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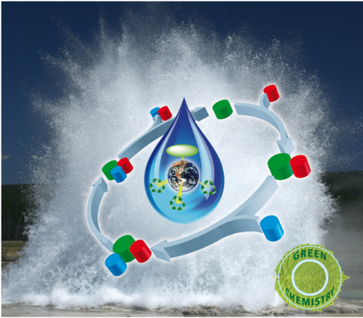

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Edited by Pierre H. Dixneuf and Victorio Cadierno

Metal-Catalyzed Reactions in Water

WILEY-VCH Verlag GmbH & Co. KGaA

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Library of Congress Card No.: applied for

British Library Cataloguing-in-Publication Data
A catalogue record for this book is available from the British Library.

Bibliographic information published by the Deutsche Nationalbibliothek
The Deutsche Nationalbibliothek lists this publication in the Deutsche Nationalbibliografie; detailed bibliographic data are available on the Internet at <http://dnb.d-nb.de>.

Print ISBN: 978-3-527-33188-8
ePDF ISBN: 978-3-527-65682-0
ePub ISBN: 978-3-527-65681-3
mobi ISBN: 978-3-527-65680-6
oBook ISBN: 978-3-527-65679-0

Cover Design Grafik-Design Schulz, Fußgönheim
Typesetting Laserwords Private Limited, Chennai, India
Printing and Binding Markono Print Media Pte Ltd, Singapore

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Preface

Metal catalysis represents a frontier field of research. The ability of metal complexes to catalyze organic reactions, and to selectively create new ones, is now the basis of the most powerful strategies leading to new synthetic methods. *Homogeneous catalysis* has brought a revolution in fine chemical synthesis, drug and cosmetic discovery, in the preparation of molecular materials and polymers, and it is more active than ever before.

Catalysis, one of the twelve principles of *Green Chemistry*, is offers selective processes with energy and atom economy and is an essential partner for sustainable manufacturing in the chemical industry. Within this context, the use of a safe, nontoxic, eco-friendly, and cheap solvent is also advised. Water is probably the most appealing candidate as an easily available, noninflammable, nontoxic, and renewable solvent. Consequently, the use of water as a solvent in synthetic organic chemistry and materials science has spread throughout the chemical community at a staggering pace during the last two decades.

The combination of metal catalysis and water has led in recent years to the development of a huge number of new and greener synthetic methodologies. Although the hydrophobic character of most organic compounds has been for long time considered as a major drawback, it is nowadays well documented that even when the reaction medium is heterogeneous, ''on water'' conditions, an enhancement on the catalyst activity and/or selectivity can be observed by using water as solvent. The low solubility and inherent instability of organometallic compounds in water is another limitation that has also been largely surpassed in recent years by designing new hydrophilic ligands and more robust, air- and water-stable catalysts. Moreover, the use of metal catalysts in water or in a two-phase system offers other advantages versus more classical organic solvents, that is, it simplifies the separation of the products, and that of catalyst, thus favoring water recycling, a very important aspect for large-scale chemical processes. New discovered techniques in nanofiltration and in recovery of metal ions from water contribute to this field. All these facts make catalysis in aqueous systems a very active field of research today, both from an academic and an industrial point of view. In fact, metal catalysis in water is now in the heart of the main fields of contemporary chemical research.

The content of this volume gathers the main aspects and potentials of metal catalysis in water, including C-C cross couplings (Chapter 1), C-H bond activations (Chapter 2), nucleophilic additions of alkynes (Chapter 3), hydroformylations (Chapter 4), oxidation processes (Chapter 5), hydrogenations (Chapter 6), rearrangements and allylations (Chapter 7), olefin metathesis reactions (Chapter 8), and nanocatalysts in water (Chapter 9).

The aim of this book is to introduce the readers to this topic through cutting-edge results from the recent literature, and the know-how shared by the chapter authors. This volume should be helpful to academic and industrial researchers involved in the fields of catalysis, new greener organic synthetic methods, water-soluble ligands, and catalysts designing and also to teachers and students interested in innovative and sustainable chemistry.

We are grateful to the Wiley-VCH team who made this project practical and to all the contributors to this volume for their effort and enthusiasm in sharing their expertise to join this *aquatic* editorial enterprise.

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1
Metal-Catalyzed Cross-Couplings of Aryl Halides to Form C–C Bonds in Aqueous Media

Kevin H. Shaughnessy

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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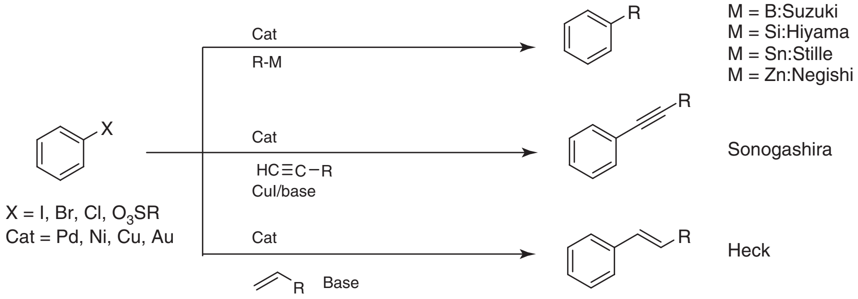


Scheme 1.1 Major classes of metal-catalyzed cross-coupling reactions.

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

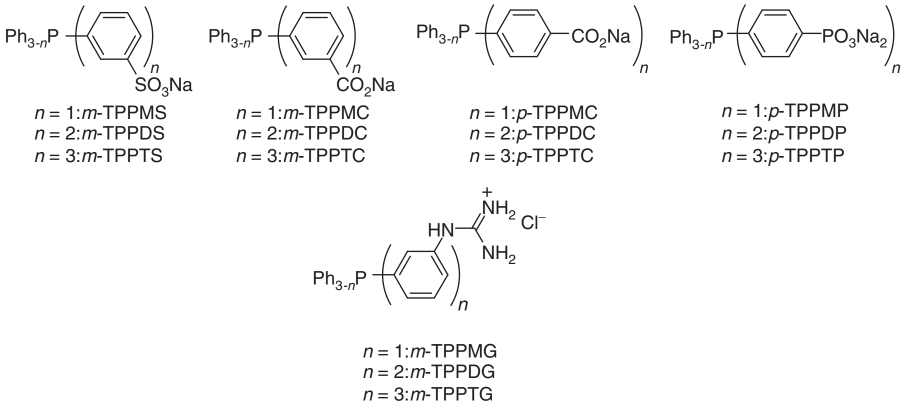
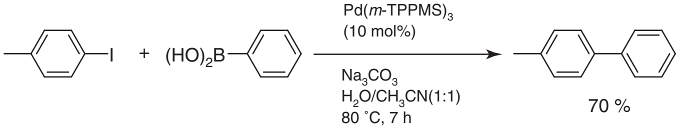


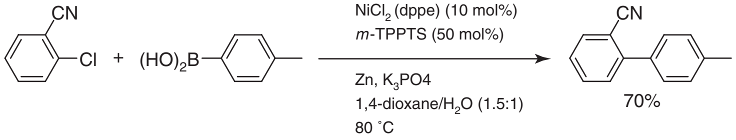
Figure 1.1 Triphenylphosphine derivatives with ionic substituents.

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.



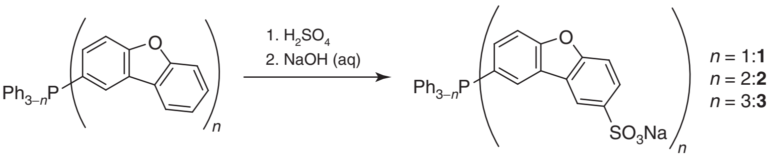
(1.1)

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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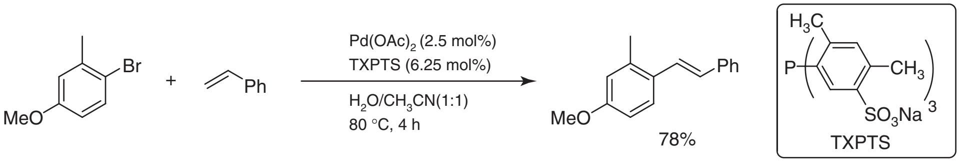
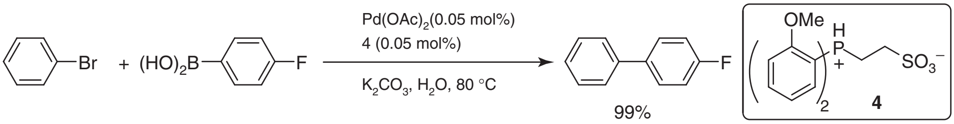


(1.4)

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.

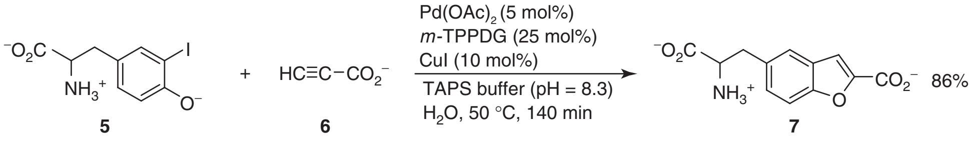


(1.5)

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

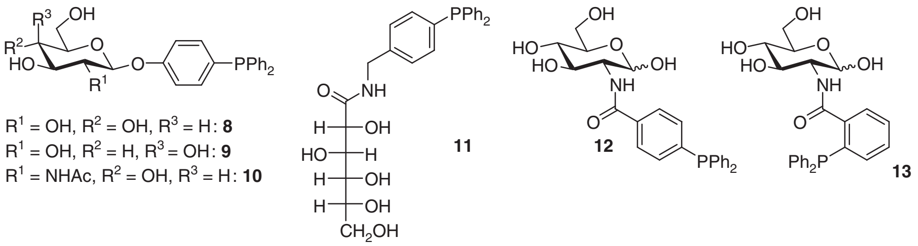


Figure 1.2 Carbohydrate-modified phosphines.

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

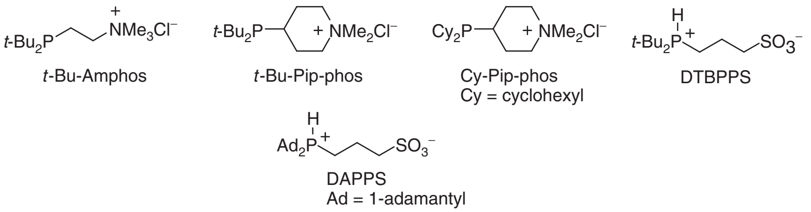
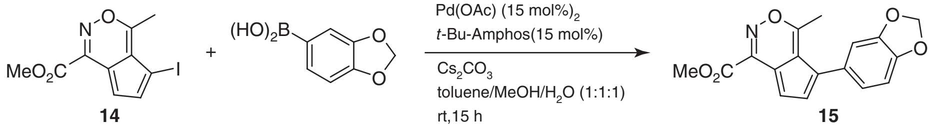


Figure 1.3 Ammonium- and sulfonate-modified trialkylphosphines.

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.

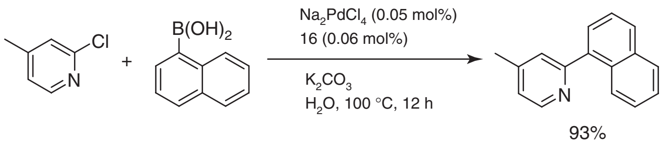


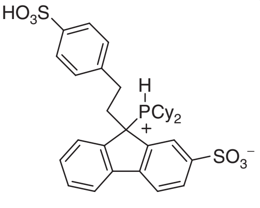
(1.7)

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].

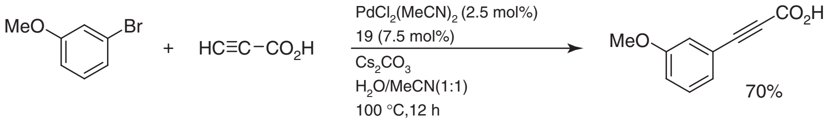




CataCXium F
16

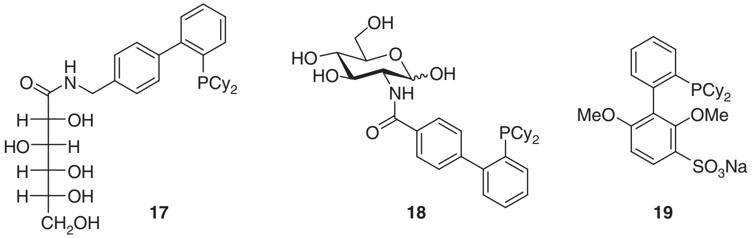
(1.8)

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)

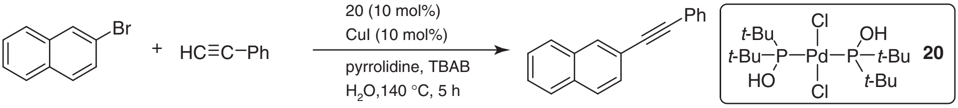
Di-(*tert*-butyl)phosphinous acid is a water-soluble ligand under basic conditions. Complex **20** is an effective precatalyst for the aqueous-phase Stille [60] and Sonogashira coupling (Equation 1.10) [61] of aryl halides, whereas complex **21** is a more effective catalyst for the Hiyama coupling (Equation 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.



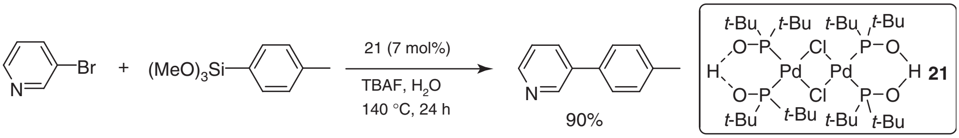
17 **18** **19**

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%.



(1.10)



(1.11)

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