TUTORIAL REVIEW

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Palladium catalyzed cross-coupling reactions for phosphorus–carbon bond formation

Adrian L. Schwan
Dept. of Chemistry and Biochemistry, University of Guelph, Guelph, Ontario, Canada N1G 2W1

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Underappreciated in the realm of palladium catalyzed cross-coupling chemistry is the formation of phosphorous–carbon bonds. This *tutorial review* summarises a collection of important contributions in the area, providing a flavour of the many types of phosphorus species that are participants in palladium catalyzed phosphorus–carbon bond formation. Recent developments include the usage of the cross-coupling reaction for preparation of phosphine ligands and the involvement of low molecular weight phosphinic acid derivatives for the synthesis of unsaturated phosphinic and phosphonic acid derivatives. Mechanistic cycles are offered in some instances. Stereochemical issues are addressed where applicable. The literature is covered to mid 2003.

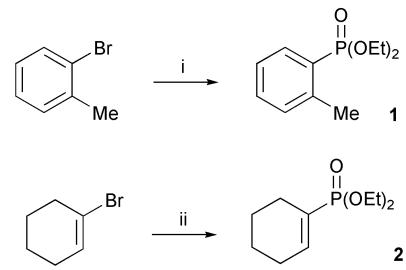
1 Introduction and early chemistry

The use of organometallic catalysis for the execution of bond forming reactions in chemistry has revolutionised organic synthesis. Palladium has proved to be a popular and reliable metal, facilitating carbon–carbon bond formation through a variety of cross-coupling reactions.[1] More recently, palladium has demonstrated its breadth and utility for the creation of heteroatom–carbon bonds.[2]

Hidden in the shadow of nitrogen–carbon and oxygen–carbon bond forming reactions are palladium-mediated reactions targeting phosphorus–carbon bond formation. As a result, these cross-couplings have not received the widespread attention afforded those reactions that target amines and ethers. However in an ironic twist, palladium catalyzed P–C bond forming reactions, among a number of applications, have found a niche for the preparation of phosphine ligands for palladium species. These ligands may in turn serve as catalysts for the creation of the more ubiquitous C–O, C–N, C–C and C–H bonds.

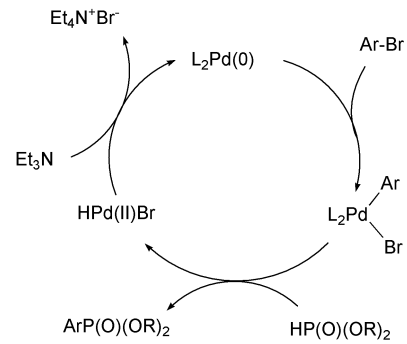
This review is intended to offer an overview of the palladium catalyzed synthesis of phosphines, phosphine oxides and phosphorus acid derivatives. The overall protocol serves as a modern alternative to radical methods, anionic chemistry and thermal methods such as the Arbuzov reaction.[3] Some of this chemistry is addressed in an earlier review by Beletskaya and Kazankova.[4] The current review focuses on, but is not limited to, aspects of reaction mechanism, recent applications of the chemistry and important new stereochemical advancements.

Pioneering work in the area appears to have been performed by the Hirao group[5] who reported the palladium catalyzed couplings of aryl and vinyl bromides with dialkyl phosphites, affording dialkyl arylphosphonates (*e.g.*, **1**) and dialkyl vinylphosphonates (*e.g.*, **2**), respectively. For those early experiments, the preferred reagents were $Pd(PPh_3)_4$ (4.5%) and Et_3N either neat or in toluene. During the formation of vinylphosphonates, the geometry of the double bond was maintained. The equations of Scheme 1 outline two examples of the reaction.[5]



Scheme 1 i) 1.1 equiv. $HP(O)(OEt)_2$, 5% $Pd(PPh_3)_4$, Et_3N, toluene, 30 h, 91%; ii) 1.1 equiv. $HP(O)(OEt)_2$, 5% $Pd(PPh_3)_4$, Et_3N, neat, 9 h, 69%.

The mechanism provided by the Hirao group at the time invokes oxidative addition of the Pd(0) into the aryl bromide bond (Scheme 2). Attack of the phosphite creates the product, while Et_3N liberates



Scheme 2

the Pd(0) from HPd(II)Br. The Pd(0) is then ready to commence the cycle again. It is unlikely that significant amounts of $(EtO)_2PO^-Et_3NH^+$ are present in the reaction mixture, even though

Adrian Schwan obtained a BSc from the University of Western Ontario in 1983. He obtained a PhD at McMaster University, studying the chemistry of nitrogen ylides and zwitterions under the supervision of John Warkentin (1988). After a postdoctoral term in organosulfur chemistry at the University of New York at Albany with Eric Block, Dr. Schwan was appointed as Assistant Professor at the University of Guelph. His contributions have predominantly been in the field of organic sulfur chemistry, with a focus on sulfenate anions and α,β-unsaturated sulfinic acid derivatives. More recent studies are in the areas of heterocycle synthesis and novel phospholipids for lung surfactant therapy. Now a Professor, Dr. Schwan is currently the Editor of the Journal of Sulfur Chemistry, is the Director of the Guelph-Waterloo Centre for Graduate Work in Chemistry and Biochemistry (GWC)² and has a burgeoning interest in organophosphorus chemistry.

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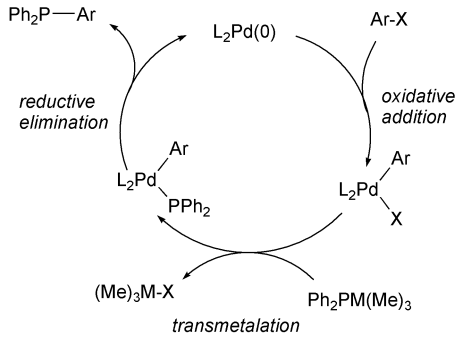
it was experimentally determined that diethyl sodiophosphonate ($(EtO)_2PO^-Na^+$) could also participate in the cross-coupling chemistry, albeit in lower yield.

Tunney and Stille described the first direct phosphine synthesis using palladium catalyzed carbon–phosphorus bond formation.[6] Those researchers showed that a wide array of iodoaryl compounds could undergo cross-coupling reactions with (trimethylsilyl)diphenylphosphines and (trimethylstannyl)diphenylphosphines in good to excellent yields.

The mechanism offered by Stille is comparable to the Hirao catalytic cycle, notwithstanding the chemical differences, but is more advanced due to increased recognition of probable intermediates in palladium chemistry. Scheme 3 outlines the common steps of oxidative addition, transmetalation and reductive elimination.[6]



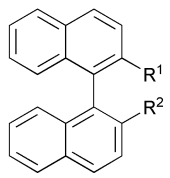
Scheme 3 M = Si, Sn.

Although modern methods have rendered the Stille protocol somewhat obsolete, it was nevertheless a contribution that prompted significant follow-up work in the area. The remainder of this review outlines the prominent methods for palladium catalyzed P–C bond forming reactions and is organised primarily by the identity of the phosphorus containing product.

2 Phosphine formation

2.1 Phosphine synthesis from phosphine oxides and lower phosphines

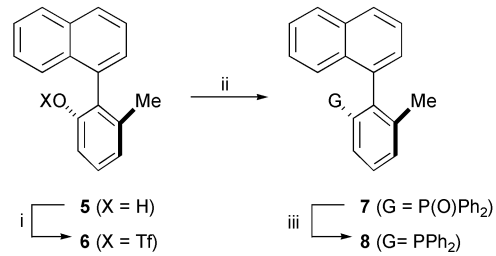
Notwithstanding phosphorus acid derivatives which are addressed later, the ability to convert aromatic alcohols into phosphorus species, primarily for the construction of (chiral) phosphine ligands, has created a valuable application of palladium catalyzed P–C bond forming reactions. Specifically, the Morgans palladium mediated phosphorylation of aryl triflates has been exploited by a number of researchers for the preparation of chiral phosphines.[7] Morgans and co-workers found that 3–4 equiv. of a phosphorylating agent such as diphenylphosphine oxide and 6 equiv. of EtN(*i*-Pr)$_2$ combined with the catalyst system of Pd(OAc)$_2$ (0.1 equiv.)/1,3-bis(diphenylphosphino)propane (dppp, 0.1 equiv.)/HCOONa (0.22 equiv.) proved suitable for the *stereospecific* conversion of (−)-BINOL ditriflate to its *mono*phosphorylated derivative in *ca*. 70% yield (Scheme 4).[7] Triflate **4** can be converted back to the alcohol through facile hydrolysis.



(-)-3 (R^1, R^2 = OTf) —i→ **(+)-4** (R^1 = OTf, R^2 = $P(O)Ph_2$)

Scheme 4 i) 3–4 equiv. HP(O)Ph$_2$, 6 equiv. EtN(*i*Pr)$_2$, 10% Pd(OAc)$_2$, 10% dppp, 22% HCOONa, DMSO, 90 °C, 16 h, 77%.

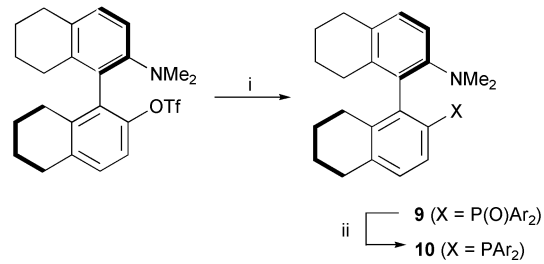
The Morgans procedure, when accompanied by a phosphorus deoxygenation step has proved exceedingly useful for the preparation of triarylphosphines. Thus phosphine **8** was prepared through the triflation, phosphinylation/reduction sequence indicated in Scheme 5.[8] The reducing silane $HSiCl_3$ is the reagent of choice and



Scheme 5 i) Tf_2O, DABCO, CH_2Cl_2, 0 °C, 94%; ii) 2 equiv. HP(O)Ph$_2$, 5 equiv. EtN(*i*Pr)$_2$, 5% Pd(OAc)$_2$, 5% dppb, DMSO, 100 °C, 6 h, 86%; iii) 5 equiv. $HSiCl_3$, 2 equiv. Et_3N, xylene, 120 °C, 24 h, 98%.

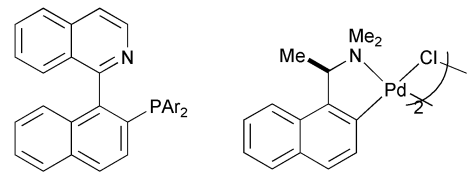
is usually combined with triethylamine to give the deoxygenated product in good to excellent yields,[8,9] although lower yields have been occasionally observed.[10,11] Phosphine **8** was evaluated for its usefulness in the Pd-catalyzed hydrosilylation of styrenes.[8] Hayashi employed synthetic chemistry analogous to that of Scheme 5, with comparable efficiency, for the preparation of 2-diarylphosphino-1,1′-binaphthyls, which were also employed as chiral ligands for the hydrosilylation of styrenes.[9]

A family of *P*,*N*-ligands were prepared using the same palladium mediated phosphinylation protocol. Deoxygenation of the phosphorus with the alternative reductant system of $CeCl_3$–LAH finalised the synthesis of ligands **10** (Scheme 6) which were used to assist the palladium catalyzed asymmetric malonation of racemic 1,3-diphenylprop-2-en-1-yl acetate.[12]



Scheme 6 i) 2 equiv. HP(O)Ph$_2$, 5 equiv. EtN(*i*Pr)$_2$, 10% Pd(OAc)$_2$, 15% dppp, DMSO, 100 °C, 16 h, 54–94%; ii) 3 equiv. dry $CeCl_3$, 4 equiv LAH, THF, 40 °C, THF, 73–93%. Ar = C_6H_5, 4-MeC_6H_4, 3-MeC_6H_4, 4-$MeOC_6H_4$, 4-*t*-BuC_6H_4, 3,5-$(Me)_2C_6H_3$.

When *P*,*N*-ligands of the type **11** are generated in a racemic form through a phosphinylation/reduction protocol, they can be co-complexed with di-μ-chloro-bis[(*R*)-dimethyl(1-phenethyl)aminato-C^2,N]dipalladium (**12**) to form diastereomeric complexes. Fractional crystallisation offers a tool for resolution of the ligands.[10] The double phosphorylation/reduction of a bis(triflate) possessing the 1,1-binaphthyl backbone has also been realised.[11]

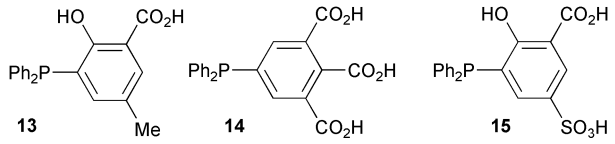


11 **12**

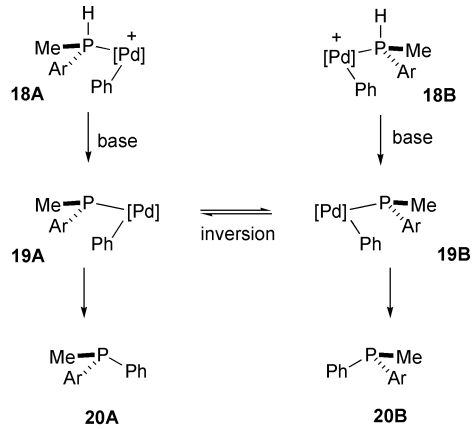
There are numerous examples of palladium catalysis chemistry that by-pass the phosphorylation/reduction requirements and offer direct formation of phosphines. Secondary and primary phosphines can act as starting phosphorus containing entities although there are fewer specific ligand syntheses. However, a noteworthy contribution outlines the preparation of a large number of highly substituted triarylphosphines, some possessing water solubility.[13] Several

phosphines including **13** were prepared by treating iodoaromatic compounds with Ph_2PH/Et_3N and only 0.1% $Pd(OAc)_2$ in refluxing MeCN. For more water soluble phosphines such as **14** and **15**, Bu_3N was employed as the base and DMA was the solvent. Also presented in this paper, some primary phosphines were successfully subjected to consecutive Pd-catalyzed P–C bond forming arylations.[13] That particular chemistry presents a synthetic route to triarylphosphines with three different aryl groups, by subjecting phenylphosphine, for instance, to consecutive phosphorus arylations with two different iodoaromatic compounds.

A wonderful example of dynamic kinetic resolution has been established through the Pd-catalyzed functionalisation of a secondary phosphine. Specifically, racemic 2,4,6-(tri-isopropyl)phenylmethylphosphine (**16**) can be enantioselectively arylated when chiral catalyst **17**, a species derived from (*R*,*R*)-Me-DuPhos, is employed.[14]

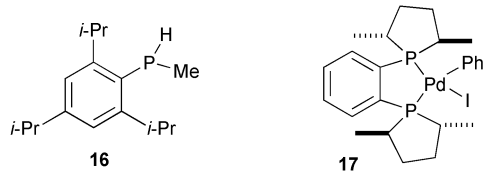


Under a particular set of conditions, *P*-chiral phosphine **20** (Scheme 7) possessing an ee of 78% was obtained in a chemical



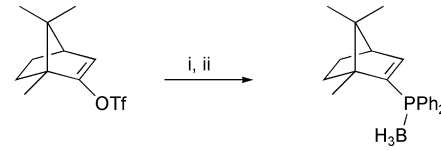
Scheme 7 [Pd] = **17** w/o PhI; Ar = 2,4,6-tri-isopropylphenyl.

yield of 84%. This result was achieved by exposing **16** to 5% **17**, NaOTMS as base and 2 equiv. phenyl iodide in toluene. Comparable results were obtained on scale-up (500 mg) of **16**, even though catalyst loading could be reduced to 2.5%.[14]



Careful mechanistic work was performed in order to establish the origin of the stereoselectivity. The authors were able to narrow the focus to the mechanistic steps indicated in Scheme 7. Given the conversion of **18** to products **20** the stereoselectivity would be controlled either by rapid interconversion of isomers **19** and differing rates of reductive elimination or by comparable rates of reductive elimination and uneven populations of **19A** and **19B**. In further experiments, whereby a known ratio of cationic diastereomers **18** (*ca.* 1::1) were deprotonated the authors obtained enantiomers **20** in a ratio of 6:1 allowing the conclusion that the inversion between diastereomers **19** is faster than or comparable to the rate of reductive elimination.[14]

Other examples of secondary phosphine functionalisation include the preparation of a polymeric phosphine ligand[15] and the conversion of vinyl triflates to vinylphosphines.[16] Although the vinylphosphines created by this protocol are quite pure, complete characterisation was achieved through conversion to the more stable borane complex (Scheme 8).[16] The double bond of the

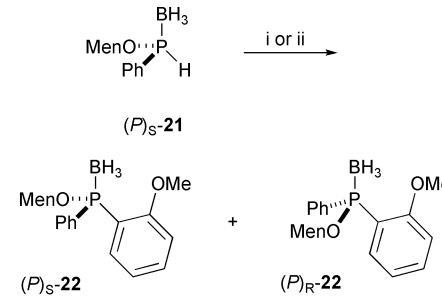


Scheme 8 i) Ph_2PH, $EtN(iPr)_2$, 5% $Pd(OAc)_2$, dppb, 40 °C. ii) BH_3-SMe_2, 84% (2 steps).

product is also readily reduced, offering a preparation of protected alkyldiarylphosphines. The palladium mediated P–C bond formation can also be prompted by microwave dielectric heating.[17] In this latter case, nickel catalysts are also suitable. In general, a number of nickel mediated P–C bond-forming reactions have been reported, many with applications to the synthesis of chiral phosphine ligands.[17–22] Noteworthy is the fact that direct use of Ph_2PH/$NiCl_2$dppe/DMF/DABCO, as first introduced by Cai,[19,20] though requiring harsher conditions, can also be more efficient than the palladium catalyzed phosphinylation/deoxygenation protocol exemplified in Schemes 5 and 6.[22]

2.2 Phosphine-borane cross coupling chemistry

To circumvent the difficulties associated with handling some phosphines, the palladium mediated P–C bond forming reaction has been extended to include phosphine-boranes. The approach was introduced by Oshiki and Imamoto[23] who showed that $(S)_P$- and $(R)_P$-menthyloxyphenylphosphine-boranes (**21**) could undergo Pd-catalyzed P–C bond formation with *o*-iodoanisole with either retention or inversion of phosphorus configuration, depending on the reaction conditions. Using 5% $Pd(PPh_3)_4$ and K_2CO_3, the two configurations could be obtained simply by utilizing either MeCN or THF (Scheme 9). Whereas retention of phosphorus stereochemistry is commonplace, the recovery of the inverted product was remarkable.

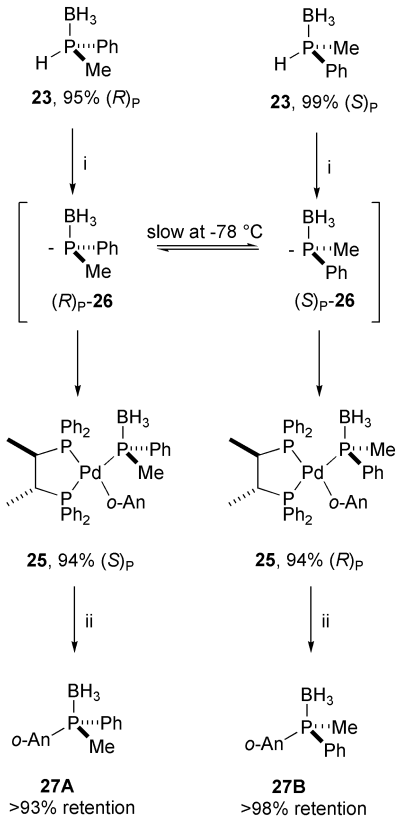


Scheme 9 i) 2 equiv. *o*-iodoanisole, 5% $Pd(PPh_3)_4$, 2 equiv. K_2CO_3, MeCN, 50 °C, 16 h, 96%, $(P)_S$-**22**:$(P)_R$-**22** = 100:0; ii) same as in i) but in THF, 50 °C, 48 h, 76%,$(P)_S$-**22**:$(P)_R$-**22** = 4:96.

The chiral menthyloxy(*o*-iodophenyl)phenylphosphine-boranes (**22**) obtained could be subsequently converted to secondary and tertiary phosphine-boranes and to optically pure C_2-symmetric biphosphine-boranes. Comparable cross-couplings were attempted with (*S*)-methylphenylphosphine-borane and although retention of configuration occurred as expected, the solvent driven inversion proceeded with reduced stereospecificity, despite variations of the reaction conditions.[23]

More recently, intermediates related to the chemistry of **21** have come under scrutiny.[24,25] An intermediate involved in the cross coupling chemistry was isolated in 1999[25] and although valuable steps of the reaction mechanism were established, stereochemical issues remained. Specifically, the reductive elimination step of many heteroatom–carbon bond forming cross-coupling reactions, including P–C bond formation, had always been surmised to

proceed with retention of configuration, direct evidence now exists. As a model for several related palladium intermediates including those involved in the conversion of **21** to **22**, diastereomeric palladium complexes **25** were synthesised by the treatment of racemic PH(Me)(Ph)(BH_3) (**23**) with (*o*-An)(I)Pd(S,S)-Chiraphos (**24**). Each resulting diastereomer (**25**) was purified and fully characterised.[24] Alternatively, isomers **25** were prepared individually in enriched form by treatment of enantioenriched phosphine boranes **23** with NaOTMS and **24** as shown in Scheme 10. If that transmetalation is performed at −78 °C, it proceeds with



Scheme 10 [Pd] = Pd(S,S)-Chiraphos i) NaOTMS, −78 °C, [Pd](*o*-An)(I) (**24**), THF; ii) D, PhC≡CPh (the conversion to **27B** was performed with 88 & 100% enriched (*R*)$_P$-**25**).

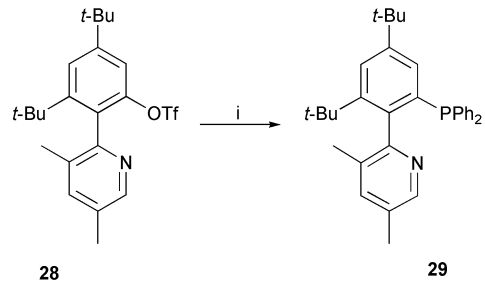
very high stereospecificity, since interconversion of anionic stereoisomers **26** is not significant. Those particular conditions are vital to the stereospecific transmetalation since different bases and(or) higher temperatures lead to interconversion of the deprotonated forms **26**.[24]

When diastereomers **25** were individually heated at 50 °C in the presence of 4 equiv. of phenyl acetylene, reductive elimination occurred to give phosphine-boranes **27**. Although complexes **25** succumbed to reductive elimination at different rates, the important issue is that during formation of **27**, there was > 93% retention of configuration (Scheme 10).[24] Products **27** represent a synthetic precursor to the commercially available DiPAMP ligand. Though not the topic of this report, it should be noted that Wolfe and Livinghouse have reported an alternative means of preparing scalemic *P*-chiral phosphine-boranes related to **27**. The study outlines the (−)-sparteine mediated kinetic dynamic resolution of lithiated *tert*-butylphenylphosphine-borane and subsequent alkylation.[26] A different desymmetrization process by those same researchers targets starting materials **23**.[27]

Aryl triflates and nonaflates are also reactive with secondary phosphine-boranes. Thus, conditions of 5% $Pd(PPh_3)_4/K_2CO_3/CH_3CN$ afford the tertiary phosphine-borane in good to excellent yields. The method is not amenable to heteroaryl triflates since the presence of the heterocyclic nitrogen decomplexes the phosphine of its borane.[28] Using altered reaction conditions, it was established that 7.5% $Pd(OAc)_2$, 22% Ph_2PMe, 20–30 mol % CuI, 1.2 equiv. $EtN(i\text{-}Pr)_2$ in THF/SMe_2 (4:1) induced the arylation of (*S*)$_P$-methylphenylphosphine-borane with nearly complete retention of configuration.[29] The proposed cuprous phosphine intermediate allows the reaction to proceed at 0 °C over three days. Eight different aryl iodides were reacted in fair to near-quantitative yield, with 94.5–99% retention of stereochemistry.[29]

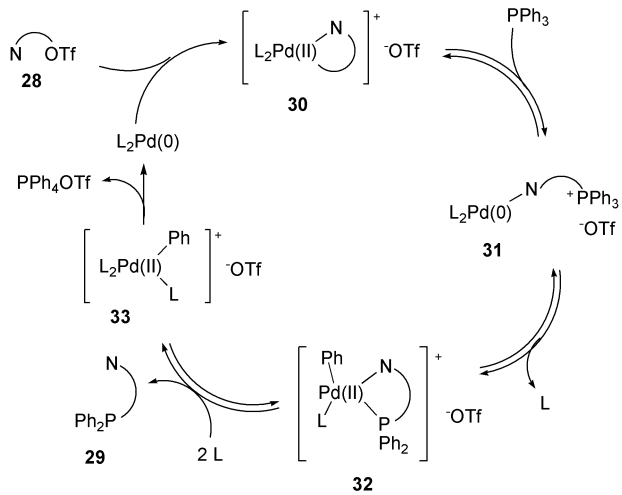
2.3 Triphenyl phosphine as a source of other triaryl phosphines

The ligand synthesis methods outlined to this point can be divided into two general types. If stabilised phosphine oxides or phosphine-boranes are employed and phosphines are desired, one is bound to a reduction step after P–C bond formation. The alternative of direct ligand formation requires the use of air sensitive primary or secondary phosphines. Circumventing both drawbacks, Chan has found direct formation of tertiary phosphorus ligands using triphenylphosphine as the diarylphosphinating agent.[30] In effect the palladium catalyzes an aryl exchange on the phosphorus, attaching a functionalised aryl unit at the expense of a phenyl group. The reaction, suitable for the conversion of aryl bromides or triflates[31] to phosphines, offers products in the 25–50% range. However, product recovery improves to 50–68% when specifically applied to the synthesis of atropisomeric biaryl *P,N*-ligands (*e.g.*, **29**, Scheme 11), presumably because the mechanism implicates and benefits



Scheme 11 i) 2.5 equiv. PPh_3, 10% $Pd(OAc)_2$, DMF, 110 °C, 4.5 d, 60%.

from a coordinative interaction of the pyridyl nitrogen (Scheme 12).[30] Furthermore the deployment of triflates such as **28**, with the



Scheme 12 L = PPh_3.

nitrogen so positioned, permits the use of other triarylphosphines beyond simply triphenylphosphine. Accordingly, a number of *p*- and *m*-substituted triarylphosphines are capable of participating in the cross-coupling reaction. On the other hand, tri(*o*-tolyl)phosphine and tricyclohexylphosphine are unreactive.[30]

Any mechanism offered for this transformation must differ from that of Scheme 2 by including the templating participation by the

proximal nitrogen while also necessitating the oxidative addition of the palladium into an already existing P–C bond. Moreover it was determined that > 2 equiv. of triarylphosphine are required for a successful reaction. As shown in Scheme 12, the mechanistic cycle begins with an oxidative addition of Pd(0) to starting triflate **28**. The complex so formed, **30** then succumbs to reductive elimination to phosphonium salt **31**. Coordinated *P,N*-complex **32** arises from internal oxidative addition of phosphonium salt **31**, a step involving loss of one aryl from the phosphorus atom and transfer of that aryl group to the palladium. Ligand substitution of more tertiary phosphine prompts the release of product **29**.[30]

After liberation of *P,N*-ligand **29**, the remaining palladium takes the form of phenyl-Pd complex **33**, which undergoes reductive elimination releasing tetraphenylphosphonium triflate and regenerating the active Pd(0). The involvement of tetraphenylphosphonium triflate was proved by its isolation from the product mixture. This species accounts for the requirement of the second equivalent of phosphine

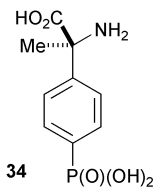
The applicability of this protocol for *P,N*-ligand synthesis is underscored since the improved yield is attributed by ligation of the nitrogen during product formation. It is noted that the phosphine-borane chemistry is limited to substrates *not* containing a nearby coordinative nitrogen. The coupling reaction has most recently been carried out with aryl bromides and triflates under solvent free conditions, although yields are only 26–43%.[32]

3 Phosphorus acid derivatives

As mentioned, the pioneering work in Pd catalyzed phosphorus–carbon bond formation was performed with dialkyl phosphites affording dialkyl alkenyl- and arylphosphonates.[5] The family of suitable substrates for this and related chemistry has expanded since the work of Hirao and some of the variations and applications of this chemistry are outlined in the sections following.

3.1 Phosphonic acid derivatives

The Hirao conditions[5] have been adopted for the preparation of a number of dialkyl arylphosphonates.[33–35] Hydrolysis of the products leads to aryl phosphonic acids.[33,34] This chemistry has been applied to the synthesis of (*S*)-α-methyl-4-phosphonophenylglycine [(*S*)-MPPG, **34**], one of a family of selective antagonists of metabolic glutamate receptors.[34] The chemistry is also an important step in the synthetic construction of the organic component (**35**) of lamellar lanthanide biphosphonates pillared with chiral crown ethers.[33]



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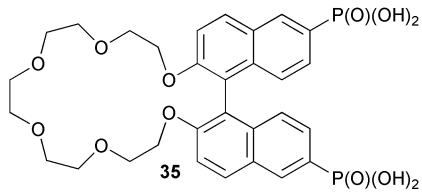

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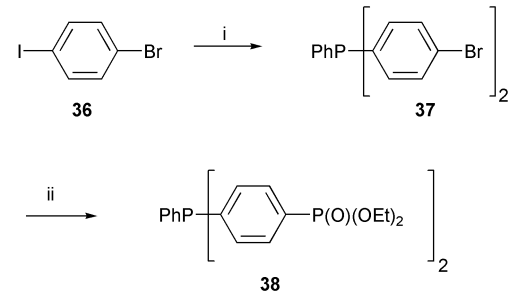
In an application of two facets of chemistry relevant to this review, the Stelzer group elaborated phenylphosphine through two palladium catalyzed P–C cross-couplings with a series of bromoiodobenzenes (*e.g.*, **36**). In a subsequent step, the remaining Br atoms of the bis(*p*-bromo) derivative **37** were engaged for C–P bond formation using diethyl phosphite and additional $Pd(PPh_3)_4$ (Scheme 13). The chemistry is equally applicable for the formation of mono or bis phosphonylated congenors. Hydrolyses of these compounds (*e.g.*, **38**) afforded water soluble phosphines. A complementary protocol for the formation of isomeric compounds whereby the phosphine and phosphonate groups assume a meta relationship was also demonstrated. Those functionalities were installed using a combination of cross-coupling chemistry to affix the phosphonate and subsequent nucleophilic displacement of a fluorine on the aromatic ring for the phosphine unit.[35]

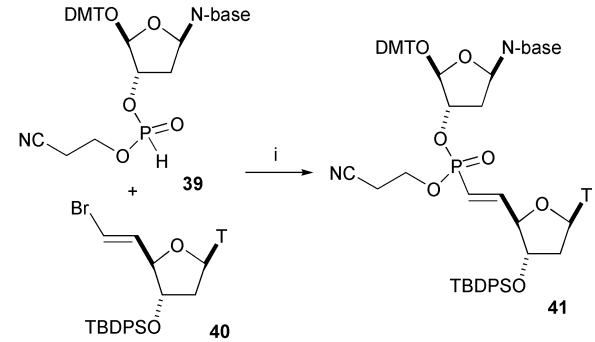


36 **37** **38**

Scheme 13 i) 0.5 equiv. $PhPH_2$, Et_3N, 1% $Pd(PPh_3)_4$, MeCN, reflux, 24 h, 63%. ii) 2.2 equiv $HP(O)(OEt)_2$, Et_3N, 1% $Pd(PPh_3)_4$, toluene, 80 °C, 3 d, 70%.

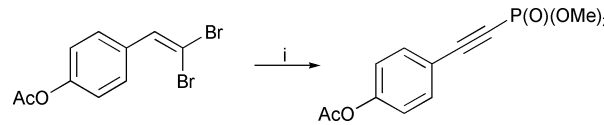
As a key step involved in the formation of exogenous synthetic oligonucleotides, the Hayes group has utilised Pd-catalyzed P–C bond formation for the fabrication of hydrolytically stable internucleotide linkages as an alternative to the natural phosphodiester tether.[36] Specifically, those researchers demonstrated the coupling of mixed dialkyl phosphonates **39** and bromoalkene **40** for the generation of a vinylphosphonate bridge as in **41**. The palladium catalyzed P–C bond forming reactions are a convenient application for this chemistry since dialkyl phosphite containing starting materials **39** are readily accessible after a single high-yielding hydrolytic treatment of commercially available materials possessing the cyanoethyl phosphoramidate protecting group.

As demonstrated in Scheme 14, the coupling conditions of $Pd(OAc)_2$, dppf, and propylene oxide in THF are not harmful to the DMT and TBDPS protecting moieties nor to the heterocyclic bases. The chemistry appears to be amenable to a solid supported protocol.[36]



Scheme 14 DMT = 4,4'-dimethoxytrityl; T = thymine; TBDPS = *tert*-butyldiphenylsilyl; i) 20% Pd(OAc)2, 40% dppf, 10 equiv. propylene oxide, THF. Four N-base examples, 31–85%.

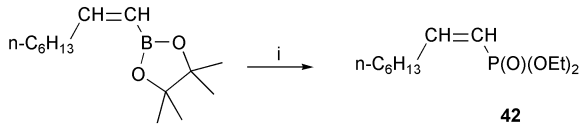
While attempting the coupling chemistry on a dibromovinyl anolog of **40**, Lera and Hayes[37] isolated an alkynylphosphonate linkage, the product of an apparent cross-coupling and HBr elimination sequence. From this result, the researchers developed a general procedure for the conversion of 1,1-dibromo-1-alkenes to alkynylphosphonates. One modification of the reaction conditions of Scheme 14 is the use of DMF as reaction solvent, a preferred choice since it reduces or eliminates the onset of a bromovinylated by-product (Scheme 15). Also, in some instances, trifurylphosphine was preferred over dppf as the added ligand.[37]



Scheme 15 i) $HP(O)(OMe)_2$, 20% $Pd(OAc)_2$, 40% dppf, 3 equiv. propylene oxide, DMF, 80 °C, 68%.

In a unique contribution to this chemistry, Kabalka and Guchhait have demonstrated the applicability of vinylboronic acids as cross-coupling partners. The increasing availability of boronic acid

derivatives and the use of triethyl phosphite as a convenient phosphorus source makes this protocol an inviting one. With 4 mol% $Pd(OAc)_2$, under an oxygen environment, the reaction proceeds in a stereospecific manner in the absence of solvent. Yields of vinylphosphonate (*e.g.*, **42**) range from 55–84%. The yields are slightly higher in the cross-coupling of *E*-isomers when compared to *Z*-isomers (Scheme 16).[38]

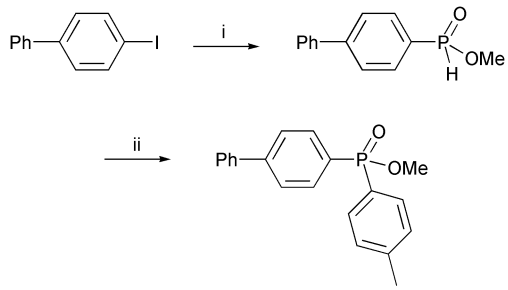


Scheme 16 i) 2 equiv. $P(OEt)_3$, 4% $Pd(OAc)_2$, O_2 atmosphere, 95 °C.

3.2 Preparation of phosphinic acids and derivatives.

Phosphinic acid derivatives possess a potentially labile hydrogen that is known to shuttle between phosphorus and oxygen atoms of the two valence isomers of phosphinic acid and their derivatives. Nevertheless, some of the cross-coupling conditions already introduced are equally applicable to a number of phosphinic acid-derived species.

Methyl phosphinate (**43**) has been shown to be a valuable building block for mono- and diaryl phosphinates, by way of palladium mediated P–C bond formation.[39] The thermal and hydrolytic sensitivity of **43** can be conveniently overcome by using excess $HC(OMe)_3$ for the conversion of H_3PO_2 to **43**, and then adding acetonitrile to make up the reaction solvent. In a thorough investigation it was found that methyl phosphinate could be monoarylated in 23–80% using the conditions shown in Scheme 17.

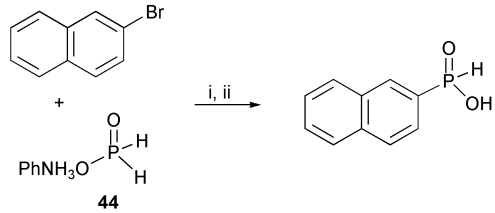


Scheme 17 i) 2.7 equiv. $H_2P(O)OMe$ (**43**), *N*-methylmorpholine, 20% PPh_3, 5% $Pd(OAc)_2$, MeCN, 23 °C, 69%; ii) MeC_6H_4–I, 3% $Pd(PPh_3)_4$, *N*-methylmorpholine, reflux MeCN, 2 h, 50% over 2 steps.

Either *N*-methylmorpholine or propylene oxide can be employed as acid scavenger. Modifying reagent ratios, using Et_3N and raising the temperature to 77 °C permits diarylation of the phosphorus in 49–59% yields.[39]

For mixed diarylation, the mono substituted product could be isolated in crude form and exposed to a different aryl iodide, base and Pd(0) in the form of $Pd(PPh_3)_4$ (Scheme 17), a reagent whose applicability had been demonstrated in earlier work addressing the synthesis of diaryl- and alkylarylphosphinates and bifunctional phosphinates.[40] The usefulness of the methodology is amply demonstrated by the synthesis of a phosphinate linked bis-amino acid for incorporation into peptides.[41]

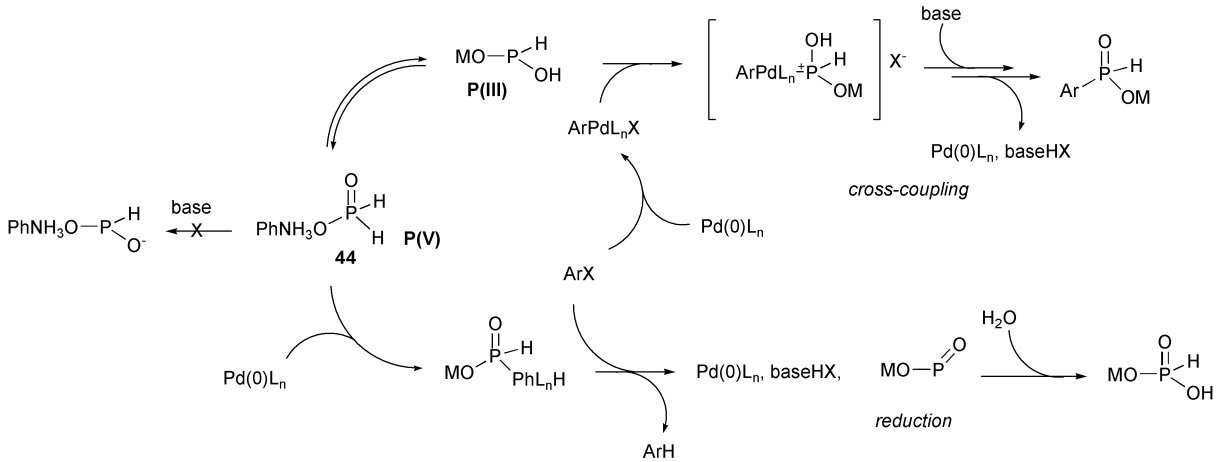
The use of hypophosphorus acid in cross-coupling was documented some time ago.[42] However, experiments with the anilinium salt of hypophosphorus acid (**44**) have recently proved viable, general and useful, and do not suffer from the reactivity issues associated with the acid or methyl phosphinate (**43**).[43] The cross-coupling is particularly easy to perform using 2 mol% of $Pd(PPh_3)_4$. Drying of the solvent (DMF or MeCN) is one of the few required precautions (Scheme 18).



Scheme 18 i) 3 equiv. Et_3N, 2% $Pd(PPh_3)_4$, DMF, 80–85 °C, 18–24 h, 71%; ii) work-up including acidification.

More intriguing is the remarkable breadth of the reaction. The acid derivative can be monofunctionalised efficiently with aryl iodides, bromides, triflates and benzyl chlorides. A mechanism for the reaction is offered in Scheme 19. The cross-coupling occurs as per mechanisms introduced earlier. Noteworthy is the possible onset of a competitive hypophosphorus acid reduction process which is encountered with highly electron rich aryl iodides. Under those circumstances, the oxidative addition step required for cross-coupling is deactivated and transfer hydrogenation becomes competitive.[43] The authors feel that oxidative insertion of the palladium occurs on the P(III) form of the phosphorus species to eventually afford product and prior deprotonation of **44** does not occur and hence is not important to the mechanism. Once the reaction is complete, the monosubstituted phosphinic acids are recovered after acidification of the reaction mixtures.[43]

More recently the applicability of anilinium hypophosphite has been extended to alkenyl bromides and triflates.[44] The yield of conversion of monosubstituted alkenes proceeds in 64–98% yields in benzene, although isolation of the alkenylphosphinic acids is more difficult and leads to more losses than observed for aryl substituted examples. The cross-coupling chemistry is vital to the synthesis of GABA (4-aminobutyric acid) analogs, compounds



Scheme 19 M = $PhNH_3^+$ or Et_3NH^+.

designed for the treatment of problems associated with the central nervous system.[44]

4 Summary

As the manipulation of phosphorus compounds becomes more manageable, so too does the development of P–C bond forming reactions. From beginnings using dialkyl phosphonates, the use of palladium catalysis for P–C bond formation has clearly made its mark as an appealing alternative to more established methods. The breadth of usable substrates offers several options for the synthetic chemist. Moreover, the recent discovery that chiral catalysts can induce the formation of enantio-enriched phosphines opens the possibility for new and imaginative studies whereby the catalytic usage of one chiral phosphine can assist in the generation of greater amounts of another chiral phosphine. Future studies promise to unveil valuable fundamental information as well as beneficial phosphines and phosphorus acids.

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