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Phosphines and Related Tervalent Phosphorus Systems

Organophosphorus Compounds as Ligands in Organometallic Catalysis

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1.1 Introduction

1.1.1 History

Phosphines and related phosphorus-containing molecules play a major role in homogeneous catalysis. The history of homogeneous metal complex catalysis, as we know it today, started in the 1960s, although there had been even industrial applications long before that. In the 1920s, a catalytic process was used for the addition of water to acetylene. The metal mercury was used in a sulfuric acid solution. The reaction was very slow and large volumes were needed; thus, this was far from attractive. A related process still in operation is the zinc-salt-catalyzed addition of carboxylic acids to acetylene. With the introduction of petrochemistry, the feedstock for acetaldehyde production changed to ethene. The reaction used until today is a stoichiometric oxidation of ethene by palladium, the so-called Wacker process, in which palladium is reoxidized with oxygen and a copper catalyst. Carbonylation catalysis came on stream in the 1930s and 1940s, although its application was retarded by World War II (WWII). Initially, the metals of choice were nickel, e.g. work by Reppe, and cobalt, especially hydroformylation by Roelen, and methanol carbonylation. Probably, Reppe (1948) was the first to use triphenylphosphine as a modifying ligand in a catalytic reaction, which concerned the addition of nickel-cyanide-catalyzed carbonylative alcohol addition to alkynes, leading to acrylates [1]. He used nickel cyanide also in the synthesis of polyketone from carbon monoxide and ethene in those early years. As of the 1960s, all these "leads" were greatly improved by ligand effects and by changing to the more active second-row transition metals palladium and rhodium. Cobalt was also modified by phosphine ligands, and in this instance, the catalyst produced more of the linear oxygenate product, which now is mainly the alcohol rather than the aldehyde (Shell) [2]. Early examples of triphenylphosphine-modified group 10 hydrogenation catalysis are due to Bailar and Itatani [3]. Ever since, more publications have appeared that reported phosphine effects on catalytic reactions.

Organophosphorus Chemistry: From Molecules to Applications, First Edition.
Edited by Viktor Iaroshenko.

1.1.2 Alternative Ligands

Before concentrating only on phosphorus ligands, we should mention that in the past three decades, ligands based on other donor atoms have become equally important and, in some areas, even more important than phosphines. In the mid-1980s, the metallocene era started for the early transition metals especially in polymerization catalysis, followed by alkoxides, amides, and salen ligands. Meanwhile, metallocene catalysts have found industrial applications. In the late transition metal area, the diimine ligands stand out together with a shift to the first-row metals for alkene polymerization, and they almost made it to a replacement of the nickel catalyst in the oligomerization of ethene. They were followed a little later by the outburst of the NHC ligands, which have beaten, in several instances, the best phosphines used so far in certain reactions. They have found commercial applications in metathesis reactions. A combination of all donor ligands in bidentates has further enriched the toolbox of homogeneous catalysis. One should not forget that the "ligand-free" systems are attractive, as they do not suffer from ligand decomposition, but their life can still be limited because of precipitation or formation of a compound with the wrong valence state. The stabilizing ligands in these cases are, for example, carbon monoxide, alkenes, halides, and other anions, for example, the Wacker process, cobalt-catalyzed hydroformylation (Exxon), nickel-catalyzed oligomerization of butene to 3-methylheptane (IFP, Dimersol process), rhodium-catalyzed carbonylation of methanol (Monsanto, now BP), and ditto for iridium (BP, Cativa process).

1.1.3 Aim of the Chapter

The aim of this chapter is to give an introduction to the use of tervalent phosphorus compounds as ligands in homogeneous catalysis. Several chapters in this work refer to that area and have their own introductions. We have tried to avoid overlap and provide some basic concepts in a nutshell while referring to those chapters that deal in more detail with this topic. In Section 1.2, we deal with the most common elementary steps used for the synthesis of phosphorus ligands. In more specific chapters, synthesis will be dealt with in much more detail than what we were able to cover here. The overview is very limited, as, for example, in our laboratories students are introduced to phosphorus ligand synthesis with a series of about 200 synthetic steps of which we think they are worthwhile for a starter in this area! In Section 1.3, the properties of phosphorus ligands will be discussed by presenting the most common yardsticks used, such as Tolman's χ and θ values for the electronic and steric parameters, respectively, and Casey's β_n, the natural bite angle for bidentate ligands. For the steric and electronic parameters, several alternatives have been developed, and all the parameters have found use particularly in catalysis [4]. Studies on the use of parameters in Linear Free Energy Relations and QUALE will be mentioned.

In Section 1.4, chiral phosphorus ligands will be introduced focusing on the types of chiral ligands available, involving the most typical phosphorus and diphosphorus ligands, and heterobidentate ligands.

The next two sections will deal with two examples of ligand effects, namely a few highlights in hydroformylation and the next one on modern cross-coupling chemistry. As both are huge areas, these parts also serve as a brief introduction to the fields. We will highlight the crucial issues concerning monodentate and bidentate ligands.

Section 1.6 includes the main decomposition pathways of phosphorus ligands, which are also discussed in dedicated chapters in books and reviews.

1.2 Synthesis of Phosphorus Ligands

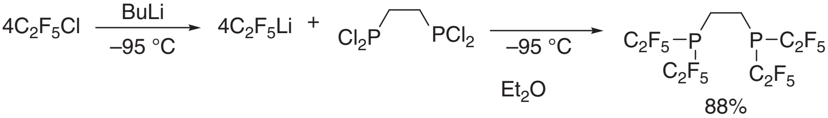
1.2.1 Introduction

Clearly, the synthesis of phosphorus ligands involves a library of organic phosphorus chemistry to which one cannot do justice in just a few pages. Chapter 7 by Stevens deals with the most important routes for the introduction of phosphonates into complex organic molecules, and more details and references can be found there. Phosphonates can be converted into phosphines, of which there exist many examples. Here, we will deal with a simple summary of the common elementary steps for making phosphorus ligands. Phosphaalkenes will not be discussed as they are not yet of proven interest in catalysis. Although phosphinines have been exploited occasionally in catalysis and have shown interesting properties, for instance, in rhodium-catalyzed hydroformylation [5], we will not discuss their synthesis. We will confine ourselves to a series of elementary steps thought to be useful for our purposes. Even that will rather be a short list of less than 40, as, for example, in my group, the students acquainted themselves in phosphine synthesis using a set of about 150–200 reactions. Although one could bring down the number as there are less reaction types, it would still be too large to list for the present purposes. Below we have ordered the reactions according to the main reaction types, which are still feasible, because the number of ways to make a P—C bond is far less numerous than that for making C—C bonds!

1.2.2 Nucleophilic Substitution by Carbanions at $P^{\delta+}$

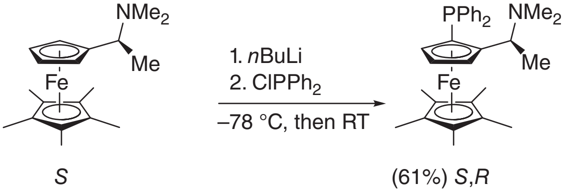
The ionic approach to the formation of a carbon–phosphorus bond has two possibilities, namely the use of phosphorus as a nucleophile or as an electrophile. The latter seems more in accord with the electronic properties of phosphorus, as a slightly positively charged phosphorus species is common and stable, whereas phosphido anions (Section 1.2.3) tend to show electron transfer reactions in addition to and before entering a nucleophilic attack. Indeed, nucleophilic substitution is the most common reaction used, although both routes have their pros and cons. One might not often directly see potential cons for a certain route. For example, an attack of a benzylic anion at a phosphorus electrophile will proceed smoothly, but the product formed, $PhCH_2PR_2$, has an acidic proton at the benzylic position, and the remaining benzyl anion may be consumed via a simple proton abstraction and, at best, the yield is only half of the expected amount. The nucleophile will often be a relatively simple Grignard or a hydrocarbyllithium reagent, and it can be used in excess, as during the workup by hydrolysis, it can be easily removed. If the nucleophile is a more complicated molecule, of which the remains can be removed only with difficulty, the use of a large excess must be avoided. Also, the carbonucleophile may substitute other hydrocarbyl groups at phosphorus (Scheme 1.3). Reaction 3 shows a less common nucleophilic substitution, but it shows its versatility.

Perfluoroalkyl groups are far less frequently used than simple aromatics, which we will encounter below. The first example shows pentafluoroethyl groups, which are not the most common substituents at phosphorus, but they are highly desirable in the studies of electronic effects in catalysis (Scheme 1.1) [6]. In this case, the diphosphine was obtained in an excellent yield. It should be borne in mind that the formation of LiF of such lithium fluoroalkyl intermediates is a highly exothermic decomposition reaction. Occasionally, such decomposition reactions take place. For instance, dry spots in the reaction vessel, caused by a flow of an inert gas, might initiate an explosive formation of LiF. Several accidents have occurred, even on a large scale, but few have been adequately reported (a safe synthesis of fluoroalkyl-containing organometallics has been reported) [7]. The phosphorus precursor is not a common reagent either; it is difficult to synthesize, but it is commercially available.



Scheme 1.1 Reaction 1, alkylation of P—Cl bonds.

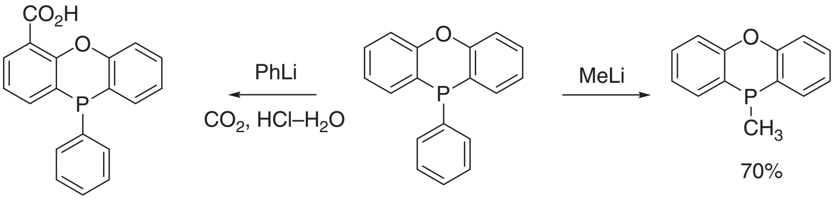
A more elaborate lithium reagent that one might not want to spoil is shown in Scheme 1.2, Reaction 2 [8]. In the next step, the amino group can be replaced by a phosphide anion under mild acidic conditions to give the so-called Josiphos ligands. Lithiation at the upper ring is facilitated by the amino group and will proceed mainly on one side to give a certain diastereoisomer if the amine consists of just one enantiomer.



Scheme 1.2 Reaction 2, synthesis of Josiphos.

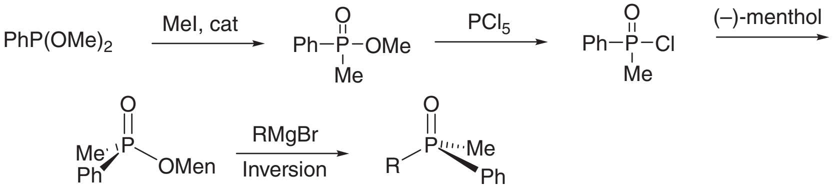
Examples of hydrocarbyl/hydrocarbyl substitution are given in Scheme 1.3, Reaction 3 [9]. Thus, on the way to the formation of the lithium nucleophiles of

10*H*-phenoxaphosphinine, one has to use the appropriate lithium rearrangement. We have pictured this reaction to show another unexpected side reaction of the otherwise successful nucleophilic substitution.



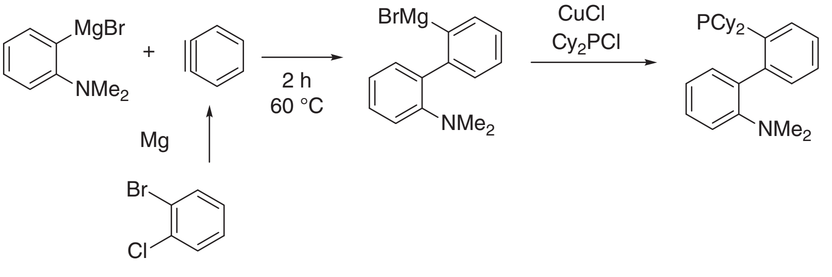
Scheme 1.3 Reaction 3, aryl–methyl exchange.

Scheme 1.4, Reaction 4 shows that phosphinates can be the electrophiles and the phosphonates can be substituted in the same way [10]. A more reactive reagent is obtained by replacing the methoxy group by chlorine. The final phosphine oxide can be reduced by $HSiCl_3$ or similar reagents such as polymethylhydrosiloxane (PMHS). Nowadays, on a small-scale synthesis, we often use refluxing $PhSiH_3$. As usual, the diastereoisomers containing the menthol group can be separated to eventually yield the *P*-chiral phosphine. Another chiral auxiliary used frequently is ephedrine.



Scheme 1.4 Reaction 4, P-chiral phosphines.

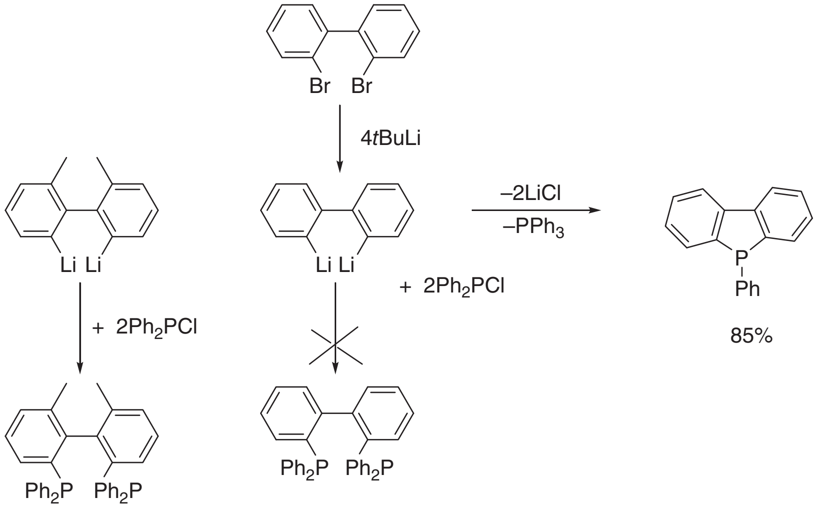
Addition of a Grignard to a carbyne is the first step in the elegant synthesis of Buchwald toward his group of ligands developed for cross-coupling reactions (Scheme 1.5, Reaction 5) [11]. The Grignard reagent adds to the carbyne generating another nucleophile that is made to react with a dihydrocarbylphosphorus



Scheme 1.5 Reaction 5, Buchwald's synthetic scheme.

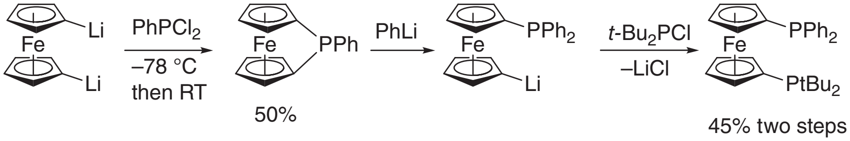
chloride. A wide variety of ligands have been made this way, and the route was optimized for use on a larger scale to promote its use in industrial applications.

The lithium reagent, as is well known, can be generated via exchange of aryl bromides with, e.g. *n*BuLi forming *n*BuBr as the by-product, which may interfere in later steps. A clean and more effective way is the often use of the more dangerous *t*BuLi, of which two equivalents per bromide are needed as it forms the unreactive isobutane and isobutene and no aliphatic bromide. An example of carbanion/carbanion substitution is depicted in Reaction 6 for dilithiobiphenyl (Scheme 1.6) [12]. The product that formed is a dibenzophosphole unless the 6,6′ position resists planarization of the molecule. The liberated PhLi reacts with Ph_2PCl to give triphenylphosphine as the second product, and thus, this is not the most convenient way to make dibenzophosphole as reaction of the dilithio intermediate with $PhPCl_2$ gives mainly one product.



Scheme 1.6 Reaction 6, phosphole synthesis.

Reaction 7 illustrates the favorable exploitation of carbon nucleophile substitution in disubstituted ferrocene derivatives (Scheme 1.7) [13]. Monosubstitution of dilithioferrocene is not a clean reaction, but here it is solved by the introduction of one extra step, namely the opening of the P—C bond by PhLi. The resulting lithium reagent can be reacted with a variety of electrophiles, including P-based ones.



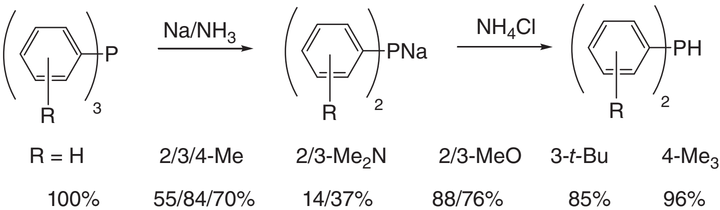
Scheme 1.7 Reaction 7.

1.2.3 Phosphorus–Carbon Bond Cleavage and Phosphido Anion Preparation

Phosphorus–carbon bond cleavage aims at the generation of phosphido anions for their use as nucleophiles toward carbon electrophiles. A few phosphido anions can be made from the triarylphosphines by cleavage with sodium in ammonia or alkali metals in tetrahydrofuran (THF) or dioxane. In addition to the desired $MPAr_2$, one obtains MAr, or in ammonia, MNH_2. Immediate continuation with this solution of the phosphido anion requires protonation of the coproduced metal aryl or metal amide. This can be done conveniently by ammonium chloride (in ammonia), *t*BuCl, or alcohols. In THF or dioxane, the aryllithium product formed may partially decompose and less than the calculated amount of alcohol may be required. Alternatively, the crude, cleaved mixture can be added with weak acids to make the diarylphosphine for storage, which is deprotonated with, e.g. *n*BuLi before its use as a phosphide anion.

The results for the sodium or lithium cleavage reactions, or for phosphines containing different aryl groups, are hard to predict. Van Doorn carried out a systematic study of substituted arylphosphines and a few alkylarylphosphines [14].

An inventory of the reductive cleavage of functionalized triphenylphosphines Ar_3P has been made in the first publication [14]. The reaction can be controlled in many cases to eventually give preparatively interesting secondary or primary phosphines (Scheme 1.8). In addition, the reaction of *ortho*-functionalized secondary phosphines leads to primary phosphines. The reducing agents Na/NH_3 and Li/THF often give complementary results; reactions such as Birch reduction or multiple cleavage of *ortho*-functionalized phosphines require protonation by the solvent and do not occur in THF. Lowest unoccupied molecular orbital (LUMO) energies and coefficients were correlated with the experimental results. Both very high and very low LUMO energies impede cleavage. Note that many of these reactions were at the time carried out on 10-g scale, which required moderate precaution with air and water; today's procedures on 100-mg scale require more stringent conditions.

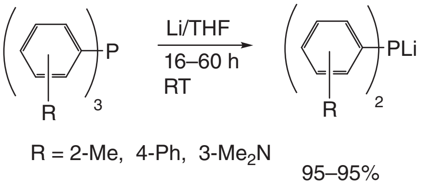


R = H	2/3/4-Me	2/3-Me_2N	2/3-MeO	3-*t*-Bu	4-Me_3Si
100%	55/84/70%	14/37%	88/76%	85%	96%

Scheme 1.8 Reaction 8 [14], P–C cleavage by sodium.

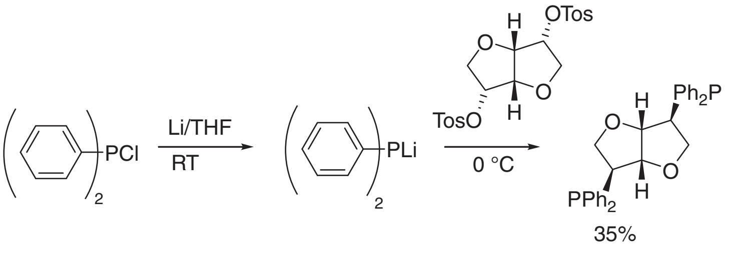
Reductive cleavage of mixed o- and p-functionalized triarylphosphines with Na/NH_3 and Li/THF strongly depends on the nature and positions of the substituents [14]. Reduction occurs readily with $PhPAr_2$ [Ar = 2,4-$(MeO)_2C_6H_3$, 2,4,6-$(MeO)_3C_6H_2$, 4-$(Me_2N)C_6H_4$] and Ph_2PAr [Ar = 2,4-$(MeO)_2C_6H$=], whereas the corresponding Ar_3P is not reduced. Cleavage of p-substituted compounds leads to the mixtures of secondary phosphines. By contrast, the cleavage of mixed o-substituted triphenylphosphines is very selective. The functionalized Ph group is split off in high yield when it carries Me, Me_2N, and MeO substituents. Reaction of $[2,4\text{-}(MeO)_2C_6H_3]_2PPh$ is not selective, owing to loss of methoxy groups. By contrast, the Ph group is split off when the mixed phosphine contains phenoxide groups, e.g. $2\text{-}NaOC_6H_4$. In a number of cases, the product of a Birch reduction with an isolated diene system is formed in NH_3 via a phosphino-stabilized cyclohexadienyl anion. This reduction does not occur in the aprotic solvent THF. Base-catalyzed isomerization leads to a conjugated double-bond system with a vinylphosphine moiety.

Reaction 9 shows an example with the use of Li/THF for the cleavage, which, for many researchers, may be more attractive, especially when working on a small scale (Scheme 1.9).



Scheme 1.9 Reaction 9, P–C cleavage by lithium [14] .

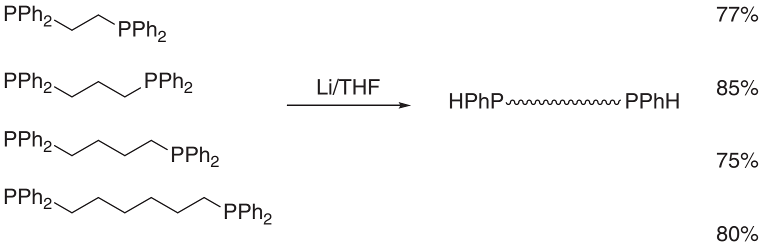
Phosphides can also be made from Ar_2PCl compounds by reacting the latter with an alkali metal in THF, and thus, this reaction can be done on small scale (Scheme 1.10) [15]. The potential by-product $Ar_2P\text{-}PAr_2$ also reacts with the alkali metal to give the phosphido metal derivative. The excess metal can be removed by decantation. The selective synthesis of Ar_2PCl often requires the well-known sequence PCl_3, Cl_2PNR_2, Ar_2PNR_2, and Ar_2PCl.



Scheme 1.10 Reaction 10, P–Cl reduction.

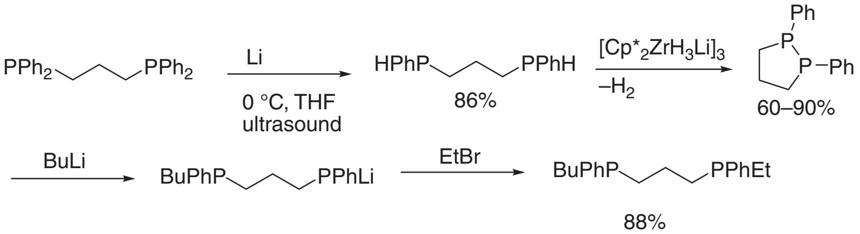
Diphosphines of bis-diphenylphosphino nature give double cleavage, and mono-cleavage has been reported but is not selective. The use of an ultrasonic bath gives the best results (Scheme 1.11, Reaction 11) [16].

The monocleaved diphosphine can be obtained with a certain percentage of di-cleaved products. Acidic workup gives the mixture of secondary phosphines that can be separated by Kugelrohr distillation. Another route to monocleaved



Scheme 1.11 Reaction 11, P–C cleavage in diphosphines.

diphosphine for 1,3-bis(diphenylphosphino)propane (dppp) involves the conversion of the dicleaved diphosphine to the cyclic 1,2-diphenyl-1,2-diphospholane, which can be ring-opened by carbonucleophiles, especially small aliphatic reagents, and thus, the scope seems limited (Scheme 1.12) [17].



Scheme 1.12 Reaction 12, reactions of 1,2-diphospholane.

Improvements of these examples are continuously reported, and one should check for more recent examples.

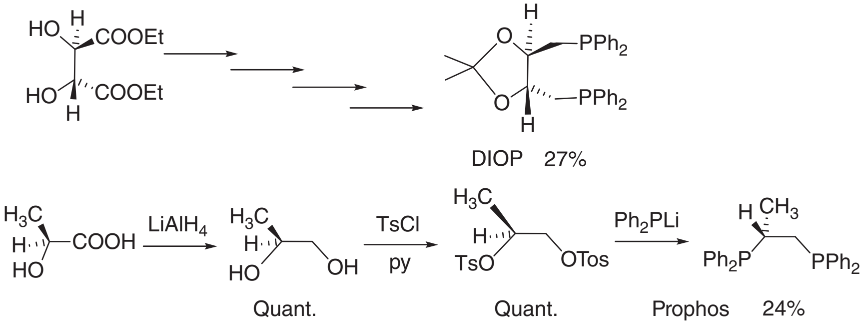
1.2.4 Phosphido Anions as Nucleophiles

The synthetic sequence of starting with an ester, reducing it to an alcohol, tosylating the alcohol, and nucleophilic displacement of the tosylate by phosphide is very useful and popular, e.g. 2,3-O-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane (DIOP) and many look-alikes were made via this route. The chiral acids are often natural products or derived thereof. One should realize, looking at the yields of this sequence, that the effectiveness of this route is limited, in particular the last step, although column separation at the end, or complex formation with nickel, always yields the pure product. The efficiencies of the substitution reactions with the use of halides as the leaving group, R_2PO anion as the nucleophile, or the BH_3 complex of the phosphido anion often give much better results. Sometimes, these results may be unexpected and, as in transition metal chemistry, it may be worth trying a number of nucleophiles and solvents. In our view, it often pays off to replace the tosylate by chloride. The side products of the simple nucleophilic substitution are, as always, elimination and radical formation (electron transfer without direct contact between phosphorus and electrophilic carbon atoms occurs; the reaction of electrophilic phosphorus halides and carbon anionic nucleophiles is more in accord with the nature of both entities).

Only alkyl halides can be substituted this way, and for aromatic electrophiles, other routes have been developed. An important reaction for the preparation of aromatic and alkene phosphine has become the metal-catalyzed coupling of sp^2-carbon and phosphorus atoms, which is discussed separately.

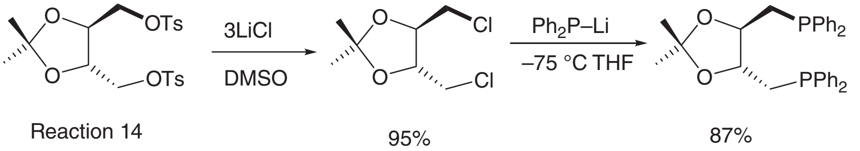
Ph_2PK is commercially available, which avoids several experimental problems. Several dihydrocarbylphosphines such as R_2PH are also commercially available, even on a large scale! As one works on a relatively small scale, nowadays the obnoxious odor of Ph_2PH does not pose a large problem either, if all glassware is submerged into a bleach solution in the fume cupboard immediately after use. Alternatively, hydrogen peroxide in water and acetic acid to aid the solubilization of the organics can be used. The smell of $PhPH_2$ is much worse than that of Ph_2PH, let alone PH_3 (inflammable in air), and more care should be taken. RPH_2 and PH_3 should be handled by experienced chemists only in well-equipped laboratories.

Scheme 1.13 gives the synthesis of DIOP [18] and 1,2-Bis(diphenylphosphino) propane - Prophos [19] and shows the low yields obtained via the substitution of tosylates. Crude Prophos was converted to a nickel complex, and after crystallization, the ligand was recovered by treatment with a cyanide salt.



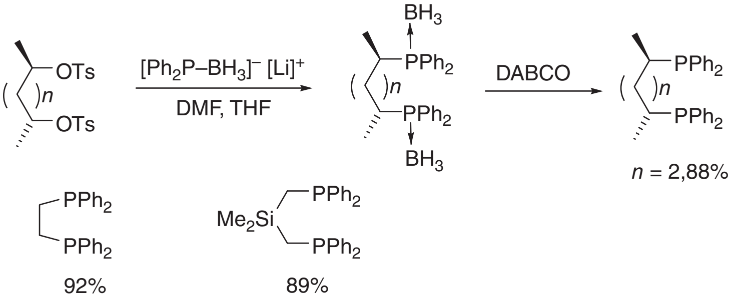
Scheme 1.13 Reaction 13, synthesis of DIOP via tosylate.

Next, we present two examples of the successful conversion of the ditosylate to the dichloride for which the substitution by the phosphide salt was much more effective, by Tani et al. [20] and Townsend et al. [21], respectively (Scheme 1.14).



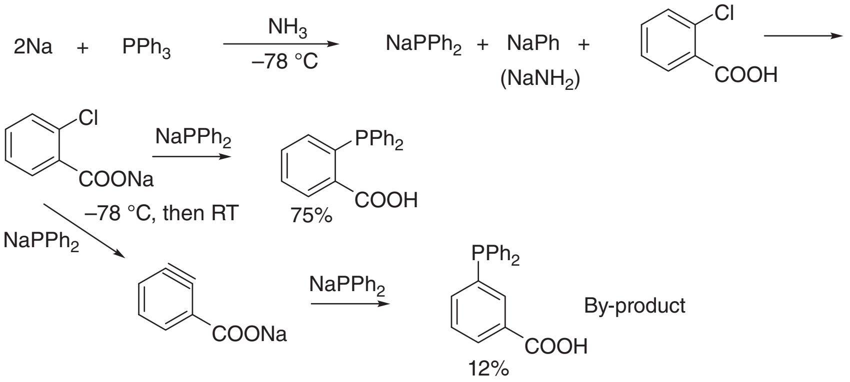
Scheme 1.14 Reactions 14. P–C coupling after conversion of tosylate to halide.

Another approach for obtaining a highly selective substitution was introduced by Livinghouse and others. It involves the conversion of the phosphido anion to its borane adduct, which becomes much less basic and less apt to electron transfer. Excellent yields are now achieved, and the borane can be removed simply by treatment with an amine (Scheme 1.15) for the less basic phosphines. Treatment with acid ($HBF_4·OMe_2$) followed by base works well for basic phosphines [22].



Scheme 1.15 Reaction 15, synthesis of diphosphines from tosylates via phosphide-boranes.

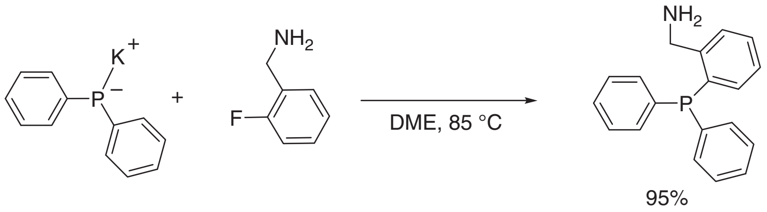
There are exceptions regarding aryl halides as is shown in Reaction 16 in which *o*-chlorobenzoic acid gives substitution by diphenyl phosphide in liquid ammonia. The acid is deprotonated by the sodium amide coproduct, formed from PhNa, and thus, this needs no separate destruction. A by-product of the substitution is the *meta*-isomer formed via a benzyne intermediate. At the time of its publication by Rauchfuss and coworkers this was already an industrial process for the synthesis of the ligand of Shell's higher olefin process (Scheme 1.16) [23].



Scheme 1.16 Reaction 16, synthesis of the SHOP ligand.

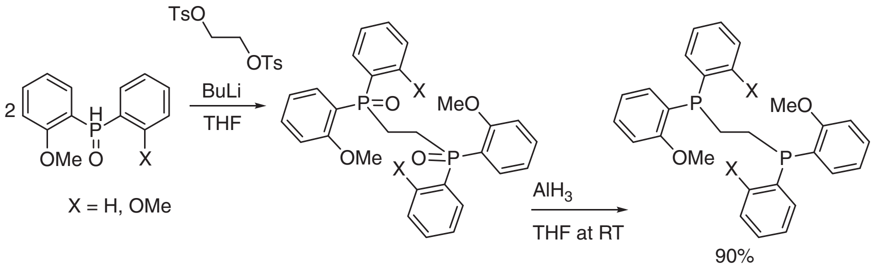
Aromatic fluorides can be substituted by phosphide groups either with or without a metal catalyst. Reaction 17 is an example of an uncatalyzed reaction. For alkyl halides, an efficient procedure involves the use of DMSO/KOH/water, and sometimes, this even works for organic fluorides (Scheme 1.17) [24].

Secondary phosphine oxides (SPOs) can also be used for tosylate substitution as is exemplified in Reaction 18 for the synthesis of 1,2-bis(diphenylphosphino) ethane (dppe). The SPOs are soft nucleophiles and not very basic, and they work well even for tosylated ethylene glycol. In this instance, the dichloride is readily available as well. A further advantage of the SPO is that it does not have an



Scheme 1.17 Reaction 17, substitution of fluoride by phosphide base.

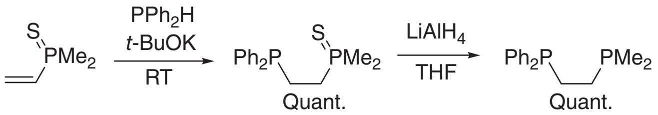
obnoxious smell such as PPh_2H. Both phosphide anions and SPOs have been used for the ring-opening substitution of epoxides (Scheme 1.18) [25].



Scheme 1.18 Reaction 18, the use of SPOs in diphosphine synthesis.

1.2.5 P—H Addition to Unsaturates

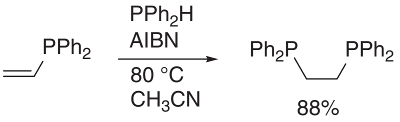
There are three main routes for the addition of secondary phosphines, SPOs, and the like to alkenes and alkynes. The first one is the Michael addition to activated double bonds such as the one shown in Reaction 19 with *t*-butoxide as the base. Through this route, one can conveniently synthesize 1,2-ethanediyl diphosphines with different substituents at each side (Scheme 1.19) [26].



Scheme 1.19 Reaction 19, Michael addition of phosphide anion.

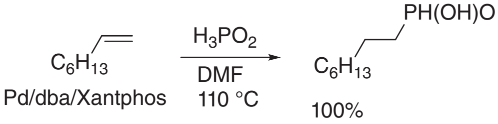
For nonactivated double bonds, one can rely on the radical addition promoted by azobisisobutyronitrile (AIBN) (Reaction 20). One adds AIBN until complete conversion has been reached [27]. Even dendrimeric oligophosphines have been prepared this way; in this instance, UV irradiation was applied together with AIBN (Scheme 1.20) [28].

The third method involves the transition-metal-catalyzed addition to unsaturated C=C bonds of which there are many examples in other chapters of this book because like many of the other reactions, it can be applied to phosphine compounds that are not R_2PH or SPO. Interestingly, for the palladium-catalyzed reactions, Xantphos often appears to be the ligand of choice [29, 30]. The example



Scheme 1.20 Reaction 20, radical addition of R_2PH to alkenes.

in Reaction 21 depicts the addition of hypophosphorus acid to 1-octene. This contains another P—H bond and could be added to another molecule, the OH group can be esterified and substituted, and the P=O group can be reduced to convert it into a phosphine. In the work referred to here by Montchamp, the product was oxidized to octylphosphonic acid (Scheme 1.21).



Scheme 1.21 Reaction 21, addition of hypophosphorus acid.

1.2.6 Reduction of Phosphine Oxides and Sulfides

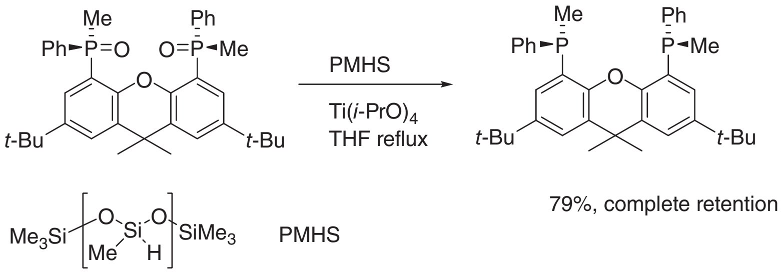
The most common method for the reduction of phosphine oxides was the use of trichlorosilane ($HSiCl_3$ or Si_2Cl_6) and triethylamine in refluxing acetonitrile (not shown). Prolonged refluxing leads to loss of trichlorosilane in that instance, as its boiling point is very low (32 °C). In the past decades, a variety of related reagents have become available that had a higher boiling point and led to a cleaner workup than trichlorosilane. For alkylphosphines, often more potent reducing agents were needed, and these have also been developed.

For chiral phosphorus centers, one should be aware that both retention and inversion have been observed for different substrates with the use of otherwise very similar reaction conditions and the same reagents.

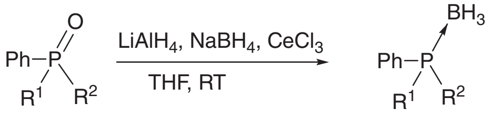
The reducing agent used in Reaction 22, PMHS, is a by-product of the silicone industry. It is a cheap, easy-to-handle, and environmentally friendly reducing agent. PMHS is more air and moisture stable than other silanes and can be stored for long periods of time without loss of activity (www.organic-chemistry.org/chemicals/reductions/polymethylhydrosiloxane-pmhs.shtm). The reduction can be catalyzed by Lewis acidic metal complexes such as titanium tetraisopropoxide, also a large industrial product. Sulfides of strongly donating phosphines are first methylated to give the thiomethylphosphonium derivative, which is then easily reduced (Scheme 1.22) [33].

For alkylphosphines, the use of metal catalysts is recommended, and for instance, cerium is an effective metal (Reaction 23). The method of Imamoto et al. is interesting because it directly produces borane-protected phosphines (Scheme 1.23) [34].

One more example concerns the transfer of sulfur from $R_3P=S$ to Bu_3P at 150 °C, which only works for nonbasic phosphines (Scheme 1.24, Reaction 24) [35].

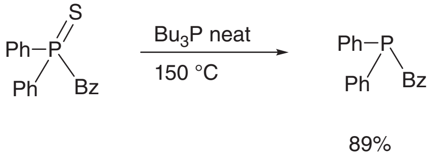


Scheme 1.22 Reaction 22, reduction of P=O [31, 32] .



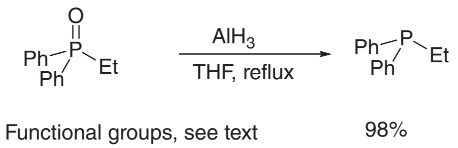
R^1	R^2	
Ph	Et	93%
*t*Bu	H	82%
o-An	Me	62%

Scheme 1.23 Reaction 23, reduction of P=O.



Scheme 1.24 Reaction 24, reduction of P=S.

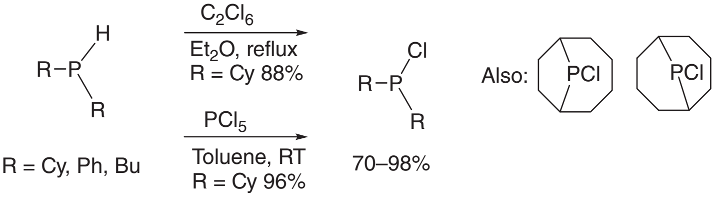
Simple AlH_3 is interesting in that many reducible functional groups are not affected. Not reduced in the presence of $P{=}O/AlH_3$ are sulfoxides, sulfones, alkyl halides, nitro aromatics, oxiranes, esters, and amides [36]. An aqueous workup is not required (Scheme 1.25).



Scheme 1.25 Reaction 25, reduction of P=O.

1.2.7 X/Y-Substitution at Phosphorus

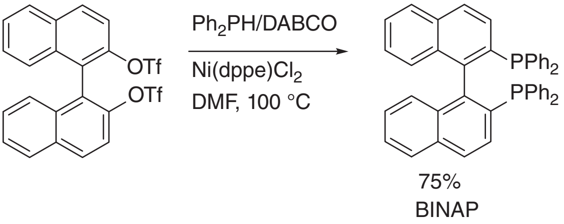
The transformation of phosphorus halides, alkoxides, and amides with the aid of C-, O-, and N-centered nucleophiles is a widely used reaction for the formation of phosphorus ligands. Of the numerous and straightforward examples, we only mention the less common yet useful conversion of R_2PH into R_2PCl, which can be carried out with $SOCl_2$, trichloroacetonitrile, hexachloroacetone, PCl_5, hexachloroethane, etc. Reaction 26 illustrates the use of the latter two reagents. For a new conversion, usually several of the reagents have to be explored for obtaining the highest yield (Scheme 1.26) [37].



Scheme 1.26 Reaction 26, conversion of PH into PCl.

1.2.8 Aryl-X in Metal-Catalyzed Cross-Coupling

As mentioned above, the substitution of alkyl halides by phosphorus nucleophiles can be carried out in a variety of ways, but substitution of aromatic halides or triflates is a rare reaction unless a catalyst of Pd, Ni, or Cu is used. The metal-catalyzed cross-coupling is the phosphorus analog of the Buchwald–Hartwig coupling for making N—C bonds, but actually, it is older and was inspired by the known metal-catalyzed C—C coupling reactions, such as Negishi and coworker [38] and Miyaura and Suzuki [39] reactions. Reaction 27 shows an example in which the nucleophile is Ph_2PH (Scheme 1.27) [40].

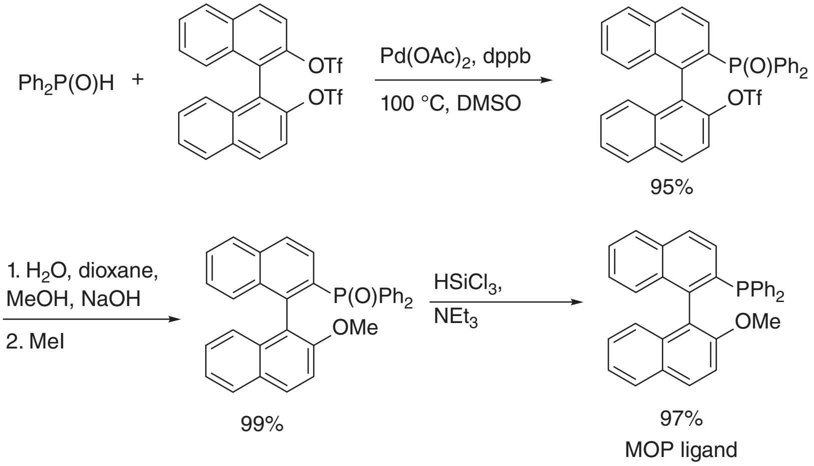


Scheme 1.27 Reaction 27, cross-coupling P—C bond formation.

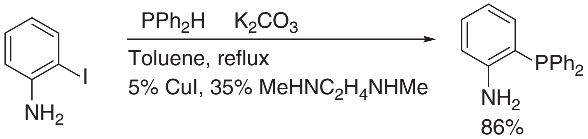
Also for the second step, $Ph_2P(O)H$ can be used and the mixed phosphine phosphine oxide is obtained. If the SPO is used in the first step, Ph_2PH or SPO does not react in a second step, and this is the way to another popular ligand for asymmetric catalysis, MOP (Reaction 28). It is obtained in excellent yield (Scheme 1.28) [41].

Copper-based catalysts, much cheaper than the palladium ones, are depicted in Reaction 29. The added diamine functions as the ligand; also for Cu ligands play an important role. Iodides often give the highest reaction rates and yields (Scheme 1.29) [42].

For a variety of cross-coupling reactions involving C—P bond formation, Xantphos gave the highest yields as was demonstrated for RPH(O)OH by Montchamp



Scheme 1.28 Reaction 28, cross-coupling P—C bond formation.



Scheme 1.29 Reaction 29, Cu-catalyzed cross-coupling P—C bond formation.

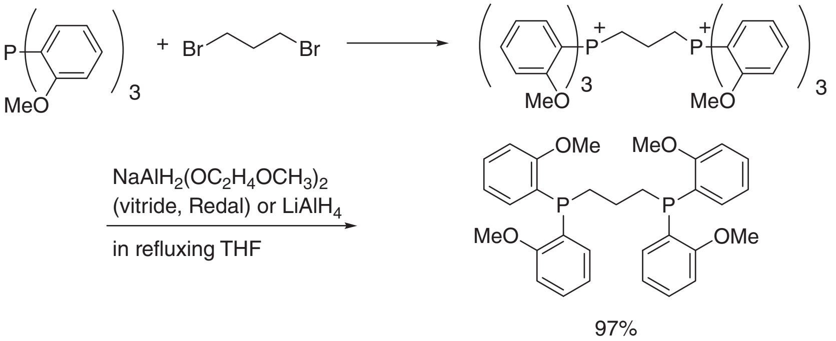
and coworkers [43]. Even benzylic alcohols can be directly cross-coupled using this catalyst with H_3PO_2 [44].

1.2.9 Quaternization and Reduction

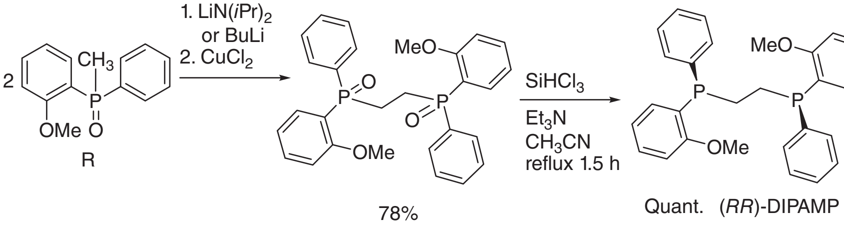
Quaternization proceeds rapidly for alkyl halides and then the group that most easily leaves the salt can be removed with a reducing agent. This "leaving" group can be benzyl, phenyl, and *o*-anisyl for instance. We mentioned an example in Reaction 30 that might have been used commercially because it is the ligand used by Shell in the temporary production of polyketone on a 500 ton yr^{-1} scale in Moerdijk, The Netherlands. Dibromopropane is quaternized with tris-*o*-anisylphosphine, and subsequently, this is treated with $LiAlH_4$, vitride, or the like, and an anisyl group is removed. High yields were reported (Reaction 31) [45]. The synthesis of Ar_3P from Grignard and PCl_3 is much easier than that of Ar_2PH (Scheme 1.30).

1.2.10 The Use of $R_2PCH_2^-$ Anions in Phosphine Synthesis

Numerous specific routes such as Diels–Alder reaction, Friedel–Crafts, phosphinine, phosphole, phospholane syntheses, etc., occur less frequently than the ones mentioned, which will not be introduced here, but we refer to standard works on these compounds. One last route we would like to mention is the use of $R_2PCH_2^-$



Scheme 1.30 Reaction 30, synthesis of Shell's polyketone ligand.

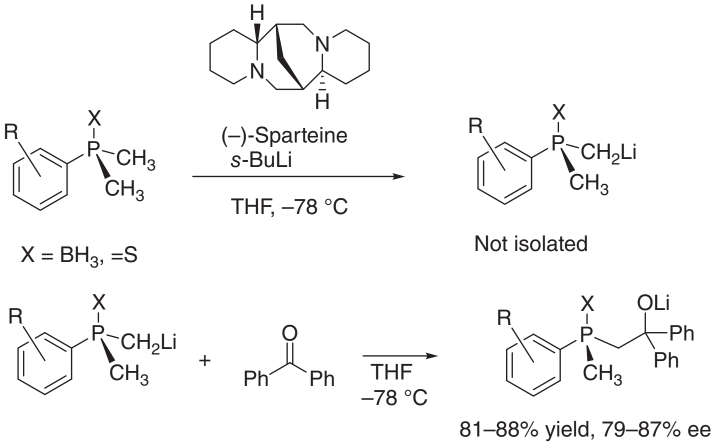


Scheme 1.31 Reaction 31, DIPAMP synthesis.

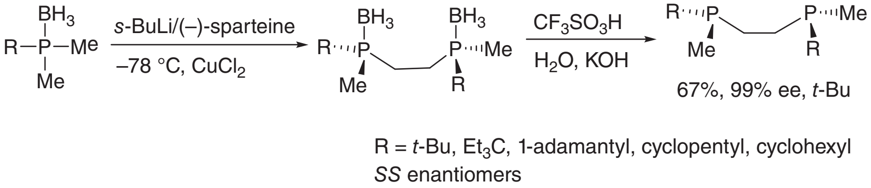
anions or the phosphine oxide, as this gives an extra tool compared to the reactions of electrophiles with the use of R_2P^- anions and SPOs. $R_2P(O)CH_2^-$ was used by Knowles to synthesize the well-known DIPAMP ligand for asymmetric hydrogenation. In this instance, the anion is not used as a nucleophile, but it is oxidized with Cu(II) to give the dimer (Reaction 31). The enantiopure starting material is made via steps mentioned above (Scheme 1.31) [46].

We finish our survey with a special application of dimethylarylphosphine that can be enantioselectively deprotonated as the borane adduct or sulfide with sparteine, a natural product and a chiral diamine, at one of its methyl groups by *s*-BuLi as depicted in Reaction 32 [47]. The anion reacts with nucleophiles as in this case with ketones on the way to chiral phosphine alcohols or phosphine–phosphite ligands. Sparteine is isolated from Scotch broom, but as this shrub has become a plague in several places, the transportation of the seeds has been restricted, which has led to shortages of sparteine. Outside its native range Europe, such as India, South America and western North America, Australia, and New Zealand, it has become an ecologically destructive, colonizing, invasive species. Synthetic analogs of opposite chirality perform slightly less well than sparteine (Scheme 1.32) [48].

The phosphinomethyl anions can be used for the synthesis of DIPAMP analogs, although in this manner one of the substituents on the P-atoms will always be a methyl group (Reaction 33). Sparteine is highly enantioselective in this reaction at low temperature, and perhaps the yield of the oxidative coupling step can further be improved nowadays (Scheme 1.33) [49].



Scheme 1.32 Reaction 32, stereoselective lithiation.



Scheme 1.33 Reaction 33, application of Reaction 32.

Sparteine has found more applications in phosphine chemistry, for instance the dynamic resolution of dihydrocarbylphosphine–borane anions, which can then be reacted with nucleophiles; the example concerns phenyl, *t*-butylphosphine [50].

1.3 Ligand Properties

1.3.1 Electronic Properties

Phosphorus ligands and their effects in catalysis have been reported an infinite number of times and their general properties have been reviewed a number of times (for recent books, see Refs. [51–53]). The electronic properties of phosphorus ligands span in a wide range, from π-acceptors as strong as CO, such as hexafluoroisopropyl phosphite to strong σ-donors such as tris-*t*-butylphosphine. A first systematic study on electronic properties was reported by Horrocks and Taylor [54] and Strohmeier and Mueller [55] who measured the infrared spectra of a range of monosubstituted metal carbonyl complexes such as $LCr(CO)_5$ and $LNi(CO)_3$ and the measured CO stretching frequency depended strongly on the donor properties of the ligand L. Figure 1.1 illustrates the well-known explanation for a linear molecule L–M–CO in a simple way. Donation by the phosphorus ligand will increase the electron density on the metal, and the

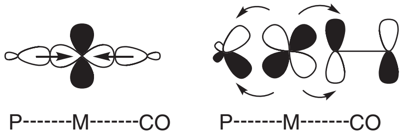


Figure 1.1 Ligand effect on the CO-stretching frequency.

increased π-back donation from M to CO in the antibonding CO orbital will weaken the CO bond and lower the frequency of the stretching mode. In case the ligand L is a π-acceptor as well, it will compete with CO for the metal d-electrons and back donation diminishes, which results in a higher CO stretch frequency.

Tolman introduced the so-called χ-value as a quantitative yardstick for electronic properties of phosphorus ligands [56]. His ligand study took place in relation with the Dupont de Nemours process for hydrocyanation of butadiene to adiponitrile. This reaction is catalyzed by Ni complexes of phosphites, and therefore, he selected $LNi(CO)_3$ as his reference compound, thus using the same metal as in the process. He measured the asymmetric stretching frequency by IR. Substitution of CO by L in $Ni(CO)_4$ is a facile reaction and does not require irradiation like many other metal carbonyls. The frequency obtained for tris-*t*-butylphosphine was the lowest, and this frequency was subtracted from the values measured for other ligands and this value (without the unit cm^{-1}) was named the χ-value. A few values are summarized in Table 1.1.

When mixed phosphorus compounds are considered, the sum of the individual contributions of the substituents can be used to calculate the χ-value of the ligand as was shown by Tolman [57]. The χ_i-value for a single substituent R is simply one-third of the χ-value of the ligand PR_3.

The π-acidity of the phosphorus ligands, which refers to the acceptance (back-donation) of electron density from filled metal orbitals to empty ligand

Table 1.1 Typical χ-values of ligands PR_3.

R=···	**χ-Value**	**IR frequency (A_1) of $NiL(CO)_3$ (cm^{-1})**
t-Bu	0	2056
n-Bu	4	2060
$4\text{-}C_6H_4NMe_2$	5	2061
Ph	13	2069
$4\text{-}C_6H_4F$	16	2072
CH_3O	20	2076
PhO	29	2085
CF_3CH_2O	39	2095
Cl	41	2097
$(CF_3)_2CHO$	54	2110
F	55	2111
CF_3	59	2115

orbitals (Figure 1.1), was initially assigned to d-orbitals on phosphorus. Today, the accepted view is that back donation takes place from the metal d-orbitals into the σ^*-orbitals of the phosphorus ligand [58].

As $Ni(CO)_4$ is very volatile, explosive, inflammable, highly toxic – maximum exposure level 1 ppb – and unstable, very few researchers still use it and its storage inside a laboratory is often forbidden. A convenient, alternative reference compound is, for instance, *trans*-$L_2Rh(CO)Cl$ [59]. The values measured for both complexes run fairly parallel. Nickel carbonyl has the advantage that even for the largest ligands, there are no steric impediments, and thus, the measured frequency is purely determined by the electronic differences of the ligands, whereas for the square-planar rhodium complex, this will not be the case for the largest ligands.

Various attempts have been undertaken to separate the π- and σ-contributions to the electronic ligand effect. The measured IR frequency differences have been used in linear free-energy relationships for which there is not a strong theoretical basis. Reaction rates of exchange processes are dominated by steric effects and then we are left with a separation of steric and electronic effects. Giering proposed in his QALE (quantitative analysis of ligand effect) studies of phosphorus ligands that three electronic parameters were needed: the σ-donor capacity (χ_d), the π-acidity (π_p), and an aryl effect (E_{ar}) [60, 61]. The last parameter has gained importance and not limited to aryl-containing phosphines, but its physical meaning has not been elucidated [62]. A more recent study concerns the development of a monodentate ligand map by Fey and coauthors that enabled them to successfully design new ligands for Ni-catalyzed hydrocyanation and Rh-catalyzed hydroformylation of alkenes [63]. The map is now based on 348 ligands; a principal component analysis (PCA) of the descriptors was used to derive an improved map of ligand space.

1.3.2 Steric Properties

Quantization of the steric properties was attempted by Tolman in the same works that described the electronic parameters [57]. Tolman defined the steric parameter θ (theta) as the cone angle of a ligand, measured in plastic CPK models with a defined M–P distance of 2.28 Å (Figure 1.2). This may look as a very crude method, but especially as a relative order, it has proven to be very useful in ligand effect studies in catalysis.

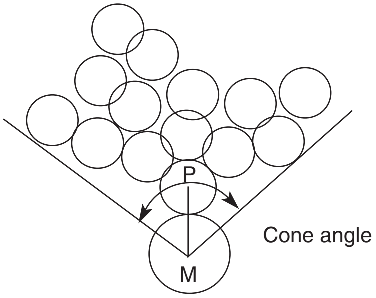


Figure 1.2 Tolman's method for determining the cone angle.

The absolute value does not have much importance, as one can see, for example, from the cone angle for PPh_3, which is 145°, whereas, in practice, in crystal structures, the P–M–P angle for two *cis* PPh_3 ligands can be as small as only 95°. On an average, this angle amounts to 100.5° in square-planar palladium(II) complexes [64]. The latter is due to nonconical shape of the ligands. For ligands with different hydrocarbyl groups, Tolman proposes to take an average of the three groups taken from the PR_3 ligands. In the past decades, computer calculations on MM2 models have been introduced, but for the application in catalysis, these methods also remain approximations. The examples of θ values of a range of phosphorus ligands are compiled in Table 1.2.

Stabilities of phosphine complexes or ligand dissociation parameters are often dominated by steric effects, particularly when the electronic effect can be kept constant. Such a study was reported by Trogler and Marzilli [65]. Thermochemistry can also give a yardstick for steric properties of phosphorus ligands [66].

The Tolman values can be readily applied, and until today, they offer a useful insight [67, 68]. Several other methods have been introduced with which one can calculate a steric parameter, aiming at better yardsticks when non-C_3 symmetric ligands are involved. An example is the calculation of the solid angle Ω, which utilizes crystal structure data. In this procedure, all atoms of the ligand are projected on a sphere equivalent to the metal surface. The coverage of the surface is a measure of the steric bulk [69, 70]. This number also takes into account remote groups on the ligand, which may be or may not be more satisfactory. This procedure can also be applied to other ligands, such as cyclopentadienyl derivatives [71]. The parameters θ and Ω fall short particularly when ligands of peculiar shape such as NHC ligands are considered. In these instances, calculation of the buried volume $\%V_{bur}$ gave better results [72, 73]. A buried volume calculation calculates the volume of the ligand atoms around a metal atom, and this can be applied for a certain sphere to obtain a standardized method [74].

Orpen and coworkers introduced another parameter, called the symmetric deformation coordinate (S4′). It involves the measurement of the distorted

Table 1.2 Typical θ values of phosphorus ligands PR_3.

R=	θ-Value (°)
H	87
CH_3O	107
n-Bu	132
PhO	128
Ph	145
i-Pr	160
C_6H_{11}	170
t-Bu	182
2-*t*-BuC_6H_4O	190
$(2\text{-}CH_3)C_6H_4$	194

angles of M–P–R and R–P–R (M = metal and R = substituent) in metal–ligand complexes [75]. The data were retrieved from almost 1300 crystal structures of metal phosphine complexes from the CSD database. The parameter S4′ was adapted for use in computational chemistry by Cundari and coworkers [76]. This parameter is just the difference between ∠M–P–R and ∠R–P–R angles (R denoting here the atom connected to P) in coordinated ligands PR_3. For bulky groups, the angles R–P–R are larger because of the repulsion of the bulky groups, and thus, S4′ is smaller for more bulky ligands.

Suresh uses the molecular electrostatic potential (MESP) to calculate and separate the electronic and steric properties of a complex [77, 78]. This requires high-level density functional theory (DFT) calculations, and Fey commented that this may be too demanding to become popular in the hands of nonspecialists in DFT [79].

Many parameters that are in use today were reviewed by Fey et al. [80]. They discuss how computational and statistical techniques can help to understand ligand effects in a quantitative way with the final goal of ligand design for catalysis and perhaps other properties of metal phosphorus ligand complexes. As an example of a study on stereoelectronic factors in iron catalysis, see a contribution by Morris and coworkers [68]. They studied aryl-substituted iron(II) carbonyl P–N–N–P complexes in the asymmetric transfer hydrogenation of ketones, and because the active catalysts contain a CO molecule, the electronic properties could be measured directly on the active catalysts, as in hydroformylation. Electron-rich complexes gave the fastest catalysts; the information on sterics was limited as too bulky ligands did not give active catalysts.

1.3.3 The Bite Angle of Bidentate Ligands

Bidentate phosphorus ligands present a special case, and in catalytic reactions, they exert an enormous influence: in square-planar complexes, bidentate ligands leave two sites in *cis* positions open, which can be used not only for insertion reactions but also for reductive elimination reactions a *cis* disposition may be indispensable. Within the class of diphosphines, it had been known for many years that the activity of complexes containing diphosphines of variable bridge length (dppm, dppe, dppp, dppb, etc.) in certain catalytic reactions can vary enormously. As early as 1970, the effect of the bite angle was extensively studied in the co-dimerization of butadiene and ethylene catalyzed by cobalt modified by a long range of ditertiary phosphine ligands [81]. Other early examples are the Pt-catalyzed hydroformylation of alkenes [82] and the cross-coupling of Grignard reagents with organohalides [83]. It was not until 1990 that Casey and Whiteker introduced the natural bite angle of bidentate ligands as a parameter to measure and compare the “bite angle” of such bidentates [84]. The concept is defined as the bite angle that the ligand would prefer in the absence of angular (electronic) preferences of a specific metal complex and steric interaction of other ligands on the metal. The natural bite angle is calculated with the aid of MM2 energy calculations for a metal complex in which the force constant of the P–M–P angle is set to zero, M is a dummy metal with a defined distance from M to P. Because the calculations were first conducted in the context of rhodium–phosphine-catalyzed hydroformylation, the M–P distance used is that taken from hydridorhodium

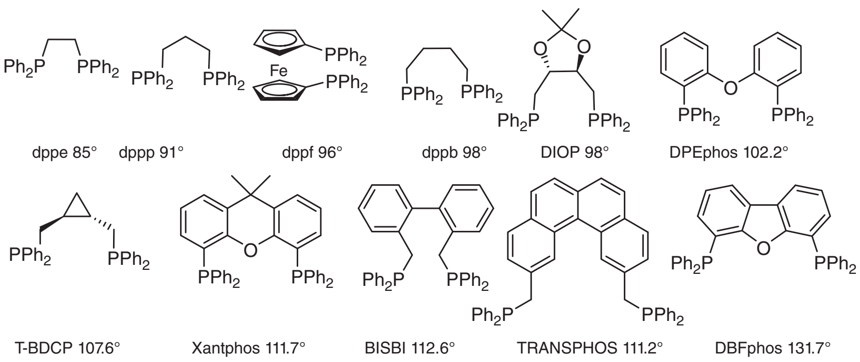
Table 1.3 Diphosphines and their natural bite angles β_n.

Ligand	X-ray values[a)] P–M–P	Molecular modeling[b)]
dppe	85.0	78.1, 84.4 (70–95)
dppp	91.1	86.2
dppb	97.7	98.6
dppf	95.6	99.1
DIOP	97.6	102.2 (90–120)
BISBI[c)]	122.2	122.6 (101–148)
		112.6 (92–155)
NORPHOS		123 (110–145)
TRANSPhos		111.2
T-BDCP		107.6 (93–131)
DPEphos	102.5	102.2 (86–120)
Xantphos	107.1	111.7 (97–135)
DBFphos		131.1 (117–147)

a) Standardized M–P distances from X-ray structures and angles recalculated.
b) Flexibility range is presented in parentheses, i.e. accessible angles within 3 kcal mol^{-1}.
c) Two conformations of backbone.

carbonyls, viz 2.315 Å. By putting the bending force constant at zero, we have not eliminated all factors that influence the bite angle, as also bending, dihedral, and nonbonding interactions do influence the bite angle. Nevertheless, β_n has proved to be a good and useful approximation, and it is mainly used as a ranking of the bidentate ligands.

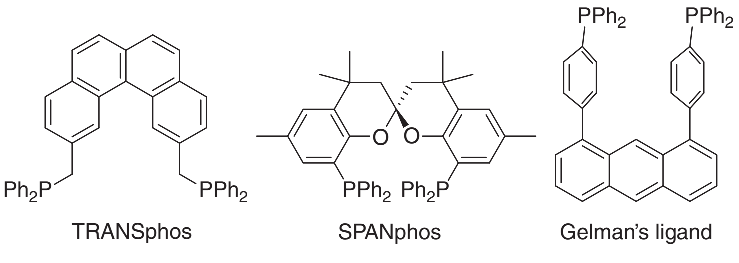
In Table 1.3, we give a number of typical examples of natural bite angles together with a few P–M–P angles as measured in crystal structures [85]. The order seen in X-ray data parallels that of the calculated bite angles. All data except those for BISBI were taken from square-planar complexes, and the deviation from an ideal 90° is in the direction one might expect from the natural bite angles. Scheme 1.34 shows a number of typical ligand structures.



Scheme 1.34 Bidentate ligands and their natural bite angles.

BISBI was introduced by Devon et al. as a ligand particularly suited to obtain linear aldehyde in Rh-catalyzed hydroformylation [86]. Casey and Whiteker showed that this was due to the wide bite angle. Not all ligands having a similar wide bite angle showed this high selectivity, and apparently, other structural details may also influence the course of the reaction. Slight variations of BISBI are difficult to realize, and to this end, van Leeuwen and coworkers introduced the Xantphos-type ligands, which will be discussed in more detail in Section 1.4. All studies show that the high selectivity for the formation of the linear alkyl intermediate is a steric effect. Xantphos ligands were initially designed for hydroformylation, but soon thereafter, they were applied successfully in Ni-catalyzed hydrocyanation, cross-coupling reactions, and many more. In hydrocyanation, it was the first phosphine ligand that gave activity; phosphites had been the ligands of choice for years. The reason for this is that the reductive elimination is the rate-limiting step in the process, and thus, electron-withdrawing phosphite ligands are needed. It was thought that a wide bite angle ligand would also be able to destabilize the square-planar intermediate, the resting state in the process waiting to undergo reductive elimination. Thus, a range of Xantphos-type ligands were applied. The reaction rate increases with the bite angle, but at too large angles, side reactions take over and an optimum value is usually reached halfway the Xantphos series. It is assigned as an electronic effect; electronic and steric effects in wide bite angle studies were reviewed by Freixa and van Leeuwen [87, 88]. The results in cross-coupling chemistry initially looked capricious until it was realized that in those systems also, the reductive elimination was rate limiting as the results were similar to those of the hydrocyanation. In the 1990s, this was an unexpected viewpoint as generally the oxidative addition to the catalyst precursor was considered to be the slow step. In the presence of an excess PPh_3 and dibenzylideneacetone (dba), this may be so for aryl bromides and iodides, but better precursors gave much faster reactions (see Section 1.5) [89].

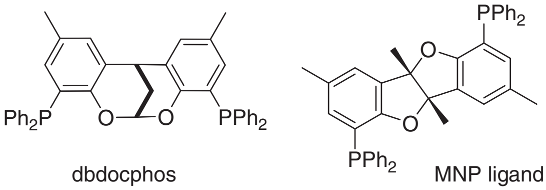
Still wider bite angles will lead to ligands that give *trans* complexes, and it was with this in mind that Venanzi and coworkers developed TRANSPhos (Scheme 1.34) [90]. The ligand is very flexible though and it forms a wide range of complexes with angles varying from *cis* to *trans*. Also, SPANphos, designed as *trans*-ligating diphosphine, can still form *cis* complexes, although when given the choice it prefers *trans* coordination (Scheme 1.35). SPANphos is chiral because of its spiro center and asymmetric catalysis has been reported. A direct chiral synthesis of the ligand was invented by Ding and coworkers. In 2004,



Scheme 1.35 "*Trans*" ligands.

Matt and coworkers reported TRANSDIP, a cyclodextrine-based diphosphine that so far only coordinates in a *trans* manner [91, 92]. Gelman developed anthracene-based diphosphines that exclusively give *trans* complexes, which are, unexpectedly, active in cross-coupling-type reactions [93]. As the more flexible ligand was the most active one, the authors supposed that *cis*-like intermediates might still be within reach for the catalyst.

In addition to monometallic complexes, SPANphos also gives bimetallic complexes, and the latter for rhodium were more active in methanol carbonylation than the monometallic complexes. The bidentate phosphine derived from dibenzodioxocin (Scheme 1.36) gives exclusive bimetallic complexes and showed the same high reaction rate in methanol carbonylation.



Scheme 1.36 Ligands for bimetallic complexes and metal nanoparticles.

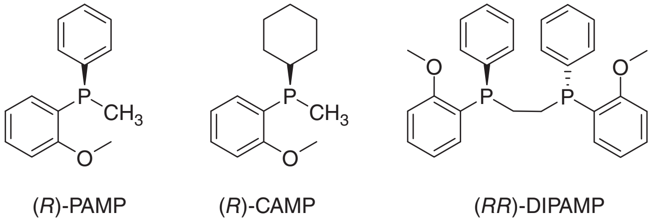
Interestingly, ligands that contain two donor atoms far apart may not be suited for organometallic complexes, not even for oligonuclear complexes, and can be used as ligands for metal nanoparticles (MNPs). The ligand named MNP ligand in Scheme 1.36 is an example of those, but also dbdocphos was used as such; the roof shape makes them good ligands to “embrace” an MNP [94]. Furthermore, the phosphine ligands clearly modify the electronic effects of RuNP as reviewed by Tschan et al. [95]. The more electron-rich the RuNPs were, the more active were the catalysts for benzene hydrogenation. Very electron-rich catalysts (Cy_3P, NHCs) were found to be less stable, and thus, the most efficient catalysts contain Cy_2ArP units as the ligands.

1.3.4 Chirality

One of the important properties of phosphines in many applications is their chirality. Here, we will only briefly mention the types of chirality one can distinguish in chiral phosphines by way of introduction.

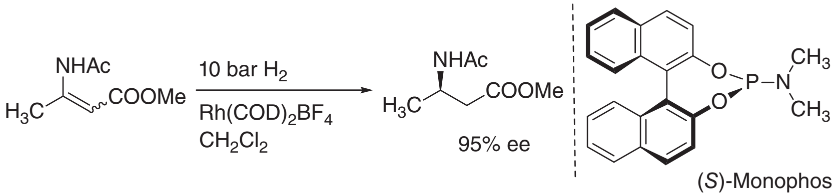
1.3.4.1 P-Stereogenic or P-Chiral Ligands

This was the first approach historically taken toward the synthesis of chiral phosphines. It requires the presence of three different substituents at the P-atom. One needs separation of the enantiomers as the diastereomers of some adduct or intermediate. The advanced methods using chiral auxiliaries developed later by Jugé et al. [96], Corey [97], and others allow the stepwise introduction of two substituents at phosphorus using a chiral auxiliary. If separation of the enantiomers is used, this might be easier on the phosphine oxides, but the reduction of phosphine oxides to phosphines is not trivial either as some methods will give retention, other methods give inversion, or mixtures of both. Oxides are conveniently made via the facile introduction of one alkyl group via an Arbuzov rearrangement, e.g. the methyl group. For instance, (phenyl)(2-methoxyphenyl)(methyl)phosphine oxide, PAMP (Scheme 1.37) could be made this way, but Knowles et al. (PAMP = phenyl anisole methylphosphine) used menthol as a chiral auxiliary and the intermediate menthoxyphosphine oxide (or menthyl phosphonates) diastereomers were separated. PAMP was used for the asymmetric hydrogenation of 2-acetamidocinnamate and gave 55% ee. Replacing phenyl by cyclohexyl, CAMP, led to an increase of the ee to 88% [98].



Scheme 1.37 Chiral ligands by Knowles.

Oxidative dimerization of the deprotonated methylphosphine derivative led to a P-chiral bidentate DIPAMP, which was found to be much more effective as an enantioselective catalyst. Thus, the idea that bidentates offered much better perspectives for enantioselective catalysis was born. This widespread idea was refuted by De Vries and Feringa in 2000, when they published studies on the highly enantioselective Monophos-type ligands (Scheme 1.38), phosphoramidites based on binol [99]. In the same year, studies on other effective monodentates were published by Pringle and coworkers [100] and Reetz and Mehler [101].



Scheme 1.38 Monophos asymmetric hydrogenation.

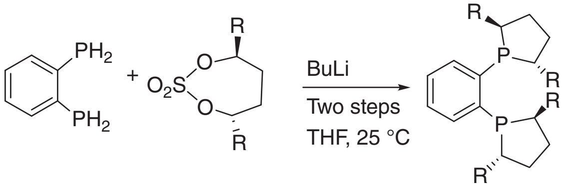
Unlike PAMP and DIPAMP, for which DIPAMP is more selective, a simple dimer of Monophos with an N–C–C–N bridge gave a slow catalyst with moderate ee (72%), and thus, in this instance, the monodentate analog is the better ligand.

1.3.4.2 Chiral Backbone

The use of a chiral backbone in bidentates is a far more general method, and it was first applied by Kagan and Dang for the synthesis of DIOP [18]. The advantage is that often natural products can be used as the chiral moiety. DIOP is derived from tartaric acid and as just one example of an often applied reaction sequence ever since, the synthetic scheme for DIOP is shown in Schemes 1.13 and 1.14. The synthesis starts from the diester of tartaric acid, a chiral, natural product.

1.3.4.3 Chiral Substituents at Phosphorus

For each group mentioned here, numerous examples exist and also for this one. Any chiral group can be connected to a phosphite or PPh_2 moiety to give a chiral ligand. Among such chiral groups, we find sugars and chiral amines, just to mention two, which also function as chiral backbones, the previous in 1.3.4.2. Here, we mention the Duphos ligands [102] as an effective group of ligands that are not derived from natural products, Scheme 1.39.



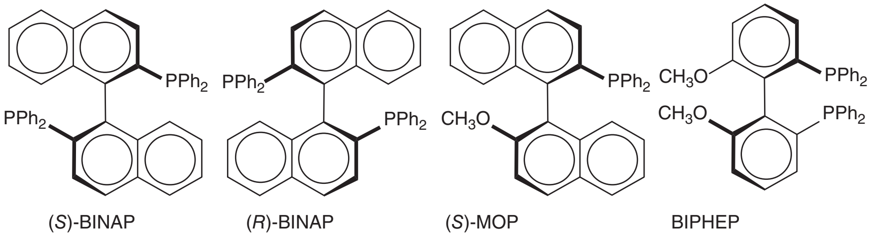
DuPHOS, 50–75%
R = CH_3, C_2H_5, iC_3H_7

Scheme 1.39 Duphos ligands, chiral substituents at phosphorus.

Many variations on this theme have been developed, such as other backbones, more substituents R, four-membered rings instead of phospholanes, etc.

1.3.4.4 Axial Asymmetry or Atropisomery

Axial asymmetry or atropisomery presents a kind of chirality closely related to the next three items, but we will treat them one by one. The famous example of an axially chiral ligand is BINAP developed by Noyori and coworkers [103]. Its first applications were with ruthenium as the metal, the "other" metal complex hydrogenation catalyst introduced by Wilkinson. The combination of rhodium and the ligands mentioned above all gave high enantioselectivities with enamide substrates, a prerequisite not needed for ruthenium. Over the years, ruthenium/BINAP turned out to be a very broadly applicable system for the asymmetric hydrogenation of all sorts of substrates, be it C=C or C=O unsaturated compounds, when conditions and co-ligands were adjusted as needed. The synthesis of BINAP starts from binol, for which the racemic mixture can be resolved enzymatically via ester hydrolysis. The enantiomerially pure binols are converted to triflates, and these are converted in two steps via cross-coupling with $HPPh_2$ into BINAP. The half product can be converted to the hemilabile monodentate MOP ligand first made by Hayashi [104], which has been used, for instance, in efficient asymmetric hydrosilylation of alkenes (Scheme 1.40).

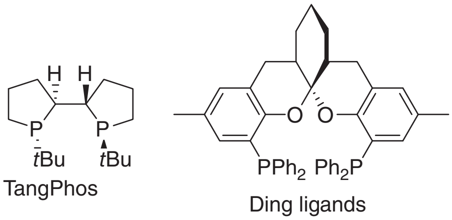


Scheme 1.40 Atropisomeric bisphosphines.

Other well-known examples of chiral axial ligands are the BIPHEP ligands introduced by Solvias. Key feature in all axially chiral ligands is that free rotation around the central axis is prohibited by the substituents in the other position ortho to the axis.

1.3.4.5 Spiro Diphosphines

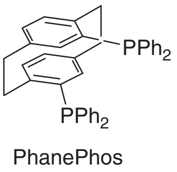
Of the spiro diphosphines, we mention two examples: TangPhos introduced by X. Zhang and SPANphos introduced by van Leeuwen. The synthesis of TangPhos is a multistep one and this hampers perhaps a wide use of it and further variations, although it has been shown to be effective in many asymmetric reactions [105]. SPANphos (Scheme 1.35) is easily obtained as the racemic mixture, which had to be separated. Ding and coworkers successfully synthesized SPANphos analogs of it equipped with an extra propanediyl bridge in a direct, enantioselective manner [106]. See Scheme 1.41.



Scheme 1.41 Spiro bisphosphines.

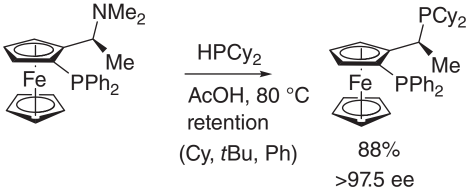
1.3.4.6 Planar Asymmetry

Planar asymmetry is represented by the ferrocenic Josiphos ligands introduced by Togni et al. [107] and [2,2]paracyclophanes forming Phanephos (Scheme 1.42) [108]. Planar chirality is well known for chromobenzene and ferrocene derivatives, in which double substitution in one ring with different



Scheme 1.42 Phanephos.

substituents creates a chiral molecule. Josiphos ligands have C_1 symmetry, whereas most other examples of the classes presented here have C_2 symmetry. Given the synthesis route employed (Scheme 1.43), one can selectively introduce two different PR_2 groups in a facile manner.

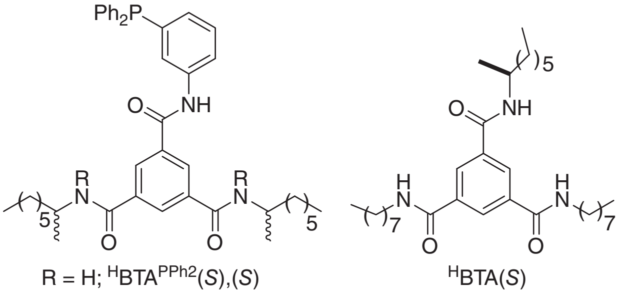


Scheme 1.43 Synthesis of Josiphos ligands.

1.3.4.7 Helical Symmetry

Helical symmetry has been neglected so far as the synthesis of covalent species with substitution on the aromatic helicene in specific positions that would afford suitable chiral diphosphines [109].

Supramolecular systems can perhaps more easily be accomplished as was shown by Raynal et al. [110], but the organized structure of such a ligand depends strongly on concentration and solvent, and this also leads to limitations. Chiral stacks of BTA units are formed (Scheme 1.44) in which phosphine-containing analogs are inserted. Addition of $Rh(nor)_2^+$ will make sure that the phosphine unit move to positions where they can form a bidentate ligand. The helical nature of the stack induces chirality in the diphosphine formed, and ees up to 88% were obtained in the hydrogenation of dimethyl itaconate.



Scheme 1.44 BTA ligands for helical symmetry.

1.4 Rhodium-Catalyzed Hydroformylation with Xantphos-Type Ligands

1.4.1 Introduction

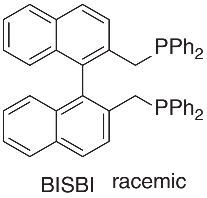
The first catalysts used for hydroformylation were based on cobalt carbonyls in the absence of other ligands. Its invention goes back to the late 1930s to Roelen in

Ruhrchemie. This knowledge was rapidly developed into a process by Exxon and others after WWII in the 1940s and first applied in the USA; the transition from the coal era to petroleum had started. Phosphine-modified Co processes were first introduced by Shell Development in the 1960s by Slaugh and Mullineaux [2]. Various Co-based systems existed that were used for both propene and higher alkene hydroformylation in industry; they are still in use for higher alkenes. In the late 1960s, Wilkinson and coworkers discovered the rhodium-based catalysts (for more details see reference [111]) for alkene hydrogenation under mild conditions. A key component was Wilkinson's catalyst $Rh(PPh_3)_3Cl$. Although this compound can be used as the precursor for hydroformylation catalysts, it is not the best choice as already described in those years. Preferably, hydrogen chloride formed from the reaction with dihydrogen should be neutralized to facilitate the formation of a rhodium hydride $HRh(CO)_n(L)_{4-n}$, as needed for hydroformylation. For triphenylphosphine as the ligand, a convenient precursor is another compound from Wilkinson's group, wrongly so, also called Wilkinson's catalyst, viz $HRh(CO)(PPh_3)_3$ [112]. A variety of metal complexes can be formed under the reaction conditions including monomers with several ligand ratios such as CO/phosphine, dimers, polar species, etc. CO is a competing ligand and thus conditions play an important role. Usually, an excess of monophosphorus ligand is needed to obtain the desired activity and selectivity. The emphasis regarding selectivity was on linear aldehyde products both for propene and for higher alkenes. Butanal finds many applications: in C8 alcohols in phthalate esters as softeners in PVC after dimerization, paints, lubricants, etc. Linear higher alcohols are applied in detergents. For styrene, the desired product is the branched one, and this is the one usually obtained with ligand-modified rhodium catalysts.

Early on, Pruett and Smith [113] showed that phosphites also led to active catalyst, and now we know that on an average, phosphites give faster catalysts than phosphines. All phosphorus ligands have shown to give active catalysts in the last 50 years, but interestingly, under hydroformylation conditions, N-based ligands do not coordinate, not even in strongly *cis*-directing P–N ligands. NHC ligands do coordinate it seems, but the spectroscopic evidence for well-defined complexes as we have for many phosphorus ligands seems to be absent.

1.4.2 Monophosphines, Characterization Studies, and Diphosphines

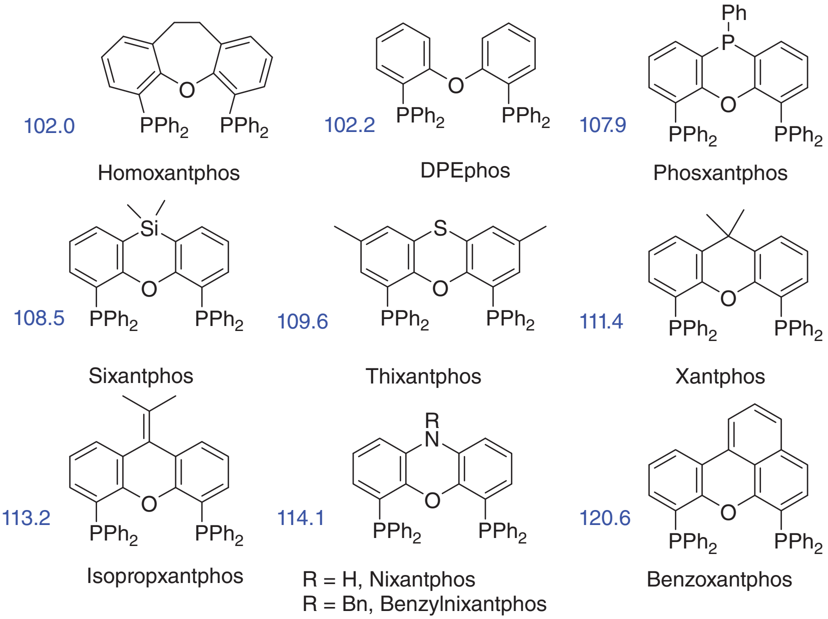
During the 1980s, several studies appeared on the possible structures of the actual catalyst precursor and all centered around a pentacoordinate rhodium hydride species with four neutral ligands, CO, and the phosphorus ligand used. The monophosphorus complex was suggested to be the most active but with low selectivity for the linear aldehyde when terminal alkenes were applied as the substrates. Trisphosphine complexes were relatively slow. Trisphosphine complexes such as $HRh(PPh_3)_3CO$ give high selectivity to the linear product, up to 95%, but they are relatively slow. These are the resting state of the catalyst in the first commercial process developed by Union Carbide Corporation (now owned by Dow), on stream since 1976. Celanese (1974) and Mitsubishi (1978) also participated early in the ligand-modified rhodium applications taking advantage of the mild conditions and high product selectivity compared to cobalt, which gives the same 10% of alkane formation as a by-product, with only fuel value. Bisphosphine biscarbonyl rhodium hydride was a good compromise for selectivity and activity. In such complexes, two phosphines can coordinate in a bis-equatorial manner or a combination of apical and equatorial positions. Especially inspiring for us was the work by Brown and Kent [114] in which there were subtle hints that perhaps the bis-equatorial species was responsible for high selectivity toward the linear aldehyde. This led to our search for bidentate ligands with a wide bite angle that would coordinate in this bis-equatorial fashion. The patent that described BISBI [86] for the first time had not yet been published. The explanatory work by Casey et al. [115] described for the first time explicitly the effect of the bite angle of a bidentate phosphine on the selectivity in rhodium-catalyzed hydroformylation. Earlier studies on DIOP [116] (for which the linear product was not the desired one, as clearly one wanted the chiral branched product!) and ferrocene-derived diphosphines (dppf) [117] already led the way to the advantageous effect of wide bite angle ligands (Scheme 1.45).



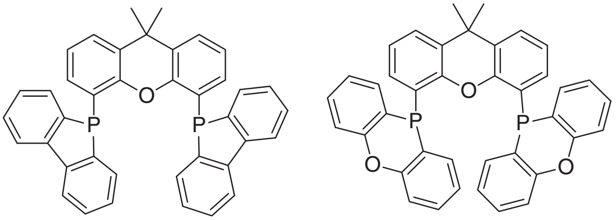
Scheme 1.45 Structure of BISBI.

Thus, in the late 1980s, we embarked on a study of wide bite angle ligands based on a xanthene backbone, as simple molecular modeling had shown that these ligands prefer bisequatorial coordination in a trigonal bipyramidal rhodium hydride complex. The parent compound was named Xantphos ((9,9-dimethyl-9*H*-xanthene-4,5-diyl)bis(diphenylphosphine)). Most interestingly, in xanthene, the C-atom in the 9-position can be easily substituted by other atoms, which leads to a closure or opening of the pincers, thus slightly modifying the natural bite angle. In Scheme 1.46, the range studied has been depicted with the calculated β_n angles [118, 119]. This subtle variation of bite angle cannot be easily achieved for other wide bite angle ligands. The oxygen atom in the bridge is important; if this were a CH or NH metalation would occur, giving the well-known pincer complexes. Most of the ligands can be synthesized by direct lithiation of the backbone followed by reaction with PPh_2Cl. Substitution at C2 and C7 by an alkyl group, as in thixantphos, enables a bromination–lithiation sequence and may give ligands a higher solubility [120].

Dibenzophosphole- and phenoxaphosphino-substituted xantphos ligands (Scheme 1.47) [121] exhibit a high activity and selectivity in the rhodium-catalyzed linear hydroformylation of terminal alkenes (l:b = >60). More interestingly and at the time unusual for rhodium catalysts, they show an unprecedented high activity and selectivity in the hydroformylation of internal octenes to linear nonanal.



Scheme 1.46 Xantphos-type ligands.



Scheme 1.47 Dibenzophosphole- and phenoxaphosphino-substituted Xantphos ligands.

We will not reproduce here tables of results; to show the importance of small changes in the ligand, it suffices to say that the rate of the ligands mentioned above ranges from 35 to 1200 (mol of aldehyde) (mol of Rh)$^{-1}$ h^{-1} under constant conditions and the linear/branched ration varies from 8 to 70. Especially rewarding is that the highest rate and selectivities occur with the same ligand. Narrow bite angles give the lowest rates and selectivities. At 108°, a plateau was reached. Electron-withdrawing ligands, which facilitate CO dissociation of the precursor complex, enhance the rate of reaction.

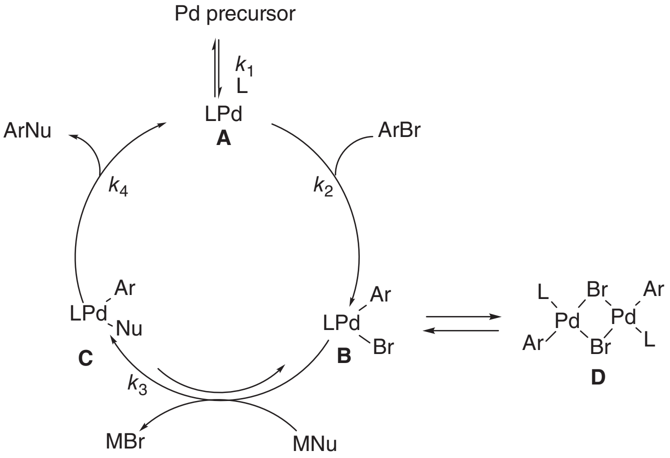
In situ studies by IR and NMR have revealed that under the conditions used, the catalyst precursor is a mixture of bisequatorial and equatorial-apical HRh(Bidentate)$(CO)_2$, and the linear branched ratios parallels the relative amount of bisequatorial hydrido species. Average conditions in these studies are temperature 80 °C, 20 bar syngas, 1 mM Rh precursor, 2.5 mM bidentate ligand, 700–1000-fold excess of alkene. For internal alkenes, somewhat higher temperatures were used. Thus, given the equilibrium phosphorus ligand – CO – an excess of ligand is needed, in spite of the fact that we are dealing with bidentate ligands. For triphenylphosphine, much larger excesses are normally used. In addition to the monomeric species mentioned, also dimeric species were observed, as already known in the work of Wilkinson as the dark orange or red solutions, but what factors govern exactly their relative occurrence is not understood; e.g. in general, Nixantphos ligands have a tendency under equal conditions to form more dimeric species.

Numerous bidentate diphosphines have been made available almost in the last five decades, many of them as enantiopure ligands for asymmetric hydrogenation and many other reactions, but all of them show natural bite angles from 75° to 95°. The Xantphos range of ligands provides a unique class with bite angles ranging from 102° to 120°. Although they were initially designed for hydroformylation in the first patent publication, they were already applied to a large number of reactions [122]. Application in hydrocyanation of alkenes led to the first catalyst based on phosphine ligands active in this reaction, and this was expected on the basis of the envisaged enhancement of the reductive elimination, known as the rate-limiting step. The rate and conversion were shown to peak at an angle of 108° for Sixantphos; both larger and smaller bite angles gave lower yields. Surprising initially was the highly favorable effect in cross-coupling reactions with palladium catalysts, initially C–C coupling reactions, soon followed by the Buchwald–Hartwig reaction. Today, around 3300, publications report the use of Xantphos-type ligands, the majority of which concerning a very wide variety of cross-coupling-like reactions. The most often used ligands are the commercially available or easy-to-make DPEphos and Xantphos, which, both in ligand-screening publications, take exceptional positions, either among the best or the worst ones! In the intermediate complexes of these catalysts, the ligands form slightly distorted *cis* complexes (sometimes *trans*) rather than the bis-equatorial coordination mode in the rhodium hydroformylation catalysts. It seems that this distortion is responsible for their unusual reactivity or selectivity in many reactions. When it was realized that the behavior of Xantphos-like ligands in cross-coupling reactions paralleled the behavior in hydrocyanation, it was suggested that reductive elimination might be a decisive step in this catalysis. In Section 1.5, we briefly present the importance of bidentates phosphines and the, nowadays, more important monodentate "biphenyl" phosphine ligands developed by Buchwald.

1.5 Cross-Coupling Catalysis with Mono- and Bidentate Phosphines

1.5.1 Introduction and Simplified Mechanism

During the past four decades, cross-coupling chemistry has grown exponentially; initially, only a few publications were known that attracted the interest of mainly organometallic chemists, but later, the power of such reactions was recognized by organic chemists in organic syntheses, such as the Heck–Mizoroki reaction, the Suzuki–Miyaura coupling, the Kumada–Corriu reaction, the Negishi reaction, and the Buchwald–Hartwig coupling reaction. The first reactions all concern C–C coupling reactions and the latter C–N coupling. Variants of the Buchwald–Hartwig reaction include coupling of oxygen, phosphorus, and more heteroatoms with carbon. The allylic substitution catalyzed initially by palladium introduced by Tsuji and developed for asymmetric applications by Trost can also be considered as a metal-catalyzed coupling reaction. The general scheme for all reactions is the same (Scheme 1.48): oxidative addition of an R^1X molecule, in which R is normally carbon-based (ArBr in the scheme), to a low-valent Pd or Ni, substitution of X by an MR^2 nucleophile R^2 (MNu in the scheme), followed by reductive elimination of R^1R^2 (ArNu). The donor atom of R^2 varies from C [123], N [124], O [124], S [125], and P [126]. For allylic substitution and the Heck reaction, the scheme is slightly different. Especially, the Heck, Suzuki, and Buchwald reactions have found ample application in organic syntheses [127] and industry [128]. The basic mechanism was published as early as 1972 by Kumada and coworkers for nickel catalysts and Grignard reagents for the Kumada–Corriu reaction [129, 130]. A simplified mechanism is shown in Scheme 1.48.



Scheme 1.48 Simplified mechanism for Pd-catalyzed cross-coupling.

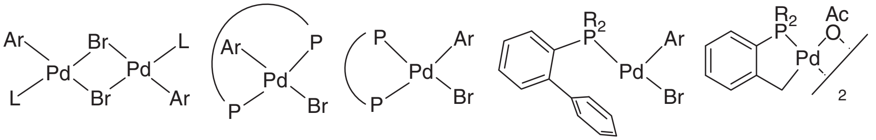
1.5.2 Oxidative Addition

Until the late 1990s, it was generally accepted that the oxidative addition Reaction 2 was the rate-limiting step, although findings were contradictory and the intermediate species are probably much more complicated. In this context, we cannot review the many systems studied, and as an example, we mention the studies by Amatore and Jutand [131] who showed that the anion present had a drastic effect on the rate of reaction in the systems they studied mostly using triphenylphosphine as the ligand. Different reactions required different anions to obtain the most efficient catalyst; for cross-coupling, halides are preferred, and for the Heck reaction, acetates are favored. Note that also in allylic substitution with palladium catalysts, some acetate is often added. They proved the importance of anion coordination to Pd(0) in step 2 using electrochemistry, as the anion makes the metal more electron-rich which will enhance oxidative addition. This suggests that oxidative addition was regarded as the rate-limiting step in those studies, but the authors caution that in the substitution reaction also, the anions can play an important role; for instance, an acetate ion can aid in substitution reactions by acting as a μ-acetato-*κ*O:*κ*O′ ligand between the two metal ions involved. The role of the precursor was also investigated by Amatore and Jutand, and by many others, but one of their papers on this serves as a good illustration here [132]. Divalent Pd precursors can be used, and this requires a reduction of palladium in order to arrive at the precursor **A**, which is not a problem if metal hydrocarbyl reagents are used as one of the coupling components, but for the Heck reactions and allylic alkylation reactions that may not be a matter of course. The metal hydrocarbyl substitutes the two halides for hydrocarbyls, which will form a coupling product via reductive elimination. The use of relatively unreactive $Pd_2(dba)_3$ complexes is widely used as a Pd(0) precursor, but as the authors have shown, this forms even more stable (bisphosphine)Pd(dba) complexes as dba stabilizes Pd(0). This interferes not only with the initial activation but may slow down the process continuously as dba remains in the medium during the reaction. Thus, the conversion of the precursor to active complex **A** (or an anion ligated **A**) may add to the observation that the oxidative addition is rate limiting in these processes. In the late 1990s, it became clear that this is not necessarily the case, especially thanks the work of Buchwald and the kinetic studies by Hartwig. Buchwald and coworkers introduced a novel Pd(0) precursor containing biaryl phosphine ligands and cyclooctadiene, which undergoes rapidly oxidative addition [133].

Most likely, the conversion of the precursor used to an active species has troubled many cross-coupling reactions for years, but the mechanistic studies have taught us that this can be easily avoided by starting with a stable intermediate such as **B**. The use of suitable precursors has done away with the old recipes in which the reaction mixtures are heated overnight in *N*,*N*-dimethylformamide (DMF). The starting complex contains a stable hydrocarbyl group such as an aryl group, the ligand in the desired stoichiometry, and a halide or pseudohalide. The hydrocarbyl group is not necessarily the same group as the one in the aryl or vinyl halide to be used as the reactant in the cross-coupling reaction, as for instance π-allylpalladium halide or acetate together with the ligand can be applied; the halide is substituted by the nucleophile and one molecule of an allylic substitution product is formed in a catalytic amount. Likewise, η^3-cinnamylpalladium chloride can be used as a precursor [134]. Dialkylpalladium (bis-trimethylsilylmethyl) coordinated by cyclooctadiene is a convenient, phosphine-free precursor, although it has to be stored at low temperature [135]. For bidentate ligands, one can synthesize an intermediate **B** exactly as it occurs in the cycle as a (L–L)Pd(Ar)Br complex separately by the slow reaction of $Pd_2(dba)_3$ with ligand and ArBr. The thus obtained complex can be used for many reactions as a useful precursor employing this ligand; for a ligand screening, this is less convenient. Application of bidentate Xantphos-type ligands gave room temperature cross-coupling with turnover frequency (TOF) of up to $600\,\text{mol mol}^{-1}\,\text{h}^{-1}$ [136]. Another approach involves the use of bulky monophosphine complexes (see Section 1.5.4 for the complete story) in a ratio 1 : 1 of Pd and L. Complexes of the formula LPd(Ar)Br may form dimers **D**

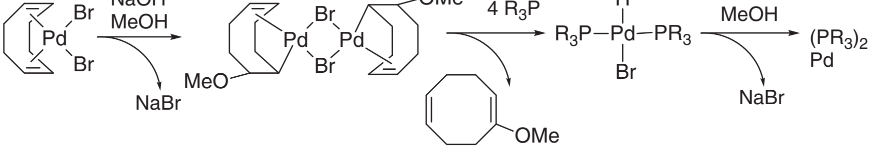
(Scheme 1.48), and if so, these must dissociate to continue the reaction. The aryl group may contain a coordinating amine group that gives more stability to the complex; with base, HCl is eliminated and reductive elimination under formation of a C—N bond gives the targeted Pd(0) intermediate [137]. In a Heck–Mizoroki reaction of acrylate and simple aryl bromides and iodides, this was found to be the resting state of the catalyst as the reaction rate was half order in Pd concentration, indicating that the oxidative addition is not. The latter was further substantiated by the electronic ligand effect as bulky phosphites gave very active catalysts. In view of the rate dependence on alkene concentration, coordination of alkene or migratory insertion was proposed as the rate-limiting step. The bulky diarylphosphine ligands introduced and developed by Buchwald and coworkers do not dimerize but are stable in the monomeric form **B**; this is a highly potent group of ligands (see Section 1.5.4) [138]. Further bulky ligands reported by Hartwig et al. are t-Bu$_3$P and NHC ligands, which also gave room temperature C—N bond formation with a TOF of 90 mol mol^{-1} h^{-1} [139].

A convenient precursor of type complex **A** containing t-Bu$_3$P is Pd(P(t-Bu)$_3$)$_2$ [140]. Another invention concerns the use of internally metallated ligand palladium complexes, in which the hydrocarbyl is eliminated via cross-coupling steps with the nucleophile [141]. In Scheme 1.49, we have collected a number of precursors discussed here. The use of an "ideal" precursor is not a guarantee that an excellent catalyst system is obtained as several other resting states outside the catalytic cycle may form, see, for instance, Alvaro and Hartwig for C—S bond formation [142].



Scheme 1.49 Suitable catalysts (precursors) for cross-coupling catalysis.

The importance of good precursors is well recognized today, and the theme continues receiving close attention. For instance, Colacot and coworkers reported a convenient synthesis of PdL$_2$ (L = bulky phosphine) precursors starting from (1,5-cod)Pd(II) salts in methanol and base [143]. An intermediate σ,π-coordinated cyclooctenyl Pd halide is formed, which undergoes β-H elimination and reductive elimination to form the desired Pd(0) catalyst (Scheme 1.50).



85–95% isolated yields; R$_3$P = t-Bu$_3$P, t-Bu$_2$NpP, o-Tol$_3$P, t-Bu$_2$PhP, Q-Phos, Cy$_3$P

Scheme 1.50 Convenient synthesis of PdL$_2$ complexes.

Generalizations in a field with so many ligands, substrates, conditions, etc., cannot be valid, certainly not for a metal as capricious as Pd, but still in the present context, we will do so. For most aryl and vinyl halides, the oxidative addition step should not delay if the halides are bromide and iodide and the ligand is a phosphine. For aryl chlorides, the oxidative addition step forms a barrier and only selected ligands will work well, mostly of the group of bulky alkylphosphines, monodentates, and to a lesser extent bidentates. We will come back to this when we have discussed the basic mechanisms of reductive elimination in Section 1.5.4.

1.5.3 Transmetallation

This step refers to Reaction 3 in Scheme 1.48 and is the replacement of the halide or pseudohalide by the hydrocarbyl nucleophile and the formation of a metal salt. The formation of the latter is the thermodynamic driving force of the reaction. Details of these reactions are scarce, but usually, it is imagined that this double decomposition takes place in a 2+2 anion–cation pairwise reaction. In most studies, it was shown that transmetallation is a complex process and more metals and more anions may be involved. Association with solvents and other reagents present may also occur. Clearly, for the Pd—C bond forming reactions, this can be a fast reaction, especially for the more reactive Grignard- or aluminum-based metal hydrocarbyls. In this instance, the conversion of **B** to **C** will be complete and all depends on the reductive elimination what the kinetics will look like.

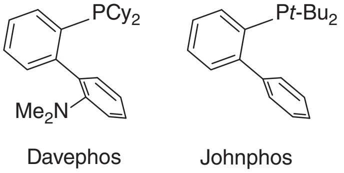
For Reactions 3 in which MNu is not a C-based anion, this reaction may not be as facile as we have presumed so far. For nitrogen-based nucleophiles as in the Buchwald–Hartwig reaction, this step may be less complete or slow, and it will appear in the rate equation. To begin with, the formation of MNu may not be complete, and the reactive species MNu may be present in an equilibrium concentration only. The latter is the case for many non-C-based nucleophiles that are added as NuH together with a base. Sometimes, deprotonation may not be complete, and Reaction 3 may not lead to full conversion. This leads to kinetic equations containing the nucleophile, halide, and base concentrations as has been found for the Buchwald–Hartwig reaction [136]. As the medium during the reactions changes with the formation of halide salts, the rate equation may be complicated.

For the cases studied with Xantphos as the ligand, the rate-determining step remains the reductive elimination, whereas the kinetic equation includes a pre-equilibrium of the halide–nucleophile exchange [89].

As concerns a possible ligand effect on such substitution reactions, no data are available, but it seems likely that exchange processes involving five-coordinate complexes are more readily accessible when wide bite angle diphosphines or monodentates, especially those that give unsaturated species, are used.

1.5.4 Reductive Elimination

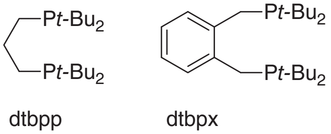
Reductive elimination (r.e.) under the formation of C—C bonds was already studied in the 1970s for bisalkyl and bisaryl group 10 metals with PPh_3 ligands and bipy. As early as 1980, Stille and coworkers proposed that the slow elimination of ethane from dimethylpalladium complexes requires dissociation of one PPh_3 [144]. We will first elaborate on this theme before mentioning the second group of fast catalysts, viz wide bite angle and sterically hindered diphosphines. It was almost 20 years later that the enhancement of reductive elimination in monodentate phosphine palladium complexes was used in cross-coupling for the first time with the use of Cy_3P and i-Pr_3P by Reddy and Tanaka [145]. This was soon followed by t-Bu_3P [146]. Symmetrically substituted L_2MR_2 complexes exhibit slower r.e. reactions than asymmetrically substituted complexes. The electronic explanation for this is that an electron-rich R group migrates to a relatively more electron-deficient carbon atom of the other R group. This is confirmed by the electronic effect that substituents on an aryl R group have on this reaction. Reductive elimination sets in as a migratory reaction, and therefore, it was named migratory-reductive elimination in cross-coupling chemistry [147]. Bulky monodentate phosphines favor the formation of mono-ligand complexes, and thus, the enhancement is not due to steric crowding but due to electronic effects as described. Intuitively, the use of bulky ligands might not be expected to lead to faster catalysts, and indeed, steps 1 and 2 may be slower in bis-ligand complexes, but they may also involve mono-ligand complexes instead. A similar favorable bulky ligand effect was observed for bulky phosphites in rhodium-catalyzed hydroformylation [148]. So far, bulky ligands would lead to the dimeric precursors $[R(L)PdX]_2$, which are still not optimal. A breakthrough was the introduction of diarylphosphines by Buchwald and coworkers that form exclusively mononuclear Ar(L)PdX complexes, equal to **B** in Scheme 1.48. The diaryl group may contain substituents, which were initially thought perhaps to act as weak donor atoms, but that turned out to be not the case. The two other substituents on phosphorus can be bulky alkyl groups or aryl groups; DavePhos and JohnPhos were the first ligands in this now extensive series of ligands (Scheme 1.51) [149, 150].



Scheme 1.51 The first "Buchwald" ligands.

Many specific conversions could be accelerated by using an optimized diarylphosphine ligand. The electron donicity of the alkyl groups was particularly important because this facilitated the oxidative addition such that aryl chlorides could also now be used as substrates, which are much more common and cheaper starting materials than aryl bromides or iodides and cause less inorganic waste by weight. The area of amination reactions with monodentate diarylphosphines was reviewed by Surry and Buchwald; this review contains a large number of practical hints [151].

We will now turn to diphosphines as ligands in cross-coupling catalysis. Important ligands in this area are, more or less in historic order, BINAP [152], dppf [153], Xantphos [122, 154, 155], and alkyl substituted ferrocene-derived ligands such as Josiphos [156]. Simple MO pictures [157] have been used to explain, as early as 1980, that wide bite angles stabilize the zero-valent state, whereas bite angles close to 90° will stabilize divalent square-planar complexes, although this does not give information about the kinetics of the transfer from one valence state to the other one. Furthermore, at this point, this was not related to chemical reactions, let alone catalysis. As we outlined elsewhere, there were several ligand-screening studies that involved bidentate diphosphines, which compared rates and/or selectivities in relation to the P–M–P angle as exhibited in crystal structures of those complexes and as calculated by MM2 [158]. The first report on the theme that concerns us here was by Hayashi et al. who found that in a C—C bond forming cross-coupling reaction, the selectivity to the C—C coupled product increased in going from dppm, dppe, dppp, to dppf, which parallels the bite angle of the bidentate ligands [159]. The reason for this effect was not clear in those days. We extended this range to the still wider bite angles of the Xantphos-type ligands [160]. It was found that not just the yield but also the rate went up with increasing bite angle until a maximum was reached around 111°. Wider bite angles gave lower selectivity and conversion, which was ascribed to the formation of five-coordinate intermediates that gave β-H elimination. Initially [122], we were puzzled by this capricious behavior, but when we realized that this paralleled the behavior in Pd-catalyzed hydrocyanation [161], it was concluded that in the cross-coupling reactions studied, the reductive elimination was also the rate-limiting step. The first proposal that a larger ligand bite angle enhances reductive elimination is probably the work by Yamamoto and coworkers who reported two cases of (diphosphine)Ni(Me)$_2$ in which elimination of ethane occurs 50 times faster for dppp than for dppe [162]. Brown and Guiry studied reductive elimination in dppf complexes of Pd, and when Fe in dppf was replaced by Ru (dppr), they noted a slight decrease in the stability of Me(Aryl)PdL for L = dppr, which was ascribed to a slightly larger interchelate ligand angle [163]. Factors influencing reductive elimination in square-planar nickel and palladium(II) complexes of bidentate phosphines have been discussed in several reviews [164]. Marcone and Moloy studied the reductive elimination of TMSCH$_2$CN from diphosphine Pd complexes for a wide range of diphosphines. The widest bite angle studied was that of DIOP, which was about 4 orders of magnitude faster than the slowest ligand in the series, dppe [165]. We may add to this that ligands having still wider bite angles such as DPEphos or Xantphos cannot be studied in this stoichiometric manner at room temperature or above because at room temperature, one observes even a fast catalytic reaction for these ligands and thus a stoichiometric reaction can be studied only at low temperatures, whereas the bis-hydrocarbylpalladium must be made *in situ*. The reactivity trend we see in Pd cross-coupling with the use of bidentate ligands has also been observed in totally different reactions, or might there be a relationship? For instance, the rate of the alternating polymerization of CO and ethene increases with the bite angle and the kinetics show that it is not a reductive elimination that is rate limiting [166]. It was thought that a slightly opening up of the chelate ring favored a faster migration. More interesting is the observation in polyketone catalysis that the molecular weight goes down as well with increasing bite angle or increasing steric hindrance [167]. In the limiting case of a wide bite angle, bulky diphosphine methyl propanoate is the product of the three ingredients of polyketone: ethene, methanol, and CO. This ligand is the so-called Lucite ligand as it is used in the Lucite process for methyl propanoate, an intermediate to methyl methacrylate [168]. This reaction is orders of magnitude faster than polymerization because the first insertion of ethene into palladium hydride is very fast, CO insertion is fast in all cases, and the chain termination reaction is a reductive elimination of an alkoxy and an acyl fragment, which strongly depends on the ligand character. The reductive elimination is extremely fast for ligands such as the Lucite ligand and actually a continuum is observed in the bite angle series in which the products change from polymers, to oligomers, to esters ("monomers") [64]. During the 1990s, it was thought that monodentates such as PPh_3 were typical ligands for giving esters, but the findings for the less-known (yet older) 1,3-bis(di-tbutylphosphino)propane (dtbpp) [169] and more stable catalyst based on bis(di-tbutylphosphino)-o-xylene (dtbpx) [170] (Scheme 1.52) showed that this might not be true. It had been proposed that *trans* monodentate phosphine acylpalladium complexes reacted in an outer-sphere mechanism with alcohol or alkoxy group to form the final product and that bidentates giving esters instead of polymers reacted with an "arm-off" mechanism. It was proven though that *trans* complexes did not react at all with alcohols [64, 171]. Thus, a reductive elimination reaction was proposed as the ester-forming step, with the steric and/or bite angle effect as the controlling step.



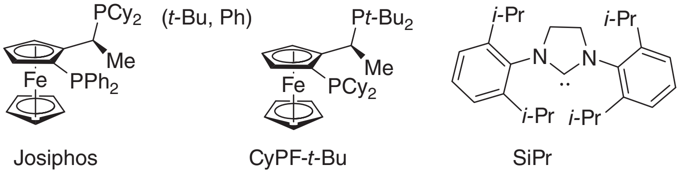
Scheme 1.52 One of the Shell ligands, dtbpp, and the Lucite ligand, dtbpx, for methyl propanoate synthesis.

Zuidema and van Leeuwen studied the ester-forming step with DFT methods, and they established that a migratory reductive elimination produced the lowest energy pathway, confirming the mechanistic proposals of the papers cited and earlier EH calculations [172].

We already mentioned the simple EH considerations that led to the relative stabilities of group 10 metal(0) and (II) complexes. We asked ourselves the question whether there is a link between reductive elimination and migratory insertion and in part the answer could have been found in a publication as early as 1991 by Calhorda et al., before the chemistry of cross-coupling and polymerization/ester formation came to bloom [173]. Calhorda analyzed the reductive elimination reaction (of sp^2 and sp^3 C—C bond formation) and came to the conclusion that it should be described as a migratory reductive elimination, as we mentioned above when discussing the monodentate Buchwald group ligands. This mechanism was particularly of importance when wider L–Pd–L bite angles could be attained during this transition, according to their calculations.

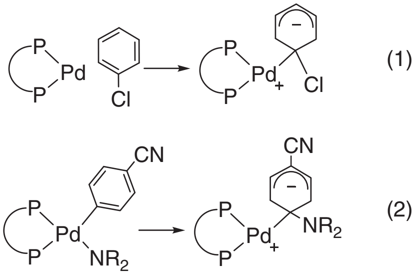
Although in the early 1990s Calhorda stressed the electronic effect of a bite angle, i.e. stabilization and destabilization of M(0) and M(II) states, it was soon clear that it is not this electronic effect that causes the fast reductive elimination in Pd carbonylation chemistry. For instance, dppp in this reaction gave one of the best polymerization catalysts for polyketone, the isopropyl derivative gives oligomer, whereas dtbpp gave methyl propionate, and yet, the bite angle is very much the same [169]. Thus, it is the steric hindrance that makes the difference, and the bite angle contributes to this as one can see from the stoichiometric reactions, already mentioned in textbooks, and thus, dtbpx with the same *t*Bu groups exerts more steric hindrance because of its wider bite angle and affords a still better ligand for making methyl propionate than dtbpp. Freixa and van Leeuwen attempted to analyze steric and electronic effects of bite angles and catalysis and concluded that hitherto steric effects dominated, although the initial inspiration for using Xantphos had been electronic in, for instance, hydrocyanation [171]. In the analysis of Birkholz et al. of "bite angle in C—N and C—C bond forming reactions," the substituents on the ligands are always phenyl groups, and thus, one can use the angles as yardstick [89]. Bickelhaupt and coworkers analyzed "electronic and steric" effects in reductive elimination of CH_3–H with relativistic DFT methods, and they underscore the importance of steric effects and not that of the bite angle *per se*, first for group 10 metals [174], but later for a very large number of catalytic systems, an interesting source for new leads [175].

Hartwig's group introduced Josiphos-type ligands in cross-coupling catalysis, for the Buchwald–Hartwig reaction, but also for other heteroatom couplings. For the analysis of ligand effects, Buchwald and Hartwig in their key contributions distinguish between the many types of reactions covered, but in this short resume, we must restrict ourselves to a brief general description of the reductive elimination, also for the Josiphos ligands. In a review in 2008, Hartwig presented four generations of ligands in C—N bond formation: monophosphines such as P(*o*-tolyl)$_3$, aromatic bidentates including BINAP and dppf, the biarylphosphines, and the return of the Josiphos ligands [176]. The latter ligands have a C3 bridge between the phosphine moieties that usually contain bulky *t*Bu and/or Cy groups, and their capacity to facilitate fast coupling reactions was ascribed to their steric bulk. Several niches for which the Josiphos ligands are important were reported. For instance, in a comparison of CyPF-*t*Bu, XPhos, and SIPr (see Scheme 1.53) for the reaction of chlorobenzenes and octylamine, CyPF-*t*Bu was by far the most selective and active catalyst. XPhos gave substantial amounts of bisarylation [156]. Likewise, excellent results were achieved for coupling of aryl bromides with ammonia and thiols.



Scheme 1.53 Ligands studied by Hartwig et al.

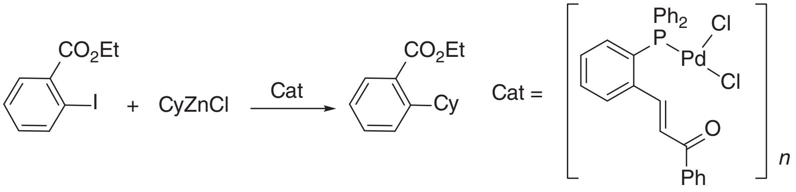
As concerns the electronic effects on the "migratory" reductive elimination, an interesting mechanism for the oxidative addition of chlorobenzene to M(0) group 10 metals was published by Fitton and Rick (Scheme 1.54, 1) [177]. A donation of electrons takes place from Pd(0) to chlorobenzene, which forms a so-called Meisenheimer intermediate, thus stabilizing the negative charge on the aryl group and finally breaking the C—Cl bond and forming the Pd—Cl bond.



Scheme 1.54 Meisenheimer intermediates in migratory reductive elimination.

Hartwig and coworkers considered the reverse reaction (Scheme 1.54, 2) for the reductive elimination, and furthermore, they showed that the substituent effects could be nicely explained by this mechanism; electron-withdrawing *Z* groups stabilize the Meisenheimer intermediate and a stronger donor on the amine will also accelerate the reaction [147a, 178].

Reductive elimination has been often accelerated by additives to the reaction mixture; one such additive is electron-withdrawing alkene. Lei and coworkers designed a monophosphine ligand that contains such an alkene as an additional donor in the molecule (Scheme 1.55) [179]. This ligand showed extremely fast cross-coupling rates for C—C bond formation in a Negishi-type reaction. The halide is a reactive iodide, and thus, the ligand can be a triaryl phosphine, but the carbon atoms are a combination of sp^3 and sp^2 C-atom, which normally do not show such a fast coupling reaction. The kinetics were studied by Lei and coworkers, and it was shown that the reaction itself was even faster, as 80% of the reaction time was needed for, as yet not understood, incubation [180]. Fairlamb published a review on alkene-enhanced reductive eliminations [181].



Scheme 1.55 Phosphino–alkene ligand enhancing reductive elimination.

Thus, there is certainly still more to discover in this field, and in spite of the successes of the bulky monodentate ligands that give such reactive catalysts, bidentate phosphines have maintained their niches in selected applications such as we mentioned for the alkyl Josiphos ligands. Even Xantphos remains unique for certain reactions, such as the carbonylative couplings with CO that seem to prefer Xantphos to other ligands [182].

1.6 Decomposition Reactions

An important practical aspect of the application of phosphorus ligands in catalysis is their stability under the reaction conditions. For catalysis, the theme is broader, as we are interested in the stability of the catalyst, but here, we confine ourselves to the decomposition reactions of the ligands. The discussion will be limited to phosphines and phosphites, although there are several more P-centered ligands as the present work shows. For a monograph on catalyst decomposition, see van Leeuwen and Chadwick, and for a recent review, see Crabtree [183, 184]. Both works contain parts on phosphorus ligand decomposition.

1.6.1 Phosphine Decomposition

1.6.1.1 Phosphine Oxidation

Before addressing P–C cleavage reactions, a few paragraphs will be devoted to other mechanisms of phosphine decomposition as there is oxidation. In the solid state, arylphosphines (unless abundantly substituted with donor groups, such as 2,4,6-trimethoxyphenyl) are not very sensitive to aerial oxidation. In solution though, they are more sensitive. In hydroformylation, the preferred ligands usually carry aryl groups, and thus, they are not very sensitive to oxidation by air. The key problem is the presence of hydroperoxides in the alkenes as allylic oxidation of alkenes rapidly takes place in air. The hydroperoxides are capable of oxidizing phosphines. As they are used in high molar quantities compared to phosphine ligands, this is a common source of failures in hydroformylation, or other alkene reactions. An “open” bottle of alkene oxidizes rather rapidly in air. Percolation of the alkene over neutral alumina suffices to remove the hydroperoxides. Alkylphosphines are very prone to oxidation by air, such as the favored ligands for aryl chloride cross-coupling reactions discussed above. Many attempts in the past decade were directed toward the use of aryl chlorides in cross-coupling chemistry with the aid of alkylphosphines, with ample success.

The high sensitivity to air of $t\mathrm{Bu}_3\mathrm{P}$ can be overcome by the protocol of Fu [185] by adding the ligand to the reaction mixture as a phosphonium salt (e.g. with BF_4^- as the counterion), which can be handled in air. The proton is removed by a base, needed anyway for the reaction, which liberates free phosphine, once the system is brought under an inert gas.

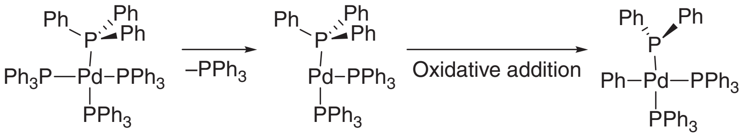
In spite of the presence of two strongly donating Cy or *t*-Bu groups, the Buchwald ligands are highly resistant to oxidation by molecular oxygen. Barder and Buchwald studied this accidentally found phenomenon in detail [186], and it turned out that in the preferred conformation of the ligand the lone pair points to the 2,6-substituted second aryl ring, which inhibits the approach of a second phosphine to a $\mathrm{R}_3\mathrm{P}^{\cdot}\cdots\mathrm{O{-}O}^{\cdot}$ phosphine–dioxygen intermediate. The

2,6-substitution plays an important role in this as unsubstituted biphenylphosphines are oxidized at least 10 times faster than the isopropyl-substituted XPhos.

Several other oxygen-containing reagents can oxidize phosphines aided by Pd complexes as the catalyst. Even water can oxidize a phosphine, producing phosphine oxide and hydrogen, which is often observed in the aqueous workup of the reaction mixture [187]. Several hard bases such as acetate and hydroxy groups can oxidize phosphines, as were found for BINAP in the presence of Pd. [188]

1.6.1.2 P–C Cleavage of Ligands

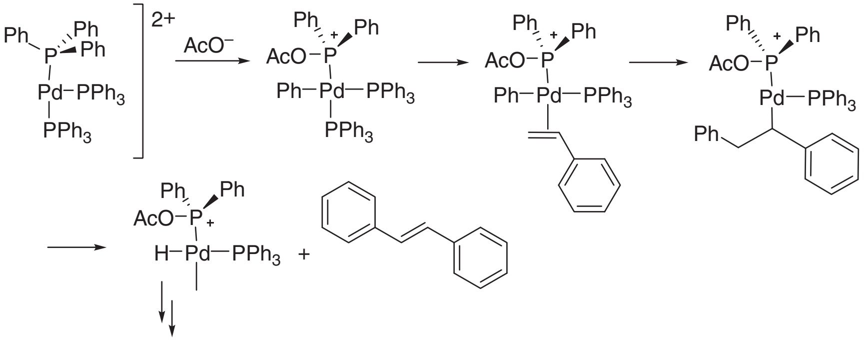
The reductive cleavage of P—C bonds with sodium at low temperatures was already used as a step in phosphine synthesis in the 1960s. Phosphine decomposition via reductive cleavage on a transition metal (Rh, Co) was reported in the early 1970s, although mechanistically, this reaction will not always be a P–C cleavage by a low-valent metal (or oxidative addition to a metal) as was shown in the first discovered examples. Replacement of Ph groups in PPh_3 by MeO, certainly not a cleavage reaction similar to that of sodium, can be carried out catalytically with high TOFs with Rh as the catalyst [189]. Aryl exchange from phosphorus to Pd, and from there into the product, was observed in the 1970s by several groups [190]. For instance, in an attempted Heck–Mizoroki reaction of 2-chlorophenol and ethyl acrylate with $Pd(PPh_3)_4$ as the catalyst at 150 °C, only ethyl cinnamate was obtained as the product in low yield and chlorophenol was completely recovered. An excess of PPh_3 prevented the reaction. The mechanism proposed was a reversible oxidative addition of arylphosphines to palladium [191], which explains the retarding effect of the excess ligand as there is no vacancy at the metal (Scheme 1.56).



Scheme 1.56 Oxidative addition of arylphosphines after creating a vacancy.

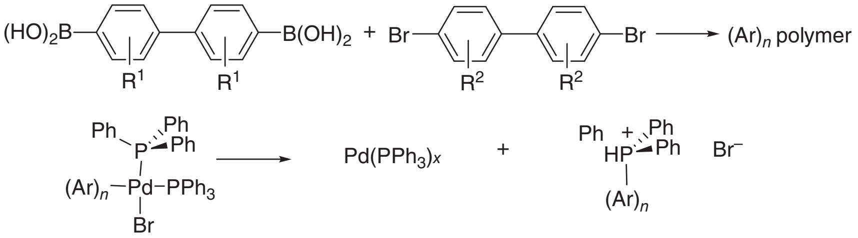
As early as 1972, Matsuda and coworkers used PPh_3 as the source of the aryl group, in which one might call a Heck–Mizoroki reaction, the arylation of alkenes (styrene, acrylates, 1-octene, and cyclohexene) with the use of stoichiometric amounts of $Pd(OAc)_2$ and PPh_3 in AcOH as the solvent at 50 °C. As a mechanism, they proposed a nucleophilic attack by, e.g. acetate at the coordinated P-atom, with simultaneous migration of phenyl to Pd. The phosphorus by-products were $PhP(O)(OH)_2$ and $Ph_2P(O)OH$, but Ph_3PO was also observed, resulting from a nonproductive oxidation (Scheme 1.57) [192].

In catalytic reactions concerning low-molecular-weight products, a small amount of aryl exchange between phosphine and substrate may not be important, but a polymer synthesis that uses the Suzuki–Miyaura cross-coupling, for instance, may mean that each polymer molecule contains an aryl end group stemming from the catalyst, or each chain may be terminated by a phosphine



Scheme 1.57 Heck reaction with PPh_3 as the aryl donor.

(or phosphonium) endcap, as was discovered by Novak and coworkers [193]. A marked inhibition in the presence of excess phosphine and/or excess iodide was observed, suggesting that a dissociative pathway was involved. The equilibrium between saturated and unsaturated metal can be displaced to the former by adding more phosphine, but this could not be applied because this led to the formation of phosphonium salts as another deactivation route (see Scheme 1.58).

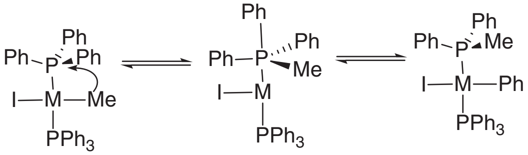


Scheme 1.58 Polymer end-capping by phosphonium salts.

The interchange reaction proceeded via the reductive elimination to form the phosphonium salt and oxidative addition again of a different P—C bond, suggesting that excess phosphine was acting as a trap for intermediate palladium(0) species, preventing the generation of the interchanged palladium-(II) complex.

Grushin studied thermal stability and reactivity toward the Pd–Ph/P–Ph exchange reactions in all halide complexes of the type $(Ph_3P)_2Pd(Ph)X$ [194]. Iodides provide by far the most labile P—C bonds. Kinetic studies of the aryl–aryl exchange reactions of $(Ph_3P)_2Pd(C_6D_5)X$ demonstrated that the rate of exchange decreases in the order I > Br > Cl (100 : 4 : 1).

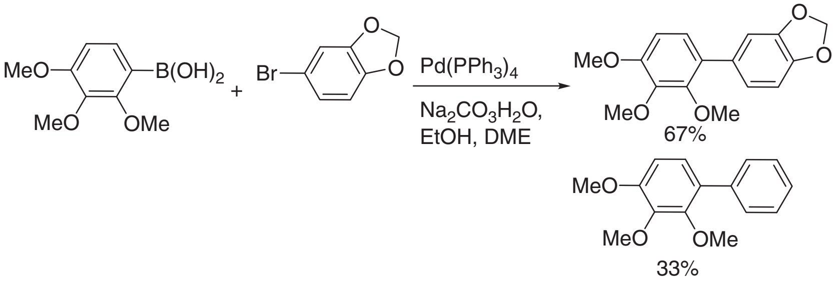
Alkyl/aryl exchange between Pd and P does not involve phosphonium salts as was proven by Norton and coworkers [195]. They found that the methyl ligand of *trans*-$CH_3Pd(PPh_3)_2I$ exchanged with a phenyl group of PPh_3 to give $PhPd(PPh_3)(PMePh_2)I$. The $PMePh_2$ formed exchanged with the PPh_3 of the starting material. The rearrangement is irreversible, does not involve a free phosphonium cation, and does not require phosphine dissociation. Such a rearrangement may involve metallophosphorane formation as shown in Scheme 1.59.



Scheme 1.59 Alkyl/aryl exchange at Pd/P under mild conditions.

Aryl exchange followed by catalyst decomposition that limited the TON of Suzuki–Miyaura and Heck–Mizoroki reactions led to the development of the *o*-tolylphosphine cyclometallated catalysts by Herrmann et al. [141]. For example, it was reported that P—C bond cleavage played an important role in the deactivation of the arylation of *n*-butyl acrylate [196, 197]. The temperatures needed were rather high, >120 °C, for both chlorides and bromides. When PPh_3 was used as the ligand and electron-rich 4-bromoanisole as the substrate, considerable amounts of butyl cinnamate were found (i.e. the aromatic group stems from the ligand used). For *o*-tolylphosphine, this was not the case.

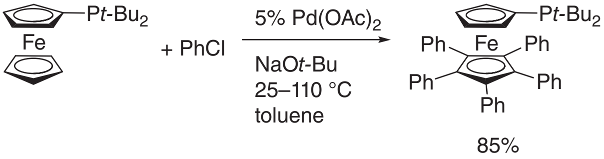
In a Suzuki–Miyaura reaction (Scheme 1.60), Marcuccio and coworkers noted that a biphenyl derivative was formed up to 33% as a by-product with the phenyl groups originating from PPh_3 and large quantities of PPh_3 could be converted this way [198]. In their attempts to find triarylphosphines that would give less phosphine aryl incorporation, they noted that tris(2-MeO-phenyl)phosphine gave the best results with only 3% of anisole-derived by-product. Addition of extra phosphine reduced by-product formation, as reported by Kong and Cheng [199], but it was not useful as the reaction was very slow under these conditions.



Scheme 1.60 Incorporation of phenyl groups of PPh_3 in the product.

A convenient test reaction for an asymmetric Heck–Mizoroki reaction is the addition of 1,2-dihydrofuran and phenylboronic acid with BINAP/Pd as the catalyst. When this was carried out in the present case, the formation of PPh_3 was observed. This takes place via P–C cleavage at the binaphthyl moiety as an oxidative addition to Pd(0) and reductive elimination of PPh_3 [200].

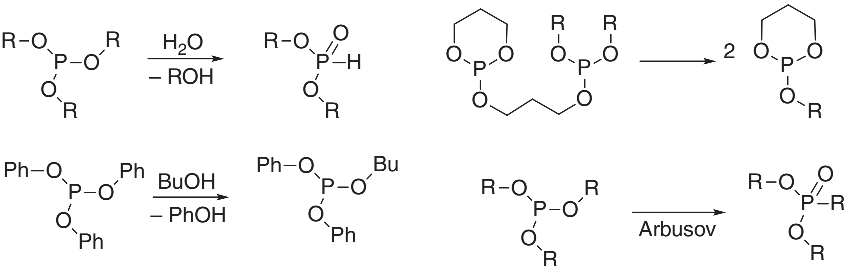
An extraordinary example of ligand participation as a reactant was reported by Hartwig and coworkers for the monodentate ligand *t*Bu_2PFc (Fc = ferrocene) used in Pd-catalyzed cross-coupling of aryl halides and aryloxides [201]. During the reaction, arylation of the unsubstituted Cp-ring took place, and surprisingly, the resulting arylated ligand appeared to be more active as a catalyst. Independent synthesis afforded $Ph_5FcPtBu_2$ containing a pentaphenylated cyclopentadienyl ring (Scheme 1.61), which indeed gave a fast catalyst for C—O bond formation.



Scheme 1.61 Formation of $Ph_5FcPt\text{-}Bu_2$ (Q-Phos) via phenylation with PhCl.

1.6.2 Phosphite Decomposition

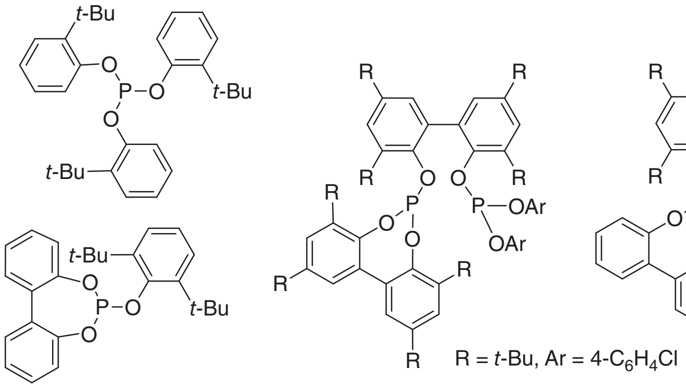
Phosphites are easier to synthesize and less prone to oxidation than phosphines. They are much cheaper than most phosphines, and a wide variety of structures can be obtained commercially. They find broad usage as antioxidants (for instance in polypropene) and flame-retarding agents. Disadvantages of the use of phosphites as ligands include several side reactions: hydrolysis, alcoholysis, transesterification, Arbuzov rearrangement, O—C bond cleavage, and P—O bond cleavage. Scheme 1.62 gives an overview of these reactions. In hydroformylation systems, at least two more reactions may occur, namely nucleophilic attack to aldehydes and oxidative cyclizations with aldehydes. Phosphines and phosphites can react with substrates such as acrylates; they can add to the acrylate and catalyze dimerization. Acrylate is the product of methoxycarbonylation of propyne, but in this case, the ligand is a bidentate diphosphine and dissociation is less likely. Enones may behave similarly, but there are very few if any reports on such side reactions. Lewis acids catalyze the Arbuzov reaction of alkyl phosphites at room temperature [202].



Scheme 1.62 Various decomposition pathways for phosphite ligands.

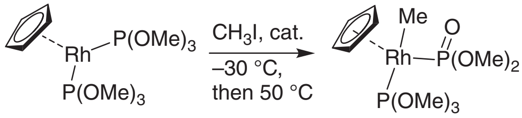
Phosphites are the preferred ligands for the nickel-catalyzed hydrocyanation of butadiene to make adiponitrile [203]. Ligand decomposition studies for this system are lacking in the literature.

Phosphites have been extensively studied for their use as ligands in rhodium-catalyzed hydroformylation. The first publication on the use of phosphites is from Pruett and Smith, from Union Carbide [113]. The first exploitation of bulky monophosphites was reported by van Leeuwen and Roobeek [148]. Diphosphites came into focus after the discovery of Bryant and coworkers at Union Carbide Corporation that certain bulky diphosphites lead to high selectivities in the rhodium-catalyzed hydroformylation of terminal and internal alkenes (see Scheme 1.63) [204].



Scheme 1.63 Typical bulky monophosphites and diphosphites.

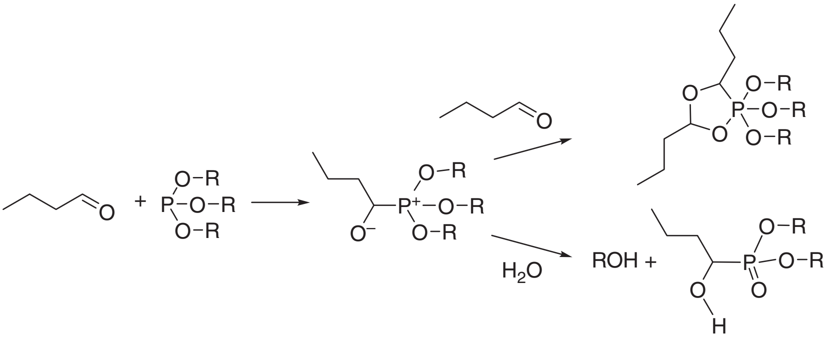
It should be noted that all phosphites reported are *aryl* phosphites (sometimes, the backbones may be aliphatic) and that the favored ones often contain bulky substituents. One of the reasons that aliphatic phosphites are used only sparingly is that they are susceptible to the Arbuzov rearrangement while the aryl phosphites are not. Acids, carbenium ions, and metals catalyze the Arbuzov rearrangement. Many examples of metal-catalyzed decomposition reactions have been reported (see Scheme 1.64) [205].



Scheme 1.64 Metal-catalyzed Arbuzov reaction leading to phosphite decomposition.

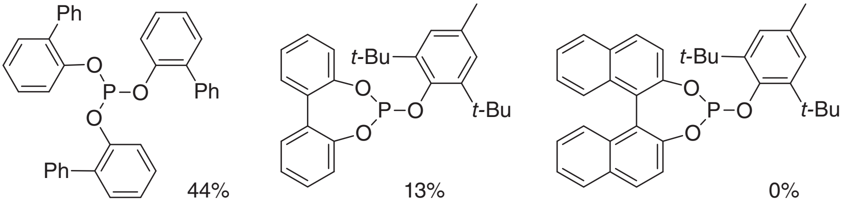
Thorough exclusion of moisture can easily prevent hydrolysis of phosphites in batch operation in the laboratory. In a continuous operation under severe conditions, traces of water may form via aldol condensation of the aldehyde product. Weak and strong acids and strong bases catalyze the reaction. The hydrolysis products are acidic and catalyze further hydrolysis. The reactivity for individual phosphites spans many orders of magnitude. When purifying phosphites over silica columns in the laboratory, one usually adds some triethylamine to avoid hydrolysis on the column.

Bryant and coworkers have extensively studied decomposition of phosphites [206]. Stability involves thermal stability, hydrolysis, alcoholysis, and stability toward aldehydes. The precise structure has an enormous influence on the stability. Surprisingly, it is the reactivity toward aldehydes that received most attention. Older literature mentions [207] several reactions between phosphites and aldehydes of which we show only two in Scheme 1.65.



Scheme 1.65 Reactions of phosphites and aldehydes.

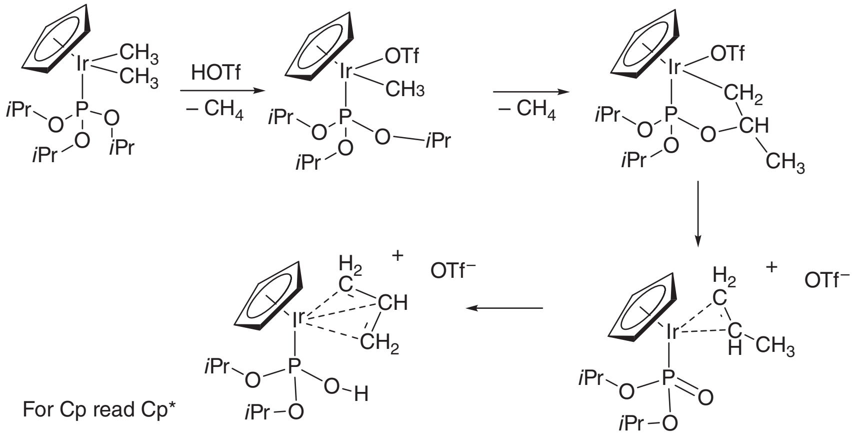
The addition of a phosphite to an aldehyde giving a phosphonate is the most important reaction [206]. The reaction is catalyzed by acid, and because the product is acidic, the reaction is autocatalytic, similar to hydrolysis. The remedy proposed is continuous removal of the phosphonate over a basic resin (Amberlyst A-21). The examples in the patents illustrate that very stable systems can be obtained when the acidic decomposition products are continuously removed. The thermal decomposition of phosphites with aldehydes is illustrated in Scheme 1.66.



Scheme 1.66 Reactivity of various phosphites toward C5-aldehyde [206]. Percentage decomposition after 23 h at 160 °C.

The role of the bulky substituents is multifold. In monophosphites, it prevents the formation of bis-ligand complexes as proposed by Roobeek and van Leeuwen [148], and van Rooy et al. [208]; for the correct and detailed spectroscopic data for the mono and bis-ligand rhodium complexes, see Crous et al. [209].

A decomposition reaction that looks like an Arbuzov reaction but actually is not was reported by Simpson [210]. The decomposition of an iridium triisopropyl phosphite complex involves a metalation of one of the propyl groups before an apparent Arbuzov reaction takes place. It is an instructive example of the complexity of the decomposition pathways that may occur (Scheme 1.67). The final complex contains a π-allyl group and a diisopropyl phosphite ligand.



Scheme 1.67 Phosphite metalation followed by Arbuzov-like reaction.

Dealkylation of trimethyl phosphite in the complexes of ruthenium is an acid-catalyzed reaction; the resulting phosphite is MeOP(OH)$_2$ [211].

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