Hydrophilic Ligands and Their Application in Aqueous-Phase Metal-Catalyzed Reactions

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1. Introduction

Water is truly ubiquitous. Approximately 80% of the earth's surface is covered by water, although only 1% of this is drinkable water. Water is the solvent of life and makes up about 60% of the mass of the human body. The majority of synthetic organic chemistry carried out in research laboratories or industrial processes utilizes organic solvents, however. Organic solvents have a number of attractive features: they will dissolve a wide range of organic compounds, they come with a variety of properties, and they are often volatile and easily removed. Unfortunately, organic solvents are often toxic, flammable, and nonrenewable and have low heat capacities. In contrast, water is nontoxic and nonflammable, has a high heat capacity, and is relatively inexpensive. Of course water has some significant drawbacks as a solvent: it is a poor solvent for most organic molecules, and it is highly reactive with many classes of reagents. Because of these drawbacks, water is rarely used as a primary solvent in synthetic organic chemistry, although there is a growing body of work related to organic chemistry in water.[1−3]

Homogeneous metal-catalyzed reactions have been growing in importance for both the synthetic and industrial communities over the past several decades. Starting with pioneering industrial processes such as the Wacker oxidation and olefin hydroformylation (oxo process) through more modern processes, such asymmetric hydrogenation, Pd-catalyzed cross-coupling chemistry, single-site Ziegler−Natta catalysts and olefin metathesis, homogeneous catalysts offer unparalleled degrees of selectivity and tunability. The use of a homogeneous catalyst presents a challenge for their implementation on a large scale. How do we recover the metal from the product? This separation can be challenging since the catalyst and product often have similar solubility characteristics. As a result, there is a strong preference for heterogeneous catalysts for industrial processes. One approach to addressing this separation issue is to heterogenize the homogeneous catalyst by attaching it to a solid support, allowing the catalyst to be recovered in the same way as traditional heterogeneous catalysts.[4−8] Unfortunately heterogenizing the catalyst on a solid support can be synthetically

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Kevin H. Shaughnessy was born in 1970 and raised in Trumbull, Nebraska. He earned his B.S. degree from the University of Nebraska—Lincoln in 1992, where he worked with Reuben D. Rieke. He then joined the group of Robert M. Waymouth at Stanford University, where he developed zirconocene-catalyzed carbometalation reactions. Upon completing his PhD (1998), he moved to Yale to work with John F. Hartwig on palladium-catalyzed enolate arylations and development of high-throughput screening assays. In 1999, he joined the chemistry faculty at The University of Alabama, where he is currently an Associate Professor of Chemistry and Director of Undergraduate Studies. His research interests have focused on the development of catalytic methodologies in alternative solvents and understanding how these solvents affect fundamental organometallic reactivity.

challenging and often results in decreased activity and selectivity. In addition, since the catalyst is typically attached to the support through the ligand, dissociation of the metal from the ligand results in leaching of the metal into the reaction solution.

Another approach that has received significant attention is to constrain the catalytic species in an organic immiscible liquid. In a biphasic reaction system, the products and catalyst reside in different immiscible phases, which are usually both liquid. The two phases are brought into contact by stirring allowing the reaction to proceed, but upon completion of the reaction the two phases can be separated by simple decantation. Because the catalyst remains in solution, it often retains its reactivity and selectivity properties. Provided there is sufficient interaction between the substrate phase and the catalyst phase, good activities can be achieved. A variety of organic immiscible solvent phases have been explored, including water, fluorous solvents,[9] supercritical CO_2,[10,11] and ionic liquids.[12]

While each of these alternative solvents has positive and negative attributes and continues to draw attention, water because of the advantages listed above is a very attractive choice as an organic immiscible solvent. In addition, water has a proven track record of use in industrial catalytic processes, such as the Wacker oxidation[13] and the Rhône-Poulenc hydroformylation of propene.[14] Because most organic molecules and solvents have little or no solubility in water, phase separation can be easily achieved. The large difference in solvent properties between water and organic solvents typically ensures that the hydrophilic catalyst and hydrophobic products will strongly partition into their relative phases. An obvious limitation for aqueous-phase metal-catalyzed processes is the limited stability of some metal−carbon bonds in water. Fortunately, late transition metals, which are the most widely used metal catalysts, have relatively nonpolar and protolytically stable metal carbon bonds.

Water has also garnered much attention as a green solvent. Green chemistry, which seeks to limit the impact of chemical processes on the environment through the use of safer and more sustainable practices, is a desirable set of goals in the design of new processes.[15] Chemical processes inevitably produce undesirable waste, and the ratio of this waste to the desired product typically increases as the complexity of the desired product increases. For example, the oil industry is very efficient at utilizing materials as measured by the *E*-factor (0.1 kg of waste/kg of product), while pharmaceutical processes tend to have high *E*-factors (25−100 kg of waste/kg of product).[16] A significant portion of this waste is due to solvents used in the reaction and purification processes.[17] While solventless processes are a desirable goal, they are unlikely to be realized in most cases. Thus, one would like to use the most benign solvent possible.[18,19] Water in its pure form is completely benign, so it would appear to be an attractive solvent. Furthermore, by simplifying the separation of the catalyst from the product, significant savings in the use of solvents and/or energy in the purification process can be realized. Water may not be the panacea solvent that it is often claimed to be, however.[20] Once contacted with organic materials, water becomes waste itself and can be very difficult to clean. The high heat capacity of water makes purification by distillation an energy intensive process. Incineration of organic-contaminated water is often required, which is complicated by the nonflammability of water. Thus the recycling of water used in chemical processes will likely be an important element in the design of aqueous-phase processes on an industrial scale.

In addition to the potential operational advantages offered by aqueous-phase or aqueous/organic biphasic catalysis, water can also offer advantages in terms of chemical reactivity and selectivity. Water is a unique solvent due to its highly structured nature enforced by intramolecular hydrogen bonding. Thus water can accelerate reactions through the hydrophobic effect first noted by Breslow,[21] whereby organic reactants in water attempt to minimize their interaction with water. The hydrophobic effect favors reactions with negative volumes of activation. Reactions of hydrophobic compounds are often accelerated in water, even if none of the reactants have appreciable water solubility (i.e., "on-water" chemistry).[22] The Lewis-basic nature of water allows it to modify the reactivity of Lewis acid species, leading in some cases to accelerated reactions.[23] Water is highly polar and provides effective solvation for ionic species that leads to solvent separated ions. Thus water can promote dissociation of anionic ligands, or attenuate the reactivity of anions in solution. Reactions carried out in water also provide the opportunity to finely tune the pH of the reaction system, which can lead to changes in reactivity in selectivity. Finally, water itself can serve as an acid, base, nucleophilic reagent, and even a H_2 source. Thus, in addition to serving as a convenient solvent, reactions in water can in some cases proceed much differently than they do in traditional organic solvents.

The most common approach to constrain a catalyst into the aqueous phase of a biphasic reaction has been to design ligands containing hydrophilic substituents. The focus of this review will be to provide an overview of the wide range of hydrophilic ligand structures that have been prepared and to describe their application in aqueous-phase metal-catalyzed processes with a focus on the most commonly used reactions: hydroformylation, hydrogenation, olefin polymerization and metathesis, and metal-catalyzed cross-couplings. The review

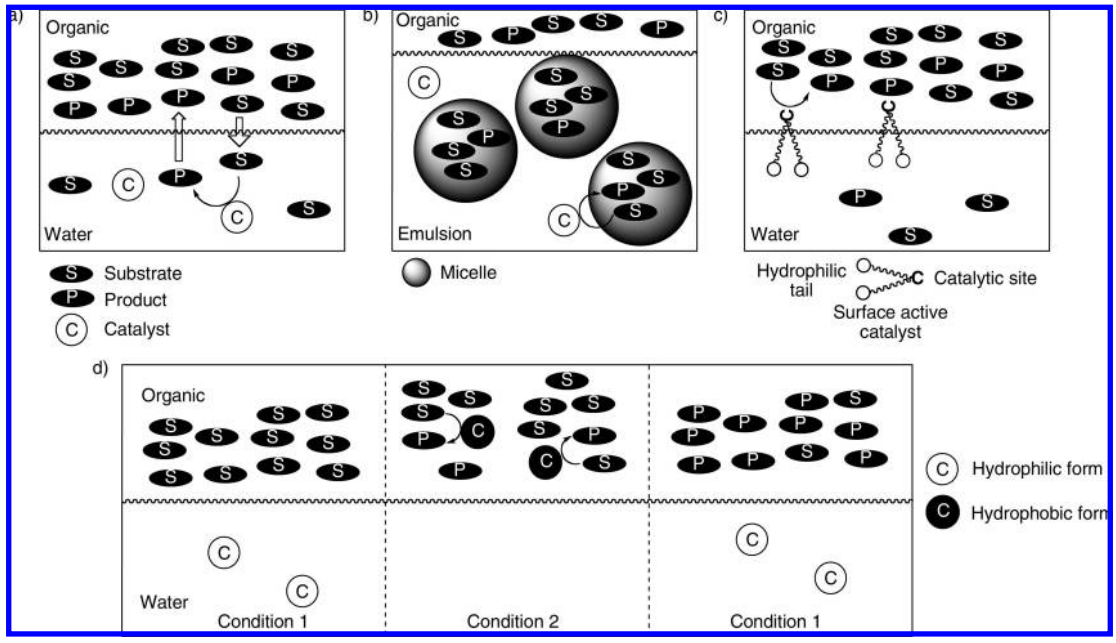


Figure 1. Possible modes for aqueous-biphasic catalysis: (a) reaction in bulk water, (b) reaction in surfactant-supported micelle, (c) use of surface active catalyst structures, (d) solvent switchable catalyst system.

will focus on advances over the past 10−15 years through mid-2008 along with key early examples of aqueous-phase catalysis.

Given the importance of this field, a number of reviews have previously been published related to aspects of aqueous-phase catalysis. A number of general reviews on aqueous-phase metal-catalyzed reactions have been published, although the majority are now more than five years old.[14,24−33] A few reviews have focused specifically on the industrial applications of aqueous-phase catalysis.[34,35] In addition, more specialized reviews on aqueous-phase hydrogenation,[36−39] olefin polymerization,[40] C−H activation,[41] and palladium-catalyzed cross-coupling reactions[42−49] have been published. Monographs by Cornils and Herrmann,[50−52] Lindström,[53] and Joó[54] also provide good overviews of this field. The goal of this review will be to provide a comprehensive update of these prior reviews, while focusing heavily on the design of water-soluble ligands, their properties, and how these properties affect aqueous-phase, metal-catalyzed reactions. Because the focus of this review is the design and application of water-soluble ligands; aqueous phase catalysis using hydrophobic ligands, solid-supported catalysts, complexes that are soluble due to the metal center being ionic, and ligand-free catalysts will not be covered.

2. Design of Hydrophilic Ligands

Constraining a catalytically active metal species in an aqueous phase is a conceptually simple process involving the design of a ligand with suitable hydrophilic functionality that will cause it to partition into the aqueous phase while providing the necessary steric and electronic properties to provide the desired catalyst stability, activity, and selectivity. In most cases a hydrophobic ligand is made hydrophilic by attaching water-solubilizing groups to known hydrophobic ligands. Most commonly ionic substituents are used, such as sulfonate, carboxylate, phosphonate, or ammonium. Nonionic hydrophilic substituents, such as polyols, carbohydrates, and polyethers, have also been used.

A major challenge in aqueous-biphasic catalysis is to bring the water-soluble catalyst into contact with the hydrophobic substrate and other reagents. For molecules with at least some degree of water solubility, the reaction can occur in the aqueous bulk through interaction of the water-soluble catalyst with the substrate dissolved in water (Figure 1a). As the substrate becomes less soluble in water, the rate of the reaction will decrease due to the lower concentration of the substrate in the aqueous phase. One approach to address this problem is to use water miscible organic cosolvents (i.e., alcohols, acetonitrile, DMF) to increase the solubility of the hydrophobic substrate in the aqueous solution. Another approach is to use surfactants or phase transfer agents (cyclodextrins or calixarenes) to carry the organic reagent into the aqueous phase by formation of water-soluble micelles with hydrophobic interiors (Figure 1b). All of these approaches can improve reaction rates, but may also complicate phase separation at the end of the reaction.

Although high water-solubility of the catalyst is desirable to facilitate partitioning of the catalyst into the aqueous phase, increased water-solubility often leads to lower catalyst activity due to poor interaction of the hydrophilic catalyst with the hydrophobic substrate. Thus, there has been significant interest in the design of surface active ligands. Typically these ligands have surfactant-like structures with long aliphatic tails connected to an ionic or neutral hydrophilic functionality. The metal coordination site is placed on the hydrophobic end of the ligand, allowing the metal to project into the hydrophobic phase or the interior of micelles (Figure 1c). In some cases the ligand itself can form micelles, in addition to supporting the metal catalyst. Again, one must balance the desire for improved activity with the need to keep the catalyst constrained in the aqueous phase.

Making the catalyst less hydrophilic increases the chance of it being leached away into the organic phase. An alternative approach is to design ligands with adjustable solvent properties (Figure 1d). Thus by changing a reaction variable, such as pH or temperature, the catalyst can be induced to partition into the organic phase to provide high activity (condition 2). At the end of the reaction, the conditions are changed to cause the catalyst to partition back into the aqueous phase to allow for easy separation (condition

1). The phase preference of amine-functionalized ligands can be controlled by changes in pH. Thus at low pH, the ammonium-functionalized catalyst is water soluble, while at high pH the amine-functionalized catalyst partitions into the organic phase. Polyether- or polyhydroxyl-substituted ligands display inverse temperature dependent solubility. At low temperature they are water soluble due to hydrogen bonding with water. As the temperature is raised, the hydrogen bonding breaks down and the catalyst partitions into the organic phase.

2.1. Synthesis of Hydrophilic Phosphines

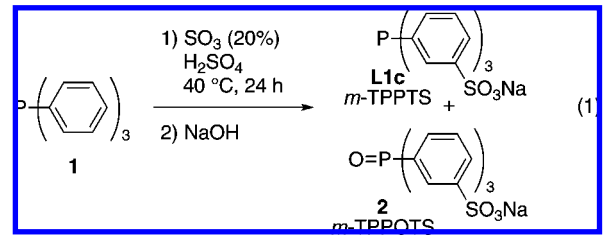
Phosphine ligands are the most widely used class of ligands in catalytic processes. Triarylphosphines are most commonly used because of their ease of preparation and stability. More recently, di- and trialkylphosphines have become important, particularly for metal-catalyzed cross-coupling reactions and olefin metathesis. A wide range of chelating phosphines with alkyl or aryl backbones are also commonly used, including important chiral diphosphines. Water-solubilized analogues of all of these ligand classes have been prepared over the years that largely mirror the relative importance of these ligand classes in homogeneous catalysis. Large numbers of hydrophilic triarylphosphines and chelating bis(diarylphosphine) ligands have been prepared, with smaller numbers of hydrophilic phosphines being reported.

2.1.1. Phosphines with Anionic Substituents

The most common class of hydrophilic phosphine ligands is those with anionic substituents appended to the organic substituents. The anionic substituents are typically weakly basic moieties, such as sulfonate, phosphonate, and carboxylate. These anionic substituents remain in their anionic form over a broad pH range, allowing them to be used to solubilize organometallic species in a variety of aqueous-phase catalytic processes. In addition, these weakly Lewis basic functionalities typically do not bind strongly to late transition metals. Therefore, these anionic substituents are usually innocent partners that do not interfere with the catalytic cycle.

The first, and still most commonly used, water-solubilizing substituent is the sulfonate group. The sulfonate group is an attractive water-solubilizing moiety because it is easily introduced and is stable under a variety of reaction conditions. Metal sulfonates are most commonly introduced to aryl substituents on phosphines by electrophilic sulfonation using SO_3/H_2SO_4, or in some cases just H_2SO_4, followed by neutralization with metal hydroxides. Sulfonation of aryl rings connected directly to the phosphorus atom occurs exclusively in the *meta*-position due to the directing effect of the protonated phosphorus center. The protonated phosphorus also deactivates the aryl ring to sulfonation, which often results in the need to use harsh conditions (20−40% oleum at elevated temperatures) and long reaction times (12−24 h). Competitive oxidation of the phosphorus center is common in these cases, particularly when attempting to achieve high degrees of sulfonation.

Chatt[55] first reported the sulfonation of triphenylphosphine using 25% SO_3 in H_2SO_4 to give the monosulfonated triphenylphosphine derivative *m*-TPPMS (**L1a**, Table 1) in modest yield. The trisulfonated derivative, *m*-TPPTS (**L1c**), was first prepared by Kuntz at Rhône-Poulenc by the reaction of triphenylphosphine (**1**) in 20% oleum at 40 °C for 24 h followed by neutralization with NaOH (eq 1).[14,56−58] This reaction gave a mixture of *m*-TPPTS (**L1c**) and the corresponding oxide (*m*-TPPOTS, **2**) in a nearly 1:1 ratio. Under optimized conditions this ratio can be improved to 75−85% *m*-TPPTS with the remainder *m*-TPPOTS.[59] The oxide can be partially removed due to the higher solubility of *m*-TPPOTS in water/methanol compared to *m*-TPPTS. An improved separation can be achieved using Sephadex columns, which allows *m*-TPPTS to be isolated free of oxide impurities and incompletely sulfonated phosphines.[60]



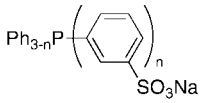
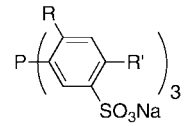
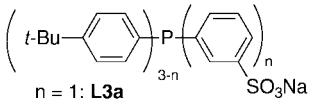
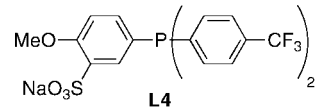
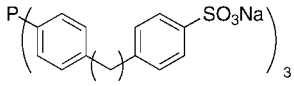
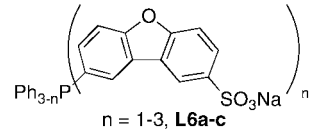
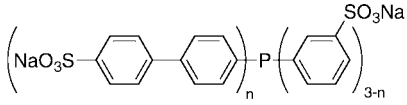
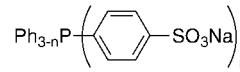
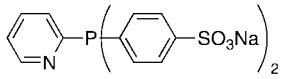
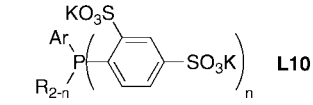
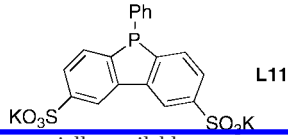
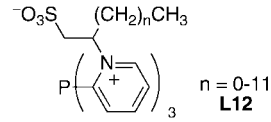
(1)

A number of sulfonation protocols have been reported to give *m*-TPPTS and related ligands in improved yield without oxidation of the phosphorus center. One approach is to allow the oxidation to occur, and then reduce the *m*-TPPOTS back to *m*-TPPTS. The sulfonates were converted to their to ethyl esters (**4**) to avoid reduction at sulfur (Scheme 1).[99] The phosphine oxide was then reduced with trichlorosilane to give the triethyl ester **5**, which gave pure *m*-TPPTS after hydrolysis of the sulfonate esters (Scheme 1). However, this process requires 4 additional steps after the sulfonation that occur in 35% overall yield. Herrmann[100] found that the use of Lewis acids, such as boric acid, protects the phosphorus center from being oxidized during sulfonation, even when the reaction was carried out under conditions necessary to achieve complete sulfonation of triarylphosphines. Oxidation primarily occurs during neutralization of the acidic reaction medium, rather than during the sulfonation itself. In concentrated sulfuric acid, the phosphorus is protonated and resistant to oxidation. As the pH is increased during workup, the triarylphosphines ($pK_a \sim 2-3$) are deprotonated, which makes them susceptible to the strongly oxidizing SO_3 that remains. By only raising the pH to approximately 3, which will deprotonate the sulfonic acids ($pK_a =$ ca. 1) but not the phosphonium, it is possible to avoid significant oxidation of *m*-TPPTS during workup.[101]

While *m*-TPPTS can be prepared using these methods in good yield and purity, preparation of the partially sulfonated ligands has proven to be more challenging. The reactivity of triphenylphosphine, *m*-TPPMS, and *m*-TPPDS toward sulfonation is similar. As a result, attempts to selectively produce the mono- and disulfonated phosphines often result in complex product mixtures. The monosulfonated ligand can be selectively prepared by carrying out the sulfonation to low conversion to give a mixture of *m*-TPPMS and unreacted PPh_3, which can easily be separated.[102] Under controlled sulfonation conditions, the synthesis *m*-TPPDS (**L1b**) can be maximized, allowing it to be isolated in 60% yield.[103] Herrmann obtained a 94% yield of *m*-TPPDS by slow addition of 65% oleum (SO_3 concentration <0.9 wt %) over 3 days to triphenylphosphine in H_2SO_4 in the presence of boric acid at 58 °C.[100]

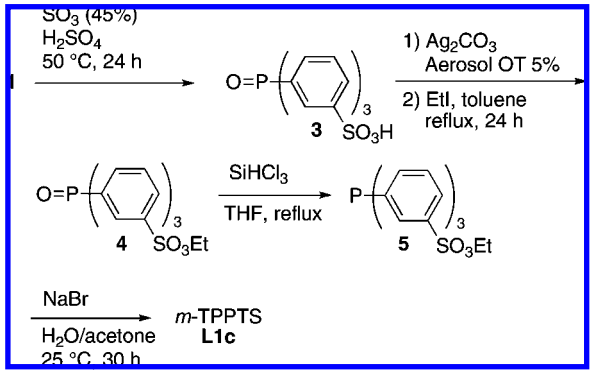
Phosphines with electron-releasing substituents on the aryl rings can be sulfonated under milder conditions than triphenylphosphine (**L2**, Table 1). Under these conditions, oxidation of the phosphorus is less likely, since the sulfonation

Table 1. Sulfonated Triarylphosphines

Ligand	Applications	Ligand	Applications
 n = 1: *m*-TPPMS (**L1a**)[a] n = 2: *m*-TPPDS (**L1b**)[a] n = 3: *m*-TPPTS (**L1c**)[a]	Aldehyde hydrogenation[61] Alkene hydrogenation[62,63] Alkene hydrocarboxylation[64,65] Alkyne hydration[66] Alkene polymerization[67,68] Allylic substitution[69,70] Butadiene telomerization[71] Carbonylation[72] Hydroformylation[14] Pauson-Khand reaction[73] Pd-catalyzed cross-coupling[74,75] Reductive Amination[76] Rh-catalyzed coupling[77,78]	 R = H, R' = OMe (**L2a**) R = OMe, R' = H (**L2b**) R = Me, R' = H (**L2c**) R = R' = Me: TXPTS (**L2d**)[a] R = Me, R' = OMe: TMAPTS (**L2e**)	Synthesis[79,80] Allylic substitution[81] Hydroformylation[82] Aldehyde hydrogenation[83] Pd-catalyzed cross-coupling[84,85]
 n = 1: **L3a** n = 2: **L3b**	Synthesis[86] Hydroformylation[87]	 **L4**	Synthesis[88]
 n = 3: **L5a** n = 6: **L5b**	Hydroformylation[89]	 n = 1-3, **L6a-c**	Hydroformylation[90] Pd-catalyzed cross-coupling[90]
 **L7a**: n = 1 **L7b**: n = 2 **L7c**: n = 3	Allylic substitution[91] Hydroformylation[91]	 n = 1: *p*-TPPMS (**L8a**)[a] n = 2: *p*-TTPDS (**L8b**)[a] n = 3: *p*-TTPTS (**L8c**)	Synthesis[92] Hydrogenation[93]
 **L9**	Synthesis[92] Rh-catalyzed alkyne arylation[78]	 **L10** Ar = Ph, Mes, 2,4-$(SO_3K)_2C_6H_4$ R = Me, *n*-Bu, Bn n = 1-2	Synthesis[94,95]
 **L11**	Synthesis[96] Suzuki coupling[97]	 n = 0-11 **L12**	Hydroformylation[98]

[a] Commercially available.

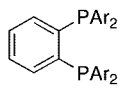
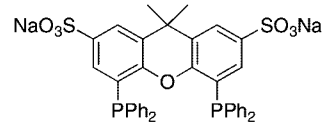
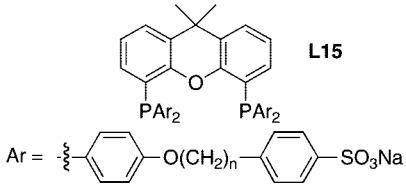
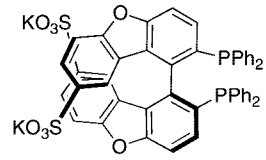
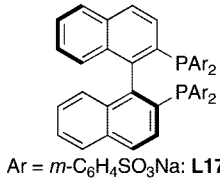
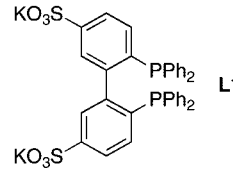
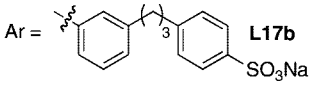
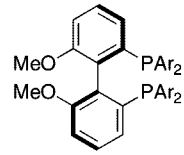
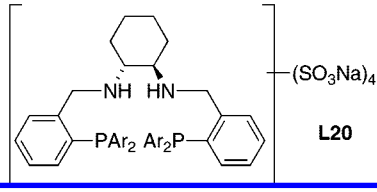
Scheme 1



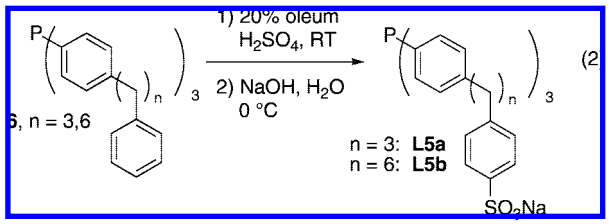
can be carried out using H_2SO_4 rather than oleum. It is also simple to prepare mono- or disulfonated triarylphosphines by incorporating electron-releasing groups on only one or two of the aryl rings.[79,80,82] Sulfonation of $Ph_{3-n}P(4\text{-}C_6H_4\text{-}t\text{-}Bu)_n$ ($n = 1-2$) resulted in exclusive sulfonation at the *meta*-position of the phenyl rings to give **L3**.[86] Incorporation of the sterically demanding *tert*-butyl groups apparently prevents sulfonation of the more electron-rich *tert*-butyl-substituted rings. Alternatively, incorporation of electron withdrawing groups will cause selective sulfonation of the unfunctionalized phenyl rings (**L4**).[88] Dibenzofuranylphosphines are readily sulfonated in 95% sulfuric acid to give **L6** due to the activating oxygen of the furan ring.[90] Sulfonation occurs selectively *para* to the furan oxygen on the ring not connected to phosphorus. Tris(4-(ω-phenylalkyl)phenyl)phosphine (**6**) was selectively sulfonated in the *para*-position of the terminal phenyl groups, which are not attached to the deactivating phosphorus center, to give **L5a,b** (eq 2).[89] Similarly, tri-(4-biphenyl)phosphine (**7**) was selectively substituted in the 4′-position of the phenyl ring not attached to phosphorus to give **L7c** under mild conditions using 95% H_2SO_4 (eq 3).[91]

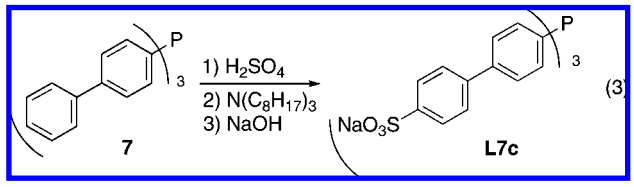
Selective sulfonation of chelating diphosphines with aromatic backbones can also be achieved in many cases (Table 2). Xantphos can be selectively disulfonated *para* to the central ring oxygen to give Xantphos-S (**L14**) in 76% yield.[104] Similarly, the oxygen of the bidibenzofuranyl backbone of **8** can be used to selectively direct the sulfona-

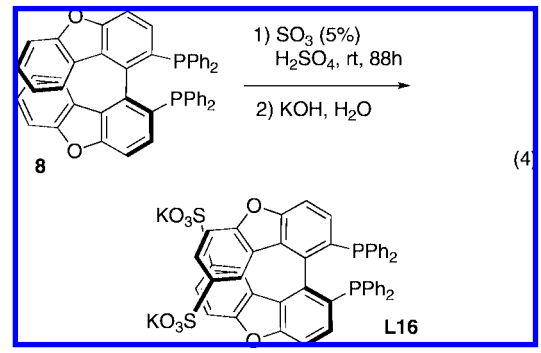
Table 2. Chelating, Sulfonated Aryldiphosphines

Ligand	Application	Ligand	Applications
 **L13**[a] Ar = *p*-$C_6H_4SO_3Na$	Hydrogenation[106] [5+2] Cyclization[107]	 Xantphos-S (**L14**)	Hydroformylationi[104] Hydrocarboxylation[108]
 **L15**	Hydroformylation[109]	 **L16**	Hydrogenation[110]
 Ar = *m*-$C_6H_4SO_3Na$: **L17a**	Hydrogenation[111] Hydroformylation[112]	 **L18**	Synthesis[96]
 **L17b**		 **L19** Ar = *p*-$C_6H_4SO_3Na$	Hydrogenation[36]
 **L20**	Hydrogenation[113]		

[a] Commercially available.





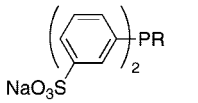
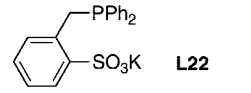
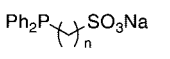
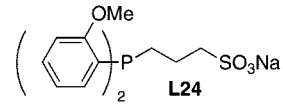
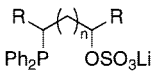
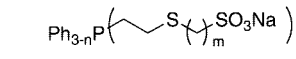
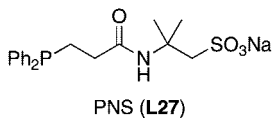
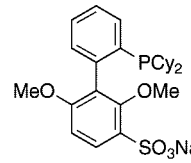
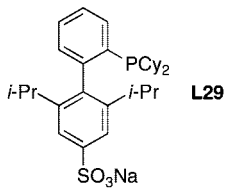
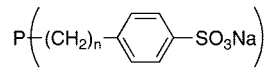
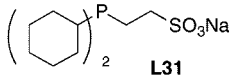
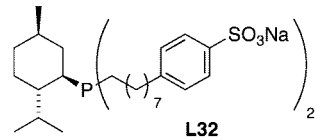
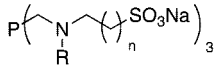
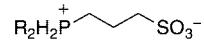
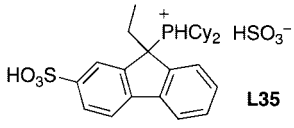
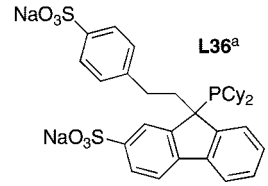
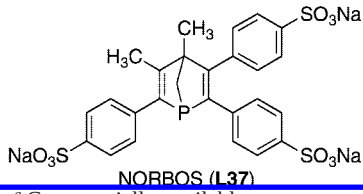


tion reaction to give **L16** (eq 4). The sulfonation of **8** could be carried out in 4 h at 50 °C using H_2SO_4, but these conditions gave racemic product. Using 5% oleum at room temperature gave **L16** without racemization, although the reaction was slow (88 h). In cases where there is not a strong directing group, products with variable degrees of sulfonation are often obtained. Sulfonation of BINAP gave primarily a tetra-substituted product (**L17a**, ca. 85%) where the more reactive phenyl substituents have been sulfonated.[105] The balance of the sample was composed of penta- and hexa-sulfonated products in which the binaphthyl backbone had also been sulfonated.

Electrophilic sulfonation of diphenylalkylphosphines (Table 3) can be carried out without oxidation of the more electron-rich phosphine center, since it remains protonated during the sulfonation reaction. Disulfonation of alkyldiphenylphosphines occurred cleanly to give protonated analogues of **L21**, but extensive oxidation occurred during workup.[114] Oxidation was avoided by protecting the phosphorus center as a borane adduct prior to neutralization with NaOH. After neutralization, treatment with allyl alcohol in water removed the borane protecting group to give **L21a**−**d**.

In cases where the phenyl ring is not directly attached to the phosphorus, sulfonation can be carried out even on trialkylphosphines without significant problems with oxidation. Sulfonation of S-phos occurred cleanly on the activated ring using sulfuric acid without oxidation of the electron rich phosphorus center to give **L28**.[126] Sulfonation of **9** using 20% oleum occurred with loss of the *para*-isopropyl group to give **L29**, again with no oxidation of the phosphorus (eq 5). Trialkylphosphines with ω-phenyl substituents can be sul-

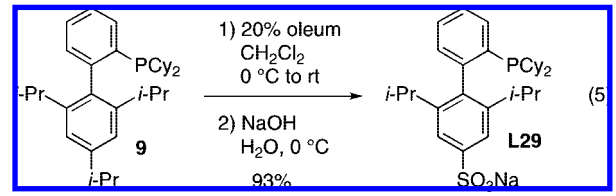
Table 3. Sulfonated Mono-, Di-, and Trialkylphosphines

Ligand	Application	Ligand	Applications
 R = Me (**L21a**) R = Et (**L21b**) R = *n*-Bu (**L21c**) R = *t*-Bu (**L21d**)	Synthesis[114]	 **L22**	Synthesis[115] Hydrodehalogenation[116]
 n = 2 (**L23a**) n = 3 (**L23b**) n = 4 (**L23c**)	Synthesis[117] Hydrodehalogenation[116] Hydroformylation[118] Suzuki coupling[119]	 **L24**	Suzuki coupling[120]
 n = 0, R = H: **L25a** n = 1, R = H: **L25b** n = 0, R = Me: **L25c** n = 1, R = Me: **L25d**	Synthesis[121]	 n = 1, m = 2: **L26a** n = 1, m = 3: **L26b** n = 2, m = 2: **L26c** n = 1, m = 3: **L26d**	Synthesis[122] Hydroformylation[118]
 PNS (**L27**)	Carbonylation[123] Hydroformylation[124] Hydrogenation[125]	 **L28**[a]	Suzuki coupling[126]
 **L29**	Sonogashira coupling[126]	 **L30**	Hydroformylation[127]
 **L31**	Metathesis[128,129]	 **L32**	Hydroformylation[130]
 n = 1, R = Me: **L33a** n = 2, R = *n*-Bu: **L33b**	Synthesis[131]	 R = *t*-Bu: DTBPPS (**L34a**) R = 1-adamantyl: DAPPS (**L34b**)	Pd-catalyzed couplings[132]
 **L35**	Suzuki coupling[133] Sonogashira coupling[133,134]	 **L36**[a]	Suzuki coupling[135,136] Sonogashira coupling[134]
 NORBOS (**L37**)	Hydroformylation[137]		

[a] Commercially available.

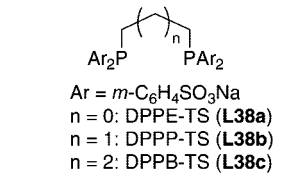
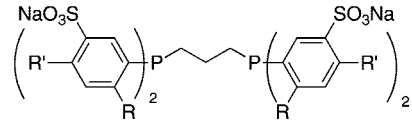
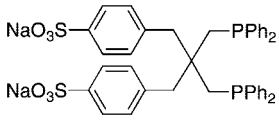
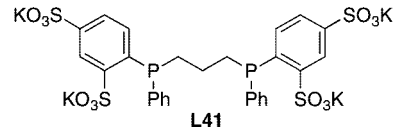
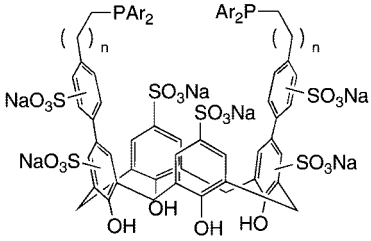
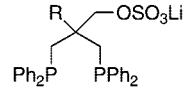
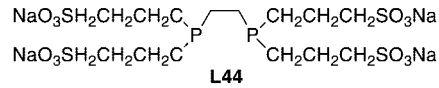
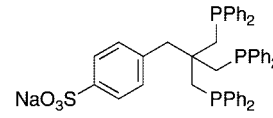
fonated with little or no oxidation at phosphorus (**L30**).[130,138] The sulfonation occurs more readily with longer alkyl chains, while the degree of oxidation also decreases with increasing alkyl chain length. These trends reflect the increased separation of the deactivating phosphonium ion from the aryl group with longer alkyl chains. Sterically demanding fluorenyl-based trialkylphosphines (**L35** and **L36**)[133,136] and a phosphanorbornadiene (**L37**)[139] could similarly be sulfonated without oxidation of the phosphorus center.

The decrease in oxidation sensitivity going from triarylphosphines to trialkylphosphines seems counterintuitive, since the more electron-rich trialkylphosphine should be more prone to oxidation. The increased basicity of the trialkylphosphines ($pK_a = 9-12$)[140] results in the phosphorus staying protonated until the SO_3 is consumed in the neutralization process, however. The less basic triarylphosphines are deprotonated before all of the SO_3 is consumed, resulting in oxidation of the phosphine.



Alkyl-bridged bis(*m*-sulfonatophenylphosphines) can be prepared by sulfonation, although careful control of the sulfonation conditions are required to maximize the yield of the tetrasulfonated product relative to partially sulfonated and oxidized products. DPPE-TS (**L38a**),[141] DPPP-TS (**L38b**),[142]

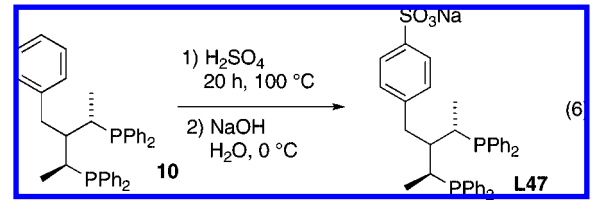
Table 4. Sulfonated, Achiral, Chelating Alkylphosphines

Ligand	Applications	Ligand	Applications
 Ar = *m*-$C_6H_4SO_3Na$ n = 0: DPPE-TS (**L38a**) n = 1: DPPP-TS (**L38b**) n = 2: DPPB-TS (**L38c**)	Synthesis[141,142] Alkene/CO copolymerization[147] Alkyne hydration[143] Alkene isomerization[148] Hydrogenation[149] Hydroformylation[150]	 R = H, R' = OMe: **L39a** R = OMe, R' = H: **L39b** R = Me, R' = H: **L39c**	Alkene/CO copolymerization[145]
 **L40**	Alkene/CO copolymerization[151]	 **L41**	Synthesis[94]
 Ar = *m*-$C_6H_4SO_3Na$ n = 1: **L42a** n = 2: **L42b**	Hydroformylation[146]	 R = Me: **L43a** R = Et: **L43b** R = CH_2OSO_3Li: **L43c**	Synthesis[121]
		 **L44**	Hydrogenation[152]
		 **L45**	Synthesis[153] Hydrogenation[154]

and DPPB-TS (**L38c**)[143] (Table 4) have all been prepared by sulfonation of the corresponding 1,ω-bis(diphenylphosphino)alkanes using oleum. The rate of sulfonation increases as the alkyl bridge becomes longer (DPPE < DPPP < DPPB) presumably due to the deactivating effect of the neighboring phosphonium salt.[144] Herrmann's[100] boric acid protocol was used to prepare **L38b** in 90% yield and 98% purity.[142] Attempts to prepare ligand **L39** by sulfonation of the activated aryl rings in fuming sulfuric acid resulted in decomposition. Tetrasulfonated ligand **L39** could be prepared in high purity (98%) by sulfonation in concentrated sulfuric acid, however.[145] Interestingly, sulfonation of a calix[4]arene-based diphosphine using the boric acid procedure gave exclusively a decasulfonated product (**L42**) in 83−88% yield.[146] The ^{1}H NMR spectrum of this compound showed that **L42** had a high degree of symmetry.

Chelating diphosphines with chiral alkyl backbones (BDPP, Chiraphos, Prophos, and CBDP, Table 5) were sulfonated using fuming sulfuric acid for a period of 2−7 days to give mixtures of products (**L46** and **L49**−**L51**, respectively) with 2−4 sulfonated rings and little oxide formation.[155] Repeated recrystallization gave the desired tetrasulfonated products. The tetrasulfonated chiral diphosphines are preferred to avoid the presence of different diastereomers due to chirogenic phosphorus centers. As seen with the achiral versions, ligands with longer bridges between the phosphines were sulfonated at higher rate (CBDP > Chiraphos > Prophos).[144] Tetrasulfonated DDPPI (**L52**) was prepared in good yield (83%) by carrying out the sulfonation in the presence of boric acid.[156]

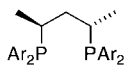
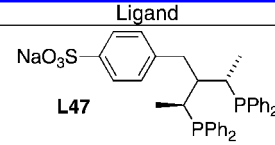
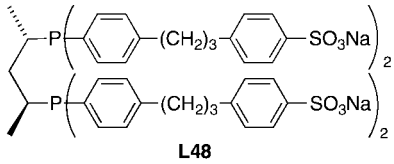
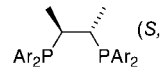
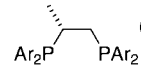
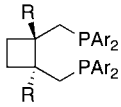
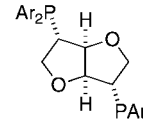
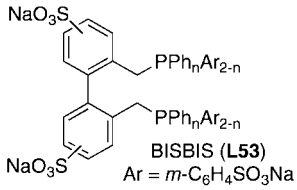
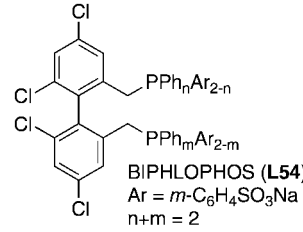
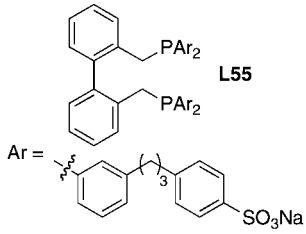
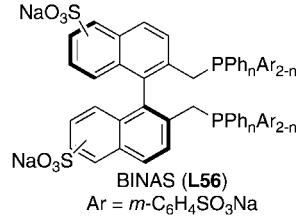
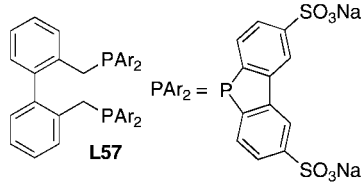
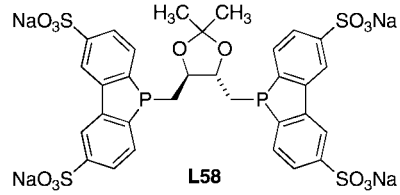
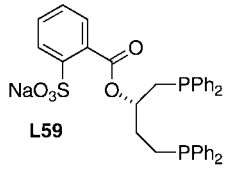
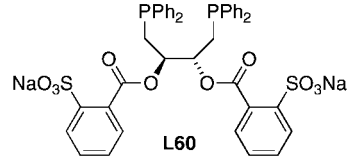
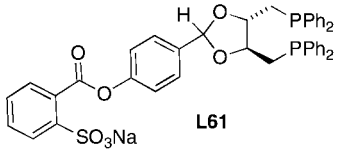
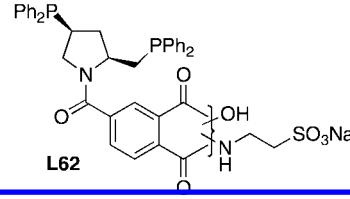
The formation of mixtures of partially sulfonated chelating diphosphines can be avoided by introducing an aryl group that is not directly attached to the phosphine. Sulfonation of **10** occurred cleanly at the benzyl group to give the monosulfonated ligand (**L47**) in 96% yield using sulfuric acid (eq 6).[157] A surface-active analogue of BDPP with ω-phenylalkyl-substituted arylphosphines was selectively tetrasulfonated to give **L48** in 84% yield (Table 5).[158] Similarly, surface active analogues of BISBI (**L55**) and BINAP (**L17b**, Table 1) were prepared by sulfonation of ω-phenylalkyl substituents.[112] Sulfonation of BISBI or BINAS resulted in the formation of mixtures of mixtures of products (**L53** or **L56**) with 4−6 sulfonate groups.[139,159] In the case of BISBI, the more electron-rich biphenyl backbone was disulfonated, while 2−4 of the phenyl rings were sulfonated. The crude mixtures were typically used without further separation. BIPHLOPHOS, which has deactivating chloro-substituents on the biphenyl backbone, gave a disulfonated product (**L54**) in which only the phenyl substituents was sulfonated. A mixture of regioisomeric products was believed to be formed under these conditions.



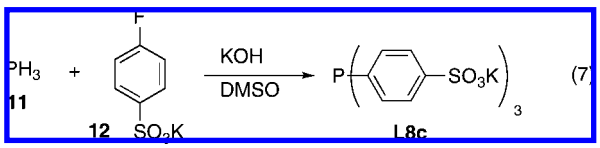
(6)

In addition to issues of phosphorus oxidation and control of the degree of sulfonation, electrophilic sulfonation results exclusively in *meta*-sulfonated phenylphosphines. Introducing the sulfonate group in the *meta*-position increases the cone angle of the phosphine, which may have a negative effect on its catalytic application. An alternate approach to preparing sulfonated arylphosphines involves S_NAr substitution of phosphorus nucleophiles on aryl fluorides with sulfonate groups in the *ortho*- or *para*-position. *para*-Sulfonated arylphosphines can be prepared by S_NAr reaction of phosphide anions with *p*-fluorobenzenesulfonate (**12**) to give *p*-TPPMS, *p*-TPPDS, and *p*-TPPTS (**L8a**−**c**, Table 1) starting from Ph_2PH, $PhPH_2$, and PH_3, respectively (eq 7).[92,93] Ligand **L9** was prepared in a similar fashion starting from 2-pyridylphosphine.[92] Reaction of phosphide nucleophiles with 2,4-disulfonato-1-fluorobenzene provided access to aryl phosphines with disulfonated phenyl substituents (**L10**).[94,95]

Table 5. Sulfonated, Chiral, Chelating, Alkylphosphines

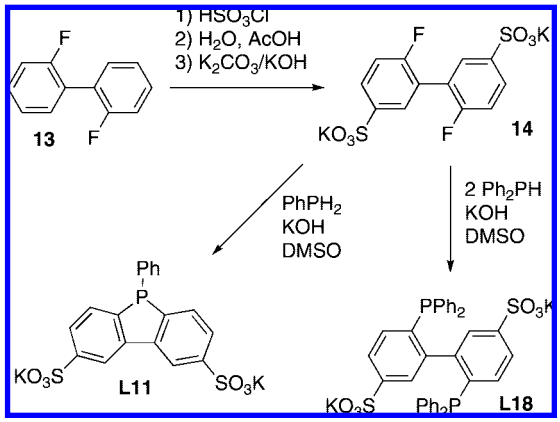
Ligand	Applications	Ligand	Applications
 (*S,S*)-BDPPTS (**L46**) Ar = *m*-$C_6H_4SO_3Na$	Synthesis[155] Hydrocarboxylation[161] Hydroformylation[162] Hydrogenation[155,163]	 **L47**	Synthesis[157] Allylic substitution[164] Hydroboration[164] Hydrogenation[164]
 **L48**	Hydrogenation[158]	 (*S,S*)-Chiraphos-TS (**L49**) Ar = *m*-$C_6H_4SO_3Na$	Hydrogenation[155]
		 (*R*)-Prophos-TS (**L50**) Ar = *m*-$C_6H_4SO_3Na$	Hydrogenation[155]
 R = H: **L51a** R = Me: **L51b** Ar = *m*-$C_6H_4SO_3Na$	Hydrocarboxylation[161] Hydrogenation[155]	 DDPPI-TS (**L52**) Ar = *m*-$C_6H_4SO_3Na$	Synthesis[156]
 BISBIS (**L53**) Ar = *m*-$C_6H_4SO_3Na$	Synthesis[165] Hydroformylation[159]	 BIPHLOPHOS (**L54**) Ar = *m*-$C_6H_4SO_3Na$ n+m = 2	Hydroformylation[160]
 **L55**	Hydroformylation[112]	 BINAS (**L56**) Ar = *m*-$C_6H_4SO_3Na$	Aryl amination[166] Hydroformylation[139]
 **L57**	Synthesis[96]	 **L58**	Synthesis[96]
 **L59**	Synthesis[167]	 **L60**	Synthesis[167]
 **L61**	Synthesis[96]	 **L62**	Hydrogenation[168]

The reaction of PhP(H)(C_6H_4-2,4-$(SO_3)_2$) with 1,3-dibromopropane gave an analogue of DPPP in which each phosphorus has a 2,4-disulfonated aryl ring (**L41**, Table 4).



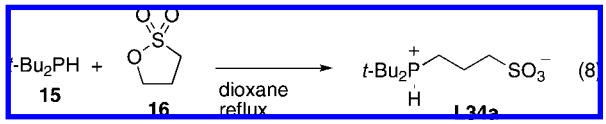
Since the sulfonate group must be installed before the phosphorus, sulfonation can be carried out on the aryl fluoride precursor without concern for undesired phosphorus oxidation. Sulfonation of 2,2′-difluorobiphenyl (**13**) occurred selectively *para* to the fluoride substituents (Scheme 2).[96] Reaction of the sulfonated difluoride **14** with diphenylphosphine gave a sulfonated 2,2′-bis(diphenylphosphino)biphenyl ligand (**L18**, Table 2**)**, while reaction with phenylphosphine gave disulfonated phenyl dibenzophosphole **L11** (Table 1). Reaction with phosphine gave 2,8-disulfonatodibenzophosphole, which was reacted with chiral dihalides or pseudohalides to give sulfonated dibenzophosphole analogues of BISBI (**L57**) and DIOP (**L58**, Table 5). Tripodal ligand **L45**

Scheme 2



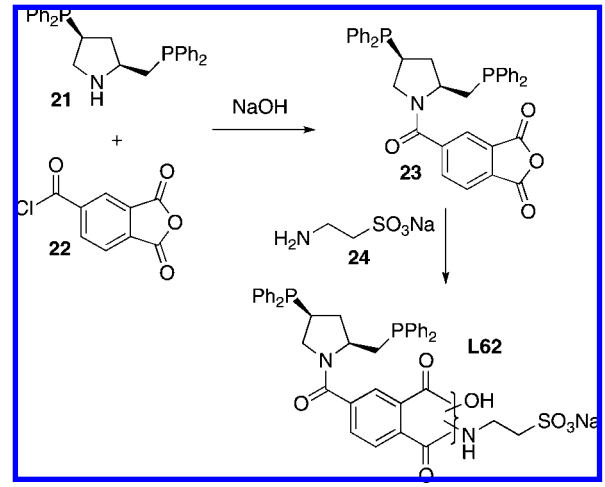
(Table 4) was prepared by sulfonation of 1-chloro-2,2-di(chloromethyl)-3-phenylpropane.[153] Reaction of the resulting sulfonated product with diphenylphosphide gave **L45**. Sulfonated aryl substituents have also been introduced by carrying out lithium/halogen exchange on 4-bromobenzenesulfonamide and reaction of the resulting aryl lithium reagent with a chlorophosphine. This approach has been applied to the synthesis of a MeO-BIPHEP derivative with *p*-sulfonatophenyl substituents on phosphorus (**L9**, Table 2).[36]

While arylsulfonates predominate as water-solubilizing agents, alkylsulfonate and -sulfate groups have also been used. Nucleophilic attack by phosphorus on ω-bromoalkanesulfonates, sultones, or cyclic sulfates provides a simple entry into diarylphosphinoalkane sulfonates and sulfates. Oehme reported the reaction of diphenylphosphide with 1,3-propane sultone to give **L23b** (Table 3).[169] Diphenylphosphine was reported to react slowly, while di-(L)-menthylphosphine was unreactive toward 1,3-propane sultone. Air-stable, zwitterionic phosphonium sulfonates (**L34a,b**) were recently prepared in good yield by the addition of sterically hindered dialkylphosphines to 1,3-propane sultone (**16**), however (eq 8).[132] Reaction of diphenylphosphide with *o*-tolylsultone gave ligand **L22**.[115] Phosphinoalkane sulfonates (**L23**, **L24**, **L31**) have also been prepared by reacting secondary phosphides with ω-bromoalkane sulfonates.[117,120,129] Bakos used the ring opening of cyclic sulfates with diphenylphosphide to prepare a family of sulfate containing mono- (**L25**) and diphosphines (**L43**, Table 4).[121] Ring opening of cyclic sulfonates with a nucleophilic functionality besides the phosphorus center has also been reported. A trizwitterionic phosphine (**L12**, Table 1) was prepared by the reaction of tri-2-pyridylphosphine with β-sultones. Börner prepared water soluble analogues of chiral diphosphines (**L59-L61**, Table 5) by the ring opening of *o*-sulfobenzoic anhydride using alcohol groups on the ligand backbones as the nucleophilic reagent.[167]

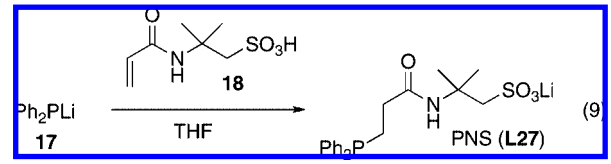


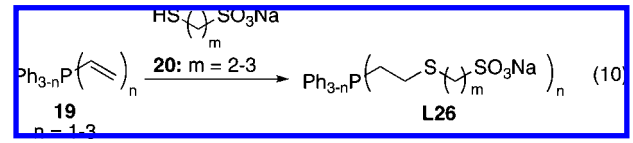
The PNS ligand (**L27**, Table 3) was prepared by Michael addition of diphenylphosphide to a commercially available sulfonated acrylamide derivative (**18**, eq 9).[124] Oehme prepared a family of alkylsulfonated phosphines (**L26**) by the addition of thioalkylsulfonates (**20**) to phenylvinylphosphines (eq 10).[122] Bis(3-sulfonatopropylphosphino)ethane (**L44**, Table 4) was prepared by the reaction of 1,2-diphosphinoethane

Scheme 3

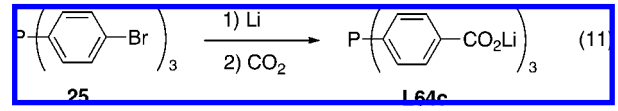


with allylsulfonate under free radical conditions.[152] Reaction of taurine (**24**) with a phthalic anhydride functionalized chiral diphosphine (**23**) provided a ligand with both carboxylate and sulfonate substituents (**L62**, Table 5, Scheme 3).[168] Tris(hydroxymethyl)phosphine (THMP) provided another entry into alkylsulfonate-substituted phosphines. Reaction of THMP with *N*-methyl taurine or 3-(*N*-butylamino)propane sulfonate gave a trialkylphosphines with three aminoalkylsulfonate side chains (**L33**, Table 3).[131]



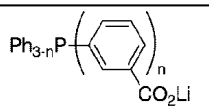
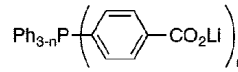
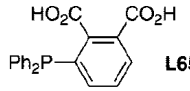
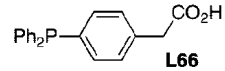
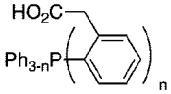
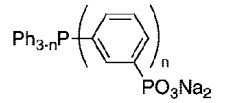
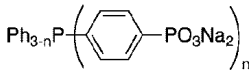
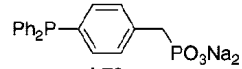
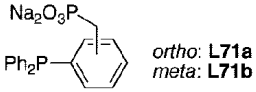
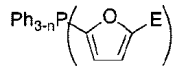
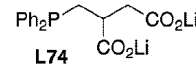
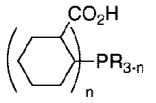
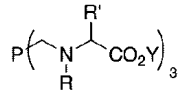
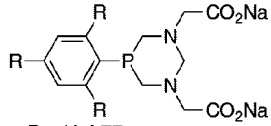
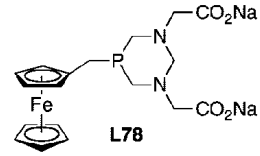
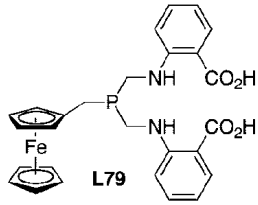
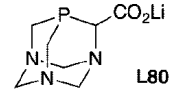
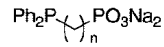
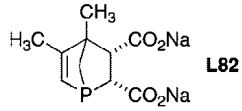
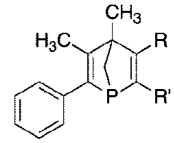
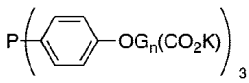
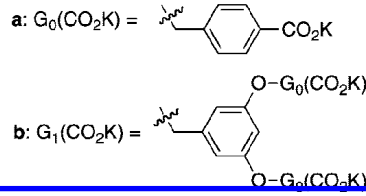


Carboxylate and phosphonate substituents have also been used to make phosphines hydrophilic, although there are fewer examples of these types of ligands than there are of sulfonated ligands. The relative lack of phosphonate and carboxylate ligands can be traced to the fact that they cannot be prepared by simple electrophilic aromatic substitution of known ligands. The carboxylated analogues of TPPTS have been prepared by lithiation of tri(bromophenyl)phosphine followed by quenching with CO_2 to give *m*- or *p*-TPPTC (**L63** or **L64**, Table 6, eq 11).[170] Nucleophilic addition of phosphides to fluorobenzoic acid derivatives has been used to prepare *o*-, *m*-, and *p*-TPPMC and TPPDC, as well as triarylphosphines with dicarboxylated aryl rings (**L65**).[171] Phosphinophenylacetic acid **L66** was also prepared by this S_NAr protocol.



The phosphonate analogues of TPPDP were first prepared by the reaction of lithiated triphenylphosphine with chlorodiethylphosphate. Hydrolysis of the diethylphosphonates with

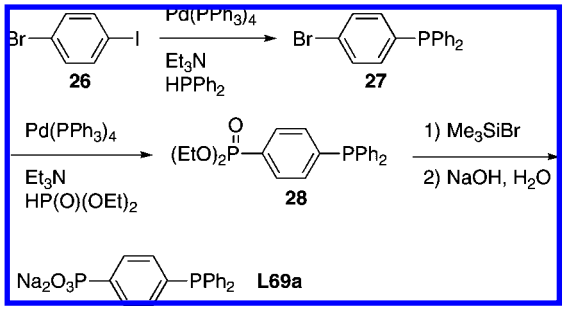
Table 6. Hydrophilic Phosphines with Phosphonate or Carboxylate Substituents

Ligand	Applications	Ligand	Applications
 n = 1: *m*-TPPMC (**L63a**) n = 2: *m*-TPPDC (**L63b**) n = 3: *m*-TPPTC (**L63c**)	Heck coupling[170] Rh-catalyzed coupling[172,173]	 n = 1: *p*-TPPMC (**L64a**)[a] n = 2: *p*-TPPDC (**L64b**) n = 3: *p*-TPPTC (**L64c**)	Heck coupling[170]
 **L65**	Synthesis[171]	 **L66**	Synthesis[171]
 n = 1: **L67a** n = 2: **L67b**	Suzuki coupling[174]	 n = 1: *m*-TPPMP (**L68a**) n = 2: *m*-TPPDP (**L68b**) n = 3: *m*-TPPTP (**L68c**)	Synthesis[175-177] Hydroformylation[178]
 n = 1: *p*-TPPMP (**L69a**) n = 2: *p*-TTPDP (**L69b**) n = 3: *p*-TTPTP (**L69c**)	Synthesis[175,176,179,180] Hydroformylation[178] Suzuki coupling[97]	 **L70**	Hydroformylation[178]
 *ortho*: **L71a** *meta*: **L71b**	Suzuki coupling[174]	 E = CO_2Li: **L72a** E = SO_2Li: **L72b** E = PO_3Na_2: **L72c**	Hydrogenation[181] Hydroformylation[181]
 **L73**: m = 1-7; n = 1-3	Synthesis[162-185] Hydrogenation[88]	 **L74**	Hydroformylation[124]
 n = 1, R = Ph: **L75a** n = 1, R = Cy: **L75b** n = 2, R = Ph: **L75c** n = 2, R = Cy: **L75d**	Synthesis[167]	 **L76a**: R=Me, R'=H, Y=Na **L76b-i**: R=Y=H R'=H (**b**), Me (**c**), Bn (**d**), *i*-Bu (**e**), CH(Me)Et (**f**), *i*Pr (**g**), -$CH_2CH_2CH_2$- (**h**), CH_2OH (**i**)	Synthesis[131] Hydroformylation[186]
 R = H: **L77a** R = Me: **L77b** R = *i*-Pr: **L77c**	Synthesis[189]	 **L78**	Synthesis[190]
 **L79**	Synthesis[190]	 **L80**	Synthesis[191]
		 **L81**: n = 2-12	Synthesis[117,192,193] Hydroformylation[178]
 **L82**	Synthesis[194]	 R = Ph, R' = PO_3Na_2: **L83a** R = H, R' = PO_3Na_2: **L83b** R = PO_3Na_2, R' = H: **L83c**	Synthesis[195]
 **L84a-c**			Suzuki coupling[196]

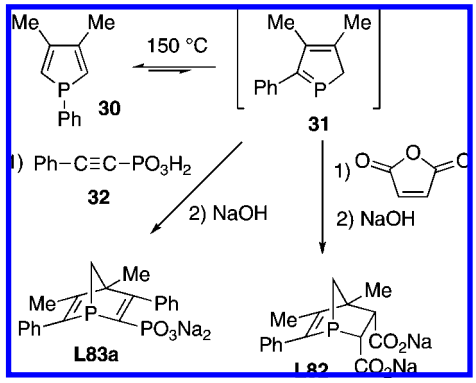
[a] Commercially available.

TMSBr gave *m*- or *p*-TPPMP (**L68a** and **L69a**, Table 6).[176,179] Mono-, di-, and triphosphonated triphenylphosphine analogues (**L69a**−**c**) have been prepared by the reaction of phosphorus nucleophiles (Ph_2PK, $PhPLi_2$, or red P) with

Scheme 4



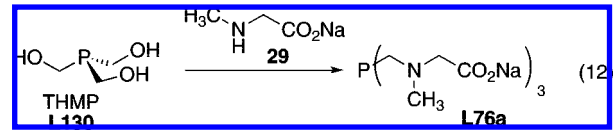
Scheme 5



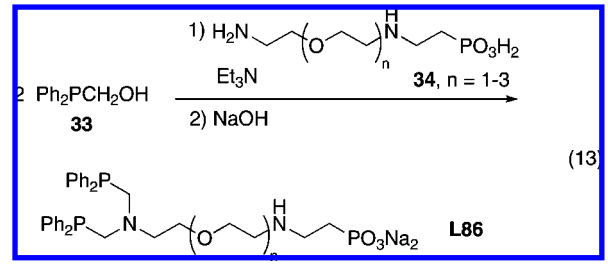
fluorophenylphosphonate esters via an S_NAr mechanism followed by hydrolysis of the phosphonate esters.[175,177,180,197] Phosphonated triphenylphosphines can also be prepared by Pd-catalyzed P−C coupling of aryl halides to introduce the phosphine, phosphonate, or both substituents (Scheme 4).[175] Methylphosphonate-substituted triphenylphosphine (**L70**) derivatives were prepared by addition of diphenylphosphide to 4-fluorobenzylphosphonamide followed by hydrolysis of the phosphonamide.[178] Alternatively, Pd-catalyzed addition of diphenylphosphine to diethyl iodobenzylphosphonate followed by hydrolysis was used to prepare the *ortho*- and *meta*-substituted analogues (**L71**).[174]

Phosphinoalkanoic acids were among the first hydrophilic ligands to be prepared. The original syntheses used the addition of phosphine, phenylphosphine, or diphenylphosphine to acrylonitrile, followed by hydrolysis to give 3-phosphinopropanoic acids (**L73**, Table 6).[182,183] Diphenylphosphinoalkanoic acids with bridges longer or shorter than 2 carbons can be prepared by the addition of diphenylphosphide to ω-haloalkanoic acids of the desired length.[184,185] More recently, organophosphide addition to itaconic acid[124] and ethyl 1-cyclohexene carboxylate[187] has been used to synthesize ligands **L74** and **L75**, respectively. Similarly, diphenylphosphide addition to ω-haloalkylphosphonates gave ω-diphenylphosphinoalkylphosphonate ligands (**L81**).[117,192,193]

Another approach used to prepare carboxylated phosphines is the condensation of hydroxmethylphosphines with amino acids. Condensation of *N*-methylglycine (**29**) with THMP gave tricarboxylated phosphine **L76a** in a similar manner to the sulfonated analogues (**L33**) previously described (eq 12).[131] Herrmann reported the synthesis of a family of amino acid-functionalized phosphines (**L76b**−**i**) by condensing THMP with amino acids.[188] Condensation of aryl or ferrocenylmethyl bis(hydroxymethylphosphines) with two equivalents of glycine in the presence of formaldehyde gave 1,3,5-diazaphosphorinanes (**L77** and **L78**).[189,190] When *o*-aminobenzoic acid was used, ring closure did not occur even in the presence of excess formaldehyde. Instead, diaminoacid ligand **L79** was obtained. Lithiation of 1,3,5-triaza-7-phosphaadamantane (PTA) and quenching with CO_2 gave carboxylated PTA ligand **L80**.[191] Diels−Alder cycloaddition of maleic anhydride with 5*H*-phosphole **31**, which was generated from **30**, followed by hydrolysis of the anhydride gave dicarboxylated phosphanorbornene ligand **L82** (Scheme 5).[194] Similarly, alkynylphosphonate ester **32** gave phosphonate-substituted norbornadiene **L83a** upon reaction with *in situ* generated phosphole **31**.[195]



The first reported example of a hydrophilic, chelating diphosphine was the phosphorus analogue of EDTA (**L85**, Table 7), which was prepared by the addition of the Reformatsky reagent derived from ethyl bromoacetate to 1,2-bis(dichlorophosphino)ethane followed by ester hydrolysis.[198] Mannich condensation of diphenylhydroxymethylphosphine (**33**) with an amphiphilic aminophosphonic acid (**34**) provided chelating diphosphine (**L86**) with an ethoxylated aminoethylphosphonate tail after treatment with sodium hydroxide (eq 13).[199] **L86** was prepared in good yield from inexpensive starting materials. Condensation of bis(hydroxymethyl)phosphinomethylferrocene with an equimolar amount of 5-aminoisophthalic acid gave a chelating 1,5-diaza-3,7-diphosphacyclooctane ligand (**L87**).[190]

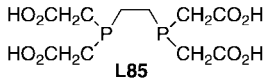
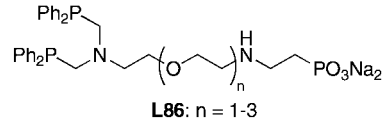
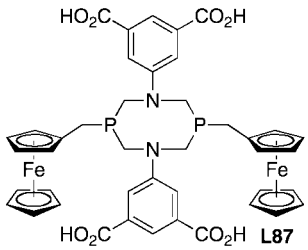
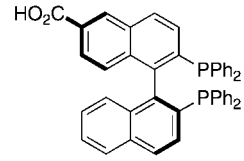
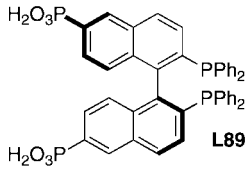
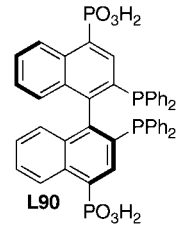
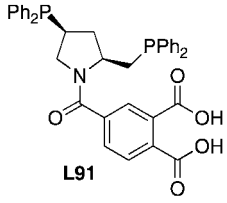
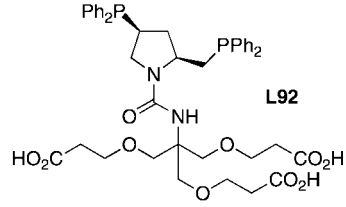
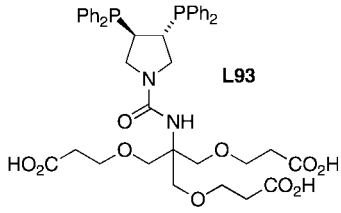
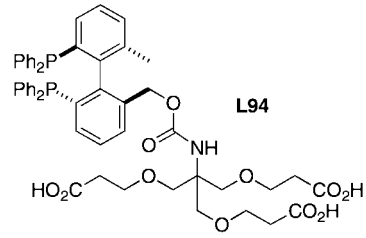
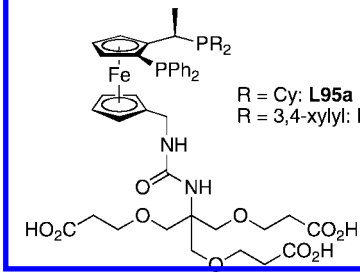


In contrast to the sulfonated phosphines, there are relatively few examples of chiral diphosphines with carboxylate or phosphonate substituents. Both BINAP-6-carboxylic acid (**L88**, Table 7)[200] and 4,4′- and 6,6′-diphosphonated versions of BINAP (**L89** and **L90**)[201,202] have been prepared, but their syntheses involve several steps from commercially available materials. In contrast, sulfonated BINAP is prepared by direct sulfonation of commercially available BINAP. Acylation of amine- or hydroxyl-functionalized phosphines with di- or polyacids is a more general method to introduce carboxylate substituents. Acylation of PPM (**20**) with trimellitic acid anhydride followed by hydrolysis of the anhydride gave the water-soluble analogue **L91** in 80% yield.[168] A series of chiral phosphines based on PPM (**L92**), Pyrphos (**L93**), BIPHEMP (**L94**), and Josiphos (**L95**) frameworks were prepared by attaching them to a tricarboxylic acid-functionalized amine through urea linkages.[203]

2.1.2. Phosphines With Cationic Substituents

Phosphines with cationic substituents present another method to prepare hydrophilic phosphines. The most commonly used cationic functionalities are ammonium ions.

Table 7. Bidentate Phosphines with Phosphonate or Carboxylate Substituents

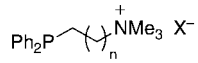
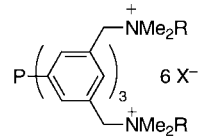
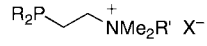
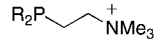
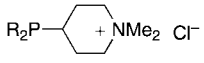
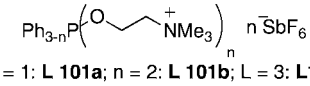
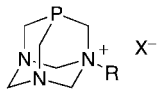
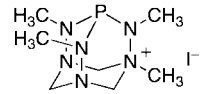
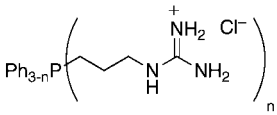
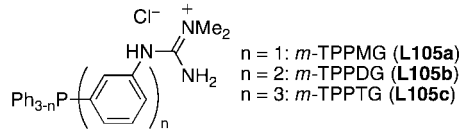
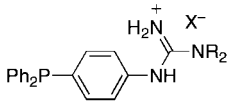
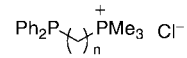
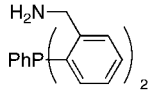
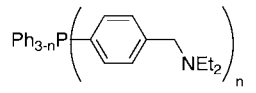
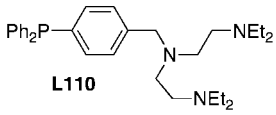
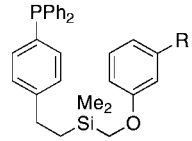
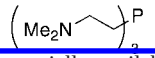
Ligand	Applications	Ligand	Applications
 **L85**	Synthesis[198]	 **L86**: n = 1-3	Carbonylation[199]
 **L87**	Synthesis[190]	 **L88**	Synthesis[200]
 **L89**	Hydrogenation[202]	 **L90**	Synthesis[201]
 **L91**	Hydrogenation[168]	 **L92**	Hydrogenation[203]
 **L93**	Hydrogenation[203]	 **L94**	Hydrogenation[203]
 R = Cy: **L95a** R = 3,4-xylyl: **L95b**	Hydrogenation[203]		

Quaternary ammonium ions can be used to give ligands that will remain ionic regardless of pH. Alternatively, incorporation of an amine functionality allows the solubility of the ligand to be controlled as a function of pH. Guanidinium ions have also been used to prepare cationic phosphines, as have phosphonium salts.

Amphos (**L96a**, Table 8) was first prepared by Baird as the iodide salt.[204] The neutral 2-phosphinoethyl dimethyl amine was prepared by phosphide addition to 2-chloroethyl dimethylamine (**35**). Attempts to quaternize the amine (**36**) with methyl iodide resulted in exclusive methylation at phosphorus. Thus, the phosphine was converted to the phosphine oxide (**37**), the amine was quaternized, and the phosphine oxide reduced with trichlorosilane (Scheme 6). This methodology has been extended to other alkyl linkers between the ammonium and phosphine groups.[205] *N*-Alkylation of a hexamine-substituted analogue of triphenylphosphine sulfide gave hexacationic ligand **L97** after removal of the sulfide protecting group.[206]

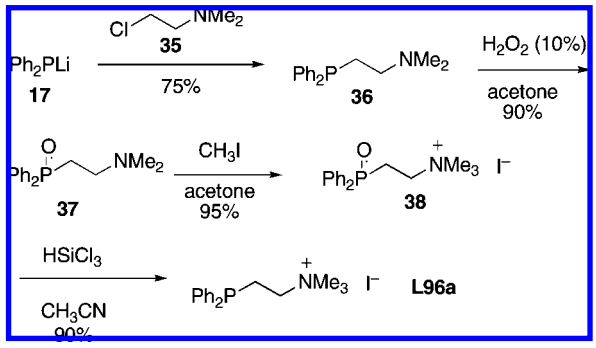
Trialkylphosphines with ammonium groups have generally been prepared by addition of phosphine nucleophiles to haloalkylamines or ammonium salts. Tri-*n*-alkylphosphines with ammonium substituents (**L98**) were prepared by the alkylation of 2-phosphinoethyltrialkylammonium salts (**40a** and **40b**, Scheme 7).[210,211] The ammonium-substituted primary phosphines **40a,b** were prepared by monoalkylation of phosphine with **35** under basic conditions.[229] Quaternization occurred exclusively at nitrogen using 1 equivalent of alkyl iodides to give **40a,b**. More sterically demanding dicyclohexyl (**L99a**) and di-*t*-butyl (**L99b**) analogues of Amphos were prepared by the reaction of borane adducts of dialkylphosphides with commercially available 2-chloroethyltrimethylammonium chloride.[129,230]

Table 8. Phosphines with Cationic or Basic Substituents

Ligand	Applications	Ligand	Applications
 n = 1: Amphos (**L96a**) n = 2: **L96b**	Hydroformylation[207,208] Hydrogenation[205,207]	 R = Me, X = I: **L97a** R = Bn, X = Br: **L97b** R = dendrimer, X = Br: **L97c**	Synthesis[206] Suzuki coupling[209]
 R = Me, R' = C_8H_{17}: **L98a** R = Me, R' = $C_{12}H_{25}$: **L98b** R = C_8H_{17}, R' = Me: **L98c**	Synthesis[210,211]	 R = Cy: Cy-Amphos (**L99a**) R = *t*-Bu: *t*-Bu-Amphos (**L99b**)[a]	Olefin metathesis[128,129] Pd-catalyzed coupling[212] Rh-catalyzed coupling[213,214]
 R = Cy: Cy-Pip-phos (**L100a**) R = *t*-Bu: *t*-Bu-Pip-phos (**L100b**)	Olefin metathesis[128,129] Pd-catalyzed coupling[212]	 n = 1: **L 101a**; n = 2: **L 101b**; L = 3: **L101c**	Alkene isomerization[215]
 R = Me, X = I: **L102a** R = Et, X = I: **L102b** R = Bn, X = Cl: **L102c** R = CH_2-2-Pyr X = Br: **L102d**	Synthesis[216,217] Hydroformylation[218] Hydrogenation[218] Nitrile hydration[219]	 **L103**	Alkene isomerization[220] Alkyne hydration[220]
 n = 1: **L104a**; n = 2: **L104b**	Heck coupling[221] Hydrocarboxylation[222]	 n = 1: *m*-TPPMG (**L105a**) n = 2: *m*-TPPDG (**L105b**) n = 3: *m*-TPPTG (**L105c**)	Synthesis[223] Hydrocarboxylation[222] Sonogashira coupling[224] Suzuki coupling[97]
 R = H, X = Cl: **L106a** R = Me, X = I: **L106b**	Synthesis[97]	 **L107**: n = 2-12	Hydrogenation[225]
 **L108**	Synthesis[174]	 n = 1: **L109a** n = 2: **L109b**	Hydroformylation[226]
 **L110**	Hydrocarboxylation[227]	 R = NMe_2: **L111a** R = NMe_3^+ I^-: **L11b**	Hiyama coupling[228]
 **L112**	Synthesis[211]		

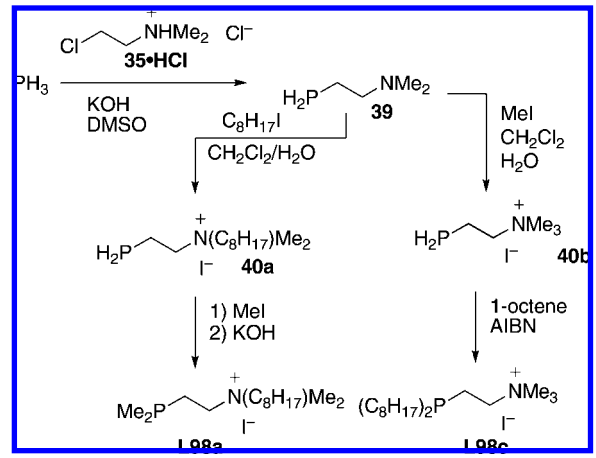
[a] Commercially available.

Scheme 6



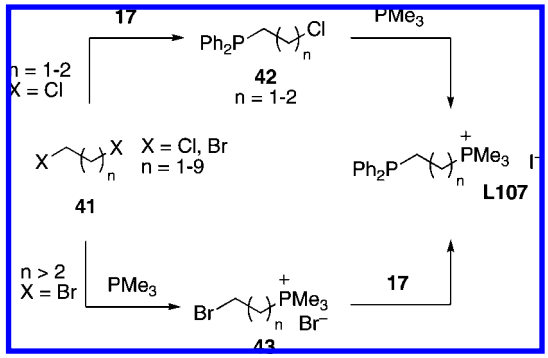
The borane adducts are better nucleophiles than the free phosphides, resulting in better yields of the substitution reaction. In addition, the borane adducts are air-stable. Cy-Pip-phos (**L100a**) and *t*-Bu-Pip-phos (**L100b**) were prepared by alkylation of dialkylphosphide borane adducts with 4-(*N*-methylpiperidyl)tosylate, followed by quaternization with methyl iodide, anion exchange, and removal of the borane

Scheme 7



protecting group. Ammonium-functionalized phosphonites, phosphinites, and phosphites (**L101**) were prepared by the condensation of *N*,*N*-dimethylethanolamine with Ph_2PCl,

Scheme 8



$PhPCl_2$, or PCl_3.[215] The amine functionality was quaternized with methyl iodide after complexation of the ligand to ruthenium to avoid competitive alkylation at phosphorus. Although PTA is water-soluble, that solubility can be enhanced by alkylation of one of the nitrogens to give PTA cations (**L102**).[216−218] Similarly, alkylation of the hexaaza analogue of PTA gave **L103**.[220]

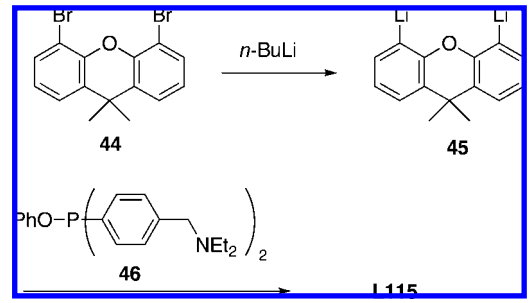
Guanidinium substituents are another class of cationic, water-solubilizing groups that have been employed. The increased hydrogen bonding ability of the guanidinium ion compared to ammonium substituents provides higher water-solubility. Mixed aryl alkylphosphines with guanidinium substituents (**L104**, Table 8) were prepared by the reaction of 3-aminopropylphosphines with 1*H*-pyrazole-l-carboxamidine in good yield (60−75%).[221] The guanidine-functionalized triphenylphosphine analogues (*m*-TPPMG, *m*-TPPDG, and *m*-TPPTG, **L105a−c**) were originally prepared by reacting the corresponding *m*-aminophenylphosphines with dimethyl cyanamide.[223] An improved synthesis of *m*-TPPMG and *m*-TPPDG used Pd-catalyzed coupling of phenyl- or diphenylphosphine with 3-iodophenylguanidine to give the guanidinium iodide product, which could be converted to the more soluble chloride by neutralization with base and then protonation with HCl.[97] This method was also used to prepare *p*-TPPMG (**L106**).

Trimethylphosphonium-substituted phosphines (**L107**) were prepared by successive addition of diphenylphosphide and trimethylphosphine to 1,*n*-dihaloalkanes.[225] For the ethylene and propylene bridges, the phosphide was first added to a large excess of the dichloride to give $Ph_2P(CH_2)_nCl$ (**42**, $n = 1-2$, Scheme 8). After removal of unreacted dihaloalkene by vacuum distillation, trimethylphosphine was added. For longer alkyl chains, this protocol was not possible due to the low volatility of the dihaloalkenes. In these cases, trimethylphosphine was added first to give an ω-haloalkyltrimethylphosphonium salt (**43**) that could easily be separated from the unreacted dihaloalkane. Treatment of the haloalkylphosphonium salt with lithium diphenylphosphide gave the desired ligands ($n = 6-12$) in good yield (80−90%).

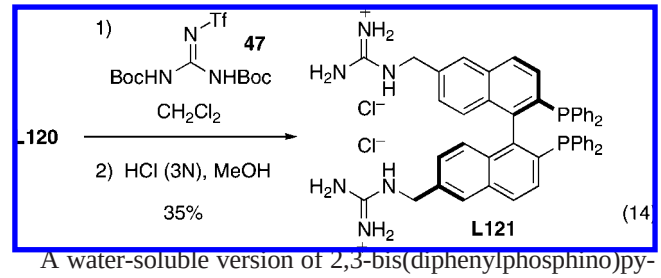
Phosphine ligands substituted with amines can partition into either the organic or aqueous phase of a biphasic system as a function of pH, which provides the best features of both homogeneous and biphasic catalysis. Arylphosphines with alkylamine substituents have been prepared by S_NAr substitution of arylphosphides and fluorobenzylamines (**L108**, Table 8).[174] Alternatively, tertiary amine-functionalized aryl Grignard reagents can be reacted with chlorophosphine precursors to give mono- or polyamine-functionalized phosphines (**L109**, **L110**, **L111a**).[226,228,231] Tri(2-dimethylaminoethyl)phosphine (**L112**) was prepared by stepwise alkylation of PH_3 with 2-chloroethyldimethylamine.[211]

A number of chelating diphosphines with amine or ammonium functional groups have also been prepared and applied in aqueous-phase catalysis (Table 9). Amphiphilic chelating diphosphines with amine substituents have been prepared in a number of ways. A methylamine-substituted analogue of DPPP was prepared by reaction of 2-(phenylphoshino)benzylamine with 1,3-dibromopropane in the presence of KO*t*-Bu to give **L114**.[211] The secondary phosphine was prepared by S_NAr substitution of phenylphosphide on 2-fluorobenzylamine. A tertiary amine-functionalized Xantphos derivative (**L115**) was prepared starting from bis(*N*,*N*-diethylaminomethylphenyl)phenoxyphosphine (**46**, Scheme 9).[232] This phosphonite was reacted with 4,6-dilithio-10,10′-dimethylxanthene (**45**) prepared from 4,6-dibromo-10,10′-dimethylxanthene (**44**) by lithium−halogen exchange. An amine-functionalized analogue of BISBI (**L116**) was prepared by the reaction of $LiP(O)(Ph)(p\text{-}C_6H_4CH_2NEt_2)$ with 2,2′-di(bromomethyl)biphenyl followed by reduction with trichlorosilane.[233] The bipyridine analogue (**L117**) was prepared by the addition of NaPPh(3-Py) to 2,2′-di(bromomethyl)bipyridyl. The 4,4′-, 5,5′-, and 6,6′-bis(aminomethyl) derivatives of BINAP (**L118−L120**) were prepared by cyanation of the corresponding bromides using copper cyanide followed by reduction of the nitrile with LAH to give the primary amine-substituted BINAP derivatives.[234,235]

Scheme 9

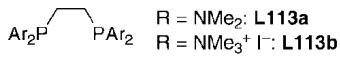
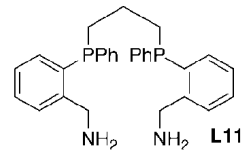
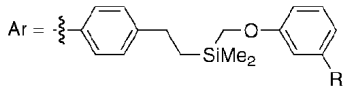
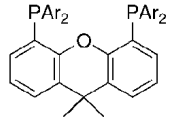
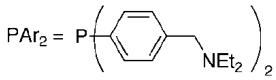
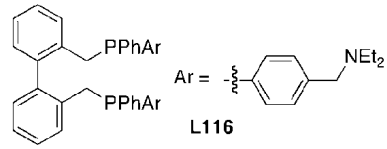
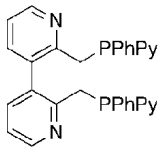
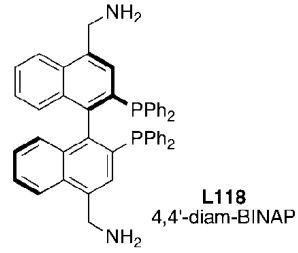
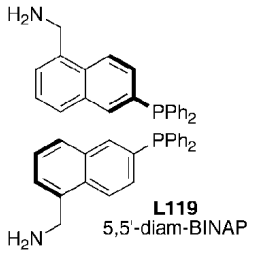
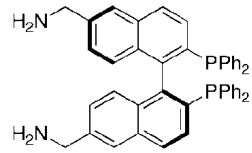
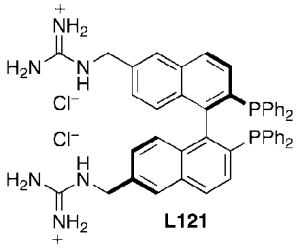
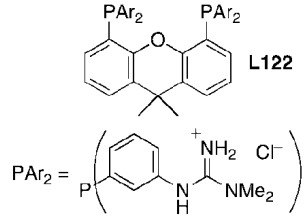
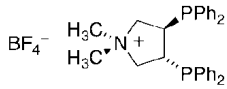
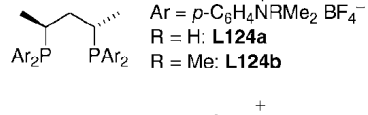
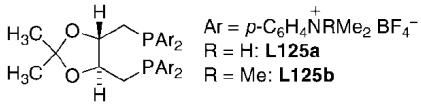
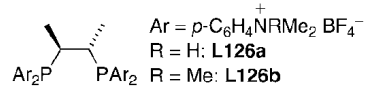
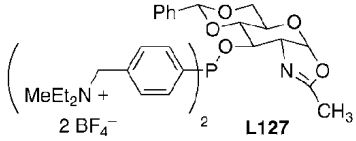
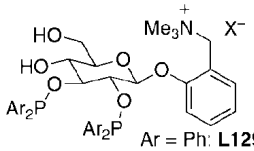
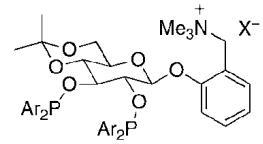


6,6′-Diguanidinium-substituted BINAP (**L121**) was prepared by the reaction of **L120** with *N*,*N*′-di-Boc-*N*″-triflylguanidine (**47**) followed by deprotection with aqueous HCl in 35% overall yield (eq 14).[237] Guanidinium-substituted Xantphos derivative **L122** was prepared by palladium-catalyzed coupling of 4,6-diphospha-10,10′-dimethylxanthene with 3-iodophenylguanidine to give the product in good yield, although it was contaminated with a small amount of 3-iodophenylguanidinium iodide.[238]



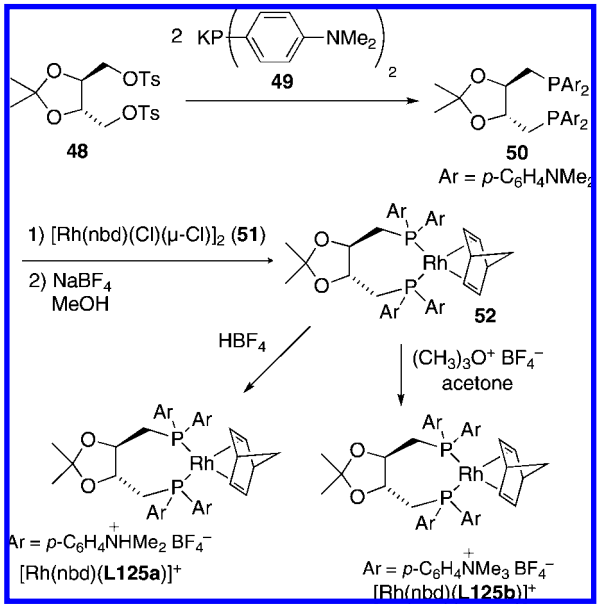
A water-soluble version of 2,3-bis(diphenylphosphino)pyrrolidine (**L123**) was prepared by methylation of the Rh(cod) complex of this ligand with trimethyloxonium tetrafluoroborate.[239] Ammonium-functionalized derivatives of BDPP (**L124**), DIOP (**L125**), and Chiraphos (**L126**) were prepared by the reaction of $KP(p\text{-}C_6H_4NMe_2)_2$ (**49**) with the appropriate chiral diol ditosylate (**48**, Scheme 10).[240] The tertiary

Table 9. Bi- and Tridentate Phosphines with Cationic or Basic Substituents

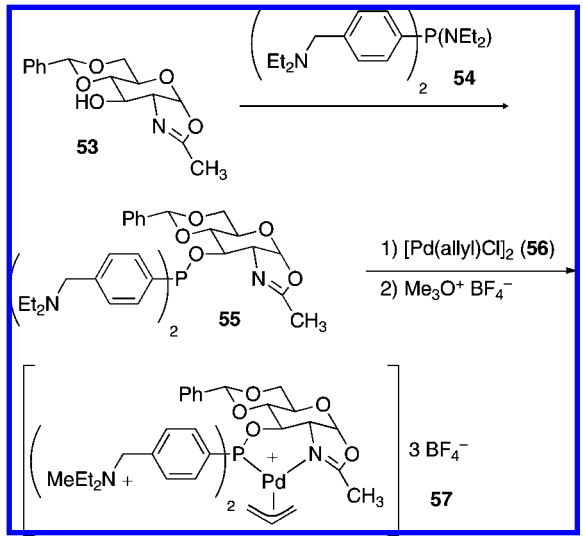
Ligand	Applications	Ligand	Applications
 R = NMe_2: **L113a** R = $NMe_3^+ I^-$: **L113b**		 **L114**	Synthesis[211]
	Hiyama coupling[226]		
 **L115** 	Hydroformylation[232]	 **L116**	Hydroformylation[233]
 **L117** Py = 3-pyridyl	Hydroformylation[233]	 **L118** 4,4'-diam-BINAP	Hydrogenation[234]
 **L119** 5,5'-diam-BINAP	Hydrogenation[234]	 **L120** 6,6'-diam-BINAP	Synthesis[235] Hydrogenation[233]
 **L121**	Hydrogenation[237]	 **L122**	Hydroformylation[238]
 **L123**	Hydrogenation[239]	 Ar = *p*-$C_6H_4NRMe_2$ BF_4^- R = H: **L124a** R = Me: **L124b**	Synthesis[240] Hydrogenation[241]
 Ar = *p*-$C_6H_4NRMe_2$ BF_4^- R = H: **L125a** R = Me: **L125b**	Synthesis[240] Hydrogenation[240]	 Ar = *p*-$C_6H_4NRMe_2$ BF_4^- R = H: **L126a** R = Me: **L126b**	Synthesis[240] Hydrogenation[240]
 **L127**	Allylic substitution[242]		
 Ar = Ph: **L129a** Ar = 3,5-$Me_2C_6H_3$: **L129b** Ar = 3,5-$(CF_3)_2C_6H_3$: **L129c**	Hydrogenation[243]	 Ar = Ph: **L128a** Ar = 3,5-$Me_2C_6H_3$: **L128b** Ar = 3,5-$(CF_3)_2C_6H_3$: **L128c**	Hydrogenation[243]

amines were quaternized with Meerwein's salt (Me_3O^+ BF_4^-) after complexation to rhodium (**51**) to prevent methylation at phosphorus. In methylene chloride, a mixture of partially methylated products was obtained. In acetone, 95% of the amines could be quaternized and the tetraammonium product could be recovered from this mixture by recrystallization. Complex **51** could also be protonated with HBF_4 to give the tetraammonium complex (**L125a**).

Scheme 10



Scheme 11

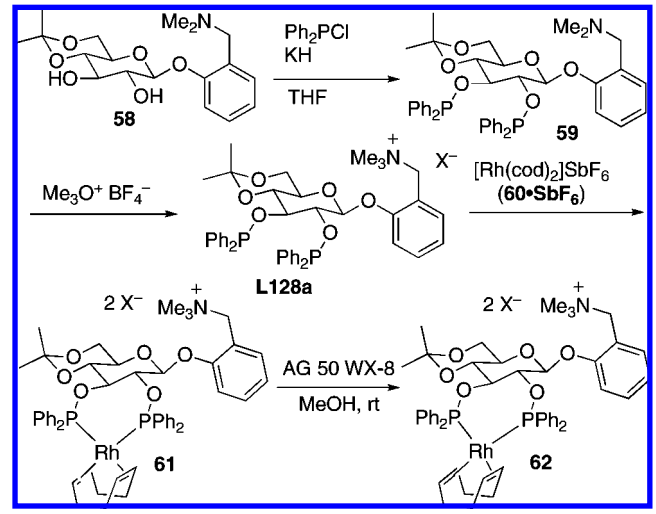


An ammonium-substituted, sugar-derived chiral phosphonite (**L127**) was prepared by the addition of bis(*N*,*N*-dimethylaminomethylphenyl)phosphinous diethyl amide (**54**) to glucosamine derived alcohol **53** (Scheme 11).[242] After complexation to palladium, quaternization of the amines was carried out using Meerwein's salt to give Pd complex **57**. RajanBabu[243] reported the synthesis of a chelating diphosphonite ligands derived from salicin. Reaction of a diarylchlorophosphine with protected amino salicin **58** followed by methylation with Meerwein's salt gave **L128a** (Scheme 12). The acetal protecting group could be removed by treating the Rh(cod) complex of **L128a** (**61**) with an acidic resin in methanol to give the Rh complex of **L129a** (**62**). It is noteworthy that with the less electron-rich phosphonite it was possible to alkylate a tertiary nitrogen in the presence of phosphorus.

2.1.3. Phosphines with Neutral Hydrophilic Substituents

While ionic functionalities are the most widely used water-solubilizing substituents for hydrophilic phosphines, there has been a growing interest in the use of non-ionic hydrophilic functional groups. Carbohydrates and other polyol substituents have been used most commonly, although polyether and polyamine structures have also been shown to be useful in aqueous-phase catalysis. Neutral hydrophilic substituents are attractive because they are often soluble in polar organic solvents as well as water, which simplifies the synthesis of the hydrophilic ligand. In addition, polyether and polyhydroxyl substituents can display inverse temperature dependent solubility, which allows ligands with these substituents to become more soluble in organic phases at higher temperature.

Scheme 12

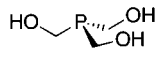
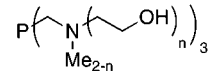
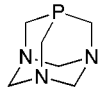
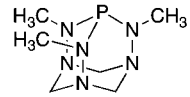
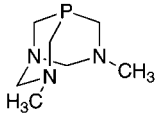
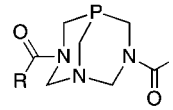
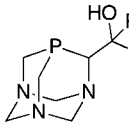
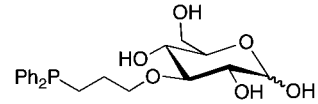
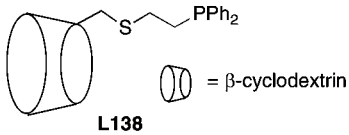
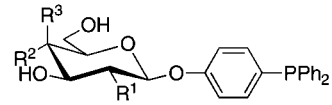
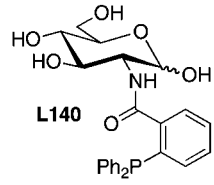
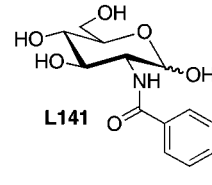
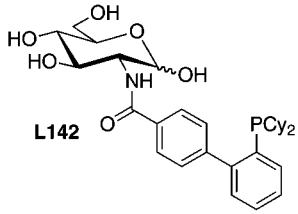
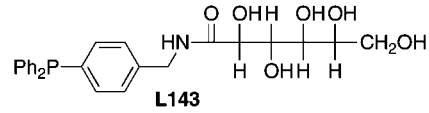
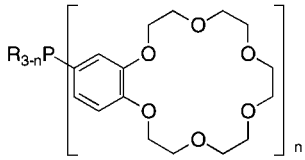
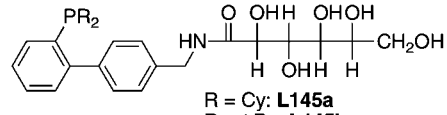
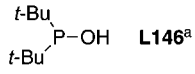


Tris(hydroxymethyl)phosphine (THMP, **L130**, Table 10) was the first hydrophilic applied to aqueous-phase catalysis.[244] The original synthesis was disclosed in the patent literature and involves the reaction of phosphine with formaldehyde in the presence of a Pt catalyst.[245] **L130** also serves as the starting material for the synthesis of other hydrophilic ligands. Condensation of THMP with *N*-methyl ethanolamine or diethanolamine gave highly water-soluble hydroxy-modified tris(aminomethyl)phosphines (**L131**).[246] 1,3,5-Triaza-7-phosphaadamantane (PTA, **L132**) can be prepared by condensation of THMP with hexamethylenetetramine (1,3,5,7-tetraazaadamantane, **L225**, Table 16).[216,247] The related THPA ligand (**L133**), first reported in 1975, was prepared by the condensation of $SP(N(Me)NH_2)_3$ with formaldehyde followed by desulfurization.[220,248]

A number of derivatives of PTA, some with improved water-solubility, have been prepared. Dimethylation of PTA and treatment with base resulted in loss of one equivalent of formaldehyde to give dmoPTA (**L134**, Table 10).[249,250] Acetylation of PTA resulted in acylation of two nitrogen centers of PTA and loss of formaldehyde to give DAPTA (**L135b**).[251] The diformamide analogue (DFPTA, **L135a**) has recently been prepared using *in situ* generated formic anhydride.[217] PTA can be selectively monolithiated on the methylene carbon between P and N, which allows further elaboration of the PTA skeleton. Treatment of lithiated PTA with aldehydes or ketones provided potentially chelating hydroxylated PTA derivatives (**L136**).[191,252]

Neutral, hydrophilic triarylphoshpines have been prepared primarily by appending the phosphine to carbohydrate structures or polyethers. The first carbohydrate-modified phosphine (**L137**, Table 10) was prepared by the addition of diphenylphosphine to O^3-allyl-O^1,O^2;O^5,O^6-diisopropylideneglucofuranose (**63**) in the presence of

Table 10. Phosphines with Neutral Hydrophilic Substituents

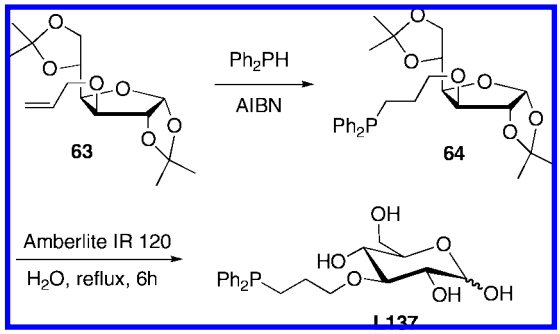
Ligand	Applications	Ligand	Applications
 THMP (**L130**)[a]	Alkene isomerization[253] Alkyne hydration[253] Hydroformylation[254] Hydrogenation[254]	 n = 1: **L131a** n = 2: **L131b**	Synthesis[131]
 PTA (**L132**)[a]	Synthesis[216] Hydroamination[255] Hydrogenation[247,256,257] Nitrile hydration[219]	 THPA (**L133**)	Alkene isomerization[220]
 dmoPTA (**L134**)	Synthesis[249,250]	 R = H: DFPTA (**L135a**) R = Me: DAPTA (**L135b**)	Synthesis[217,251] Nitrile hydration[219]
 R = R' = Ph: **L136a** R = H, R' = Ph: **L136b** R = H; R' = *p*-C_6H_4OMe: **L136c**	Synthesis[191,252]	 **L137**	Synthesis[258]
 **L138**	Synthesis[259]	 R^1 = NHAc, R^2 = OH, R^3 = H: **L139a** R^1 = OH, R^2 = OH, R^3 = H: **L139b** R^1 = OH, R^2 = H, R^3 = OH: **L139c**	Heck coupling[260] Suzuki coupling[260]
 **L140**	Synthesis[261] Suzuki coupling[262]	 **L141**	Synthesis[261] Suzuki coupling[262]
 **L142**	Suzuki coupling[263]	 **L143**	Suzuki coupling[264]
 R = Ph, n = 1: **L144a** R = Ph, n = 2: **L144b** R = Me, n = 2: **L144c**	Hiyama coupling[265] Stille coupling[266]	 R = Cy: **L145a** R = *t*-Bu: **L145b**	Suzuki coupling[267]
 **L146**[a]	Conjugate Addition[268] Hiyama coupling[269] Sonogashira coupling[270] Stille couping[271]		

[a] Commercially available.

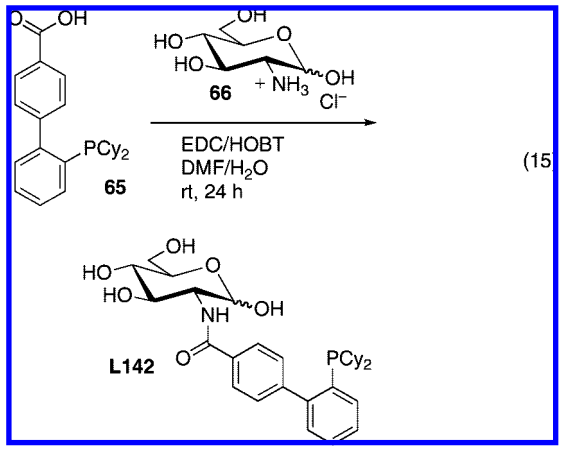
AIBN (Scheme 13).[258] The acetonide protecting groups of **64** were removed using an acidic resin to give the glucopyranose-modified phosphine (**L137**). Reetz[259] reported the synthesis of a β-cyclodextrin modified phosphine (**L138**) by the reaction of diphenyl-2-thioethylphosphine with monotosylated β-cyclodextrin. This ligand was designed to provide both water-solubility and molecular recognition of hydrophobic substrates. Beller reported a series of 4-(diphenylphosphino)phenylglycosides (**L139a**−**c**) formed by the reaction of (4-hydroxyphenyl)diphenylphosphine with acetate protected 1-α-D-glucosyl bromide, 1-α-D-glucosaminyl chloride, and 1-α-D-galactosyl bromide followed by deprotection in basic methanol.[260] The β-linked glycosides were formed selectively in each case.

Phosphines attached through the glycosidyl bond are prone to cleavage of the sugar from the phosphine by hydrolysis. An alternative attachment strategy utilizes amide formation between a carboxylated triphenylphosphine derivative and a protected glucosamine derivative followed by hydrolysis to give *o*- and *p*-glucosamide-substituted phosphines (**L140** and **L141**) in good yields (80−88%).[261] Amide coupling of 4′-carboxy-2-(dicyclohexylphosphino)biphenyl (**65**) with D-

Scheme 13



glucosamine (**66**) gave glucosamide **L142** (eq 15**)**.[263] Gluconamide-based ligand **L143** was prepared in quantitative yield by the reaction of (4-aminomethylphenyl)diphenylphosphine with D-glucono-1,5-lactone.[264] Condensation of 4′-aminomethyl-2-(dicyclohexylphosphino)biphenyl with gluconic acid gave gluconamide **L145**;[267] **L145** and **L142** were the first hydrophilic analogues of the 2-biphenylphosphines pioneered by Buchwald.[126,272−276] Crown-ether-functionalized phosphine **L144** was prepared by lithiation of 3-bromobenzo-18-crown-6 followed by quenching with $R_{3-n}PCl_n$ (R = Me, Ph; $n = 1-2$).[266]



Chelating diphoshines with neutral hydrophilic substituents have been predominately based on polyhydroxylated substituents, such as carbohydrates or short chain alcohols (Table 11). Chelating diphosphines with ω-hydroxyalkyl substituents were prepared by the free-radical hydrophosphination of formaldehyde or ω-hydroxyalkenes with the diprimary phosphine, $H_2P(CH_2)_nPH_2$ ($n = 2-3$) to give **L147**-**L149**.[152,277] Hydrophilic derivatives of DuPhos were prepared starting from D-mannitol. In the case of BASPHOS (**L150**), mannitol (**67**) was deoxygenated at C3 and C4, followed by protection of the primary alcohols and conversion to the cyclic sulfate (**68**, Scheme 14).[278] The sulfate was reacted with 1,2-bis(phosphino)benzene (**69**) to give the THP protected version of **L150** (**70**). Complexation to rhodium and removal of the THP protecting groups gave the Rh complex of **L150** (**71**). Ligands **L151a** and **L151b** were prepared in a similar manner, but the deoxygenation was performed on the primary hydroxyl groups of D-mannitol.[279]

Carbohydrates represent an attractive framework for the synthesis of hydrophilic, chiral diphosphines, as they are readily available in enantiomerically pure form, are hydrophilic, and can be readily functionalized. Glucose-derived bisphosphonite **L152** (Table 11) was prepared initially as the acetonide protected diphosphonite.[280] After complexation with Rh(cod), the acetonide group could be removed with 40% aqueous HBF_4 without hydrolysis of the phenylglycoside or phosphonite linkages. Trehalose-derived diphosphonite ligands with α,α'- and β,β'-linkages (**L153** and **L154**) were independently reported by Uemura[282] and RajanBabu.[284] In each case, the diphosphonites were prepared by reacting Ar_2PCl with protected trehalose derivatives. After complexation to Rh, the protecting groups were removed under acidic conditions. Glycosyl oxime-derived P−N chelating ligands (**L155a**−**d**) were prepared by the condensation of 2-(diphenylphosphino)benzaldehyde with the corresponding hydroxylamine glycoside.[285] Chelating diphosphines attached to cyclodextrin rings were prepared by the condensation of $[Ph_2P(CH_2OH)_2]Cl$ with amine functionalized cyclodextrin derivatives to give **L156** and **L157**.[286]

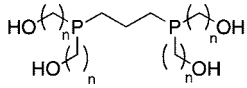
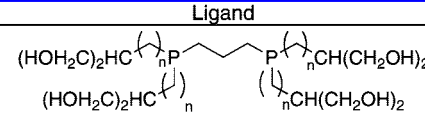
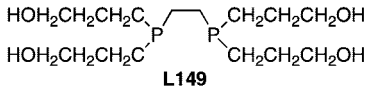
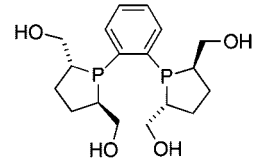
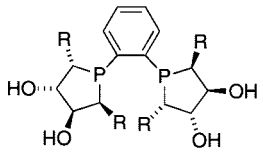
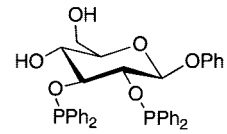
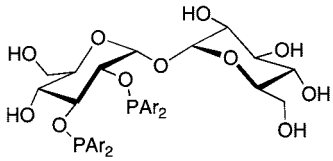
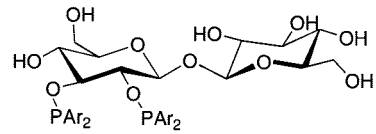
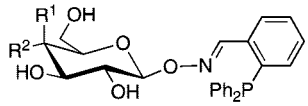
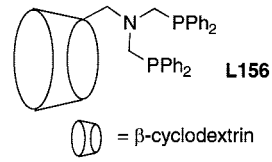
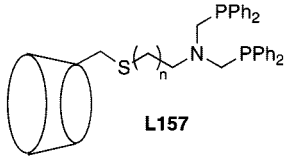
2.1.4. Ligands Supported on Water-Soluble Polymers

One common strategy to heterogenize phosphine ligands is to attach them to insoluble resins, such as cross-linked polystyrene.[7] Soluble polymeric supports have also received attention as tunable macromolecular supports for ligands and catalyst systems.[287,288] Poly(sodium acrylate) is a highly water-soluble polymer. Polyacrylate-supported phosphines are readily prepared by condensation of amine-modified phosphines with poly(acrylic acid), followed by deprotonation with base. This strategy has been applied to the synthesis of a poly(acrylate)-supported triphenylphosphine (**L158**, Table 12)[289] as well as supported chiral diphosphines (**L159** and **L160**).[290,291] Alper utilized poly(4-pentenoic acid), which was prepared by hydrocarboxylation of 1,2-polybutadiene, as a support for a chelating diphosphine (**L161**).[292] A polyammonium-supported triphenylphosphine derivative was prepared by reductive amination of polyethyleneimine (PEI) with (4-carboxyphenyl)diphenylphosphine followed by protonation of the amines to give **L162**.[289]

Polyethylene glycol (PEG) is a popular non-ionic, hydrophilic support for reagents and ligands because it soluble in water as well as certain organic solvents (i.e., CH_2Cl_2 and DMF), yet is insoluble in nonpolar organic solvents, such as diethyl ether. A wide variety of PEG-modified phosphines have been prepared for use in aqueous-phase catalysis. Jin has prepared a family of PEG-modified phosphines (**L163**−**L165**, Table 13) by using hydroxyl or amine functionalities on the phosphine as initiators for the polymerization of ethylene oxide (EO).[294−296] A similar approach was used to prepared a tri-PEG-substituted tripodal ligand (**L166**, Scheme 15). EO polymerization was carried out using molybdenum complex **69** as the initiator.[297] After methyl termination of the PEG-modified complex (**70**), the molybdenum was removed by photolytic oxidation using N_2O. An alternative approach to a PEG-modified triphenylphosphine (**L163**) derivative involved the Pd-catalyzed coupling of a PEG-substituted aryl iodide and diphenylphosphine.[298] Alternatively, diphenyl(4-hydroxyphenyl)phosphine, prepared by Pd-catalyzed coupling of 4-iodophenol and diphenylphosphine, could be coupled with PEG using Mitsunobu conditions. Amphiphilic PEG-substituted phosphinites, phosphonites, and phosphites have been prepared by the condensation of monoalkylated PEG with chlorophosphines (**L167** and **L168**).[299,300]

PEG substituents are often appended to phosphines using a nucleophilic group on the ligand to react with a PEG containing an electrophilic site on one end. Amphiphilic ligand **L169** was prepared by chlorinating the hydroxyl

Table 11. Bi- and Tridentate Phosphines with Neutral Hydrophilic Substituents

Ligand	Applications	Ligand	Applications
 **L147**: n = 1-8	Alkene/CO copolymerization[277]	 **L148**: n = 3-6	Alkene/CO copolymerization[277]
 **L149**	Hydrogenation[152]	 BASPHOS (**L150**)	Hydrogenation[278]
 R = Me: **L151a** R = Et: **L151b**	Hydrogenation[279]	 **L152**	Synthesis[280] Hydrogenation[281]
 Ar = Ph: **L153a** Ar = 3,5-$Me_2C_6H_3$: **L153b**	Hydrogenation[282-284]	 Ar = Ph: **L154a** Ar = 3,5-$Me_2C_6H_3$: **L154b**	Hydrogenation[282-284]
 R^1 = OH, R^2 = H: **L155a** R^1 = H, R^2 = OH: **L155b** R^1 = H, R^2 = β-glucosyl: **L155c** R^1 = H, R^2 = α-galactosyl: **L155d**	Hydrogenation[285]	 **L156** = β-cyclodextrin	Hydroformylation[286] Hydrogenation[286]
 **L157** = β-cyclodextrin	Hydroformylation[286] Hydrogenation[286]		

terminus the commercially available IGEPAL surfactant.[301] The resulting PEG-Cl was reacted with diphenylphosphide to give **L169**. PEG-supported triphenylphosphine **L170** was prepared by the reaction of (4-hydroxyphenyl)diphenylphosphines with PEG dimesylate under basic conditions.[302] PEG-Phos (**L171**) was prepared by the reaction of bis(TBDMS)-protected (*S*)-BICOL (**71**) with PEG bromoacetate (**72**, Scheme 16).[303] Deprotection and reaction with HMPT gave the PEG-modified chiral phosphoramidite (**L171**).

The *diam*-BINAP-PEG ligand (**L173**) was prepared by the condensation of **L120** with a substoichiometric amount of the mono-PEG ester of glutaric acid to give the mono-PEG-substituted product.[237] The PEG-modified (*R*)-Prophos ligand (**L176**) was prepared by reaction of MeO-PEG-Cl (**78**) with 1,2-isopropylidene glycerol (**77**, Scheme 17).[308] The PEG-modified glycerol was deprotected, converted to a ditosylate (**80**), and reacted with $LiPPh_2$ to give the desired ligand (**L176a**). A similar approach was used to prepare DIOP-PEG (**L178**). Monomethyl PEG was alkylated with chloroacetaldehyde dimethyl acetal, which was then reacted with 1,4-(*R*,*R*)-threitol ditosylate.[310] The resulting PEG-threitol ditosylate was then reacted with diphenylphosphide to give

Scheme 14

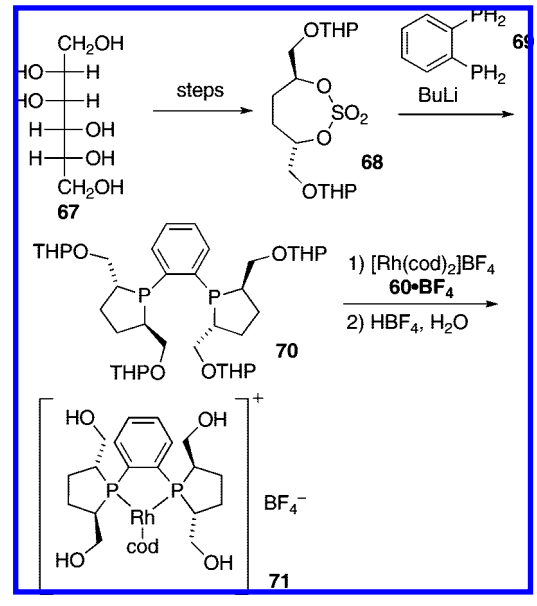
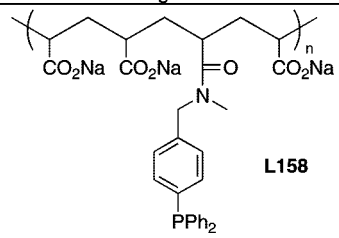
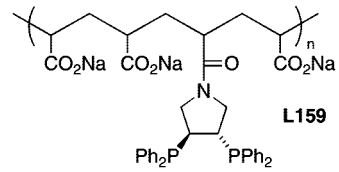
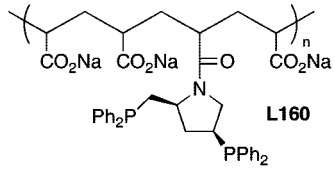
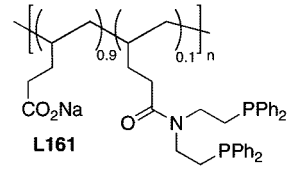
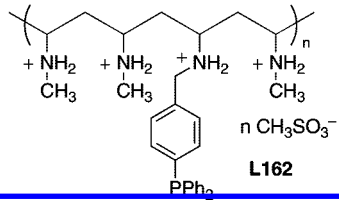


Table 12. Phosphines Supported on Ionic, Water-Soluble Polymeric Supports

Ligand	Applications	Ligand	Applications
 **L158**	Synthesis[289] Hydroformylation[293]	 **L159**	Hydrogenation[290]
 **L160**	Hydrogenation[291]	 **L161**	Hydroformylation[292]
 **L162**	Synthesis[289] Hydroformylation[293]		

L178. A unique PEG-containing polymeric phosphine was prepared by the copolymerization of 5,5′-diamino-BINAP, terephthaloyl chloride, and PEG to give a polymer in which the BINAP unit is incorporated into the polymer backbone (**L175**).[307]

In addition to PEG, other hydrophilic polymers have been used as supports for phosphines. Poly(oxazolines) have been used as water-soluble supports for phosphines. An amine-modified poly(oxazoline) was condensed with (4-carboxyphenyl)diphenylphosphine to give ligand **L177**.[309] A chiral pyrrolidine-based diphosphine was attached to an acid-modified poly(oxazoline) using DCC to give polymer-supported ligand **L180**.[314] Bergbreiter reported the synthesis of a hydrophilic polyacrylamide-supported phosphine (**L179**) by the reaction of (3-aminopropyl)diphenylphosphine with poly(*N*-isopropyl)acrylamide-*co*-(*N*-acryloxysuccinimide).[312]

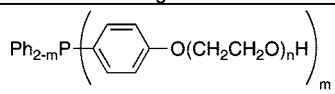
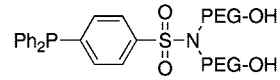
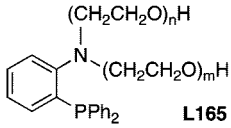
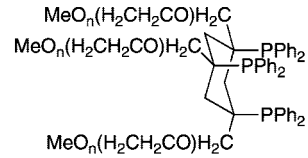
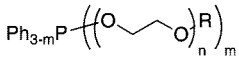
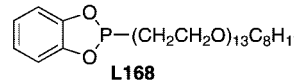
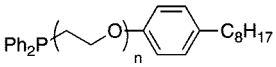
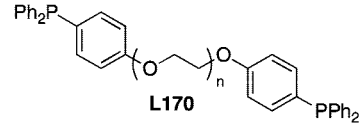
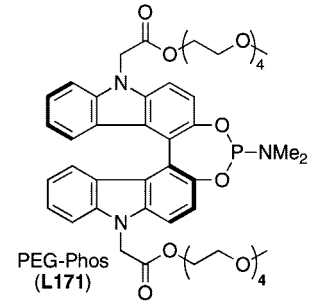
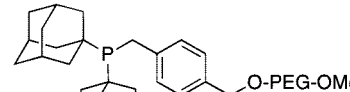
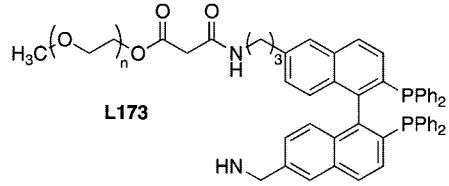
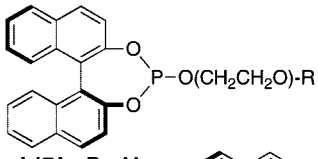
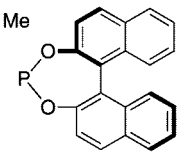
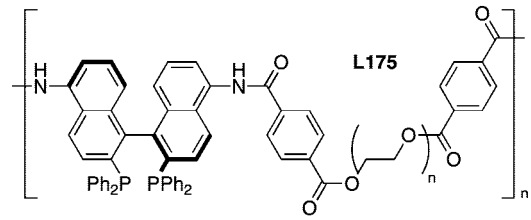
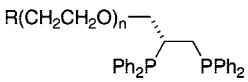
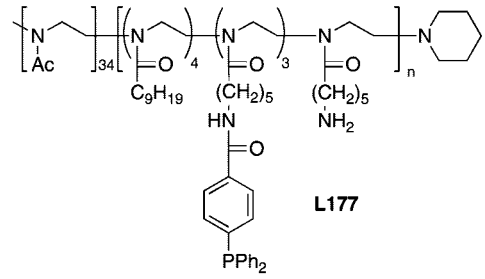
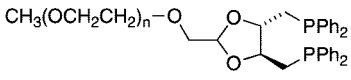
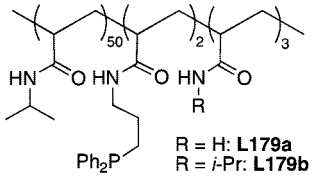
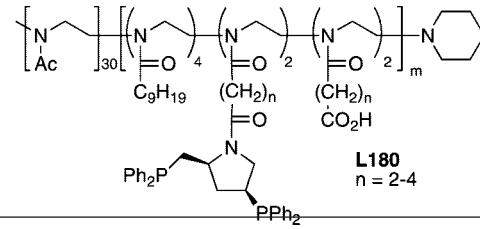
2.2. Synthesis of Hydrophilic Nitrogen Ligands

Phosphine ligands have received the majority of attention in the development of hydrophilic ligands, which mirrors the major role that phosphines have played in the development of homogeneous catalysis. Nitrogen-based ligands also play important roles as ligands in many catalytic processes. The stability of nitrogen to oxidation, makes nitrogen ligands more attractive than phosphines for catalytic reactions carried out under oxidizing conditions. In addition, there are a large number of chiral ligands that can be prepared from readily accessible chiral diamines. For these reasons there is a growing family of nitrogen based hydrophilic ligands in the literature.

Bipyridine ligands are widely used as nitrogen ligands in complexation chemistry and catalysis. The sulfonated analogues of 2,2′-bipyridine and 1,10-phenanthroline have proven challenging to synthesize in contrast to the relative ease of synthesis of sulfonated phosphines. Because the protonation of nitrogen further deactivates the pyridine ring to electrophilic sulfonation, very harsh conditions are required. Sulfonation of 1,10-phenanthrene with ammonium hydrogensulfate at 365 °C gave a mixture of 3-sulfonated bipyridine (**L181a**, 4%), 5-sulfonated bipyridine (**L181b**, 30%), uncharacterized polysulfonated material (19%) and decomposition products, from which the 3- and 5-sulfonated products were isolated.[315] Sulfonation of 2,2′-bipyridine with 30% oleum at 220 °C for 24 h or concentrated sulfuric acid at 300 °C for 10 h gave the 5-sulfonated product **L183a** in modest yields.[316,317] 2,2′-Biquinoline can be sulfonated using 20% oleum at 100 °C to give disulfonated biquinoline (**L185**) in 25% yield. The position of the sulfonates was not determined, but sulfonation would presumably occur at the more activated benzene ring rather than the pyridine ring. Bathophenanthroline and bathocuproine can be disulfonated using 20% oleum at 100 °C to give the products (**L182a,b**) as a mixture of regioisomeric disulfonated products in good yield.[318] These compounds are commercially available from most major vendors. Introduction of a sulfonic acid in the 4 position requires an S_NAr-type substitution with a sulfur nucleophile. Treatment of 4,4′-dichloro-2,2′-bipyridine *N*,*N*′-dioxide (**81**) with sodium sulfite followed by deoxygenation with V^{2+} gave **L184** in 50% overall yield (Scheme 18).[316]

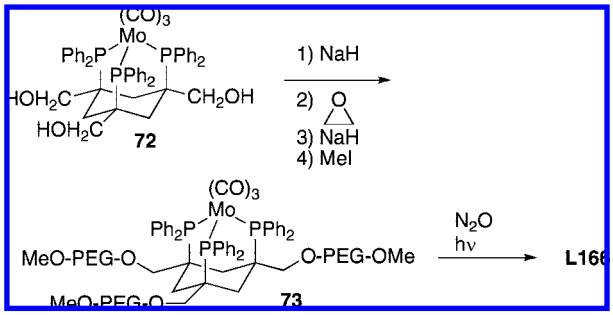
4,4′-Dicarboxylated 2,2′-bipyridine **L186** (Table 14) was prepared by oxidation of the corresponding 4,4′-dimethyl-2,2′-bipyridine, which can be obtained by oxidative coupling of 4-picoline, with $KMnO_4$.[321] 2,2′-Biquinoline-4,4′-dicarboxylic acid (**L187**) was originally prepared by the condensation of isatin and acetoin under basic conditions.[322] **L186** and **L187** and their sodium salts are commercially available. A calixarene bearing two dicarboxylated bipyridine (**L192**) ligands was prepared by the alkylation of calixarene phenolic positions with a bromomethyl-substituted bipyridine dicarboxylate diester.[330] Hydrolysis gave water-soluble ligand **L192**. Palladium-catalyzed coupling of diethyl phosphonate with 4,4′-dibromo- or 5,5′-dibromo-2,2′-bipyridine gave the diphosphonated bipyridines **L188a** and **L188b** in 82% and 87% yield, respectively.[324] A large excess of triphenylphosphine was required to avoid deactivation of the palladium catalyst by bipyridine, however. Phosphonated ligand **L189** was prepared by condensation of diethyl 4-aminophenylphosphonate and 4,4′-di(chlorocarbonyl)bipyridine.

Table 13. Hydrophilic Phosphines Supported on Non-Ionic Water-Soluble Polymers

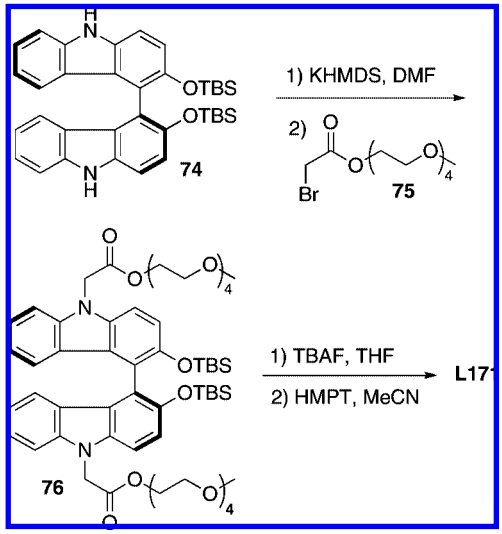
Ligand	Applications	Ligand	Applications
 m = 1: **L163a** m = 2: **L163b** m = 3: **L163c**	Hydroformylation[294] Hydrogenation[298]	 **L164**	Hydroformylation[295]
 **L165** n + m = 35, 45	Hydroformylation[296]	 **L166**	Hydroformylation[297]
 m = 1: **L167a** m = 2: **L167b**	Hydroformylation[299]	 **L168**	Hydroformylation[300]
 **L169** n = 1-13	Hydrogenation[301]	 **L170**	Synthesis[302]
 PEG-Phos (**L171**)	Hydrogenation[303]	 **L172**  **L173**	Sonogashira coupling[304] Suzuki coupling[305] Hydrogenation[237]
 **L174a**: R = Me **L174b**: R = 	Hydroformylation[306] Hydrogenation[306]	 **L175**	Hydrogenation[307]
 R = OCH_3: **L176a** R = NEt_2: **L176b**	Hydrogenation[308]	 **L177**	Hydroformylation[309]
 **L178**	Synthesis[310] Hydrogenation[311]		
 R = H: **L179a** R = *i*-Pr: **L179b**	Synthesis[312] Allylic substitution[313] Sonogashira coupling[313]	 **L180** n = 2-4	Hydrogenation[314]

Placing the water-solubilizing group directly on the pyridine ring changes the electronic nature of the ligand. An alternative is to have the ionic substituent isolated from the pyridine ring by an alkyl chain. Liang and co-workers have prepared a family of amine and pyridine ligands (**L190**) with alkyl sulfonate groups by the Michael addition of an amine-functionalized pyridine (**83**) with sodium vinyl sulfonate (eq 16).[326] Copper-catalyzed coupling of alkynyl

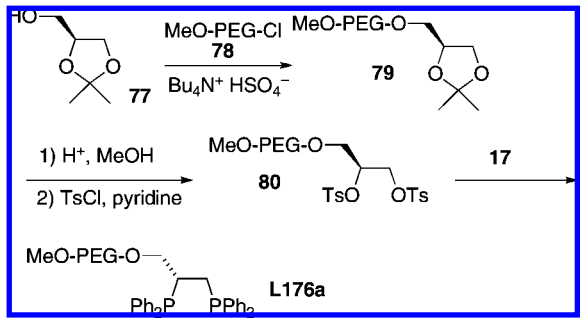
Scheme 15



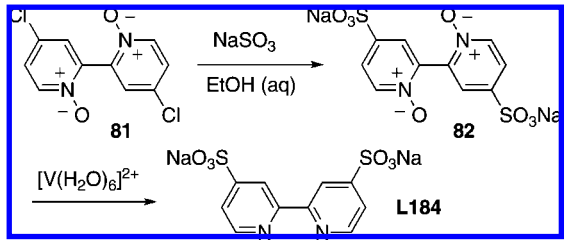
Scheme 16



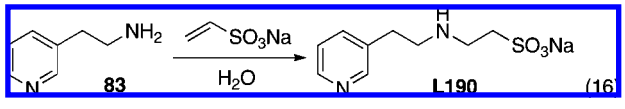
Scheme 17

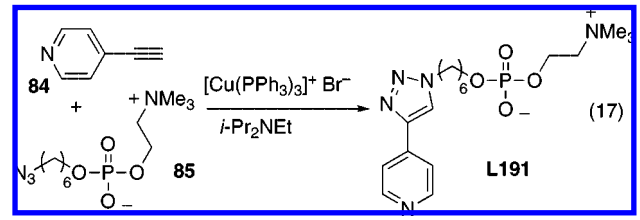


Scheme 18

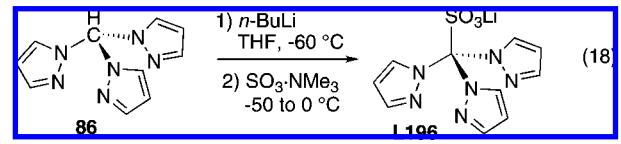


pyridine **84** with azide-functionalized phosphoryl choline derivative **85** provided zwitterionic phosphoryl choline-modified pyridine ligands (**L191**, eq 17).[337] The resulting pyridine ligands were soluble in water, methanol, and methylene chloride.





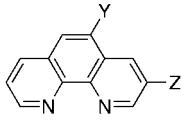
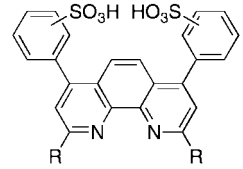
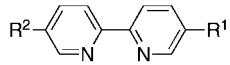
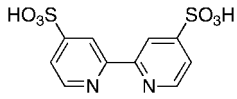
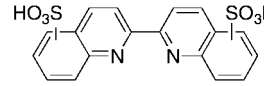
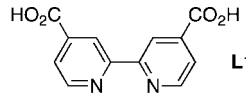
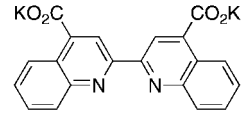
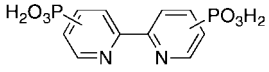
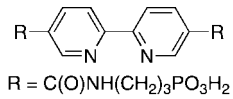
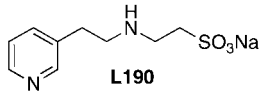
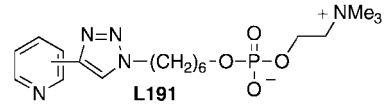
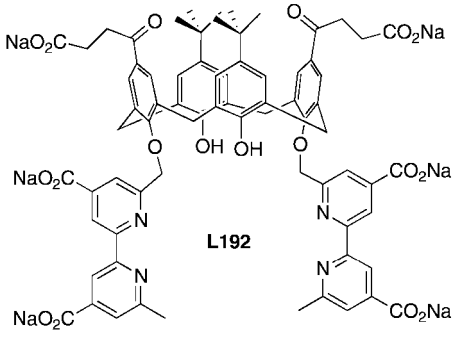
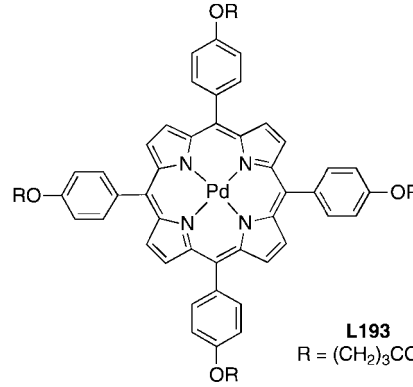
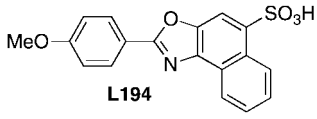
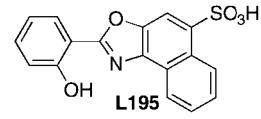
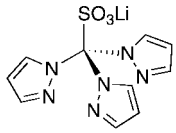
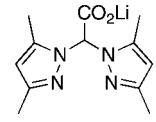
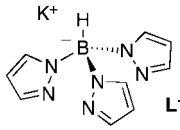
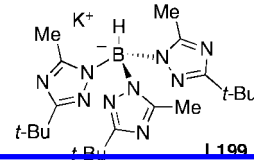
A number of azole ligands with anionic substituents have also been prepared. Porphyrins are important ligands in bioinorganic chemistry, but have received less attention in catalysis. A water-soluble porphyrin complex of palladium (**L193**) was prepared by the condensation of a *p*-alkyl ester-functionalized benzaldehyde derivative with pyrrole.[331] After metalation with $PdCl_2$, the pendant ester groups were hydrolyzed to give **L193**. Sulfonic acid-functionalized oxazole ligands (**L194** and **L195**) were prepared by the condensation of benzaldehyde derivatives with commercially available 1-amino-2-hydroxy-4-naphthalenesulfonic acid.[332] Two examples of hydrophilic bis- and tris(pyrazolyl)methanes have been reported. Deprotonation of tris(pyrazolyl)methane (**86**) with butyl lithium and quenching with $SO_3 \cdot NMe_3$ gave the sulfonated ligand **L196** (eq 18).[333] A similar strategy starting with bis(pyrazolyl)methane and quenching with CO_2 gave carboxylate-modified ligand **L197**.[334] Tris(pyrazolyl)borate (**L198**) is a water-soluble ligand, but forms water-insoluble complexes with many metal ions.[335] The water-solubility can be increased by replacing the pyrazole heterocycles with triazoles (**L199**).[336]



Imine-based ligands can be readily prepared by the condensation of amines with mono- or dialdehydes. Preparation of hydrophilic versions of these ligands is in principle straightforward, as *p*-aminobenzoic acid and *p*-sulfanilic acid are readily available. In addition, 2,6-disubstituted anilines can be sulfonated to give more sterically demanding ligands. Condensation of *p*-aminobenzoic acid with 2,3-butanedione in anhydrous methanol gave dicarboxylic acid-substituted diazabutadiene ligand **L200** in good yields (Table 15).[338,339] Similarly, condensation of pyridine-2-carboxyaldehyde with aminobenzoic acid or sulfanilic acid derivatives in anhydrous methanol gave pyridine imine ligands **L201** and **L202**.[339−341] A tridentate pincer-type ligand **L203** was prepared similarly starting with pyridine-2,6-dicarboxaldehyde.[340]

The resulting hydrophilic imines are moderately to highly moisture sensitive. In some cases, such as **L202b** and **L202e**, the ligands could not be isolated due to their sensitivity to hydrolysis.[341] The metal complexes of these ligands are stable in water, however. Thus, the ligands can be metalated in an aprotic, polar solvent (i.e., DMSO or DMF) to give complexes that can be used in an aqueous environment. Benzaldehyde imines with sulfonate (**L204**) or carboxylate (**L205**) substituents were prepared in a similar manner.[342] The oxime of 4-hydroxybenzaldehyde (**L206**) has been used to provide a water-soluble palladacycle.[344] These imines are stable in water in contrast to the pyridine carboxaldehyde imines.

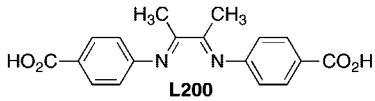
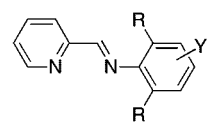
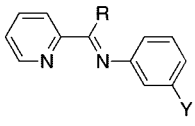
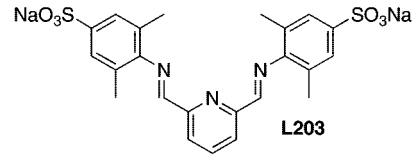
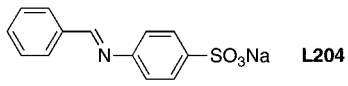
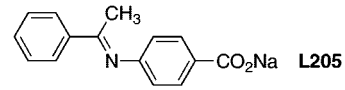
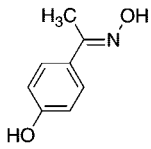
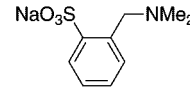
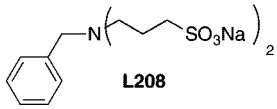
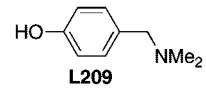
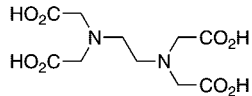
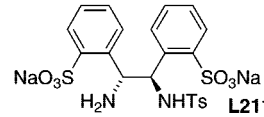
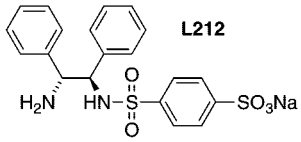
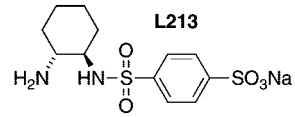
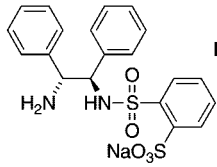
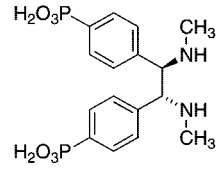
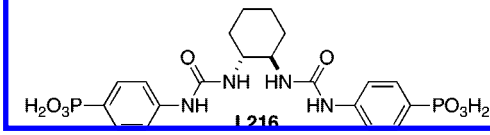
Table 14. Pyridine and Azole-Based Ligands with Anionic or Acidic Substituents

Ligand	Applications	Ligand	Applications
 Y = SO_3Na, Z = H: **L181a** Y = H, Z = SO_3H: **L181b**	Synthesis[315]	 R = H: **L182a**[a] R = Me: **L182b**[a]	Synthesis[318] Alcohol oxdiation[319] Alkene oxidation[320] Alkene/CO copolymerization[147]
 R^1 = SO_3Na, R^2 = H: **L183a** R^1 = R^2 = SO_3Na: **L183b**	Synthesis[316,317] Alkene oxidation[320]		
 **L184**	Synthesis[316]	 **L185**	Synthesis[316]
 **L186**[a]	Synthesis[321]	 **L187**[a]	Synthesis[322] Alcohol oxidation[323] Reductive Amination[76]
 4,4'-PO_3H_2: **L188a** 5,5'-PO_3H_2: **L188b**	Synthesis[324] Hydrogenation[325]	 **L189** R = $C(O)NH(CH_2)_3PO_3H_2$	Synthesis[324] Hydrogenation[325]
 **L190**	Synthesis[326] Heck coupling[327] Suzuki coupling[328]	 **L191**	Olefin metathesis[329]
 **L192**	Synthesis[330]	 **L193** R = $(CH_2)_3CO_2K$	Suzuki coupling[331]
 **L194**	Suzuki coupling[332]	 **L195**	Suzuki coupling[332]
 **L196**	Synthesis[333]	 **L197**	Synthesis[334]
 **L198**[a]	Synthesis[335]	 **L199**	Synthesis[336]

[a] Commercially available.

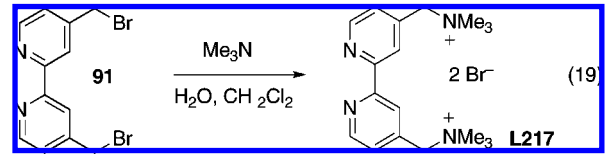
Amine-based ligands with anionic substituents have begun to receive interest, particularly chiral diamine ligands. *N*,*N*-Dimethyl-*o*-sulfonatobenzylamine (**L207**, Table 15) was prepared by reductive amination of commercially available *o*-formylbenzene sulfonate.[342] Similarly, *N*,*N*-dimethyl-(4-hydroxyenzyl)amine (**L209**) was prepared by reductive amination of 4-hydroxybenzaldehyde. The reaction of benzylamine with an excess of 1,3-propane sultone was used to prepare ligand **L208**. Monotosylated chiral diamines are highly effective ligands in enantioselective reduction of carbonyl and imine substrates.[354,355] Sulfonation of DPEN (**87**) with fuming sulfuric acid followed by neutralization gave sulfonated diamine **88** (Scheme 19).[349] Sulfonation occurred exclusively in the *ortho*-position. Reaction with tosyl chloride gave sulfonated chiral ligand **L211**. Alternatively, the sulfonate substituent can be appended to the sulfonamide substituent (Scheme 20).[351] Ligands **L212** and **L213** were prepared by reaction of DPEN (**87**) with

Table 15. Hydrophilic Imine and Amine Ligands with Anionic Substituents

Ligand	Applications	Ligand	Applications
 **L200**	Synthesis[338]	 R = H; 3-SO_3Na: **L201a** R = H; 3-CO_2Na: **L201b** R = H; 4-SO_3Na: **L201c** R = H; 4-CO_2Na: **L201d** R = Me; 4-SO_3Na: **L201e**	Synthesis[339,340]
 R = H, Y = CO_2H: **L202a** R = Me, Y = CO_2H: **L202b** R = Ph, Y = CO_2H: **L202c** R = H, Y = SO_3Na: **L202d** R = Me, Y = SO_3Na: **L202e** R = Ph, Y = SO_3Na: **L202f**	ATRAP[341]	 **L203**	Synthesis[340]
 **L204**	Suzuki coupling[342]	 **L205**	Synthesis[342]
 **L206**	Hiyama coupling[343] Suzuki coupling[344] Heck coupling[345]	 **L207**	Suzuki coupling[342]
 **L208**	Suzuki coupling[342]	 **L209**	Suzuki coupling[342]
 EDTA (**L210**)	Aryl halide homocoupling[346] Hydrogenation[347,348] Suzuki coupling[246]	 **L211**	Synthesis[349] Hydrogenation[350]
 **L212**	Synthesis[351] Hydrogenation[352]	 **L213**	Synthesis[351] Hydrogenation[352]
 **L214**	Synthesis[351] Hydrogenation[352]	 **L215**	Hydrogenation[353]
 **L216**	Hydrogenation[325]		

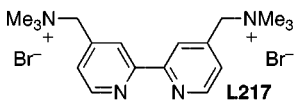
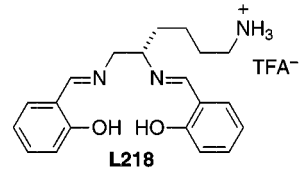
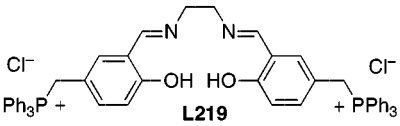
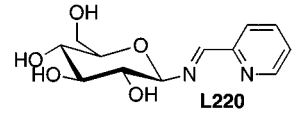
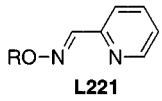
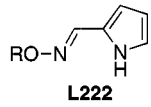
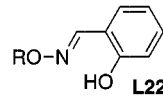
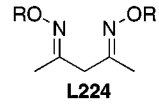
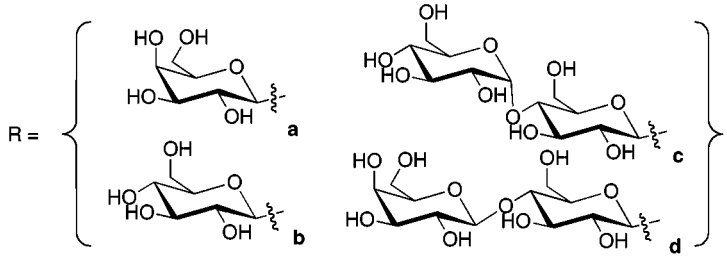
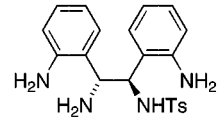
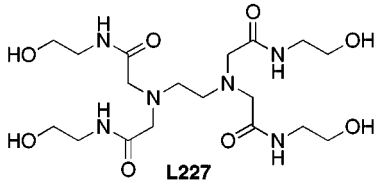
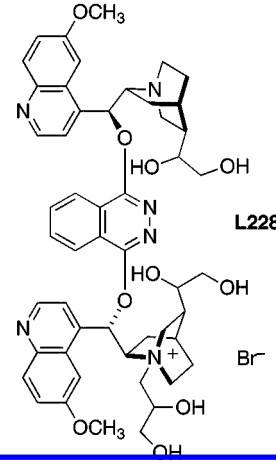
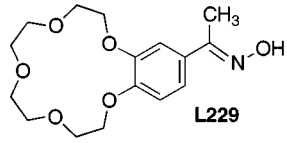
(p-$ClO_2SC_6H_4S)_2$ (**89**) followed by oxidation of the disulfide. Ligand **L214** was prepared by the addition of DPEN to benzene-1,2-disulfonic acid anhydride. Phosphonic acid-modified chiral diamine ligands have also been reported. Pd-catalyzed P−C bond formation was used to prepare a diphosphonated *N*,*N*′-dimethyl-DPEN analogue **L215**.[353] Ligand **L216** was prepared by the addition of (*R*,*R*)-diaminocyclohexane to a phosphonate-functionalized isocyanate.[325]

There are few examples of nitrogen-based ligands with cationic substituents, presumably due to the difficulty in selectively preparing mixed ammonium or phosphonium amines. 4,4′-Di(bromomethyl)-2,2′-bipyridine (**91**) can be prepared and isolated with out self-alkylation.[356,357] Quaternization with trimethylamine gave water-soluble ligand **L217** in quantitative yield (eq 19, Table 16).[358] Salen ligands have played an important role in catalysis and coordination chemistry. The first example of a hydrophilic salen derivative was prepared starting from a 1,2,6-triaminohexane (**92**) derived from L-lysine.[359] Condensation with salicaldehyde (**93**) in the presence of Cu^{2+} followed by deprotection and demetalation gave **L218** in 33% yield over two steps (Scheme 21). A phosphonium-modified salen ligand was prepared by the condensation of 4-(trimethylphosphoniummethyl)salicaldehyde with 1,2-diaminoethylene (**L219**).[360] Monoquaternization of $(QN)_2PHAL$ with allyl bromide gives a moderately water-soluble ligand for Os-catalyzed asymmetric dihydroxylation.[361] Under the reaction conditions, the olefinic sites in the ligand were dihydroxylated to give a cationic polyol (**L228**) that had good water solubility.

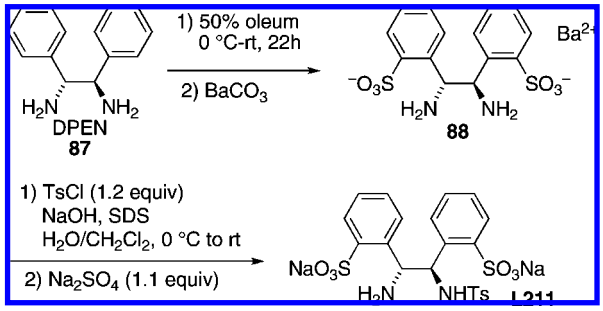


A glucosyl-modified pyridyl imine ligand (**L220**, Table 16) was prepared by the condensation of peracetylated

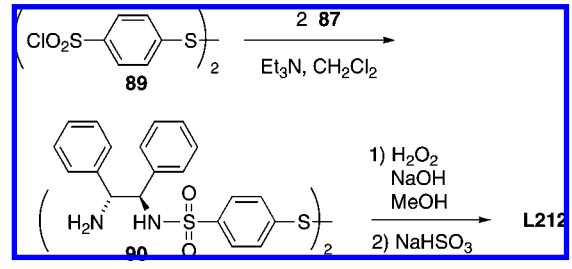
Table 16. Nitrogen Ligands and Complexes with Neutral or Cationic Substituents

Ligand	Applications	Ligand	Applications
 L217	Hiyama coupling[365] Suzuki coupling[358]	 L218	DNA cleavage[359]
 L219	Alcohol oxidation[366] Alkane oxidation[360] Epoxidation[360]	 L220	Hydrogenation[362]
 L221		 L222	
 L223		 L224	
			Hydrogenation[285]
 L225[a]	Olefin polymerization[367]	 L226	Hydrogenation[368]
 L227	Allylic oxidation[363] Allylic substitution[369]	 L228	Asymmetric dihydroxylation[361]
 L229	Hydrolysis[364]		

Scheme 19

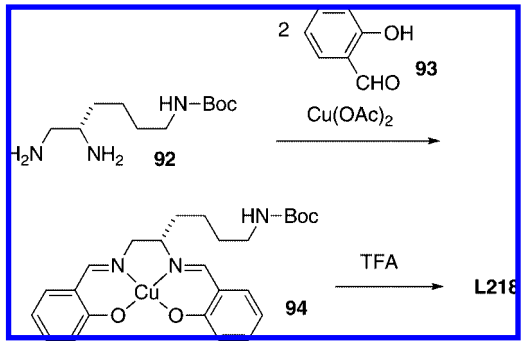


Scheme 20

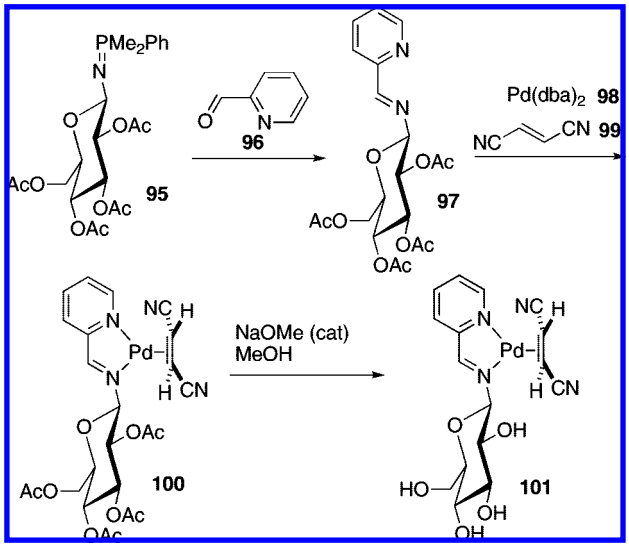


glucosyl iminophosphorane (**95**) with pyridine-2-carboxaldehyde (**96**, Scheme 22).[362] After complexation with Pd^0 to give **100**, the ligand could be deprotected under basic conditions to give the palladium complex **101**. A family of sugar-modified chelating imine ligands (**L221**−**L224**) were prepared by the condensation of aldehydes with hydroxylamine derivatives of D-glucose, D-galactose, D-maltose, and D-lactose.[122] The condensation reactions were carried out with the unprotected aldosyl hydroxylamines in water to give the imine products in good yield. Unlike the sulfonated imines derived from pyridyl-2-carboxaldehyde, these imine ligands

Scheme 21



Scheme 22

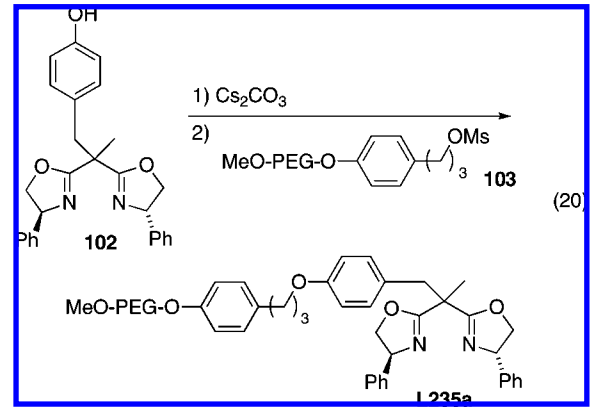


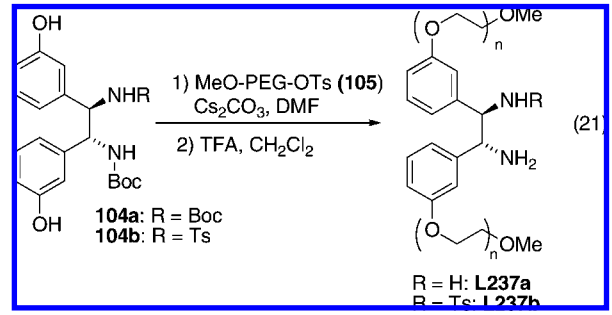
are stable in water. The tetraamide (**L227**) formed by condensation of ethanolamine and EDTA tetramethyl ester is a highly water-soluble neutral diamine ligand.[363] The oxime of 4′-acetylbenzo-15-crown-5 (**L223**) was prepared by standard methods to give a neutral imine ligand that has been used to prepare hydrophilic palladacycle complexes.[364]

Water-soluble polymers have also been used as supports for nitrogen-based ligands. A water-soluble polymer-supported analogue of Ts-DPEN was prepared by copolymerization of the 4-vinylsulfonamide of DPEN with *p*-styrene sulfonate to give **L230** (Table 17).[370] A number of PEG-modified nitrogen ligands have been prepared. (4-Pyridyl)tetraglyme (**L231**) was prepared by reacting 4-hydroxypyridine with tetraglyme under Mitsunobu conditions in modest yield (40%).[371] Dipyridyl PEG **L233** was prepared in excellent yield (95%) by the reaction of 4-hydroxymethylpyridine with PEG-ditosylate.[298] Similarly, bis(2-pyridyl) methanol was treated with NaH and PEG-ditosylate to give **L234**.[372]

PEG-modified bis(oxazoline) ligand **L235** was prepared by the reaction of the 4-hydroxybenzyl derivative of the bis(oxazoline) (**102**) with 3-(4-MeOPEG-phenyl)propyl mesylate (**103**, eq 20).[373] PEG-supported DPEN (**L237a**) and TsDPEN (**L237b**) ligands were prepared by the reaction of MeO-PEG mesylate (**105**) with *N*-Boc-protected 1,2-di(3-hydroxyphenyl)ethylene diamine (**104a**) or the monotosylamide (**104b**) analogue (eq 21).[376,377]

Several examples of PEG-supported alkaloid ligands applicable to asymmetric dihydroxylation reactions have





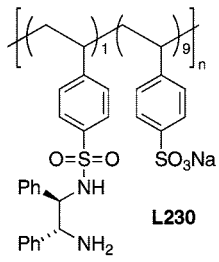
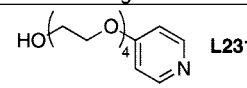
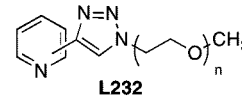
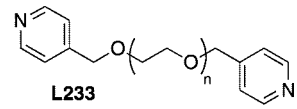
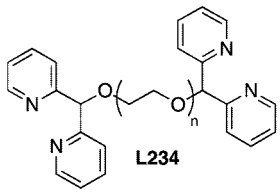
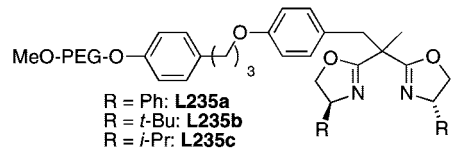
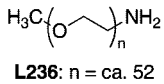
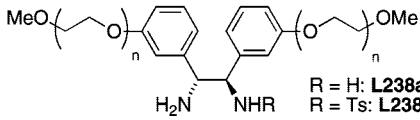
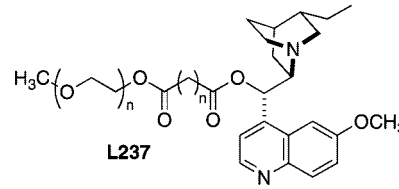
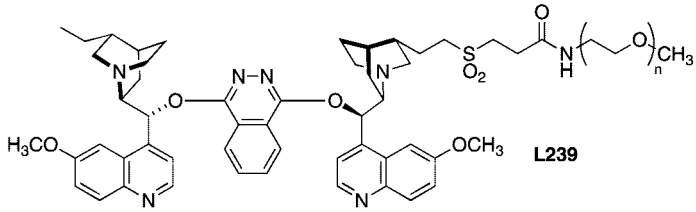
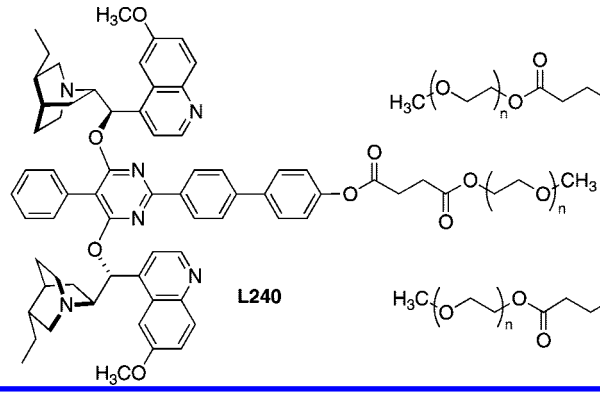
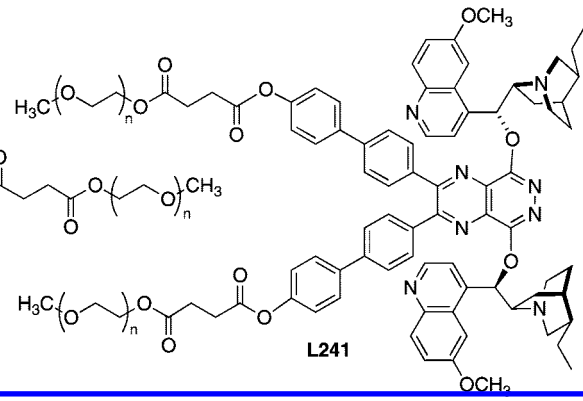
been reported. Ligand **L238** was prepared by acylation of dihydroquinidine with the PEG monoester of glutaric acid.[375] PEG-supported $(DHQD)_2PHAL$ derivative **L239** was prepared by the free radical addition of 3-mercaptopropionic acid (**107**) to the vinyl group of the quinidine center of **106** (Scheme 23).[379] The free acid (**108**) was then coupled to MeO-PEG-NH_2 (**L236**), followed by oxidation of the sulfur linkage. Bolm prepared ligands **L240** and **L241** from modified bis-quinine or -quinidine ligands with phenolic sites located away from the reaction site.[380] The PEG group was introduced by acylation of the phenolic sites with the MeO-PEG monoester of succinic acid.

2.3. Synthesis Hydrophilic Carbene Ligand Precursors and Complexes

Since their initial preparation by Arduengo,[381] imidazol-2-ylidenes and other *N*-heterocyclic carbenes (NHCs) have become very useful ligands in metal-catalyzed reactions, as well as reagents in organic synthesis.[382−385] Their strong σ-donor ability, variable steric demand, and ability to form stable metal complexes make them highly attractive ligands in metal-catalyzed reactions. Free imidazol-2-ylidene and related compounds are strong bases (imidazolium pK_a = ca. 25),[386] which makes them incompatible with water. The imidazolium precursors to *N*-heterocyclic carbenes are stable in water, as are the resulting metal-carbene complexes in most cases. In addition, formation of the metal−carbene complex can often be accomplished in protic solvents. Recently, there have been a growing number of reports of hydrophilic precursors to NHCs and their metal complexes.

To date, there are only two examples of NHC precursors with anionic substituents. NHC precursors **L242a,b** were prepared by the ring opening of 1,3-propane sultone with *N*-arylimidazoles to give the zwitterionic imidazolium salt (Table 18).[387] Condensation of mesitylamine-3-sulfonate (**109**) with glyoxal gave **110**, which was reduced by catalytic hydrogenation using Pd/C to give diamine **111** (Scheme 24). The imidazolinium preligand (**L243a**) was formed by

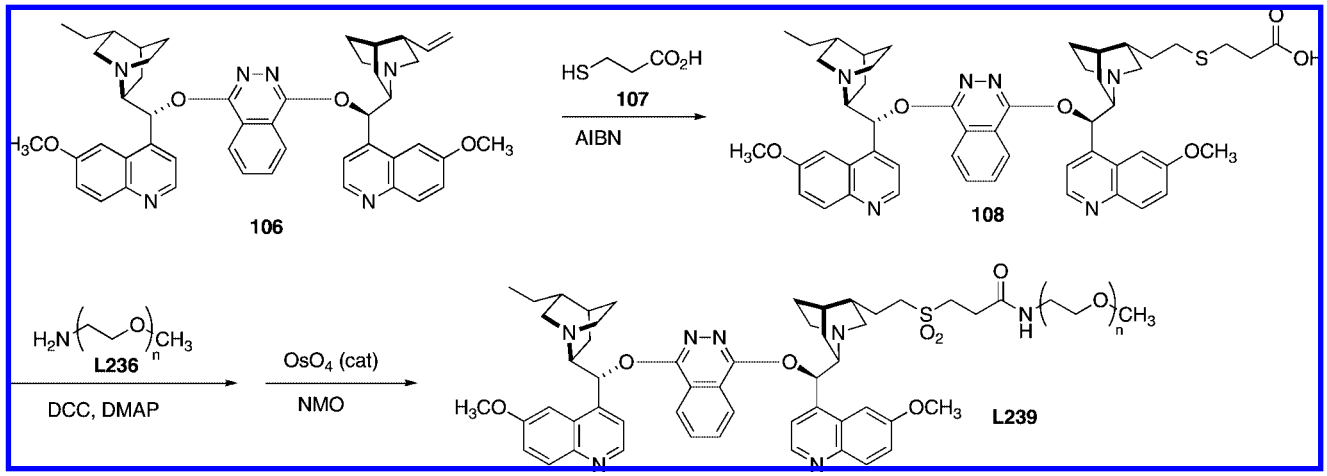
Table 17. Nitrogen Ligands Supported on Water-Soluble Polymeric Supports

Ligand	Applications	Ligand	Applications
 **L230**	Hydrogenation[370]	 **L231**	Olefin metathesis[371]
		 **L232**	Olefin metathesis[329]
		 **L233**	Hydrogenation[298]
 **L234**	Suzuki coupling[372]	 R = Ph: **L235a** R = *t*-Bu: **L235b** R = *i*-Pr: **L235c** R = Bn: **L254d**	Synthesis[373] Mukaiyama aldol[374]
 **L236**: n = ca. 52	Olefin polymerization[367]		
 R = H: **L238a** R = Ts: **L238b**	Synthesis[376,377] Hydrogenation[378]	 **L237**	Asymmetric dihydroxylation[375]
 **L239**			Asymmetric dihydroxylation[379]
 **L240**		 **L241**	Asymmetric dihydroxylation[380]

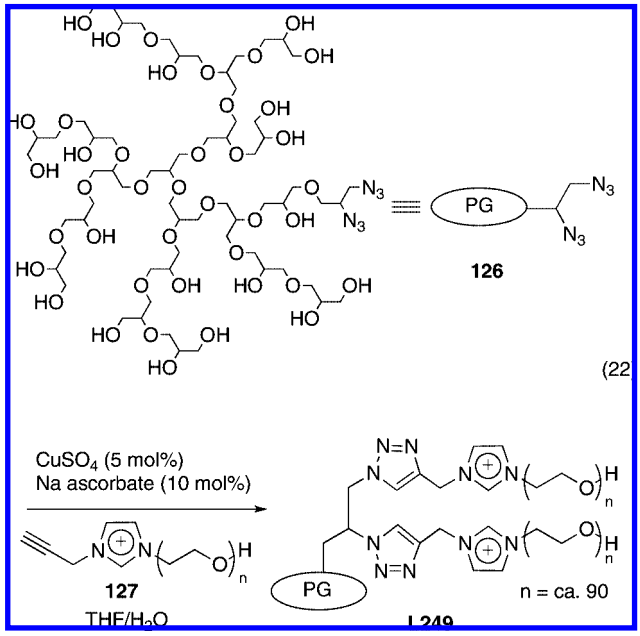
condensation of **111** with triethyl orthoformate.[388] Attempts to condense the less nucleophilic 2,6-disubstituted sulfanilic acids **112** with glycol were unsuccessful, but the necessary diamine could be prepared starting from 1,4-dioxane-2,3-diol (**113**, Scheme 25). Reduction and ring closing gave imidazolinium salts **L243b** and **L243c**. Alternatively, the bis(imine) (**114a,b**) could be reacted with chloromethylpivalate (**115**) to give the imidazolium salts **L243d** and **L243e**.

Özdemir was the first to report an aqueous-phase, metal-catalyzed reaction using a hydrophilic NHC ligand.[389] Ru-complex **L244** was prepared starting from neutral tetraaminoethylene **116**, which was reacted with $[RuCl(\mu\text{-}Cl)(\eta^6\text{-}C_6Me_6]_2$ (**117**) to give the neutral diamine-substituted imidazolin-2-ylidene complex **118** (Scheme 26). Protonation with anhydrous HCl in ether gave the water-soluble diammonium salt **L244**. A diquaternary ammonium salt-modified benzylidine ligand has been used to prepare a water-soluble Grubbs−Hoveyda metathesis catalyst.[390] The styrene precursor of this unusual hydrophilic alkylidene ligand was prepared by chloromethylation of 2-isopropoxybenzaldehyde followed by methylenation to give **119** (Scheme 27). Alkylation of **119** with *N*,*N*,*N*′,*N*′-tetramethylethylene diamine gave the styrene precursor **120**, which was reacted with the second generation Grubbs catalyst to give **L245**. Grubbs has also reported two PEG-modified imidazolinium precursors that have been used to prepare olefin metathesis catalysts. Imidazolinium **L247** was prepared by the reaction of *N*-PEG-4-chloromethylbenzamide with *N*-mesitylimidazole in the presence of sodium iodide.[392] Imidazolinium **L246** with the PEG substituent on C4 of the ring was prepared starting from *N*,*N*′-dimesityl-2,3-diamino-1-propanol (**123**). Reaction of **123** with MeO-PEG mesylate (**124**) followed

Scheme 23



by closure of the imidazolinium ring with triethyl orthoformate gave **L246** (Scheme 28).[391] Imidazolium **L248** was prepared by the dialkylation of imidazole with 3,4,5-tri-PEG-substituted benzyl chloride.[393] Hyperbranched poly(glycerol)-supported ligand precursor **L250** was prepared by cycloaddition of propargylimidazolium salt **127** and a diazido-substituted hyperbranched support (**126**, eq 22).[394]



Carbohydrate-modified imidazoliums **L250a,b** were prepared by reacting *N*-mesitylimidazole with pivalate-protected β-D-1-galactosyl bromide or acetate protected β-D-glucosyl bromide followed by deprotection with KCN in methanol to give **L250a** and **L250b** as the α-anomers exclusively.[395] Polymer-supported rhodium complex **L251** was prepared by reacting 2-hydroxylethyl-substituted imidazol-2-ylidene complex of Rh with carboxylic acid modified poly(oxazoline) using DCC.[396] Copolymerization of an oxazoline-modified bis(NHC)Pd complex was used to prepare poly(oxazoline)-supported Pd complex **L252**.[397]

2.4. Overview of Hydrophilic Ligand Properties

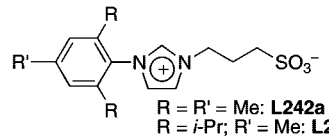
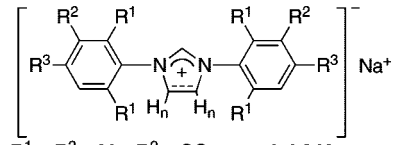
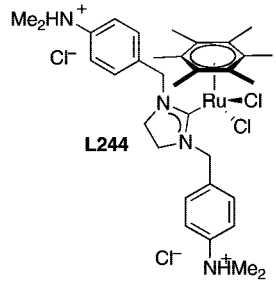
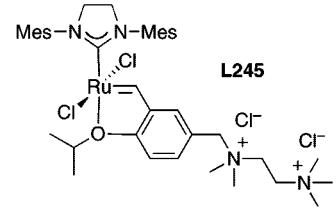
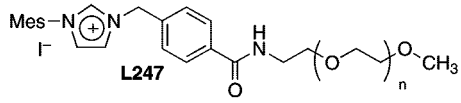
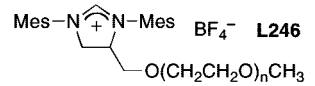
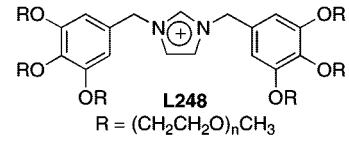
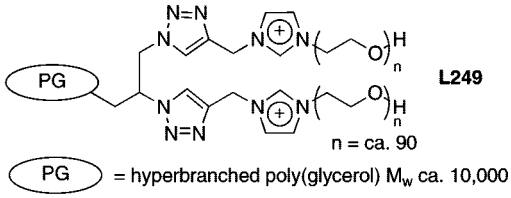
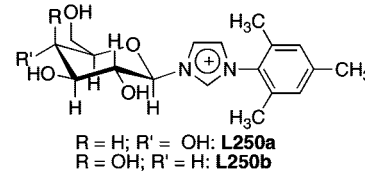
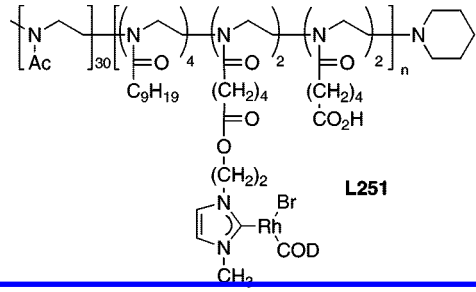
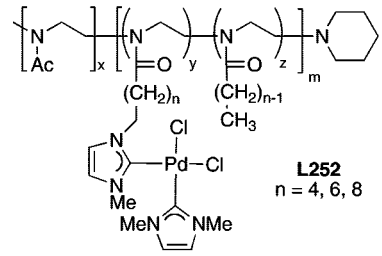
2.4.1. Water Solubility

Although a large number of hydrophilic phosphines have been reported, the water-solubility has been reported for only a small subset of these ligands (Table 19). The solubility of hydrophilic phosphines depends primarily on the ratio of non-hydrogen atoms to water-solubilizing groups and to a lesser extent on the identity of the water-solubilizing group. Monosulfonated *m*-TPPMS has a maximum water solubility of 0.2 M (18 C/sulfonate), while *m*-TPPTS can be dissolved with concentrations up to 1.9 M (6 C/sulfonate).[14] Increasing the number of carbon atoms relative to the number of ionic groups decreases the solubility, as one would expect. Thus surface active trisulfonated ligand **L9a** (15 C/sulfonate) has a similar solubility to *m*-TPPMS, despite being trisulfonated.[89] Phosphonate groups provide more soluble ligands than sulfonate for a given carbon number (i.e., *m*-TPPMS vs *m*-TPPMP),[178] but carboxylate and sulfinate groups provide similar water solubility to sulfonate (**L72a−c**).[181] Ligands **L72a−c** with furyl groups of were more soluble than closely related triphenylphosphine derivatives, possibly due to hydrogen bonding of the furyl oxygen with water.

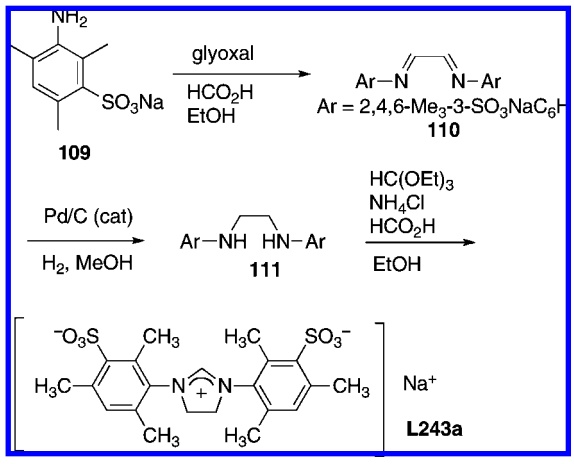
Diphenylalkylphosphines with water-solubilizing groups show roughly comparable solubilities to the triaryl analogues at similar degrees of substitution (**L81** compared with **L68**).[178] Carbohydrate[258] and hydroxyl[131] substituents can provide appreciable solubility if present in sufficient numbers (**L131** and **L137**). The PTA ligand is surprisingly soluble (1.5 M) given that the only functionality present are tertiary amine and phosphine groups.[251] Interestingly, the diacetylated PTA derivative (DAPTA) has a maximum water-solubility of 7.4 M, which is significantly higher than the solubilities of the parent PTA (1.5 M) or TPPTS (2.0 M). DFPTA is significantly less soluble in water (1.1 M) than DAPTA, however.[217] The benzaldehyde adduct of PTA (**L136a**) was reported to more soluble in water (4.2 M) than PTA,[252] although a similar compound derived from *p*-anisaldehyde (**L136c**) was reported to be significantly less water-soluble (0.04 M).[191]

Incorporation of tertiary amines into triarylphosphines or chelating phosphines gives ligands that partition exclusively into the organic phase above pH 6. Thus **L109a** and **L109b** partition exclusively in to the ether phase of an ether/water solution. Below pH 6, the ligands begin to partition into water as they become protonated. Ligand **L109a** completely partitions into the aqueous phase below pH 2, while the diamine-functionalized ligand **L109b** completely partitions into water around pH 3.[399] Triamine-functionalized ligand **L110** shows a broader pH range over which the ligand changes from primarily partitioning into water (pH <2.5) to primarily into the organic phase (pH > 8).[231] Even at pH

Table 18. Hydrophilic Carbenes, Carbene Precursors, and Metal−Carbene Complexes

Ligand	Applications	Ligand	Applications
 R = R' = Me: **L242a** R = *i*-Pr; R' = Me: **L242b**	Synthesis[387]	 $R^1 = R^3 = Me, R^2 = SO_3^-, n = 2$: **L243a** $R^1 = Me, R^2 = H, R^3 = SO_3^-, n = 2$: **L243b** $R^1 = i\text{-}Pr, R^2 = H, R^3 = SO_3^-, n = 2$: **L243c** $R^1 = Me, R^2 = H, R^3 = SO_3^-, n = 1$: **L243d** $R^1 = i\text{-}Pr, R^2 = H, R^3 = SO_3^-, n = 1$: **L243e**	Suzuki coupling[388]
 **L244**	Alkyne hydration[389]	 **L245**	Olefin metathesis[390]
 **L247**	Olefin metathesis[392]	 **L246**  **L248** $R = (CH_2CH_2O)_nCH_3$	Olefin metathesis[391] Hydrosilylation[393] Suzuki coupling[393]
 **L249** n = ca. 90 PG = hyperbranched poly(glycerol) M_w ca. 10,000	Suzuki coupling[394]	 R = H; R' = OH: **L250a** R = OH; R' = H: **L250b**	Synthesis[395]
 **L251**	Hydroformylation[396]	 **L252** n = 4, 6, 8	Synthesis[397] Heck coupling[398] Suzuki coupling[398]

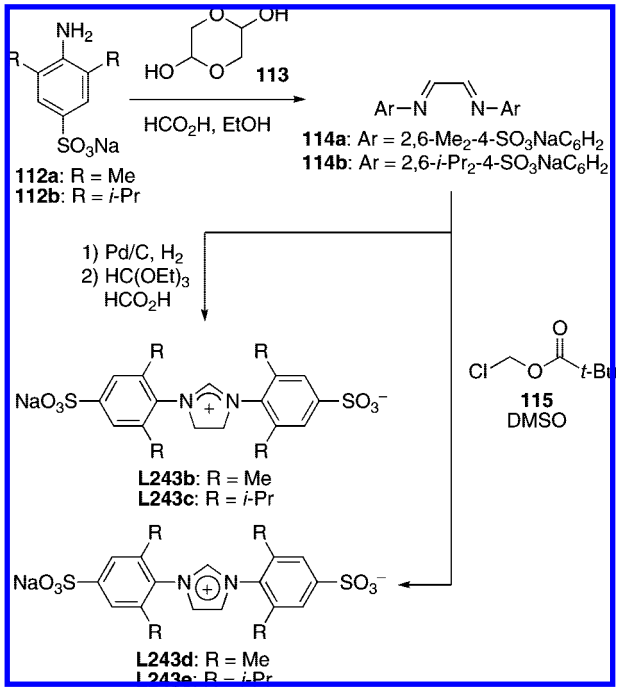
Scheme 24



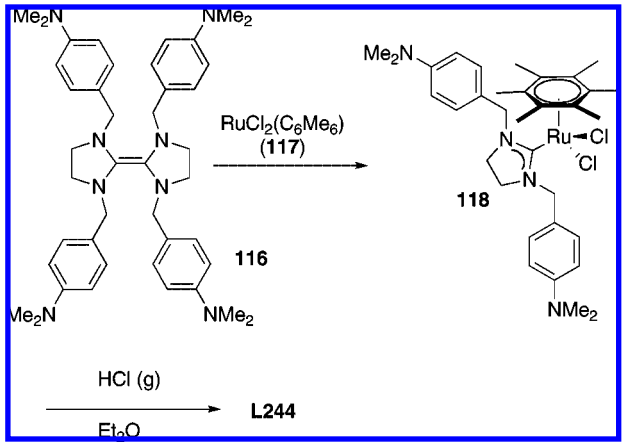
8, only about 90% of the ligand has partitioned into the organic phase. The fact that some ligand remains in the incorrect phase at high and low pH is attributed to the surface active properties of the ligand that lead to micelle formation. *p*-TPPMC (**L64a**) also shows pH responsive partitioning properties. The transition from the organic layer to aqueous later occurs as the pH is raised from 8 (92% in organic phase) to 12 (100% in aqueous phase).[399]

PEG-substituted hydrophobic molecules often display inverse temperature dependent solubility in water. At low temperatures, the PEG species is soluble in water due to hydrogen bond interactions between the PEG oxygens and water. When the solution is heated, the hydrogen bonding becomes less efficient leading to precipitation of the PEG-supported molecule, which is known as the cloud point. In a two phase system, this decrease in water solubility will result in the PEG-supported species partitioning into the organic phase. Jin and Fell have demonstrated that PEG-supported phosphine ligands display inverse temperature-dependent solubility.[294,295,299] For example, ligands **L163**−**L165** and **L167** have cloud points ranging from 30 to 95 °C depending on the number and length of the PEG units present. Increasing the length of the PEG support

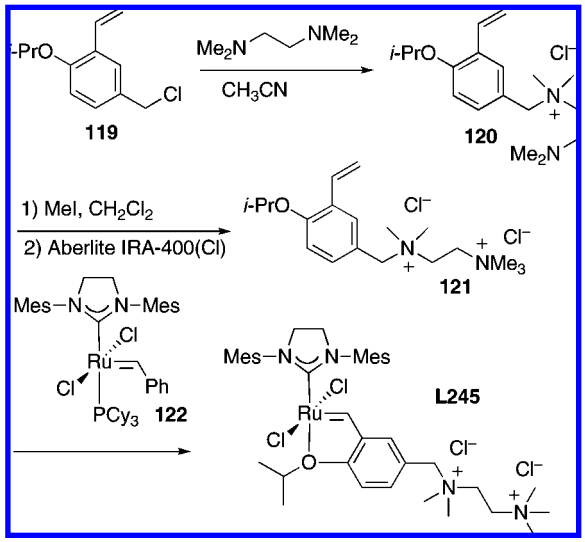
Scheme 25



Scheme 26



Scheme 27



increases the cloud point, thus requiring higher temperature to drive the PEG-supported ligand out of water. For example,

Scheme 28

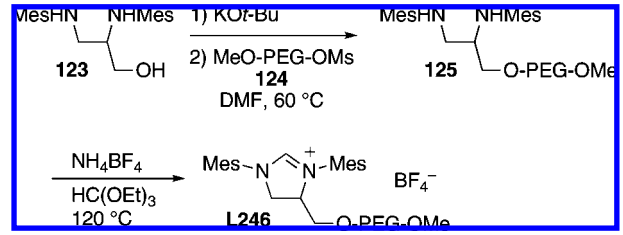


Table 19. Water-Solubility of Hydrophilic Phosphines

ligand	solubility (M)	atoms/WSG[a]
m-TPPMS (**L1a**)	0.2[14]	18
m-TPPTS (**L1c**)	1.9[14]	6
L5a	0.2[89]	15
L6a	0.2[90]	25
L6b	1.2[90]	16
L6c	>1.2[90]	13
m-TPPMP (**L68a**)	1.0[178]	18
m-TPPDP (**L68b**)	>2.0[178]	9
p-TPPDP (**L69b**)	>2.0[178]	6
L72a, $n = 1$	0.8[181]	17
L72a, $n = 2$	1.8[181]	8
L72a, $n = 3$	2.4[181]	5
L72b, $n = 1$	1.8[181]	17
L72b, $n = 2$	2.3[181]	8
L72c, $n = 2$	1.7[181]	8
L72c, $n = 3$	2.6[181]	5
L81, $n = 2$	1.1[178]	14
L81, $n = 10$	0.7[178]	20
L137	0.5[258]	4
L33a	5.8[131]	5
L33b	1.4[131]	9
L131a	2.5[131]	5
L131b	6.0[131]	3
PTA (**L132**)	1.5[251]	2
DFPTA (**L135a**)	1.1[217]	2.5
DAPTA (**L135b**)	7.4[251]	3.5
L102c	2.4[217]	4.3
L136a	4.2[252]	3.25
L136c	0.04[191]	3.75

[a] Ratio of non-hydrogen atoms (minus P and atoms in water-solubilizing group) to the number of water-solubilizing groups.

L163 has a cloud point of 26 °C with an octameric PEG, 52 °C for $n = 16$, and 75 °C for $n = 25$. As will be discussed in section 3.1.2, the temperature dependent partitioning of the ligand can be seen in the hydrogenation of a water-soluble substrate. Below the cloud point, hydrogenation activity is observed. If the temperature is raised above the cloud point, the catalyst partitions into the organic phase and no further hydrogenation occurs until the temperature is lowered again.

Many water-soluble ligands have surfactant-like structures that cause them to be surface active, which means they will tend to accumulate at the boundary between the aqueous and organic phases. As will be discussed below, this can be desirable in terms of catalyst activity with hydrophobic substrates as it provides a mechanism for the catalyst and substrate to interact. *m*-TPPTS and *m*-TPPDS behave as electrolytes in solution and do not display surface active character.[87] In contrast, *m*-TPPMS, is surface active and will form micelles above its critical micelle concentration (CMC) of about 0.01 M.[400] Increasing the hydrophobicity of the ligand lowers the CMC. Amphiphilic ligand **L3a** has a CMC of 2×10^{-5} M, while the disulfonated analogue (**L3b**) has a CMC of 0.02 M.[86,87] In general, ligands with high water-solubility and the water-solubilizing groups near the coordination site will not be surface active, while those with lower water-solubility that have both hydrophobic and hydrophilic

regions will show surface activity. As mentioned, some surface activity can significantly improve catalyst activity. Ligands that readily form micelles can lead to stable emulsions that make separation of the aqueous and organic phases more difficult, however.

2.4.2. Steric and Electronic Effects of Water-Solubilizing Groups

Introduction of water-solubilizing groups can also affect the steric and electronic properties of the ligand, which can affect the activity of catalysts derived from these ligands. Unfortunately, this data is not available for the vast majority of hydrophilic ligands. The steric demand of *m*-TPPTS has been measured by a number of approaches, with a range of values reported. Using Tolman's correlation of ^{31}P NMR chemical shift and cone angle (θ) a cone angle value of 145° for *m*-TPPTS was obtained, which is the same as is obtained for PPh_3.[59,401] Using the correlation between the ^{31}P NMR shift of *trans*-L_2PdCl_2 gave a value of 166° for *m*-TPPTS, while PPh_3 gave a value of 145°.[138] Cone angle values ranging from 152° to 178° were obtained from crystal structures of free *m*-TPPTS and its complexes with iron and tungsten carbonyls.[83,402,403]

The structure of the *m*-TPPTS trianion calculated at the HF/3-21G* level of theory gave a cone angle value of 160° for *m*-TPPTS coordinated to a metal with a bond distance of 2.28 Å.[87] Using DFT level theory (B3LYP) the cone angle of *m*-$TPPTS^{3-}$ was calculated to be 183°.[91] Calculation of the gas phase structure of highly charged molecules, such as *m*-TPPTS, is challenging due to the strong charge repulsion effects. Using the structure of Pd(*m*-TPPTS) calculated at the local density theory level (LDFT-DZVP2), the cone angle of *m*-$TPPTS^{3-}$ was determined to be 155°.[85] The optimized Pd−P bond length was used in this calculation, rather than Tolman's idealized 2.28 Å. When the sulfonate charge was neutralized by attachment of a proton or sodium ion, the calculated cone angle increased to 164° and 165°, respectively. The trianion has a smaller cone angle due to the charge repulsion between the sulfonates, which increases the dihedral angle between the M-P bond and the phenyl ring. At the LDFT-DZVP2 level of theory, *m*-TPPTS was calculated to have a smaller cone angle than PPh_3 (172°). The calculated cone angle for Na_3TXPTS (**L2d**) was calculated to be 206°, which was also smaller than tri-(2,4-xylyl)phosphine (TXP, 214°). Bakos found a similar trend for the calculated cone angles of **L2d** (192°) and TXP (210°), although the difference was more significant.[404] Based on this limited data, the steric effect of the *meta*-sulfonate group is probably small and dependent on the particular system and the method of measurement.

Changing from the sulfonate substituent of *m*-TPPTS to the carboxylate of *m*-TPPTC does not change the cone angle of the ligand. Both *m*-TPPTS and *m*-TPPTC gave cone angles of 166° based on ^{31}P chemical shifts of their *trans*-L_2PdCl_2 complexes.[173] Using this method, the cone angle of *m*-TPPDG was determined to be 148°. The cone angle of *m*-TPPDS has not been determined under identical conditions, but a calculated value (HF/3-21G*) of 157° has been reported for *m*-TPPDS.[87] Thus, the steric impact of the guanidinium moiety is similar to that of sulfonate or carboxylate. In contrast, incorporation of a crown ether functionality fused to the 3,4-positions of the phenylphosphine did not have an impact on the steric demand of ligand **L144a** and **L144b**.[266]

To avoid changes in the steric environment of triarylphosphines when water-solubilizing substituents are introduced, attachment in the *para*-position is necessary. The cone angle of *p*-TPPTS (**L8c**) was determined to be 139.2° from crystallographic data, which is slightly smaller than the value of PPh_3 (141.5°) and significantly smaller than *m*-TPPTS (170.0°) obtained by the same method.[93] Tri-(4′-sulfonatobiphenyl)phosphine (**L7c**) and PPh_3 were both calculated (DFT/B3LYP) to have identical cone angles of 163°.[91] Similarly, sulfonation of aryl rings not adjacent to the phosphine center has little effect on the ligand steric parameter. Sulfonated of tri-(ω-(4-sulfonatophenyl)alkyl)-phosphines (**L30**) have nearly identical cone angles as the non-sulfonated precursors as determined from the ^{31}P NMR chemical shift of *trans*-L_2PdCl_2 complexes.[138]

Introduction of ionic substituents in proximity to the coordination site also affects the electron-donating ability of the ligand. The electron donating ability of *m*-TPPTS is less than that of PPh_3 as determined by the CO stretching frequency of *trans*-$L_2Rh(CO)Cl$ complexes.[85,87] Decreasing the number of sulfonate substituents or adding other electron-releasing substituents, such as methyl or methoxy, does not affect the electronic parameter as determined from CO stretching frequencies. Calculated electronic parameters (LDFT-DZVP2), such as the charge on phosphorus or the HOMO energy level, show that electron releasing groups do compensate for the withdrawing effect of the sulfonate substituent. Thus, TXPTS has a lower charge on phosphorus and a higher energy HOMO than *m*-TPPTS, although PPh_3 is still more electron-donating than TXPTS.[85]

As expected, separating the water-solubilizing group from the coordination site through nonconjugated spacers insulates the coordinating atom from the electronic effect of the water-solubilizing group. A sulfonated triarylphosphine (**L7c**, Table 1) with identical electronic properties to PPh_3 has been made by sulfonation of tri-(4-biphenyl)phosphine, which occurs selectively in the 4′-position.[91] Since the two phenyl rings are not conjugated, the sulfonate group does not affect the electron-donating ability of the phosphine. Separation of the phosphine center from the sulfonated aryl ring with methylene spacers can also insulate the phosphorus from the electronic effect of the sulfonate. A single methylene spacer is insufficient, as tri-(4-sulfonatobenzyl)phosphine is less electron-donating than tribenzylphosphine based on the higher carbonyl stretching frequency for its $LNi(CO)_3$ complex.[138] Adding additional methylene spacers between the sulfonated phenyl substituent and the phosphorus resulted in the sulfonated phosphines having identical electronic parameters to their non-sulfonated precursors, however.

When the ionic substituent is attached to the phosphorus center through short alkyl chains, the charge on the ionic substituent does affect the electron donating ability of the phosphorus center through an field effect. Alkylphosphines with alkyl ammonium substituents (**L98a,b** and **L100a,b**) are less electron-donating than similar neutral trialkylphosphines based on both CO stretching frequencies of metal carbonyl complexes and calculated electronic parameters.[129,405] In contrast, phosphines with alkylsulfonate substituents are more electron-donating than neutral trialkylphosphines. The nickel tricarbonyl complex of dicyclohexylphosphinoethylsulfonate (**L31**) gave a lower CO stretching frequency than that of *t*-Bu_3P, which is one of the most electron donating ligands known.[129]

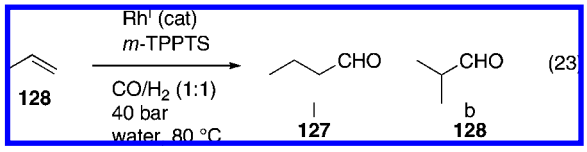
A comparison of *m*-TPPTS and *m*-TPPTC shows that the *m*-TPPTC ligand is more electron-donating than *m*-TPPTS based on the CO stretching frequency of the corresponding $L_2Mo(CO)_4$ complexes and the $^1J_{Se-P}$ coupling constants of the corresponding phosphine selenides.[173] Incorporation of phosphonate or sulfonate substituents in the *para*-position appears to make the phosphorus center slightly more electron-donating, in contrast to the effect seen with *meta*-sulfonated phosphines.[97] Surprisingly, the cationic guanidinium substituent in *m*-TPPDG results in a ligand that is more electron-donating than PPh_3 or *m*-TPPTS.

3. Catalytic Applications of Hydrophilic Ligands

3.1. Hydroformylation

3.1.1. Aqueous-Phase Hydroformylation of Lower Olefins

The starting point for the field of aqueous-phase catalysis can be traced to the development of the Rhône-Poulenc process for the hydroformylation of propene. At the time, Co-based catalysts dominated propene hydroformylation, but Rh-phosphine catalysts were known to be more active. The high cost of Rh compared to Co made its recovery critical for industrial application. A continuous, aqueous-biphasic process was developed in which the Rh could be isolated in water, while the water immiscible aldehyde products were recovered by decantation. For example, $[Rh(cod)(\mu\text{-}Cl)]_2$ and an excess of *m*-TPPTS catalyzed the hydroformylation of propene at 80 °C and 40 bar CO/H_2 pressure to give a 95% yield of *n*-butanal (**129**) along with 4% of isobutanal (**130**) after 4 h for a linear/branched (l/b) ratio of 24:1 (eq 23).[14,56,57] Although propene is only slightly soluble in water, it is sufficiently soluble to allow the reaction to proceed at a reasonable rate. Upon completion of the reaction, a two phase mixture is obtained that separated readily without foam formation. The aqueous phase contained the Rh−TPPTS complex and excess TPPTS along with a small amount of aldehydes, while the organic layer contained the products and a small amount of water. This process was commercialized in a plant in Oberhausen, Germany, in 1984. Initial capacity was 100,000 tons/year. The process saved 23,000 tons of propene annually compared to the Co process.



An excess of *m*-TPPTS is required to stabilize the catalyst system and give optimal activity.[406] Kalck reported that the catalyst derived from $[Rh(\mu\text{-}St\text{-}Bu)(CO)(m\text{-}TPPTS)]_2$ provided a more productive catalyst than $HRh(CO)(m\text{-}TPPTS)_3$, which is the species formed under the Rhône-Poulenc conditions.[407] The initial activity of the sulfide-bridged catalyst was lower than that of the monomeric species, but the sulfide-bridged dimer retained activity longer and ultimately gave a higher conversion to product.

In addition to *m*-TPPTS, a variety of other mono- and bidentate ligands have been applied to the hydroformylation of propene. Benzofuran-based ligands (**L6a**−**c**, Table 1) gave catalysts with significantly lower activity and l/b ratio than those derived from *m*-TPPTS.[90] The lower activity was attributed to **L6a**−**c** being more electron-rich than TPPTS, which would be expected to lead to a less active catalyst.[408] The authors suggested the lower l/b ratio was due to **L6a**−**c** being smaller than *m*-TPPTS. NORBOS (**L37**, Table 3) was found to give a much more active catalyst for propene hydroformylation than *m*-TPPTS when compared under identical conditions (**L37** = 118 mol of aldehyde/mol of Rh·min; *m*-TPPTS = 20 mol of aldehyde/mol of Rh·min), although *m*-TPPTS gave a higher selectivity for the linear aldehyde (94%) compared to **L37** (81%).[139] A low L/Rh ratio of 3.4 was used in this comparison, which is significantly below the optimal conditions for *m*-TPPTS (L/Rh = 20−100)

THMP (**L130**, Table 5) provided a moderately active Rh catalyst for the hydroformylation of 1-pentene.[254] Due to its very small cone angle, the THMP-based catalyst actually gave a slight preference for the branched product (l/b = 0.75). Amino acid-derived ligands **L76b**−**i** derived from THMP gave a rhodium catalyst with slightly higher activity for propene hydroformylation than the THMP-derived catalyst.[188] The l/b ratio was strong dependent upon the pH of the reaction solution. At pH = 2, low l/b ratios (0.8−1.2) were obtained, while higher pH (pI + 2 for the ligand) gave l/b ratios of 1.5−1.9. The catalyst derived from **L76b** was recycled, but the activity and l/b selectivity of the catalyst decreased with each use.

Chelating phosphines have shown improved activity as well as linear selectivity for the Rh-catalyzed, aqueous-phase hydroformylation of propene. The BISBIS ligand (**L53**, Table 5) gave an activity of 98 mol of aldehyde/mol of Rh·min and an l/b ratio of 97:3.[159] Changing the ligand backbone from biphenyl to binaphthyl (BINAS, **L56**), resulted in a significant increase in the activity of the resulting catalyst to 178 mol of aldehyde/mol of Rh·min as well as a slight increase to 98% linear selectivity.[139] In a pilot plant study, the Rh/**L56** catalyst system was shown to give nearly constant conversion to product over a 2 month period using P/Rh ratios of 10−50:1.[409] The Rh/**L53** system also showed good activity and recyclability with 1-butene.[410] Xantphos is a large bite-angle ligand that is known to give high linear selectivity in hydroformylation.[411] The sulfonated Xantphos ligand (**L14**, Table 1) gave a less active catalyst under low pressure (10 bar CO/H_2) than *m*-TPPTS, but gave a higher l/b ratio (30:1 compared to 16:1 for *m*-TPPTS).[104] The Xantphos/Rh catalyst could be recycled and the catalyst activity and l/b selectivity increased with each cycle. This increase was attributed to slow formation of the catalytically active species. Once formed, the catalyst was quite robust as it could be recycled in the absence of CO for 5 cycles.

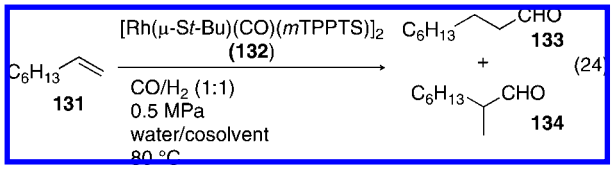
3.1.2. Strategies for Hydroformylation of Higher Olefins

While the Rhône-Poulenc system works well for propene, higher alkenes ($\geq C_6$) tend to give very low activity for aqueous-biphasic hydroformylation due to the very low solubility of these alkenes in water. For example, 1-octene is more than 3 orders of magnitude less soluble in water than 1-butene.[412] The high water-solubility of TPPTS, and the resulting Rh complexes, results in the catalysis taking place primarily in the aqueous reaction phase. A Co/*m*-TPPTS system showed good activity for 1-hexene hydroformylation at 100 °C, although very high catalyst loadings were used.[413] The chelating sulfonated phosphine DPPE-TS (**L38a**) gave a catalyst with slightly lower activity and similar l/b ratio to that obtained with *m*-TPPTS for the hydroformylation of 1-octene in water.[141] Sulfonated Xantphos (**L14**) showed modest activity for the hydroformylation of 1-hexene in water and high l/b ratio as well as 100% selectivity for

aldehyde formation.[104] A sulfonated, tridentate phosphine (**L45**) showed modest activity for the hydroformylation of 1-hexene (46% conversion) at 80 °C in 1:1:1 water/methanol/isooctane with a 2:1 l/b ratio, but the aldehyde selectivity was only 54%.[153]

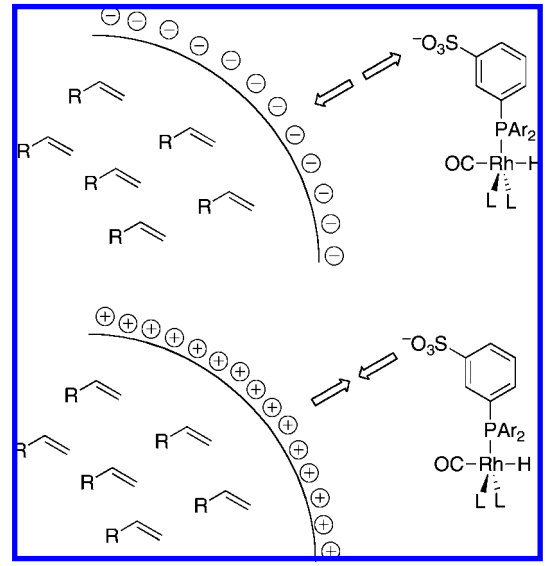
One approach to improving the activity for higher olefins in the Rh/*m*-TPPTS system is to use a water-miscible organic cosolvent to increase the solubility of the alkene in the aqueous phase, or of the catalyst in the organic phase. No aldehyde products were observed when 1-dodecene was hydroformylated with Rh/TPPTS (16:1 L/Rh) at 100 °C for 2 h in water. Addition of ethanol or propanol to the system (1:1 ROH/H_2O) resulted in 25% and 42% conversion to aldehyde under identical conditions.[414] Sulfonated tri(4-biphenyl)phosphine **L7c** was designed to give a water-soluble ligand with identical steric and electronic properties to PPh_3.[91] The catalyst derived from Rh(acac)$(CO)_2$ and **L7c** gave lower conversion (54%) for the hydroformylation of 1-decene in water/ethanol (80/20) than the *m*-TPPTS-derived catalyst (96%). The lower activity was attributed to **L7c** being more electron-donating than *m*-TPPTS.

Hydroformylation of 1-octene in water using [Rh(μ-S*t*-Bu)(CO)(*m*-TPPTS)]$_2$ (**132**) as the catalyst gave low conversions (<24%) after 15 h at 80 °C (eq 24).[415] Adding cosolvents, such as methanol, ethanol, or acetone, to the reaction system significantly increased the catalyst activity. For example, using water/methanol (3:1) as the solvent, the reaction reached 90% conversion in 10 h. The linear selectivity decreased with addition of the cosolvent, however. Since alcohols are more soluble in aldehydes than olefins, the cosolvent leaches into the product phase unless an additional hydrophobic cosolvent is used.[416] This leaching may also lead to increased solubility of the Rh complex in the organic phase. In addition, alcohol cosolvents can lead to undesirable reactions, such as acetal formation, unless the reaction pH is kept high.



The use of compressed CO_2 to promote the separation of miscible liquids has received significant attention in separations and for catalyst recovery.[417] 1-Octene is approximately 10,000 times more soluble in the monophasic 70:30 THF/water solvent system than in water alone (2.7 ppm).[418] Introduction of pressurized CO_2 results in phase separation to give a CO_2-expanded THF layer and a water layer with little CO_2. At a CO_2 pressure of 32 bar, *m*-TPPMS partitions into the water layer with a distribution coefficient of 2000. At this CO_2 pressure, nonanal has approximately a 1000:1 preference for the CO_2/THF layer.[419] Thus, hydroformylation of 1-octene can be carried out in a miscible THF/water solvent system using Rh/*m*-TPPTS as the catalyst system. At 80 °C with 31 bar CO/H_2 (1:1), the *m*-TPPMS/Rh (10:1 L/Rh) catalyst system gave 85% conversion to aldehydes (390 mol of aldehydes/mol of Rh·h) and a 2.4:1 l/b ratio. These results were similar to those obtained with PPh_3 under the same conditions (91% yield, 457 mol of aldehydes/mol of Rh·h, 2.7:1 l/b ratio). Separation could be achieved by replacing the syn gas pressure with CO_2. The catalyst was used for three reaction cycles with no change in the turnover frequency.

Scheme 29

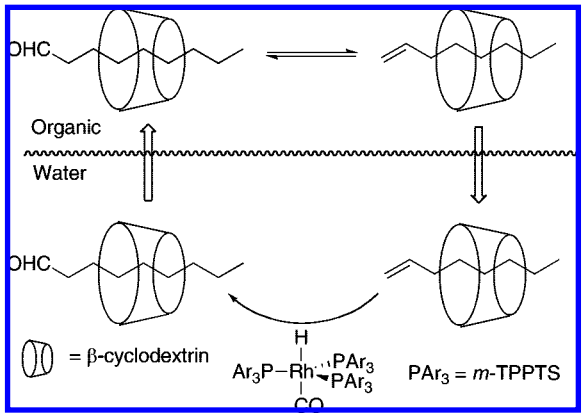


An alternative approach to increasing the hydroformylation activity of higher olefins in water is to use surfactants to provide micelles in which the hydrophobic substrate can be sequestered. The micelles serve to significantly increase the water/organic interfacial area. Cationic surfactants, such as cetyltrimethylammonium bromide (CTAB), significantly improve the activity for hydroformylation of 1-dodecene in water. With no surfactant, no conversion was seen after 2 h, but addition of CTAB increased the yield of aldehyde to 61% in the same time using a Rh/*m*-TPPTS catalyst system.[414] Reactions run with the cationic surfactant gave an l/b ratio to 6, which was higher than that obtained with ethanol as a cosolvent (3.4). The CTAB surfactant has also been used in hydroformylation of hydrophobic olefins catalyzed by **L2a,b**/Rh[82] and **L53**/Rh in water.[420] Dicationic surfactants provide even higher levels of catalyst activity and increased l/b ratio than CTAB in the hydroformylation of higher olefins using Rh/*m*-TPPTS.[421−423] No conversion of 1-dodecene was observed with the anionic surfactant sodium dodecylsulfate (SDS), while neutral surfactants (Tween 20 and Spam 40) gave only low conversion (3−4%).

The unique accelerating effect of cationic surfactants suggests they play more than just a simple role of forming micelles in which the hydrophobic substrate can be dispersed in the aqueous phase. It has been proposed that the cationic surface of the micelles derived from CTAB attract the anionic Rh-*m*-TPPTS complex (Scheme 29). Thus the local concentration of the catalyst at the micelle surface is much higher than it would be in the case of a neutral surfactant, while an anionic surfactant would be expected to repel *m*-TPPTS.[414]

A similar trend was observed in hydroformylation of 1-octene using cross-linked polystyrene-PEG latexes as promoters. Latexes with ammonium groups on the PEG terminus gave the highest conversion, while sulfonate- and alcohol-terminated PEG latexes were ineffective promoters.[424] All three latexes dissolved significant amounts of 1-octene and showed a preference for uptake of octane over nonanal, thus the difference in effectiveness appears to be related to the interaction of the catalyst and the latex. 1-Methyl-3-octylimidazolium bromide ([C_8mim][Br]) has also been used as a cationic promoter of hydroformylation.[425] Hydroformylation of 1-octene in the presence of 0.5 M [C_8mim][Br] using the standard Rh/*m*-TPPTS hydroformy-

Scheme 30



lation system gave a TOF of 1,105 mol/mol of Rh·h, while the TOF was 10 mol/mol of Rh·h in the absence of the imidazolium salt. [C_6mim][Br] gave only a small increase in activity (47 mol/mol of Rh·h), while [C_{10}mim][Br] gave a higher TOF (1,239 mol/mol of Rh·h) but gave a stable emulsion that could not be separated at the end of the reaction.

Despite the apparent superiority of cationic surfactants in TPPTS/Rh-catalyzed hydroformylation, positive results have been seen in microemulsions generated from neutral surfactants. Ethoxylated fatty alcohol surfactants (Lutensol ON, $C_{10}H_{21}(OCH_2CH_2)_nOH$) have shown the ability to promote hydroformylation of higher olefins.[426] Lutensol ON 70 gave the best results, while other Lutensol surfactants gave irreversible emulsions that made phase separation difficult. The use of anionic surfactants have also been reported, although in at least one case the amount (0.5−10 wt %) of SDS surfactant did not affect the yield or selectivity of the reaction. This result raises the question of whether the SDS had any positive effect.[141] Hydroformylation of 1-octene with polycarboxylate-supported phosphine **L158** was accelerated in the presence of SDS, however.[293] In the absence of SDS, 25% conversion was obtained after 15 h; while with 10 mM SDS 100% conversion occurred after only 6 h.

An alternative approach to solubilizing higher olefins in water is the use of cyclodextrins as inverse phase transfer catalysts. Cyclodextrins (CD) are able to form inclusion complexes with hydrophobic substrates and carry them into the aqueous-phase to react with the water-soluble catalyst (Scheme 30). This concept was first demonstrated by Monflier, who showed that per-methylated β-cyclodextrin increased the rate of hydroformylation of hydrophobic alkenes, such as 1-decene, by up to a factor of 10.[427] The degree of methylation is an important parameter in these systems. Dimethylated β-cyclodextrin (DM-β-CD) was found to give higher yields in the hydroformylation of higher olefins than β-cyclodextrin (β-CD) using [Rh(μ-S*t*-Bu)(CO)(*m*-TPPTS)]$_2$ as the catalyst.[428] The higher effectiveness of the DM-β-CD compared to unmodified β-CD was attributed to the higher organic solubility of DM-β-CD. Randomly methylated β-CD containing an average of 12.6 methyl groups/CD ring (RAME-β-CD) was found to be a highly effective promoter for hydroformylation of higher olefins catalyzed by Rh/*m*-TPPTS.[429−431] The effectiveness of RAME-β-CD is believed to be due to its surface-active behavior and the lower stability of the aldehyde inclusion complex compared to β-CD. RAME-β-CD was also found to be effective in the Rh/**L14**-catalyzed hydroformylation of

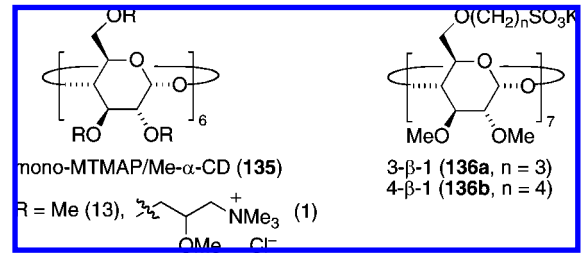


Figure 2. Cyclodextrin derivatives with ionic substituents.

1-octene and 1-decene.[432] Octene conversion increased from 19% without RAME-β-CD to 90% with the cyclodextrin. Aldehyde selectivity and l/b ratio also increased when the CD was used. The highest l/b ratio was achieved with RAME-α-CD. The steric congestion of the CD-supported olefin and Rh/**L14** complex is believed to account for the increased linear selectivity.

Monflier reported the application of an α-CD derivative functionalized with quaternary ammonium ions (MTMAP-α-CD, **135**) in higher olefin hydroformylation (Figure 2).[433] The cationic CD was designed to favorably interact with the anionic *m*-TPPTS-supported catalyst. MTMAP-α-CD gave somewhat better results for the hydroformylation of 1-decene than RAME-α-CD, particularly at longer reaction times. A heptaalkylsulfonate analogue of β-CD 3-β−1, **136a**) also gave higher activity for hydroformylation of 1-decene than did RAME-β-CD.[434] The aldehyde selectivity was much lower (60%) than with RAME-β-CD, however. The aldehyde selectivity and l/b ratio obtained with **136a** were nearly identical to those obtained without cyclodextrin present. Using a β-CD with a butylsulfonate water-soluble element (**136b**) in place of the propylsulfonate of **136a** gave a high hydroformylation rate (250 mol of aldehydes/mol of Rh·h compared to 210 mol of aldehydes/mol of Rh·h), with no change in the aldehydes or l/b selectivity.[435]

Sulfonated chelating diphosphines have also been studied in the presence of cyclodextrin mass transport promoters.[150] In the absence of CD, conversion decreased in the series DPPE-TS (**L38a**) > DPPP-TS (**L38b**) > DPPP-TS (**L38b**), which corresponds with increasing chelate ring size, while the l/b ratios were comparable for these three ligands. In the presence of RAME-β-CD, higher activity was seen for all three ligands, but the trend was reversed **L38a** < **L38b** < **L38c**. The cyclodextrin also decreased the l/b ratio from 2.6−3 in the absence of CD to 1.2−1.9 in the presence of the CD. These results are in contrast to sulfonated Xantphos (**L14**) where the cyclodextrin resulted in higher regioselectivity. Studies of the interaction of the catalyst interacting with RAME-β-CD showed that the cyclodextrin induced opening of the chelate to give a monodentate rhodium complex, which displayed lower regioselectivity.

Reetz has attached chelating phosphines to cyclodextrins (**L156** and **L157**, Table 11) in order to keep the catalyst near the mass transfer agent.[286] The catalyst derived from **L157** gave complete conversion of 1-octene to aldehyde after 18 h at 80 °C with >99% selectivity and a 3:1 l/b ratio. In contrast, *m*-TPPTS/Rh gave <1% conversion under the same conditions. Nearly identical results were obtained with **L156**. Recovery of the catalyst and reuse showed that the aqueous solution retained only about 50% of the original activity. In addition, up to 90 ppm of Rh was observed in the organic phase after the reaction. Shimizu has reported hydroformylation using phosphine ligands with sulfonated calix[4]arenes appended to them (**L42**).[146,436] The calixarene acts as a mass

transport promoter in a similar fashion to the cyclodextrins. A combination of Rh(acac)$(CO)_2$/**L42a** gave 55% conversion of 1-octene with 40% yield of aldehyde at 100 °C after 12 h. In comparison, *m*-TPPTS/Rh gave only a trace of aldehyde, which could be increased to 21% yield in the presence of DM-β-CD. The catalyst derived from **L42b** was used for 3 reaction cycles and the yield of aldehyde increased from 73% to 86% from the first to third cycle. The l/b ratio also increased slightly from 1.7 to 2.0.

Chaudhari addressed the issue of mass transport by using both hydrophobic (PPh_3) and hydrophilic (*m*-TPPTS) ligands for the hydroformylation of 1-octene in water.[437] In the absence of PPh_3, little hydroformylation activity was observed. The activity increased dramatically (>100-fold) upon addition of 0.33 equiv of PPh_3/Rh. A concern when adding a hydrophobic ligand is that some of the Rh would leach into the organic phase. The organic phase contained <5 ppm of Rh after the catalytic reaction and no catalytic activity was seen with the recovered organic phase, however. Thus Chaudhari concluded that the catalysis occurred at the water/organic interphase and that the catalyst was retained in the aqueous phase. In contrast, Kalck concluded that the catalysis occurs in the organic phase with a similar mixed ligand system based on a dimeric Rh precatalyst.[438,439] The l/b ratio in this system was 3/1, which was consistent with the hydroformylation occurring in the organic phase. A higher l/b ratio would be expected if the reaction occurred in the aqueous phase.[440] Significant amounts of PPh_3-Rh complexes were observed in the organic phase, which suggested that significant leaching would occur in this system. Furthermore, Kalck showed that the equilibrium between $[Rh(\mu\text{-}S\textit{t}\text{-}Bu)(CO)(\textit{m}\text{-}TPPTS)]_2$ and $[Rh(\mu\text{-}S\textit{t}\text{-}Bu)(CO)(PPh_3)]_2$ strongly favored the PPh_3 complex. The discrepancy between the results of Chaudhari and Kalck are difficult to reconcile. It should be noted that the rhodium precursor in Chaudhari's system was $[Rh(cod)Cl]_2$, while Kalck used $[Rh(\mu\text{-}S\textit{t}\text{-}Bu)(CO)(\textit{m}\text{-}TPPTS)]_2$ as the precatalyst. Thus it is possible that the equilibrium between the *m*-TPPTS- and PPh_3-bound complexes may different for the two rhodium precursors.

Another approach that has received much attention is the development of ligands that can act as surfactants themselves. While *m*-TPPTS has essentially no surface activity, *m*-TPPMS shows surface activity as evidenced by the formation of emulsion layers and foaming of solutions of *m*-TPPMS.[441] The CMC for *m*-TPPMS is 0.01 M.[400] Interestingly, the carboxylate analogue of *m*-TPPTS, *m*-TPPTC (**L62c**, Table 6) provides a much more effective catalyst for hydroformylation of higher olefins in water. Using *m*-TPPTS, only 2% conversion was seen after 3 h in the hydroformylation of 1-octene at 80 °C. In contrast, *m*-TPPTC gave 94% conversion with 87% aldehyde selectivity under the same conditions.[442] With 1-decene, *m*-TPPTC gave only 16% conversion, however. Surface tension studies showed that *m*-TPPTC behaved as a surfactant with a CMC of approximately 0.01 M, which may account for the higher activity of catalysts derived from *m*-TPPTC compared to *m*-TPPTS. In the presence of RAME-β-CD, **L62c** gave complete conversion of 1-octene at 80 °C after 3 h, while *m*-TPPTS gave 91% conversion. The aldehyde selectivity and l/b ratios are nearly identical. With 1-dodecene, *m*-TPPTC gave 88% conversion in the presence of RAME-β-CD, while *m*-TPPTS gave only 31% conversion with similar selectivity.

Amphos (**L96**, Table 8) is an early example of a more surfactant like ligand than *m*-TPPTS. Rh[207] and Co[208] catalysts derived from **L96** gave good conversion for hydroformylation of 1-hexene. The Co system gave roughly equal amounts of linear, branched, and alcohol products. In the Rh system, a higher l/b ratio was observed (3.4−4.6). Good activity was seen over the pH range of 5.8−6.8, but both activity and aldehyde selectivity decreased below pH 5. Diphenylphosphinoalkylsulfonates (**L23** and **L26**, Table 3) gave TON values of up to 50,000 mol/mol of Rh for the hydroformylation of 1-decene in water.[118] The use of CTAB and SDS were explored, but did not give better activity in most cases, although a non-ionic surfactant showed some positive effects. Diphenylphosphinoalkylphosphonates (**L81**, Table 6) and *p*-TPPDP (**L69b**) were tested in the hydroformylation of 1-octene in water at 120 °C.[178,193,443] The best ligands in this study were $Ph_2P(CH_2)_nPO_3Na_2$ (**L81**, $n = 10$, 12), which gave >90% yield of aldehyde with >4:1 l/b ratio. More hydrophilic ligands with shorter alkyl chains or **L69b** gave primarily olefin isomerization, although aldehyde yields were still higher than obtained with *m*-TPPTS. *m*-TPPTS gave 83% internal octenes and only 17% aldehyde products. A polycarboxylated chelating diphosphine (**L161**) gave good activity in the hydroformylation of 1-dodecene (45% conversion after 1.5 h at 90 °C).[292]

Reaction of tripyridylphosphine with sultones gave surfactant ligands **L12** (Table 1) that were good promoters of high olefin hydroformylation.[98] The best ligand for the hydroformylation of 1-tetradecene had hexyl ($n = 5$) tails on the sulfobetaine substituent. The activity of the catalyst dropped off dramatically if the ligand became less ($n = 3$) or significantly more ($n = 9$) hydrophobic. Despite the surface active character of the ligand, it could be recovered quantitatively by simply allowing the phases to separate upon completion of the hydroformylation reaction. Partially sulfonated ligands with *t*-butylphenyl substituents (**L3a** and **L3b**) gave higher activity and l/b ratio in the hydroformylation of higher 1-alkenes.[87] Disulfonated ligand **L3b** was superior to *m*-TPPDS, which shows that the *t*-butyl group has a beneficial effect presumably due to increased surface active character for the ligand. Ligand **L3b** gave the best results with 1-hexene, while the monosulfonated **L3a** ligand was most effective for the more hydrophobic 1-dodecene substrate.

A variety of phosphine architectures with ω-(4-sulfonatophenyl)alkyl substituents have been prepared as surface active ligands to improve activity of high olefin hydroformylation. The first examples were trialkylphosphines **L30**, in which the arylsulfonate substituents was separated from the phosphorus center by an alkyl chain.[127] In the hydroformylation of 1-octene in water at 120 °C for 15 h, **L30** ($n = 2$) gave 70% conversion, while *m*-TPPTS gave only 30% conversion. The l/b ratio was lower with **L30** due to the smaller size the ligand, however. The catalyst activity increased with increasing alkyl chain length, consistent with the importance of surfactant character on improving catalyst activity. Triarylphosphines with 4-(ω-(4-sulfonatophenyl)alkyl)phenyl substituents (**L5a,b**, Table 1) were prepared to give surface active ligands that had more similar properties to PPh_3 than **L30**.[89,444] Higher hydroformylation activity for 1-octene was obtained with **L5a** and **L5b** than *m*-TPPTS, with the most dramatic effect being at low (2:1) L/Rh ratios. The selectivity for aldehyde and l/b ratio was also higher for **L5a** and **L5b** than *m*-TPPTS. The solution properties of **L5a,b** were unclear based on initial studies. The hydrodynamic radius of the ligands suggested no aggregation, except

in the presence of salt. In contrast, studies with a hydrophobic dye suggested micellar character.

Chelating diphosphines with 3-(ω-(4-sulfonatophenyl)alkyl)phenyl substituents based on BINAP (**L17b**) and BISBI (**L55**) were applied to the hydroformylation of 1-octene in water at 120 °C.[112] The BINAP-based ligand gave similar or lower activity catalysts compared to *m*-TPPTS. In contrast, the BISBI-based ligand showed somewhat higher efficiency than the *m*-TPPTS-based complex. With a 7:1 P/Rh ratio, the **L55**/Rh complex gave a 73% yield of aldehyde after 5 h with a 94:6 l/b ratio. The *m*-TPPTS-derived catalyst gave a 54% yield and a 76:24 l/b ratio under the same conditions. Analysis of the organic and aqueous phases from these reactions showed no measurable Rh in the organic phase for either *m*-TPPTS or **L55**, while the aqueous phase contained the same amount of Rh as originally charged in each case. Similarly, surface active derivatives of Xantphos (**L15**) were found to give more active catalysts for the hydroformylation of 1-octene in water than **L14**, while delivering the same high linear aldehyde selectivity (>95%).[109] The catalyst derived from **L15** was able to be used for 4 reaction cycles with no decrease in activity or selectivity. No aggregation was seen for **L14** based on its hydrodynamic radius of 1 nm, while **L15** gave a hydrodynamic radius of 63 nm. Vesicles formed by **L15** could be observed by electron microscopy.

By attaching ligand sites to amphiphilic polymers, it is possible to ensure that the catalyst remains close to the substrate containing micelle. Poly(oxazoline)-supported triphenylphosphine (**L177**) was applied to the hydroformylation of 1-octene in water.[309] The supported ligand gave approximately twice the TOF than the hydroformylation carried out with Rh/*m*-TPPTS in the presence of a poly(oxazoline) lacking the supported phosphine. Although the polymer support appeared to constrain the Rh to the aqueous-phase, catalyst activity of recovered catalyst was significantly lower. On the second cycle, the catalyst had 59% of the original activity and dropped to 13% activity after two more cycles. A rhodium-carbene catalyst was attached to an amphiphilic, water-soluble oxazoline polymer (**L251**) and applied to the hydroformylation of 1-octene.[396] The polymer-bound Rh complex was only 50% as active as the small molecule analogue, however. When the catalyst was recycled, its activity increased over the next two cycles until it was nearly identical to that of the small molecule analogue. As the activity increased, the l/b ratio decreased from 2.6 to 1.2. The monomeric catalyst gave an l/b ratio of 0.67. The slow increases in catalyst activity was believed to be due to slow conversion of the Rh−Br precatalyst into the catalytically active Rh−H species. The Rh-NHC catalyst gave poor chemo- and regioselectivity, with significant amounts of olefin isomerization occurring.

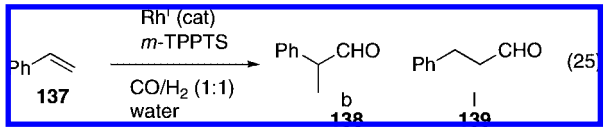
The largest weakness of aqueous-biphasic catalysis is the mass transport issue. The ideal catalyst would have controllable solubility properties, so that it could be induced to go into the substrate phase under one set of conditions, but return to the aqueous phase under an alternate set of conditions. One approach is to carry out the reaction using an ionic ligand (**L33**) in a polar solvent (NMP) under homogeneous conditions.[445] Upon completion of the reaction, water can be added to give a biphasic mixture with the aldehyde products in the organic phase and the catalyst in the aqueous phase. Another variation on this theme is to use pH responsive ligands that can be converted from lipophilic to hydrophilic by changing pH. Amine functionalized ligands **L109a** and **L109b** gave nearly identical performance to that of PPh_3 in the Rh-catalyzed hydroformylation of 1-octene in toluene.[226] These ligands partition completely into the organic phase of a organic/aqueous biphase at pH values above 5.5, but can be partitioned completely into the aqueous-phase below pH 3 for **L109b** and pH 2 for **L109b**.[399] Using this pH responsive solubility, hydroformylation could be carried out in toluene followed by extraction of the active species into acidic water (pH = 2). Approximately 2% of the rhodium remained in the organic phase. Raising the pH to 7 allowed the catalyst to be extracted into a new organic phase (1.5% Rh loss) and reused. Under optimized conditions, the recovered catalyst retained 86% of its original activity. A triamine functionalized ligand **L110** gave similar results.[231] The loss of activity is likely due to decomposition of the catalyst under the strongly acidic and basic conditions used for recovery.

pH-responsive chelating diphosphines with biphenyl (**L116**) and bipyridyl (**L117**) backbones were prepared to provide more selective catalysts for hydroformylation higher alkenes.[233] **L116** gave a more active catalyst for the hydroformylation of 1-octene in toluene than did the unfunctionalized BISBI ligand, while **L117** gave a slightly less active catalyst than BISBI. The selectivity for linear aldehyde was similar for all three ligands. **L116** could be extracted into pH 1.8 water from toluene with about 95% efficiency. When the sodium bicarbonate was added to raise the pH, a green precipitate formed and only about 5−10% of the rhodium could be extracted into a new organic phase. The recycling of **L117** occurred much more efficiently with only 1% loss on each step. The recovered catalyst retained 72% of its original activity. Amine-functionalized Xantphos derivative **L115** gave much better results.[232] Upon extraction into water and then recovery into a new organic phase, 98% of the rhodium was retained. The recovered catalyst solution retained 86% of the original activity. While these results are an improvement, the loss of 14% of the original activity and 2% of the rhodium makes this impractical for industrial application.

Surfactants with PEG as the water-solubilizing substituents display interesting inverse temperature-dependent solubility when the correct hydrophobic/hydrophilic ratio is maintained. The Jin group has prepared a variety of triphenylphosphine derivatives with PEG substituents (**L163** − **L165**) that have cloud points ranging from 26 to 95 °C.[294−296] Ligand **L164** has a cloud point of 68 °C. At 70 °C, the catalyst derived from **L164** and Rh gave a TOF 21 mol of aldehyde/mol of Rh·h for the hydroformylation of 1-decene in water/toluene (3:2). Increasing the temperature to 80 °C gave a slight increase in activity to 53 h^{-1}, but at 90 °C the TOF increased to 163 h^{-1}. The catalyst derived from **L165** (cloud point = 92 °C) showed a similar trend, which an increase in the TOF from 318 h^{-1} to 418 h^{-1} upon increasing the temperature from 90 to 100 °C. At room temperature the catalyst derived from **L165** is located exclusively in the aqueous phase, which could be used for 20 reaction cycles with only a 5% loss in catalytic activity. Similar results have been reported using phosphonites, phosphonates, and phosphites derived from PEG.[299,300]

3.1.3. Aqueous-Phase Hydroformylation of Styrene Derivatives

While hydroformylation of 1-alkenes typically occurs to preferentially give the more desirable linear aldehydes, styrene hydroformylation typically gives branched products. Since these branched aldehydes are potential precursors to pharmaceutically active 2-phenylpropanoic acids, the branched isomer is generally preferred. *m*-TPPTS/Rh catalysts showed good activity for styrene hydroformylation in aqueous-biphasic systems at lower temperatures (50 °C) than are typical for 1-alkenes with similar carbon numbers (eq 25). Styrene hydroformylation with a family of furylphosphines functionalized with sulfinate, carboxylate, and phosphonate water-solubilizing groups (**L72a**, $n = 2$) generally gave more active catalysts than *m*-TPPTS.[181] As was seen with higher 1-alkenes, more surface active ligands generally gave better results. In the carboxylated series, **L72a** ($n = 2$) with two carboxylated furyl substituents gave optimal activity, while the more water-soluble **L72a** ($n = 3$) and less water-soluble **L72a** ($n = 1$) gave lower activity catalysts. Only in the case of the sulfinate-substituted ligands **L72b** did activity increase with increasing water-solubility. Chelating ligand DPPPTS (**L38b**) gave a 72% conversion of styrene at 80 °C with a 81:19 b/l ratio, but only a 61% selectivity for aldehyde.[446] Adding methanol as cosolvent improved both the chemo- (100% aldehyde) and regioselectivity (93:7 b/l).



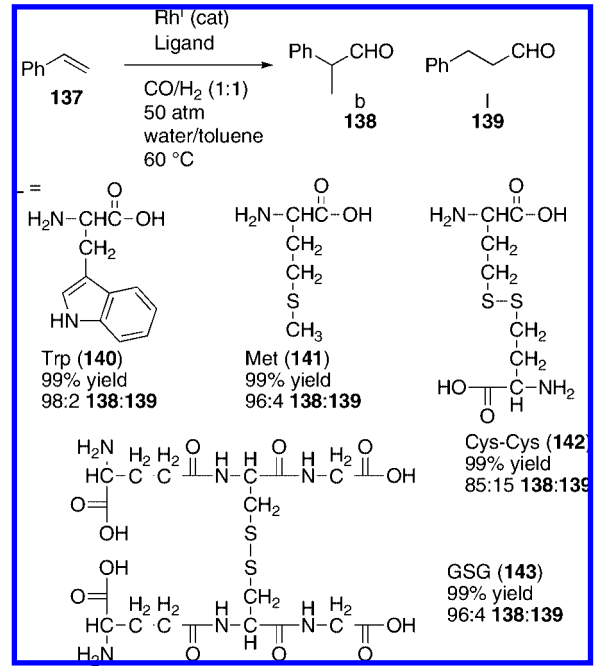
A catalyst formed by the combination of $Rh(CO)_2(acac)$ and human serum albumin (HSA) was found to give an effective catalyst for the hydroformylation of styrene in water.[447,448] Complete conversion with >99% aldehyde selectivity and 19:1 b/l ratio was achieved at 60 °C after 24 h. This catalyst was also applied to 1-octene hydroformylation, although the l/b ratio was low (1.1). The catalyst also showed good recyclability with no loss of activity until the sixth cycle. After ten cycles the catalyst solution still maintained 75% of the original activity. Based on this success, simple amino acids or peptides were sought that would show similar activity.[449] Tryptophan and methionine in combination with Rh both gave quantitative conversion to aldehyde after 16−21 h at 60 °C with high selectivity (Scheme 31). The disulfides of L-cystine (**142**) and glutathione (**143**) as well as vancomycin also gave active and highly selective catalysts. The vancomycin-derived catalyst gave exclusively the branched aldehyde isomer.

Since the branched product is formed selectivity, there has been an interest in designing catalysts for asymmetric hydroformylation of styrene. A challenge to accomplishing the asymmetric hydroformylation in water is avoiding racemization of the aldehyde once formed as the reaction systems are typically at least slightly basic (Scheme 32). The first attempt to promote asymmetric hydroformylation of styrene in water used surface active menthyl-substituted ligand **L32**.[130] Ligand **L32** was found to give a more active catalyst for styrene hydroformylation than *m*-TPPTS and gave comparable b/l ratios (2:1). No enantioselectivity was observed with this ligand, however.

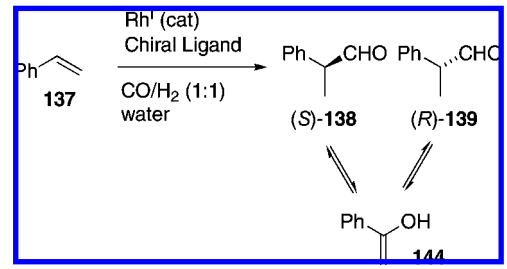
The chelating BINAS ligand (**L53**) gave good conversion and regioselectivity for the branched product, but only 18% ee in toluene/methanol/water.[450] The non-sulfonated parent ligand (NORPHOS) gave 32% ee under similar conditions in toluene. Chiral ligands **L46** and **L51a** also gave ineffective catalysts for the asymmetric hydroformylation of styrene.[162,446] A 17% ee (67% conversion) was obtained at 50 °C using **L51a** under buffered conditions (pH 7). If the solution was not buffered, a lower ee (9%), but higher conversion (76%) was obtained. Ligand **L46** showed better enantioselectivity (44% ee) at 65 °C, but the conversion was only 10% after 8 h. At 30 °C, 66% ee was obtained, but with only 2% conversion after 72 h. The enantioselectivity values with **L46** and **L51a** were comparable to those obtained in organic solvents with the non-sulfonated parent ligands BDPP and CBDP. A PEG-substituted, binaphthol-based phosphite (**L174a,b**) gave a maximum of 25% ee for styrene hydroformylation at 40 °C with 100% conversion.[306]

Water can serve as more than just the solvent in hydroformylation reactions. Because rhodium complexes also catalyze the water-gas shift reaction, water can be used as the hydrogen source. Hydroformylation of 1-hexene at pH 6 and 80 °C under CO, but in the absence of H_2, using $HRh(CO)(m\text{-TPPTS})_3$ as the catalyst gave heptanal at the rate of 6.6 mol/mol of Rh·h.[440,451] The rate could be increased to 28 mol/mol of Rh·h by using the dimeric $[Rh(\mu\text{-}St\text{-}Bu)(CO)(m\text{-TPPTS})]_2$ catalyst precursor. The optimal activity (40 mol/mol of Rh·h) was achieved at pH 4.8. Interestingly, the presence of olefin significantly increased the production of hydrogen over the water-gas shift reaction alone.

Scheme 31



Scheme 32



3.2. Hydrogenation

3.2.1. Olefin Hydrogenation

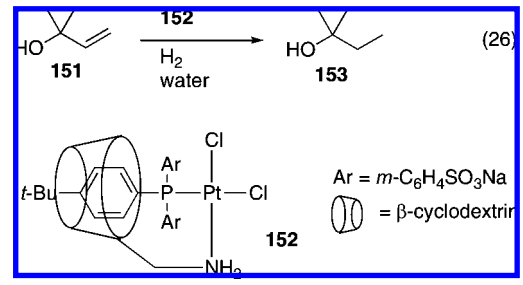
One of the earliest examples of the use of a hydrophilic ligand for aqueous-phase catalysis was reported by Chatt.[244] Chatt applied rhodium complexes of THMP (**L130**, Table 11) to the hydrogenation of 1-octene in ethanol and water. Rapid hydrogenation occurred in ethanol, but no activity was seen in water, even with maleic acid. Chatt concluded that, "these complexes show no obviously useful catalytic properties." THMP complexes of ruthenium and iridium have shown some promise in hydrogenation reactions, however. Cp*Ru(THMP)(CO)Cl gave a modestly active catalyst for the hydrogenation of sorbic acid in water/hexane to give a mixture of hexanoic acid and 2- and 3-hexenoic acids.[452] The THMP-based catalyst was more active than the analogous *m*-TPPTS complex. Ir(cod)(THMP)Cl catalyzed the reduction cinnamaldehyde with good selectivity for reduction of the aldehyde to give cinnamyl alcohol at 100 °C and 100 atm of H_2.[254]

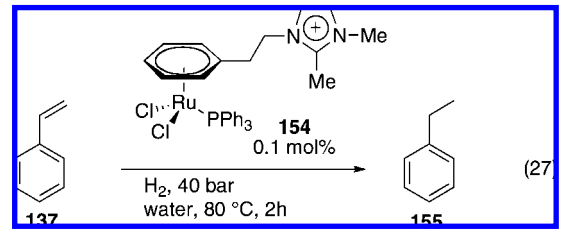
Early examples of alkene hydrogenation in aqueous-biphasic systems using sulfonated triaryl phosphines were reported independently by Manassen,[453] Joó,[454] and Wilkinson.[441] Manassen found that the complex derived from *m*-TPPMS and $RhCl_3 \cdot 3H_2O$ gave low activity for hydrogenation of cyclohexene in water, but improved activity was obtained by adding methanol or ethanol as a cosolvent. Joó applied RuH(OAc)(*m*-TPPMS)$_3$ to the hydrogenation of unsaturated acids in water. Activities between 92 and 198 mol/mol of Ru·h were obtained at pH 4.8, but the activity decreased at lower pH. Wilkinson reported that RhCl(*m*-TPPMS)$_3$ was moderately active for hydrogenation of terminal 1-alkenes in water without cosolvent, although alkene isomerization was a competitive process. The rhodium complex was more active than HRuCl(*m*-TPPMS)$_3$. HRu(CO)Cl(*m*-TPPMS)$_3$ was found to give modest activity for hydrogenation of styrene (3 h^{-1}) and cyclohexene (1 h^{-1}) at 100 °C under 1000 psi of H_2.[455]

$[RuCl_2(m\text{-TPPMS})_2]_2$ provided an effective catalyst for the hydrogenation of phenylacetylenes to styrene or alkylbenzene derivatives.[456] The reactions were strongly affected by pH. Low activity for hydrogenation of both diphenylstilbene and 1-phenylpropyne were seen at low pH, but the activity increases dramatically above pH 6. The product selectivity also shows dramatic changes as the pH was raised above 6. At low pH, the hydrogenation of diphenylacetylene gave *Z*-stilbene with high selectivity (Scheme 33). Above pH 8, a 2:1 mixture of 1,2-diphenylethane and *E*-stilbene was produced with essentially no *Z*-stilbene present. Similarly, reduction of 1-phenylpropyne gave a 2:1 mixture of *Z*-1-phenyl-1-propene and allylbenzene at pH <5, while above pH 8, a mixture of *E*-1-phenyl-1-propene, propylbenzene, and allylbenzene was produced with <5% *Z*-alkene. These results correlate with different Ru-hydride species observed when the dichloride complex was treated with H_2 at different pH values in the presence of excess *m*-TPPMS.[457,458] Below pH 6, $[Ru(H)Cl(m\text{-TPPMS})_2]_2$ (**146**) and Ru(H)Cl(*m*-TPPMS)$_3$ were formed; while above pH 8 the only species seen was $RuH_2(m\text{-TPPMS})_4$ (**147**).

$RuCl_2(m\text{-TPPTS})_3$ showed modest activity (ca. 3 h^{-1}) for hydrogenation of 1-heptene, styrene, and cyclooctene in water at 150 °C and 1 atm of H_2.[63] This complex also showed some activity for the hydrogenation of benzene, which could be improved by adding $ZnCl_2$. The activities with the *m*-TPPTS complex were lower than obtained by Joó[454] with a Ru^{II}/*m*-TPPMS catalyst (60 °C, 1 atm of H_2), which may be due to the higher surface active character of *m*-TPPMS. Similar activity was obtained using $W(CO)_3(CH_3CN)_2$(*m*-TPPTS) for the hydrogenation of 1-hexene (<2 h^{-1}) at 100 °C and 1000 psi of H_2 in the presence of CTAC.[459] No activity was observed when the surfactant was not used. Ruthenium carbonyl clusters with the formula $Ru_3(CO)_{12-x}(m\text{-TPPTS})_x$ gave much more active hydrogenation catalysts than monomeric Ru/*m*-TPPTS complexes.[460] Hydrogenation of 1-octene with $Ru_3(CO)_{11}$(*m*-TPPTS) gave a TOF of 76 mol/mol of Ru·h at 60 °C with 60 atm of H_2, while styrene was hydrogenated at a rate of 490 mol/mol of Ru·h. Benzene was also hydrogenated with this system at a rate of 45 mol/mol of Ru·h, although this reaction appeared to be catalyzed by Ru colloidal species. Very high activities and good productivities were obtained using $RhCl_3 \cdot 3H_2O$/*m*-TPPTS in the partial hydrogenation of linseed oil (MELO: TON = 6,500 mol/mol of Rh; TOF = 39,000 mol/mol of Rh·h) and sunflower seed (MESO: TON = 9,700 mol/mol of Rh; TOF = 117,000 mol/mol of Rh·h) methyl esters.[461] A cationic surfactant (DTAC) was used for the MELO substrate, but was not required for MESO due to the presence of Lecithin in the crude sunflower oil, which act as an emulsifier.

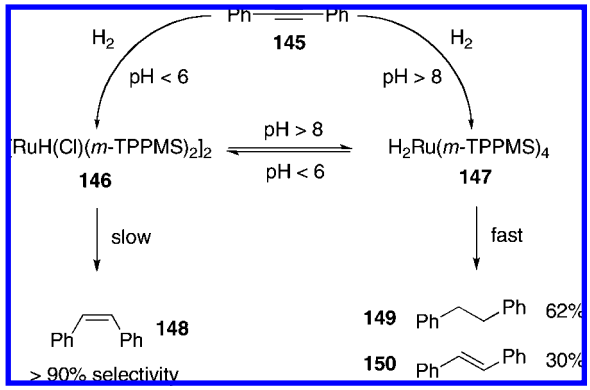
Hydrogenation of allylbenzene with an iridium complex of PEG-supported triphenylphosphine (**L163**, Table 13) gave conversion rates that were 10 times slower than the homogeneous reaction in CH_2Cl_2.[298] The water-soluble PEG-supported catalyst was also slower than the hydrophobic PPh_3 complex in water. The surface active ligand **L3a** was used in combination with an amine-functionalized cyclodextrin and Pt^{II} to produce a supramolecular catalyst (**152**, eq 26) that showed high activity (2,600 mol/mol of Pt·h) for the hydrogenation of 2-methyl-3-buten-2-ol.[462] An alternative approach to generating hydrophilic ruthenium hydrogenation catalysts involved appending an imidazolium salt to the arene ligand of Ru(arene)$Cl_2(PPh_3)$ (**154**, eq 27).[463] The resulting complexes were highly active for the hydrogenation of styrene (TON = 500 mol/mol of Ru·h) and could be used for 3 reaction cycles without loss of activity.





The rhodium complex generated from $[Rh(nbd)Cl]_2$ and Amphos (**L96a**, Table 8) showed comparable activity to the triphenylphosphine complex for hydrogenation of maleic acid in methanol, but the rate in water was much slower.[207] The

Scheme 33

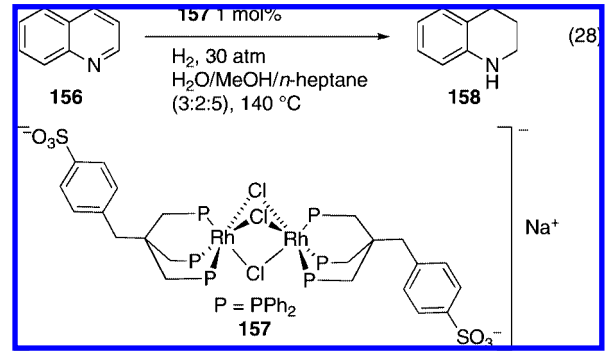


lower rate in water may be due to the lower solubility of H_2 in water compared to methanol or the lower stability of the dihydride complex in water. The Amphos complex was less active for styrene hydrogenation in methanol than the PPh_3 complex. The phosphonium analogue of Amphos (**L107**, Table 8) did show good activity in water for the hydrogenation of 1-hexene, although isomerization to 2-hexenes was a significant side reaction in most cases.[225] The propyl-bridged ligand (**L107**, $n = 3$) gave higher conversion to hexane than the ligands with shorter or longer alkyl bridges. The longer chain ligands gave stable emulsions that were difficult to break.

Surface active diphenylphosphines with ionic alkyl substituents have proven to be useful for the hydrogenation of higher alkenes in water. Rh-catalyzed hydrogenation of 1-decene using alkylcarboxylate functionalized ligand **L73** ($n = 1$, $m = 5$) gave good activity (902 mol/mol of Rh·h) under 4 atm of H_2 pressure at 80 °C, while a longer alkyl bridged homologue ($m = 7$) gave lower activity.[186] Ligand **L81** ($n = 12$, Table 6) gave an active Rh complex for hydrogenation of decene when the ligand was present in excess.[192] Complete conversion was seen with 1 atm of H_2 at room temperature using 2.5 mol % Rh overnight. The PNS ligand (**L27**, Table 3) was used in the Rh-catalyzed hydrogenation of alkenols.[125] Good conversion was seen with good to excellent selectivity for hydrogenation over isomerization to the ketone.

Arene−Ru complexes of chelating ligand **L13** (Table 2) showed activity toward hydrogenation of styrene in water, but evidence suggests that the active species may be ruthenium nanoparticles.[106] A chloride-bridged ruthenium dimer complex with tripodal ligand **L45** (**157**) showed good activity for the hydrogenation of 1-decene and allylbenzene, both of which were completely hydrogenated after 1 h using 1 mol % catalyst at 140 °C and 30 atm of H_2 (TON = 100 mol/mol of Ru).[154] Complex **157** was also effective for the highly selective hydrogenation of benzo[*b*]thiophene and quinoline (eq 28). A tetrasulfonated analogue of DPrPE (**L44**, Table 4) gave a moderately active (25 mol/mol of Rh·h) rhodium catalyst for the hydrogenation of 1-hexene in water at 60 °C and 50 psi of H_2.[152] An analogous ligand (**L149**, Table 11) with alcohol substituents in place of the sulfonates gave an unstable rhodium complex that gave very low hydrogenation activity.

Functionalized alkenes often provide higher reactivity in water since they are typically more soluble than unfunctionalized alkenes. The *m*-TPPMS analogue of Wilkinson's catalyst showed good activity for the hydrogenation of unsaturated acids and diacids in water.[464] Fumaric acid was



particularly reactive (1270 mol/mol of Rh·h), while maleic acid gave only 53 turnovers/h. This relative reactivity was opposite to that normally seen for Wilkinson's catalyst. A similar trend was observed with $RhCl(PTA)_3$ (PTA = **L132**, Table 10).[465] When the reactivity of fumaric and maleic acid was studied as a function of pH, it was found that maleic acid has minimal reactivity from pH 2 to 5, while fumaric acid has maximal reactivity over this pH range.[464]

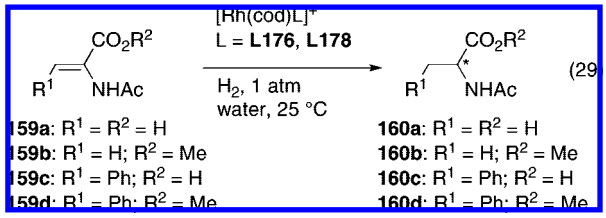
Hydrogenation of water-soluble alkenes in a water/organic biphase using PEG-modified ligands (**L167** and **L168**, Table 13) could be controlled thermally.[299,306] Below the cloud point of the ligand, the catalyst partitions into the aqueous phase and hydrogenation activity was observed. If the temperature was raised above the cloud point, the catalyst partitioned into the organic phase and no activity was seen. Lowering the temperature below the cloud point restarts the reaction. Thus, by changing the temperature over a 20 °C range that crosses the cloud point, the catalyst went from active to inactive. Rh-catalyzed hydrogenation of α-acetamidocinnamic acid was performed using a series of furylphenylphosphines with carboxylate, phosphonate, and sulfinate water-solubilizing groups (**L72a**−**c**, Table 6).[181] The sulfinate-substituted ligands gave completely inactive catalysts. In the carboxylate-substituted ligands, catalyst activity decreased with increasing numbers of carboxylate groups. The phosphonate-substituted ligands all gave quantitative conversion under 3 bar H_2 at room temperature in 2−3 h.

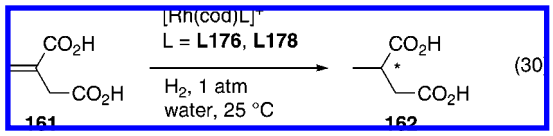
3.2.2. Enantioselective Hydrogenation of Alkenes

Beginning with the seminal work of William Knowles at Monsanto, the enantioselective hydrogenation of prochiral alkenes has been one of the most widely studied asymmetric transformations.[466] A large number of water-soluble ligands have been developed in an effort to provide aqueous-phase, enantioselective hydrogenation catalysts. While in most cases, the activity and/or enantioselectivity of the water-soluble catalysts are inferior to their hydrophobic analogues, some highly enantioselective ligands have been reported.

PEG-modified analogues of Prophos (**L176**, Table 13) and DIOP (**L178**) were applied to the hydrogenation of *N*-acyl dehydroamino acids and their esters (**159**, eq 31).[308,310,311] The [Rh(cod)(**L178**)]ClO_4 catalyst gave good turnover numbers in ethanol (700−1600 mol/mol of Rh·h), but the reactions were slower in water (100−700 mol/mol of Rh·h). The reactions in water were faster with a longer PEG tail on the ligand, however. Enantioselectivity values were modest in ethanol (42−69%), but were much lower in water (12−30% ee). Similar results were obtained with itaconic acid (**161**, eq 31). The cationic rhodium complex derived from **L176** was more enantioselective than the **L178**-derived catalyst. Dehydroamino acids (**159a,c**) gave ee values ranging

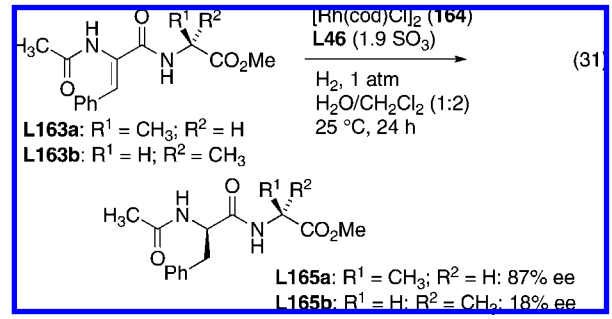
from 80−86%, but the enantioselectivity for itaconic acid (**161**) reduction was much lower (14%). Although the mechanism is unclear, water appears to have a more deleterious effect on the enantioselectivity of 1,4-chelates (**L178**) than the 1,2-chelates (**L176**).





Water-soluble analogues of the PPM ligand (**L62**, Table 5; **L91**, Table 7) gave improved enantioselectivity in the Rh-catalyzed hydrogenation of dehydroamino acids compared to **L178**.[168] Although these ligands again gave lower enantioselectivity in water than in ethanol, the differences were smaller than observed with **L176** and **L178**. For example, hydrogenation of **159c** gave 87% ee in ethanol and 82% in water. A poly(oxazoline)-supported PPM ligand (**L160**, Table 12) in combination with $[Rh(cod)_2]BF_4$ gave good enantioselectivity (85%) and conversion rate (110−142 mol/mol of Rh·h) for the hydrogenation of **159d**, while the free acid (**159c**) gave very slow conversion (1 mol/mol of Rh·h).[291] Higher enantioselectivity in water was obtained with the Rh complex of 2,3-diphenylphosphinopyrrolidinium ligand **L123**.[239,291] Hydrogenation of **159c** gave *N*-acylphenylalanine **160c** in quantitative yield and 87% ee in water, which is nearly identical to the selectivity in methanol. Again, the 1,4-chelate ligand **L63** gave lower enantioselectivity in water than a 1,2-chelate (**L123**). Pyrphos has also been supported on poly(acrylic acid) (**L159**, Table 12).[290] Hydrogenation of **142c** with **L159** and $[Rh(nbd)_2]OTf$ in water/ethyl acetate gave the product in 76−81% yield and 76−82% ee. The phosphine loading on the polymer was varied from 3.9 to 0.95% P, but the phosphorus loading did not significantly affect the yield or selectivity of the reaction.

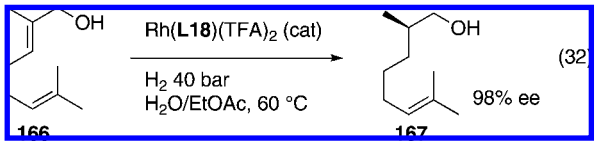
The Sinou group has reported a number of studies of the hydrogenation of *N*-acylated dehydroamino acids with sulfonated phosphines derived from BDPP (**L46**, Table 5), Chiraphos (**L49**), Prophos (**L50**) and CBDP (**L51**).[155,467−469] The order of enantioselectivity for the hydrogenation of dehydrophenylalanine **159c** in 1:1 water/ethyl acetate was **L51** (34% ee) < **L46** (65% ee) < **L50** (70% ee) < **L49** (87% ee), with all ligands giving quantitative conversion to product. The enantioselectivity increased with decreasing degree of sulfonation. For example, **L46** with an average degree of sulfonation of 1.9 gave the hydrogenated product in 80% ee compared to 65% for the tetrasulfonated ligand. Running the hydrogenation in water without cosolvent resulted in significantly lower enantioselectivity (33%, **L46**) than in water/ethyl acetate (65%). The hydrogenation could also be carried out under transfer hydrogenation conditions using ammonium formate, although the conversion rate with **L51** was slow (65% yield, 17 h) and the enantioselectivity was modest (43%). Again, better enantioselectivity was seen with ligands forming smaller chelate rings. Hydrogenation of dehydrodipeptide **163a** with partially sulfonated **L46** (1.9 SO_3Na)/Rh in water/CH_2Cl_2 gave an 87% ee for the reduced dipeptide product (**165a**) if the alanine configuration was *S*, while the *R* precursor (**163b**) gave only a 18% ee under identical conditions (eq 31).[470]



Since sulfonation of the phenyl groups on phosphorus appears to have a negative impact on stereoselectivity, other water-soluble ligand architectures have been explored. A surface active analogue of BDPP (**L48**, Table 5) gave essentially the same enantioselectivity for hydrogenation of **159c** as **L46** and the unsulfonated BDPP ligand in methanol (72−75%), although longer reaction times were required.[158] In water/ethyl acetate (1/1), the catalyst derived from **L48** gave 69% ee and 100% yield after 1.5 h. In contrast, the **L46**-derived catalyst gave only 20% ee and 32% yield after 20 h. Ligand **L47**, which has the arylsulfonate group attached to the backbone, has been applied to the hydrogenation of unsaturated acids and dehydroamino acids in methanol.[157,164] The best results were obtained in the hydrogenation of dimethyl itaconate with [M(**L47**)(nbd)]OTF (M = Ir, 77% ee; *m* = Rh: 68% ee), but dehydroamino acids gave low to modest enantioselectivity (4−57% ee). The hydrogenation chemistry of this ligand in water has not been reported. Ligands **L59**−**L61** (Table 5), which also contain the sulfonate substituents on the backbone, were applied to the hydrogenation of dehydroamino acids in methanol and water.[471] In methanol, [Rh(cod)(**L61**)]BF_4 was highly active ($t_{1/2}$ < 2 min) for the hydrogenation of **159c** and gave a 70% enantiomeric excess. The Rh complexes of **L59** and **L60** were slightly less active ($t_{1/2}$ = 2.4−4.6) and gave lower enantioselectivity (44 and 31% ee, respectively). In water, the catalysts derived from **L59**−**60** were much less active ($t_{1/2}$ = 22−45 min) and less enantioselective (7−38% ee) than in methanol. Adding SDS to the reaction as a surfactant raised the enantioselectivity of the **L61** catalyst from 38% to 66%, but had a lesser effect on the catalysts derived from **L59** and **L60**.

Chiral analogues of BDPP (**L124a,b**, Table 9), DIOP (**L125a,b**), and Chiraphos (**L126a,b**) with proton or methyl quaternized ammonium groups showed good to excellent enantioselectivity in water or aqueous acid solutions.[241,472] Hydrogenation of **159c** with the cationic rhodium complex of **L124a** in methanol gave complete conversion after 20 min and 97% ee. In aqueous HBF_4, the reaction was slower (3 h), but the enantioselectivity was the same, while **L124b** gave an 86% ee (6 h). The catalyst derived from **L124a** could be recovered with minimal loss of Rh (0.5−3.7 ppm Rh) and no loss of enantioselectivity over 4 cycles of the reaction. The catalyst derived from **L126a** gave 87% ee in methanol and 90% ee in aqueous HBF_4 with comparable conversion rates. **L125a** gave a less enantioselective catalyst (59% ee) in water, and underwent hydrolysis of the ketal functionality in aqueous HBF_4.

Ligands with axially chiral biaryl backbones have become powerful chiral ligands. Hydrophilic versions of these ligands have also been applied to aqueous-phase hydrogenation reactions. Sulfonated BINAP (**L17a**, Table 2) in combination with Rh gave complete conversion and 70% ee in the hydrogenation of **159a** in water.[105,111] In contrast to ligands with alkyl bridges, using methanol as the solvent decreased the enantioselectivity (58% ee in MeOH). With Ru/**L17a** based catalysts, higher enantioselectivity was obtained in methanol than water. Sulfonated MeO-BIPHEMP derivative **L19** provided a highly enantioselective catalyst (Rh(**L19**)$(TFA)_2$) for hydrogenation of a range of substrates in water.[36] Geraniol (**166**) was reduced to citronellal (**167**) in 98% ee in water/ethyl acetate (eq 32), while hydrogenation of **168** gave 98.5% ee and a TOF of 48 mol/mol of Ru·h (eq 33). Both the enantioselectivity and activity were comparable with the parent unsulfonated ligand in methanol.



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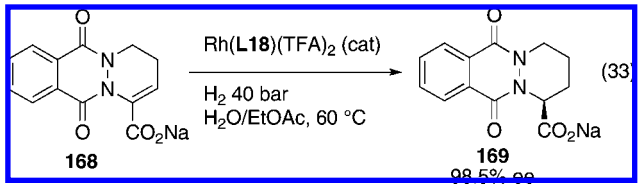

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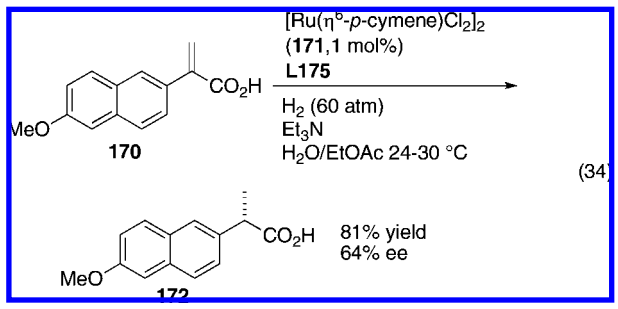
Diammonium- and diguanidinium-substituted analogues of BINAP (**L120** and **L121**, Table 9) complexed to Rh ($[LRh(cod)]^+$) gave high enantioselectivity (95 and 94% ee, respectively) for the hydrogenation of **159c** in ethylene glycol.[237] Hydrogenation of the vinyl naphthalene precursor to naproxen (**170**) using a hydrophilic PEG-based polymer incorporating BINAP in the polymer backbone (**L175**, Table 13) gave 86% ee and 92 mol/mol of Ru·h in methanol in the presence of triethyl amine (eq 34).[307] Without triethylamine, no reaction was observed. In ethyl acetate/water the enantioselectivity dropped to 64% and the TOF was 51 mol/mol of Ru·h. PEG-modified phosphoramidite ligand (**L171**, Table 13) complexed to Rh ($[Rh(\mathbf{L171})_2(cod)]BF_4$) gave high enantioselectivity for the hydrogenation of dehydroamino acid **159c** in methanol (90% ee) or water (82% ee), although the reaction in water was much slower (TOF = 1200 and 55 mol/mol of Rh·h in MeOH and H_2O, respectively).[303] Adding 10 wt % SDS to the reaction in water improved both the enantioselectivity (89%) and activity (600 mol/mol of Rh·h).



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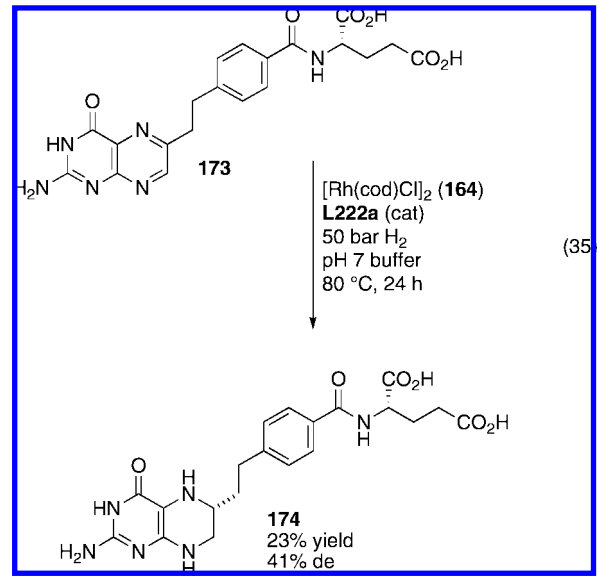
Bis(phospholane) ligands based on the DuPhos structure are another family of privileged ligands in the enantioselective hydrogenation literature.[466] The Holz[278] and Zhang[279] groups have independently reported hydroxylated ligands **L150** and **L151** (Table 11) that provide excellent enantioselectivity in both methanol and water for a wide range of substrates. $[Rh(cod)(\mathbf{L150})]BF_4$ gave a 99.6% ee for the hydrogenation of dehydroamino acid **159a**. The combination of $[Rh(cod)_2]PF_6$ and **L151a,b** provided >99% ee for the hydrogenation of **159a** in methanol. The **L151b** complex also gave >99% ee for the hydrogenation of itaconic acid in methanol and methanol−water mixtures. No change in ee was observed as the solvent was changed from methanol to 3% methanol in water.

Carbohydrate-based ligands have been applied to enantioselective hydrogenation with good success. Diphosphonites derived from an ammonium-substituted salicin derivative (**L128** and **L129**, Table 9) gave good enantioselectivity for the hydrogenation of dehydroamino acids (**159a**) in THF, but the reactions were not selective in water or water/ethyl acetate.[243] Trehalose-derived ligands **L153** and **L154** in combination with rhodium provided catalysts that gave excellent enantioselectivity for hydrogenation of dehydroamino acids in water with SDS surfactant.[282,283] In the absence of SDS, the reactions were slower and gave lower enantioselectivity.[284]

A series of carbohydrate-imine-based ligands (**L155**, Table 11; **L221**−**L224**, Table 16) were tested in the diastereoselective hydrogenation of folic acid (**173**) to tetrahydrofolic acid (**174**, eq 35).[285] These ligands gave moderately selective catalysts in combination with $[Rh(cod)Cl]_2$ or $[Cp^*RhCl_2]_2$. The best selectivity was achieved with **L222a** and $[Rh(cod)Cl]_2$, which gave tetrahydrofolic acid in 41% de, but only 23% yield. Higher yields (99%) could be achieved with **L155a**/$[Rh(cod)Cl]_2$, but the diastereoselectivity was only 9% de. Chiral ligands **L92**−**L95** have also been applied to the diastereoselective hydrogenation of disodium folate.[203] The best activity was obtained with **L95b** (184 mol/mol of Rh·h), which also gave modest diastereoselectivity (31% de). BIPHEMP-based ligand **L94** gave a more selective catalyst (46% de), but was less active (27 mol/mol of Rh·h). Lowering the reaction temperature from 70 to 30 °C increased the diastereoselectivity to 47% de with **L95b**, but at the cost of a significantly slower reaction (8 mol/mol of Rh·h).



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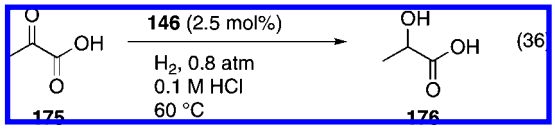
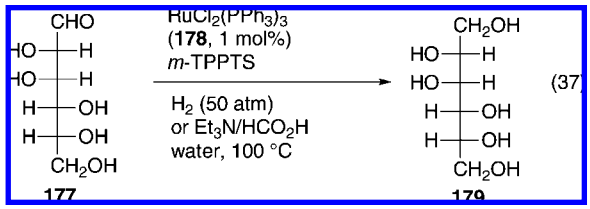
3.2.3. Carbonyl and Imine Hydrogenations

Reduction of carbonyls and imines to give alcohol and amine functionality is an important transformation in synthetic chemistry, particularly if the reduction can be done with control of stereochemistry. The reductions can be done using H_2 as the hydrogen source or by transfer hydrogenation using hydride sources, such as formate or isopropanol. Water is an attractive solvent, particularly for transfer hydrogenation processes. Early reports showed that the $[RuH(Cl)(m\text{-TPPMS})_2]_2$ (**146**) catalyst system could be used for the reduction of α-keto acids, such as pyruvic acid (**175**), to the corresponding α-hydroxy acids (eq 36).[454,473]

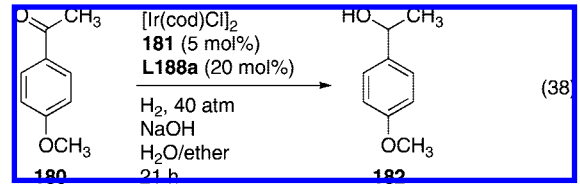


Ruthenium complexes of *m*-TPPMS provided selective catalysts for the reduction of aldehydes using formate as the reductant.[474] Benzaldehyde derivatives were reduced to give benzyl alcohols in high yield at 80 °C in 1.5−8 h. Unsaturated aldehydes, such as cinnamaldehyde, were selectively converted to the corresponding unsaturated alcohol. The reaction is believed to occur in the aqueous bulk. Since both cationic phase transfer agents and cyclodextrins inhibit the reaction. The Ru/*m*-TPPTS catalyst system was applied to the reduction of aldoses to alditols (eq 37).[475] D-Mannose was more reactive than D-glucose, and reduction under dihydrogen was found to be faster than transfer hydrogenation with formate. The Ru/*m*-TPPTS catalyst was applied to the combined hydrolysis and hydrogenation of inulin to give D-mannitol and D-glucitol at low pH (1−3).[476] Amphiphilic PEG-modified phosphines (**L169**, Table 13) gave selective ruthenium catalysts for the hydrogenation of prenal to prenol using hydrogen.[301]

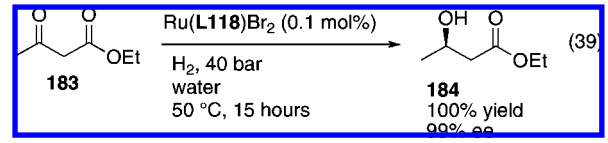


$RuCl_2(PTA)_4$ also provided a highly selective catalyst for the reduction of aldehydes.[247,477] The PTA complexes were less active than the corresponding *m*-TPPMS complex, however. Benzaldehyde gave 64% conversion after 5 h at 80 °C, while the *m*-TPPMS complex gave complete conversion after 1.5 h at 80 °C. The PTA complex was highly selective for aldehyde reduction with unsaturated aldehyde substrates, such as crotonaldehyde and cinnamaldehyde. In fact, 1-decene could not be reduced under these conditions.

Ruthenium complexes also are effective for the reduction of ketones. $RuCl_2(\eta^6\text{-}p\text{-cymene})(m\text{-TPPMS})$ is an active catalyst for the reduction of ketones under transfer hydrogenation conditions with isopropanol as the reductant.[478] Cyclohexanone was reduced with a rate of nearly 2000 mol/mol of Ru·h in isopropanol, although most other substrates gave rates ranging from 100−400 mol/mol of Ru·h. Low activity was obtained in water/organic biphasic systems, however. The aqueous catalyst solution could be reused for an additional reaction cycle with no loss of activity, but attempted use on a third cycle gave much lower activity. The iridium complex formed from $[Ir(cod)Cl]_2$ and phosphonated bipyridine ligands (**L188a** and **L189**, Table 14) gave good yields for the reduction of aryl ketones in water at neutral pH using 5 mol % catalyst (eq 38).[325] Electron-rich acetophenone derivatives gave low yields, however. Increasing the pH to 9 allowed the reduction of 4′-methoxyacetophenone to occur in >99% conversion after 8 h. The iridium complex derived from chiral diamine ligand **L216** (Table 15) was unstable under the reaction conditions. A Ru^{II}−PTA complex gave good activity (139 mol/mol of Ru·h) for the hydrogenation of acetophenone under H_2 in pH 6.9 buffer.[479]



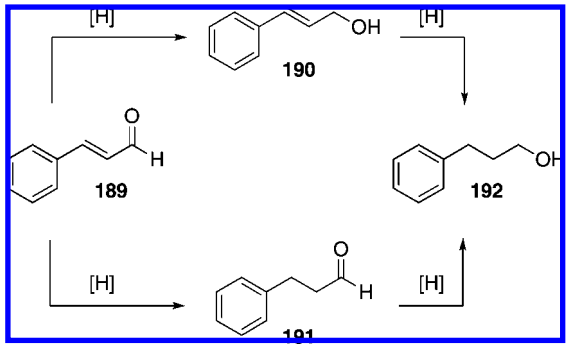
Reduction of prochiral ketones provides the possibility of producing chiral alcohols with high levels of stereocontrol in aqueous solvents. While alkene reduction in water typically gave low enantioselectivity, a variety of highly selective systems have been reported for ketone reduction. Amine-substituted BINAP ligands (**L118**−**L120**, Table 9) gave active and selective catalysts for the reduction of ethyl acetoacetate (**183**) in methanol when complexed to ruthenium (eq 39).[234−236] Complete conversion and enantioselectivities in excess of 98% ee were obtained with all three ligands in methanol. The protonated forms of **L118** and **L119** gave the same results in water as were observed in methanol. The catalysts could be recycled in both the methanol and water without loss of activity or enantioselectivity for several cycles, although the water reactions could be recycled for more cycles (6−8) than in methanol (3).



Guanidinium (**L121**) and PEG-substituted (**L173**, Table 13) derivatives of **L120** in combination with Ru also gave good selectivity in the hydrogenation of β-ketoesters in ethylene glycol and methanol.[237] The Ru complex of **L121** could be recycled in ethylene glycol, although activity and enantioselectivity decreased with each cycle. In contrast, the catalyst derived from PEG-substituted ligand **L173** maintained activity and enantioselectivity over 4 cycles for reactions run in methanol. Chiral PNNP ligand **L20** (Table 2) in combination with $Ir(cod)Cl(PPh_3)$ gave good yields and high enantioselectivity (88−93% ee) in the transfer hydrogenation of aryl ketones in aqueous isopropanol.[113] Increasing the water/isopropanol ratio gave a slight increase in enantioselectivity, but significantly decreased the reaction rate.

The DPEN ligand and its tosyl amide (TsDPEN) have been shown to be highly effective ligands for enantioselective reduction of ketones.[354,355] Diphosphonated DPEN analogue **L216** (Table 15) gave high activity catalysts in combination with $[Ir(cod)_2]BF_4$ (0.5 mol %) for the reduction of acetophenone using H_2 in 1:1 water/methanol, but the enantioselec-

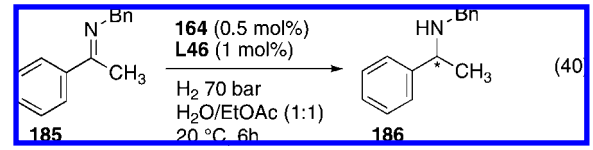
Scheme 34

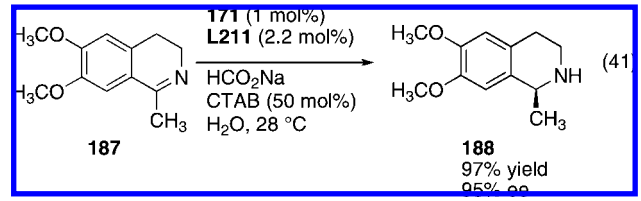


tivity was modest (50%).[353] The aqueous catalyst solution could be used for 4 reaction cycles with no loss in activity or enantioselectivity. Sulfonated analogues of DPEN have been shown to give effective rhodium catalysts for transfer hydrogenation of aryl ketones in water. TsDPEN derivative **L211** with sulfonates on the phenyl substituents provided an effective catalyst in combination with [Ru(η^6-*p*-cymene)Cl_2]$_2$ for the reduction of aryl ketones in water using sodium formate and SDS as a PTC.[349] Complete conversion and 95% ee was obtained using 1 mol % Rh at 40 °C after 24 h. Similar results were obtained with **L212** and **L213**, which both gave high yields and enantiomeric excesses ≥95%.[351,352] Electron-rich ketones, such as 4′-methoxyacetophenone, were less reactive, but gave similar enantioselectivity. The complex derived from **L213** was more active with electron-rich substrates than the catalyst derived from **L212**. TsDPEN supported on sulfonated polystyrene (**L230**) was also an effective ligand (100% conversion, ≥97% ee) for Ru-catalyzed (1 mol %) transfer hydrogenation of aryl ketones using sodium formate.[370] The catalyst-containing aqueous phase could be reused without loss of activity.

Neutral diamine-substituted TsDPEN **L226** (Table 16) gave optimal activity (97% conversion, 0.2 mol % Rh, 0.5 h) and selectivity (97% ee) in combination with [Cp*RhCl]$_2$ for transfer hydrogenation of acetophenone in water.[368] The iridium analogue along with [Ru(η^6-*p*-cymene)Cl_2]$_2$ gave less active catalysts, but the same enantioselectivity. Interestingly, [Cp*RhCl]$_2$ in combination with the sulfonated ligand **L213** gave a catalyst with low activity and enantioselectivity (10% ee). PEG-modified TsDPEN (**L237b**) in combination with [Ru(η^6-*p*-cymene)Cl_2]$_2$ provided a catalyst that gave good activity (100 mol/mol of Ru·h) and high enantioselectivity (90−95% ee) with a range of aryl ketone substrates, including electron-rich acetophenone derivatives.[377,378] The DPEN analogue (**L237a**) in combination with chiral, chelating diphosphines gave a more active catalyst (1000 mol/mol of Ru·h) and similar to better enantioselectivity using dihydrogen.[376] Catalysts derived from **L237a**, BINAP or Phanephos and [Ru(η^6-C_6H_6)Cl_2]$_2$ gave the most enantioselective catalysts. The catalyst was used for three reaction cycles with no decrease in conversion or enantioselectivity.

Sulfonated BDPP (**L46**) combined with [Rh(cod)Cl]$_2$ was applied to the hydrogenation of the *N*-benzylimine of acetophenone (**185**) in water/ethyl acetate under H_2 (eq 40)..[480] The yield of amine **186** and the enantioselectivity of the reaction increased with decreasing degree of sulfonation of the ligand. With an average degree of sulfonation of 3.75, 55% yield and 19% ee was obtained. With an average degree of sulfonation of 1.65, the amine was recovered in 94% yield and 96% ee. The non-sulfonated ligand gave a good yield (87%), but low enantioselectivity (18%) in water/ethyl acetate. The nature of this sulfonate effect was unclear. The effect did not appear to be due to steric or electronic factors, matching the charge on rhodium, or anion effects.[163] Although Noyori has reported that transfer hydrogenation of imines using Ru(TsDPEN) complexes do not work well in alcohol solvents,[481] aqueous-phase imine transfer hydrogenation was successfully demonstrated in water using **L211** (eq 41).[350] High yield and good enantioselectivity (85−95% ee) were achieved with a 3,4-dihydroquinoline (**187**) derivative using [Ru(η^6-*p*-cymene)Cl_2]$_2$ and **L211** in water with formate as the reducing agent. A number of surfactants were explored, but they gave only slight improvements over the reaction run without surfactant.



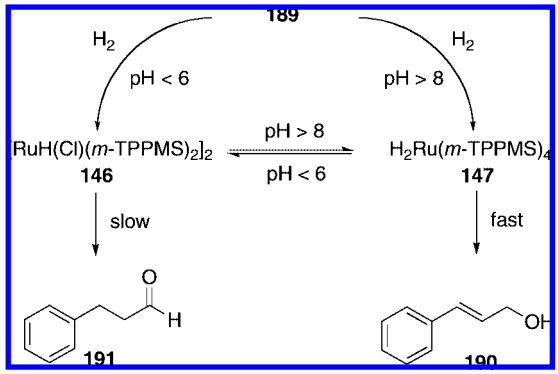


3.2.4. Regiochemical Control in Reduction of Enones and Enals

Hydrogenation of α,β-unsaturated aldehydes, such as cinnamaldehyde (**189**), can give the unsaturated allylic alcohol (**190**) by reduction of the aldehyde, the saturated aldehyde (**191**) by reduction of the alkene, or the fully reduced saturated alcohol (**192**) by reduction of both sites (Scheme 34). Water-soluble catalyst systems have been developed that show selectivity for either alkene or aldehyde reduction depending on the identity of the metal as well as the pH of the reaction medium.

Reduction of cinnamaldehyde under transfer hydrogenation conditions (HCO_2Na) using $RuCl_2$(*m*-TPPMS)$_2$ as the catalyst (1.5 mol %) gave a 98% yield of cinnamyl alcohol after 5 h.[482] Similar results were obtained using $RhCl_3$/3*m*-TPPTS and the Ru- or Os-hydride of complexes of *m*-TPPMS and *m*-TPPTS as the catalyst precursors under standard hydrogenation conditions.[61,483,484] In contrast, reduction of cinnamyl alcohol with RuH(CO)Cl(L) (L = *m*-TPPMS or *m*-TPPTS) gave low selectivity using H_2 with the fully reduced 3-phenylpropanol as the major product.[455] The *m*-TPPMS complex appeared to reduce the aldehyde faster than the alkene, while there was little selectivity in the *m*-TPPTS reaction. Hydrogenation of cinnamaldehyde under comparable conditions in toluene using Ru/PPh_3 complexes gave low selectivity with the fully reduced alcohol being the major product in most cases.[484] Hydrogenation of cinnamaldehyde in toluene/water using $RuCl_3$/*m*-TPPTS or Ru(H)$_2$(*m*-TPPTS)$_4$ gave high selectivity for cinnamyl alcohol, although low conversion.[485] Adding supercritical CO_2 improved the conversion, but slightly lowered the selectivity. Recovery of the catalyst phase and reuse resulted in lower activity and a lower selectivity. The recovered catalysts gave nearly equal amounts of cinnamyl alcohol and dihydrocinnamaldehyde. The lower selectivity was proposed to be due to coordination of cinnamyl alcohol to the active species leading to a change in selectivity.

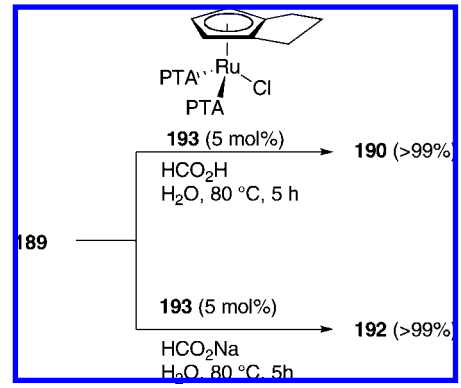
Scheme 35



Joó has studied the hydrogenation of cinnamaldehyde as a function of reaction pH. At low pH (3) with Ru/*m*-TPPMS or *m*-TPPTS catalysts, alkene reduction occurred selectively with low rate to give dihydrocinnamaldehyde (**191**, Scheme 35). Dihydrocinnamaldehyde remained the major product until about pH 8, where a reversal of selectivity was seen leading to preferential formation of cinnamyl alcohol (**190**). The reaction rate was also higher at pH ≥9.[93,457,458] The reversal of selectivity and increase in hydrogenation activity correlated well with a change in the speciation of the ruthenium complexes as the pH is changed. At low pH, Ru(H)Cl(*m*-TPPMS)$_3$ (**146**, 90%) and [Ru(H)Cl(*m*-TPPMS)$_2$] (10%) were the only species detected. As the pH was raised above 6, these complexes decrease in concentration and Ru(H)$_2$(*m*-TPPMS)$_4$ (**147**) begins to form. Above pH 9, Ru(H)$_2$(*m*-TPPMS)$_4$ was the only species present. Thus, Ru(H)$_2$(*m*-TPPMS)$_4$ must be a high activity catalyst that selectively reduced the aldehyde, but is unreactive toward alkenes. At low pH, Ru(H)Cl(*m*-TPPMS)$_3$ and/or [Ru(H)Cl(*m*-TPPMS)$_2$] were low activity catalysts that selectively reduced alkenes.

Selective aldehyde reduction was also seen in the reduction of cinnamaldehyde and crotonaldehyde to the corresponding allylic alcohols with RuCl$_2$(PTA)$_4$, although the rate of conversion was slow.[247,477] Changing the catalyst to [Rh(PTAH)(PTA)$_2$Cl]Cl (PTAH = *N*-protonated **L132**) resulted in highly selective reduction of the alkene to give dihydrocinnamaldehyde in 94% yield, with 3% of cinnamyl alcohol and 3% of the fully reduced 3-phenylpropanol product.[149] High alkene selectivity was also seen in the reduction of benzylidene acetone with Cp*Ru(PTA)$_2$Cl under both hydrogenation and transfer hydrogenation conditions.[256,486] In contrast, cinnamaldehyde gave low selectivity with this catalyst system. The product selectivity for cinnamaldehyde reduction under transfer hydrogenation conditions was found to be dependent on the reaction pH when using CpRu(PTA)$_2$Cl.[257] Using formic acid as the reducing agent gave exclusively 3-phenylpropanol as the product. When the reaction was run at higher pH by using sodium formate, the major product formed was dihydrocinnamaldehyde. When the cyclopentadienyl group was changed to Dp, the catalyst (**193**) gave exclusively cinnamyl alcohol when using formic acid, while 3-phenylpropanol was the only product formed with sodium formate (Scheme 36). With benzylidene acetone, selective reduction of the alkene was seen with both formic acid and sodium formation using CpRu(PTA)$_2$Cl; while DpRu(PTA)$_2$Cl (**193**) gave a 1:1 mixture of alkene and ketone reduction products when formic acid was used, but only 3-phenyl-2-butanone using sodium formate.

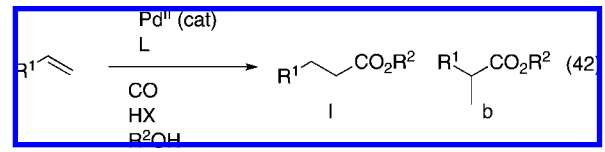
Scheme 36



3.3. Other Reactions of Alkenes and Alkynes

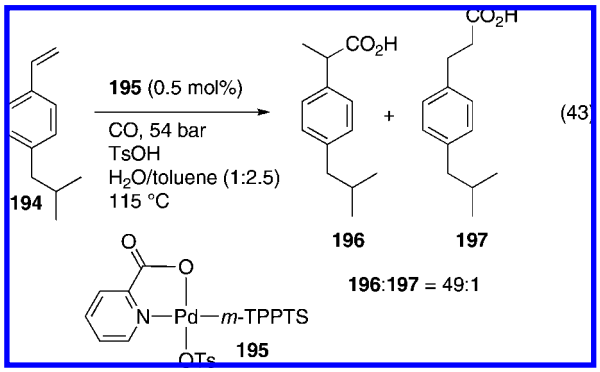
3.3.1. Hydrocarboxylation of Alkenes

Olefin hydrocarboxylation or hydroesterification is the addition of H and an ester functionality across a double bond, typically using a palladium catalyst (eq 42). The reaction is related to hydroformylation, but the metal acyl is cleaved by nucleophilic attack rather than hydrogenolysis. The reactions are typically run using catalysts with hydrophobic ligands in alcohol solvents that serve as the nucleophilic reagent as well as the solvent. In water, olefins are converted to carboxylic acids, which provides access to fatty acids from 1-alkenes and 2-arylpropanoic acids from styrene derivatives.



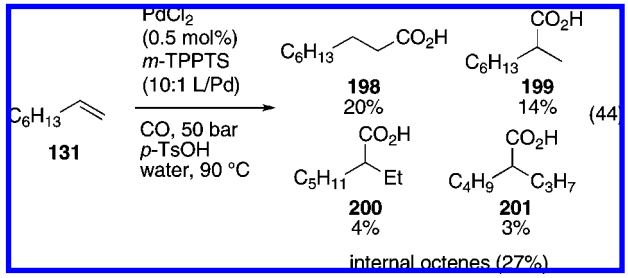
The catalyst derived from PdCl$_2$ and *m*-TPPTS showed modest activity for the hydrocarboxylation of styrene (40 mol/mol of Pd·h) and 4-isobutylstyrene (3 mol/mol of Pd·h) at 65 °C under 50 bar of CO pressure in the presence of toluene sulfonic acid.[65,487] A 3:1 b/l ratio was obtained. In the case of 4-isobutylstyrene (**194**), the major product was ibuprofen (**196**). Higher catalyst activity and selectivity for the desired branched acid was achieved by using Pd(nicotinate)(OTs)(*m*-TPPTS) (**195**)/2*m*-TPPTS as the catalyst precursor to give 2-arylpropionic acids with >90% selectivity (TOF = 100−550 mol/mol of Pd·h, eq 43).[64,488] Increasing the *m*-TPPTS/Pd ratio decreased the catalyst activity and selectivity for the branched product. Interestingly, changing the ligand from *m*-TPPTS to **L110** using PdCl$_2$(PhCN)$_2$ as the palladium source resulted in a reversal of the regioselectivity from 90% branched product to 70% linear acid.[489] Guanidinium-functionalized ligand **L104a** in combination with Pd(OAc)$_2$ gave a modestly chemoselective (20−54% acids) and regioselective (1.5−2:1 l/b) catalyst for the hydrocarboxylation of styrene in water.[222] The *m*-TPPTG (**L105c**) ligand gave a catalyst that produced only acids, although the regioselectivity remained low (1.5−2:1). Chelating, chiral diphosphines **L46** and **L51** in combination with Pd(OAc)$_2$ gave active catalysts for styrene hydrocarboxylation, but the enantioselectivity was low (14−43%ee), with **L46** giving the highest enantioselectivity.[161]

The PdCl$_2$/*m*-TPPTS system was also effective for the hydroesterification of propene to a mixture of butanoic and 2-methylpropanoic acid (1.5:1). At 100 °C, the turnover



(43)

frequency was 1,300 mol/mol of Pd·h, which is significantly faster than the rate for the Pd/PPh_3-derived catalyst in aqueous dioxane (246 mol/mol of Pd·h). Similar to results seen in hydroformylation, less soluble higher alkenes gave lower activity. Hydrocarboxylation of 1-octene using this system in water gave low conversion and poor product selectivity (eq 44).[490] In addition to the linear (**198**) and branched acids (**199**, 1.5−2:1), smaller amounts of 2-ethyl- and 2-propyl-substituted acids (**200** and **201**) were formed due to isomerization of the olefin prior to hydrocarboxylation. Sulfonated Xantphos (**L14**) in combination with Pd gave good activity for the hydrocarboxylation of ethylene and propene (100−300 mol/mol of Pd·h) at 120 °C and 30 bar CO. Styrene was hydrocarboxylated at 70 °C to avoid competitive thermal polymerization.[108] Both styrene and propene gave identical l/b ratios of 1.5−1.85:1, which shows that the regioselectivity was controlled by the ligand rather than the substrate.



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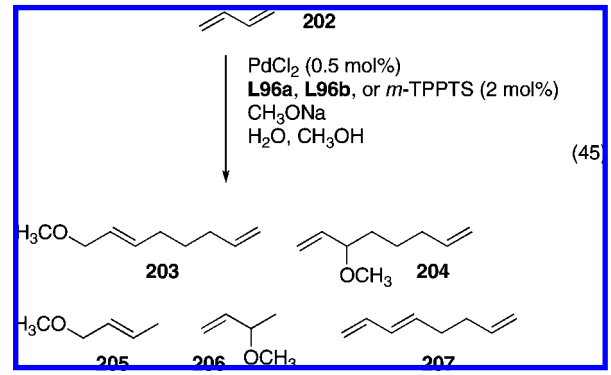
3.3.2. Polymerization of Alkenes and Alkynes

Ziegler−Natta-type polymerization in water using early transition metal complexes is not possible due to the very low protolytic stability of these catalyst species. Late transition metal olefin polymerization catalysts would appear more amenable to aqueous-phase polymerization, since they are less oxophilic and protolytically unstable. The majority of work on olefin oligomerization and polymerization in water has focused on the use of palladium and nickel catalyst systems. The initial work focused primarily on oligomerization of reactive substrates, such as butadiene and norbornene, as well as olefin/CO copolymerization. Examples of homopolymerization of ethylene in water using water-soluble catalysts have recently been reported to give polyethylene latexes.

Telomerization of butadiene with methanol in water using ammonium-substituted ligands **L96a,b** or *m*-TPPTS in combination with $PdCl_2$ gave a mixture of methoxy-substituted C8 dienes, butenyl methyl ethers and octatriene products, with 1-methoxy-2,7-octadiene (**203**) as the major product (eq 45).[205] The *m*-TPPTS catalyst system was more selective for **203** than the **L96** system, but ligands **L96a,b** gave similar selectivity and activity. The catalyst solutions could be recovered and reused to give the same selectivity, but lower activity. Telomerization of butadiene in water to give octadienols with Pd/*m*-TPPTS was accelerated by adding long chain dimethylamines.[71] Telomerization of butadiene in water with ethylene glycol using Pd/*m*-TPPTS gave a high selectivity (75%) for the monotelomere products (**208** and **209**, eq 46).[491] This selectively was higher than was obtained using $Pd(acac)_2/PPh_3$ in homogeneous phase, where only 50−60% selectivity for the monotelomere product was achieved.[492] The high selectivity was believed to be due to the low solubility of the product in water, which prevented further reaction to give ditelomeric products (**210**, **211**). Using the Pd/*m*-TPPTS system, butadiene was telomerized with sucrose to give alkyl-substituted derivatives (**214**) that are of interest as surfactants (eq 47).[493,494]



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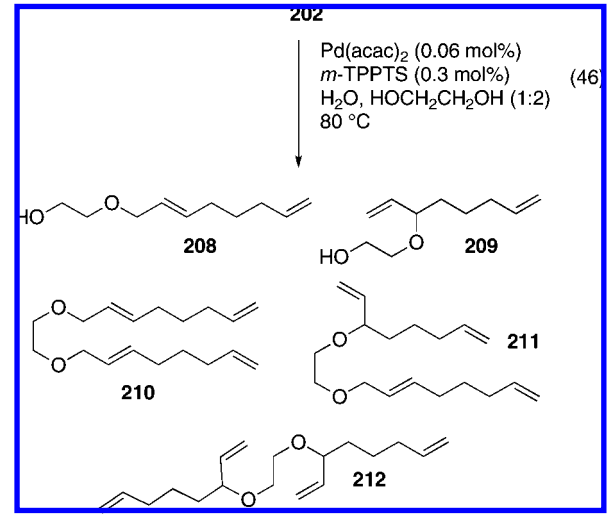

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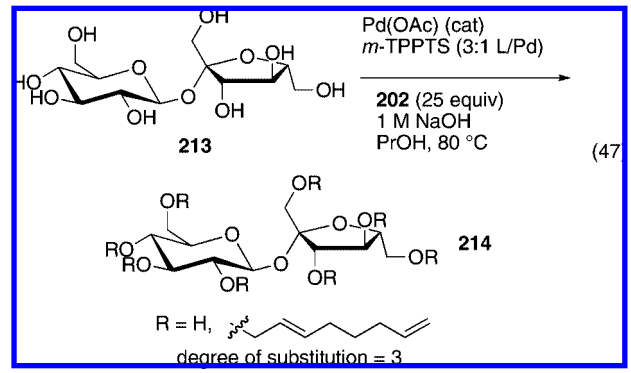
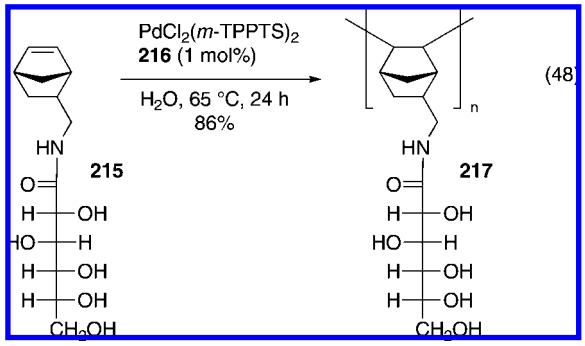
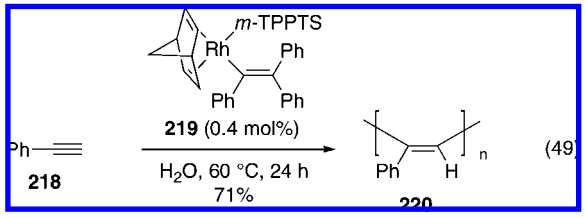


(47)

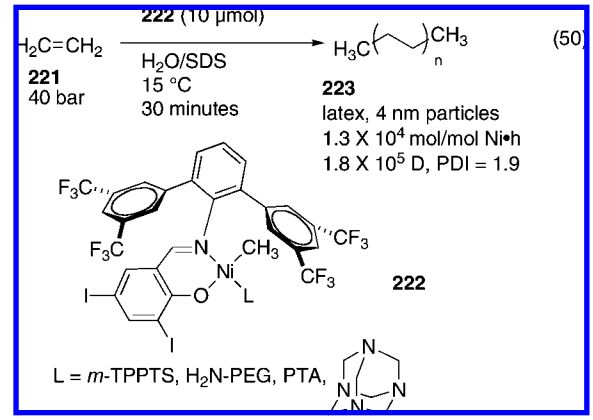
Polymerization of strained olefins, such as norbornene, can be achieved with cationic palladium catalysts. Several

examples of this class of polymerization have been reported in water using hydrophilic catalysts. A gluconamide-functionalized norbornene (**215**) was polymerized using $PdCl_2$(*m*-TPPTS)$_2$ (**216**, 1 mol %) in water at 65 °C to give an 86% yield of the polymer (**217**) with an average degree of polymerization (DP) of 17 (eq 48).[67] A lactobionamide norbornene derivative gave 66% conversion and an average DP of 12. The neoglycopolymers are of interest as potential antiviral compounds. Polymerization of norbornene in aqueous/organic emulsions was carried out using a catalyst derived from Pd(η^3-allyl)(L)Cl/LiB(C_5F_6)$_4$ (L = PCy_3, *m*-TPPTS).[495] The *m*-TPPTS catalyst was less active than the PCy_3 complex due to the unfavorable partitioning of the *m*-TPPTS catalyst into the hydrophobic monomer droplets and lower inherent activity of the *m*-TPPTS-derived catalyst. After 24 h, complete conversion could be achieved to give particles of similar size to those produced by the PCy_3 catalyst. Polymerization of phenylacetylene derivatives in water was carried out with a Rh/*m*-TPPMS catalyst (**219**) in water (eq 49). Phenylacetylene was polymerized at 60 °C to give a 77% yield of the polymer (**219**) with an M_n values of 8,200 Da and a PDI of 1.7.[496] The molecular weight was much lower than was achieved in THF (110,000 Da). Water soluble monomers, sodium 4-ethynylbenzoate and 2-[(2-methoxy)ethoxy]ethyl 4-ethynylbenzoate could also be polymerized to give water-soluble polyacetylenes.

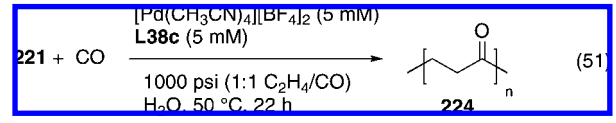




Polymerization of simple olefins such as ethylene in water using emulsions of hydrophobic catalysts has been explored as a way to generate polyethylene latexes.[40] In these systems, the catalyst must be widely dispersed in the aqueous medium in order to achieve the smallest possible latex particles. The highest degree of catalyst separation could be achieved using a water-soluble catalyst, which would be completely dispersed in water. An *in situ* catalyst generated from *p*-TPPMS (**L8a**), chloranil, and Ni(cod)$_2$ (1:1:1.1) gave an active catalyst (1−2,000 mol of ethylene/mol of Ni·h) for polymerization of ethylene in water/isopropanol (9:1) with SDS (0.035 M).[497] The resulting polymer had low molecular weight (1.4−6 × 10^3 Da) and broad polydispersity indices (M_w/M_n = 4−7). Particle sizes were in the 20 nm range for the latex. Improved productivity and increased molecular weight were obtained using salicylimine-derived nickel complexes (**222**, eq 50) with hydrophilic ligands.[68,367] Using the **222**/*m*-TPPTS system, ethylene was polymerized in water containing SDS with an activity of 1.2 × 10^4 mol of ethylene/mol of Ni·h. The polymer molecular weight (M_w) was 2 × 10^4 Da with a polydispersity of 1.9. The particle sizes of the polymer averaged 4 nm. Similar results were obtained using amine-terminated PEG as the hydrophilic ligand, although larger particles (15 nm) were formed.



The copolymerization of alkenes with CO in water has received more attention than the homopolymerization reaction. Sen initially reported that [Pd(**L38b**)(H_2O)][BF_4]$_2$ and [Pd(**L182a**)(H_2O)][BF_4]$_2$ gave active catalysts for the copolymerization of ethylene and CO (1000 psi, 1:1 ethylene/CO) at 50 °C to give 470 and 80 g of polymer/g of Pd respectively (eq 51).[147] The activity in water was much lower than is observed in $MeNO_2$/MeOH (2:1) with [Pd(DPPP)(H_2O)][BF_4]$_2$ (28 kg of polymer/g of Pd). [Pd(**L38b**)(H_2O)][BF_4]$_2$ was more active in the copolymerization of propylene and CO (200 g of polymer/g of Pd, M_w = 14,000 Da). Varying the alkyl bridge in the ligand showed that **L38c** gave the most active catalyst, while **L38b** gave good activity and much higher molecular weight.[498] The ethyl-bridged ligand **L38a** gave a low activity catalyst.



Improved activity for ethylene/CO copolymerization was obtained using a catalyst derived from **L38c** and Pd(CH_3CN)$_2$(OTs)$_2$ in the presence of toluene sulfonic acid (4 kg of polymer/g of Pd·h, 7,700 Da).[142] Using ligand **L40** (Table 4) complexed to Pd(TFA)$_2$ in the presence of TsOH and benzoquinone gave somewhat higher activity (7.2 kg of polymer/g of Pd·h).[151] Further improved activity was obtained by adding electron donating substituents to the sulfonated aryl substituents. Ethylene/CO copolymerization using ligands **L39a**, **L39b**, and **L39c** in combination with Pd(CH_3CN)$_2$(OTs)$_2$ gave 1.67, 8.22, and 1.71 kg of polymer/g of Pd·h respectively at 70 °C with 40 bar of ethylene/CO (1:1).[145] At 90 °C and 60 bar of ethylene/CO, the **L39b** complex gave a maximum activity of 32 kg of polymer/g of Pd·h. This catalyst also produced high molecular weight product at 70 °C (125,000 Da) and 90 °C (60,000 Da). Chelating alkylphosphines with hydroxyl substituents (**L147** and **L148**, Table 11) complexed to Pd(OAc)$_2$ also showed good activity for ethylene/CO copolymerization.[277] Under identical conditions, **L147** and **L148** gave higher activity catalysts than **L39b**. Activity generally increased with

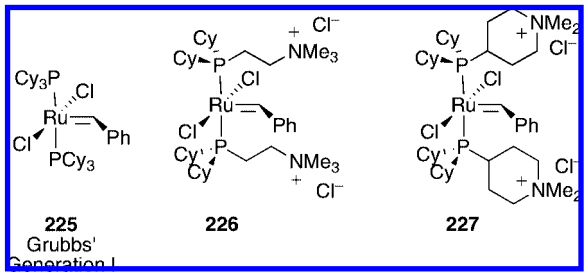


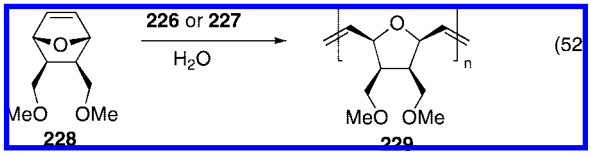
Figure 3. Hydrophilic examples of Grubbs first generation olefin metathesis catalyst.

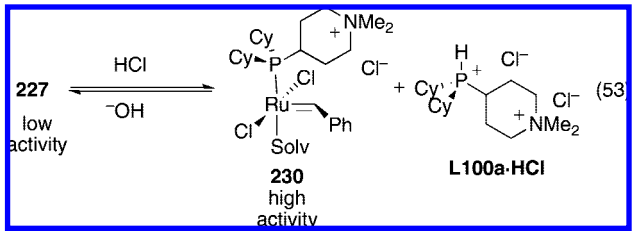
increasing length of the hydroxyalkyl substituents on phosphorus, and **L148** gave more active catalysts than **L147**. The molecular weights with **L147** and **L148** were an order of magnitude higher than with **L39b** (100,000 Da vs 10,000 Da).

3.3.3. Metathesis

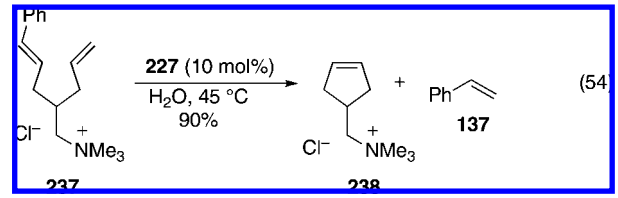
Olefin metathesis catalyzed by molybdenum− and ruthenium−alkylidene complexes has become a widely used synthetic method for the preparation of polymers and small molecules.[499] While the molybdenum complexes developed by Schrock are highly active, they are also sensitive to water. In contrast, the ruthenium catalysts developed by Grubbs are quite stable in water and can be used to promote olefin metathesis of hydrophilic and hydrophobic substrates.

The first examples of water-soluble olefin metathesis catalysts were ruthenium alkylidenes (**226** and **227**) with Cy-Amphos (**L99a**) or Cy-Pip-phos (**L100a**) coordinated (Figure 3).[129] The resulting complexes were completely soluble in water and methanol, although decomposition was observed after two days in water. Water-soluble ruthenium complexes were active for the polymerization of functionalized oxanorbornene substrates in methanol, water, and aqueous emulsions (eq 52). Addition of acid to complex **226** or **227** resulted in loss of a phosphine ligand as a phosphonium salt to give a highly active ROMP catalyst (eq 53).[128,500] ROMP activity increased by a factor of 10 in the presence of HCl.





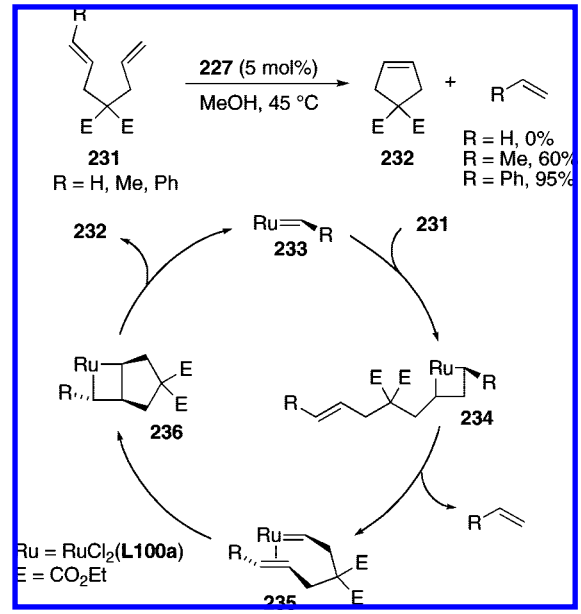
Ring-closing metathesis with **226** and **227** was unsuccessful with α,ω-dienes (**231**, R = H) in methanol or water due to the poor stability of the ruthenium−methylidene produced during the catalytic cycle in protic solvents (Scheme 37).[501] Use of dienes with one secondary alkene (**231**, R = Me, Ph) gave better results, as the propagating catalyst species was a more stable substituted alkylidene. Good to excellent yields were obtained with hydrophobic dienes in methanol, with the **L100a** complex giving better yields. A quaternary ammonium-substituted diene (**237**) gave 90% yield of the cyclized product using complex **226** in water (eq 54). Water-soluble unsaturated alkylidene complexes were prepared by reacting $[RuCl_2(m\text{-TPPTS})_2]_2$ with phenylacetylene or 1,1-diphenyl-2-propynol.[502] The *m*-TPPTS-Ru-alkylidene complexes were active for the ring-opening cross metathesis of cyclopentene and methyl acrylate in methanol or ether/water biphase.



Imidazolin-2-ylidene complexes of ruthenium alkylidenes (second generation catalysts) are more active than the diphosphine catalyst precursors (Figure 4). The first example of a water-soluble NHC metathesis catalyst was prepared by the coordination of PEG-modified pyridine **L231** (Table 16) to the second generation Grubbs catalyst to give **239a**.[371] The resulting complex was soluble in both water and methylene chloride. Complex **239a** was an inactive ROMP catalyst at neutral pH, but catalyzed ROMP of PEG-modified oxanorbornene substrates to give PEG-grafted polymers at low pH (≤2). The acidic conditions were presumably needed to promote dissociation of the pyridine ligands. Similar results were obtained with **239b** derived from **L232**.[337] Again, the catalyst was only active at low pH or in the presence of Cu^{II} salts. Interestingly, metathesis catalyst **L239c** derived from a phosphoryl choline-functionalized pyridine ligand (**L191**) gave complete conversion for ROMP of a PEG-substituted oxynorbornene substrate (S/cat. = 50:1) under both neutral (pH = 7) and acidic (pH = 1.5) conditions.

Complex **240** with a PEG-modified imidazol-2-ylidene ligand derived from **L247** was prepared to provide a more active catalyst in which the water-solubilizing group was permanently attached to the metal center.[392] Complex **240** was significantly more active for the polymerization of a challenging *endo*-norbornene substrate (**2242**, eq 55) than the water-soluble first generation catalyst (**226**). Complex

Scheme 37



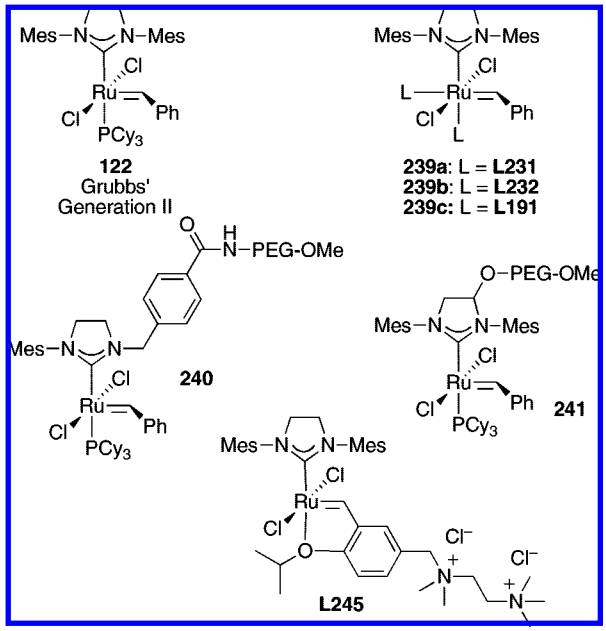
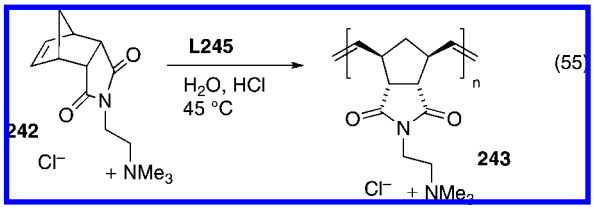
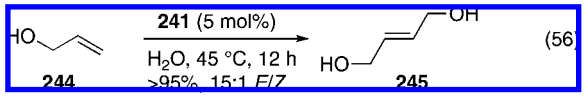


Figure 4. Examples of hydrophilic second and third generation Grubbs catalysts.

240 gave greater than 90% conversion of the monomer after 24 h, while **226** had only reached 13% conversion. Complex **240** also showed modest activity toward RCM in methanol. To improve the activity and stability of the water-soluble catalyst, imidazolinium salt **L246** was prepared and coordinated to a ruthenium alkylidene to give **241**. The **L246** ligand was designed to have mesityl groups on both nitrogens, as is the case for the hydrophobic second generation catalyst (**122**).[391] Complex **241** gave complete conversion in 2 h without acid promoters in the ROMP of *endo*-norbornene **242**. Complex **241** was also the first water-soluble complex to catalyze RCM of α,ω-dienes in water as well as the cross metathesis of allyl alcohol (eq 56) and the isomerization of *cis*-2-butene-1,4-diol to the *trans*-isomer. Complex **L245** with quaternary ammonium-substituted alkylidene ligand was prepared to give a water-soluble metathesis catalyst that was a monodisperse small molecule.[390] Complex **L245** gave similar activity for ROMP, RCM and CM reactions in water as **241**.

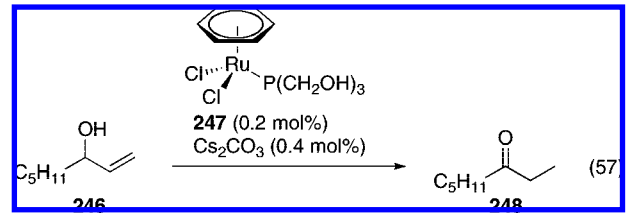




3.3.4. Other Reactions of Alkenes in Aqueous Solvents

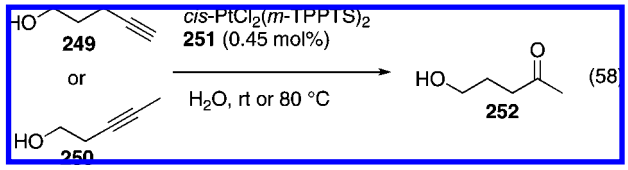
Olefin isomerization is a side reaction noted in many examples of aqueous-phase hydrogenation and hydroformylation reactions discussed above. In the absence of hydrogen, selective olefin isomerization is often possible. Nickel-catalyzed isomerization of allylbenzene to *E*- and *Z*-1-phenylpropene in water was studied using *m*-TPPTS and **L38c**.[148] The *m*-TPPTS catalyst gave very low conversion, but high selectivity for the *E*-olefin (11:1) in water/toluene. The chelating ligand **L38c** gave higher activity with complete conversion after 48 h (2 mol % Pd), although the *E*/*Z* selectivity was lower (4−6:1). Higher initial activity was obtained using 1:1 water/methanol as the polar phase.

Isomerization of allylic alcohols is an effective way to prepare ethyl ketones. The aqueous phase isomerization of 1-octen-3-ol (**246**) to 3-octanone (**247**) was first reported using $RuCl_2(\eta^6\text{-arene})(THMP)$ and $[RuCl(\eta^6\text{-arene})(THMP)_2]Cl$ (**247**, arene = benzene, *p*-cymene, C_6Me_6; THMP = **L130**) in the presence of Cs_2CO_3 (eq 57).[253] The mono-THMP complex was more active (29−67 mol/mol of Ru·h) than the bis(THMP) complex (4−6 mol/mol of Ru·h). The benzene complexes were most active in both cases. Catalyst activity dropped significantly when the aqueous catalyst-containing phase was recycled, although 100% conversion could be achieved for up to 3 cycles with long reaction times (64 h). Ru−arene complexes of **L102** and **L133** gave good activity for the isomerization of 1-octen-3-ol in water (100−200 mol/mol of Ru·h).[220] For the benzene complex, **L133** gave a more active catalyst than **L102**. The situation was reversed for the *p*-cymene complex, where the **L102** complex gave the highest activity (200 mol/mol of Ru·h) of all the catalysts tested. Higher activity was obtained using cationic phosphonite, phosphonate, and phosphite ligands (**L101a**−**c**) complexed to $RuCl_2(\eta^6\text{-}p\text{-cymene})$ in the presence of KO*t*-Bu.[215] In the isomerization of 3-penten-1-ol, ruthenium complexes of **L101a**, **L101b**, and **L101c** gave activities of 388, 1,188, and 15 mol/mol of Ru·h, respectively. The catalyst containing aqueous phase could be recycled for each catalyst, although longer reaction times were required for the recycled catalyst. The catalyst derived from **L101c** was used 10 times to give quantitative yield in each cycle, although the reaction time was increased from 35 min in the first cycle to 210 min in the last cycle. The catalyst derived from $CpRu(m\text{-TPPMS})_2Cl$ converted **246** to **248** with a rate of 2,226 mol/mol of Ru·h.[503]



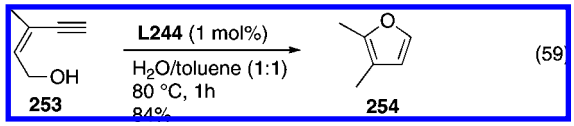
Hydration of alkynes provides another route to ketones that can be carried out efficiently in water. Hydration of 4-pentyn-1-ol (**249**) or 3-pentyn-1-ol (**250**) both gave 5-hydroxy-2-pentanone (**252**) as the only product in less than 1 h at 80 °C using *cis*-$Pt(m\text{-TPPTS})_2Cl_2$ (**251**) in water (eq 58).[504] The high regioselectivity with 3-pentyn-1-ol suggests a directing effect by the hydroxyl substituents. Chelating, sulfonated diphosphines with small bite angles provided more active catalysts. Hydration of 4-pentyn-1-ol using $LPtCl_2$ complexes (L = **L38a**−**c**, 0.21 mol % Pd) in water gave initial activities of >2300 (**L38a**), 69 (**L38b**), and <0.5 (**L38c**) mol/mol of Pt·h at room temperature.[143] Addition of NaCl increases the rate of the catalysts derived from **L38b** and **L38c** to 200 mol/mol of Pt·h (21 mol % NaCl), while chloride inhibits the **L38c** catalyst (300 mol/mol of Pt·h).

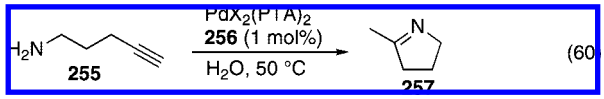
As seen with other reactions, hydrophobic substrates prove more challenging. $RuCl_2(\eta^6\text{-arene})(THMP)$ gave a low



activity catalyst for the hydration of phenylacetylene at 90 °C (1 mol/mol of Ru·h), but higher activity was seen with 1-hexyne (2.5 mol/mol of Ru·h).[253] While phenylacetylene gave acetophenone exclusively, 1-hexyne gave a mixture of 2-hexanone and hexanal (2.2−5.2:1 hexanone/hexanal). Gold-catalyzed hydration of alkynes using Au(C≡C-3-C_4H_3S)(*m*-TPPTS) as the catalyst precursor gave good activity in aqueous methanol (1,500 mol/mol of Au·h), but lower activity in water (410 mol/mol of Au·h).[66] The aqueous catalyst solution could be recovered and reused, although catalyst activity decreased with each cycle.

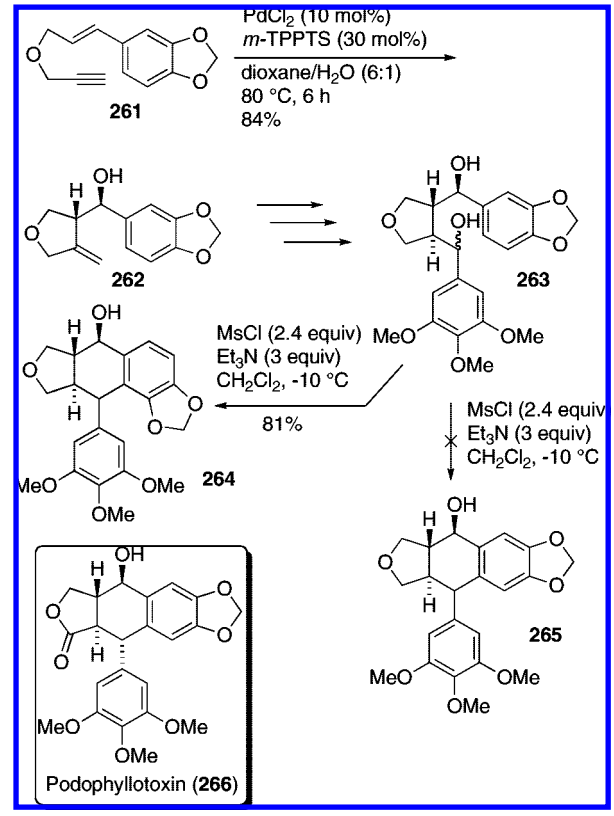
Intramolecular attack on the metal-bound alkyne by pendant nucleophiles provides access to furan or pyrrolidine rings in an atom economical rearrangement. Hydrophilic ruthenium−carbene complex **L244** (Table 18) catalyzed the cyclization of **253** to 2,3-dimethylfuran (**254**) in water at 80 °C in good yield (eq 59).[389] Cyclization of **253** has also been reported using ligands **L102** and **L133** complexed to Ru, Rh, and Ir.[220] The best catalyst was Ir(**L133**)(cod)Cl, which gave quantitative yield of the furan product in 30 min at 80 °C. The catalyst containing phase was used for 10 reaction cycles with minimal decrease in reaction yield, although the reaction time was increased from 1 h in the first cycle to 4 h in the tenth. Palladium and platinum complexes of PTA were tested in the cyclization of 4-pentyn-1-ylamine (**255**) in water, methanol, and DMSO at 50 °C (eq 60).[255,505] $Pd(PTA)_2X_2$ (**256**, X = Cl, Br) gave higher activity than the corresponding platinum complexes of PTA in all three solvents. The highest rate for all three catalysts was achieved in water.

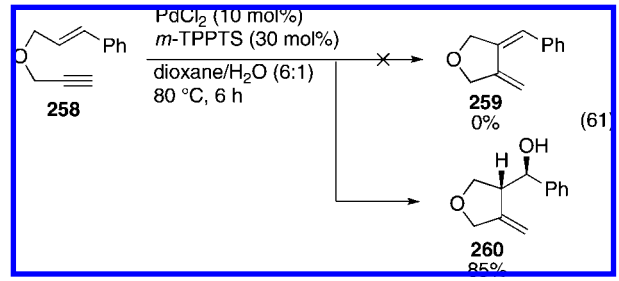




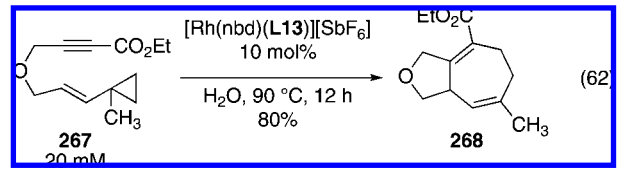
Cycloisomerization of unsaturated molecules provides a perfectly atom economical entry into complex cyclic organic structures. Cycloisomerization of cinnamyl propargyl ether **258** using $PdCl_2$ (10 mol %) and *m*-TPPTS (30 mol %) at 80 °C in dioxane/water (6:1) did not give the expected cycloisomerization product (**259**), but rather gave an unexpected hydroxy-substituted product **260** in 85% yield as a single diastereomer (eq 61).[506] The hydroxide was introduced by Pd-catalyzed hydration of the styrenic olefin in a highly stereoselective manner. This methodology was applied to the synthesis of a key intermediate for the synthesis of podophyllotoxin (**266**, Scheme 38). Cycloisomerization of **261** gave **262** as a single diastereomer, which was further elaborated to intermediate **263**. Friedel−Crafts cyclization of **263** was expected to give **265**, which only lacks the lactone carbonyl of podophyllotoxin. The regioisomeric cyclization product **264** was obtained, however.

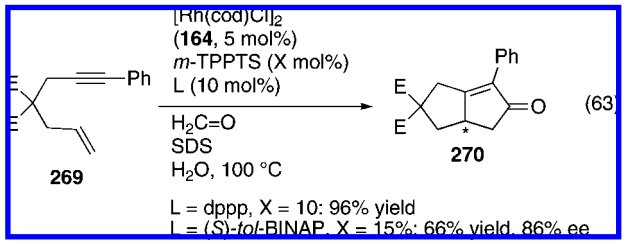
Scheme 38



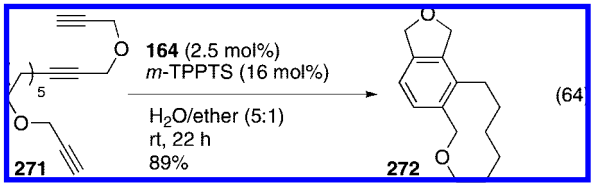


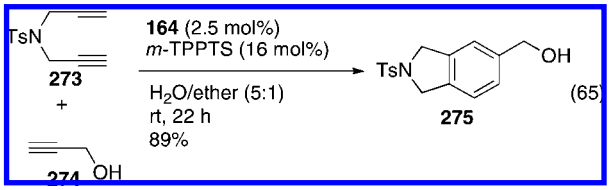
Rhodium-catalyzed [5 + 2] cycloisomerization of diene cyclopropane substrate **267** was carried out in water using sulfonated DPPBz (**L13**) to give **268** (eq 62).[107] The reaction gave comparable yields in water to those obtained with Wilkinson's catalyst in THF. The aqueous-catalyst phase could be used for 5 reaction cycles before a decrease in yield occurred. Rh-catalyzed Pauson−Khand cycloaddition of enyne **269** using formaldehyde as a water-soluble CO source provided access to bicyclic cyclopentenone **270** in water at 100 °C using SDS as a surfactant (eq 63).[73] The optimal catalyst system was comprised of $[Rh(cod)Cl]_2$ (10 mol %) and a mixture of *m*-TPPTS and DPPP (1:1:1 Rh/*m*-TPPTS/DPPP), which gave 97% of the cyclopentenone product. Use of either ligand alone gave lower conversion rates. Use of (*S*)-*tol*-BINAP in place of DPPP gave the product in both good yield (60−85%) and high enantioselectivity (75−95% ee).[507]





An interesting example of the use of substrate partitioning to control the selective cycloisomerization of di- and triynes was reported by Shinokubo, Oehima, and co-workers.[508] Cyclization of triynes, such as **271**, to give polycyclic arenes typically are carried out under ultradilute conditions to avoid intermolecular reactions. By using a water-soluble catalyst, the [2 + 2 + 2]-cyclization would occur in the aqueous phase where the concentration of the substrate would be low, while a high concentration substrate was present in the organic phase. Cyclization of triyne **271** in water/ether (5:1) using [RhCl(cod)]$_2$/*m*-TPPTS as the catalyst gave the desired tricyclic arene **272** in excellent yield (89%) with a 0.5 M concentration of **271** in the ether layer (eq 64). Products with larger rings could also be produced in good yields (89%) as a mixture of regioisomers. This methodology was also applied to the intermolecular [2 + 2 + 2] cyclization of a diyne (**273**) and propargyl alcohol, which often gives low yields due to oligomerization of the diyne. An 84% yield of **275** was obtained in the cyclotrimerization of **273** and propargyl alcohol (**274**) using the biphasic protocol (eq 65).





3.4. Aqueous-Phase Palladium-Catalyzed Cross-Coupling

Palladium-catalyzed cross-coupling of organic halides or pseudohalides with a nucleophilic reagent is one of the fundamental organometallic reaction classes used in organic synthesis (Figure 5). Since their development in the early 1970s, these reactions have become widely used in both academic and industrial laboratories, as well as being applied in the synthesis of a number of fine chemicals and pharmaceuticals. The history of using aqueous solvent systems in Pd-catalyzed cross-coupling goes back to the early development of the Suzuki coupling, which utilized aqueous base to activate the organoboron nucleophile.[509] The first example of the use of a water-soluble ligand for Pd-catalyzed cross-coupling in water was reported by Casalnuovo in 1990.[74] Since that time numerous reports of Pd-catalyzed coupling in aqueous solvents using a wide range of hydrophilic ligand designs have been reported. Several recent reviews of this area have been published,[42−44,47−49,510] so this overview will focus on the role of ligand design in developing catalysts with improved activity, lifetime, and recyclability.

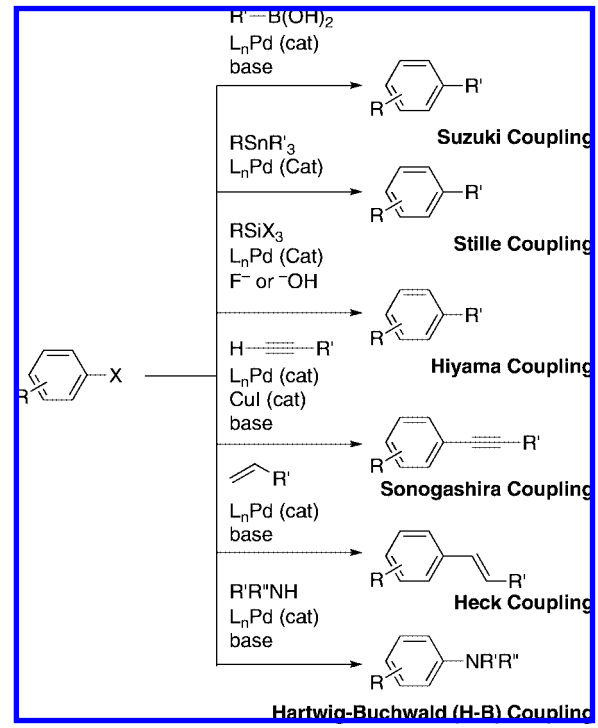
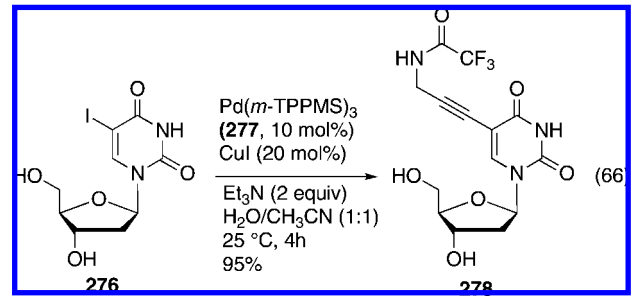


Figure 5. Examples of palladium-catalyzed cross-coupling reactions.

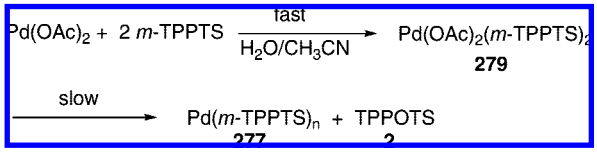
3.4.1. Cross-Coupling of Aryl Halides Using Hydrophilic Triarylphosphines

Casalnuovo's initial report of the cross-coupling of aryl iodides and activated aryl bromides in water/acetonitrile used Pd(*m*-TPPMS)$_3$ as the catalyst.[74] Examples of Suzuki, Sonogashira, Heck, and phosphonylation of aryl halides were reported. Of particular note were examples of Heck and Sonogashira couplings of 5-iodo-2′-deoxyuridine (**276**), 5-iodo-2′-deoxycytidine-5′-monophosphate, and 5-iodo-2′-deoxyuridine-5′-triphosphate (eq 66). Good yields were obtained in most cases, although elevated temperatures (80 °C) and high catalyst loadings (5−15 mol %) were used. The scope of aryl halides was limited to aryl iodides and a couple examples of activated aryl bromides (4-bromopyridine, 4-bromobenzoic acid).



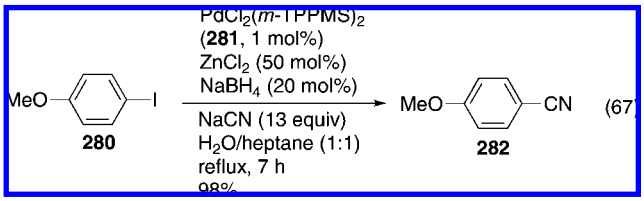
Casalnuovo's initial report inspired a number of groups to explore aqueous-phase, Pd-catalyzed cross-coupling reactions. Catalysts derived from $PdCl_2$ and *m*-TPPMS or *m*-TPPDS were also found to be effective for Stille coupling of aryltrichlorostannanes and aryl iodides in water.[511,512] The Genêt group reported that the catalyst derived from *m*-TPPTS and $Pd(OAc)_2$ was active for Suzuki and Sonogashira

Scheme 39

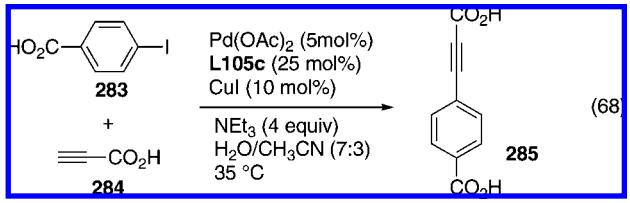


couplings of aryl iodides at room temperature, while Heck couplings required higher temperatures in some cases (25−66 °C).[75,513,514] Mechanistic studies showed that the $Pd(OAc)_2$/*m*-TPPTS mixture was converted to $Pd(m\text{-TPPTS})_3$ + *m*-TPPOTS by similar mechanism to that observed with PPh_3 (Scheme 39).[515]

A study of solvent effects in the Heck coupling of iodobenzene and ethyl acrylate using various palladium sources and *m*-TPPTS showed that the best results were obtained with $Pd(OAc)_2$ and DMF or DMF/water.[516] Notably, higher yields were obtained in DMF/water in the absence of *m*-TPPTS. Cyanation of aryl iodides was efficiently catalyzed by $PdCl_2(m\text{-TPPMS})_2$ in the presence of $NaBH_4$ and $ZnCl_2$ in a water/heptane biphase to give benzonitrile derivatives in good to excellent yields (eq 67).[517] The *m*-TPPMS ligand gave more effective catalysts than *m*-TPPMP (**L62a**) or crown-ether modified ligand **L144.**

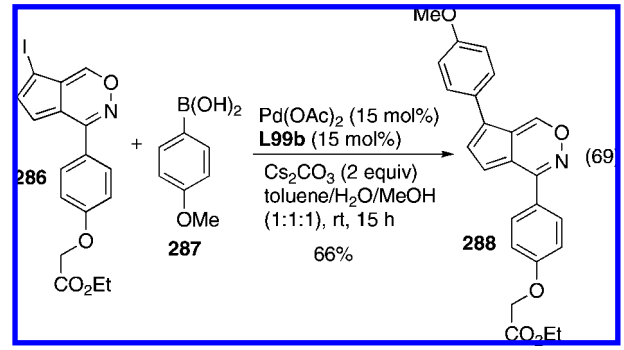


Sulfonated benzofuran ligands (**L6a**−**c**) gave effective catalysts for the Heck and Suzuki coupling of aryl iodides in water or water/acetonitrile, but the catalysts were less active than the *m*-TPPTS-derived catalyst.[90] Coupling of iodobenzene and cyclohexenone gave 71% yield of coupled product at 80 °C using **L6c**/$Pd(OAc)_2$ (5 mol %), while *m*-TPPTS/$Pd(OAc)_2$ gave 98% yield at 27 °C. Guanidinium-substituted triarylphosphines were found to be active for the Sonogashira coupling of 4-iodobenzoate (**283**) and propiolate (**284**) under mildly basic conditions (Et_3N) in water at 35 °C (eq 68).[224] *m*-TPPDG (**L105b**) gave a more active catalyst than *m*-TPPTG (**L105c**) or *m*-TPPTS. It was proposed that the cationic ligands would be more effective for the coupling of anionic substituents than the anionic *m*-TPPTS ligand.



The carboxylated analogue of *m*-TPPTS (*m*-TPPTC, **L62c**) was also effective for the Sonogashira coupling of 2-iodoanilines and phenols.[173] Using *m*-TPPTC, it was possible to carry out the reaction to completion at 70 °C in water/acetonitrile with only 1 mol % Pd. More complex dendrimeric carboxylic acid-substituted phosphines **L84a**−**c** (Table 6) gave similar results.[196] Heck coupling of iodobenzene and ethyl acrylate catalyzed by $Pd(OAc)_2$/*m*-TPPTC (0.1 mol % Pd, 5:1 L/Pd) occurred with complete conversion after 1 h at 110 °C in water/NMP using diisopropylamine as the base.[170] Reactions with styrene required 1 mol % catalyst and gave lower conversions (84%) after 4 h. The *m*-TPPTC/Pd catalyst showed better activity than *p*-TPPTC (**L64c**), *m*-TPPTS, or *m*-TPPTG (**L105c**). The catalysts derived from the latter three ligands showed similar initial activity, but became deactivated before complete conversion was obtained.

Suzuki coupling of 4-iodoanisole and phenylboronic acid using 0.07 mol % $PdCl_2$(**L23a**)$_2$ in toluene/ethanol/water (1:1:1) gave good initial conversion, but became inactive after one hour at 70% conversion.[518] Silica immobilized surfactants increased the catalyst activity and lifetime, allowing reactions to be carried out to >90% conversion. No catalytic activity remained when the aqueous phase was recycled, however. Good yields (65−80%) were obtained in the Suzuki coupling of a complex heterocyclic iodide (**286**) using *t*-Bu-Amphos (**L99b**) in combination with $Pd(OAc)_2$ in only 15 min at room temperature (eq 69).[519] No activity was seen using $Pd(OAc)_2$/P(*o*-tol)$_3$ at 50 °C in dioxane under standard Suzuki conditions.



Neutral hydrophilic phosphines have also been applied to cross-coupling of aryl iodides. Glucosamine-functionalized triphenylphosphines (**L140** and **L141**) gave good yields in the Suzuki coupling of very activated 4-nitrophenyl iodide in water/ethanol/toluene (2:2:3) at 60 °C.[262] The moderately high temperature with such an activated substrate suggests that the catalysts derived from **L140** and **L141** were not particularly active. Good activity was achieved in the coupling of $PhSnCl_3$ and aryl iodides using crown ether-functionalized ligand **L144b**.[266] Polymer-supported triarylphosphine **L179** gave active palladium catalysts for the coupling of hydrophobic and hydrophilic aryl iodides and alkynes in water/acetonitrile at 80 °C.[313] The soluble polymer-supported catalyst could be recovered in the aqueous phase and reused without loss of activity. Reactions in water−sodium 4-iodobenzoate went to completion in 36 h at 10 °C.

Aryl iodides are typically highly reactive in Pd-catalyzed cross-coupling due to their facile oxidative addition to Pd^0, so almost any catalyst system can be expected to show activity with these substrates. As noted above, the water-soluble ligands inhibit the palladium catalyst in several cases. Aryl iodides are also significantly more expensive on large scale than corresponding aryl bromide or chloride substrates. The bromides, and particularly chlorides, are less reactive, so they represent more challenging substrates when designing catalyst systems.

Several of the ligand systems that were initially reported to give active catalysts for aryl iodide cross-couplings could

also be applied for couplings of aryl bromides at elevated temperatures. The Suzuki coupling has received the most attention, as this is typically the easiest reaction to catalyze with aryl bromides. Aryl bromides can be coupled to arylboronic acids in water/acetonitrile (1:3) at 80 °C using $Pd(OAc)_2$ (5 mol %) and *m*-TPPTS (15 mol %) to give biaryls with complete conversion and good to excellent yields after 1−8 h.[520] The aqueous-phase containing the catalyst could be reused for 4 reaction cycles in the coupling of an activated aryl bromide, 4-bromobenzaldehyde, and phenylboronic acid before the yield began to decrease.

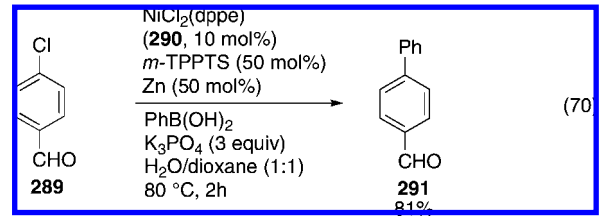
Careful optimization allowed the Sonogashira coupling of 2-bromo-1,4-dimethoxybenzene to be carried out with 0.5 mol % Pd at 80 °C.[521] Heck couplings of activated aryl bromides as well as aryl iodides with ethylene using $PdCl_2$(*m*-TPPMS)$_2$ (1 mol %) was achieved in modest yield at 100 °C, but deactivated aryl bromides gave low yields.[522] Diphenylphosphinoalkane sulfonate **L23a** in combination with $Pd(OAc)_2$ gave good yields in the coupling of aryl bromides using just 0.07 mol % catalyst at 78 °C in the presence of CTAB in 1:1:1 toluene/ethanol/water.[119] Palladium complexes of **L111a** and **L113a** (1 mol %) gave complete conversion at 140 °C in the Hiyama coupling of 3-bromopyridine and trimethoxyphenylsilane.[228] Complexes derived from the cationic analogues **L111b** and **L113b** gave good, but lower levels of conversion (85−90%). Catalysts derived from all four ligands showed no activity when the aqueous layer was reused.

The Pd^0L_n complex of *m*-TPPDG (**L105b**) gave complete conversion after 60 h in the coupling of (3-bromophenyl)-diphenylphosphine oxide and 4-tolylboronic acid using 1 mol % Pd at 90 °C in 3:1:1 toluene/ethylene glycol/water.[97] Higher activity was achieved with *p*-TPPMP (**L69a**), which gave complete conversion after 10 h. Phosphole ligand **L11** gave an inactive catalyst under these conditions. Hexacationic ligand **L97** gave a highly active catalyst for the coupling of methyl 4-bromobenzoate with 4-tolylboronic acid in water/methanol.[209] Using 0.01 mol % $Pd(dba)_2$ (2:1 P/Pd), complete conversion was achieved within 1 h at 65 °C. The Pd/**L97** catalyst was less effective with electron rich aryl bromides, such as 4-bromoanisole, however.

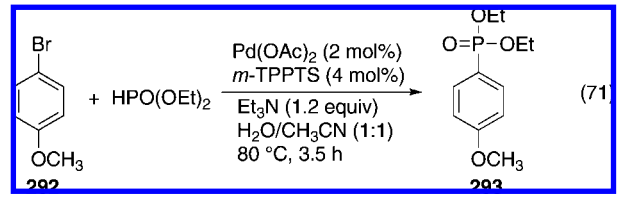
Triphenylphosphine glycoside (**L139**) in combination with $Pd(OAc)_2$ provided a more active catalyst for the Suzuki coupling of 4′-bromacetophenone and phenylboronic acid at 78 °C in water than *m*-TPPTS.[260] No examples were reported with nonactivated aryl bromides, however. Similarly, gluconamide phosphine **L143** gave a more active catalyst than *m*-TPPTS or *m*-TPPMS for Suzuki coupling of activated aryl bromides at 80 °C.[264] Bromobenzene gave only 68% yield after 16 h using 0.1 mol % catalyst, however. Glucosamine-substituted phosphine **L140** in combination with $Pd(OAc)_2$ gave a quantitative yield for the Suzuki coupling of 4-bromoanisole at 70 °C after 2 h using 1 mol % Pd.[261] Aqueous-phase Hiyama coupling of aryl bromides and arylsiloxanes using PdL_2Cl_2 precatalysts (L = **L144a,b**) gave good yields using 1 mol % Pd, but required high temperatures (140 °C).[265]

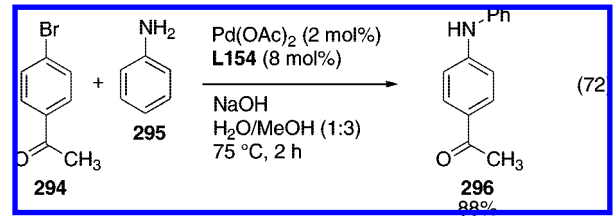
The sterically demanding ligands TXPTS (**L2d**) and TMAPTS (**L2e**) have significantly larger cone angles than *m*-TPPTS, as well as being somewhat more electron-donating.[85] Ligands **L2d** and **L2e** provided more active catalysts for the Suzuki, Sonogashira, and Heck couplings of aryl bromides at moderate temperatures (50−80 °C).[84] The difference in activity between TXPTS and *m*-TPPTS was small for the Suzuki coupling of aryl bromides at 50 °C, while in the Heck and Sonogashira couplings of 4-bromotoluene, TXTPS gave yields that were twice as high as those obtained with the *m*-TPPTS catalyst under identical conditions.

Triarylphosphine−palladium complexes typically show low activity for the oxidative addition of aryl chlorides.[523] There are no examples of cross-couplings of aryl chlorides in water using triarylphosphines in combination with palladium. Genêt and co-workers have shown that a catalyst derived from $NiCl_2$(DPPE) (**290**, 10 mol %), *m*-TPPTS (50 mol %), and zinc (50 mol %) gave good to excellent yields in the Suzuki coupling of aryl chlorides at 50 °C in dioxane water (eq 70).[524] The reaction was largely limited to activated aryl chlorides, although 4-chlorotoluene was coupled with phenylboronic acid in NMP/water at 80 °C to give a 70% yield of 4-methylbiphenyl.



In addition to carbon nucleophiles, palladium can catalyze the coupling of aryl halides and heteronucleophiles. Examples of these reactions in aqueous solvents have been rare, however. Palladium-catalyzed coupling of aryl iodides and bromides with diethyl phosphonate using a $Pd(OAc)_2$/*m*-TPPMS system (2.5 mol % Pd) gave good yields of arylphosphonate esters (**292**) in water/acetonitrile at 80 °C (eq 71).[525] To date, the only example of C−N bond formation using a hydrophilic phosphine has been reported by Boche.[166] Using a catalyst derived from BINAS (**L56**) and $Pd(OAc)_2$ (2 mol % Pd, 8:1 L/Pd), good yields were obtained in the coupling of 4′-bromoacetophenone (**294**) and aniline or *N*-methylaniline at 75 °C in water/methanol (eq 72). Although examples of aryl amination in the presence of water have been reported using hydrophobic ligands,[526,527] no further examples with hydrophilic ligands have been reported in the decade since Boche's initial report.



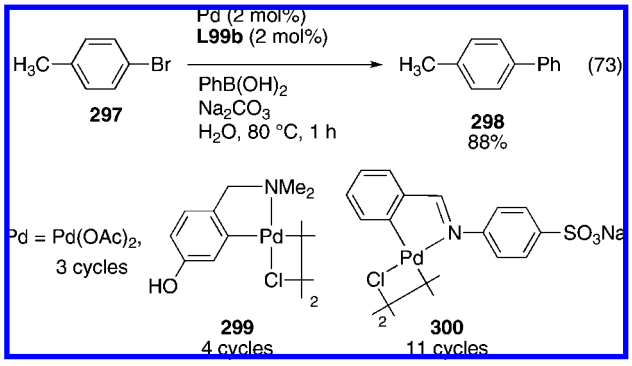


3.4.2. Cross-Coupling with Hydrophilic, Sterically Demanding Alkylphosphines

The majority of the early work in aqueous-phase cross-coupling chemistry involved exploring triarylphosphine ligands with a variety

of water-solubilizing groups. While catalysts derived from these ligands showed good activity for coupling of aryl iodides and aryl bromides at elevated temperature, there has been a growing interest in designing catalyst systems that provide good activity for unactivated aryl bromide and chloride substrates at low temperature and with low catalyst loadings. Over the past decade, ligands with large steric demand and strong electron donor properties have been shown to give high activity catalysts for cross-coupling reactions of unactivated substrates at moderate temperatures. Only recently have hydrophilic examples of these types of ligands been reported that can promote cross-coupling of aryl bromides at ambient temperatures as well as in a few cases couplings of aryl chlorides.

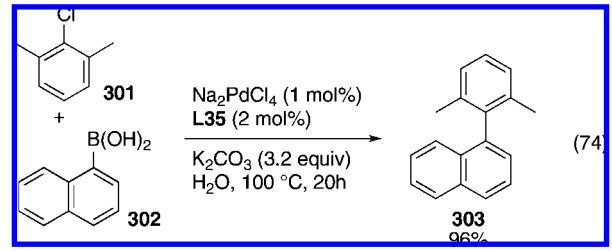
Sterically demanding trialkylphosphines, such as *t*-Bu_3P, provide effective catalysts for a range of coupling reactions of aryl bromides and room temperature and aryl chlorides below 100 °C. Quaternary ammonium-substituted trialkylphosphines *t*-Bu-Amphos (**L99b**) and *t*-Bu-Pip-phos (**L100b**) were developed as water-soluble ligands with similar steric and electronic properties to *t*-Bu_3P. Catalysts derived from *t*-Bu-Amphos and *t*-Bu-Pip-phos and $Pd(OAc)_2$ provided the first example of the Suzuki coupling of unactivated aryl bromides at room temperature in an aqueous solvent system (1:1 water/acetonitrile).[230] Cy-Pip-phos (**L100a**) gave a less active catalyst, however. The *t*-Bu-Amphos/Pd catalyst system gave good activity for Sonogashira and Heck couplings of aryl bromides at 50 and 80 °C, respectively.[212] Neither ligand provided active catalysts for the coupling of unactivated aryl chlorides, however. Both **L99b** and **L100b** have larger calculated cone angles than *t*-Bu_3P, while **L100a** was smaller than *t*-Bu_3P.[405] All three cationic ligands are weaker electron donors than *t*-Bu_3P presumably due to the cationic ammonium functionality. Increasing cone angle correlated well with catalyst activity for the Suzuki coupling of aryl bromides with these ligands, while activity toward aryl chlorides correlated with increasing electron donating ability.



The *t*-Bu-Amphos/$Pd(OAc)_2$ system gave turnover values of 10,000 mol/mol of Pd at room temperature and 730,000 mol/mol of Pd at 80 °C for the coupling of 4-bromotoluene and phenylboronic acid.[230] The aqueous catalyst solution could be used for three reaction cycles before the yield began to decrease substantially. Using hydrophilic palladacycles derived from **L204** and **L208** (**299** and **300**) in combination with *t*-Bu-Amphos gave a highly stable catalyst system that could be recycled multiple times (eq 73).[342] In the coupling of 4-bromotoluene and phenylboronic acid in water at 80 °C, the *t*-Bu-Amphos/$Pd(OAc)_2$ again gave 3 reaction cycles before the activity decreased significantly (1 h/cycle). Palladacycle **299** gave 4 cycles of quantitative yield with *t*-Bu-Amphos and then began to lose activity. The sulfonated imine complex **300** in combination with *t*-Bu-Amphos gave a quantitative yield of product for 11 reaction cycles, 85% yield in cycle 12, and then 50% in cycle 13 (1 h/cycle).

In order to achieve good activity for the coupling of aryl chlorides, more electron-donating ligands than **L99** and **L100** will be required. Replacement of the cationic ammonium functionality with an anionic group should give a more electron-donating ligand. Phosphonium alkylsulfonates **L34a,b** were prepared as anionic versions of **L99b**.[132] These ligands provided active catalysts for the Sonogashira coupling of aryl bromides at 23 °C, while the **L99b**/$Pd(OAc)_2$ system required 50 °C to give comparable conversion rates. More significantly, coupling of 4-chloroanisole with phenylacetylene at 80 °C in water/acetonitrile using **L34a**/$Pd(OAc)_2$ (1 mol %) gave a 73% yield of the coupled product. PEG-supported diadamantylphosphine **L172** has been shown to provide active catalysts for Suzuki and Sonogashira couplings of aryl bromides in dipolar aprotic solvents, but have not been applied to aqueous-phase coupling.[304,305]

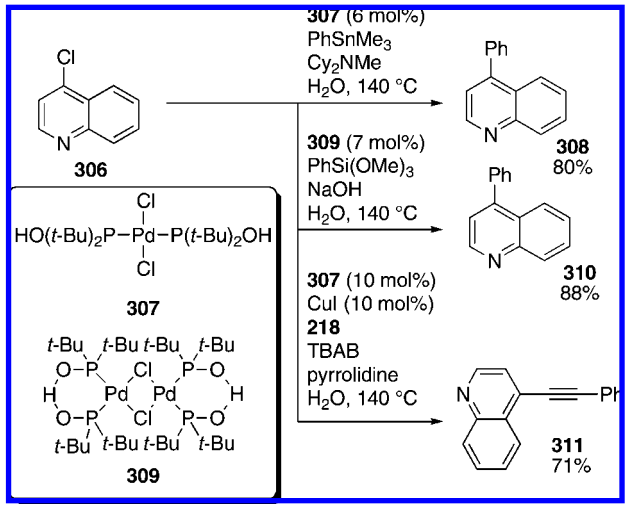
Sulfonated sterically demanding 9-fluorenyldialkylphoshines (**L35** and **L36**) have been found to give highly effective palladium catalysts for Suzuki and Sonogashira couplings of aryl bromides in water.[133−135,388,528,529] Ligand **L35** in combination with $NaPdCl_4$ gave excellent yields in Suzuki couplings of aryl bromides and chlorides using 0.1−1 mol % Pd in water. Unhindered aryl bromides and activated aryl chlorides could be coupled at room temperature, while unactivated aryl chlorides and hindered substrates required elevated temperatures (50−100 °C, eq 74). This catalyst system also gave excellent results in the Sonogashira coupling of aryl bromides at 100 °C in water/isopropanol. No aryl chlorides were reported for the Sonogashira coupling, however. The catalyst derived from **L36** gave excellent yields in the Suzuki coupling of aryl and heteroaryl chlorides using low catalyst loadings (0.01−0.05 mol %) at 100 °C in water/butanol (1:3).



Sterically demanding mixed aryl alkylphosphines have also shown promise for aqueous-phase cross-coupling of aryl bromides and chlorides. Sterically hindered diarylphosphinopropane sulfonate ligand **L24** in combination with $Pd(OAc)_2$ (0.05 mol % Pd, 1:1 L/Pd) gave good yields for Suzuki coupling of aryl bromides at 80 °C, although 4-bromoanisole gave incomplete conversion.[120] This catalyst system could also be applied to activated aryl chlorides to give modest yields of coupled products using 1−2 mol % Pd at 150 °C with microwave heating.

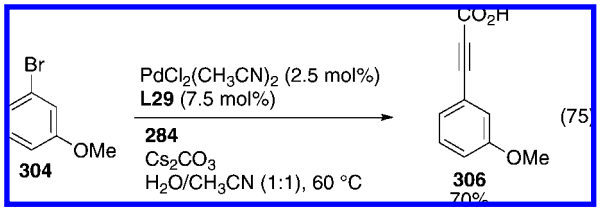
Buchwald has developed a family of ligands based on dialkyl(2-biphenyl)phosphines that give active catalysts for cross-coupling reactions of aryl bromides and chlorides.[126,272−276] Miyaura prepared gluconamide-modified version of this class of ligands (**L145a,b**).[267] The catalyst derived from **L145a** and $Pd(OAc)_2$ gave comparable activity to triphenylphosphine gluconamide (**L143**) for the Suzuki coupling of 4-bromoanisole at 80 °C, but at room temperature the **L145a**-derived catalyst was more active. The **L145a**/Pd catalyst also

Scheme 40



showed activity toward 4-chlorobenzoic acid at 80 °C, while the catalyst derived from **L143** was completely inactive. The **L145b**/Pd catalyst was generally a less effective ligand than **L145a**. A glucosamine analogue of **L145a** has also been reported (**L142**).[263] The catalyst generated from **L142** and $Pd(OAc)_2$ (1 mol % Pd, 3:1 L/Pd) was moderately active for the Suzuki coupling of activated aryl chlorides at 80 °C in toluene/ethanol/water (3:2:2). Good yields were obtained with activated aryl chlorides, but 4-chlorotoluene gave only 23% conversion under these conditions.

Buchwald has reported the use of ligands **L28** and **L29** in the aqueous-phase Suzuki and Sonogashira coupling of aryl bromides and chlorides.[126] The catalyst derived from **L28** and $Pd(OAc)_2$ (1 mol % Pd) gave excellent yields for Suzuki coupling of aryl chlorides, including some examples at room temperature. The catalyst derived from **L29** was effective for the Sonogashira coupling of aryl bromides and chlorides in water/acetonitrile at 60−100 °C. For the first time, propiolic acid was coupled with an aryl bromide in water (eq 75). No examples of deactivated aryl chlorides were reported, however.

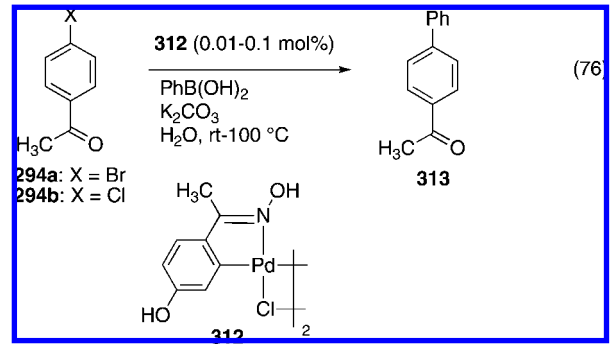


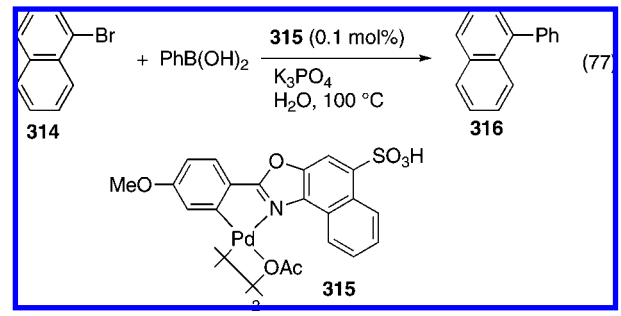
Dialkylphospinous acids have been applied to the cross-coupling of aryl bromides and chlorides at elevated temperatures in water. Under the reaction basic coupling conditions the phosphinous acid is deprotonated to give water-soluble catalyst species. Stille,[271] Hiyama,[269,530,531] and Sonogashira[270] couplings of aryl bromides and chlorides can be catalyzed by Pd complexes of t-Bu_2POH (Scheme 40) at elevated temperatures. The coupling reactions are typically carried out at 130−140 °C using high catalyst loadings (6−10 mol %). The aryl chloride examples reported are limited to activated aryl or heteroaryl chlorides. Pd-catalyzed conjugate addition of arylsiloxanes to enones has also been reported using **309** (5 mol %) at 120 °C in water to give β-arylketones in good yields.[268]

3.4.3. Cross-Coupling with Hydrophilic Nitrogen or NHC Ligands

Phosphines have dominated the palladium-catalyzed cross-coupling landscape since the initial development of these reactions in the 1970s, but recent efforts to develop phosphine-free systems have gained growing momentum. This trend can also been seen in the development of ligands for aqueous-phase cross-coupling reactions. While still dominated by phosphines, a growing number of hydrophilic nitrogen and *N*-heterocyclic carbene ligands have been applied to Pd-catalyzed cross-coupling reactions in recent years.[385]

Palladacyclic complexes have shown significant promise as catalyst precursors in cross-coupling reactions.[532−534] The palladacycle derived from oxime **L206** (**312**) was an effective precatalyst for the Suzuki coupling of aryl bromides and chlorides (eq 76).[344,535] At 100 °C, the coupling of 4-bromoacetophenone (**291a**) and phenylboronic acid was complete in 15 min (90% yield) using 0.01 mol % Pd, although similar results were obtained with $Pd(OAc)_2$ without a ligand. At room temperature, complex **312** gave a 98% yield after 5 h in 3:1 MeOH/H_2O, while $Pd(OAc)_2$ gave a 50% yield after 23 h. Complex **312** catalyzed the Hiyama coupling of aryl iodides and bromides and vinylsiloxanes in water at 100−120 °C.[343] $Pd(OAc)_2$ gave comparable results, but complex **312** could be used for 6 cycles in the vinylation of 4′-bromoacetophenone compared to 4 cycles with $Pd(OAc)_2$. Leaching increased significantly as the catalyst activity decreased. Complex **312** also catalyzes the Suzuki coupling of activated aryl chlorides in refluxing water in good to excellent yields using TBAB as a promoter. This complex was also effective for the Heck coupling of aryl iodides and activated aryl bromides in water at 100−120 °C.[345,536] The palladacyclic complex derived from sulfonated naphthoxazole ligand **L194** (**315**) was an effective precatalyst (0.1 mol %) for the Suzuki coupling of aryl bromides in water under aerobic conditions at 100 °C (eq 77).[332] Unactivated aryl chlorides gave little or no conversion with **315** as the precatalyst, though.





The complex formed from $PdCl_2$ and EDTA (**L210**) was an effective catalyst for the Suzuki coupling of aryl iodides

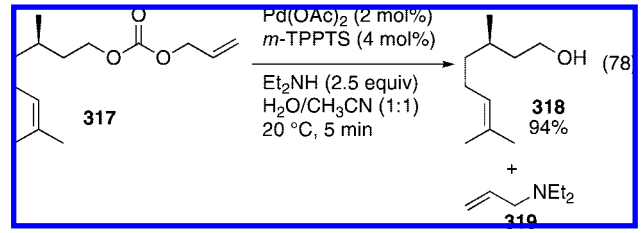
(20−100 °C) and aryl bromides (60−100 °C) in water using 0.1 mol % Pd.[246] This catalyst system showed modest activity for the reductive homocoupling of aryl bromides using ascorbic acid as the reducing agent.[346] Yields ranged from 35% to 84% for reactions run in refluxing water/ethanol (5:1) using 3 mol % Pd. PEG-supported dipyridylmethane ligand **L234** was used with $Pd(OAc)_2$ for the Suzuki coupling of aryl bromides and $NaBPh_4$ in PEG/H_2O (1:1) at 110 °C.[372] Good yields were obtained with aryl bromides. The catalyst was more effective for coupling reactions run in PEG alone, however. Alkylsulfonate-functionalized pyridine ligand **L190** was used as a promoter for the room temperature Heck and Suzuki coupling of aryl iodides in water.[327,328] Good yields were obtained, but high palladium loadings (3−5 mol %) were required along with very high loadings of **L190** (50−100 mol %).

Dicationic bipyridine ligand **L217** gave an active catalyst for the Suzuki coupling of activated aryl bromides at 80 °C in water.[358] The aqueous catalyst solution could be used for 5 reaction cycles to give the product in high yield, although reaction time increased with each cycle. Activated aryl chlorides could also be coupled at 100−140 °C. Ligand **L217** in combination with $Pd(NH_3)_2Cl_2$ also gave an effective catalyst for the Hiyama coupling of phenylsiloxanes and aryl bromides in water at 120 °C.[365] The palladium complex of tetracarboxylated porphyrin (**L193**) gave good yields in the Suzuki coupling of aryl bromides at 100 °C in water under air. Recovery of the aqueous phase gave a less active catalyst.[331] The nature of the active species in this system is presumably colloidal palladium, since the coordinatively saturated palladium−porphyrin complex cannot catalyze the reaction.

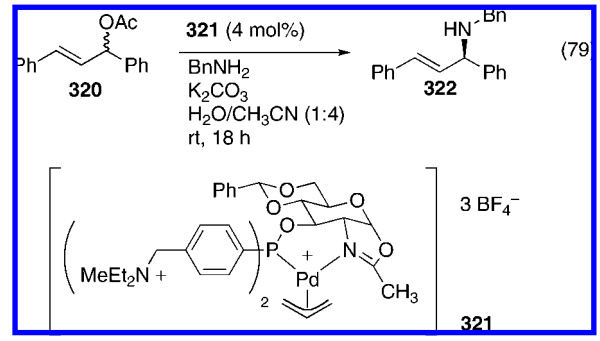
Hydrophilic palladium−NHC complexes have only recently been reported for cross-coupling reactions in water. The first example to be reported was the Heck coupling of iodobenzene and styrene using poly(oxazoline)-supported Pd−NHC complex **L252**.[397,398] The catalyst showed modest activity at 90 °C and could be used for 3 reaction cycles, although the activity dropped with each cycle. Complex **L252** was also effective for the Suzuki coupling of iodobenzene and activated aryl bromides. The first monomeric, hydrophilic carbene precursors applied to cross-coupling reactions were **L243a**−**c**.[388] 4-Chlorotoluene and 4-tolylboronic acid were completely converted to the biaryl product using **L243a**/$NaPdCl_4$ in water at 100 °C after 16 h. The isopropyl analogue (**L243c**) gave a less active catalyst and palladium precipitation occurred rapidly. The unsaturated analogue (**L243e**) did give an effective catalyst, however. Hyperbranched NHC precursor **L249** gave an active palladium precatalyst for the Suzuki coupling of aryl bromides in water at 80−100 °C.[394]

3.4.4. Pd-Catalyzed Reactions of Allyl and Benzyl Substrates

Palladium-catalyzed allylic substitution reactions (Trost−Tsuji allylation) are widely used synthetic methods in chemistry.[537] Early examples of aqueous-phase, Pd-catalyzed coupling reactions involved the development of catalysts for the removal of allyl carbonate from protected alcohols. Pd/*m*-TPPTS catalyst systems were found to be effective for this transformation using primary amines as the nucleophilic reagent (eq 78).[70,86,538,539] Hydrophobic allyl carbonates show low activity, which can be improved by the use of cosolvents or surfactants. Alternatively, cyclodextrin phase transport catalysts can be used.[540−542] Sterically demanding analogues of *m*-TPPTS provide optimal activity in these systems since the ligand does not form an inclusion complex with the cyclodextrin.

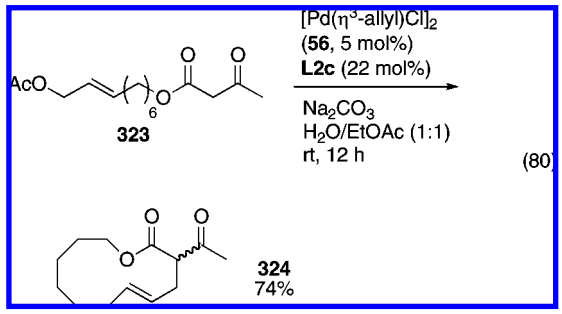


The Pd/*m*-TPPTS catalyst system has also been applied to synthetic applications of the allyl substitution reaction. $Pd(OAc)_2$ in combination with large excesses of *m*-TPPTS (6−12 equivalents) provided effective catalysts for the reaction of allyl carbonates with malonates in water/acetonitrile at 50 °C. The linear substitution product was formed preferentially (9:1).[69,543] Enantioselective allylation of malonates was achieved using a palladium complex of **L127** (**321**) in water or water/acetonitrile (eq 79).[242] Good yields (66−85%) of the coupled product (**322**) were achieved along with good enantioselectivity (77−85%). The catalyst solution could be used again, but the enantioselectivity degraded somewhat (60% ee in water).

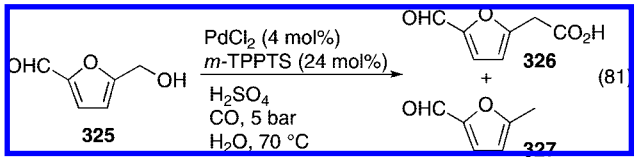


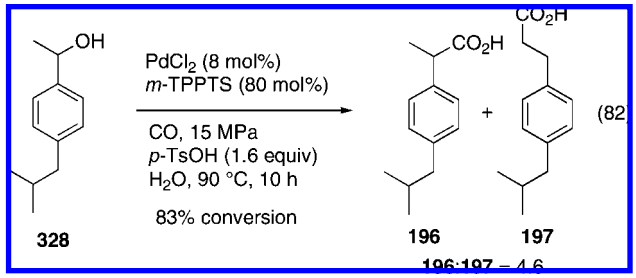
Shinokubo and Oshima took advantage of the unique properties of aqueous-biphasic reactions to carry out the synthesis of macrolactones by an intramolecular allylic substitution reaction.[81] In a homogeneous reaction, this type of transformation must be done at high dilution to avoid intermolecular reactions. Since the aqueous phase will have a low concentration of hydrophobic substrate, independent of the water/substrate ratio, the reaction could be run under effective low concentration conditions without the use of large volumes of solvent by using a water-soluble catalyst. Reaction of allylcarbonate **323** in water/ethyl acetate at room temperature using $[Pd(\eta^3\text{-allyl})Cl]_2$ and *m*-TPPTS gave a 66% yield of the macrolactone (**324**) as a 1:1 mixture of olefin stereoisomers (eq 80). If the reaction was run in THF at 0.05 M using PPh_3 as the ligand, a 36% yield of the macrolactone was obtained.

Benzylic and allylic alcohols can be directly activated in water without the need to convert the OH into a good leaving group. This concept was first demonstrated in the carbonylation of hydroxymethylfurfural (**325**) catalyzed by $PdCl_2$/*m*-TPPTS in acidic water.[72] Under optimized conditions, 90% conversion of **325** to a mixture of acid **326** and 5-methylfurfural (**327**, 3:1 ratio of **326**/**327**) was obtained (eq 81).

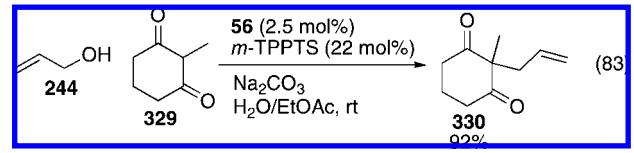


The reaction proceeded by acid promoted oxidative addition of the alcohol to Pd^0 followed by carbonylation and hydrolysis of the Pd-acyl. Product **327** was formed by competitive protonation of the Pd−alkyl intermediate. This method could be extended to benzyl alcohol, which was carbonylated to phenylacetic acid in modest yield.[72,544] Carbonylation of the precursor to ibuprofen (**328**) with Pd/*m*-TPPTS in the presence of TsOH gave 93% conversion of the alcohol to a mixture of ibuprofen (**196**) and the regioisomeric acid product (**197**) in a 72:28 ratio (eq 82).





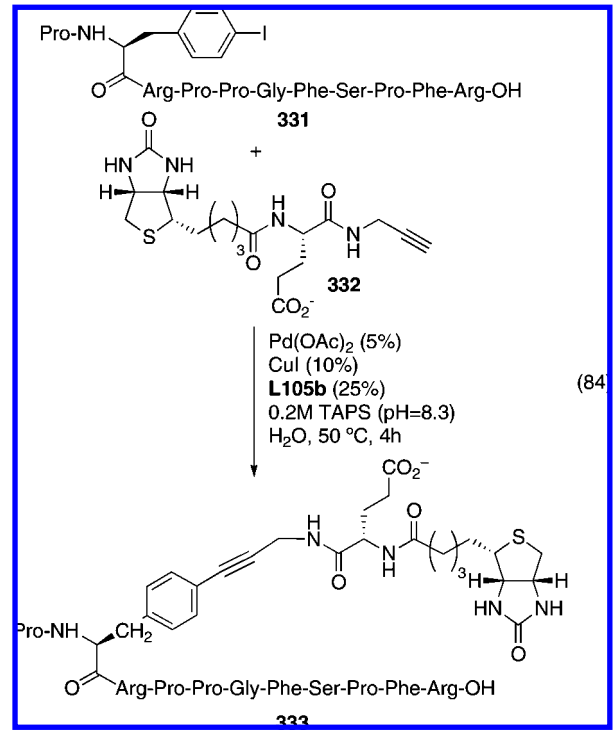
Kobayashi reported that allylic alcohols could be used in allylic substitution reactions catalyzed by $Pd(PPh_3)_4$ in water in the presence of organic acids without activation of the OH group.[545] This reactivity in water is different from what is seen in organic solvents, where allyl alcohols react slowly. While desirable from an atom economy and simplicity standpoint, the use of an acid promoter would limit the choice of nucleophiles that could be used. When $[Pd(\eta^3\text{-allyl})Cl]_2$ and *m*-TPPTS were used as the precatalyst, no acid promoter was needed.[546] Reaction of allyl alcohol (**244**) with 2-methylcyclohexan-1,3-dione (**329**) in water/ethyl acetate in the presence of 2.5 mol % $[Pd(\eta^3\text{-allyl})Cl]_2$/*m*-TPPTS (4:1 L/Pd) and catalytic sodium carbonate gave the allylated product (**330**) in 92% yield (eq 83). In ethyl acetate alone, no reaction occurred. A range of allyl alcohols and diketone or amine nucleophiles could be coupled in good yields with this catalyst system. Based on computational studies it was proposed that Pd coordination to the alkene of the allyl alcohol activated the OH. The departing hydroxide was stabilized through hydrogen bonding interactions with the aqueous solvent. Coupling of 1,1-dimethylallyl alcohol with haloanilines using Pd/*m*-TPPTS gave good yields of the *N*-allylated product in water at neutral pH, while the reaction gave low conversion in toluene.[547] Under basic conditions, selective Heck coupling occurred.



3.4.5. Pd-Catalyzed Modification of Biomolecules in Water

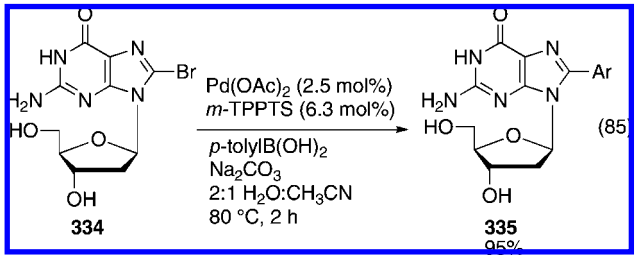
While the motivation for developing water-soluble catalyst systems is typically to encourage the catalyst to separate into the water layer allowing it to easily be removed from the hydrophobic substrate, one can also envision hydrophilic catalysts as ideal reagents for the modification of hydrophilic substrates. Biomolecules are often hydrophilic to some extent, since they reside in an aqueous environment Modification of these compounds in traditional organic solvents often requires protection of the hydrophilic sites on the biomolecule to make it sufficiently hydrophobic to dissolve in the desired reaction solvent. Upon completion of the reaction, the biomolecule must be deprotected to regain it is biologically useful function. It would be more efficient to directly modify the biomolecule in its unprotected form using a water-soluble catalyst system, thus avoiding the protection/deprotection sequence.

Dibowski and Scmidtchen reported Sonogashira coupling of a iodophenyl-containing bradykinin derivative (**331**) with alkyne (**332**) using $Pd(OAc)_2$ and *m*-TPPDG (**L105b**) in TAPS buffer (pH 8.3) at 35 °C gave the alkyne linked biotin peptide conjugate (**333**) in 75% yield (eq 84).[223] This concept has been extended to functionalization of biologically active iF-RAS proteins containing specific iodophenylalanine modifications with alkenyl or alkynyl biotin derivatives using $Pd(OAc)_2$ and *m*-TPPTS.[548,549] Heck and Sonogashira couplings were carried out on the modified iF-RAS proteins at 5 °C at mM concentration of substrates and catalyst. The addition of DMSO (1.6 M) and $MgCl_2$ (80 mM) was critical to the success of the reaction. A 2% yield of the biotin modified protein was obtained in the Heck coupling and 25% in the Sonogashira coupling.



Modified nucleosides, nucleotides, and oligonucleotides where the natural base has been covalently modified are of interest as biochemical probes, disease models, and potential pharmaceuticals. Palladium-catalyzed modification of halogenated nucleoside derivatives is a common approach to introduce organic fragments by C−C or C−N bond formation.[550,551] The typical approach for nucleoside modification is to protect the nucleoside functionality (alcohol and or amine), carry out the desired reaction in an organic solvent, and deprotect the resulting product. The protection/deprotection step is atom inefficient. Moreover, this approach is not practical for modification of nucleotides or oligonucleotides.

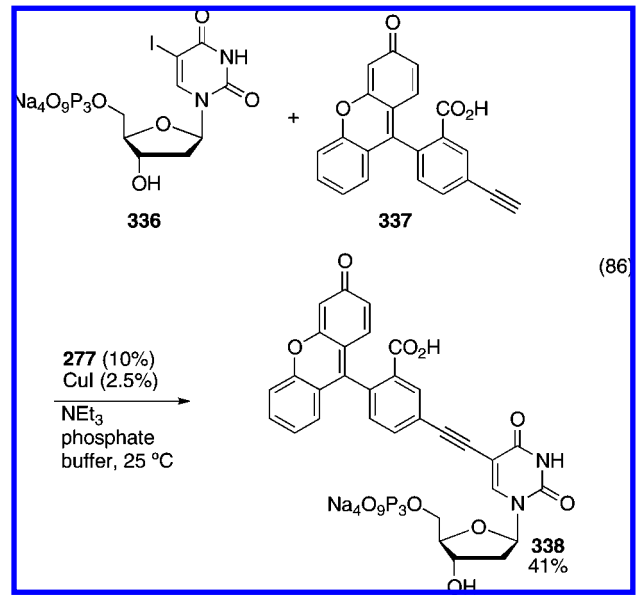
Casalnuovo was the first to report aqueous-phase modification of halonucleosides with a water-soluble catalyst.[74] Suzuki and Sonogashira couplings of 5-iodo-2′-deoxyuridine and 5-iodo-2′-deoxycytidine mono- and triphosphates were catalyzed by Pd(*m*-TPPMS)$_3$ to give the products in modest to excellent yields (47−95%). Using water-soluble catalysts derived from Pd(OAc)$_2$ and *m*-TPPTS or *m*-TXPTS good to excellent yields of *C*-arylated nucleoside derivatives were obtained in the Suzuki coupling of halonucleosides and arylboronic acids in water/acetonitrile.[552] Coupling of 8-bromo-2′-deoxyguanosine (**3334**) with 4-tolylboronic acid gave 8-*p*-tolyl-2′-deoxyguanosine (**335**) in 95% yield (eq 85). Good yields (70−95%) were obtained with a range of arylboronic acids with 8-bromo-2′-deoxyadenosine and 5-iodo-2′-deoxyuridine, as well as the ribose analogues. The guanosine substrates gave the slow rates due to binding of the guanosine base to palladium resulting in catalyst inhibition.[553] The Suzuki coupling of halonucleosides can also be carried out in water as the only solvent in good yield.[554]

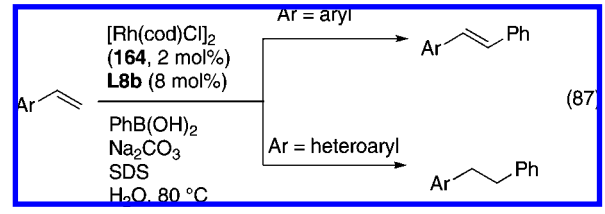


Nucleotides are more challenging substrates for standard cross-coupling methodologies because they are highly hydrophilic and cannot readily be made soluble in typical organic solvents. Burgess and co-workers used an aqueous-phase Sonogashira coupling of 5-iodo-2′-deoxyuridine-5′-triphosphate (**336**) with an alkyne-functionalized fluorescent dye (**337**) catalyzed by Pd/*m*-TPPMS at room temperature in phosphate buffer to give a dye-functionalized nucleotide (**338**) in 41% yield (eq 86).[555] Suzuki coupling of 8-bromoguanosine and its mono- and triphosphate catalyzed by Na$_2$PdCl$_4$/*m*-TPPTS gave good yields of arylated products in water at 80 °C.[556] Yields for the guanosine and guanosine-5′-phosphate were similar, but the triphosphate gave somewhat lower yields. Reaction times were also longer with the phosphorylated substrates.

3.5. Rh-Catalyzed Cross-Coupling

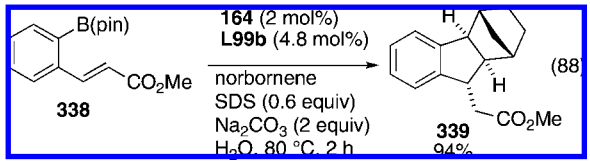
Rhodium catalyzes the addition of organometallic reagents, such as boronic acids, to electron deficient olefins, alkynes, or carbonyls.[557,558] Recent efforts have shown that many of these reactions can be carried out in aqueous solvent systems. The first example of a Rh-catalyzed reaction using hydrophilic ligands in water was the arylation of alkenes with arylboronic acids using a catalyst derived from [Rh(cod)Cl]$_2$ and *p*-TPPDS (**L8b**, Table 1).[77] Under optimized conditions, styrene was coupled with phenylboronic acid using 4 mol % Rh in water with SDS at room temperature to give stilbene in 80% yield (eq 87). Surfactant (SDS) was required to allow the reaction to proceed at a sufficient rate to avoid competitive hydrolytic deborylation. When vinylpyridines were used, saturated 1-aryl-2-pyridylethane products were obtained. It is noteworthy that little or no reaction was observed when the reaction was run with cosolvents or in organic solvents using either sulfonated or hydrophobic ligands. In organic solvents, only electron-deficient olefins underwent this reaction. The catalyst derived from [Rh(cod)Cl]$_2$ and *m*-TPPTC (**L62c**) was found to give a more active catalyst for these reactions than *m*-TPPTS, although both ligands gave lower yields than were achieved in the absence of ligand.[172]



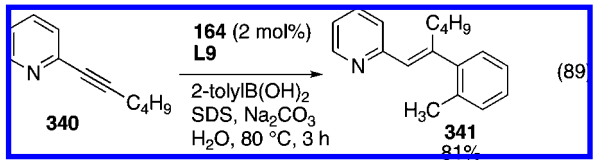


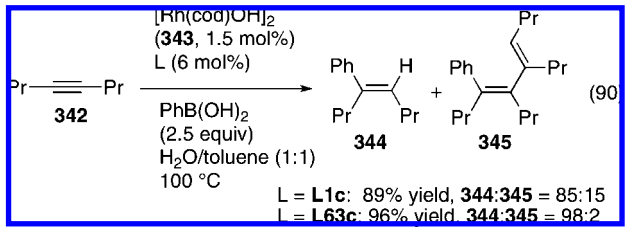
Reaction of 2-borylstyrene derivatives (**338**) with norbornene using [Rh(cod)Cl]$_2$ with *p*-TPPDS (**L8b**) or *t*-Bu-Amphos (**L99b**) in water with SDS provided bicyclic indane derivatives (**339**, eq 88).[214] The *p*-TPPDS-derived catalyst gave complete conversion after 2 h, but only 27% yield of the indane product. The remaining borylstyrene had been protodeborylated. The *t*-Bu-Amphos-derived catalyst gave complete conversion with 100% selectivity for the indane product. Reaction of methyl-2-borylcinnamate with norbornene in water in the presence of Rh/*t*-Bu-Amphos (2 mol %), SDS, and sodium carbonate gave indane product **339** in 94% yield as a single diastereomer.

Arylation of 2-alkynylpyridines using arylboronic acids was carried out using catalytic [Rh(cod)Cl$_2$]$_2$ in combination with a pyridyl analogue of *m*-TPPDS (**L8b**) in water with SDS at 80 °C.[78,559] Coupling of 2-methylboronic acid and 1-hexynylpyridine gave **341** exclusively as the *E*-isomer in

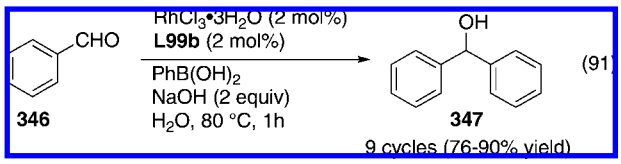


81% yield using 4 mol % Rh (eq 89). The alkyne must be in the 2-position for the reaction to occur, but does not need to be conjugated to the pyridine. The catalyst derived from $[Rh(cod)OH]_2$ and either *m*-TPPTS or *m*-TPPTC (**L62c**, Table 6) promoted the arylation of dialkyl and aryl alkyl acetylenes in good yields in water/toluene at 100 °C.[173,560,561] In the coupling of 4-octyne and phenylboronic acid, the *m*-TPPTS/Rh complex gave an 89% yield and 85:15 ratio of **344/345**, while the *m*-TPPTC/Rh complex gave the same yield and a 98% selectivity for the monomeric product (**344**, eq 90). The aqueous catalyst solution could be recovered and used for 4 reaction cycles during which the yield and product selectivity remained unchanged.





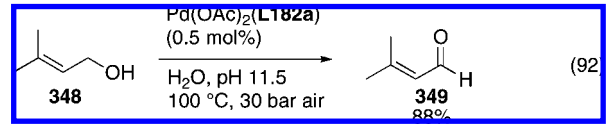
Rhodium-catalyzed 1,2- and 1,4-addition of nucleophiles to aldehydes or enones provides an attractive alternative to the use of main group metals that is compatible with aqueous-phase catalysis. Conjugate addition of arylboronic acids to cyclohexenone using a catalyst derived from $[Rh(cod)Cl]_2$ and *m*-TPPTS or *m*-TPPTC gave quantitative yield of the product after 1 h at 80 °C.[172] Although these results were quite promising, the ligands actually served as catalyst inhibitors. In the absence of ligand, $[Rh(cod)Cl]_2$ catalyzes the 1,4-addition in 15 min. While the water-soluble ligands inhibited the reaction, they do allow the expensive rhodium catalyst to be recovered and reused. Use of the same aqueous catalyst solution for 4 reaction cycles gave identical yields and product selectivities. Rh^{I} or Rh^{III} sources in combination with *t*-Bu-Amphos (**L99b**) catalyze the addition of aryl- and vinylboronic acids to aryl- and aliphatic aldehydes in water at 80 °C in 50−90% yield.[213] The $RhCl_3 \cdot 3H_2O$/*t*-Bu-Amphos catalyst system (2 mol % Rh) was used for 9 reaction cycles (1 h/cycle) during which the product yields were 79%, 83%, 90%, 85%, 90%, 90%, 86%, 74%, and 76% (eq 91).



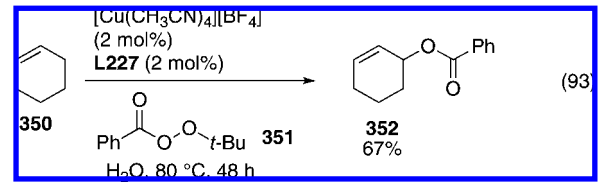
3.6. Aqueous-Phase Catalytic Oxidation

Metal-catalyzed oxidation of organic substrates have received a resurgence of interest as they offer improved atom economy compared to traditional stoichiometric metal-mediated oxidations. Water is an attractive solvent for metal-catalyzed oxidations as the oxidants and/or their byproducts are often water-soluble, which allows them to be easily separated from the organic product. Since phosphines are prone to oxidation, these reactions typically rely on hydrophilic nitrogen-based ligands.

Metal-catalyzed aerobic oxidation of alcohols to ketones using O_2 as the oxidant in water is a highly attractive reaction in terms of environmental sustainability. Oxidation of primary and secondary alcohols using the $Pd(OAc)_2$ (0.25−0.5 mol %) complex of sulfonated bathophenanthroline (**L182**) under 30 bar of air pressure at 100 °C gave ketone or aldehyde products in high yield and selectivity (eq 92).[319] Because oxygen is more soluble in water than nitrogen, nitrogen diluted oxygen (8% O_2), which in combinations with organic materials is not explosive, could be used when the reaction was carried out at high pressure (30 bar). Dicarboxylated biquinoline ligand **L187** gave a less active catalyst under similar conditions.[323] A Mn^{III} complex of phosphonium-substituted salen ligand **L219** catalyzed the oxidation of primary and secondary alcohols to aldehydes and ketones in water/acetonitrile using $NaIO_4$ as the oxidant.[366] Good to excellent yields of the oxidized products were obtained in less than 1 h at room temperature.

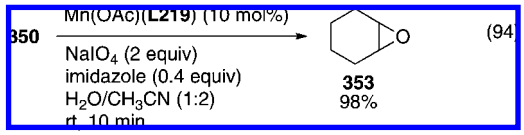


Direct C−H activation of hydrocarbons to give functionalized molecules has been a long-standing goal in organometallic catalysis. The combination of EDTA-tetraamide **L227** and $[Cu(CH_3CN)_4]BF_4$ was applied to the Kharasch−Sosnovsky allylic oxidation of alkenes in water at 80 °C (eq 93).[363] Slow conversion to the allylbenzoate products was obtained with cyclic and linear alkenes. More hydrophobic substrates were less reactive, as is commonly seen in aqueous-phase catalysis. The aqueous catalyst solution could be reused and gave higher yields in subsequent reactions. The Mn^{III} complex of salen **L219** showed good activity for the oxidation of alkanes with $NaIO_4$ to give mixtures of alcohol and ketone products in modest yield.[360] Oxidation of cyclooctane gave 65% conversion to a 1:1 mixture of cyclooctanol and cyclooctanone after 40 min at room temperature.

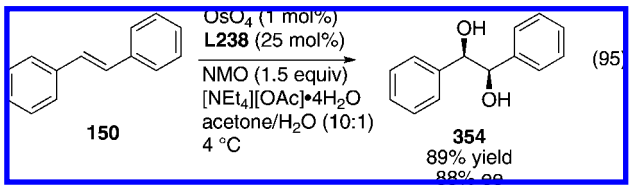


Alkene oxidations to epoxide or diol structures are widely used strategies in organic synthesis. The water-soluble manganese complex of **L219** (10 mol % Mn) gave good yields of epoxides with high chemoselectivity from mono- and disubstituted alkenes in water/acetonitrile using $NaIO_4$ as the oxidant in 10−20 min.[360] Cyclohexene was epoxidized to give cyclohexene epoxide (**353**) with 100% selectivity for the epoxide product (eq 94). Epoxidation of styrene gave a 93% yield of styrene epoxide with acetophenone (2%)

produced as a side product. All other reactions gave complete selectivity for the epoxide product.



Recovery of the OsO_4/cinchona alkaloid catalyst system in the asymmetric dihydroxylation of alkenes is important given the cost of the osmium and alkaloid catalyst components as well as the toxicity of OsO_4. A series of PEG-supported cinchona alkaloid derivatives have been prepared to allow the catalyst to be recovered. Quinidine derivative **L238** was the first PEG-supported ligand reported for the asymmetric dihydroxylation reaction. It gave good yields (89%) and enantioselectivity (88% ee) in the dihydroxylation of *E*-stilbene (**150**) in water/acetone (1:10, eq 95). Notably, the reaction was complete in 5 h compared to 48 h for a polymer-supported quinidine ligand (87% yield, 82% ee).[375] PEG-modified $(DHQD)_2PHAL$ ligand **L239** gave improved enantioselectivity for the dihydroxylation of *E*-stilbene (99%) compared to **L238**.[379] Similar results were obtained with **L241** in the dihydroxylation of *E*-stilbene (91% yield, 99% ee). Each of the catalysts derived from **L238**−**L241** could be recovered by precipitation with diethyl ether or *t*-butyl methyl ether. For example, **L241** was used for six reaction cycles during which the enantioselectivity slowly degraded from 99% to 96%.



Although reactions with ligands **L238**−**L241** were run in partially aqueous solvents, they are not truly aqueous-phase reactions. A series of cationic cinchona alkaloid ligands were prepared by allylation of the one quinidine nitrogen of $(DHQD)_2PHAL$ or $(QD)_2PHAL$.[361] Under asymmetric dihydroxylation conditions, the olefinic sites of the ligand would be dihydroxylated to give the cationic polyol ligand **L228**. The combination of **L228** and OsO_4 gave good yields (88−93%) and excellent enantioselectivity (97%) for the dihydroxylation of styrene derivatives promoted by NMO in 1:1 *t*-BuOH/H_2O. Addition of hexane upon completion of the reaction gave a biphasic mixture, in which the catalyst partitioned into the aqueous-phase. The aqueous catalyst phase was used for five reaction cycles during which there was no change in the yield and only a slight decrease in enantioselectivity from 97 to 95% ee.

4. Conclusions and Perspectives

In the three decades since the report of the Rhône-Poulenc aqueous-phase hydroformylation process, aqueous-phase catalysis has been applied to a wide range of catalytic processes. This work has demonstrated that nearly any catalytic reaction involving late transition metals can be adapted to the use of water as a solvent provided the reagents themselves are water stable. To support these efforts a large variety of hydrophilic ligands have been developed. The majority of hydrophilic ligands are based on the triarylphosphine core, but recent years have seen increasing efforts to develop hydrophilic analogues of other useful ligand classes, such as sterically demanding alkylphosphines, nitrogen ligands, and *N*-heterocyclic carbenes. Further efforts along these lines will allow further development of aqueous phase catalysis. Despite the significant progress that has been made, there remain few examples of industrial processes that use water-soluble catalyst systems, thus further effort is needed develop industrially viable systems. These must be demonstrated to be economically advantageous over current processes.

The major driver for the development of aqueous-phase catalyst systems has been to simplify the separation of the catalytic active species from the hydrophobic product stream, which is of significant importance for industrial application of homogeneous catalysts. The majority of metals widely used in catalysis (Ru, Rh, Ir, Pd, Pt) are expensive and rare, which makes their recovery an important requirement of their large-scale use. In addition, product specifications typically require low levels of metal or ligand derived impurities. Thus simplifying the catalyst separation by use of an aqueous-biphasic catalyst system can lower the economic and environmental costs associated with separation of the catalyst from the product. The other major driver is that water is potentially a more environmentally benign solvent than traditional organic solvents. For water to be a truly green replacement, issues related to handling water contaminated with organic impurities must be addressed. Thus aqueous-phase catalyst systems that provide comparable activity and selectivity to homogeneous processes have the potential to provide significant savings if implemented.

The final advantage offered by the use of aqueous-phase catalysts, which has received less attention, is the ability to use water's unique properties to fundamentally change the nature of the reaction. A simple, but very useful, example is the formation of macrocycles in water by taking advantage of the low solubility of organic substrates in water. By using a water-soluble catalyst, the reaction occurs in water where substrate concentration is very low, even though the substrate/solvent ratio is relatively high. Water can also serve as a reaction promoter. Oxidative addition of allyl and benzyl alcohols to palladium(0) occurs readily in water, while this process is slow in organic solvents. The hydrogen bonding ability of water plays a key role in activating the hydroxide leaving group. The ability to control the pH of the reaction medium can also be used to dramatically change catalyst activity and selectivity, particularly in processes that involve metal-hydride species. Water does not always have a benign or beneficial effect on aqueous-phase catalysis, however. Asymmetric reactions in aqueous solvents using hydrophilic catalysts often give lower enantioselectivity than can be achieved in homogeneous systems. The loss of selectivity could be related to the solvent medium or to changes that occur in the ligand properties when the hydrophilic substituents are added.

As the field of aqueous-phase catalysis moves forward into the future, one of the key questions to be addressed is how does water affect the fundamental organometallic reaction steps that make up catalytic cycles. By better understanding the role of water in catalytic processes, and how this differs from typical organic solvents, the unique properties of water can be better utilized. In this way, not only can water be

used as a substitute for organic solvents, but it can be used to create new types reactivity or selectivity that are not observed in organic solvents. To date the majority of the effort in this area has focused on development of new ligand architectures and adapting new reactions to the aqueous phase. While continuing advancement along these fronts will be important, fundamental studies of organometallic reactivity related to catalysis in aqueous environments will be critical to the rational development of novel aqueous-phase catalytic reactions.

5. Abbreviations

$(DHQ)_2$PHAL	bis(dihydroquinine)-1,4-phthalazine diether
$(QD)_2$PHAL	bis(quinidine)-1,4-phthalazine diether
$(QN)_2$PHAL	bis(quinine)-1,4-phthalazine diether
(*S*)-*tol*-BINAP	(*S*)-2,2′-bis(di(4-tolyl)phosphino)-1,1′-binaphthalene
3-β-1	heptakis(2,3-di-*O*-methyl-6-*O*-sulfopropyl)-β-cyclodextrin
4-β-1	heptakis(2,3-di-*O*-methyl-6-*O*-sulfobutyl)-β-cyclodextrin
Amphos	(2-(diphenylphosphino)ethyl)trimethylammonium chloride (**L96a**)
BASPHOS	1,2-bis(2′,5′-dihydroxymethylphospholanyl)benzene
BDPP	2,4-bis(diphenylphosphino)pentane
BICOL	4,4′-bicarbazole
BINAP	2,2′-bis(diphenylphosphino)-1,1′-binaphthalene
BINAS	sulfonated-2,2′-bis(diphenylphosphinomethyl)-1,1′-binaphthalene (**L56**)
BIPHLOPHOS	4,4′,6,6′-tetrachloro-2,2′-bis(diphenylphosphino)-1,1′-biphenyl
BISBI	2,2′-bis(diphenylphosphinomethyl)-1,1′-biphenyl
BPHEMP	2,2′-bis(diphenylphosphino)-1,1′-biphenyl
CBDP	*trans*-1,2-bis(diphenylphosphino)cyclobutane
CD	cyclodextrin
Chiraphos	2,3-bis(diphenylphosphino)butane
CM	cross metathesis
CMC	critical micelle concentration
CTAB	cetyltrimethylammonium bromide
Cy-Amphos	(2-(dicyclohexylphosphino)ethyl)trimethylammonium chloride (**L99a**)
Cy-Pip-phos	4-(dicyclohexylphosphine)-*N*,*N*-dimethylpiperidinium chloride (**L100a**)
DAPTA	3,7-diacetyl-1,3,7-triaza-5-phosphabicyclo[3.3.1]-nonane (**L135b**)
DCC	dicyclohexylcarbodiimide
DDPPI	[1,4:3,6-dianhydro-2,5-dideoxy-2,5-bis(diphenylphosphino)-L-iditol
DFPTA	3,7-diformyl-1,3,7-triaza-5-phosphabicyclo[3.3.1]-nonane (**L135a**)
DIOP	(4*S*,5*S*)- or (4*R*,5*R*)-4,5-bis(diphenylphosphinomethyl)-2,2-dimethyl-1,3-dioxolane
DM-β-CD	dimethylated β-cyclodextrin
Dp	bicyclo[3.3.0]octa-1,3-dien-5-yl
DPEN	(*S*,*S*)- or (*R*,*R*)-1,2-diamino-1,2-diphenylethane
DPPB	1,4-bis(diphenylphosphino)butane
DPPB-TS	1,4-bis(di(3-sulfonatophenyl)phosphino)butane (**L38c**)
DPPE	1,4-bis(diphenylphosphino)ethane
DPPE-TS	1,4-bis(di(3-sulfonatophenyl)phosphino)ethane (**L38a**)
DPPP	1,4-bis(diphenylphosphino)propane
DPPP-TS	4-bis(di(3-sulfonatophenyl)phosphino)propane (**L38b**)
DTAC	dodecyltrimethylammonium chloride
EO	ethylene oxide
HSA	human serum albumin
MELO	methyl esters of linseed oil
MESO	methyl esters of soybean oil
M_n	number average molecular weight
MTMAP-α-CD	methylated mono[2-*O*-(2-methoxy-3-trimethylammoniopropyl)]-α-cyclodextrin chloride
nbd	norbornadiene
NHC	*N*-heterocyclic carbene
NORPHOS	2,2′-bis(diphenylphosphinomethyl)-1,1′-binaphthalene
PDI	polydispersity index
PEG	poly(ethylene glycol)
PEI	poly(ethylene imine)
PNS	*N*-(2-methyl-3-sulfonatoprop-2-yl) 3-(diphenylphosphino)propionamide
PPM	4-(diphenylphosphino)-1-(diphenylphosphinomethyl)pyrrolidine
Prophos	(*S*)- or (*R*)-1,2-bis(diphenylphosphino)propane
PTA	1,3,5-triaza-7-phosphaadamantane (**L132**)
PTAH	*N*-protonated 1,3,5-triaza-7-phosphaadamantane (**L133**)
Pyrphos	(*S*,*S*)- or (*R*,*R*)-3,4-bis(diphenylphosphino)pyrrolidine
RAME-β-CD	randomly methylated β-cyclodextrin
SDS	sodium dodecylsulfate
S-phos	2-(dicyclohexylphosphino)-2′,6′-dimethoxy-1,1′-biphenyl
TAPS	*N*-tris(hydroxymethyl)methyl-3-aminopropanesulfonic acid
t-Bu-Amphos	(2-(di-*tert*-butylphosphino)ethyl)trimethylammonium chloride (**L99b**)
t-Bu-Pip-phos	4-(di-*tert*-butylphosphino)-*N*,*N*-dimethylpiperidinium chloride (**L100b**)
TFA	trifluoroacetate
THMP	tris(hydroxymethyl)phosphine (**L130**)
THPA	2,4,10-trimethyl-1,2,4,5,7,10-hexaaza-3-phosphatricyclo-[3.3.1.$1^{3,7}$]decane (**L133**)
m- or *p*-TPPMC	(3- or 4-carboxyphenyl)diphenylphosphine (**L63a** or **L64a**)
m- or *p*-TPPDC	di-(3- or 4-carboxyphenyl)phenylphosphine (**L63b** or **L64b**)
m- or *p*-TPPTC-	tri-(3- or 4-carboxyphenyl)phosphine (**L63c** or **L64c**)
m- or *p*-TPPMG	(3- or 4-guanidiniumphenyl)diphenylphosphine (**L105a** or **L106**)
m- or *p*-TPPDG	di-(3- or 4-guanidiniumphenyl)phenylphosphine (**L105b**)
m- or *p*-TPPTG	tri-(3- or 4-guanidiniumphenyl)phosphine (**L105c**)
m- or *p*-TPPMP	(3- or 4-phosphonylphenyl)diphenylphosphine (**L68a** or **L69a**)
m- or *p*-TPPDP	di-(3- or 4-phosphonylphenyl)phenylphosphine (**L68b** or **L69b**)
m- or *p*-TPPTP	tri-(3- or 4-phosphonylphenyl)phosphine (**L68b** or **L69b**)
m- or *p*-TPPMS	(3- or 4-sulfonatophenyl)diphenylphosphine (**L1a** or **L8a**)
m- or *p*-TPPDS	di-(3- or 4-sulfonatophenyl)phenylphosphine (**L1b** or **L8b**)
m- or *p*-TPPTS	tri-(3- or 4-sulfonatophenyl)phosphine (**L1c** or **L8c**)
TsDPEN	(*S*,*S*)- or (*R*,*R*)-*N*-tosyl-1,2-diamino-1,2-diphenylethane
Xantphos	4,5-bis(diphenylphosphino)-9,9-dimethylxanthene

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