Heck coupling of aryl halides and vinyltriethoxysilane to give stilbenes (Equation 1.40) [193]. Sequential addition of different aryl halides was possible to give unsymmetrical stilbene products.



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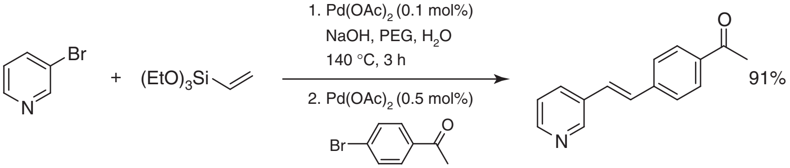

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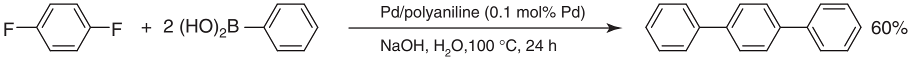
Dendrimers have been used as supports for palladium nanoparticles. The water-soluble poly(amido amine) (PAMAM) dendrimer will coordinate metal ions, which can then be reduced to metal nanoparticles supported within the dendrimer. Palladium nanoparticles generated from G4 PAMAM dendrimer and 40 equiv of $Pd(OAc)_2$ were effective for the Stille coupling of aryl iodides [194]. Nanoparticles generated from $Pd(OAc)_2$ in the absence of the dendrimer showed improved catalyst activity, however. The dendrimer supported nanoparticles could be recycled, whereas the nanoparticles generated in the absence of dendrimer rapidly lost activity.

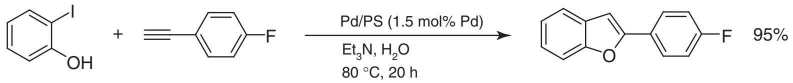
Polyvinylpyrrolidinone (PVP) is an effective stabilizer for palladium nanoparticles. Palladium nanoparticles supported by PVP were moderately active in the Suzuki coupling of aryl iodides and activated aryl bromides using either microwave heating or ultrasound activation [195]. Using a mesoporous silica support for the Pd/PVP catalyst allowed the catalyst to be used for nine cycles with no change in catalyst activity [196]. No palladium leaching to the organic phase was observed until the sixth cycle. Later cycles had <5 ppm leaching of palladium into the organic phase. Palladium nanoparticles supported by polyaniline nanofibers were highly active for Suzuki couplings of aryl bromides and inactivated aryl chlorides [197]. Even 1,4-difluorobenzene could be arylated to give *p*-terphenyl (Equation 1.41).



(1.41)

Hydrophobic polymers can also be used to support palladium nanoparticles. Thermal decomposition of $Pd(OAc)_2$ in the presence of linear polystyrene in aqueous potassium carbonate gave 2.3 nm nanoparticles supported on the polystyrene matrix [198]. The catalyst was active for the Suzuki coupling of aryl iodides and bromides at 80 °C in water and the Sonogashira coupling of aryl iodides. 2-Iodophenols could be coupled with alkynes to give benzofurans in excellent yields (Equation 1.42).

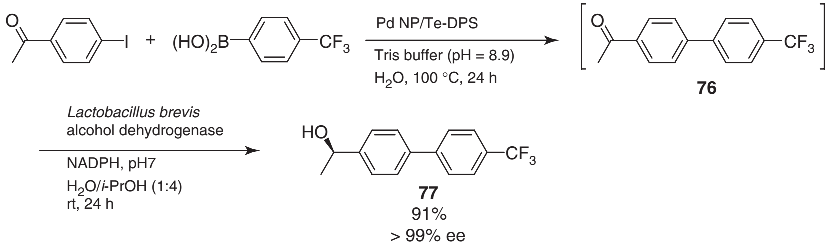
The water-insoluble catalyst could be recovered by filtration and reused 10 times in the Suzuki coupling of 4-bromotoluene with no loss in activity.



(1.42)

In order to achieve high catalyst activity, it is important that the support allows easy access for substrates and reagents to the catalyst particle. Water-insoluble, cross-linked polymers need to be able to swell to allow access to their interiors. Cross-linked polyacrylamide-*co*-polyacrylic acid acts as a hydrogel and is significantly swollen by water. When exposed to a palladium salt, the hydrogel absorbs the palladium, which expels water and further cross-links the polymer [199]. After reduction of the palladium, the hydrogel can be reswollen with water. The hydrogel-supported catalyst is a recyclable catalyst for the Suzuki coupling of aryl iodides and bromides. Core–shell nanospheres of polystyrene-*co*-poly[2-methacrylic acid 3-bis-(carboxymethylamino)-2-hydroxypropyl ester] serve as a pH-responsive support for palladium nanoparticles [200]. The nanoparticles are dispersed in the hydrophilic shell. Under basic conditions typically used in cross-coupling reactions, the polymer shells are well dispersed in water. On lowering the pH, the carboxylate-functionalized shell is protonated causing it to contract and the polymer spheres to precipitate allowing for easy recovery and recycling. Good yields were obtained with hydrophilic aryl bromides and iodides.

Natural polymers, such as proteins and cellulosic material, are highly functionalized, allowing them to attract palladium and support nanoparticles. Cacchi and coworkers prepared a palladium nanoparticle catalyst supported on thermally stable DNA binding proteins (Te-Dps) [201]. The resulting protein-stabilized nanoparticles catalyzed the Suzuki coupling of aryl iodides and bromides in modest to good yields. The catalyst was used in a one-pot cascade reaction involving a Suzuki coupling to generate a 4-arylacetophenone derivative **76** that was then enantioselectively reduced to alcohol **77** using the alcohol dehydrogenase from *Lactobacillus brevis* (Scheme 1.4). The resulting alcohols were isolated in good yield and >99% ee. Palladium nanoparticles supported on wool are effective catalysts for the Suzuki coupling of aryl bromides at 80 °C [202]. The wool-supported catalyst could be reused for 10 reaction cycles with minimal loss in catalyst activity and no measurable loss of palladium content in the wool.



Scheme 1.4 One-pot Suzuki coupling/enzymatic reduction cascade reaction.

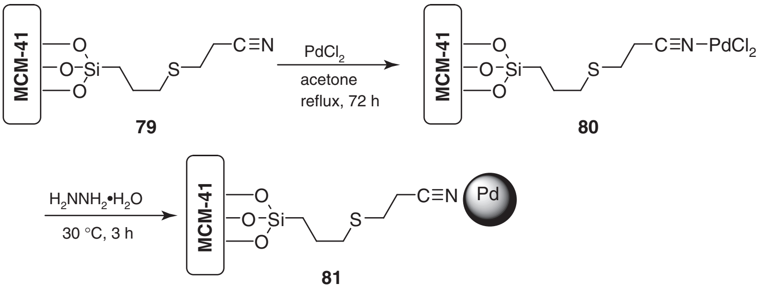
Chitosan-supported nanoparticles were formed by adsorption of Pd(II) ions into chitosan, followed by reduction with hydrazine [203]. The resulting catalyst was effective for the Suzuki coupling of aryl iodides and bromides at 150 °C under microwave irradiation in water/TBAB. The chitosan-supported catalyst could be recovered by filtration and reused with no loss in activity over five cycles. PEG-modified chitosan was also explored as a support for palladium nanoparticles [204]. The PEG–chitosan catalyst allowed the Suzuki coupling of hydrophobic aryl bromides in water without the use of TBAB. The recyclability of the catalyst was significantly diminished, however. A significant decrease in yield was observed after only two reaction cycles.

Highly stable gold nanoparticles can be prepared by reduction of $HAuCl_4$ in the presence of poly(2-aminothiophenol) [205]. The resulting nanoparticles catalyze the Suzuki coupling of aryl chlorides in water at 80 °C in good yield. The catalyst could be used for six reaction cycle with yields ranging from 87 to 84% from the first to sixth cycle.

1.4.2.3 **Inorganic-Supported Nanoparticle Catalysts**

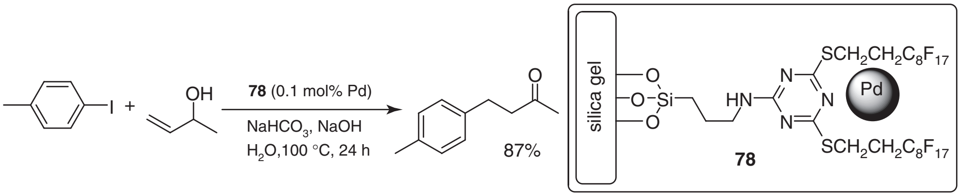
Palladium on carbon has a long history as a catalyst. In recent years, there has been renewed interest in using Pd/C as a recyclable catalyst in cross-coupling reactions. Palladium supported on carbon shows high activity in the Suzuki coupling [206–210]. The Pd/C catalyst could be recovered by filtration or centrifugation, but loses its activity after three cycles [207]. In a direct comparison, Pd/C outperformed Pd-supported on alumina [211]. The increased activity of Pd/C was attributed to the higher surface area and the fact that the surface is hydrophobic rather than hydrophilic. The Pd/C catalyst has also been successfully applied to the Hiyama coupling of aryl bromides and iodides with $PhMeSiCl_2$ in water at 100 °C [212].

Metal oxides are the most widely used inorganic catalyst supports. Silica was used to promote the Suzuki coupling of aryl bromides catalyzed by $Pd(OAc)_2$ in water/PEG [213]. The silica is believed to act as a support for the palladium nanoparticle catalyst. PEG was critical in stabilizing the active catalyst. In the presence of PEG, the catalyst could be reused 18 times with little loss in activity, whereas catalyst activity decreased significantly after the first run when PEG was not used. Including coordinating groups on the silica surface can enhance the binding of the palladium nanoparticles to silica. Palladium nanoparticles generated on a fluorous pyrazole modified silica gel (**78**) were active and highly recyclable catalysts for the Heck coupling of aryl iodides and allyl alcohols (Equation 1.43) [214]. Using 0.1 mol% Pd, catalyst **78** could be used up to eight times with no loss in activity. As noted above, palladium supported on alumina provides a less active catalyst than Pd/C due in part to the polar surface of the metal oxide. Mesoporous silica (Mobile crystalline material (MCM)-41) surface modified with a cyanoethyl thioether (**79**) has been used to support palladium nanoparticles (**81**, Scheme 1.5) [215]. The MCM-supported catalyst was used in the Sonogashira coupling of aryl iodides in water. Reuse of the catalyst for five cycles was demonstrated for several substrate combinations. Alumina and titania particles functionalized with hydrophobic or



Scheme 1.5 Synthesis of MCM-41-supported palladium nanoparticle catalyst.

amphiphilic surface groups provide higher activity catalysts for Suzuki coupling reactions of aryl bromides than unfunctionalized hydrophilic particles [211].



(1.43)

A variety of other metal oxide supports have been explored for aqueous-phase cross-coupling reactions. Palladium on CeO_2 catalyzed the Suzuki coupling of aryl bromides in water/ethanol at room temperature [216]. The Pd/CeO_2 was highly recyclable giving yields between 98 and 100% over 10 reaction cycles. Palladium on $BaSO_4$ catalyzed the Suzuki coupling of aryl bromides at 80 °C [217]. In recycling studies, the catalyst efficiency dropped off after the second use. Palladium nanoparticles supported on magnetite particles were applied to the Hiyama coupling of aryl bromides and aryltrialkoxysilanes in water at 100 °C [218]. Good yields were obtained with a range of aryl bromide and aryl siloxane substrates. The magnetically recoverable catalyst was used for five reaction cycles with the yield decreasing from 91% in the first cycle to 80% in the final cycle. A polyoxotungstate-supported catalyst was prepared by reduction of Keggin-type polyoxometalate $K_5[PPd(H_2O)W_{11}O_{39}] \cdot 12H_2O$ [219]. The resulting material catalyzed the Suzuki coupling of aryl bromides and chlorides as well as the Stille, Heck, and Buchwald–Hartwig couplings of aryl bromides.

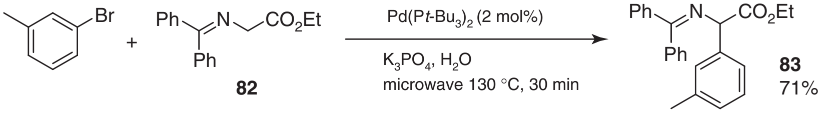
Zeolites that contain defined voids capable of sequestering palladium nanoparticles are attractive solid supports. The catalyst is isolated, so that particle agglomeration does not occur, yet the pores of the zeolite allow for access to the catalyst by substrates. Zeolite-supported palladium catalysts can be prepared by exchanging palladium(II) ions into Na–Y zeolite followed by reduction to Pd(0) nanoparticles [220]. The resulting material catalyzed the Suzuki coupling of aryl bromides in water at room temperature. The catalyst could be used for 15 reaction cycles with a slow decrease in yield from 98 to 82%. Inductively coupled plasma analysis of the catalyst after use showed no measurable loss in palladium content. Palladium(II)-exchanged Na–Y zeolite was also used in the Heck coupling of aryl bromides and iodides in a microemulsion composed of Triton X10, heptane, 1-butanol, water, and 1,2-propanediol [221]. The zeolite-supported catalyst showed higher activity than Pd/C or $Pd(OAc)_2$ without support.

1.5
Special Reaction Conditions

1.5.1
Microwave Heating

Microwave irradiation allows for rapid and even heating of reaction mixtures, unlike traditional thermal heating. The speed of heating can dramatically accelerate reaction rates compared to thermal heating. For microwave heating to be effective, the solvent must have a strong dipole. Water is an ideal solvent for microwave-promoted reactions because of its strong interaction with microwave radiation. Microwave heating is often used with catalysts requiring high reaction temperatures ($> 100\,^\circ C$) to provide high reaction rates.

Microwave heating was first applied to aqueous-phase palladium-catalyzed Suzuki coupling of PEG-supported aryl bromides as part of a rapid throughput synthesis approach [186]. Using microwave heating, high yields were obtained with a ligand-free catalyst in PEG/water with a reaction time of 2–4 min. Suzuki coupling of aryl chlorides catalyzed by Pd/C was carried out at 120 °C using microwave heating [184, 185, 209]. Microwave irradiation gave rates that were 30 times higher than conventional heating and 3 times higher than ultrasound irradiation in the aqueous-phase Suzuki coupling catalyzed by palladium nanoparticles supported on PVP [195]. Catalyst loadings as low as 2.5 ppm have been used for the Suzuki coupling of aryl bromides under microwave irradiation [222]. Microwave irradiation has been applied to Hiyama [101], Sonogashira [127], and Heck [102] couplings as well as α-arylation [223] of protected glycine derivative **82** in water to give amino acid **83** (Equation 1.44). Copper-catalyzed Sonogashira couplings of aryl iodides can be carried out in <1 h under microwave irradiation compared to 24 h for conventional heating [133].



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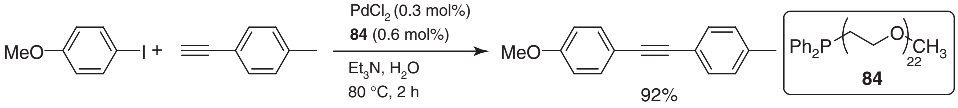
1.5.2
Ultrasound

Ultrasound irradiation has been shown to accelerate many reactions, allowing them to be completed with shorter reaction times than thermal activation of reactions. As a result of shorter reaction times and lower reaction temperatures, ultrasound-promoted reactions often give fewer side products than reactions promoted by heating. In the aqueous-phase Suzuki coupling of aryl iodides catalyzed by palladium supported on PVP, ultrasound-promoted reactions occurred 10 times faster than thermally promoted reactions (80 °C) [195]. Ultrasound has also been used to promote the $Pd(OAc)_2$-catalyzed Heck coupling of aryl iodides in water/ethanol using SDS as a surfactant [179].

1.5.3
Thermomorphic Reaction Control

PEG- or polyol-substituted compounds often display thermoregulated solvation. At low temperature, extensive hydrogen bonding with water allows them to partition primarily to the water layer of a water/organic biphasic system. As the temperature is increased, the hydrogen bonding is disrupted and the molecule becomes more hydrophobic and partitions into the organic phase. Thus, a catalyst with thermoreversible solvation properties can be partitioned into the organic phase at high temperatures, and the catalyst partitions back into the aqueous phase when the reaction temperature is lowered. In this way, catalysis can be carried out under nearly homogeneous conditions in the organic phase, while allowing the water-soluble catalyst to be recovered at ambient temperature.

Diphenylphosphino-substituted PEG (**84**) provides effective catalysts for the thermoregulated Suzuki [224, 225] and Sonogashira [226] couplings of aryl bromides and iodides (Equation 1.45). The ligand has a cloud point of 93 °C. In the Suzuki coupling, a significant increase in yield was seen above the cloud point (100 °C, 99%) compared to 90 °C (44%). The catalyst derived from this ligand is completely soluble in water at room temperature, but partitions into the substrate phase on heating to 100 °C leaving a colorless water layer. On cooling to room temperature, the catalyst partitions back into the water phase and the water-insoluble product precipitates. In the Sonogashira coupling, the temperature effect was even more dramatic. At 72 °C, a 30% yield was obtained in the coupling of 4-iodonitrobenzene and phenylacetylene. At 74 °C, the yield was 70% under otherwise identical conditions. The catalyst system could be used for four cycles before significant loss of activity in both the Suzuki and Sonogashira reactions.



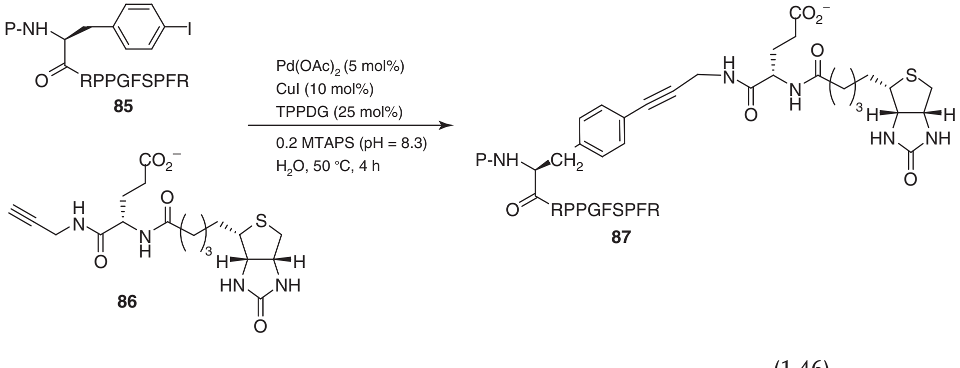
(1.45)

1.6
Homogeneous Aqueous-Phase Modification of Biomolecules

The motivation for using water as a solvent in metal-catalyzed cross-coupling is often to improve the safety of a system or to allow recycling of a catalyst that partitions into the aqueous phase. Water is also an attractive solvent when the substrates are highly polar biomolecules. By using a water-soluble catalyst system, the coupling can be carried out under homogeneous conditions with hydrophilic biomolecules, such as proteins or nucleosides. In this way, cumbersome protection/deprotection strategies designed to make the molecules more lipophilic can be avoided.

1.6.1
Amino Acids and Proteins

Schmidtchen and coworkers first demonstrated the use of palladium-catalyzed cross-coupling on unprotected peptides [227]. Using a $Pd(OAc)_2$/TPPDG catalyst, iodophenyl bradykinin derivative **85** was coupled with alkynes under biocompatible conditions. The alkynylated products were obtained in high yield without degradation of the peptide. Biotin peptide conjugate **87** was synthesized by coupling alkyne-containing biotin derivative **86** with the iodophenyl-substituted peptide **85** (Equation 1.46). Cross-linked peptides were prepared by the coupling of a trialkynyl core with iodophenyl-modified peptides having 17–33 amino acid residues [228]. Quantitative yields were obtained at pH 5.5 except in cases where the peptide contained free thiols or thioethers.

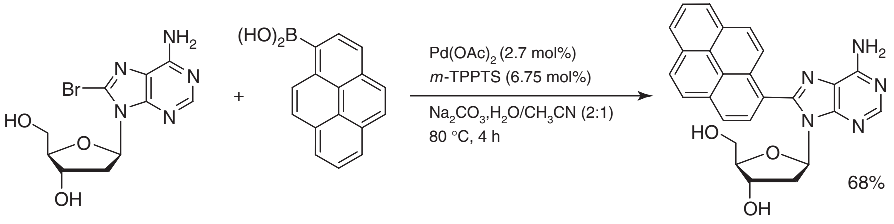


(1.46)

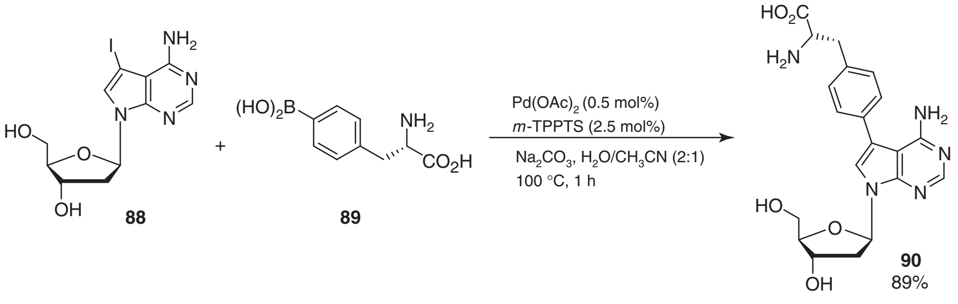
These methodologies have been extended to enzymes. Sonogashira [229] and Heck [230] modifications of an iF-RAS protein were performed using a $Pd(OAc)_2$/*m*-TPPTS catalyst to add biotin groups to specific residues on the enzyme. The site of functionalization had been modified by incorporation of a 4-iodophenylalanine residue. The reactions could be carried out at low temperature ($< 5\,^{\circ}C$) and in the presence of additives required to stabilize the protein, such as $MgCl_2$, glycerol, or NaCl. Isolated yields of the coupled enzyme were around 25%. The enzyme retained catalytic activity after the coupling reaction. A catalyst derived from $Pd(OAc)_2$ and disodium 2-amino-4,6-dihydroxypyrimidine was used in the Suzuki coupling of an iodophenyl-modified serine protease enzyme at 37 °C [16, 85].

1.6.2
Nucleosides and Nucleotides

Palladium-catalyzed coupling of halonucleosides and halonucleotides dates back to Casalnuovo's first report of aqueous-phase cross-coupling reactions [25]. More than a decade later this initial work was extended to the Suzuki coupling of the less reactive 8-halopurine nucleosides using palladium salts in combination with *m*-TPPTS or TXPTS (Equation 1.47) [231]. Interestingly, sterically demanding alkylphosphines, such as *t*-Bu-Amphos, gave ineffective catalysts for Suzuki coupling of halonucleosides. This system has been applied to the Suzuki coupling of 7-deazapurine ribonucleosides [232] and synthesis of amino acid–nucleoside conjugate **90** by coupling 7-iodo-7-deazopurine (**88**) and phenylalanylboronic acid (**89**) (Equation 1.48) [233, 234]. The Pd/TTPTS system was an effective catalyst for the Suzuki arylation of 8-bromoguanosine mono- and triphosphate [235, 236].

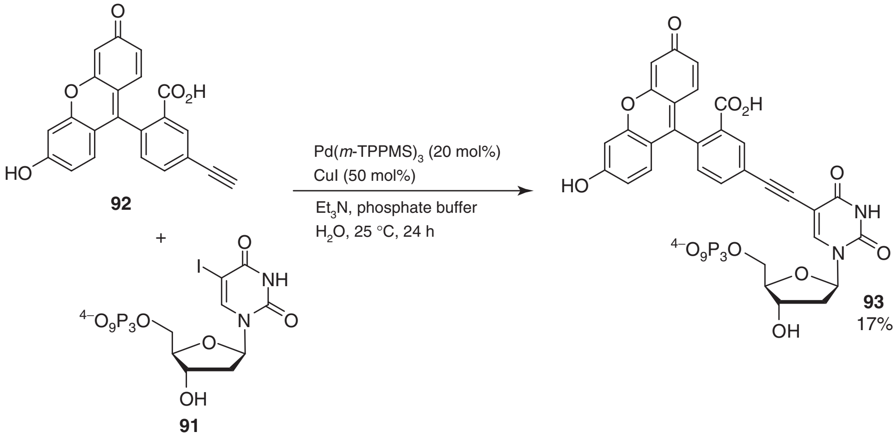


(1.47)



(1.48)

Sonogashira couplings of unprotected nucleosides can be carried out using $Pd(OAc)_2$/*m*-TPPTS [237, 238]. Improved activity for the coupling of 8-bromopurine nucleosides is seen when TXPTS is used as the ligand in place of *m*-TPPTS [239]. Sonogashira coupling of 5-iodouridine triphosphate (**91**) catalyzed by Pd(*m*-TPPTS)$_3$ was used to attach dye probe **92** to the nucleobase to give dye-modified nucleoside **93** (Equation 1.49) [240]. Heck coupling of 5-iodo-2′-deoxyuridine has been reported using a ligand-free $Pd(OAc)_2$ catalyst [241].



(1.49)

1.7
Conclusion

The field of aqueous-phase cross-coupling reactions has grown from a niche effort to an area receiving significant attention. The initial motivations of decreasing the cost and environmental impact of catalytic processes remain the driving forces behind current research. There is still strong interest in developing efficient and recoverable catalysts for use in pharmaceutical and other fine chemical synthetic processes. An interesting development in recent years is that water can promote cross-coupling reactions of hydrophobic substrates. Reactions carried out on water with hydrophobic substrates and catalysts can in many cases occur faster than traditional homogeneous phase reactions, while avoiding organic solvents. Challenges for future developments in this area will be to develop catalysts with scope and activity comparable to the best organic-phase catalyst systems. Good progress has been made in recent years in developing catalysts capable of activating aryl chlorides, but most systems remain limited to aryl iodides or bromides. In addition, the majority of work on aqueous-phase catalysis has focused on the Suzuki and Hiyama couplings, which occur with a wide range of catalyst systems. Further development of efficient catalysts for Heck reactions, as well as carbon–heteroatom bond formation, is needed.

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