# Catalytic Synthesis of Phosphines and Related Compounds

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**Abstract:** Phosphines play an important role in organometallic chemistry, homogeneous catalysis and synthetic chemistry. Traditionally, phosphines are mainly prepared by one of the following methods: reaction of halophosphines with organometallic reagents, reaction of phosphides with halides, addition of RR'PH to C-C multiple bonds, Friedel–Crafts reactions and reduction of phosphine oxides. In the past one decade or so, powerful catalytic methods have emerged, allowing a variety of structurally and electronically diverse phosphines to be accessed more easily and efficiently. This review, not attempted to be comprehensive, aims to summarise, and demonstrate the utility of, important catalytic methods that have been employed in the synthesis of phosphines and related organophosphorus compounds. The review focuses on reactions involving hydrophosphination, hydrophosphorylation, P-C coupling, C-C coupling and olefin metathesis.

## 1. INTRODUCTION

Organophosphorus compounds are widely used in chemical, agrochemical and pharmaceutical industries [1]. Derivatives of phosphoric acids are fundamental to living systems and many phosphorus compounds containing P-C bonds have been found to display bioactivities. Of more relevance to homogeneous catalysis, organometallic chemistry and organic synthesis are phosphines, which have extensively been utilised as ligands and reagents in the synthesis of bulky chemicals and numerous fine chemical intermediates [2]. There are various traditional methods for the synthesis of phosphines, of which the most useful and versatile will be briefly summarised [1a].

Reaction of halophosphines with organometallic reagents is one method of phosphine synthesis. Phosphinous halides ($R_2PCl$) and phosphonous dihalides ($RPCl_2$) are excellent starting materials in which alkyl or aryl groups can displace the halides through Grignard or lithium reagents to give $R_2R'P$ or $RR'_2P$ [3]. The halophosphines can be prepared by Friedel-Crafts reaction, $PCl_3$ addition to C=C double bonds and the carefully controlled reaction of $PCl_3$ with organometallic reagents. For the synthesis of symmetrical tertiary phosphines $R_3P$, $PCl_3$ is the reagent of choice. Alternatively, phosphines can be synthesised from metal phosphides. The anions derived from $PH_nR_{3-n}$ (n = 1-3) by the reaction with metals such as Na and K are highly nucleophilic and reactive towards alkylating reagents, such as R'Cl yielding $PR_{3-n}R_n'$ [4]. A third way of phosphine synthesis is by addition of $PH_nR_{3-n}$ to C=C and C≡C multiple bonds *via* radical or ionic pathways [5]. Phosphine can also add to α,β-unsaturated nitriles and carbonyl compounds under basic conditions [6]. Reduction of phosphine oxides is the final traditional method of phosphine synthesis. It has been known since 1964 that silicon hydrides are efficient reducing agents for phosphine oxides and the reductions occur in high yield under mild conditions [7]. Trichlorosilane is now used as a standard reducing agent in phosphine synthesis.

All of the methods discussed have some disadvantages and none could be applied to all the preparation conditions. This review will highlight how catalytic methods have been developed in the past few years, creating more accessible routes to electronically and structurally diverse phosphines. The coverage of literature is not attempted to be comprehensive; instead the focus is placed on catalytic methodologies that have been devised and utilised for the synthesis of phosphines important to catalysis and synthetic chemistry. The phosphines and related compounds discussed in this review have been limited to those containing at least one P-C bond and the synthesis of phosphonium salts is not included. The main areas covered are hydrophosphination, P-C coupling, C-C coupling and olefin metathesis.

## 2. HYDROPHOSPHINATION AND HYDROPHOSPHORYLATION

### 2.1 Reaction with C=X bonds (X = C, N, O)

The first example of hydrophosphination of an alkene catalysed by a transition metal was the Pd(0)-catalysed hydrophosphination of acrylonitrile [8e]. The tris(cyanoethyl)phosphine (tcep) has previously been well-studied [9], and the complex [Pt(tcep)$_3$] was found to catalyse the addition of $PH(CH_2CH_2CN)_2$ to $H_2C$=CHCN. The reaction proceeded to completion after 1 h to give tcep, identified by $^{31}$P NMR (Fig. 1). Other $d^8$ and $d^{10}$ metal-tcep complexes including Pd, Ir, and Ni were also found to catalyse the hydrophosphination of acrylonitrile [8b], but Pt remained the most efficient.

More recently, the hydrophosphination of ethyl acrylate was reported in which the addition of $PH_3$ to $H_2C$=$CHCO_2Et$ yields $P(CH_2CH_2CO_2Et)_3$ in over 90% selectivity according

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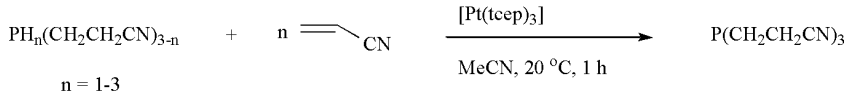



**Fig. 1.**

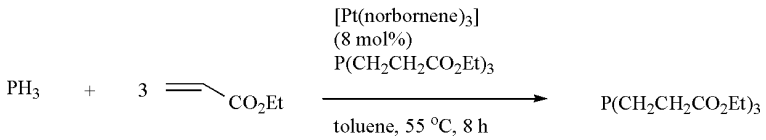



**Fig. 2.**

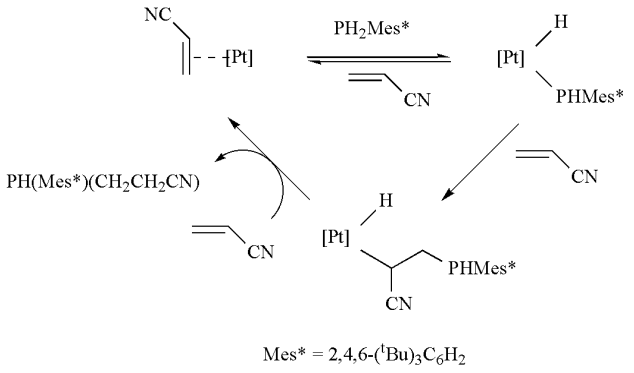



**Fig. 3.**

to $^{31}$P NMR (Fig. 2) [8a]. Once again, platinum complexes of the product ligand are effective catalysts for the reaction itself.

The following insight into the mechanism of these reactions was gained [8]. As substrates, activated, Michael acceptor olefins were required. The resting states of the catalysts were presumably the olefin complexes [$PtL_2$(olefin)] (L = phosphine). Regarding acrylonitrile hydrophosphination, parallel mechanisms involving mononuclear and dinuclear intermediates were proposed [8b]. With these hydrophosphination reactions, potentially useful ligands for homogeneous catalysis have been prepared [8].

Mechanistic studies on Pt-catalysed acrylonitrile hydrophosphination were also carried out using diphosphine complexes [Pt(diphos)($CH_2CHCN$)] (diphos = dppe; $Cy_2PCH_2CH_2PCy_2$) with the aim of developing Pt-catalysed asymmetric hydrophosphination with chiral bidentate ligands such as Binap or Duphos [10a]. It was concluded that the general mechanism involved P-H oxidative addition, selective acrylonitrile insertion into a M-P rather than a M-H bond, and acrylonitrile induced C-H reductive elimination of the resulting alkyl hydride complex (Fig. 3). The product-forming reductive elimination appeared to be irreversible, but in some cases both the oxidative addition and insertion step were reversible. In the key P-C bond forming step, the rate and reversibility are sensitive to the nature of the ligands in the Pt(II)-phosphido complex, with hydrophosphination faster for smaller phosphine substrates. The insertion did not appear to proceed by displacement of phosphide by the olefin but rather by a classical insertion pathway, involving acylonitrile pre-coordination or a concerted insertion.

Further studies from the same group concluded that for asymmetric hydrophosphination a chiral bidentate ligand would be required that would bind tightly to the metal and not be as readily displaced as dppe [10b]. The catalyst chosen was [Pt{(*R*,*R*)-Me-Duphos}(*trans*-stilbene)], with shorter Pt-P bond distances consistent with tight binding and a rigid Me-Duphos structure to prevent displacement by monodentate phosphines. With this chiral catalyst the preparation of *P*-chiral phosphines from racemic secondary

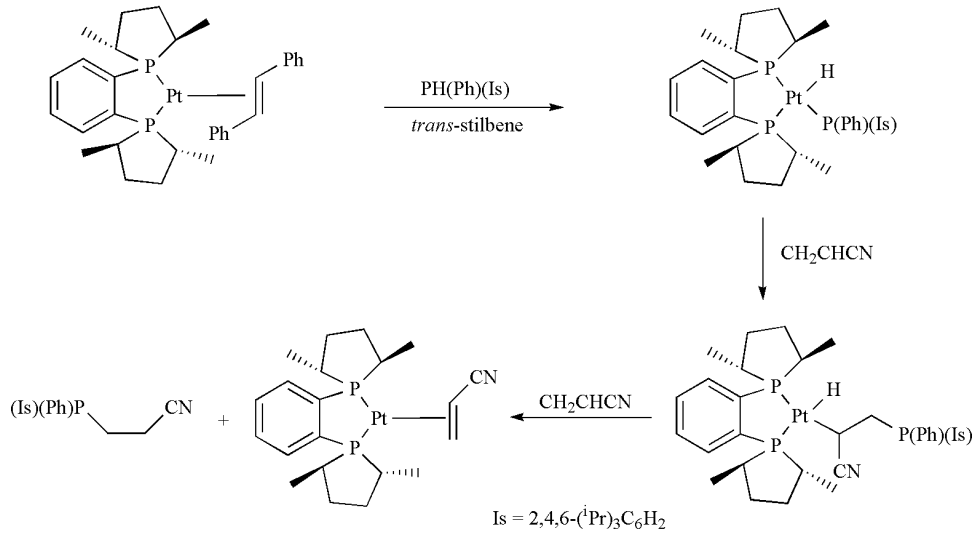
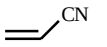
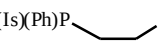
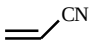
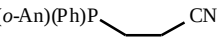
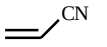
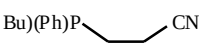
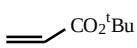
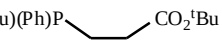
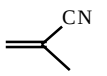
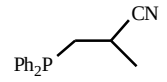
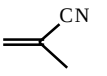
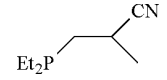
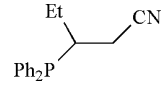
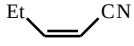
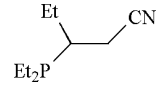



**Fig. 4.**

**Table 1.**

| Entry | Alkene | Phosphine | Product | Selectivity (%)[b] | % ee |
|---|---|---|---|---|---|
| 1 |  | PH(Ph)(Is) |  | >90 | 17 |
| 2 |  | PH(Ph)(*o*-An)[c] |  | 80 | 5 |
| 3 |  | PH(Ph)($^i$Bu) |  | 60 | 5 |
| 4 |  | PH(Ph)($^i$Bu) |  | 95 | 20 |
| 5 |  | $PHPh_2$ |  | 95 | 27 |
| 6 |  | $PHEt_2$ |  | 80 | 0 |
| 7 |  | $PHPh_2$ |  | 95 | 4 |
| 8 |  | $PHEt_2$ |  | 100 | 18 |

[a] 5 mol% catalyst precursor. [b] Selectivity = percentage of illustrated phosphine product. [c] *o*-An = *o*-$MeOC_6H_4$

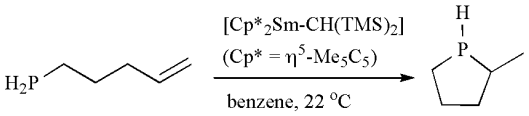



**Fig. 5.**

phosphines was attempted. Treatment of the catalyst with 1.1 equiv of PH(Ph)(Is) (Is = 2,4,6-($^i$Pr)$_3$C$_6$H$_2$) in THF at room temperature gave the phosphido hydride complex [Pt(H){P(Ph)(Is)}(Me-Duphos)] as a single diasteromer (Fig. 4). Introduction of acrylonitrile at –78 °C in toluene led to the formation of 4 alkyl hydride isomers, observed by NMR at –20 °C. On warming to room temperature the *P*-chiral tertiary phosphine PPh(Is)($CH_2CH_2CN$) was formed with 63-71% ee [11]. Compared to this stoichiometric reaction, the catalytic reaction was very slow with a lower ee of 17% (Table 1, entry 1.). When less bulky phosphines were used, the reactions were faster but proceeded with lower ee's (Table. 1, entries 2,3). In contrast, the bulkier phosphines PH(Me)(Mes*) (Mes* = 2,4,6-($^t$Bu)$C_6H_2$) did not lead to hydrophosphination products. The results of the stoichiometric reactions suggested that the slow step was oxidative addition of P-H bonds. To promote oxidative addition, bulkier alkenes than acrylonitrile were used. This resulted in faster rates and increased selectivity but with still a modest enantioselectivity at phosphorus (Table 1, entry 4). Achiral phosphines and disubstituted olefins gave tertiary phosphines with similar poor stereocontrol at carbon with ee's between 0 and 27% (Table 1, entries 5-8). It was hypothesised that phosphines PH(R)(R') with R and R' differing greatly in size and variations in the olefin substrate could increase enantioselectivity at phosphorus and carbon.

The intramolecular version of the metal-catalysed additions of P-H to C=C bonds also exits. The organolanthanide-catalysed hydrophosphination/cyclisation of phosphinoalkenes has been reported in the synthesis of five-membered phosphines [12]. One example is shown in Fig. 5. Four stereoisomers can in principle result from the alkenyl phosphine cyclisation, because inversion at phosphorus is slow [13]. Here, $^{31}$P NMR exhibited two product resonances in a 2:1 ratio.

Organophosphonates $RP(O)(OR')_2$ are a useful class of compounds in synthetic and biological applications. Their synthesis *via* the hydrophosphorylation of alkenes by $HP(O)(OR')_2$, catalysed by metal complexes, had never been realised, until the high reactivity of the five-membered cyclic

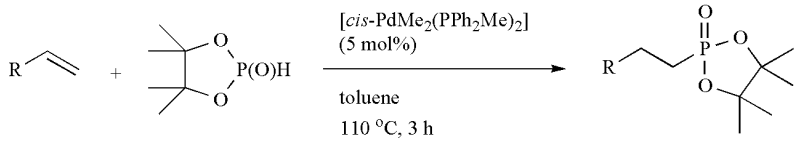



**Fig. 6.**

**Table 2.**

| Entry | Alkene | Yield (%) |
|---|---|---|
| 1 |  | quant |
| 2 |  | quant |
| 3 |  | quant |
| 4 |  | 83 |
| 5 |  | 87 |

hydrogen phosphonate, 4,4,5,5-tetramethyl-1,3,2-dioxaphospolane-2-oxide (TMDPO), was taken advantage of [14]. When treated with 1-octene in toluene, and heated at 110 °C for 3 h in the presence of [*cis*-$PdMe_2(PPh_2Me)_2$], the corresponding adduct was formed in 63% yield (Fig. 6). Besides palladium catalysts, $[Ni(PPh_3)_4]$ and $[RhCl(PPh_3)_3]$ showed moderate activity under similar conditions with 26 and 49% yields respectively. When noncyclic and six-membered cyclic hydrogen phosphonates were used, the corresponding adducts did not form. Screening of palladium catalysts revealed that $[PdMe_2(dppb)]$ (dppb = $Ph_2P(CH_2)_4PPh_2$) also worked efficiently in 1,4-dioxane. As seen from Table 2, the reaction can be extended to aliphatic and aromatic terminal alkenes and some cyclic alkenes.

Hydrophosphination and hydrophosphorylation are not restricted to C=C bonds. A similar self-replication to the examples shown in Figs. 1 and 2 is also found in the addition of $PH_3$ to formaldehyde to give tris(hydroxymethyl)phosphine (Fig. 7) [8d]. A range of Pt(IV), Pt(II), and Pt(0) compounds including $Na_2[PtCl_6]$, $K_2[PtCl_4]$, $[PtCl_2\{P(CH_2OH)_3\}_2]$ and $[Pt\{P(CH_2OH)_3\}_4.H_2O]$ were used as catalysts. It was hypothesised that a common Pt-

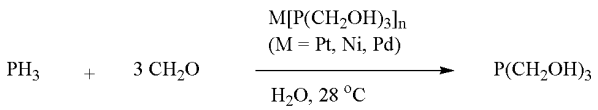



**Fig. 7.**

$P(CH_2OH)_3$ complex was involved for each. In addition to platinum, $[Ni\{P(CH_2OH)_3\}_4]$ and $[Pd\{P(CH_2OH)_3\}_4]$ could be used as catalysts.

In back to back communications, the enantioselective hydrophosphorylation of aromatic aldehydes, a potentially useful method for asymmetric synthesis of α-hydroxyphosphonic acids, was developed using a chiral Ti-Lewis acid derived from *L*-tartrate [15a], that is the Sharpless catalyst [16]. Upon treatment with diethylphosphite, benzaldehyde and the electron deficient *para*-chlorobenzaldehyde underwent hydrophosphorylation to give the (*R*)-configured product in good yield and modest enantioselectivity (Fig. 8).

In the following paper, it was discovered that decreasing the Lewis acidity of the catalyst by tuning the donor ability of the solvent was found to be effective for obtaining higher enantioselectivity [15b]. Also, changing the metal in the catalyst to a more basic one was an alternative method for the achievement of high enantioselectivity. In this context, the modified binaphthol-derived La-alkoxide catalyst developed by Shibasaki was used, due to its basic character and potential usefulness in asymmetric synthesis [17,18]. The reactions of several aromatic aldehydes with diethylphosphite were examined in the presence of Shibasaki's catalyst in the synthesis of (*S*)-(-)-α-hydroxyphosphonates. At −40 °C, high yields were obtained, but at –78 °C the yield of product decreased (Fig. 9). The degree of enantioselectivity depended strongly on the electronic nature of the substituent in the *para*-position on the aromatic ring, with a drop in ee from 82% to 17% on

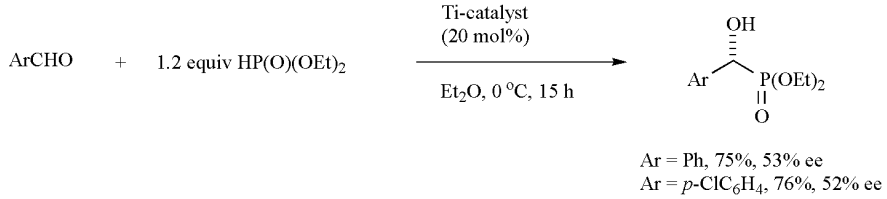



**Fig. 8.**

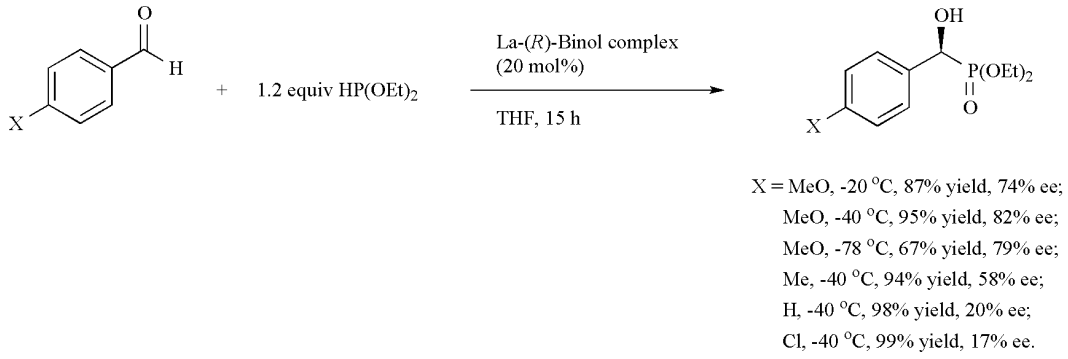



**Fig. 9.**

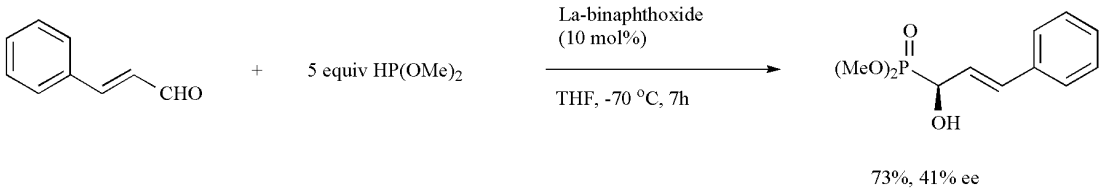



**Fig. 10.**

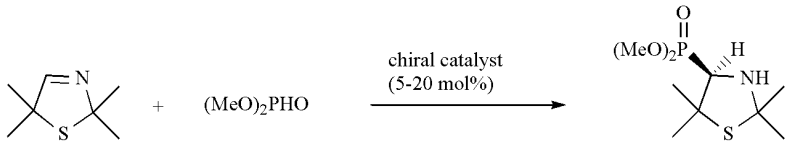



**Fig. 11.**

**Table 3.**

| Entry | Catalyst (mol%)[a] | Temp (°c) | Time (h) | Yield (%) | % ee |
|---|---|---|---|---|---|
| 1 | $Ti(O^iPr)_2$(TAD)[b] | 65 | 4 | 57 | 46 (*R*) |
| 2 | $Ti(O^iPr)$(Binol) | 65 | 5 | 62 | 29 (*R*) |
| 3 | (*R*)-SmK(Binol) | 50 | 40 | 97 | 93 (*R*) |
| 4 | (*R*)-GdK(Binol) | 50 | 50 | 77 | 95 (*R*) |
| 5 | (*R*)-DyK(Binol) | 50 | 50 | 76 | 97 (*R*) |
| 6 | (*R*)-YbK(Binol) | r.t | 50 | 86 | 98 (*R*) |
| 7 | (*R*)-YbK(Binol)[c] | 50 | 40 | 63 | 95 (*R*) |

[a] 20 mol% catalyst. [b] TAD = (-)-(*R,R*)-TADDOL. [c] 5 mol% catalyst.

replacing MeO with Cl. A linear Hammet correlation plot demonstrated that the Lewis acidity of the aromatic aldehyde and the basicity of the catalyst were important in obtaining high enantioselectivity.

With the aim of developing allylic hydroxyphosphonates, La-(*R*)-binaphthoxide was used as a catalyst in the hydrophosphorylation of cinnamaldehyde with dimethylphosphite [19]. (*S*)-Hydroxyphosphonates were obtained in good yields and modest enantioselectivity using 10 mol% catalyst. Reactions run between –75 and -25 °C showed little variation in enantioselectivity; however, temperatures above –15 °C reduced the selectivity (Fig. 10).

Hydrophosphorylation of C=N bonds in cyclic imines has been carried out using organolanthanide complexes as catalysts [20]. Initially, the enantioselective hydrophosphorylation of 2,2,5,5-tetramethyl-3-thiazoline to yield 4-thiazolidinyl-phosphonate was performed using chiral Ti-diol complexes with up to 62% yield and 46% ee (Fig. 11). With the success of heterobimetallic lanthanoid complexes in a wide range of enantioselective reactions [21], these catalysts were applied to the hydrophosphorylation reaction replacing the chiral Ti-diol complexes in an effort to optimise optical purity. A substantial increase in ee values were obtained by using Sm, Gd and Dy. The highest enantioselectivty was obtained with 20 mol% [(*R*)-YbK(Binol)] (Binol = (*R*)-(+)-binaphthol), which gave 86% yield and 98% ee at room temperature in 50 h. Reduction of catalyst loading to 5 mol% still gave a 63% yield with maintenance of high ee (95%) at 50 °C in 40 h (Table 3) [20b].

## 2.2 Reaction with C≡C triple bonds

The catalytic addition of P-H bonds to terminal alkynes is expected to produce three types of alkenylphosphines *via* addition of the phosphorus atom to the substituted end of the terminal alkyne or the non-substituted end, the latter possessing *E*- or *Z*-configuration (Fig. 12). Alkenylphosphines provide potential access to functionalised ligands *via* modification of the double bond. The standard synthesis of vinylphosphines involves the reaction of vinyl magnesium or lithium derivatives with halophosphines but suffers from lack of tolerance to functional groups.

The first example of hydrophosphination of alkynes came with the report that oxidative addition of $Ph_2P(O)H$ to the compound $[M(PEt_3)_3]$ (M = Pd, Pt) afforded [*cis*-$MH\{P(O)Ph_2\}\{PPh_2(OH)\}(PEt_3)$] complexes at room

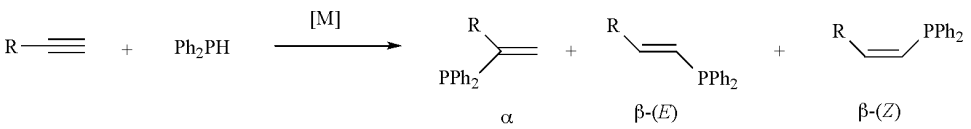



**Fig. 12.**

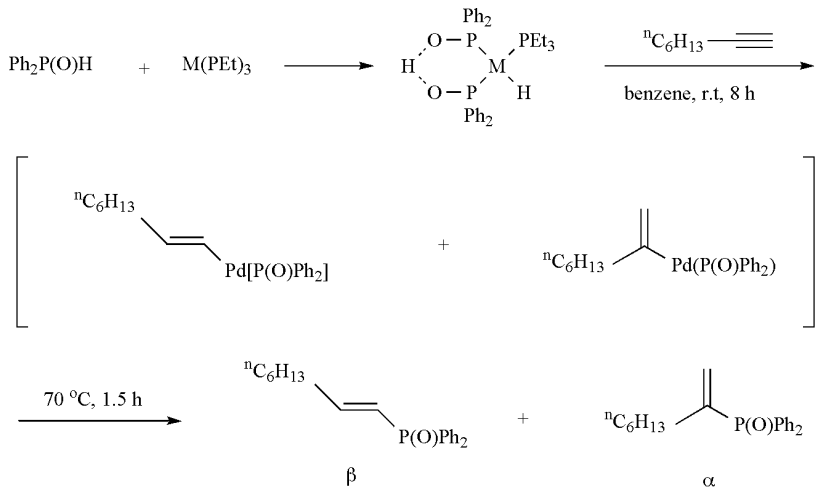



**Fig. 13.**

temperature in benzene [22a]. The Pd(II) complex was found to undergo an insertion reaction with 1-octyne to give 1- and 2-(diphenylphosphinoyl)-1-octenes (Fig. 13).

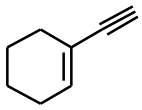
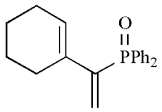
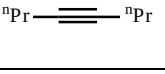
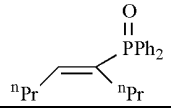
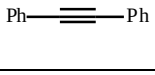
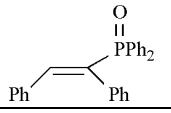
With this observation, the Pd-catalysed regio- and stereo-selective hydrophosphination of alkynes was explored [22a]. When an equimolar mixture of $Ph_2P(O)H$ and 1-octyne in benzene were heated at 35 °C in the presence of 5 mol% $[Pd(PPh_3)_4]$ for 20 h, 82% of hydrophosphination product was obtained with a β:α ratio of 96:4 and 100% stereoselectivity for the β-(*E*) product (Table 4, entry 1). The nature of the phosphine ligand only marginally affected regio- and stereo-selectivities. Less basic phosphines ($PPh_3$, $PPh_2Me$) were favourable for β-formation while more basic phosphines ($PMe_3$, $PEt_3$) not only favoured α-formation but gave β as *E*/*Z* mixtures. Other terminal alkynes could be used in this hydrophosphination, including acetylene. Aromatic alkynes such as phenylacetylene and 4-ethynyltoluene were used as substrates, and two phosphinyl groups could be introduced to diyne compounds such as 1,8-nonadiyne. The reaction was tolerant of functionalities including cyano and hydroxy groups, and the internal alkynes, 4-octyne and diphenylacetylene were successfully hydrophosphinated (Table 4).

The selective formation of β-adducts could be reversed with the addition of phosphinic acid [22b]. The reactions catalysed by palladium complexes bearing less sterically

**Table 4**[a] .

| Entry | Alkyne | Product | Yield (%) |
|---|---|---|---|
| 1 | $^nC_6H_{13}$—≡ | $^nC_6H_{13}$, O, PPh$_2$ | 82 |
| 2 | HC≡CH | O, PPh$_2$ | 51 |
| 3 | Ph—≡ | *p*-Me-C$_6$H$_4$, O, PPh$_2$ | 79 |
| 4 | *p*-Me-C$_6$H$_4$—≡ | NC(CH$_2$)$_3$, O, PPh$_2$ | 83 |
| 5 | NC(CH$_2$)$_3$—≡ | HO(CH$_2$)$_2$, O, PPh$_2$ | 73 |
| 6 | HO(CH$_2$)$_2$—≡ | Ph$_2$P(O), (CH$_2$)$_5$, PPh$_2$(O) | 86 |
| 7 | ≡—(CH$_2$)$_5$—≡ | Ph$_2$P(O), (CH$_2$)$_5$, PPh$_2$(O) | 61 |

**(Table 4). contd….**

| | | | |
|---|---|---|---|
| 8 |  |  | 91 |
| 9 |  |  | 61 |
| 10 |  |  | 85 |

[a] Conditions: 5 mol% [$Pd(PPh_3)_4$], 35 °C in benzene, 20-22 h.

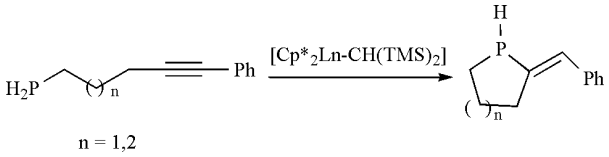


**Fig. 14.**

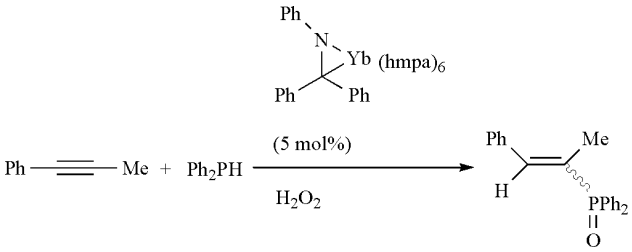


**Fig. 15.**

demanding and more basic phosphine ligands were more sensitive to the effect of this phenomena. For example, when the catalyst [$PdMe_2(PEt_3)_2$] was used in the hydrophosphination of 1-octyne with $Ph_2P(O)H$, a reversal of the β:α ratio from 87:13 to 9:91 was observed upon addition of 5 mol% $Ph_2P(O)OH$. This reversal of regioselectity could be generally applied to various aliphatic and aromatic terminal alkynes, with cyano and hydroxy groups again tolerated.

The Pd-catalysed additions of diphenylphosphine oxide to alkynes shown in Table 4 proceeded slowly at ambient temperature [22a,b]. Later it was discovered that rhodium was a novel catalyst for this reaction and enabled the addition of $Ph_2P(O)H$ to a variety of alkynes, producing the corresponding (*E*)-alkenylphosphine oxides exclusively in excellent yields [22c]. For instance, in the hydrophosphination of 1-octyne, the β−(*E*)-product was formed in 100% yield using the Wilkinson-type catalyst $RhI(PPh_3)_3$ at 25 °C in 1 h.

Phosphines have also been shown to add to C≡C bonds. The organolanthanide complex discussed earlier (Fig. 5) catalysed the hydrophosphination of alkynes both *intra*-molecularly and *inter*molecularly [12]. For instance, catalysts of the type [$Cp^*_2Ln\text{-}CH(TMS)_2$] promoted the cyclisation of primary alkynyl phosphines to yield secondary phospholanes and phosphinanes (Fig. 14). However, the products were somewhat unstable and could only be characterised *in situ* by NMR.

More recently, catalytic intermolecular hydrophosphination of alkynes with $Ph_2PH$ has been achieved with Yb-imine complexes to yield α,β-unsaturated alkenylphosphines and phosphine oxides in high yields after oxidative work up [23]. When diphenylphosphine and equimolar amounts of 1-phenyl-1-propyne were added to a THF solution of 5 mol% [$Yb(\eta^2\text{-}Ph_2CNPh)(hmpa)_6$] (hmpa = hexamethylphosphoramide) at room temperature, the corresponding alkenylphosphine oxide was formed quantitatively (*E*:*Z* = 80:20) after oxidation with $H_2O_2$ (Fig. 15). Generally with respect to regiochemistry, the $Ph_2P$ group was introduced into the opposite side to the aryl substituents of the aromatic alkynes exclusively, and into the less hindered side of aliphatic alkynes. Regarding stereochemistry, this was dependent on the substrate, with (*E*)- and (*Z*)-isomers preferentially formed with aromatic and aliphatic alkynes, respectively. This method was also applicable to other C-C multiple bonds, such as conjugated dienes, allenes and styrene derivatives to be discussed in section 2.3. Direct synthesis of alkenylphosphine oxides by using diphenylphosphine oxide was unsuccessful due to oxidation of the catalyst to give a trivalent lanthanide species and diphenylphosphine.

Vinylphosphines have recently been prepared by Pd- and Ni-catalysed direct diphenylphosphine addition to alkynes [24]. An interesting aspect of the reaction is that the regioselectivity depends dramatically on the nature of the catalyst. β-(*Z*)- and α-Alkenylphosphines could be selectively reached *via* catalytic addition of $Ph_2PH$ to phenylacetylene with 5 mol% [$Pd(PPh_3)_4$] and [$Ni(acac)_2$]/$(EtO)_2P(O)H$, respectively (Fig. 16). Interestingly, the addition of acetic acid to the reaction catalysed by [$Pd(PPh_3)_4$] favoured the α-adduct, and [$Ni(acac)_2$], without the addition of a small amount of $(EtO)_2P(O)H$, gave rise to the β-(*E*)-adduct. This phenomena is similar to that observed in the hydrophosphination of 1-octyne with $Ph_2P(O)H$ where a reversal of regioselectivity was observed under the influence of the phosphinic acid $Ph_2P(O)OH$ [22b]. High selectivity was also obtained for the catalytic addition of $Ph_2PH$ to $^t$BuC≡CH and PhC≡CPh, and the reaction could also be applied to other internal alkynes.

As part of a study into the synthesis of unsymmetrical, rigid, chelating diphosphine ligands, the base-catalysed additions of coordinated secondary phosphines/phospholes to

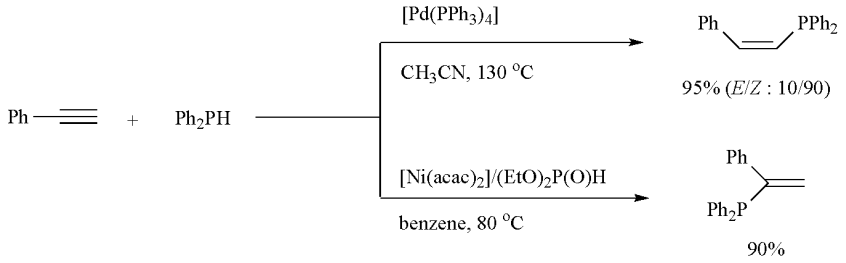



**Fig. 16.**

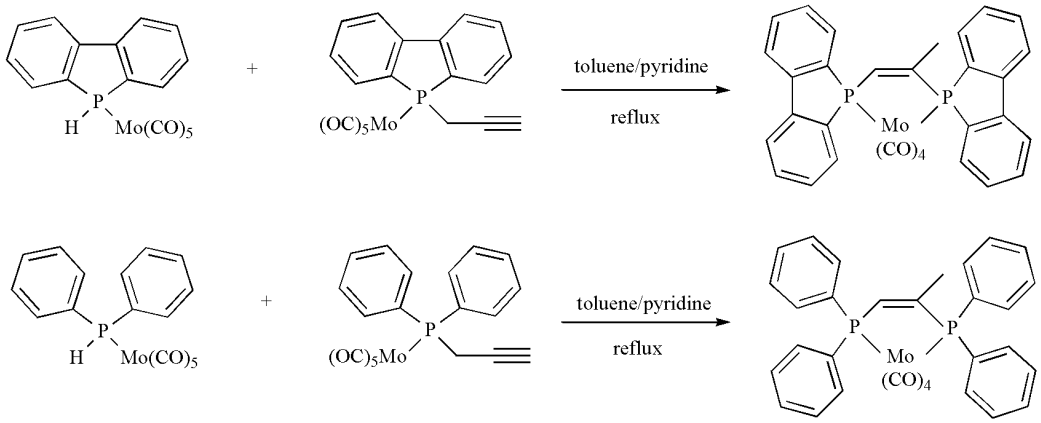



**Fig. 17.**

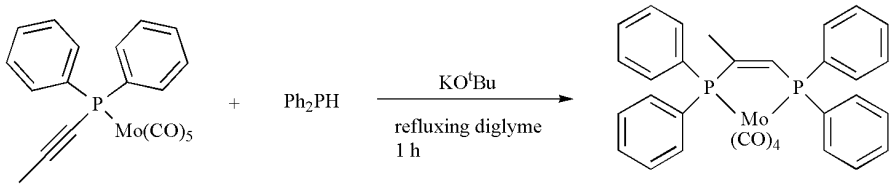



**Fig. 18.**

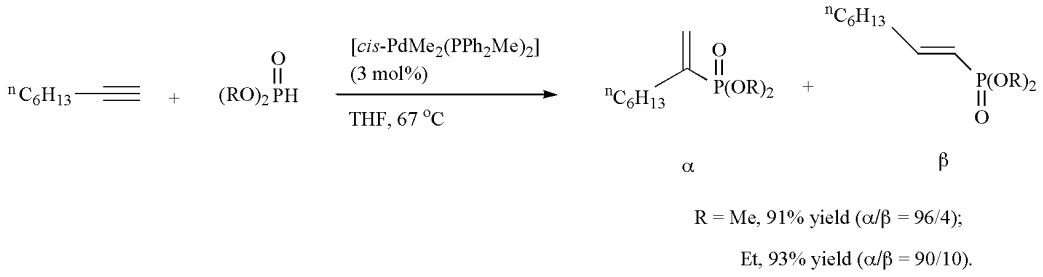



**Fig. 19.**

coordinated tertiary phosphinoalkyne complexes were reported (Fig. 17) [25].

The coordinated phosphinoalkyne [{MeC≡CP(Ph)$_2$}-Mo(CO)$_5$] was also shown to react with diphenylphosphine under more forcing conditions, in refluxing diglyme, to give one product isolated in 73% yield (Fig. 18) [25b].

Transition metal catalysts can be used in the hydrophosphorylation of alkynes. Heating a THF solution of 1-octyne and HP(O)(OR)$_2$ in the presence of 3 mol% [*cis*-PdMe$_2$(PPh$_2$Me)$_2$] at 67 °C for 5 h afforded the corresponding alkenylphosphonates in high yields (Fig. 19) [26a]. The hydrophosphorylation occurs *via* oxidative addition of HP(O)(OR)$_2$ to Pd(0), and in general, Pd(0)-complexes or readily reducible Pd(II)-complexes that have less basic ligands are able to efficiently catalyse the reaction. Such catalysts include [*cis*-PdMe$_2$(PPh$_3$)$_2$], [Pd(CH$_2$=CH$_2$)(PPh$_3$)$_2$] and [Pd(PPh$_3$)$_4$], whereas PdCl$_2$, [Pd(OAc)$_2$], [PdCl$_2$(PPh$_3$)$_2$] and [PdCl$_2$(PhCN)$_2$] were totally inactive. Both aliphatic and aromatic terminal alkynes are suitable substrates for this reaction, providing a new methodology for the general synthesis of alkenylphosphonates, not readily accessible by conventional methods [27]. Compared to terminal alkynes, the hydrophosphorylation of internal alkynes proceeded a little slower.

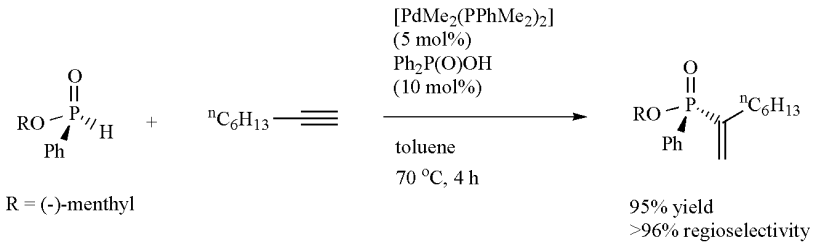
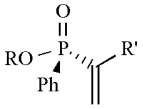
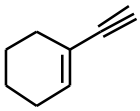
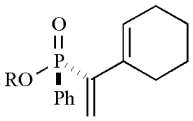
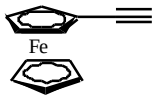
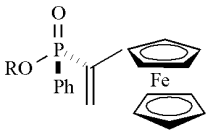
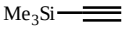
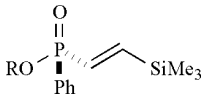
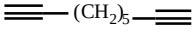
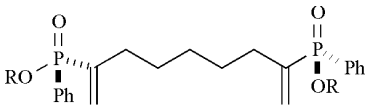
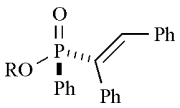



**Fig. 20.**

**Table 5.**

| Entry | Alkyne | Adduct | Yield (%) |
|---|---|---|---|
| |  |  | |
| 1 | | R' = $^{n}C_6H_{13}$ | 96 |
| 2 | | R' = H | 93 |
| 3 | | R' = Ph | 91 |
| 4 | | R' = 1-naphthyl | 81 |
| 5 |  |  | 89 |
| 6 |  |  | 60 |
| 7 |  |  | 89 |
| 8 |  |  | 65 |
| 9 |  |  | 85 |

More recently, the oxidative addition of ($R_p$)-phenylphosphinate to Pt(0) was shown to proceed with retention of configuration [26b]. On this basis, the metal-catalysed stereospecific hydrophosphination of various alkynes with ($R_p$)-phenylphosphinate was successfully developed. Extensive screening revealed [$PdMe_2(PPhMe_2)_2$]/$Ph_2P(O)OH$ to be the catalyst of choice for the addition to 1-octyne, with the α-adduct produced in high yield and regioselectivity (Fig. 20). As shown in Table 5, the stereospecific hydrophosphination was general in application. With the exception of entry 7, which gave a β-*trans*-adduct, other alkynes of both aliphatic and aromatic nature including those bearing chloro, cyano, carbonylalkoxy, olefinic and alkoxy functionalities, all afforded the ($R_p$)-vinylphosphinates in high yields and selectivities. It is noted that reactions of $Ph_2P(O)H$ shown in Table 4 lead to β products.

The first Rh-catalysed hydrophosphorylation of alkynes was recently described, taking advantage of the highly reactive five-membered cyclic hydrogen phosphonate TMDPO, [26c]. High yields of the corresponding (*E*)-alkenylphosphonates were obtained with excellent regio- and stereo-selectivities. For instance, a mixture of the phosphonate and one equiv of phenylacetylene in acetone, in the presence of 3 mol% [$RhCl(PPh_3)_3$] at room temperature, gave (*E*)-2-phenyl-1-ethenylphosphonate in quantitative yield after 1 h (Fig. 21). Notably, the reaction takes place with a complete regiochemical reversal to the Pd-catalysed

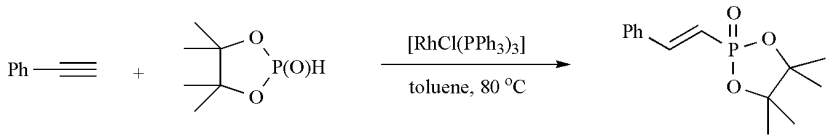
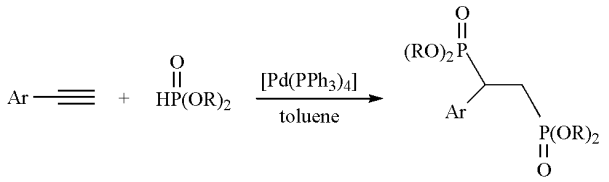



**Fig. 21.**




Ar = 2-pyridyl, 4-pyridyl, 4-nitrophenyl, 4-cyanophenyl, 2-thiazolyl

**Fig. 22.**

counterpart using acyclic phosphonates (Fig. 19). Again, the hydrophosphorylation proved generally applicable to a variety of alkynes including unsubstituted acetylene, and substituted terminal aliphatic and aromatic alkynes. Functional groups such as chloro, cyano, hydroxy, thienyl and silyl were all tolerated.

The synthesis of functional bisphosphonates *via* bis-hydrophosphorylation of alkynes with dialkylphosphonates has been realised through palladium catalysis [28]. Refluxing a mixture of 1 equiv of a terminal alkyne with 3 equiv of dialkylphosphonate in the presence of 5 mol% [$Pd(PPh_3)_4$] in toluene over a period of 19-71 h afforded a variety of vicinal bisphosphonates in between 41 and 90% yield (Fig. 22).

### 2.3 Reaction with allenes and dienes

Pd-dppf complexes (dppf = 1,1'-bis(diphenylphosphino)ferrocene) have been used to promote the addition of TMDPO to terminal allenes in the regio- and stereo-selective formation of allylphosphonates [29a]. Heating a mixture of 1,2-heptadiene and TMDPO in the presence of a catalytic amount of [$PdMe_2$(dppf)] gave the allylic phosphonate in high yield and stereoselectivity (Fig. 23). Other regioisomers were formed but only in negligible amounts. The method was applied to other terminal allenes, and each time the *trans* allylic adducts resulted, even though they required addition to the more sterically congested face of the terminal double bond (Table 6).

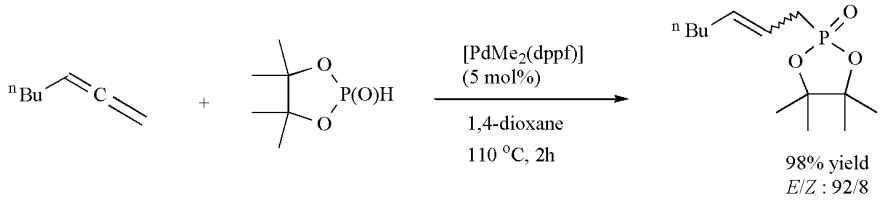
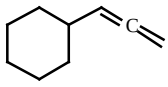
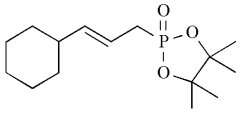
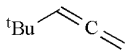
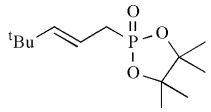
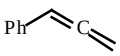
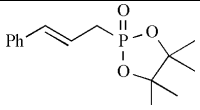
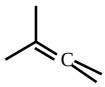
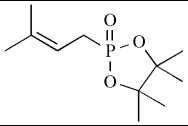
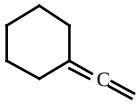
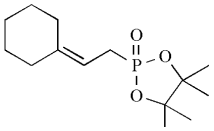
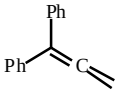
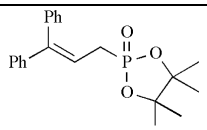



**Fig. 23.**

**Table 6.**

| Entry | Allene | Product | Conditions | % Yield (*E*/*Z*) |
|---|---|---|---|---|
| 1 |  |  | 100 °C, 6 h | 61 (94/6) |
| 2 |  |  | 100 °C, 4 h | 81 (>99/1) |
| 3 |  |  | 100 °C, 1 h | 87 (>99/1) |
| 4 |  |  | 100 °C, 4 h | 66 |
| 5 |  |  | 80 °C, 18 h | 89 |
| 6 |  |  | 80 °C, 18 h | 92 |

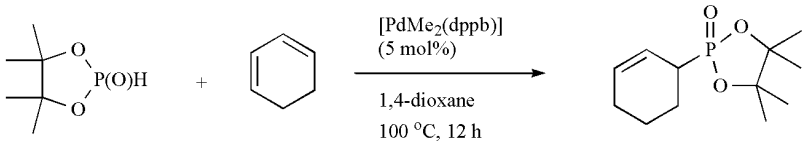
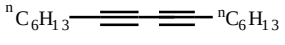
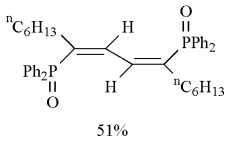
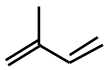
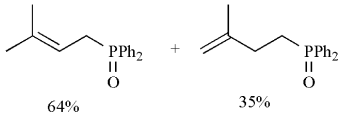
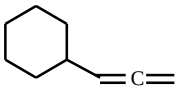
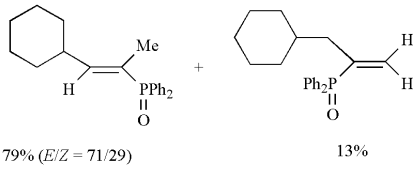



**Fig. 24.**

**Table 7**

| Entry | Substrate | Conditions | Product and yield (%) |
|---|---|---|---|
| 1 |  | -35 °C, 3 h |  51% |
| 2 |  | 0 °C, 1.5 h |  64% 35% |
| 3 |  | rt, 0.5 h |  79% (*E*/*Z* = 71/29) 13% |

TMDPO has also been used in the Pd-catalysed 1,4-hydrophosphorylation of 1,3-dienes, affording the corresponding allylphosphonates selectively and in high yields [29b]. When a mixture of 1,3-cyclohexadiene and TMDPO was heated in the presence of [$PdMe_2$(dppb)], the corresponding 1,4-addition product, allylphosphonate, was obtained in 76% isolated yield (Fig. 24). The same procedure was successfully applied to 2,3-dimethyl-1,3-butadiene with 80% yield, and 1,3-butadiene using [$PdMe_2$(dppf)] to give a quantitative yield with *E*/*Z* = 83/17.

The Yb-imine complex illustrated in Fig. 15 is also capable of catalysing hydrophosphination of allenes, dienes and diynes [23]. Using 10 mol% [Yb($\eta^2$-$Ph_2CNPh$)$(hmpa)_6$] and 2 equiv of $Ph_2PH$, the corresponding alkenylphosphine oxides were isolated after oxidative workup (Table 7).

## 3. P-C COUPLING

### 3.1 Formation of aryl C-P bonds

The Pd-catalysed C-C bond forming reactions have been widely exploited by organic chemists in recent years [2,30]. However, the analogous P-C forming reactions are much less known. Nevertheless, P-C coupling makes a significant contribution to the catalytic synthesis of phosphines. The Michaelis-Arbusov reaction is a well-known method for the formation of C-P bonds, but is generally not applicable to the formation of aryl C-P bonds [1a, 31]. Consequently, some of the early work in catalytic P-C coupling was concerned with the synthesis of aryl C-P bonds.

It was found in the 1980's that arylphosphonates, arylphosphinates and arylphosphine oxides could be synthesised by coupling aryl halides with a H-P bond [32]. Thus, aryl bromides reacted with 1.1 equiv of a phosphorus oxide in the presence of triethylamine and 5-10 mol% [$Pd(PPh_3)_4$] to yield the desired products in good yields (Fig. 25). Various groups such as halogen, cyano, naphthyl, pyridyl and nitro functionalities were tolerated in the synthesis of phosphonates, but lower yields were obtained for phosphine oxides when the aryl bromide contained electron donating groups.

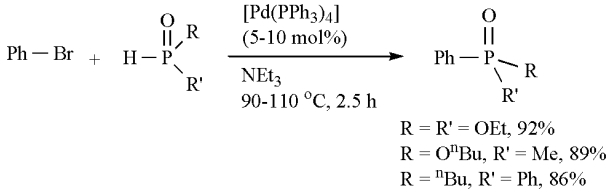



**Fig. 25.**

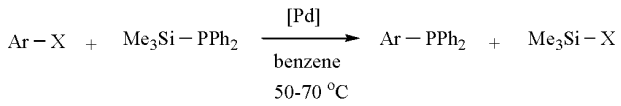



**Fig. 26.**

Aryl phosphines were also obtained *via* the Pd catalysed coupling of aryl halides with Si-P and Sn-P bonds, for example, (trimethylsilyl)diphenylphosphine and (trimethylstannyl)diphenylphosphine, under relatively mild conditions (Fig. 26) [33]. Substituted aryl iodides were generally phosphinated in yields of up to 94% regardless of the electronic nature of the substituent. However, aryl bromides could only be phosphinated at higher temperatures (105 °C) in moderate yields between 40 and 65%. Methyl ethers, esters, ketones, nitriles, anilides and certain halogens were tolerated but not nitro, aldehyde, hydroxyl or amino groups. Stannylphosphines reacted about twice as fast as silylphosphines, but being cheaper and less toxic the latter were preferred. The catalysts used were $[PdCl_2(PPh_3)_2]$ and $[PdCl_2(MeCN)_2]$.

Pd-catalysed substitution of triflates derived from Tyrosine-containing peptides was later shown to be effective in forming C-P bonds [34]. Tyrosyl peptides could be converted to their corresponding triflates in excellent yields with *N*-phenyltriflimide. Addition of $(EtO)_2P(O)H$ in the presence of $[Pd(PPh_3)_4]$ gave good to excellent yields of the diethyl arylphosphonates (Fig. 27).

Following these successes, a number of aryl phosphines and related compounds have been made *via* the P-C coupling route. A convenient and general route to monoarylphosphinic acid methyl esters as well as symmetrical and unsymmetrical methyl diarylphosphinates was realised utilising such palladium catalysis [35]. Even though methylphosphinate rapidly decomposes, methyl arylphosphinates were obtained using 2-5 mol% $[Pd(OAc)_2]$ in 46-80% yield (Fig. 28). Symmetrical diarylphosphinates were obtained in 49-59% yield by reducing the amount of methylphosphinate. A sequential process without isolation of the mono aryl derivative installed dissimilar aryl substituents, Ar and Ar'. The first aryl substituent was introduced in the same manner as for methyl arylphosphinates. The excess methylphosphinate was filtered off, and the crude material then allowed to react with the second aryl iodide with 3 mol% $[Pd(PPh_3)_4]$ to furnish the products in 44-51% yield. Aryl bromides and triflates reacted similarly to, though more slowly than, iodides in most cases. The procedures are compatible with a variety of functionalities, including nitriles, alcohols, and formate esters.

Tertiary arylphosphine oxides can be accessed by Pd-catalysed P-C coupling reaction of an aryl halide with $[P(CH_2OH)_4][Cl]$ [36]. For example, when 4-bromofluorobenzene and 5 equiv of $[P(CH_2OH)_4][Cl]$ were combined in the presence of 3 mol% Herrmann-Beller palladacycle catalyst [37], the coupling products were

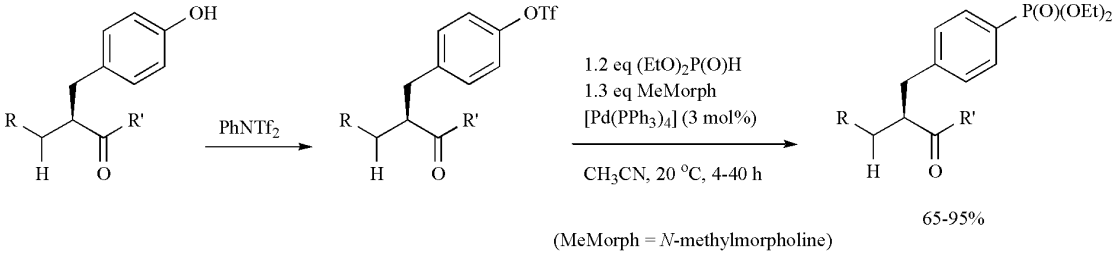



**Fig. 27.**

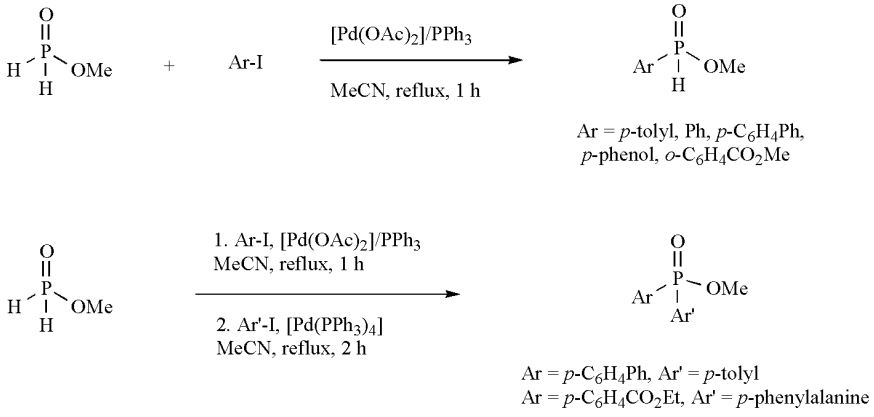



**Fig. 28.**

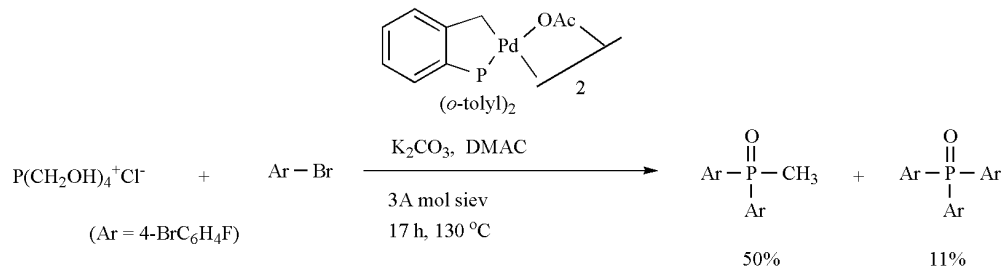



**Fig. 29.**

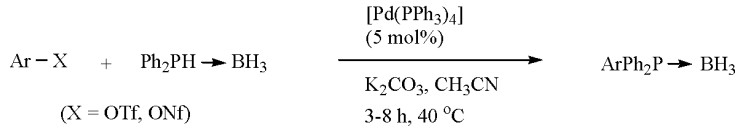



**Fig. 30.**

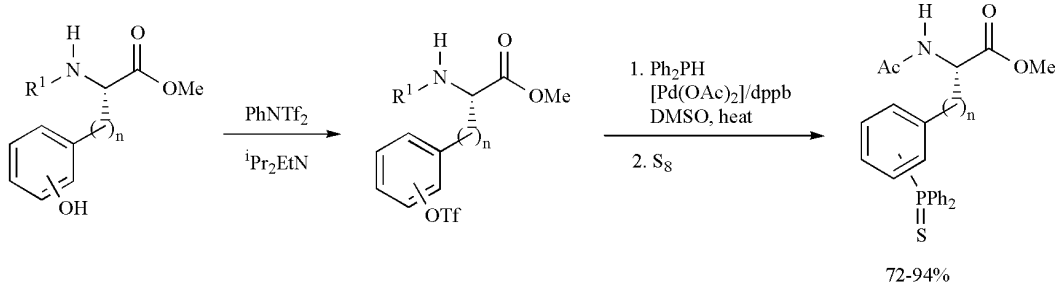



**Fig. 31.**

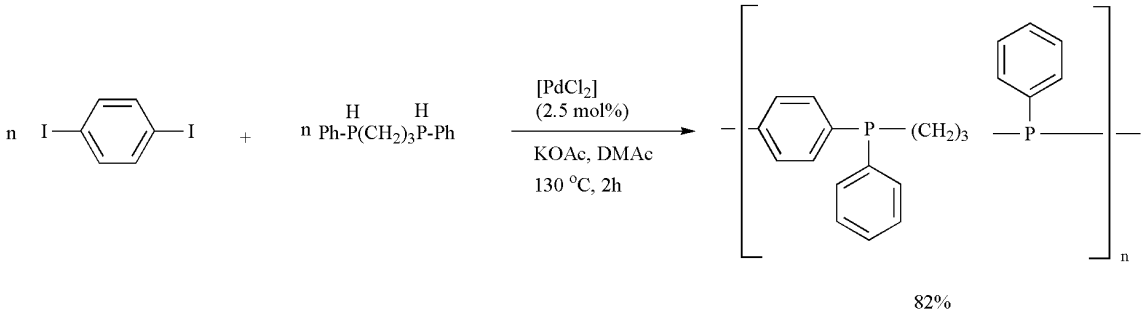



**Fig. 32.**

obtained in 61% yield (Fig. 29). This is an interesting reaction, as hydroxymethylphosphines are easier to handle than simple phosphorus precursors such as $PR_3$ (R = H, alkyl).

Borane-protected phosphines could also be brought to couple with aryl nonaflates or triflates to form unsymmetrical triarylphosphine boranes, useful precursors to the analogous phosphines (Fig. 30) [38]. An advantage of the approach is that the problem of oxidation to the phosphine oxide is eliminated. However the methodology suffers in that the phosphine boranes are sensitive to amines.

Phosphine-containing amino acids were accessed *via* the Pd-catalysed coupling of amino acid triflates with diphenylphosphine (Fig. 31) [39]. Reaction of the triflate with $Ph_2PH$ in the presence of $[Pd(OAc)_2]$/dppb gave the phosphine amino acid in good yield; however, racemistion of the α-carbon occured. Replacement of the acetate with a $^t$Boc protecting group allowed the reaction to be run without racemisation. The air-sensitive phosphine group was converted to a phosphine sulfide (stable to chromatography), which can easily be removed by Raney-Ni. In comparison with the synthesis of BINAP *via* coupling of $Ph_2PH$ with the binaphthol ditriflate in which a nickel catalyst was required (discussed in section 3.4), using a nickel catalyst in Fig. 31 resulted in cleavage of the acid protecting group, along with formation of the phosphine product. Pd was a more suitable catalyst here; but it is interesting to note the reaction depicted in Fig. 31 did not work in DMF, in which the BINAP synthesis was conducted and failed when attempted with a Pd catalyst.

P-C coupling has been applied to the synthesis of polymeric phosphines. The Pd-catalysed coupling reaction of diiodobenzenes with secondary phosphines afforded poly(arylenediphosphine)s [40]. For example, 1,4-diiodobenzene and 1 equiv of 1,3-bis(phenylphosphino)propane in *N*,*N*-dimethylacetamide (DMAc) in the presence of $[PdCl_2]$ gave a polymeric product in 82% yield (Fig. 32). The

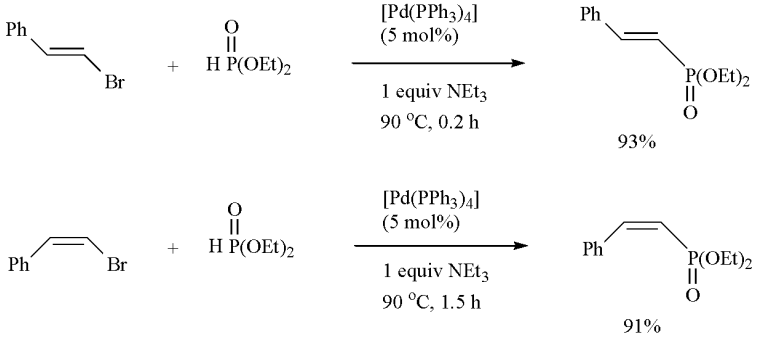



**Fig. 33.**

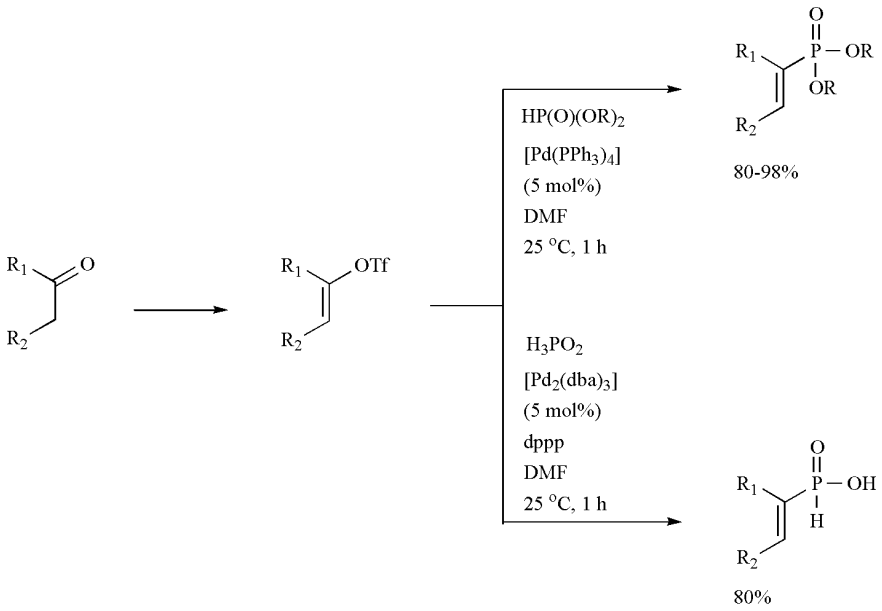



**Fig. 34.**

polycondensation reaction was performed with several aryl dihalides, with some functional group tolerance. The poly(arylenediphosphine)s consisted of repeating units analogous to DPPP, one of the very useful chelating phosphine ligands in catalysis.

Arylation reactions discussed above have been extensively exploited for the synthesis of several classes of catalytically important phosphines, such as those that are water-soluble and those that contain binaphthyl units. These reactions are dealt with separately in sections 3.3 and 3.4.

### 3.2 Formation of vinyl C-P bonds

The synthesis of vinylphosphonates *via* P-C coupling can be traced back to 1970, with the direct reaction of vinyl bromides and trialkylphosphites in the presence of nickel halides [41]. However, conversion was low and the stereochemistry of the products were not clarified. Ten years later, the stereoselective synthesis of vinylphosphonates *via* the reaction of vinyl bromides with dialkylphosphonate in the presence of $[Pd(PPh_3)_4]$ was reported [42]. (*E*)- and (*Z*)-β-bromostyrenes gave (*E*)- and (*Z*)-styrylphosphonates in 93% and 91% yields respectively (Fig. 33).

The preparation of α,β−unsaturated phosphonates and phosphinates from alkenyl triflates *via* Pd(0)-catalysed coupling with dialkylphosphites or hypophosphorus acid was later described (Fig. 34) [43].

1- and 2-alkoxy or dialkylaminovinyl phosphonates were synthesised using reactions of the corresponding vinyl halides with di- and tri-ethylphosphites in the presence of catalytic amounts of nickel salts and palladium complexes [44]. $[Pd(PPh_3)_4]$ is the catalyst of choice for 1-alkoxy or 1-dialkylaminovinyl phosphonates, and $[NiBr_2]$ was preferred in the synthesis of 2-alkoxy or 2-dialkylaminovinyl phosphonates (Fig. 35).

(*E*)-Vinylphosphonates were also obtained under mild conditions *via* the Pd-catalysed cross coupling of (*E*)-vinyl iodides with dialkylphosphates (Fig. 36) [45]. The former are not easily available and their preparation by the reaction of vinylzirconocenes with iodide is the key feature. (*E*)-Vinyl bromides could also be made from the vinylic zirconium

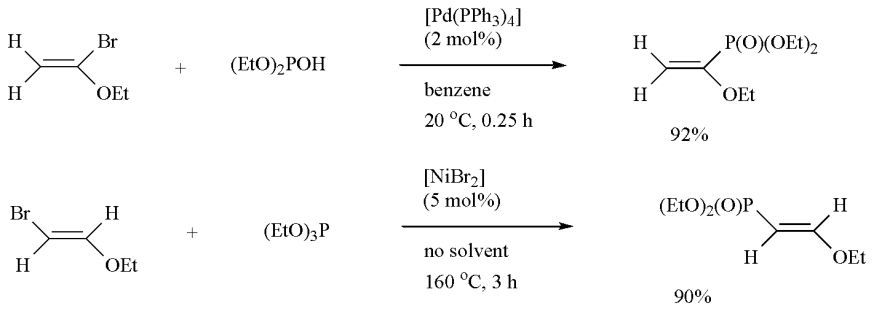



**Fig. 35.**

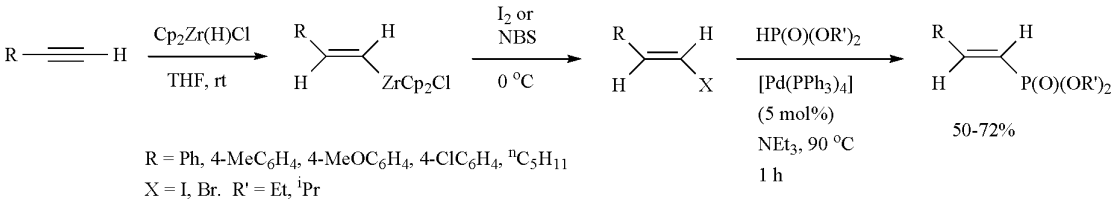



**Fig. 36.**

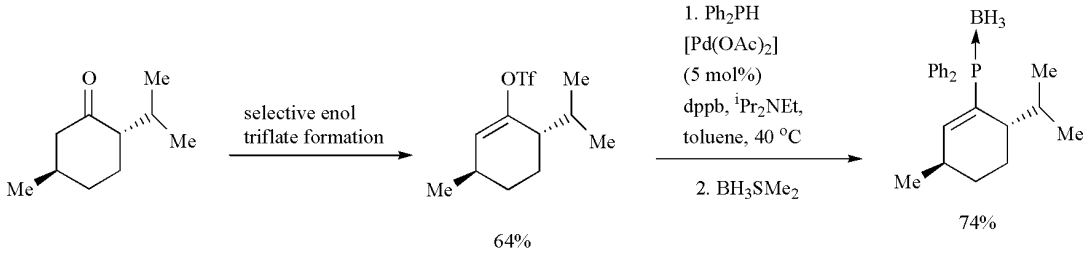



**Fig. 37.**

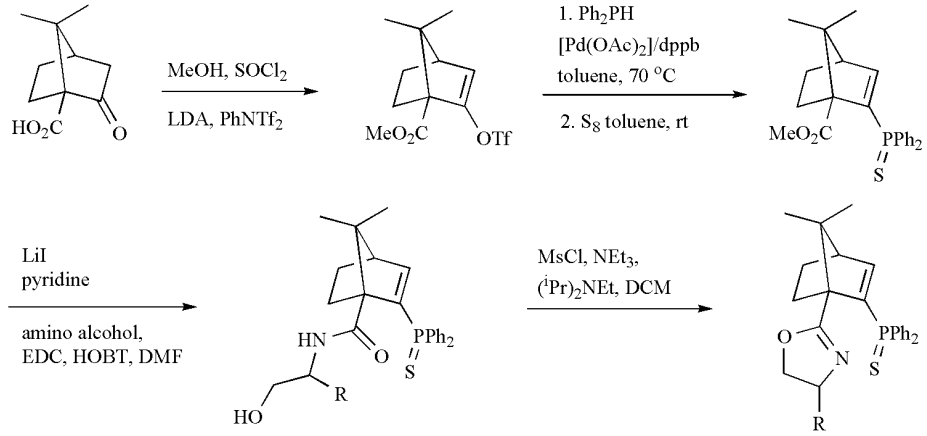



**Fig. 38.**

complex by reacting with *N*-bromosuccinimide (NBS). These were coupled with the dialkylphosphites to give (*E*)-vinylphosphonates with slightly lower yields than their iodo counterparts.

The direct conversion of vinyl triflates to chiral phosphines has recently been reported [46]. Selective enolization of a variety of chiral ketones was followed by trapping of the enolate as the vinyl triflate, and subsequently through Pd-catalysis, the corresponding vinylphosphines were obtained which could be reduced to alkylphosphines (Fig. 37). This approach for chiral phosphines is attractive, as the triflates are readily available from the pool of chiral ketones.

The development of this transformation has led to the synthesis of novel phosphine ligands using commercially available chiral ketones. Chiral P,N-ligands were synthesised from (1*S*)-(+)-ketopinic acid using Pd-catalysed coupling of a vinyl triflate and either a diaryl or dialkylphosphine (Fig. 38) [46b]. The ketopinic acid was converted to the methyl ester, which was converted to the corresponding vinyl

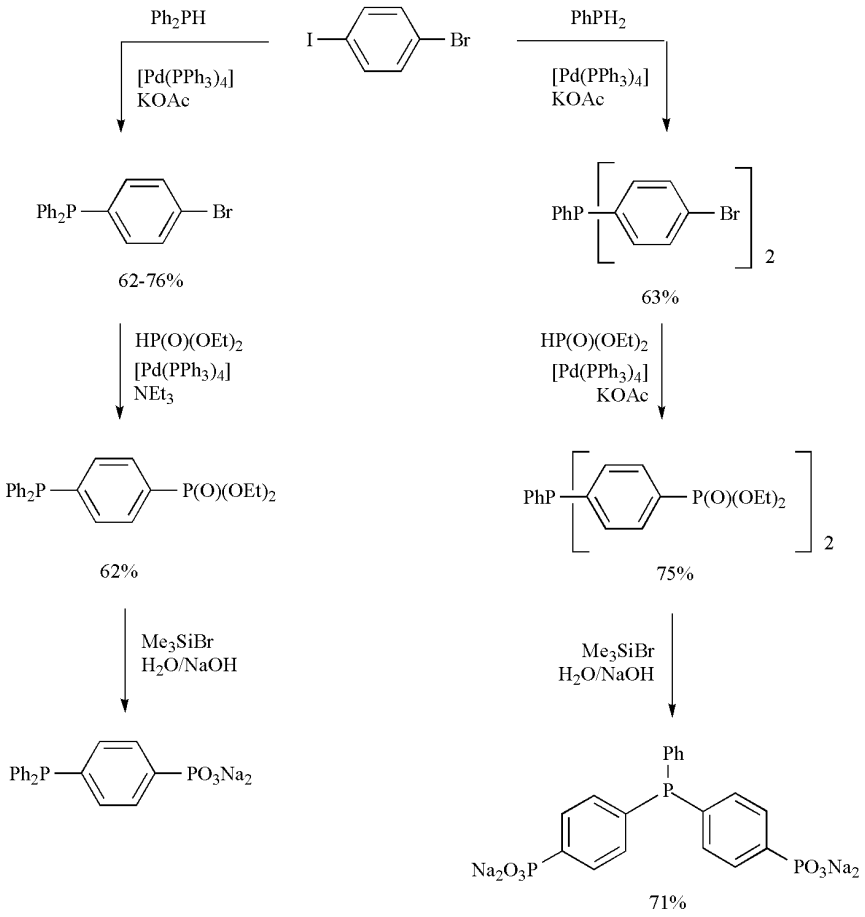



**Fig. 39.**

triflate. Pd-catalysed coupling with diphenylphosphine was followed by protection of the phosphine as its sulfide, to which the oxazoline unit was added. The free phosphine was generated by reaction with Raney Ni.

### 3.3 P-C Coupling in the Synthesis of Water-Soluble Phosphines

Water-soluble phosphines have been extensively investigated for catalysis in the past one decade or so, the best example being probably TPPTS [TPPTS = P(*m*-$C_6H_4SO_3Na)_3$] [2a]. TPPTS is made by sulfonation of phosphines with oleum and has successfully been applied to commercial biphasic hydroformylation. Sulfonated arylphosphines can also be obtained by nucleophilic aromatic substitution with $PH_3$ or primary and secondary phosphines in the superbasic medium DMSO/KOH [47a,b]. An alternative to these methods is to use Pd-catalysed P-C coupling. Thus, phosphines of the type $Ph_2PAr$ and $PhPAr_2$, containing mono- and di-substituted aromatic rings that possessed polar substituents, were obtained in good yields by Pd(0)-catalysed cross coupling of phenyl- or diphenylphosphine with substituted bromo- or iodo-benzenes [47c,d]. $[Pd(OAc)_2]$ and $[Pd(PPh_3)_4]$ can be used as catalysts, and as expected, the C-Br bonds reacted much slower than the C-I variants. An interesting application of the P-C coupling chemistry to the synthesis of water-soluble phosphines is observed in the consecutive Pd-catalysed P-C coupling reactions shown in Fig. 39 [47e]. (*p*-Bromophenyl)diphenylphosphine and bis(*p*-bromophenyl)phenylphosphine were first obtained in high yields by reaction of *p*-bromoiodobenzene with diphenylphosphine and phenylphosphine respectively in the presence of 0.1 mol% $[Pd(PPh_3)_4]$. The base used was KOAc and the mixture was heated in DMAc at 130 °C for 5 d. The *m*- and *o*-isomers were also accessible by this procedure. From here, the phosphonic ester group was introduced by an additional P-C coupling reaction that involves diethylphosphite in toluene at 80 °C for 2-3 d. The final ionic derivatives were obtained by transesterification with $Me_3SiBr$ and hydrolysis with aqueous NaOH.

Cationic phosphines containing a guadininium group show pronounced solubility in water due to their highly polar functions and are also accessible *via* P-C coupling. Monocationic guanidiniumphenylphosphines were synthesised in high yields by reaction of *p*-iodophenylguanidines with $Ph_2PH$ in the presence of a catalytic amount of $[Pd(OAc)_2]$ (Fig. 40) [47f]. Due to the strongly basic character of the guanidinium groups, no extra base was required, unlike the P-C coupling reactions previously

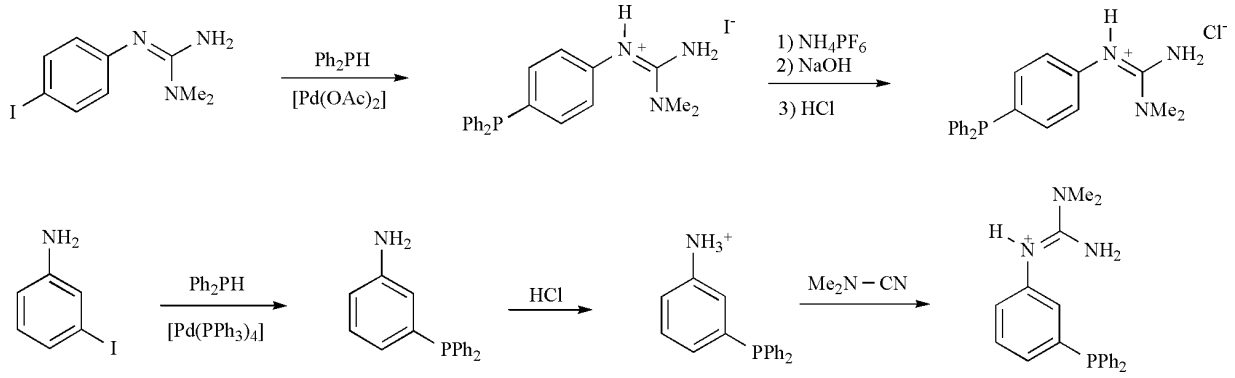


**Fig. 40.**

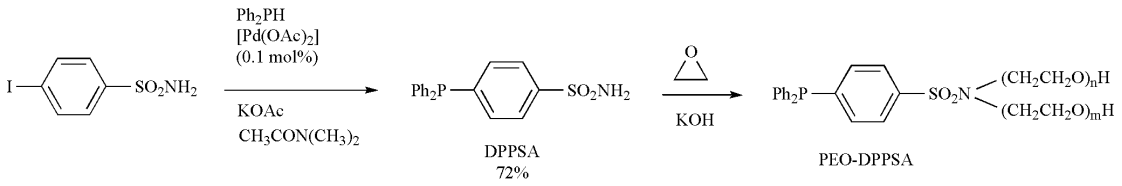


**Fig. 41.**

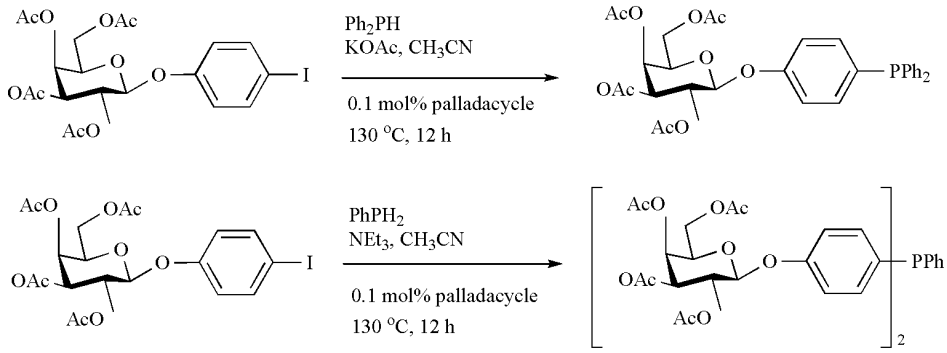


**Fig. 42.**

described [47a,b]. The synthesis of monocationic guanidiniumphenylphosphines could also be achieved by introducing the guanidinium group in the last step. *m*-Aminophenylphosphine was prepared from the Pd-catalysed coupling of diphenylphosphine with *m*-iodoaniline [47d]. Subsequent addition of aqueous HCl and the introduction of the guanidinium group by the well-established addition of anilinium salts to cyanamides [48] gave the guanidinium phosphines in high yields (Fig. 40) [47g]. The synthesis of dicationic guanidiniumphenylphosphines was carried out similarly to that of the monocationic phosphine, using *p*-iodophenylguanidine and phenylphosphine as substrates and $[Pd(PPh_3)_4]$ as catalyst. If the bromophenylguanidine was employed instead of its iodo analogue, the P-C coupling reaction proceeded much slower.

P-C coupling was also used to prepare a novel, non-ionic, water-soluble phosphine, PEO-DPPSA (Fig. 41) [49]. Coupling between *p*-I-$C_6H_4SO_2NH_2$ and $Ph_2PH$ using $[Pd(OAc)_2]$ as catalyst gave DPPSA, and subsequent ethoxylation with ethylene oxide catalysed by KOH gave PEO-DPPSA.

Water-soluble, carbohydrate-substituted phosphines have been made in a similar manner (Fig. 42) [50]. These phosphines are a new class of hydrophilic ligands for two-phase catalysis, which resemble PEO-DPPSA but contrast to the well-known sulfonated phosphines in that the hydrophilic character of the ligands is attributed to a neutral carbohydrate moiety. The phosphines were synthesised by the coupling of a carbohydrate-substituted aryl iodide with $Ph_2PH$. The reaction proceeded smoothly to one single product in 85% yield in the presence of 0.1 mol% Herrmann-Beller palladacycle catalyst. However, when $[Pd(OAc)_2]$ was used, a mixture of various phosphine products was observed. The reaction of $PhPH_2$ with 2 equiv of the carbohydrate-substituted aryl iodide was also useful, leading to a bis-glycosylated triphenylphosphine in 48% yield (Fig. 42).

Polymers can play an important role as recoverable catalyst support in aqueous/organic biphasic catalysis. Using

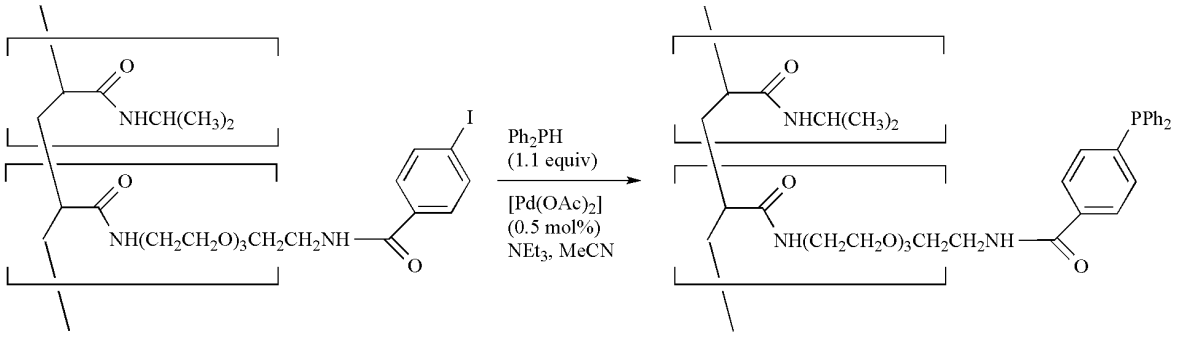



**Fig. 43.**

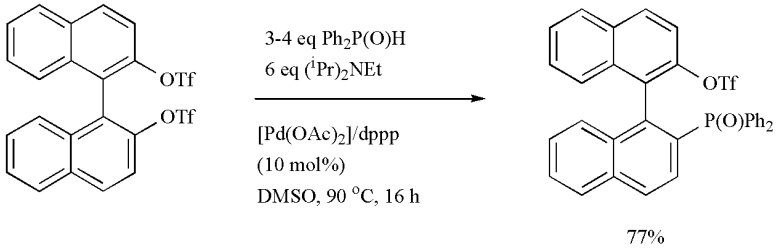



**Fig. 44.**

the now well-known chemistry of Pd(0)-catalysed P-C coupling of aryl halides with $Ph_2PH$, an extension to include polymer bound aryl iodide substrates resulted in a simple route to polymeric phosphines (Fig. 43) [51]. Exposure of the polymer bound aryl iodide to $Ph_2PH$ and $[Pd(OAc)_2]$ in $CH_3CN$ led to 98% conversion to the polymer bound triarylphosphine. The fact that the catalyst tolerates an excess of phosphine and the soluble polymeric phosphines are effective ligands for palladium in their own synthesis make this a self-replicating ligand synthesis. These ligands are typically prepared by nucleophilic substitution. The example illustrated here shows that P-C coupling is an easy alternative in preparing polymeric triarylphosphines.

### 3.4 Synthesis of BINAP-Type Ligands

The pioneering work, which demonstrated the potential of Pd-catalysed reactions in the synthesis of phosphines containing an axially chiral binaphthyl skeleton, came in 1990 with the Pd(0)-catalysed stereospecific functionalisation of chiral 1,1'-bi-2-naphthol *via* its triflate (Fig. 44). [52]. This work had obvious relevance given the success of BINAP-type ligands for catalytic asymmetric induction around that time [2c]. Starting with the chiral binaphthol ditriflate and diphenylphosphine oxide in the presence of $[Pd(OAc)_2]$/dppp, monophosphorylation occurred to give the product in 77% yield with no loss of enantiopurity. With no observation of bisphosphorylation products, the procedure fell short in the synthesis of BINAP, but showed that substitution reactions of this type could potentially be used to stereospecifically functionalise the axially chiral binaphthyl unit.

The preparation of chiral monodentate phosphine ligands was described later, in which the monophosphorylation of the chiral binaphthyl ditriflate was achieved by a slight modification of the procedure shown in Fig. 44. Using $[Pd(OAc)_2]$/dppb, the ditriflate could be monophosphorylated with $Ph_2P(O)H$ and $An_2P(O)H$ (An = *p*-$MeOC_6H_4$) to give the corresponding products in 93-95% yield. Hydrolysis of the remaining triflate, followed by alkylation with an alkyl halide in the presence of base proceeded in high yields (91-98%). Reduction of the phosphine oxide gave 2-(diarylphenylphosphino)-2'-alkoxy-1,1'-binaphthyls (MOPs) in good to excellent yields (63-97%) (Fig. 45) [53].

Furthermore, alkyl substituents could be introduced at the 2'-position at the (diphenylphosphino)binaphthyl skeleton by a Ni-catalysed cross coupling reaction with a Grignard reagent using $[NiCl_2(dppe)]$ (Fig. 46). The reactions in Figs. 45 and 46 proceeded without racemisation in the synthesis of an array of electronic and sterically diverse MOPs, with *R*- and *S*-configuration from (*R*)- and (*S*)-Binaphthol [53].

In the search for a methodology for the preparation of carboxylated phosphines and their oxides, some of which bear a close relationship to the MOPs shown in Fig. 45, secondary phosphines were coupled with aryl triflates through Pd-catalysis [54]. Various phenyl triflates were first coupled with $Ph_2PH$ using $[PdCl_2(PPh_3)_2]$/dppp. However, the corresponding phosphine oxides were obtained rather than the phosphines. A plausible explanation given for the formation of the oxides is that $Ph_2PH$ was completely oxidised to $Ph_2P(O)H$ during the initial stages of the reaction. Hence, the key phosphinylation reagent is $Ph_2P(O)H$. A limitation was discovered for naphthyl triflates,

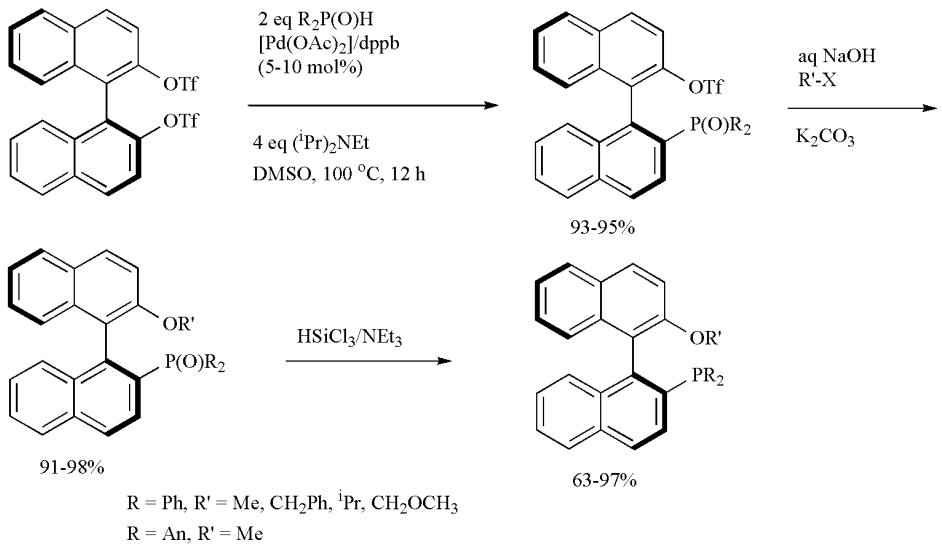



**Fig. 45.**

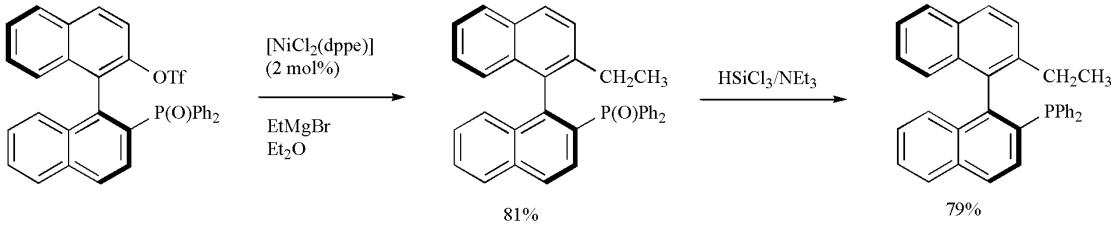



**Fig. 46.**

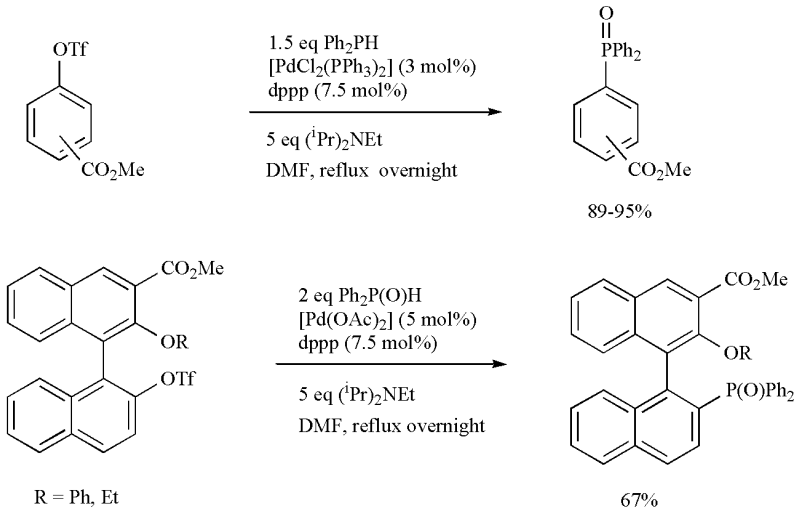



**Fig. 47.**

which failed to react under the conditions employed. Application of the Ni-protocol discussed below [56] was also not successful. However, the desired conversion was achieved using conditions comparative to those shown in Fig. 44, in which $Ph_2P(O)H$, instead of $Ph_2PH$ was used as substrate (Fig. 47).

Previously in the synthesis of BINAP, problems arose due to a low yielding bromination reaction in which hot hydrogen bromide was evolved. Also, a resolution step was necessary that resulted in a low yield for the entire sequence [55]. An efficient approach to the synthesis of BINAP would be to react diphenylphosphine directly with the chiral binaphthyl ditriflate. However, a few problems exist with such a strategy. In nucleophilic replacement chemistry, using reagents such as $LiPPh_2$ would likely result in the attack at the sulfur of the triflate group instead of the carbon centre. Alternatively, palladium catalysis could be used; but a

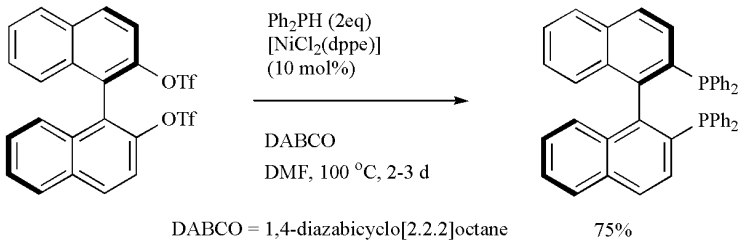



**Fig. 48.**

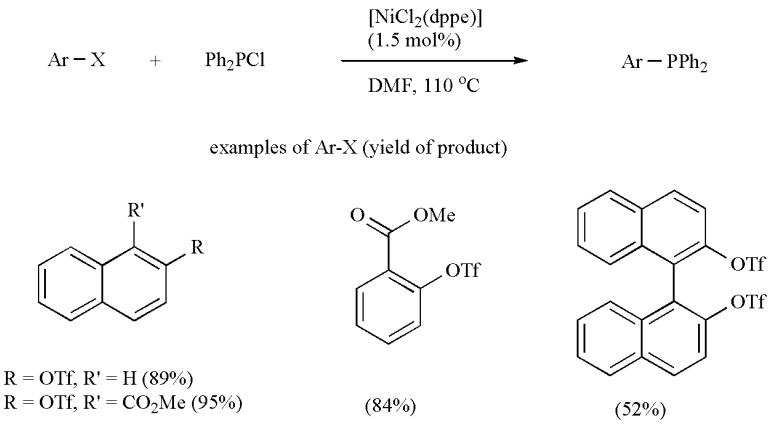



**Fig. 49.**

potential problem is catalyst poisoning by $Ph_2PH$ or more probably by BINAP. Hence, in the first known example of an aryl triflate to arylphosphine conversion using $Ph_2PH$ as a reagent, nickel was chosen over palladium as the catalyst on the basis that it is smaller and harder, and according to hard-soft acid-base theory, should be less probable to bind to BINAP. Heating a mixture of a chiral binaphthyl ditriflate and diphenylphosphine in DMF provided the desired chiral BINAP in 75% yield with no racemisation (Fig. 48) [56]. Notably the reaction was not possible with palladium.

Tertiary phosphines could also be prepared from aryl triflates by Ni-catalysed cross coupling with $Ph_2PCl$ in the presence of Zn (Fig. 49) [57]. The methodology appears to be general for the synthesis of a range of phosphines, in which aromatic sulfonates, aromatic halogens, benzylic bromides and vinyl bromides/iodides could be used as substrates. The cross coupling occured with *ortho*-substituted substates, with tolerance to amides but not carboxylic acids. Noteworthy is the preparation of the *S*-isomer of BINAP by this methodology, which has the advantage of avoiding the pyrophoric $Ph_2PH$ as starting material. $Ph_2PCl$ is relatively inexpensive and available for large-scale use.

Recently, water-soluble BINAP-derivatives have been synthesised by the P-C coupling reaction [58]. Pd(0)-catalysed coupling of diethylphosphonate with brominated and bis-brominated BINAP oxide, obtained *via* the bromination of a BINAP oxide in the presence of pyridine, led to the mono- and bis-phosphorylated BINAP oxides in *ca* 50% yield. Reduction of the phosphine oxide followed by hydrolysis of the dialkylphosphonate group gave rise to the water-soluble, phosphonic acid-substituted BINAP derivatives (Fig. 50).

Binaphthyl based P,N-ligands have also been made available *via* similar reactions. For instance, carboxylated binaphthyl phosphines were prepared from racemic binaphthol using the conditions described earlier [53], which could then be used as starting materials in the synthesis of $C_1$-symmetric chiral phosphino-oxazoline ligands (Fig. 51) [59]. The overall synthesis furnished both (*S*,*S*) and (*S*,*R*) diastereoisomers at the same time, and utilised racemic binaphthyl building blocks avoiding the expensive enantiomerically pure compounds. All the phosphorus-containing intermediates existed as oxides, which are air stable, with the free phosphine obtained by reduction in the last step.

In another example of chiral P,N-ligand synthesis, the amino triflate shown in Fig. 52 was coupled with $Ph_2P(O)H$ in the presence of $[Pd(OAc)_2]$/dppp in DMSO, affording the binaphthyl aminophosphine oxide in 76% yield [60]. The triflate was obtained by optical resolution of the corresponding amino alcohol, which was methylated and triflated. Reduction of the oxide with $HSiCl_3$ in the presence of $NEt_3$ yielded 90% of the free phosphine.

## 4. SYNTHESIS OF PHOSPHINES *VIA* C-C COUPLING

### 4.1 Non-Catalytic C-C Coupling

Catalytic C-C coupling in the synthesis of phosphine ligands is relatively rare, but examples of non-catalytic reactions are well known [1a,61]. A few recent examples in the latter category are presented first, which lead to the

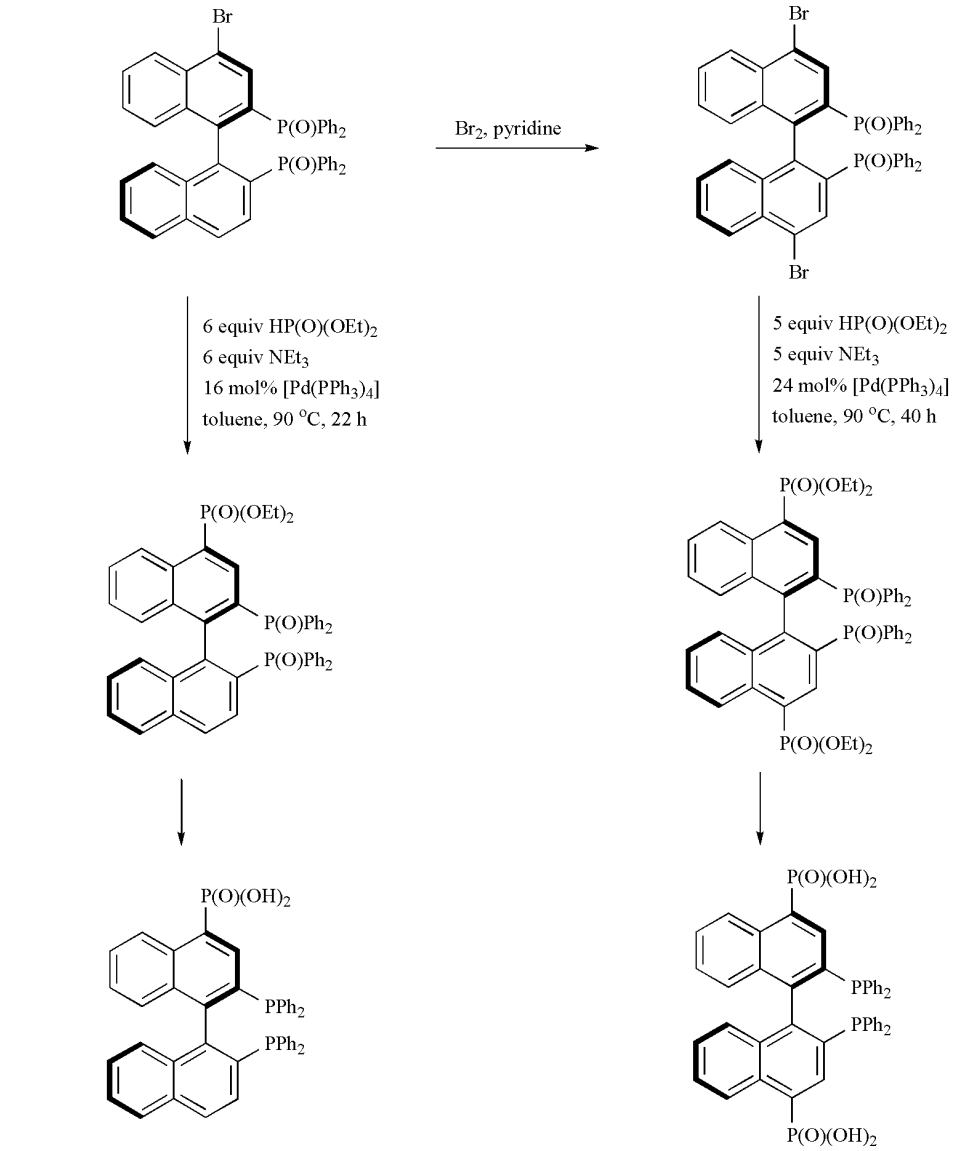



**Fig. 50.**

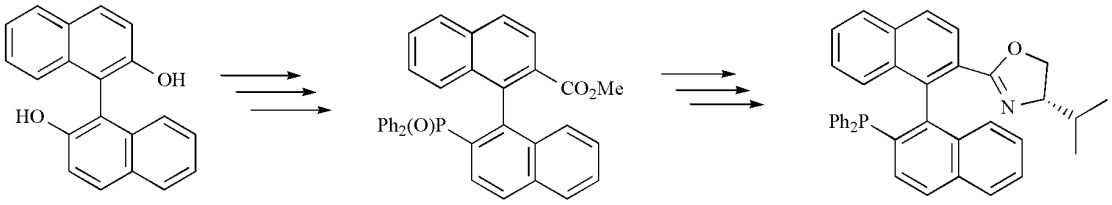



**Fig. 51.**

synthesis of interesting chiral phosphines. Using the related chemistry of phosphine-boranes [61,62], air-stable bis(phosphine-boranes) were prepared by oxidative coupling of dimethylalkylphosphine-boranes, available *via* a three step, one-pot procedure from $PCl_3$ (Fig. 53) [63]. The chirality was introduced when the phosphine-boranes were deprotonated in the presence of (-)-sparteine [64]. The tertiary bis(phosphine-boranes) were obtained in 30-40% overall yield with ee's in excess of 99%. Deboronation with trifluoromethanesulfonic acid or tetrafluoroboronic acid yielded almost quantitatively a new class of $C_2$-symmetric *P*-chiral bis-phosphines that contained an ethane backbone. Bis-phosphines with a methane backbone were similarly prepared (Fig. 53). Enantioselective deprotonation of dimethylalkylphosphine-boranes, followed by treatment with alkylphosphorus dichloride afforded optically pure bis(phosphine-boranes) in 13-28% yield after recrystallisation from ethanol. The boronato group was removed as before in almost quantitative yields.

Transition metal complexes of pyridyl-substituted phosphines have been shown to be effective catalysts in

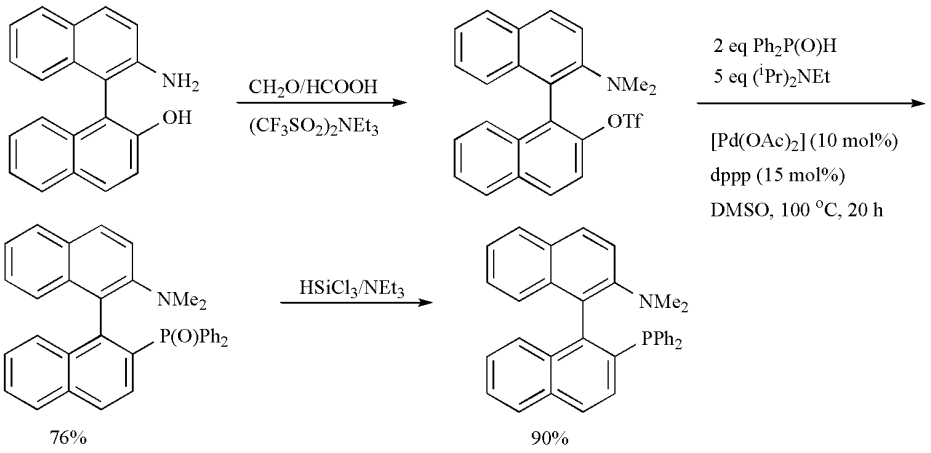



**Fig. 52.**

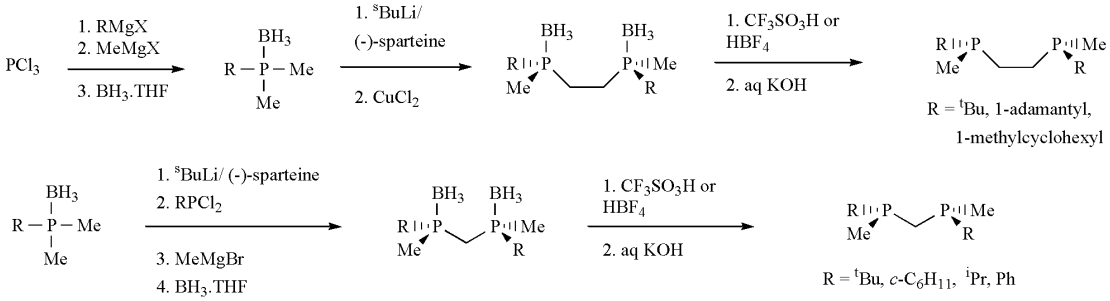



**Fig. 53.**

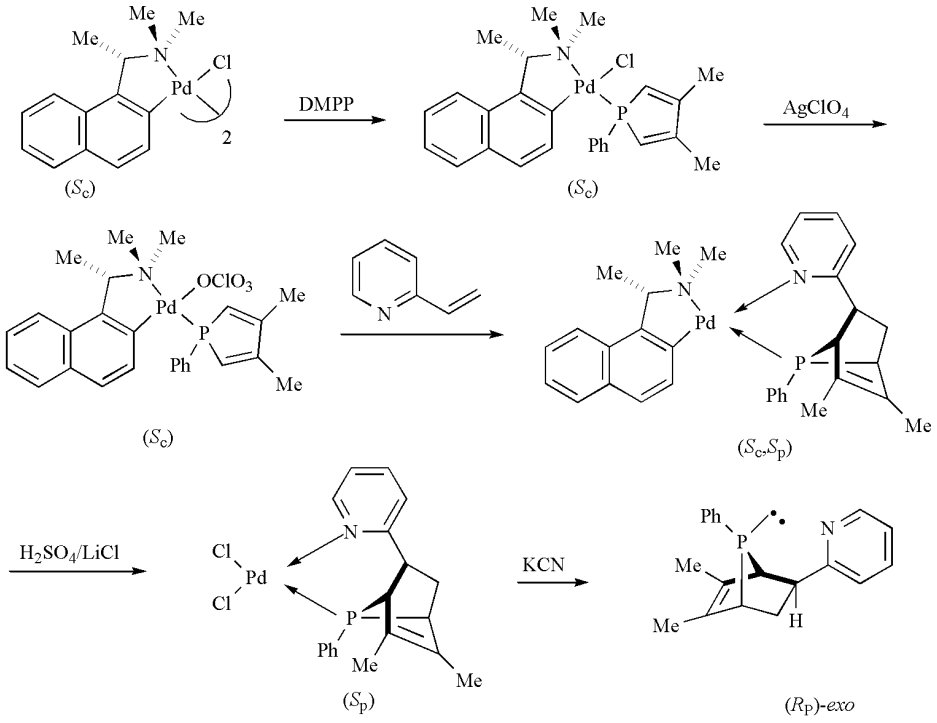



**Fig. 54.**

reactions such as carbonylation, epoxidation and cycloadditions [65]. These rarely involve the optically active phosphines containing resolved tertiary phosphorus stereocentres, perhaps due to the difficulty of synthesis or optical resolution. An efficient approach to various stereoisomeric forms of the *P*-chiral pyridyl phosphines is by means of an unusual exo-endo stereochemically controlled asymmetric Diels-Alder reaction between 2-vinylpyridine and 3,4-dimethyl-1-phenylphosphole (DMPP) (Fig. 54) [66]. The chiral organopalladium complex is used as both a reaction promoter and stereochemical controller. It is noted that the apparent inversion of configuration during liberation of the free ($R_p$)-*exo* compound is merely a consequence of the Cahn-Ingold-Prelog rules [67].

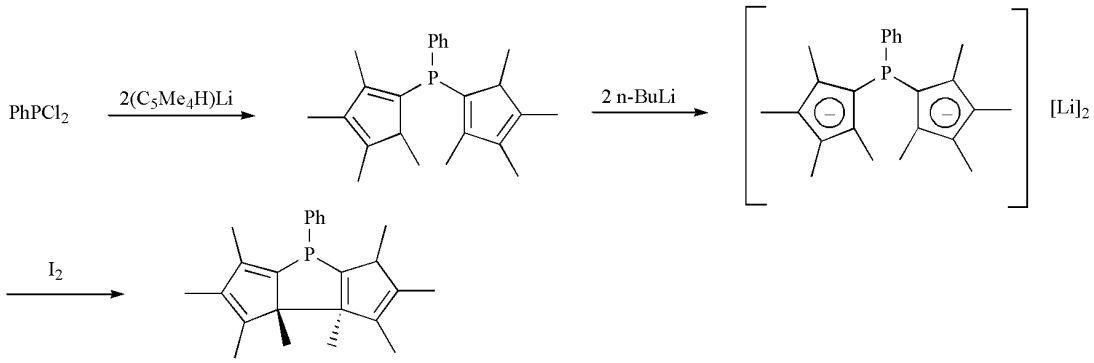
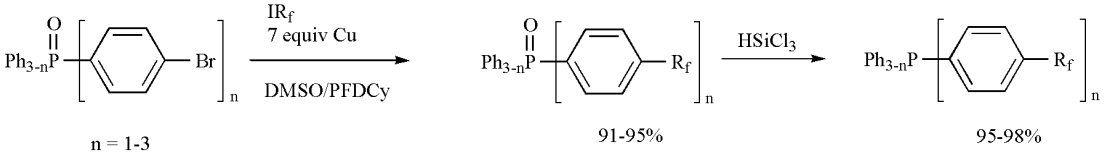



**Fig. 55.**




PFDCy = perfluoro-1,1-dimethylcyclohexane; $R_f = C_6F_{13}, C_8F_{17}$

**Fig. 56.**

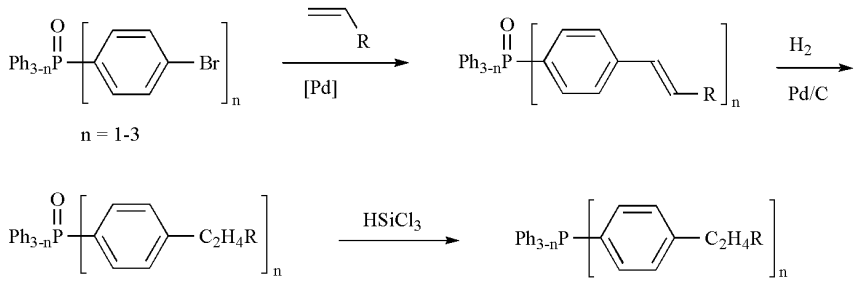



**Fig. 57.**

The intramolecular C-C coupling of tetramethylcyclopentadienyl groups in the synthesis of a monodentate chiral phosphine was reported [68]. $PhP[(C_5Me_4)_2]$ was obtained by oxidation of the lithium complex $Li_2[PhP(C_5Me_4)_2]$, which couples the two cyclopentadienyl groups to form a five-membered heterocyclic ring. The C-C coupling occurs in an asymmetric manner in which the two methyl groups adopt a *trans* rather than *cis* relationship (Fig. 55). The asymmetric nature of the coupling is indicated by the observation that $PhP[(C_5Me_4)_2]$ is characterised by eight inequivalent methyl groups in the $^1H$ NMR spectrum. The chiral nature of the compound was confirmed by X-ray crystallography.

## 4.2 Catalytic C-C Coupling

Catalytic C-C coupling reactions can be employed to modify known phosphorus compounds, leading to compounds or ligands of new properties. Thus, well-known transition metal catalysed C-C and C-X bond forming reactions (X = N, O) have recently been utilised for the easy synthesis of a variety of arylphosphine ligands in which the aryl groups are stereoelectronically modified [69]. These ligands were aimed for catalysis in water, supercritical $CO_2$ ($scCO_2$), ionic liquids and fluorous solvents, which are emerging fast as suitable media in organic synthesis but require catalysts/ligands of special solubility properties [70]. The approach utilises a common haloarylphosphine oxide as a starting block $OPPh_{3-n}(C_6H_4Br)_n$ (n = 1-3) to couple with substrates such as perfluoroalkyl halides, olefins and aryl halides. For instance, perfluoroalkylated arylphosphines could be prepared in excellent yield by the Cu-mediated coupling of $OPPh_{3-n}(p\text{-}C_6H_4Br)_n$ with a perfluoroalkyl iodide ($IR_f$) in the presence of bipy in DMSO (Fig. 56). The presence of bipy allowed the reaction to be performed at lower temperatures without affecting conversion or yield, and may have facilitated metallation of Cu by $IR_f$ [69a].

Phosphines bearing fluoroalkylated chains with $CH_2CH_2$-spacers, and the alkyl varieties, including those containing $CO_2R$ and CN groups, were synthesised by the Heck arylation of the corresponding olefins (Fig. 57) [69b]. Typically, a phosphine oxide $OPPh_{3-n}(p\text{-}C_6H_4Br)_n$ (n = 1-3) was mixed with 1.1 equiv of an olefin $H_2C{=}CHR$, 1.3 equiv NaOAc and 0.5–1 mol% Herrmann-Beller palladacycle in DMF. The coupling reaction proceeded at 125 °C to give the olefinated phosphine oxides in over 90% yield. These were hydrogenated using Pd/C under 10 bar $H_2$, and the free phosphine obtained by reduction with silane. The phosphines synthesised could in effect be "tuned" to various green solvents. If the olefin contained a $^nC_8F_{17}$ or a $CO_2Na$ group

(obtained *via* hydrolysis of $CO_2R$), then the resulting phosphine would be suitable to $scCO_2$/fluorous and aqueous media, respectively.

The versatility of these processes can also be seen in the preparation of water-soluble ligands without $CH_2CH_2$-spacers by alkoxycarbonylation of $OPPh_{3-n}(p\text{-}C_6H_4Br)_n$ (n = 1-3) and subsequent hydrolysis [69d]. To a solution of $OPPh_2(p\text{-}C_6H_4Br)$, 2.5 mol% $[PdCl_2(PPh_3)_2]$, 1.5 equiv $NEt_3$ in DMF/MeOH, CO was introduced at 75 bar and the reaction mixture stirred at 125 °C overnight. This yielded the phosphine oxide, which could be reduced by silane to the free phosphine in 92% yield (Fig. 58).

There are some advantages to these new methodologies. They are versatile in that phosphines of varying solubility properties can be easily made. Further, the key steps of the reactions are catalytic and avoid using hazardous organometallic reagents. In the specific example of fluorinated phosphines, the new method produces in general better yields than other approaches. For example, 90% of the expensive perfluoroalkyl reagents were effectively incorporated into the desired product. The alternative procedure of a metathesis reaction of fluoroalkylated aryl halides with $PPh_{3-n}Cl_n$ gave the fluoroalkylated phosphines in less than 50% yield [71a-c], and earlier the alkylated aryl phosphines were prepared in an overall yield of 30% [71d]. In most cases with the new method, the coupling step and reduction both proceeded in over 90% yield.

The examples of the aforementioned phosphines contain *para*-substituted phenyl rings. Arylphosphines with *ortho*-substituents, especially those containing 2-biphenyl units, are of interest in catalytic reactions where steric effects are desirable, and have been shown to be effective ligands in a number of transition metal-catalysed reactions, such as Pd-catalysed coupling reactions [72]. The previous methodologies could be extended to the preparation of functionalised biphenyl-based phosphines *via* the Suzuki coupling of $OPPh_2(o\text{-}C_6H_4Br)$ with various arylboronic acids [69e]. Some examples are seen in Fig. 59, where the catalyst was formed *in-situ* from 3 mol% $[Pd_2(dba)_3]$ and 4 equiv of $PPh_3$. Clearly, sterically and electronically diverse arylphosphines as well as phosphines containing special solubility properties can be accessed by the well-established catalytic C-C coupling chemistry, which is tolerant of many functionalities. However, a limitation of the approaches is that they rely on halogenated arylphosphines as substrates.

Suzuki coupling has recently been successfully employed in the synthesis of chiral, binaphthyl-based phosphine ligands [73]. First, coupling of a bromide-containing

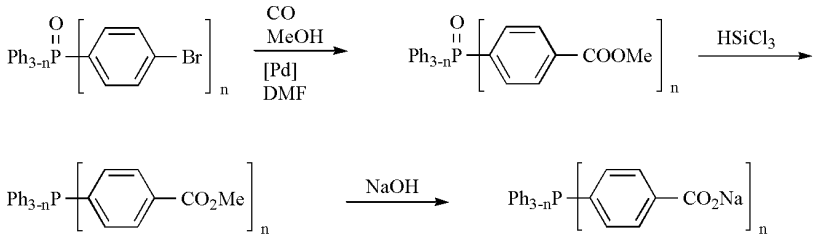
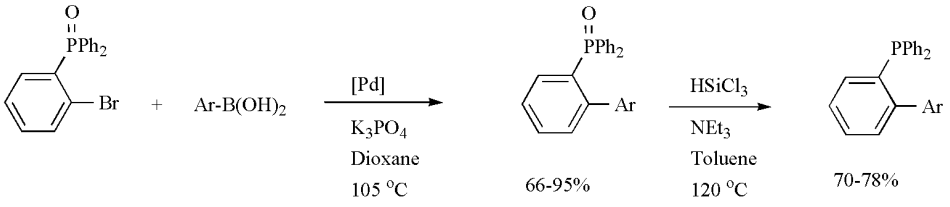



**Fig. 58.**




Ar = $C_6H_5$, *o*-$C_6H_4Me$, *o*-$C_6H_4OMe$, *o*-$C_6H_4SMe$, 2-naphthyl

**Fig. 59.**

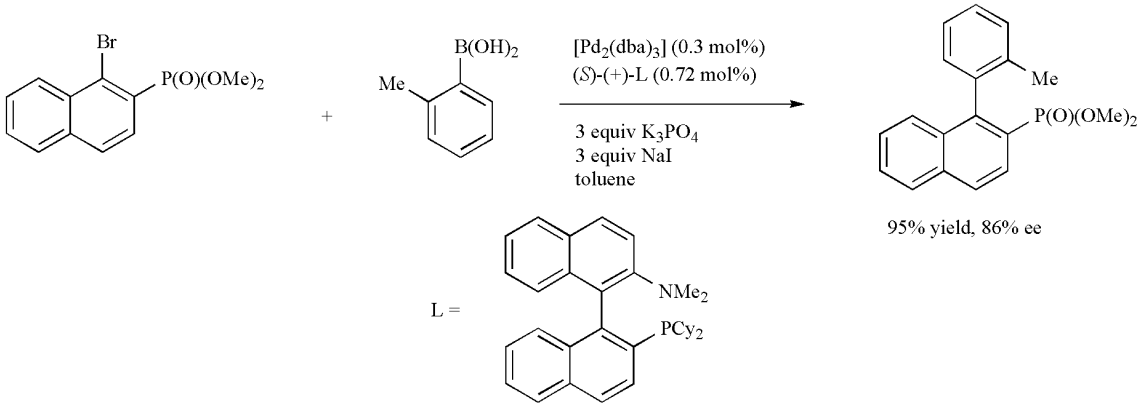



**Fig. 60.**

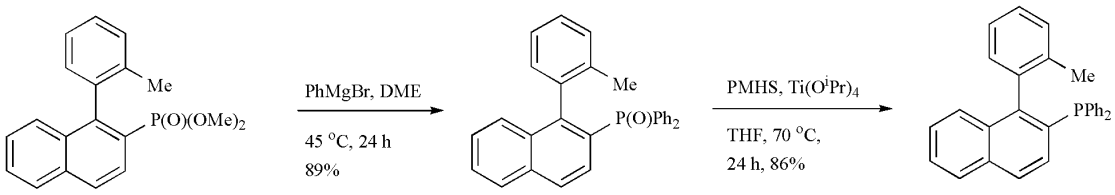



**Fig. 61.**

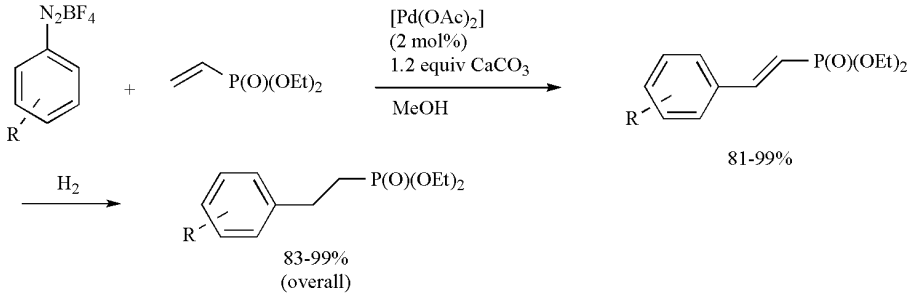



**Fig. 62.**

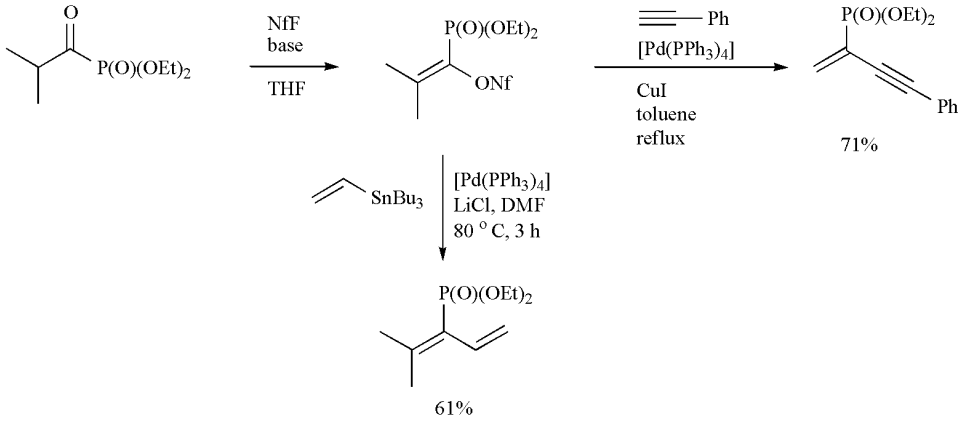



**Fig. 63.**

phosphonate with 1.5 equiv *o*-tolylboronic acid using $[Pd_2(dba)_3]$, in the presence of an electron-rich, chiral phosphine (L/Pd = 1.2) at 60 °C for 24 h, yielded the axially chiral phosphonate in 95% yield and 86% ee (Fig. 60).

The chiral phosphonate was then subject to further functionalisation. When heated with PhMgBr in DME at 45 °C for 24 h, the phosphine oxide was obtained in 89% yield. This could be reduced to the new chiral phosphine in 86% yield and 99% ee (Fig. 61).

Functionalisation of vinyl phosphorus compounds *via* the Heck reaction has also been reported. An example is seen in the synthesis of aryl vinylphosphonates using the Heck coupling of aryldiazonium salts with vinylphosphonates [74] (Fig. 62). Typically, an aryldiazonium salt bearing either an electron withdrawing or donating group was combined with 0.85 equiv of a vinylphosphonate in the presence of 2 mol% $[Pd(OAc)_2]$. When allowed to stir at 50 °C in methanol, the resulting aryl vinylphosphonates were obtained in yields up to 99% in less than 2 h. The reaction was stereoselective, with the *E*-isomers formed exclusively. This reaction allows the one-pot preparation of Wadsworth-Emmons reagents. The overall reaction would involve the Heck arylation followed by hydrogenation of the C=C double bond.

Fig. 63 shows the application of the Sonogashira and Stille coupling reactions in the synthesis of novel organophosphorus species [75]. The vinylphosphonates, *i.e.* α-phosphonovinyl nonaflates, were prepared from acylphosphonates. When followed by the Pd-catalysed Sonogashira cross coupling with acetylenes, the corresponding phosphonoenynes were furnished, not accessible using conventional methods [76]. Alternatively, when coupled with vinyl stannane in the presence of Pd(0), a phosphonodiene was obtained.

## 5. OLEFIN METATHESIS IN THE SYNTHESIS OF PHOPHORUS COMPOUNDS

### 5.1 RCOM for Phosphines, Phosphine Oxides and Phosphine Boranes

The use of ring closing olefin metathesis (RCOM) in organic synthesis has seen considerable growth in the past

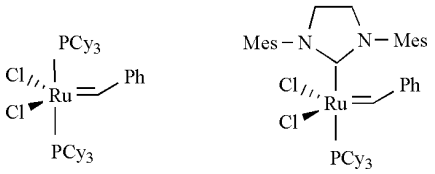


**Fig. 64.**

decade. This is partly due to the emergence of well-defined catalysts such as the Grubbs ruthenium carbene catalyst and the further discovery of the second generation, *N*-heterocyclic carbene-substituted**,** air stable ruthenium catalysts [77] (Fig. 64).

The first example of the metathesis of phosphorus-containing olefins utilised a cyclometallated tungsten complex [78]. Allyldiphenylphosphine or diallylphenyl-phosphine in the presence of 5 mol% tungsten catalyst at 80 °C in chlorobenzene yielded the metathesis products (Fig. 65). However, the isolated yields were low (*ca* 20%). These reactions were also attempted with the Grubbs catalyst, which was found to be ineffective [79].

However, the Grubbs catalyst was found to be effective on phosphine oxides in RCOM for the synthesis of five-,six-, seven-membered cyclic products [79]. Some examples are given in Fig. 66. The reactions were carried out in refluxing $CH_2Cl_2$ in the presence of 2-6 mol% catalyst. Reduction to the corresponding phosphines occured with retention of stereochemistry. This method was also extended to the synthesis of a bisphospholene oxide using 10 mol% catalyst in refluxing $CH_2Cl_2$ for 3 d.

The application of the Grubbs catalyst to constructing borane complexes of cyclic phosphines was also explored. As a result, five-, six-, and seven-membered complexes of cyclic phosphines as well as a bisphospholene, borane analogues of the oxides shown in Fig. 66, were synthesised in good yields by metathesis of the corresponding phosphine-borane olefins (Fig. 67) [80]. These examples and those above illustrate the power of RCOM and the Grubbs catalyst in the synthesis of protected phosphorus heterocycles.

Cyclic phosphinates are also accessible *via* RCOM [81]. The reactions shown in Fig. 68 proceeded efficiently in refluxing $CH_2Cl_2$ in the presence of the Grubbs catalyst to yield five-, six-, and seven-membered phosphinates in high yields.

### 5.2 RCOM in the Synthesis of Heterocycles

Heterocyclic systems that include phosphorus linked to an oxygen or a nitrogen atom are common to a diverse array

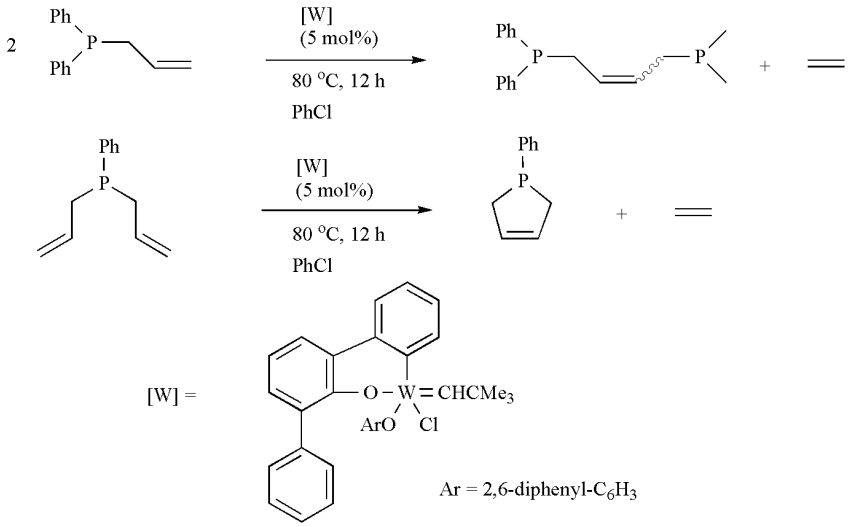


**Fig. 65.**

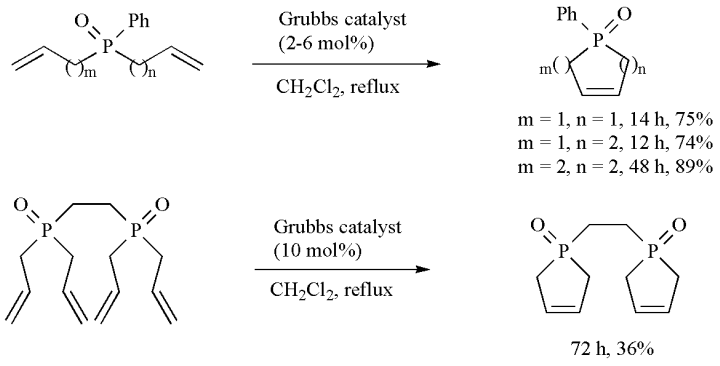


**Fig. 66.**

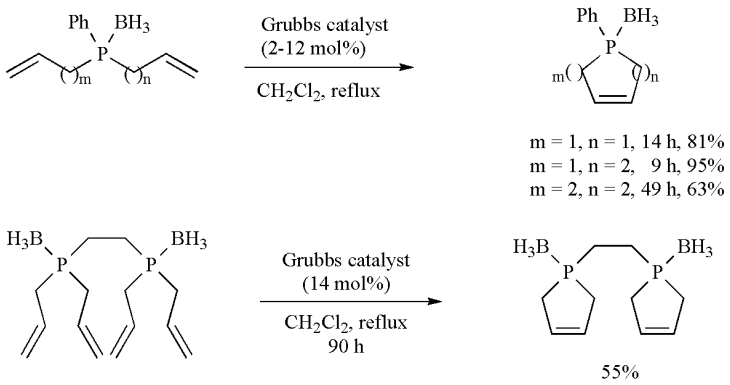



**Fig. 67.**

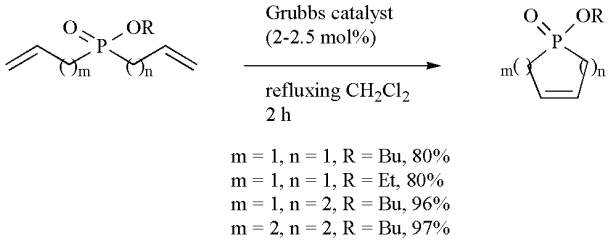



**Fig. 68.**

of important biological molecules [1a,82]. RCOM reactions promoted by the Grubbs catalyst have been performed on phosphonate templates in the synthesis of P/O heterocycles [83]. Fig. 69 shows the cyclisation of allyl- and homoallyl-phosphonates [83a]. Initial studies on the metathesis reaction of the diallyl allylphosphonate (m = n = 1, R = H) gave a modest yield of 39% using 3 mol% catalyst in benzene. Changing the solvent to $CH_2Cl_2$ improved the yield to 74%. The RCOM on the dicrotyl allylphosphonate (m = n = 1, R = Me) gave product in nearly quantitative yield after 30 min reflux in $CH_2Cl_2$ using the same catalyst. This suggests substitution may prevent loss of product due to further reaction of the unreacted allyloxy group. In these reactions, metathesis occurred between the allylphosphonate and either of the two allyloxy groups, possibly due to a preference for formation of six- over seven-membered rings. Metathesis of the diallyl homoallylphosphonate (m = 2, n = 1) and dihomoallyl allylphosphonate (m = 1, n = 2) also occurred in good yields, in the synthesis of seven-membered cyclic phosphonates shown in Fig. 69.

The reaction of vinylphosphonates was less selective, giving a mixture of the product arising from the vinyl and one allyloxy group and that between the two allyloxy groups, as shown in Fig. 70 [83b]. In the former, cleavage of the allyloxy group occurred during chromatographic purification.

Elsewhere, a series of cyclic phosphorus-containing heterocycles were prepared in a one-step procedure by RCOM of various dienes (Fig. 71) [84]. The synthesis of the

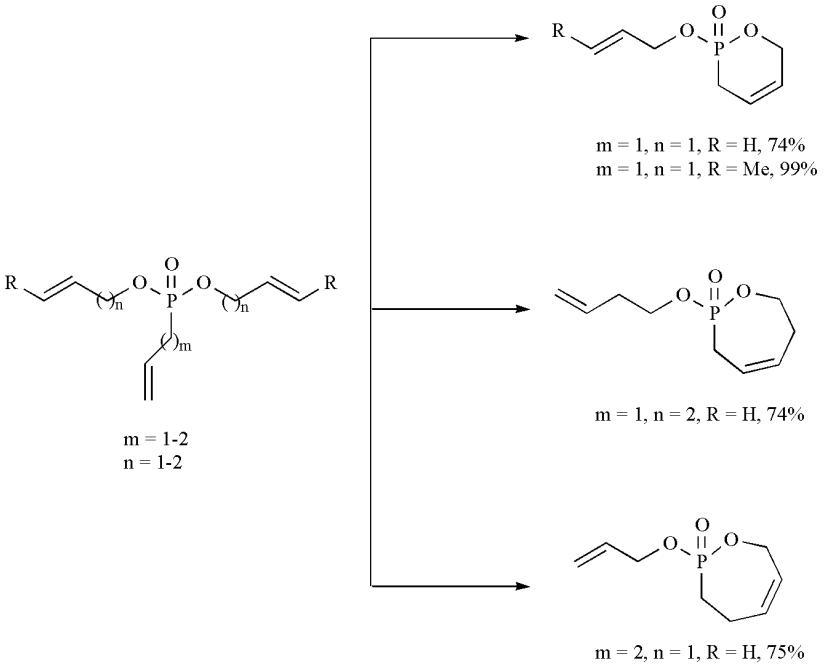



**Fig. 69.**

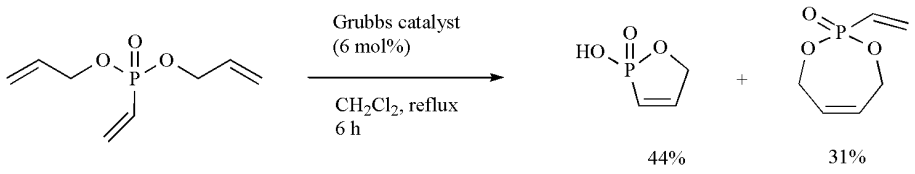



**Fig. 70.**

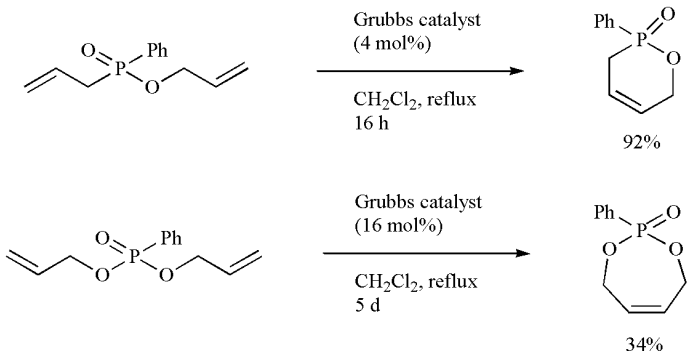



**Fig. 71.**

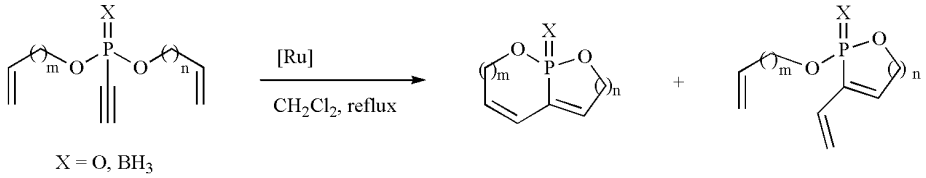


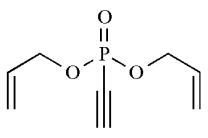
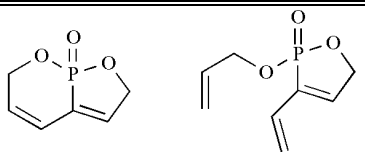
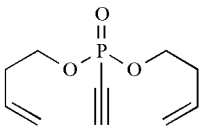
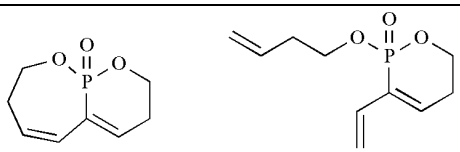

**Fig. 72.**

six-membered heterocycle was completed in 92% yield. The cyclic products containing a methyl group on position 3 and 6 could also be prepared in high yields (up to 96%) but a higher catalyst concentration was required (8 mol% Grubbs catalyst). The cyclisation of the symmetrical diallyl phenylphosphonate was sluggish with only 34% of the seven-membered product obtained after 5 d in the presence of 16 mol% catalyst.

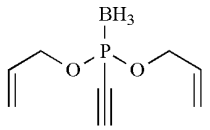
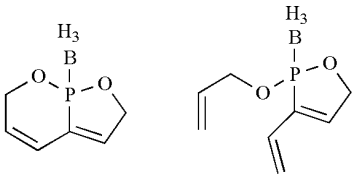
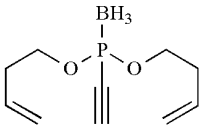
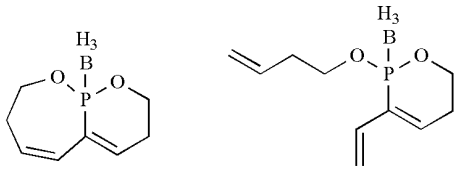
The RCOM of symmetrical (n = m) and asymmetrical (m ≠ n) bis(alkenyl)ethynylphosphonates was also reported (Fig. 72) [85]. In the presence of the Ru-*N*-heterocyclic carbene catalyst (Fig. 64), the fused bicyclo ring products as well as the monocyclic phosphonates were afforded. The analogous symmetrical borane complexes also underwent RCOM, again leading to bi- and mono-cyclic products. Some specific examples are found in Table 8.

Metathesis of the symmetrical diolefinic substrate with 1 mol% catalyst in refluxing $CH_2Cl_2$ led to the monocyclic product exclusively (Table 8, entry 1). Attempted conversion to the bicyclo product using 5 mol% catalyst and prolonged reaction times was unsuccessful. In contrast, the dibutenylic substrate afforded the bicyclo and monocyclo products in a

**Table 8.**

| Entry | Substrate | Products |
|---|---|---|
| 1 |  |  0 % 98% |
| 2 |  |  76% 18% |

**(Table 8.) contd…..**

| | | |
|---|---|---|
| 3 |  |  99% |
| 4 |  |  74% 23% |

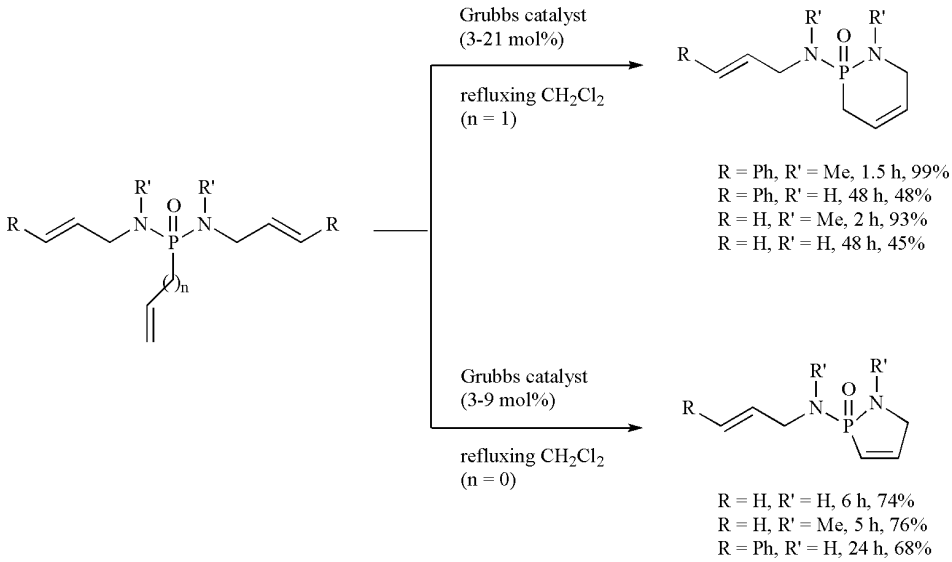



**Fig. 73.**

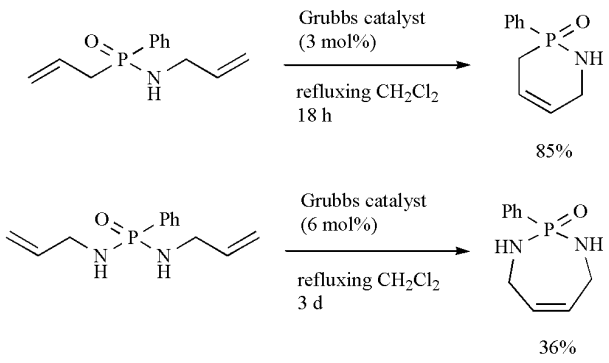



**Fig. 74.**

4/1 ratio under the same conditions (entry 2). Interestingly, when the catalyst concentration was increased to 5 mol% the bicyclo product was obtained in near quantitative yield. As seen from entries 3-4, the boronato complexes reacted in a similar fashion to the phosphonates, though much slower.

The methodology illustrated in Figs. 69 and 70 can be extended to the synthesis of six-membered allylphosphonamides and five-membered vinylphosphonamides [83b]. As shown in Fig. 73. The RCOM reaction of the *N*-methyl substituted allylphosphonamide (R' = Me) gave excellent yields of the six-membered products (up to 99%) with 3 mol% Grubbs catalyst. However, the reactions with substrates containing free N-H groups (R' = H) were sluggish and required a higher amount of catalyst (18-21 mol%) to give moderate yields between 45-48%. On the other hand, the reaction of both the N-H and N-Me vinylphosphonamides gave good yields of five-membered products. Substitution on the allylamino double bond (R = Ph) slows the reaction for vinylphosphonamides and higher catalyst concentrations were required.

The synthesis of closely related nitrogen-containing heterocycles was also reported [84]. The formation of the six-membered product shown in Fig. 74 required only 3 mol% catalyst to yield 85% product in 18 h. However, the reaction of the symmetrical phosphonamide yielded only

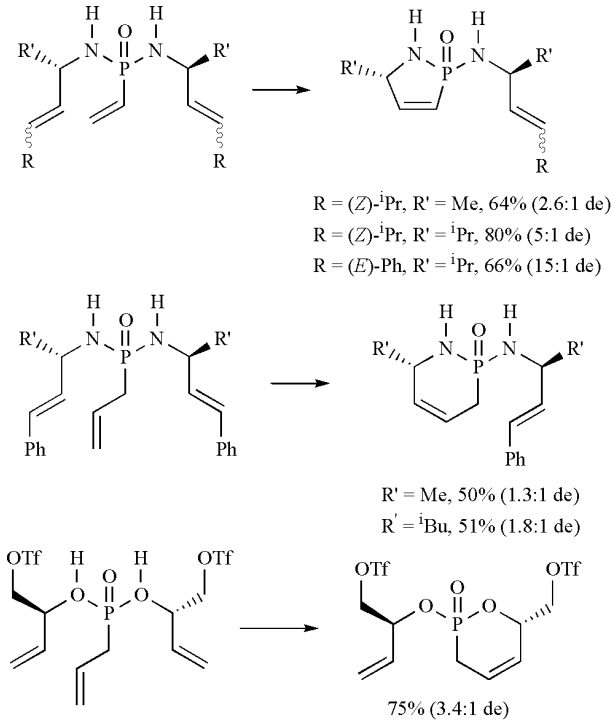



**Fig. 75.**

36% product after 3 d in the presence of 6 mol% catalyst, which supports the previous observation that the formation of a seven-membered ring combined with the presence of free allylic N-H groups is not favourable [83b].

The RCOM reaction has been utilised in the synthesis *P*-chiral heterocycles. Fig. 75 illustrates examples of diastereotopic differentiation of psuedo-$C_2$-symmetric phosphorus templates for *P*-chiral phosphonamides and phosphonates using the Grubbs catalyst [86]. In the synthesis of the five-membered phosphonamides high yields but low diastereoselectity (de = 2.6:1) were obtained from the (*Z*)-configured, $^i$Pr-substituted substrates. Increasing the size of substituent R' to $^i$Pr increased the diastereoselectivity to 5:1. However, substitution on the double bond played a more prominent role in selectivity. Changing R from (*Z*)-$^i$Pr to (*E*)-Ph resulted in a slower reaction, but selectivity increased to 15:1. Formation of the six-membered phosphonamides resulted in almost complete loss of selectivity, although the yields were good, at *ca* 50%. In the desymmetrisation of the allylphosphonate, the six-membered product was isolated in 75% yield with a modest selectivity of 3.4:1 (Fig. 75).

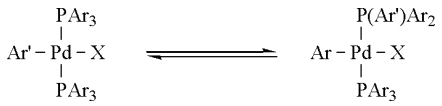


**Fig. 77.**

The examples so far have primarily involved *intra*molecular RCOM. Examples of *inter*molecular olefin metathesis in the synthesis of organophosphorus compounds are also known. Fig. 76 shows the synthesis of substituted allyl and vinyl-phosphonates by this reaction [87]. The products were prepared in good yields using the *N*-heterocyclic carbene catalyst. Cross metathesis of vinylphosphonates provided exclusive (*E*)-olefin stereochemistry, and the allylphosphonates were also prepared with good stereoselectivity. An additional example of an *inter*molecular reaction is already shown in Fig. 65.

## 6. OTHER REACTIONS

This section summarises a few reactions that lead to useful phosphorus compounds but could not readily be categorised in accordance with the previous sections.

### 6.1 P-C Cleavage/Coupling Reactions

Aryl/aryl exchanges between Pd-bound Ar' with P-bound Ar (Fig. 77) are frequently observed in Pd-catalysed cross coupling reactions and represent one of the pathways of catalyst decomposition [2a,88]. The reaction formally involves the cleavage of an existing P-C bond and formation of a new one *via* a process probably similar to the palladium-catalysed P-C coupling reaction of aryl halides.

The reaction is usually undesirable, as it leads to by-products and catalyst decomposition. A novel use of these reactions for the synthesis of functionalised aryl phosphines has recently been reported [89]. As shown in Fig. 78 and

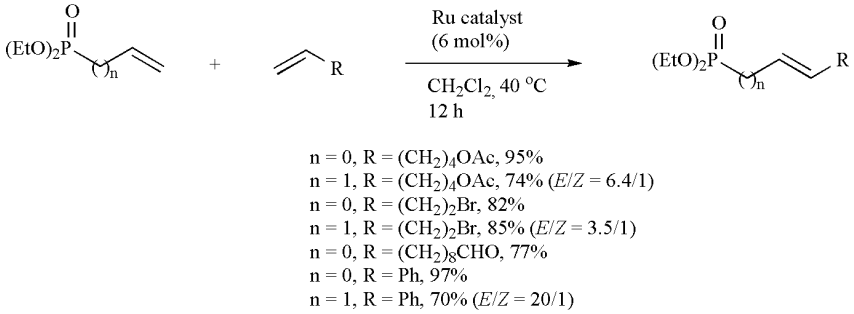



**Fig. 76.**

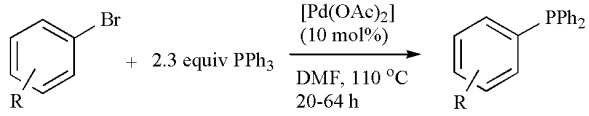
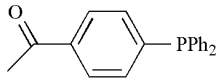
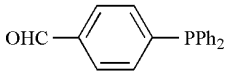
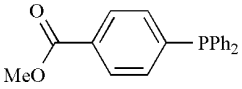
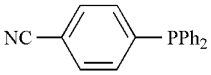
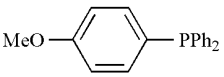
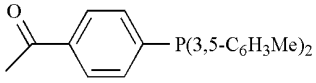
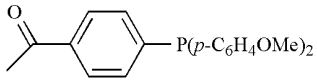
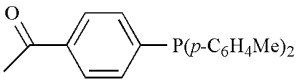



**Fig. 78.**

**Table 9.**

| Entry | Products | Time (h) | Yield (%) |
|---|---|---|---|
| 1 |  | 20 | 40 |
| 2 |  | 64 | 32 |
| 3 |  | 36 | 30 |
| 4 |  | 48 | 36 |
| 5 |  | 24 | 27 |
| 6 |  | 32 | 34 |
| 7 |  | 34 | 33 |
| 8 |  | 33 | 39 |

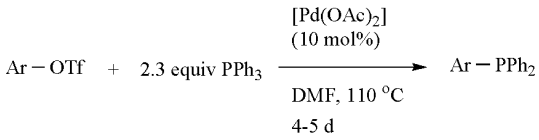



**Fig. 79.**

Table 9, heating a mixture of an aryl bromide and the readily available $PPh_3$ resulted in the replacement of one of the phenyls with the aryl group. In addition to $PPh_3$ (entries 1-5), other triarylphosphines (entries 6-8) were suitable phosphinating agents. Although slow with low yields, the method tolerated ketone, aldehyde, ester, nitrile, ether and chloride functional groups [89a].

This method has also led to the catalytic synthesis of biaryl P,N ligands from their corresponding O,N triflates [89b]. The synthesis of the new P,N ligands was achieved with triphenylphosphine as the phosphinating agent using the conditions shown in Fig. 79. Substituted triarylphosphines were also effective phophinating agents. Some examples are found in Table 10. In comparison with the methods for introducing a diarylphosphino group discussed in the P-C coupling section, using triarylphosphines avoids the use of rather air and moisture sensitive reagents such as $Ph_2PH$ and $Ph_2PCl$.

## 6.2 Oxidation/Reduction

Bisphosphine monoxides (BPMO's) are useful ligands for reactions such as hydroformylation and

**Table 10**

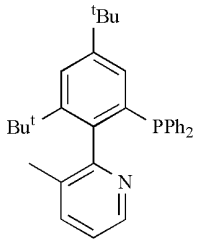
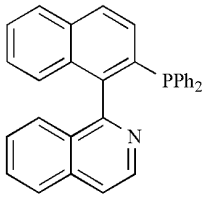
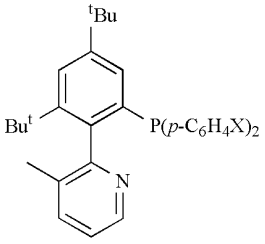
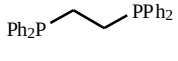
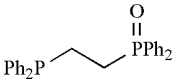
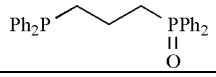
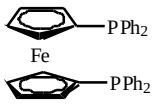
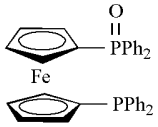
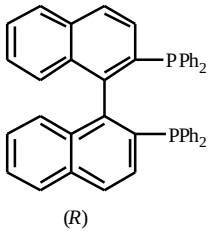
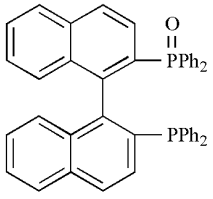
| Entry | Product | Time (d) | Yield (%) |
|---|---|---|---|
| 1 |  | 4.5 | 68 |
| 2 |  | 4.5 | 53 |
| 3 |  | 4.5 (X = Me)<br>3.5 (X = OMe) | 60<br>60 |

**Table 11.**

| Substrate | Reaction Conditions[a] | $[Pd(OAc)_2]$ Weight % | Time (h) | Product | Yield (%) |
|---|---|---|---|---|---|
|  | A | 0.1-0.5 | 7-22 |  | 78-90 |
|  | A | 0.2 | 6 |  | 73-77 |
|  | B, C | 0.5 | 24 |  | 50-65 |
|  | D | 0.5 | 72 |  | 80 |

[a] Conditions: A: 1,2-dichloroethane, 10-20% NaOH, 1.5-2 equiv $C_2H_4Br_2$, reflux. B: NaI (*ca* 9 mol equiv/Pd). C: $CH_2Cl_2$, 20% NaOH, 3 equiv $C_2H_4Br_2$, reflux. D: $CH_2Cl_2$, *ca* 5% NaOH, 4 equiv $C_2H_4Br_2$, r.t for 48 h then reflux with 8% NaOH for 1 more day.

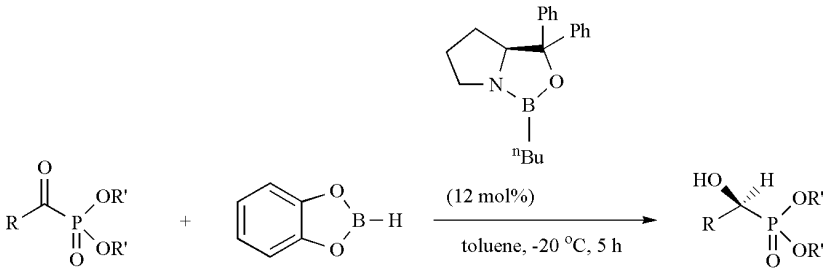



**Fig. 80.**

hydroxycarbonylation [90]. The simplest method for synthesising these ligands would be selective mono-oxidation of readily available bidentate phosphines. However, with conventional oxidants (e.g., $O_2$, $H_2O_2$, $Br/H_2O$) the reaction is non-selective leading to a mixture of products. BMPO's can now be synthesised utilising anaerobic palladium-catalysed biphasic oxidation in the presence of 1,2-dibromoethane/alkali, which gives rise to the mono-oxidised product with high selectivity [91]. As can be seen in Table 11, various well-known bidentate phosphine ligands were successfully mono-oxidised; but worthy of note is that the conditions used were substrate-specific in order to obtain high yields. A variety of catalysts were successful, including $PdCl_2$, $[Pd(OAc)_2]$ and $[K_2PtCl_4]$. In general, palladium catalysts were more efficient than their platinum counterparts. The catalytic oxidation involves an intramolecular redox process, that is Pd(II)/P(III) to Pd(0)/P(V), and is promoted by $OH^-$. The catalytic cycle is completed by re-oxidation of the resulting Pd(0) complex to the catalytically active Pd(II) complex by 1,2-dibromoethane, the latter being transferred to ethylene. In certain cases the mono-oxidation was promoted by iodide. The preferential formation of the BMPO's is probably due to their weakened coordinating capability compared with the parent bisphosphines.

α-Hydroxyphosphonates are an important class of phosphonates. They are biologically active, with the absolute configuration at the α-position influencing the properties of the compounds significantly. These compounds can be obtained by the hydrophosphorylation reactions shown in Figs. 8-10, and they can also be obtained by reduction of the corresponding carbonyl species discussed here. In a stereospecific synthesis of chiral, dialkyl α-hydroxyphosphonates, various α-ketophosphonates underwent oxazaborolidene-catalysed reduction with *ca* 1 equiv of catecholborane (Fig. 80) [92]. As shown in Table 12, all reactions proceeded with good to excellent yields and ee's. The reaction was valid for the synthesis of α-hydroxy*aryl*- (Table 12, entries 1-13) as well as α-hydroxy*alkyl*- (Table 12, entries 14-17) phosphonates. The reduction proceeded with predictable stereochemistry with the (*S*)-configurated

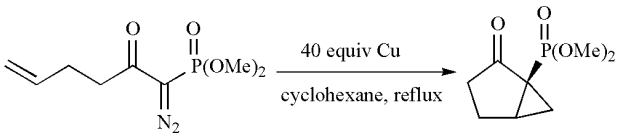



**Fig. 81.**

**Table 12**

| Entry | R | R' | Yield (%) | ee (%) |
|---|---|---|---|---|
| 1 | Ph | $^{i}$Pr | 92 | 65 |
| 2 | 2-F-Ph | $^{i}$Pr | 68 | 91 |
| 3 | 2-Cl-Ph | $^{i}$Pr | 96 | 97 |
| 4 | 2-Br-Ph | $^{i}$Pr | 82 | 95 |
| 5 | 2-I-Ph | $^{i}$Pr | 79 | 92 |
| 6 | 3-Cl-Ph | $^{i}$Pr | 84 | 77 |
| 7 | 4-Cl-Ph | $^{i}$Pr | 98 | 70 |
| 8 | 2-Me-Ph | $^{i}$Pr | 89 | 97 |
| 9 | 2-MeO-Ph | $^{i}$Pr | 82 | 51 |
| 10 | 4-Me-Ph | $^{t}$Bu | 85 | 76 |
| 11 | 4-MeO-Ph | $^{i}$Pr | 76 | 55 |
| 12 | 2,6-F-Ph | $^{i}$Pr | 96 | 99 |
| 13 | 2,4-Cl-Ph | $^{i}$Pr | 85 | 94 |
| 14 | Me | $^{t}$Bu | 89 | 81 |
| 15 | $^{i}$Pr | $^{t}$Bu | 91 | 80 |
| 16 | $^{i}$Pr-$CH_2$ | $^{t}$Bu | 85 | 90 |
| 17 | Ph-$(CH_2)_2$ | $^{i}$Pr | 85 | 95 |

catalyst leading to (*S*)-configuration at the new stereogenic centre. Within the series of α-arylketophosphonates as starting materials (entries 1-13), the 2-substituted compounds gave better enantioselectivity than 3- or 4-substituted derivatives. However, the size of the substituent appeared to have no effect.

### 6.3 Catalytic Synthesis of Phosphonates *via* α-Diazophosphonates

The first example of a transition metal-catalysed reaction of a α-diazophosphonate was the intramolecular cyclopropanation of allyl α-diazodialkylphosphonoacetate using Cu powder (Fig. 81) [93].

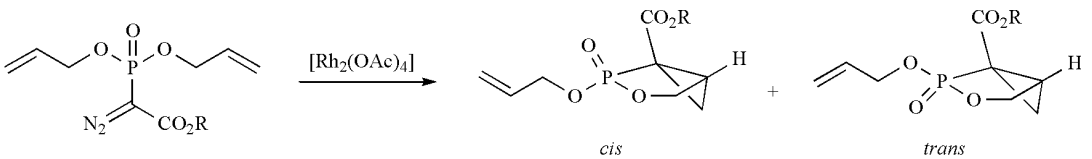
More recently, the intramolecular cyclopropanation reaction of an alkyl α-diazo diallylphosphonoacetate using $[Rh_2(OAc)_4]$ as catalyst to yield novel *P*-heterocycles was described [94]. The reactions proceeded in good to excellent yields giving mixtures of the *P*-heterocycles in *cis*- and *trans*-configuration with modest levels of diastereoselectivity. The R group in the starting material influenced the degree of diastereoselectivity obtained, with R = $^{t}$Bu giving the highest ratio (Fig. 82).

α-Phosphonylated γ,δ-unsaturated sulfides were obtained when diazomethylphosphonate was treated with 1.2 equiv of allylic sulfide in the presence of 10 mol% $[Cu(acac)_2]$ or 5 mol% $[Rh_2(OAc)_4]$ in $CH_2Cl_2$ at r.t (Fig. 83) [95]. The reaction proceeded by a [2,3]-sigmatropic Wittig rearrangement of the sulfonium ylide intermediate, affording the isolated product in yields between 60-75%.

Recently, consecutive catalysis involving $[Rh_2(OAc)_4]$ and Grubbs catalyst was utilised in the synthesis of cyclic α-thiophosphonates (Fig. 84) [96]. This strategy incorporated a [2,3]-sigmatropic rearrangement of the sulfur-ylides generated from α-diazophosphonates and a ring closing metathesis of the resulting α-thiophosphonates. The starting α-diazophosphonates were treated with 5 equiv of diallyl sulfide in the presence of 10 mol% $[Rh_2(OAc)_4]$ in refluxing $CH_2Cl_2$ to produce the α-thiophosphonates in moderate to good yields. These underwent metathesis using 5-15 mol% Grubbs catalyst in refluxing $CH_2Cl_2$ to yield the cyclic α-thiophosphonates in moderate to excellent yields.

## 7. CONCLUDING REMARKS

Homogeneous catalysis has emerged as a powerful alternative to the traditional methods of phosphine synthesis, allowing a variety of known as well as previously unavailable phosphorus compounds to be accessible in a more efficient, simpler and safer manner. As revealed in the previous sections, alkyl, vinyl and allyl phosphines and related compounds can readily be prepared *via* hydrophosphination, and functionalised aryl and vinyl phosphines including those that possess special solubility properties are accessible through P-C coupling. Novel phosphines can also be made available using established C-C coupling chemistry. Concerning cyclic phosphines, the utility of RCOM in the synthesis of various P-, P,O- and P,N-heterocycles has clearly been demonstrated. The asymmetric version of these reactions has also appeared, which includes the use of chiral catalysts and enantiopure substrates. The synthesis of binaphthyl-based chiral phosphorus ligands *via* P-C and C-C coupling reactions and that of functionalised *P*-chiral




R = Me, 97% (de = 2.5:1)
R = Et, 93% (de = 3.7:1)
R = Bn, 88% (de = 4.0:1)
R = $^{t}$Bu, 96% (de = 5.5:1)

**Fig. 82.**

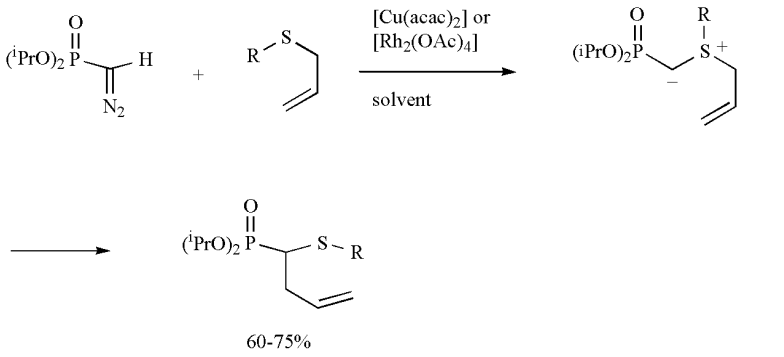



**Fig. 83.**

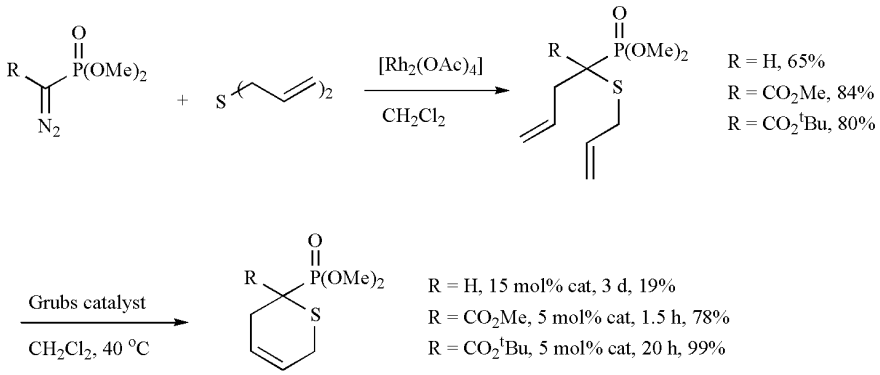



**Fig. 84.**

compounds *via* hydrophosphination are particularly noteworthy in this context.

Whilst traditional methods will probably remain as the dominant approach to phosphine synthesis, catalysis can be expected to play an increasing role in the construction of designer phosphorus compounds and ligands, or libraries of them. Indeed, with phosphines often an integral variant within homogeneous catalysis, the synthesis of novel phosphines could lead to improved as well as new catalytic processes, and paradoxically, new phosphines.

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