Applications of phosphine-functionalised polymers in organic synthesis

Meritxell Guinó[a] and King Kuok (Mimi) Hii[b]

Received (in Cambridge, UK) 14th March 2006
First published as an Advance Article on the web 25th September 2006
DOI: 10.1039/b603851b

This *tutorial review* deals with recent advances in the use of phosphine-functionalised polymers in organic synthesis. In the first part of the review, some recent applications of polymer-supported palladium catalysts are reviewed, particularly recyclable catalysts for C–C and C–X bond formation with aryl bromide and chloride substrates. In the second half, novel applications of phosphine-functionalised polymers as reagents, scavengers, organocatalysts and linkers in organic chemistry are presented. Emphasis is placed on the synthesis of biologically active molecules.

1. Introduction

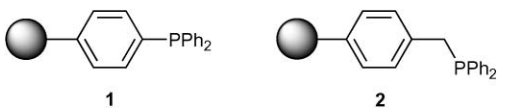
Phosphorus is a unique element, occupying important roles in organic and inorganic chemistry. Much of its synthetic versatility is associated with its ability to adopt +3 and +5 oxidation states, whilst forming up to five covalent bonds with C, H, N and O.

Phosphine-functionalised resins were originally produced in the 1970s to provide an insoluble support for metal catalysts. This was followed quickly by their use in organic (Wittig) reactions. More than three decades later, interest in these functionalised polymers continues unabated, especially when they proved to be compatible with several new technologies, *e.g.* microwave irradiation and automated synthesis.

[a]*The School of Pharmacy, University of London, 29/39 Brunswick Square, London, UK WC1N 1AX. E-mail: meritxell.guino@pharmacy.ac.uk*
[b]*Department of Chemistry, Imperial College London, South Kensington, London, UK SW7 2AZ. E-mail: mimi.hii@imperial.ac.uk*

This review aims to highlight areas of chemistry enabled by the use of phosphine-functionalised polymers, particularly in the last five years. Triphenylphosphine polystyrene (PS-TPP, **1**; also known as PS-PPh_3) and diphenylphosphinomethyl polystyrene (**2**, PS-PPh_2) are the most commonly employed (Fig. 1). For ease of comparison between applications, these will constitute the majority of the current discussion.

Polymers **1** and **2** are readily available from several commercial sources, typically with a loading of between 1.2–1.4 mmol g^{-1}, with 2% cross-linking provided by divinylbenzene. Alternatively, they may be prepared in one of three ways: (i) nucleophilic substitution of halogenated polymer (typically Merrified resin) with diphenylphosphide;[1a] (ii) activation of



1 **2**

Fig. 1 The two most popular phosphine-functionalised polymer supports.

Meritxell Guinó

Meritxell Guinó received her BSc degree from Universitat de Barcelona, Spain in 2001. Moving to King's College London, UK, she pursued a MSc project with Dr. Yolanda de Miguel in the Department of Chemistry, then undertook further postgraduate studies with Dr. Mimi Hii and Yolanda de Miguel on the application of polymer-supported scavengers and catalysts in organic reactions. After receiving her PhD degree in 2005, she was appointed as a postdoctoral research assistant at The School of Pharmacy, London, working in the research group of Dr. Mark Searcey on the synthesis of duocarmycin-related DNA alkylating agents.

King Kuok (Mimi) Hii

Mimi Hii received both her BSc and PhD degrees from University of Leeds, UK, where she conducted postgraduate study with Professor Bernard L. Shaw, FRS. This was followed by EPSRC-funded postdoctoral work with Dr. John M. Brown, FRS at Oxford University, where she also held a Junior Research Fellowship at Wadham College. She initiated independent research in 1997 upon the award of the Ramsay Memorial Fellowship and ICI Strategic Research Funding. In the following year, she was appointed to a Lectureship at the Department of Chemistry, King's College London. Following the demise of the 175 year old department in 2003, she moved to a Senior Lectureship at Imperial College, London. Her research interests lie in the area of transition metal-catalysed organic synthesis, including asymmetric catalysis.

4-bromopolystyrene by bromine–metal exchange, followed by trapping with $ClPPh_2$;[1b] or (iii) radical polymerisation of 4-styryldiphenylphosphine with styrene.[1c] This last method of synthesis is used to control the amount of cross-linking, which determines the physical properties of the resultant polymer (*e.g.* mechanical stability and swelling in organic solvents).

2. Applications of phosphine-functionalised polymer resins in catalysis

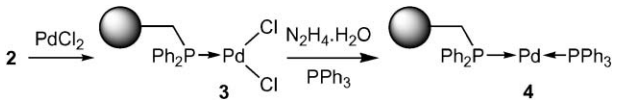
Trivalent organophosphorus compounds (*e.g.* phosphine and phosphites) are good π-ligands and can coordinate to many catalytically important metals (*e.g.* Ru, Rh, Ni, Pd). In certain cases, phosphorus ligands can be structurally altered to fine tune catalytic activity and selectivity. Various aspects of polymer-supported transition metal catalysts have been reviewed in recent years, including their preparation and characterisation,[2] as well as their applications in medicinally-oriented organic synthesis[3] and industrial research.[4] The preparation of polymeric palladium catalysts and their applications in asymmetric catalysis have also been recently reviewed.[5] In the following sections, we will provide an overview of new applications, particularly in the area of palladium catalysis. Employment of these polymer supports as metal scavengers and organocatalysts will also be described.

2.1 Immobilisation of homogeneous palladium catalysts

One of the main motivations for using polymer-supported tertiary phosphine ligands in catalysis is to facilitate the recovery of metal catalysts at the end of a reaction. However, the attachment of a homogeneous catalyst onto an insoluble support also engenders several practical and cost issues that must be carefully assessed when determining the overall effectiveness of the strategy. Firstly, separation of a polymer-bound catalyst from a reaction mixture is attractive only if the metal is expensive or toxic, and when other means of purification (*e.g.* distillation, recrystallisation) are not viable or are costly. Secondly, the recovered metal complex should be reusable, preferably several times, without any decrease in its activity. Thirdly, encapsulation of the catalyst may affect the access of reagents to active metal sites. Therefore, careful adjustment of the reaction conditions (solvent, temperature) becomes necessary.

Several major advances have been made in the field of palladium catalysis in the last few years, particularly in the discovery of ligands and reaction protocols that can afford synthetically and industrially useful turnover numbers in a wide range of C–C and C–X bond forming processes.[6] Concurrent with these discoveries, there are a burgeoning number of reports that describe the immobilisation of these catalysts onto polymer supports.

The first polymer-bound palladium catalyst for C–C bond forming reactions was reported in the late 1970s.[7] The catalyst was prepared by the reaction of palladium dichloride with polymer **2**. The resultant dichloropalladium(II) complex, **3**, was reduced by hydrazine hydrate in the presence of triphenylphosphine to give palladium(0) complex **4**, the heterogeneous analogue of $Pd(PPh_3)_4$ (Scheme 1). Both **3** and **4** have been employed in palladium-catalysed reactions.

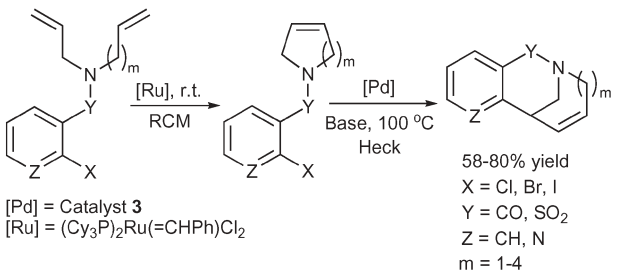


Scheme 1 Formation of polymer-supported palladium catalysts **3** and **4**.

2.1.1 The Heck reaction. The unique physical properties afforded by the immobilised palladium catalyst **3** were exploited in novel one-pot ring closing metathesis (RCM)–intramolecular Heck tandem reactions for the synthesis of bridged tricyclic ring systems (Scheme 2).[8] The ruthenium and palladium catalysts are mutually incompatible in the homogeneous solution. However, the process of immobilisation effectively encapsulates the palladium catalyst within the macroporous structure of the polymer, allowing the ruthenium-catalysed RCM reaction to proceed in the solution phase at room temperature. When the temperature is raised (110 °C), the polymer beads swell, thus allowing contact between the reactants and the palladium catalyst, initiating the Heck cyclisation. Five bridged ring systems can be successfully constructed using this catalyst system, with yields of between 58–80%.

2.1.2 Suzuki–Miyaura cross-coupling reaction. The palladium-catalysed cross-coupling reaction of aryl halides with aryl boronic acids, known as the Suzuki–Miyaura reaction, is an important C–C bond forming reaction in organic synthesis, particularly for the synthesis of biaryls. Rather surprisingly, the first example of a polymer-assisted Suzuki reaction was reported only comparatively recently, in 1997, where the PS-Pd(0) catalyst **4** was used for the coupling of a number of organoboranes with alkenyl bromides, iodobenzene and aryl triflates (21 examples).[9] Yields comparable to those obtained with the homogeneous catalyst $Pd(PPh_3)_4$ were reported. Furthermore, the heterogeneous catalysts may be reused up to 10 times.

A year later, the activity of palladium catalysts generated from polymers **1** and **2**, and several palladium precursors were examined, including $PdCl_2$, $Pd(PPh_3)_4$, $Pd(NCMe)_2Cl_2$, $Pd(NCPh)_2Cl_2$, $Pd(dba)_2$ and Na_2PdCl_4.[10] The catalysts were used to induce the coupling reaction between phenylboronic acid and 4-bromopyridine. As was observed previously, the immobilised catalysts showed a similar activity to the



Scheme 2 Bimetallic, catalytic RCM–Heck cascade reaction.

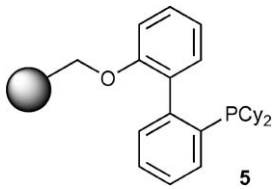
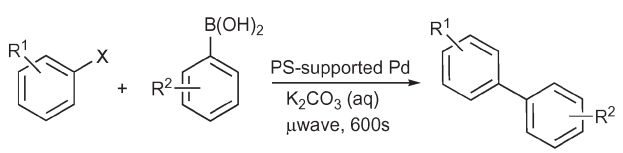


Fig. 2 A polymer-supported dialkylphosphinobiphenyl ligand.

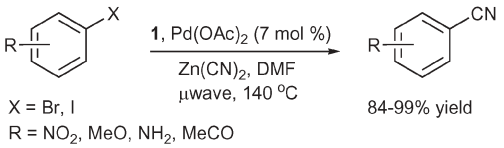
corresponding homogeneous analogues. Neither the nature of the polymer support (**1** or **2**) or the Pd/P ratio were found to have any effect on the reaction outcome. This contrasts with a previous study, conducted by Hallberg *et al.*, where similar catalysts were used in the Heck arylation reaction.[11] In fact, the choice of the Pd salt/complex used in the catalyst preparation was found to be important. It was found that catalyst **3**, generated by refluxing **2** and $Pd(COD)Cl_2$ in benzonitrile, can be used in the Suzuki cross-coupling reactions of 4-tolylboronic acid with activated chloroarenes and chloropyridine derivatives to give high yields of the biaryl products (85–92%).[12] However, with electron-rich chloroarenes, very low yields were obtained. For these unactivated substrates, Buchwald and Parrish reported the preparation of a polymer-supported dialkylphosphinobiphenyl ligand **5** (Fig. 2), which can be used in cross-coupling reactions of chloroarenes with aryl boronic acids or amines.[13] Although the catalyst can only be reused up to four times, it represents the first example of a recyclable catalyst for reactions involving chloroarenes.

Microwave irradiation is increasingly being adopted as an energy source in synthetic chemistry. Offering a highly focused and intense source of thermal or dielectric energy, it can dramatically shorten reaction times. In recent years, solid-supported catalysis has often been combined with microwave irradiation to minimise reaction time and its work-up. This is particularly useful in relieving bottlenecks in parallel synthesis programmes for the production of libraries of drug-like compounds. The combination of microwave irradiation and polymer-supported palladium catalysis was first described in 2004 (Scheme 3), where the performance of commercially available **1**-Pd(II) was compared against other similar polymer-based catalysts in Suzuki cross-coupling reactions.[14] Remarkably, the reaction took only 10 minutes to complete. Analytically pure product could be obtained following the removal of the catalyst by filtration and sequestration of excess boronic acids by solid phase extraction (SPE) using a silica-supported carbonate base. Thus, purification of the products could be achieved rapidly and conveniently. However, the reuse of the catalysts was not discussed.

2.1.3 Coupling of aryl halides with soft nucleophiles. The substitution of aryl halides by soft nucleophiles, such as



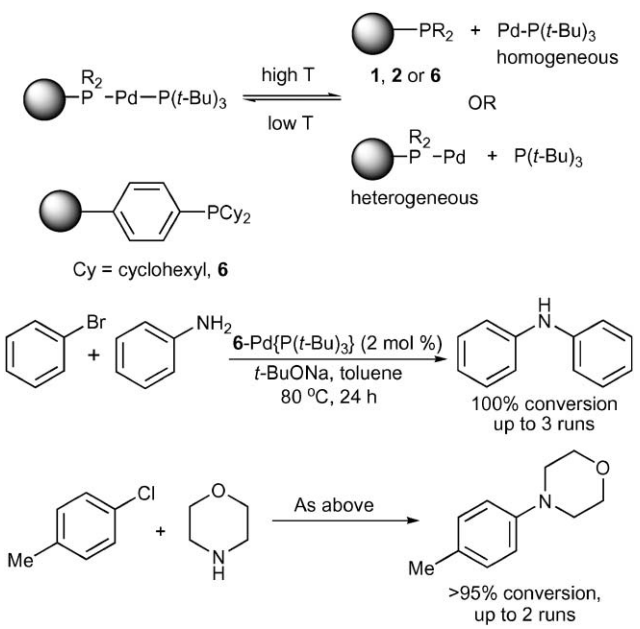
Scheme 3 Suzuki cross-coupling reactions under microwave irradiation using polymer-supported palladium catalysts.



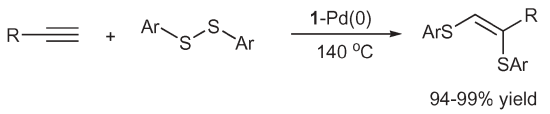
Scheme 4 Cyanation of aryl halides under microwave irradiation.

amines, alcohols, enolates and cyanide, may also be achieved through palladium catalysis. Srivastava and Collibee demonstrated that the cyanation of aryl halides can occur under microwave irradiation using a polymer-bound palladium catalyst generated by mixing $Pd(OAc)_2$ with **1** in DMF (Scheme 4).[15] The aryl nitriles can be synthesised within an hour in high yields without the need for purification. However, the reaction appears to be limited to aryl iodides and electron deficient bromides, and the reuse of the catalyst was not discussed.

In all of the above examples, the functionalised polymer was used to provide a phosphine donor, as well as a means of immobilisation. To increase the catalytic activity of polymer-supported palladium catalysts towards less active aryl halides, a different approach was adopted, whereby commercially available resins **1**, **2** and a dicyclohexylphosphine-functionalised polymer, PS-PCy_2 (**6**), were used to capture a coordinatively unsaturated *t*-Bu_3P–Pd complex for aryl amination reactions.[16] Using this design, catalytically active species could be generated either *via* the release of the coordinatively unsaturated palladium complex into the homogeneous phase or by dissociation of the tri-*tert*-butylphosphine ligand to generate a catalytically active, heterogeneous species (Scheme 5). These catalysts were used to effect C–N bond formation between aryl halides and aromatic amines. The catalyst derived from polymer **6** displayed the best turnover. Moreover, an unactivated aryl chloride substrate can be employed under fairly mild reaction conditions. The catalyst



Scheme 5 Dissociative pathways for generating palladium catalysts.



Scheme 6 Use of immobilised Pd(0) catalyst for the addition of aromatic disulfides to alkynes.

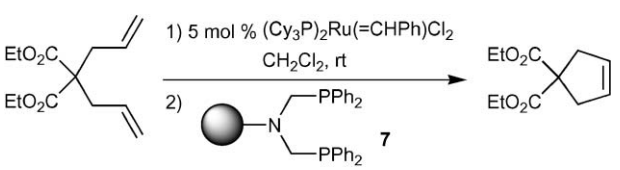
can be reused up to three times with no apparent loss of catalytic activity.

2.1.4 Palladium-catalysed addition of disulfides to alkynes. Tertiary phosphines can induce reductive cleavage of aromatic disulfides to thiols. The reaction generates a mixture of aryl thiolate anion and (arylthio)phosphonium cation, which undergo hydrolysis to generate a second equivalent of thiol. Recently, the reaction was conducted in the presence of terminal alkynes and a polymer-supported palladium(0) catalyst, prepared by the adsorption of $Pd_2(dba)_3$ onto polymer resin **1**. This resulted in the addition of diaryl disulfides across the triple bond, affording dithiol products in high yields and with a high stereoselectivity without the need for special purification (Scheme 6).[17] A similar reaction of alkynes with Ph_2Se_2 was less successful, although (*Z*)-vinyl selenide derivatives could be obtained in 60–70% yield.

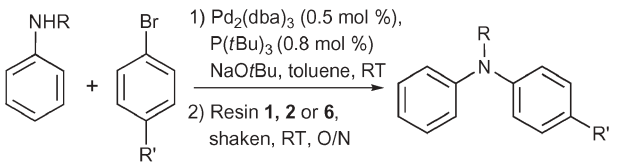
2.2 Phosphine-functionalised polymers as scavengers

As homogeneous catalysis becomes increasingly common in the fine and pharmaceutical industries, the removal of metal impurities from product streams is an important issue. Purification by crystallization, distillation or extraction are not always feasible, while chromatography is impractical on a large scale. In recent years, there has been significant interest in the development of functionalised, solid supports as heavy metal scavengers. The use of a phosphine-functionalised polymer to sequester metal catalysts was first reported by Westhus *et al.*[18] The polymeric scavenger **7** contains a chelate phosphine moiety, which was used to remove Grubbs' catalyst following a RCM of bis(allyl)malonate (Scheme 7). The efficiency of the scavenger was measured by the %Ru content in the product using atomic absorption spectroscopy, and was found to be between 0.11–0.24%.

A number of immobilised polymer resins have been marketed in recent years as palladium scavengers. All of them contain chelating N- and/or S-donor groups, and their use was initially demonstrated only in Suzuki cross-coupling reactions. Recently, it was shown that commercially available resins **1**, **2** and **6** can be used to capture coordinatively unsaturated palladium catalysts from Buchwald–Hartwig aryl amination reactions (Scheme 8);[19] the scavenger being removed by filtration. Following an aqueous wash, the residual palladium



Scheme 7 Scavenging of Grubbs' catalyst.



Scheme 8 Scavenging palladium following aryl amination reactions.

in the product was analysed by ICP-AES. Scavenging efficiencies of up to 98.5% were achieved.

2.3 Phosphine-functionalised polymers as organocatalysts

Phosphorus(III) is mildly basic and is also sufficiently nucleophilic to reversibly form phosphonium bonds to electrophilic carbon and protons. These properties have been exploited in synthesis to activate certain molecules towards electrophilic or nucleophilic reactions.

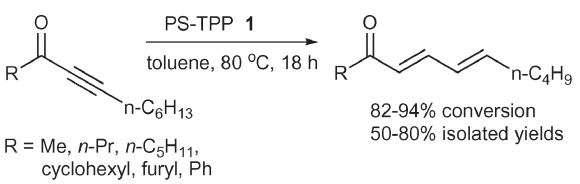
One of the significant advances in recent years has been the discovery of organocatalysts that can replace metal catalysts in bond forming reactions. Theoretically, organocatalysts are easier to prepare, more stable, cheaper and most importantly, do not leave metal residues. Polymer-supported phosphorus reagents have been successfully adopted in a number of these reactions.

2.3.1 Isomerisation catalyst. PS-TPP (**1**) catalysed the conversion of a mixture of (*E*/*Z*)-nitro-olefins to the (*E*)-isomer in quantitative yields and high purity.[20] It has also been used as a mild organocatalyst for the stereoselective isomerisation of α,β-ynones to (*E*,*E*)-α,β-γ,δ-dienones (Scheme 9).[21] The catalyst could be recovered and reused.

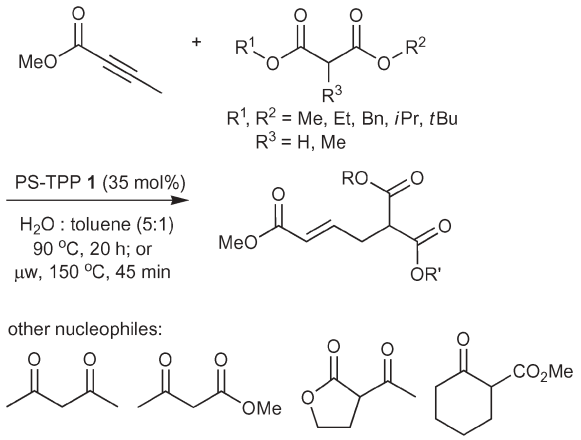
2.3.2 Nucleophilic additions. 1 catalysed the γ-addition of a number of pronucleophiles, such as malonate, 1,3-diketones and keto esters, to methyl 2-butynoate in an aqueous medium with good yields under thermal or microwave heating (Scheme 10).[22] The catalyst could be reused twice before significant degradation occurred through leaching and oxidation of the phosphine.

Triphenylphosphine supported on JandaJel (JJ), a polystyrene resin cross-linked by 1,4-bis(4-vinylphenoxy)butane, has been used to catalyse the aza-Baylis–Hillman reaction between *N*-tosyl imines and methyl vinyl ketone (Scheme 11).[23] The presence of polar functional groups and the loading levels of the polymer were found to affect the catalyst's efficiency.

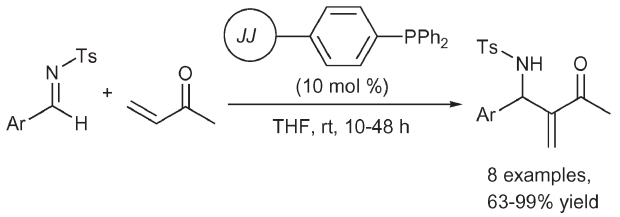
2.3.3 Electrophilic additions. The reaction of methyl bromoacetate with resin **1** generates polymer-supported acetonyltriphenylphosphonium bromide (PS-$PPh_3CH_2CO_2Me^+Br^-$, PS-ATPB). This has been explored as a source of mild



Scheme 9 Isomerisation of ynones catalysed by **1**.



Scheme 10 Trost's γ-addition catalysed by **1**.

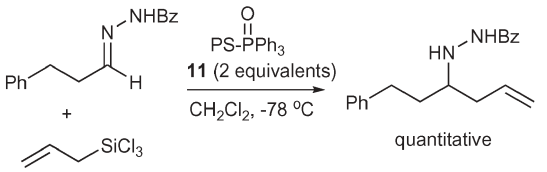


Scheme 11 Aza-Baylis–Hillman reaction catalysed by triphenylphosphine supported on JandaJel.

Brønsted acid in protecting group chemistry. For example, a catalytic amount of PS-ATPB has been used in the protection (and deprotection) of primary, secondary and tertiary alcohols as cyclic or acyclic enol ethers,[24a] and in the protection of aldehydes as acetals or thioacetals.[24b]

Similarly, polymer-bound PS-CH_2PPh_2HBr (**8**) can be generated by the treatment of resin **2** with hydrobromic acid and used as a mild Brønsted acid for the activation of enol ethers and glycals.[25] Furthermore, the procedure may be adapted to allow the chemoselective manipulation of acid-labile protecting groups. This was demonstrated by the selective deprotection of the amine and alcohol groups present in compound **9** (Scheme 12). Using resin **8**, the *N*-TBS protecting group could be removed selectively in the presence of a THP ether group. Following protection of the aniline group with a carbamate (allyloxycarbonyl, Alloc), the THP ether was selectively removed to reveal the allyl alcohol **10** in high yield.

2.3.4 Lewis base catalysis. Polymer **11**, the oxidised form of **1**, replaced sulfoxides as an efficient neutral coordinate organocatalyst (NCO) for the allylation of *N*-acylhydrazones by allyltrichlorosilane (Scheme 13).[26] The organophosphorus reagent is more stable than the sulfoxides under oxidative and acidic conditions, and is also more active. Two equivalents of **11** are required for the transformation, and could be recovered by simple filtration, although catalyst reuse was not discussed.



Scheme 13 Phosphine oxide polymer **11** as an organocatalyst for the allylation of *N*-acylhydrazones.

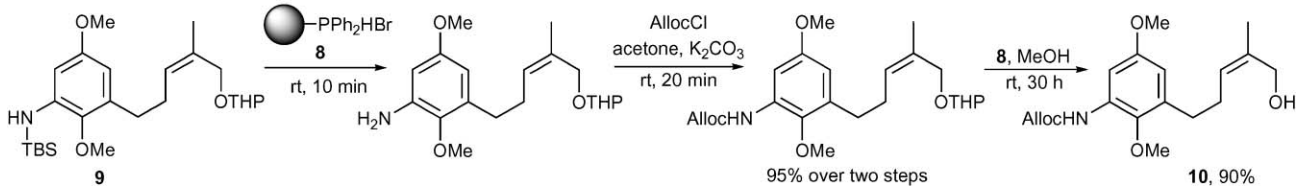
3. Applications of phosphine-functionalised polymer reagents in organic synthesis

Phosphine-functionalised polymer reagents are widely used in organic synthesis, particularly in Wittig and Mitsunobu type processes. The strong affinity of P(III) to oxygen and nitrogen is exploited to effect functional group transformations, often under pH neutral and mild reaction conditions. The phosphorus atom is rarely incorporated into the product during organic synthesis, thus the generation of phosphorus by-products is inevitable. These are notoriously difficult to remove, especially when the desired product is highly polar. Thus, the immobilisation of organophosphorus reagents onto insoluble solid supports is particularly attractive, as it facilitates the easy removal and recovery of the phosphorus reagents (and their by-products) *via* a simple filtration.

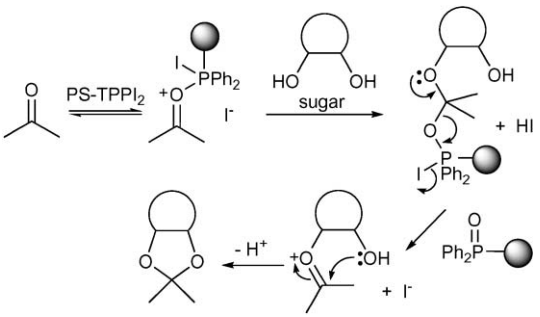
The use of PS-TPP (**1**) in organic synthesis was briefly reviewed in 1999, describing its use as a Wittig reagent and that of PS-TPP/CCl_4 and PS-$TPPX_2$ (where X = Br, I) in functional group transformations.[27] In the following sections, we will highlight some recent applications, particularly for the synthesis of biologically active molecules and the construction of small-molecule libraries for medicinal discovery programs.

3.1 Phosphine-functionalised polymers as dehydrating agents

Recently, **1** has been used to support I_2, and the resultant phosphonium salt (PS-$TPPI_2$) was used as both a Lewis acid and a dehydrating agent in the thermodynamic acetonation of nine sugars (Scheme 14).[28] L-arabinose, D-fructose, D- and L-galactose, D-glucose, D-mannose, D-ribose, L-sorbose and D-glucitol were transformed into the corresponding *O*-isopropylidene sugar derivatives at room temperature within 15 minutes in excellent yields (90–97%). More importantly, the work-up procedure was simple and the formation of water was avoided.



Scheme 12 Polymer **8** as a mild Brønsted acid for selective protection/deprotection reactions.



Scheme 14 Acetonation of sugars using PS-TPPI$_2$.

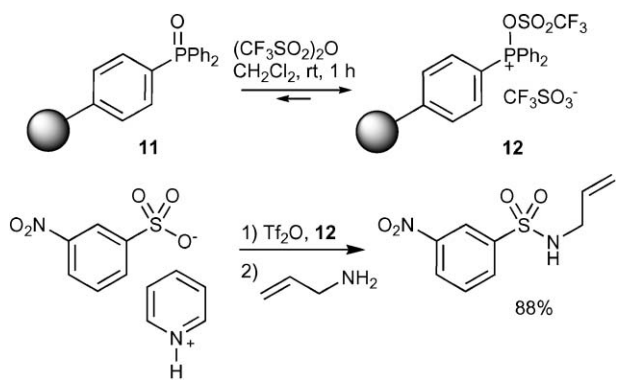
Triphenylphosphine oxide polymer **11** reacts with triflic anhydride to generate a phosphonium ditriflate **12**, which was used by Caddick *et al.*[29] as a coupling reagent for the synthesis of sulfonamides (Scheme 15). The major advantage of **12** is its recyclability; hence, a diverse range of sulfonamides could be generated from one batch of resin and reused at least five times without loss of activity. The generality of **12** as a coupling reagent was subsequently demonstrated by the synthesis of amides, esters (from primary and secondary alcohols), ethers, a tripeptide, a nitrile, an epoxide, an anhydride, an azide and a thioacetate. In the presence of DMAP, secondary alcohols were esterified successfully with retention of configuration.[30]

3.2 Wittig reactions

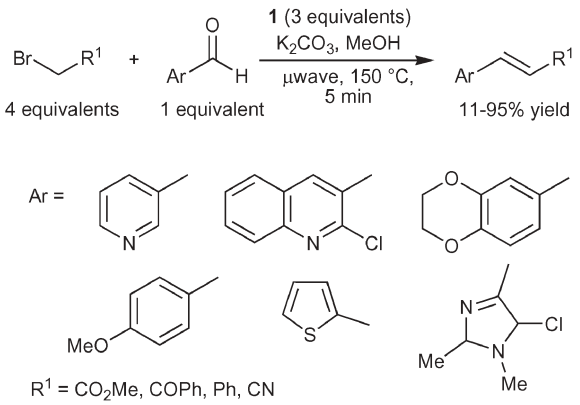
Using triphenylphosphine resin as the phosphine reagent, Westman reported the development of a one-pot, three-step Wittig reaction, whereby microwave dielectric heating was applied directly to a mixture of **1**, aromatic aldehyde and alkyl halide.[31] Good yields of fifteen cinnamate, chalcone and stilbene derivatives could be obtained in high purities in just five minutes without the need for pre-formation or isolation of the phosphorus ylide (Scheme 16).

3.3 Cumulated P-ylides

Similar to Wittig reagents, cumulated P-ylide $Ph_3P{=}C{=}C{=}O$ is a versatile C2-building block that is widely used in domino and multi-component reaction systems for the construction of heterocycles from functionalised carbonyl compounds. Recently, this reagent has been successfully attached to a polymer support by the reaction of **1** with benzyl bromoacetate.



Scheme 15 Use of phosphonium ditriflate **12** as a coupling reagent.



Scheme 16 One-pot Wittig reactions using microwave heating.

The resultant phosphonium salt was treated with a strong base, to afford the polymer-supported P-ylide **13** as a yellow, fairly air-stable resin.

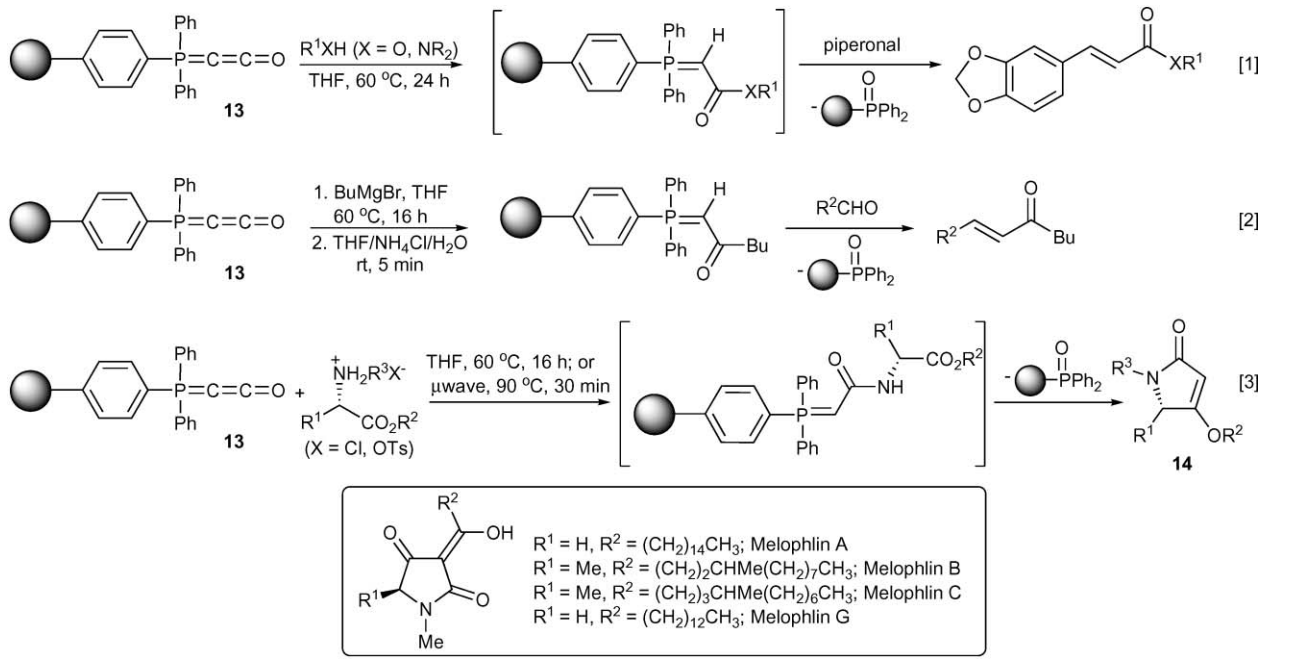
The immobilised ylide **13** was used in the synthesis of a number of α,β-unsaturated esters, amides and ketones *via* a three-component reaction with an aldehyde and an alcohol, amines or a Grignard reagent, respectively (Scheme 17, eqn. 1 and 2).[32] Similarly, the reaction with unprotected α-ammonium esters in one-pot under thermal or microwave conditions furnished optically pure 5-substituted tetramates **14** with yields ranging between 40–93% (Scheme 17, eqn. 3). This has been employed to synthesise four *N*-methyl-3-acyltetramic acids from their corresponding α-amino esters—Melophlin A, B, C and G, a class of marine natural products possessing cytotoxic and antibiotic activities.[33] In all cases, the phosphine oxide by-product **11** could be removed easily by filtration.

3.4 Staudinger reactions

The Staudinger reaction involves the substitution of an organoazide (R-N_3) by a tertiary phosphine to produce a iminophosphorane ($R_3P{=}NR$), which hydrolyses to give primary amines with retention of stereochemistry. The reaction is particularly useful for azides which contain functional groups that are sensitive to reducing reagents. As the final product is highly polar, their purification from phosphorus by-products can be difficult. The use of polymer-supported reagents circumvents this problem by eliminating the need for column chromatography, especially when the molecule also contains acid-sensitive groups. These advantages were exploited in a solid phase-assisted synthesis of phosphorylated aminonucleosides. **1** was used to convert azido nucleoside to an iminophosphorane intermediate, which is stable under the conditions of phosphorylation. Cleavage from the solid support was accomplished using concentrated ammonia under mild conditions to afford the product in good purity (Scheme 18). The method was used to prepare five phosphorylated aminonucleosides with yields between 70–75%.[34]

3.5 Aza-Wittig reactions

The reaction between **1** and an organoazide (R–N_3) compound produces a supported iminophosphorane ($R_3P{=}NR$) that undergoes Wittig reactions with aldehydes to furnish a C=N



Scheme 17 Applications of polymer-supported cumulated P-ylide **13** in organic synthesis.

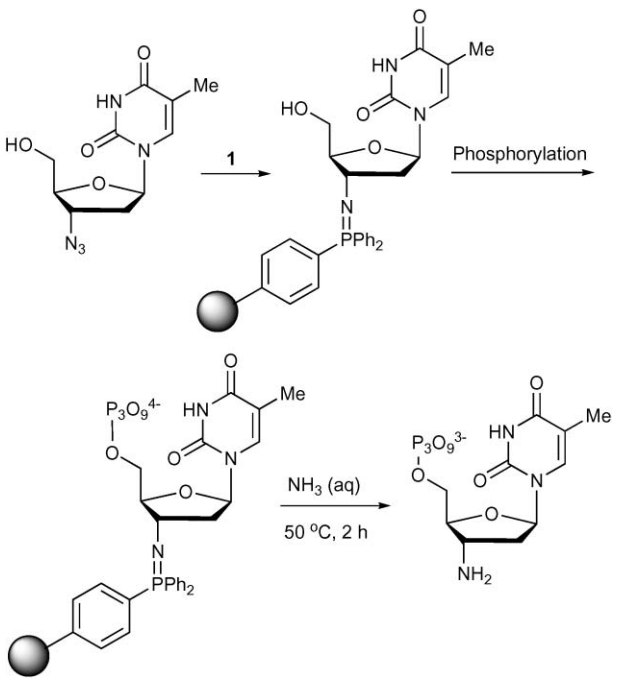
bond, which may be transformed into primary amines using a polymer-supported cyanoborohydride or secondary amines by 1,2-addition reactions with organometallic reagents. Quantitative yields may be achieved and the reactions can be performed in one-pot.[35] The phosphine oxide product **11** was recovered by filtration, from which **1** could be regenerated by using trichlorosilane as a reducing agent.

The supported iminophosphorane was used in a tandem aza-Wittig/heterocumulene annulation to give nitrogen heterocycles. The synthesis of quinazolines **15** and, more recently, 3-amino-1,2,4-benzothiadiazine 1,1-dioxides **16** were achieved in medicinal chemistry programs (Scheme 19).[36]

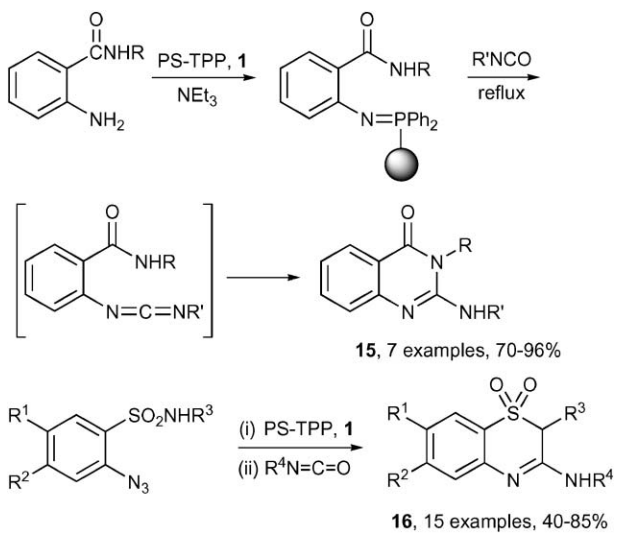
A polymer-assisted aza-Wittig reaction was employed in tandem with a retro-Diels–Alder reaction to access the bicyclic core structure of marine natural product Phloeodictine A1 (Scheme 20).[37] As well as the ease of purification, the use of polymer-support resin **1** avoids unfavourable isomerisation of the double bond in **17**.

3.6 Mitsunobu reactions

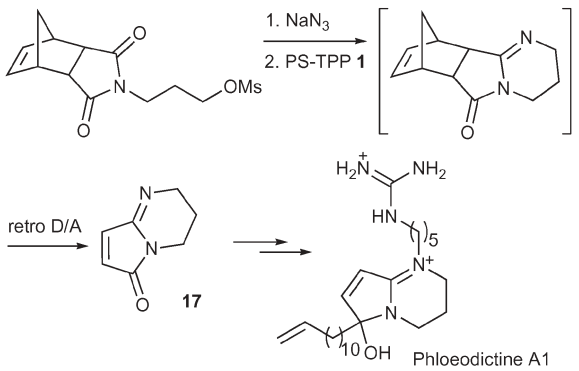
Application of PS-TPP (**1**) resin in Mitsunobu reactions had been reported earlier, in 1983, for the synthesis of esters. This was followed by a curious 15 year gap before the reagent was deployed again for the synthesis of 15 aryl ethers.[38]



Scheme 18 Solid phase synthesis of amino nucleosides.



Scheme 19 Heterocyclic synthesis by aza-Wittig reactions.



Scheme 20 Synthesis of the bicyclic core structure of Phloeodictine A1.

Two important studies uncovered some interesting facts: (i) The immobilisation of the phosphorus reagent has a beneficial effect on the reaction. It was speculated that unfunctionalised phenyl groups of the polystyrene resin decrease the polarity of the microenvironment, thus facilitating the reaction by increasing the reactivity of the ion pair;[39] (ii) The stereochemistry of Mitsunobu reactions remains unaffected by using PS-supported phosphine. The reaction proceeds with inversion of stereochemistry, even with sterically hindered alcohols.[40]

Although the excess phosphorus reagents/side product generated by the Mitsunobu reaction can be removed by immobilisation, the presence of the dicarboxylate hydrazine side product still necessitates purification by chromatography. This problem can be eliminated by substituting diethylazodicarboxylate (DEAD) with di-*tert*-azodicarboxylate (DTAD). Both the reagent and its side product can be decomposed at the end of the reaction into gaseous or water-soluble by-products (CO_2 and $NH_2NH_2{\cdot}2TFA$) by the addition of TFA. The simplicity of the procedure can be easily adapted for automation. Hence, following the initial 15-year hiatus, the use of resin **1** in Mitsunobu reactions is enjoying a resurgence of interest. In the last five years, it has been used widely for the generation of target compounds in several discovery programmes, particularly for the formation of aryl ether bonds. This has included the preparation of key intermediates **18** for the synthesis of an antisense nucleotide, where *Z*-protected amino- or guanidino-groups were introduced onto the phenoxazine ring using a solid phase-assisted Mitsunobu reaction (Fig. 3).[41] A double Mitsunobu reaction was also employed in the selective O-alkylation of 6,7-dihydroxyquinazoline **19** in a 3-step process.[42] In another example, eight

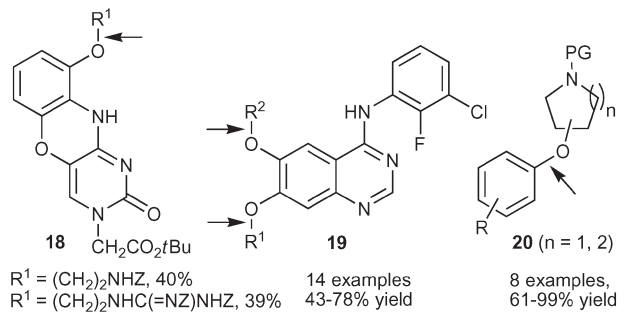
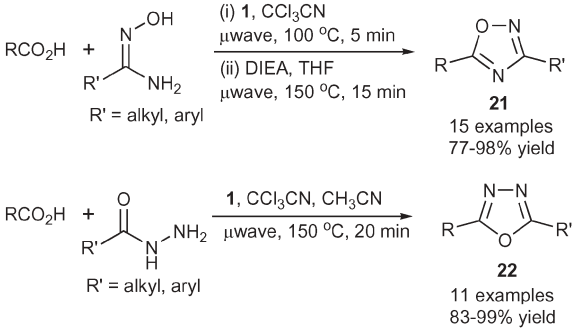


Fig. 3 Aryl ether bonds formed by Mitsunobu reactions.

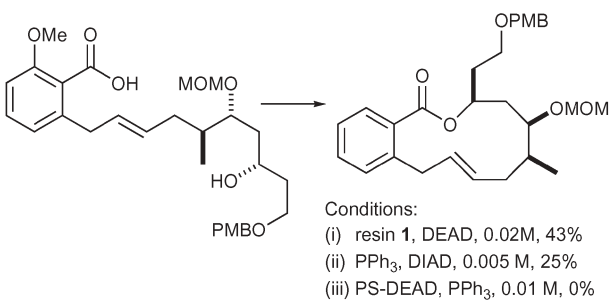


Scheme 21 Synthesis of oxadiazoles **21** and **22** utilising resin **1** and microwave heating.

compounds of general structure **20** were prepared by Mitsunobu coupling between phenol and *N*-Boc-protected amino alcohols. The reactions were found to proceed more efficiently if **1** was pre-treated with DEAD prior to the addition of a mixture of the substrates and triethylamine.[43] The author rationalised that the addition of the tertiary amine prevents protonation of the basic phenolate anion by the amino alcohol, thus promoting the rate-limiting S_N2 step.

Resin **1** was used in a parallel synthesis programme for generating a library of 1,2,4-oxadiazoles **21** in one pot (Scheme 21).[44] In these reactions, unstable carboxylic acid chlorides may be generated *in situ* by subjecting a mixture of a carboxylic acid, **1** and CCl_3CN to microwave irradiation for five minutes. Subsequent treatment of the product with alkyl or aryl amidoximes in the presence of a base and further irradiation furnished the desired heterocycles in good to excellent yields. Recently, a number of 1,3,4-oxadiazoles **22** were similarly produced by replacing amidoximes with acid hydrazides.[45]

Intramolecular Mitsunobu reactions are also used extensively in natural product syntheses, particularly for the formation of macrocycles. In a total synthesis of Salicylihalamide A (a highly potent cytotoxic marine natural product), the formation of the 12-membered macrolactone core structure was achieved by a solid phase-assisted Mitsunobu reaction utilising polymer resin **1** (Scheme 22).[46] Ring formation was envisaged to be particularly difficult as the macrocycle contains a double bond at an allylic position with an *E*-geometry, which may impose steric hindrance on the cyclisation. It was subsequently found that the macrolactonisation was greatly



Scheme 22 Macrolactonisation of the core structure of Salicylihalamides.

enhanced by using the phosphine-functionalised polymer. Using PPh_3 and di-*iso*-propylazodicarboxylate (DIAD) under homogeneous conditions at high dilution (0.005 M), only 25% of the product was obtained. In comparison, use of the polymer-supported triphenylphosphine allowed the concentration to be raised to 0.02 M, affording a higher 43% yield. In contrast, no product was formed using immobilised azodicarboxylate reagent.

4. Phosphine-functionalised polymers as an almost traceless linker

The use of polymer-bound triphenylphosphine **1** as an almost traceless linker was first demonstrated by Hughes in 1996, with the solid phase synthesis of three small organic molecules from 2-nitrobenzyl bromide.[47a] Two years later, he reported the use of this strategy in a split-and-mix synthesis of a library of fifty bis-amides **23** (Scheme 23).[47b]

The linker was also used by Slade *et al.* for the synthesis of an 80-member library of 2-alkylthiobenzimidazoles **24** from a subset of amines and electrophiles.[48] HPLC analysis revealed that most compounds were obtained in $> 80\%$ purity.

5. Conclusions and outlook

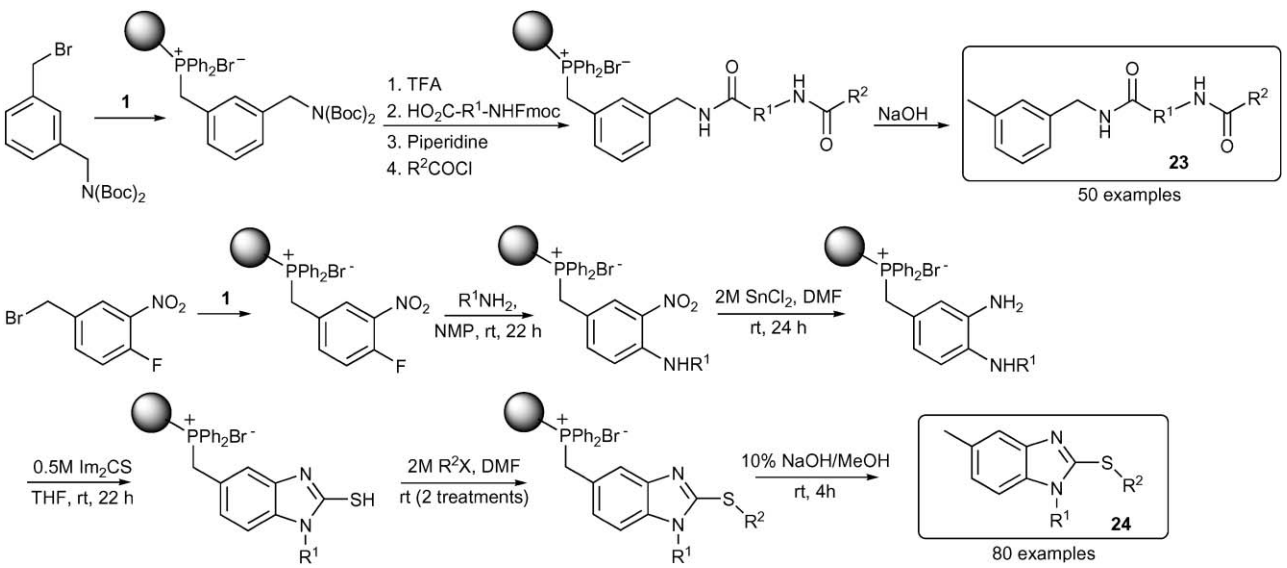
Recent applications of polymer-supported tertiary phosphines in organic synthesis have been highlighted.

The attachment of metal catalysts to anchored phosphines continues to attract interest, particularly in the area of palladium catalysis where the recyclability and reuse of the expensive polymer-bound catalysts is important. Microwave irradiation has been employed simultaneously as an effective means of shortening reaction times. The process of catalyst preparation and immobilisation was found to have a profound effect on the catalytic activity. The origin of this is unclear, although a recent review has cast some useful insights into the nature of the catalytically-active palladium species generated from homogeneous and heterogeneous catalysts.[49] Finally, catalyst decomposition and leaching still pose considerable restrictions on the reusability of these heterogeneous catalysts, especially when the reactions involve unactivated aryl chlorides. To overcome part of this problem, a method of 'incarcerating' Pd(0) precursors within a polymer matrix has recently been reported that can drastically reduce the amount of metal leaching. However, the addition of a phosphine ligand is necessary to effect Suzuki reactions with unactivated aryl halides.[50] The presence of phosphorus impurities in the product was not discussed.

An emerging area is the use of these polymer resins as organocatalysts, which have received significant attention, particularly in the last two years. Several bond formations, including carbon–carbon bonds, can be achieved without the mediation of heavy metals. Furthermore, as the organophosphorus catalyst is covalently attached to the insoluble support, contamination of the product can be avoided. However, degradation of the phosphine by oxidation could potentially limit its reusability.

The transposition of organophosphorus reagents onto polymer supports continues unabated. The biggest successes have been recorded in Wittig chemistry, as well as solution phase Mitsunobu reactions, where polymer resin **1** has been used to generate several molecular libraries of medicinal interest, as well as in natural product synthesis.

Despite the extensive use of organophosphorus reagents in synthetic chemistry,[51] only a fraction of them have been conducted using phosphine-functionalised polymer resins. With this in mind, we predict that the search for new applications of polymer-supported phosphorus reagents will continue for the foreseeable future. Concurrently, several studies have shown that a polymer's microenvironment often has a profound effect on reaction outcome. Thus, it is envisaged that future developments will include a greater emphasis on 'performance' polymer resins with better mechanical and chemical stabilities, such that polymer degradation, leaching behaviour and swelling of the resin beads may be improved, leading to faster and cleaner reactions.



Scheme 23 Resin **1** as an almost traceless linker.

References

1 (*a*) M. J. Farrall and J. M. J. Frechet, *J. Org. Chem.*, 1976, **41**, 3877; (*b*) G. L. Thomas, C. Boehner, M. Ladlow and D. R. Spring, *Tetrahedron*, 2005, **61**, 12153; (*c*) M. K. W. Choi, H. S. He and P. H. Toy, *J. Org. Chem.*, 2003, **68**, 9831.
2 N. E. Leadbeater and M. Marco, *Chem. Rev.*, 2002, **102**, 3217.
3 N. E. Leadbeater, *Curr. Med. Chem.*, 2002, **9**, 2147.
4 N. End and K. U. Schöning, *Top. Curr. Chem.*, 2004, **242**, 241.
5 Y. Uozumi, *Top. Curr. Chem.*, 2004, **242**, 77.
6 B. Schlummer and U. Scholz, *Adv. Synth. Catal.*, 2004, **346**, 1599.
7 M. Terasawa, K. Kaneda, T. Imanaka and S. Teranishi, *J. Organomet. Chem.*, 1978, **162**, 403.
8 R. Grigg and M. York, *Tetrahedron Lett.*, 2000, **41**, 7255.
9 S. B. Jang, *Tetrahedron Lett.*, 1997, **38**, 1793.
10 I. Fenger and C. Le Drian, *Tetrahedron Lett.*, 1998, **39**, 4287.
11 C. M. Andersson, K. Karabelas, A. Hallberg and C. Andersson, *J. Org. Chem.*, 1985, **50**, 3891.
12 K. Inada and N. Miyaura, *Tetrahedron*, 2000, **56**, 8661.
13 C. A. Parrish and S. L. Buchwald, *J. Org. Chem.*, 2001, **66**, 3820.
14 Y. Wang and D. R. Sauer, *Org. Lett.*, 2004, **6**, 2793.
15 R. R. Srivastava and S. E. Collibee, *Tetrahedron Lett.*, 2004, **45**, 8895.
16 M. Guinó and K. K. Hii, *Tetrahedron Lett.*, 2005, **46**, 7363.
17 V. P. Ananikov, M. A. Kabeshov and I. P. Beletskaya, *Synlett*, 2005, 1015.
18 M. Westhus, E. Gonthier, D. Brohm and R. Breinbauer, *Tetrahedron Lett.*, 2004, **45**, 3141.
19 M. Guinó and K. K. Hii, *Tetrahedron Lett.*, 2005, **46**, 6911.
20 P. Stanetty and M. Kremslehner, *Tetrahedron Lett.*, 1998, **39**, 811.
21 Y. G. Wang, H. F. Jiang, H. L. Liu and P. Liu, *Tetrahedron Lett.*, 2005, **46**, 3935.
22 R. Skouta, R. S. Varma and C. J. Li, *Green Chem.*, 2005, **7**, 571.
23 L. J. Zhao, C. K. W. Kwong, M. Shi and P. H. Toy, *Tetrahedron*, 2005, **61**, 12026 and references cited therein.
24 (*a*) Y. S. Hon, C. F. Lee, R. J. Chen and P. H. Szu, *Tetrahedron*, 2001, **57**, 5991; (*b*) Y. S. Hon, C. F. Lee, R. J. Chen and Y. F. Huang, *Synth. Commun.*, 2003, **33**, 2829.
25 J. Jaunzems, D. Kashin, A. Schonberger and A. Kirschning, *Eur. J. Org. Chem.*, 2004, 3435.
26 C. Ogawa, H. Konishi, M. Sugiura and S. Kobayashi, *Org. Biomol. Chem.*, 2004, **2**, 446.
27 D. H. Drewry, D. M. Coe and S. Poon, *Med. Res. Rev.*, 1999, **19**, 97.
28 S. Pedatella, A. Guaragna, D. D'Alonzo, M. De Nisco and G. Palumbo, *Synthesis*, 2006, 305.
29 S. Caddick, J. D. Wilden and D. B. Judd, *J. Am. Chem. Soc.*, 2004, **126**, 1024.
30 K. E. Fairfull-Smith, I. D. Jenkins and W. A. Loughlin, *Org. Biomol. Chem.*, 2004, **2**, 1979.
31 J. Westman, *Org. Lett.*, 2001, **3**, 3745.
32 R. Schobert, C. Jagusch, C. Melanophy and G. Mullen, *Org. Biomol. Chem.*, 2004, **2**, 3524.
33 R. Schobert and C. Jagusch, *Tetrahedron*, 2005, **61**, 2301.
34 T. Schoetzau, T. Holletz and D. Cech, *Chem. Commun.*, 1996, 387.
35 K. Hemming, M. J. Bevan, C. Loukou, S. D. Patel and D. Renaudeau, *Synlett*, 2000, 1565–1568.
36 (*a*) W. Zhang, J. P. Mayer, S. E. Hall and J. A. Weigel, *J. Comb. Chem.*, 2001, **3**, 255; (*b*) C. Blackburn, A. Achab, A. Elder, S. Ghosh, J. Guo, G. Harriman and M. Jones, *J. Org. Chem.*, 2005, **70**, 10206.
37 B. J. Neubert and B. B. Snider, *Org. Lett.*, 2003, **5**, 765.
38 A. R. Tunoori, D. Dutta and G. I. Georg, *Tetrahedron Lett.*, 1998, **39**, 8751.
39 S. D. Alexandratos and D. H. J. Miller, *Macromolecules*, 1996, **29**, 8025.
40 P. D. White, A. R. Tunoori, D. Dutta and G. I. Georg, *Comb. Chem. High Throughput Screening*, 2000, **3**, 103.
41 C. Ausin, J. A. Ortega, J. Robles, A. Grandas and E. Pedroso, *Org. Lett.*, 2002, **4**, 4073.
42 C. S. Harris, L. F. Hennequin, J. G. Kettle and O. A. Willerval, *Tetrahedron Lett.*, 2005, **46**, 7715.
43 M. E. Lizarzaburu and S. J. Shuttleworth, *Tetrahedron Lett.*, 2002, **43**, 2157.
44 Y. Wang, R. L. Miller, D. R. Sauer and S. W. Djuric, *Org. Lett.*, 2005, **7**, 925.
45 Y. Wang, D. R. Sauer and S. W. Djuric, *Tetrahedron Lett.*, 2006, **47**, 105.
46 C. Herb and M. E. Maier, *J. Org. Chem.*, 2003, **68**, 8129.
47 (*a*) I. Hughes, *Tetrahedron Lett.*, 1996, **37**, 7595; (*b*) I. Hughes, *J. Med. Chem.*, 1998, **41**, 3804.
48 R. M. Slade, M. A. Phillips and J. G. Berger, *Mol. Diversity*, 1998, **4**, 215.
49 N. T. S. Phan, M. van der Sluys and C. W. Jones, *Adv. Synth. Catal.*, 2006, **348**, 609.
50 H. Hagio, M. Sugiura and S. Kobayashi, *Org. Lett.*, 2006, **8**, 375.
51 *Organophosphorus Reagents*, ed. P. J. Murphy, Oxford University Press, Oxford, 2004, pp. 51–97.