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Polymer-supported triphenylphosphine: application in organic synthesis and organometallic reactions

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This comprehensive review highlights the diverse chemistry and applications of polymer-supported triphenylphosphine (PS-TPP) in organic synthesis since its inception. Specifically, the review describes applications of the preceding reagent in functional group interconversions, heterocycle synthesis, metal complexes and their application in synthesis, and total synthesis of natural products. Many examples are provided from the literature to show the scope and selectivity (regio, stereo, and chemo) in these transformations.

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1. Introduction

One of the latest advances in recent years has been the utility of solid-phase synthesis as a strategy to prepare chemical libraries,[1] biologically active molecules, and natural products.[2,3] Adaptation of solution phase synthetic techniques to use on solid supports offers some key advantages over solution-phase chemistry such as ease of purification, recyclability of the solid matrix, and use of excess reagents to achieve complete reaction conversion. Consequently, polymer-supported

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reagents have found many applications in synthetic organic chemistry. As such, the use of supported reagents in medicinal chemistry has been nicely showcased by Ley in the multi-step synthesis of drug targets and natural products such as sildenafil (Viagra),[4] epimaritidine[5] and epibatidine.[6] One of the most useful reagents to which many chemical transformations can be credited is polymer-supported triphenylphosphine (diphenyl-polystyrylphosphine or polystyryldiphenylphosphine (1), PS-PPh$_2$), an analogue of the ubiquitous triphenylphosphine (PPh$_3$). The latter is a common reagent used in many chemical transformations where in many cases it gets oxidized to triphenylphosphine oxide (Ph$_3$PO). Removal of Ph$_3$PO from the product requires tedious chromatographic separation and/or crystallization processes which renders PPh$_3$ impractical. As an alternative, polystyrene-supported triphenylphosphine was introduced. This reagent has an advantage over the its soluble counterpart because it can be separated along with any oxidation byproduct by filtration. The reagent can be easily prepared in one step and for convenience is commercially available from several chemical suppliers (100–200 mesh, extent of labeling: ~3 mmol g^{-1} triphenylphosphine loading). The immobilized reagent was first reported in 1971 and has been extensively used ever since.[7] However, the full synthetic potential of the reagent and variations thereof is still being established and several

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research groups around the globe are still aggressively pursuing such endeavors as demonstrated by the recent surge of research articles published by various groups on a wide range of transformations mediated by this reagent. The PS-PPh$_2$ reagent has not yet been thoroughly reviewed in the literature except in some instances where it was briefly featured as a part of reviews of much wider scope.[8–10] Thus, in this comprehensive review, an attempt to give an overall detailed picture of the synthetic utility of PS-PPh$_2$ has been made by taking many examples from the literature covering almost 50 years. The review focuses on the preparation of PS-PPh$_2$ and its utility in functional group interconversions, transition metal complexes and their reactions, heterocyclic synthesis, and preparation of natural products. Special focus has been dedicated to the impact of the structural framework of the substrate, substitution pattern, and configuration on reaction times and conditions, as well as on the stereo-, chemo, and regiochemical outcome of the reaction. Therefore we have discussed the synthetic schemes and entries in every table for the various transformations in detail. The scope of the review will be limited to PS-PPh$_2$ and its reactions.
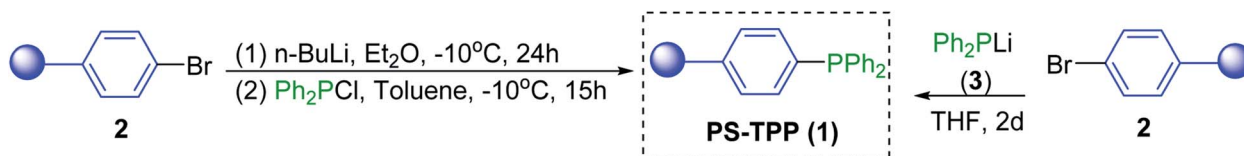
2. Preparation of polystyryldiphenylphosphine (1)

Generally, one of the simplest approaches to immobilize a phosphine ligand on a polymer support involves direct reaction of the desired ligand with a functionalised polymer such as bromopolystyrene or Merrifield's resin. Polystyrene resins are commercial available in a variety types, cross-link densities, and particle sizes. The cross-linked diphenyl-polystyrylphosphine (PS-PPh$_2$, 1) can be prepared from bromopolystyrene (2) via a lithium–halogen exchange process by initial lithiation of the polymer support 2 to form lithiated polystyrene (Scheme 1), followed by reaction with chlorodiphenylphosphine (PPh$_2$Cl).[7,11–13] There are however drawbacks associated with this approach. Reaction of cross-linked bromopolystyrene with butyllithium often leads to unwanted side-reactions involving the C=C bonds of the divinylbenzene crosslinking. Consequently, the product resin becomes contaminated and shows poor swelling properties. More efficient preparation of the polystyryl-lithium species that precludes attack of the divinylbenzene crosslinking moiety involves reaction of cross-linked polystyrene with the 1 : 1 complex of *n*-butyl-lithium and *N*,*N*,*N*′*N*′-tetramethylethylenediamine (TMEDA).[14] An alternative preparation of PS-PPh$_2$ (1) involves reaction of cross-linked bromopolystyrene (2) with lithium diphenylphosphide (3).[7,12,13,15] This method represents the more common route for the attachment of monodentate phosphines to polymer resins. PS-PPh$_2$ is insoluble in all typical organic solvents and is readily available through several chemical vendors as 2% divinylbenzene crosslinked polystyrene beads (100–400 mesh size) with loading ranges from 1.0 mmol P per g to over 3.0 mmol P per g. The reagent can be handled like a typical solid and is amenable to long term storage, although preferably under inert atmosphere to avoid aerial oxidation.

Scheme 1 Synthesis of DVB–crosslinked polystyryldiphenylphosphine **1**.

3. Polystyryldiphenylphosphine-mediated functional group interconversions

3.1. Wittig reagents

3.1.1. Carbonyl olefination with *p*-polystyryldiphenyl-benzyl-phosphonium chloride. The Wittig reaction[16] represents on of the most used chemical methods for olefin synthesis involving phosphines in solution. Not surprisingly, the first reported application of PS-TPP involved a Wittig reaction. Castells was the first to report the use of polymer-bound triphenylphosphine in this capacity to synthesize stilbene (40–60% yield) from the reaction of benzaldehyde with *p*-polystyryldiphenyl-benzyl-phosphonium chloride, prepared by reacting PS-TPP with neat benzyl chloride.[7] A concurrent investigation by Heitz and Michels[17] on polymer-supported Wittig synthesis of olefins using polystyrene crosslinked with 0.5 and 2.0 wt% of divinylbenzene (DVB) found that higher yields were possible with a 0.5% crosslinked polystyrene support. This was because only about 75% of the pore volume in a swollen polymer crosslinked with 2% DVB was accessible to substrates with molar masses 300–400, according to gel-chromatographic studies. Heitz and Michels[18] also investigated steric control of the Wittig reaction on triphenylphosphane resins. They found that the adduct formed from the reaction of the aldehyde with the ylide can be selectively converted either to the *trans*- or *cis*-olefin as the major product in the mixture. The formation of the *cis*-olefin is kinetically controlled and favored in salt-free medium while the *trans*-olefin is thermodynamically controlled and predominates if the adduct is formed at low temperature ($-78\ ^{\circ}C$) as the lithium salt is generated by adding lithium perchlorate as a Lewis acid. The study was, however, very limited in scope as the diastereoselectivity was poor and only reported for three olefins. Another concurrent study on the preparation and application of polymeric phosphoranes in the Wittig reaction was reported by Mckinley and Rakshys using the standard 2% crosslinked polystyryldiphenyl phosphine.[19] Although the carbonyl–olefination reactions proceeded with methylene, ethylene, and benzylidene

polymeric ylides using aromatic and aliphatic aldehydes and ketones, the conversion of the carbonyl compound was incomplete and yields were generally low (24–72%). It is noteworthy that these earlier papers reported syntheses of alkenes in fluctuating yields, depending on the polymer used and particular reaction conditions. Thus, further improvements were required for a useful methodology of general applicability.

3.1.2. Polymer-supported phase transfer catalysed Wittig reaction. Phase transfer catalysed reactions[20] have been used extensively in organic synthesis, although they have been used to a much lesser extent in polymer chemistry. Thus, chemical reactions that combine the advantages of both experimental techniques are of interest. Hodge *et al.* described a phase transfer catalysed Wittig reaction between aldehydes **6** and polymer-bound phosphonium salt residues **5**, prepared from PS-TPP and various organic halides **4** (Scheme 2).[21,22] The reaction proceeds at room temperature and the small molecules are tethered to the polymer with bonds which are stable to both acid and base. The Wittig reaction was carried out in CH_2Cl_2 with 50% aqueous NaOH and a phase transfer catalyst (tetrabutylammonium iodide (TBAI) or cetyltrimethylammonium bromide (CTAB)). These conditions offered the highest reported olefin **7** yields compared to those reported by earlier work on polymer-supported Wittig reagents.[17–19,23,24]

As shown in Table 1, high yields of essentially pure alkenes were obtained from arylalkylphosphonium salts and various aldehydes (entries 1–9). However, while the alkylphosphonium salt (entry 10) reacted with a moderate yield with a reactive aldehyde, alkylphosphonium salts did not react with any aldehydes (entry 11). The Wittig reactions were performed with both, crosslinked and linear PS-TPP, although the former was more convenient since the resulting oxidized byproduct could be directly removed by filtration whilst the latter and it oxide were soluble and required precipitation workup. This renders linear polymers generally unsuitable. The isomeric ratios (*cis* : *trans*) were not determined for all olefins, although the measured ones were comparable to those obtained under conventional phase transfer catalysed conditions (entry 1; *E* : *Z* (100 : 0); entry 3; *E* : *Z* (57 : 43); entry 4; *E* : *Z* (44 : 56)). A point
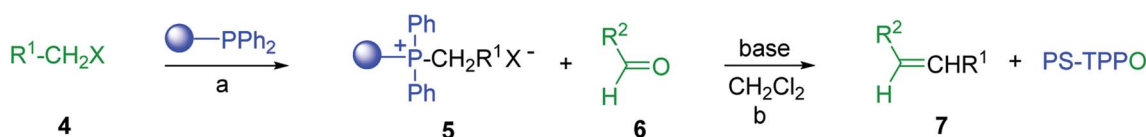
Scheme 2 Polymer-supported phase transfer catalysed Wittig reaction. Reagents and conditions: (a) PS-TPP, chlorobenzene; (b) **5** : **6** (1.5 : 1 equiv.), 50% NaOH, TBAI or CTAB (2 mol%), 2–16 h.

Table 1 Reactions of polymer–bound phosphonium salts **5** derived from PS–TPP (**1**) and aldehydes **6** under phase–transfer conditions

Entry	Halide **4** (R^1-X)	Aldehyde **6**	Catalyst	Yield **7** (%)
1	Benzyl chloride	9-Formylanthracene	CTAB	98
2	Benzyl chloride	Benzaldehyde	CTAB	92
3	Benzyl chloride	*p*-Methyl-benzaldehyde	CTAB	100
4	Benzyl chloride	*p*-Chloro-benzaldehyde	TBAI	97
5	Benzyl chloride	Furan-2-aldehyde	CTAB	90
6	Benzyl chloride	Heptaldehyde	TBAI	93
7	4-*t*-Butylbenzyl chloride	Formaldehyde	CTAB	95
8	2-Bromoethylnaphthalene	β-Naphthaldehyde	CTAB	65
9	2-Bromoethylnaphthalene	Formaldehyde	CTAB	67
10	Allyl bromide	*p*-Chloro-benzaldehyde	None	78
11	MeI or *n*-hexyl bromide	*p*-Chloro-benzaldehyde	TBAI	0

that merits comment is that the Wittig reaction can take place without any added catalyst, albeit more slowly, producing much lower yields as well. Ketones also failed to react with the phosphonium salts.

3.1.3. Wittig reagents bound to crosslinked polystyrenes with variable crosslinking densities. Building on the earlier work describing polymer-supported Wittig reagents, Ford *et al.* reported a detailed study on the impact of varying the extent of crosslinking of the polystyrene support on yields of Wittig products.[13] The polymer-supported reagents with 0.5% and 2% cross-linked polystyrenes that had been used earlier were too gelatinous and unsuitable for large-scale filtration.[17] Thus, more highly crosslinked and rigid polystyrene supports were being sought out, although on the expense of lower Wittig yields, since penetration of reagents into all of the functional sites and out of the more highly cross-linked polymer matrices would be expected to be poor especially with large substrates. Ford described the use of Wittig reagents supported on polystyrenes with up to 20% cross-linking and with reactants as bulky as 10-nonadecanone (Table 2, entries 8 and 9) and the 3-keto steroid, cholest-4-en-3-one (Table 2, entries 10 and 11). The Wittig reagents were prepared on 2%, 8%, and 20% DVB crosslinked polystyrene from the reaction of crosslinked PS-TPP

and either MeI (**8a**) or BnBr (**8b**), to afford the methyl-(**9a**) and benzylphosphonium (**9b**) salts, respectively (Scheme 3).

As shown in Scheme 3 and Table 2, Wittig reactions of the methylidenephosphoranes, generated from phosphonium salts **9** under basic conditions, were complete after 6 h at room temperature, followed by heating for 24 h at 60 °C. The chemical yields in all cases depended on the polymer as follows: 2% crosslinked polymer produced higher yields than >20% cross-linked polymer >8% crosslinked polymer. A similar trend was observed for olefins generated from polymer-bound benzyl-phosphonium salts. In this case, *E/Z* diastereomeric ratios ranged from 72/28 to 43/57. In general, reactions of the phosphoranes **9** with aldehydes and ketones afforded olefins in 73–96% yields with the 2% crosslinked polymer, 52–77% yields with the 8% cross-linked polymer, and 72–87% yields with the 20% cross-linked macroporous polymer. Ford showcased the utility of phosphonium salts on 2% cross-linked polystyrene and on 20% cross-linked macroporous polystyrene in the synthesis of ethyl retinoate.[25] The preparation of olefins from polymer-supported phosphonium salts derived from PS-TPP (**1**) and various carbonyl compounds and elaboration thereafter has also been exploited by Ley for the synthesis of β-hydroxyamines.[26]

Table 2 Alkenes from polymer–bound methylphosphonium salts **8a**

Entry	Copolymer, % crosslinking	Carbonyl compound **10**	Wittig product **11**	Yield (%)
1	2	$(CH_2)_5C{=}O$	$(CH_2)_5C{=}CH_2$	99
2	2	$PhCH{=}CHCHO$	$PhCH{=}CHCH{=}CH_2$	95
3	8	$PhCH{=}CHCHO$	$PhCH{=}CHCH{=}CH_2$	52
4	20	$PhCH{=}CHCHO$	$PhCH{=}CHCH{=}CH_2$	83
5	2	$Ph_2C{=}O$	$Ph_2C{=}CH_2$	94
6	8	$Ph_2C{=}O$	$Ph_2C{=}CH_2$	61
7	20	$Ph_2C{=}O$	$Ph_2C{=}CH_2$	74
8	2	$(n\text{-}C_9H_{19})C{=}O$	$(n\text{-}C_9H_{19})C{=}CH_2$	96
9	20	$(n\text{-}C_9H_{19})C{=}O$	$(n\text{-}C_9H_{19})C{=}CH_2$	62
10	2	Cholest-4-en-3-one	3-Methylenecholest-4-ene	91
11	20	Cholest-4-en-3-one	3-Methylenecholest-4-ene	87
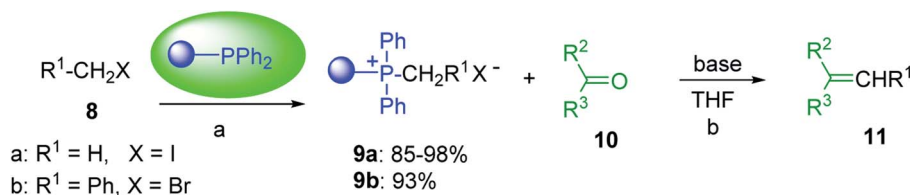
Scheme 3 Polymer-supported Wittig reactions. Reagents and conditions: (a) PS–TPP **1** : halide **8** (1 : 2 molar ratio), DMF, 70 °C, 2 d; (b) **9** : sodium methylsulfinylmethylide (1 : 3 molar ratio), THF/DMSO (1 : 1), −10 °C, 6 h, then **10** (1 molar equiv.), RT, 6 h, then reflux 24 h.

3.1.4. Mono-olefination of symmetrical dialdehydes with polymer-supported Wittig reagents derived from PS-TPP and various halides. Castells and co-workers exploited the pseudo high dilution environment provided by polymer supported phosphonium salts to effect mono-olefination of symmetrical dialdehydes (Scheme 4).[27] The olefination reactions were carried out using 1 : 1 molar ratio of polymer supported phosphonium salts **13** and **19** to dialdehydes (isophthalaldehyde (**14**) and terephthalaldehyde (**15**)). The phosphonium salts were prepared from PS-TPP **1** and benzyl bromide (**12a**), benzyl chloride (**12b**), or methyl bromoacetate (**18**). The Wittig reaction afforded olefins in variable yields as *E/Z* geometric isomers (**16** and **17**), and in the case of phosphonium salt **19** as single diastereomers (**20** and **21**). The exclusive mono-olefinization was attributed to the formation of a betaine intermediate with one of the two aldehydes which blocks all active sites on the polymer, preventing the second carbonyl group from reacting. Interestingly, mono-olefinization still took place even when

excess phosphonium salt to dialdehyde (2 : 1 molar ratio) was employed.

3.1.5. Preparation of vinyl ethers and thioethers *via* Wittig reagents. Polystyryldiphenyl-methoxymethyl- (**23a**), methylthiomethyl-phosphonium (**23b**), and benzyl-phosphonium chlorides (**23c**) were prepared by Akelah[23] by treating PS-TPP (**1**) with chloromethylmethylether (**22a**), chloromethylthioether (**22b**), and benzyl chloride (**22c**) respectively (Scheme 5). These reagents were employed for the conversion of carbonyl compounds and formate esters into vinyl-ethers (**24a**), thioethers (**24b**), and alky-β-styrylethers (**25**) in high yields.

3.2. PS-TPP halophosphorane complexes

3.2.1. Polymer-supported dichlorophosphorane. Polymer-supported dichlorophosphoranes (**26** and **28**) were first prepared in 1974 from PS-TPP (**1**) and its related benzyl analogue **27** by initial oxidation with peracetic acid to the corresponding polymer-bound phosphine oxides, followed by
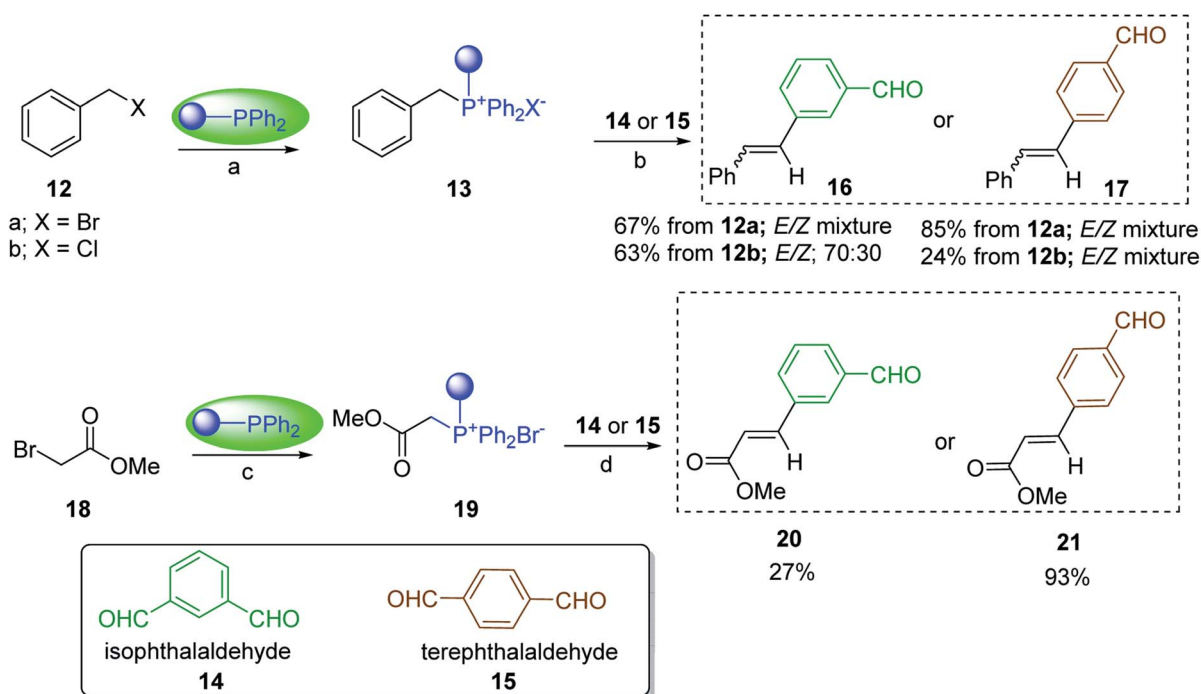
Scheme 4 Mono-olefinization of dialdehydes. Reagents and conditions: (a) PS-TPP : BnBr (or BnCl); (1 : 6.5 (or 1 : 16.3 for BnCl) molar ratio), benzene, reflux, 16 h (with BnBr) or 5 h (with BnCl); (b) **13** : **14**: (or **15**); (1 : 1 molar ratio), ethylene oxide (10.5 equiv.), benzene, 68 h at RT, then reflux at 45–50 °C for 6 h; (c) PS-TPP : methyl bromoacetate (**18**); (1 : 3.6 molar ratio), benzene, 7 d; (d) **18** : **14** or **15**; (1 : 1 molar ratio), ethylene oxide (14.3 equiv.), benzene.
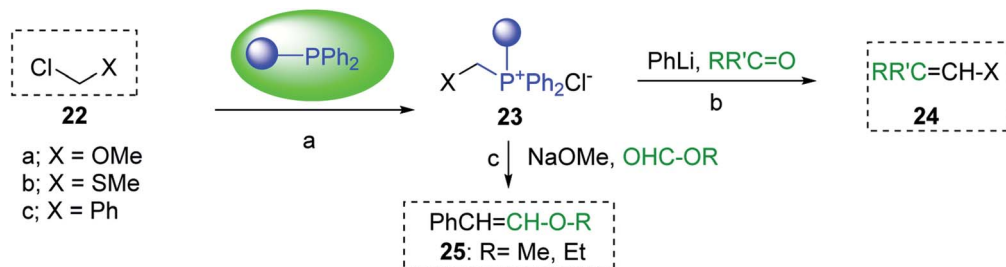
Scheme 5 Preparation of vinyl ethers, thioethers, and alky-β-styrylethers. Reagents and conditions: (a) **23a**; PS-TPP : MeOCH$_2$Cl : carbonyl (1 : 1.5 : 1), toluene, 50 °C, 48 h; **23b**; PS-TPP : MeSeCH$_2$Cl : carbonyl (1 : 1.5 : 1), toluene, 50 °C, 48 h; **23c**; PS-TPP : BnCl (1 : 2), toluene, 50 °C, 24 h; (b) **24a** : PhLi (1 : 1), ether, RT, 24 h; **24b** : PhLi (1 : 1), THF, RT, 24 h; (c) **25**: PS-TPP : **23c** (1 : 1), NaOMe, MeOH, RT.

treatment with carbon oxychloride (phosgene) to provide the desired halophosphorane complexes **26**, and **28** (Scheme 6).[28]

Reagents **26** and **28** were used successfully for the synthesis of acid chlorides from carboxylic acids (Table 3, entries 1–3 and 5–7), a nitrile from a primary amide (entry 4), a chloroalkene from a ketone (entry 10), an imidoyl chloride from an anilide (entry 8), and an alkyl chloride from an alcohol (entry 9). The recovered resin-bound phosphine oxide was rephosgenated back to the halophosphorane reagent for reuse.

3.2.2. Condensation of *N*-alkoxycarbonyl α-amino acids with primary amines using PS-TPP and CCl$_4$. The combination of PS-TPP and carbon tetrachloride comprises a convenient coupling system for the amidation of *N*-alkoxycarbonyl α-amino acids and primary amines.[29] Such a process is often beset with shortcomings associated with epimerization of the *N*-terminal residue and purification of the product. However, the preceding method reported by Landi and Brinkman is not afflicted by the aforementioned problems. The reagent system proved effective for *N*-Boc (*t*-butoxycarbonyl) and *N*-Fmoc (9-fluorenylmethoxycarbonyl) amino acids, as well as *N*-CBz (benzyloxycarbonyl) substrates (Table 4). Typically, the procedure involved refluxing an equimolar mixture of the *N*-protected amino acid and the amine with 4-methylmorpholine (**29**) (1.1 equiv. or 2.2 equiv. if the amine was an acid salt) and PS-TPP (2 equiv.) in a binary solvent mixture of CH$_2$Cl$_2$ and CCl$_4$ (2 : 1). Interestingly, although earlier work of Relles[28] and Hodge[30] described the formation of acid chlorides from the reaction of polymer-supported dichlorotriphenylphosphorane with carboxylic acids, these intermediates were not present or involved in the current condensation. The active electrophile was found to be a resin-bound mixed phosphinic anhydride.

3.2.3. Preparation of dipeptides using PS-TPP and CCl$_4$. Polymer-supported triphenylphosphine and carbon tetrachloride have also been successfully used for the synthesis of dipeptides. Appel described the synthesis of three small peptides from *N*-protected amino acid and amino acid ester salts using PS-TPP and CCl$_4$. The reaction was heated at 40 °C in acetonitrile as solvent to afford the peptides in 70–76% yields (Table 5).[31]

3.2.4. Preparation of acid chlorides and alkyl chlorides using PS-TPP and CCl$_4$. The PS-TPP–CCl$_4$ reagent system has also been applied successfully to convert carboxylic acids into acid chlorides,[30,32] and thiols[32] as well as alcohols[15,30,32] into alkyl chlorides (Scheme 7). The reactions do not generate HCl and thus the conditions are essentially neutral.

Some representative examples of the conversion of carboxylic acids into acid chlorides, and alcohols/thiols into alkyl chlorides are summarized in Table 6. Generally, a carbon tetrachloride solution of the carboxylic acid, alcohol, or thiols in the presence of excess PS-TPP (1.3–2 molar equiv.) was heated at reflux for 1–5 h and the oxidized polymer resin was removed at the end of reaction period by filtration. Carbon tetrachloride was used as a co-reagent and as a solvent. A range of aliphatic and aromatic carboxylic acids, thiols, and alcohols were suitable substrates and gave good yields (50–98%), except for the secondary alcohol, cyclohexanol (entry 13). In this case, some elimination occurred, giving a mixture of chlorocyclohexane and cyclohexene. The acetonide protecting group (entry 12) remained intact, underscoring the advantage of neutral conditions. Interestingly, substrate selectivity based on size was not a factor in determining the reaction rate considering that substrates need to diffuse into the polymer to react. For
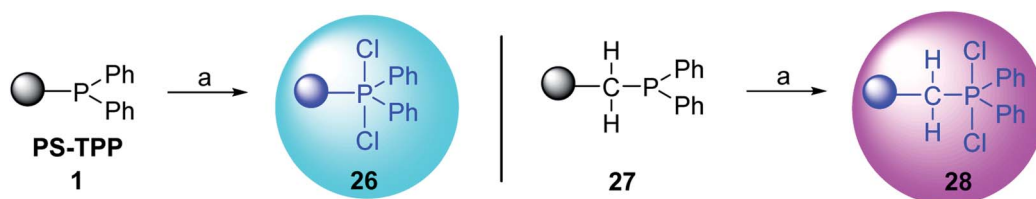
Scheme 6 Preparation of halophosphorane complexes. Reagents and conditions: (a) (i) 40% peracetic acid in acetic acid, CH$_2$Cl$_2$, 25 °C, 3 h; (ii) phosgene (excess), 25 °C, 1 h.

Table 3 Chemical conversions using cross-linked polymeric phosphine dichlorides[a]

Entry	Polymeric phosphine dichloride	Reactant	Product	Yield (%)
1	26	$PhCH_2CO_2H$	$PhCH_2COCl$	100
2	26	p-$CH_3C_6H_4CO_2H$	p-$CH_3C_6H_4COCl$	98
3	26	$HO_2CC_6H_4CO_2H$ (p)	$ClOCC_6H_4COCl$ (p)	91
4	26	$PhCH_2CONH_2$	$PhCH_2CN$	78
5	28	$HO_2CC_6H_4CO_2H$ (p)	$ClOCC_6H_4COCl$ (p)	95
6	28	$HO_2CC_6H_4CO_2H$ (p)	$ClOCC_6H_4COCl$ (p)	98
7	28	$HO_2CC_6H_4CO_2H$ (m)	$ClOCC_6H_4COCl$ (m)	87
8	28	$PhCH_2CONHC_6H_5$	$PhCH_2C(Cl){=}NC_6H_5$	93
9	28	$PhCH_2OH$	$PhCH_2Cl$	88
10	28	$PhCH_2COCH_3$	$PhCH_2C(Cl){=}CH_2$	75

[a] Reagents and conditions: 1 : 1 molar ratios of polymeric phosphine dichloride : reactant, CH_2Cl_2, RT, 30 min.

instance, 5β-cholan-24-ol (entry 14), which represents a relatively large substrate, reacted satisfactorily with the reagent. Mechanistically, the polymer-supported reactions involving the conversion of alcohols into alkyl chlorides seem to follow similar pathways to those observed for the free Ph_3P reagent as judged by the quantity of phosphine (2 equiv.) consumed per mole of alkyl chloride and by the quantity of chloroform produced at the end of the reaction. Formation of the polymeric chlorinating species appears to be the slow step, although the PS-TPP reactions have been shown to be faster than those using Ph_3P due to a microenvironmental effect.[32,33] The suggested mechanism also required that polymer supported phosphine residues react together.[33] This is consistent with Sherrington's work in which the conversion of alcohols into alkyl chlorides was retarded or even inhibited when highly crosslinked PS-TPP (>15% crosslink ratio of styrene to DVB) was utilized.[34] Although highly crosslinked polymers favour the formation of chloroalkanes because the alcohol penetrates the matrix more easily, the inherent rigidity and lack of backbone mobility hinders the approach and reaction of non-adjacent phosphine residues,

and therefore inhibit the preceding transformation. As a result, the aforementioned chlorination reactions are best carried with Ph_3P supported on polystyrene of low crosslink ratio (1–2%).[35]

3.2.5. Synthesis of amides from carboxylic acids and amines using PS-TPP and CCl_4. Hodge et al. also demonstrated that carboxylic acids could be directly converted into amides by treatment with carbon tetrachloride and PS-TPP in the presence of at least 2 molar equivalents of the amine (Table 7).[32] The reaction was reminiscent to that reported earlier by Appel and Willms whereby several peptides were prepared using the same reagent.[31] Amides were prepared in 1,2-dichloroethane (DCE) containing 10% CCl_4 by volume (entries 1, 2 and 5) or in CCl_4 under reflux for 3 h to afford the amides in 57–94% yield. The same system was used by Hodge to convert primary carboxamides and oximes into nitriles or imidoyl chlorides in good yields.

3.2.6. Polymer-supported triphenylphosphine-carbon tetrabromide and triphenylphosphine dibromide: conversion of alcohols into alkyl bromides. Hodge et al. reported the use of polymer-supported triphenylphosphine dibromide (PS-TPP–

Table 4 Condensation of N-alkoxycarbonyl α-amino acids and primary amines

Entry	R^1	R^2	Amine	Yield (%)
1	CH_2CO_2Bn	Bn	L-Phenylalanine-OMe·HCl	96
2	$CH_2C_6H_4(OBu\text{-}t)\text{-}4$	$CH_2C_{13}H_9$	L-(−)-α-Methylbenzylamine	89
3	CH_2OBn	t-Bu	L-(−)-α-Methylbenzylamine	99
4	CH_2CO_2Bn	Bn	D-Phenylalanine-OMe·HCl	100
5	Bn	t-Bu	L-(−)-α-Methylbenzylamine	88
6	CH_2CO_2Bn	t-Bu	L-(−)-α-Methylbenzylamine	96
7	$CH_2CO_2Bu\text{-}t$	t-Bu	L-Phenylalanine-OMe·HCl	100
8	$(CH_2)_2SMe$	t-Bu	L-(−)-α-Methylbenzylamine	79
9	$(CH_2)_4NHCO_2CH_2C_6H_4Cl\text{-}2$	t-Bu	L-(−)-α-Methylbenzylamine	78

Table 5 Preparation of dipeptides with polymeric triphenylphosphine and CCl_4[a]

Entry	N-Protected amino acid	Amino acid ester	Peptide	Yield (%)
1				76
2				70
3				70

[a] Reagents and conditions: 3 : 1 : 1 : 2 molar ratios of PS-TPP/CCl_4 : N-protected amino acid : amino acid ester : Et_3N, acetonitrile, 40 °C, 1 d.
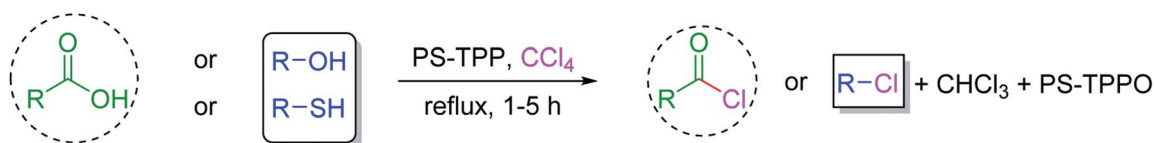
Scheme 7 Reactions of carboxylic acids, thiols, and alcohols with PS–TPP in CCl_4.

Br_2) and the combination of polymer-supported triphenyl-phosphine and carbon tetrabromide (**30**) (PS-TPP–CBr_4) to convert alcohols into alkyl bromides (Table 8).[36] The former reagent had been used earlier for the cleavage of ethers,[37] and to prepare imidoyl bromides, ketenimines, and carbodiimides.[38]

The required PS-TPP–Br_2 was prepared from PS-TPP and bromine in $CHCl_3$ and was used to convert a range of alcohols to bromides at reflux temperature. However, the use of PS-TPP–CBr_4 was more advantageous since HBr is not a byproduct and reactions were faster (5–40 min), cleaner, and did not
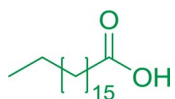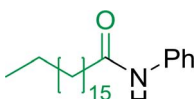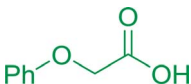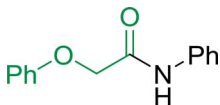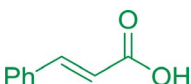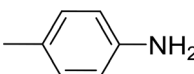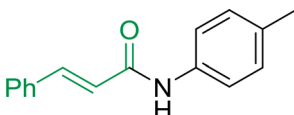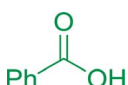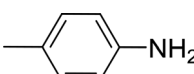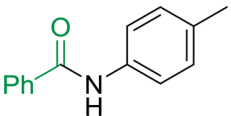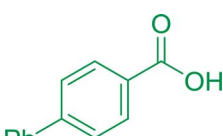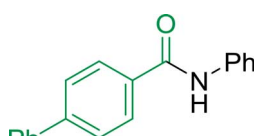
Table 6 Conversion of carboxylic acids into acid chlorides and alcohols into alkyl chlorides[a]

Entry	Carboxylic acid/alcohol	Acid chloride/alkyl chloride	Yield (%)
1	n-Octanoic	Octanoyl chloride	63
2	Phenoxyacetic	Phenoxyacetyl chloride	50
3	Stearic	Stearoyl chloride	82
4	Cinnamic	Cinnamoyl chloride	77
5	Benzoic	Benzoyl chloride	90
6	α-Furoic	2-Furanoyl chloride	82
7	β-Naphthoic	2-Naphthoyl chloride	84
8	n-Octanol	1-Chlorooctane	98
9	2-n-Butoxyethanol	1-(2-Chloroethoxy)butane	94
10	Benzyl alcohol	Benzyl chloride	88
11	Hexadecyl alcohol	1-Chlorohexadecane	98
12	4-Hydroxymethyl-2,2-dimethyl-1,3-dioxolane	4-(Chloromethyl)-2,2-dimethyl-1,3-dioxolane	78
13	Cyclohexanol	Chlorocyclohexane	40
14	5β-Cholan-24-ol	24-Chloro-5β-cholane	78
15	Octadecanethiol	1-Chlorooctadecane	78
16	3-Phenylpropanethiol	(3-Chloropropyl)benzene	82
17	Phenylmethanethiol	Benzyl chloride	95

[a] Reagents and conditions: 1.3 : 2 molar ratios of PS-TPP : carboxylic acid or alcohol, CCl_4, 77 °C, 1–5 h.

Table 7   Preparation of amides from carboxylic acids and amines[a]
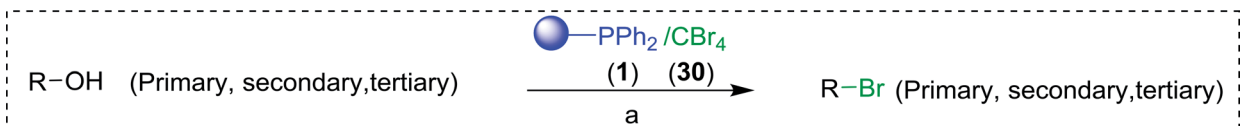
Entry	Acid	Amine	Amide	Yield (%)
1		Ph–NH$_2$		86
2		Ph–NH$_2$		57
3				72
4				83
5		Ph–NH$_2$		94

[a] Reagents and conditions: 2.2 : 1 : 2 molar ratios of PS-TPP : carboxylic acid : amine, DCE/10% CCl$_4$ or CCl$_4$, reflux, 3 h.

require heating in the case of primary and some secondary alcohols (Table 8, entries 1–8). Bulky substrates (entries 9–11) required more vigorous conditions but nevertheless still gave good yields of the bromides. Inversion of configuration was observed with trinorbornan-*endo*-2-ol (entry 10) and (−)-bornan-2-ol (entry 11).

3.2.7. Synthesis of dibromoalkenes by reaction of carbonyl compounds with PS-TPP and CBr$_4$. Aldehydes and ketones react with dibromomethylene ylides **32**, generated from the reaction of carbon tetrabromide with Ph$_3$P (Scheme 8, reaction 1), to give 1,1-dibromoalkenes **34** (reaction 2). Additionally, the carbonyl group may react with the accompanying triphenylphosphine

Table 8   Conversion of alcohols to bromides with PS-TPP and CBr$_4$[a]

Entry	Alcohol	Bromide product	Yield (%)
1	1-Octanol	1-Bromooctane	98
2	Benzyl alcohol	Benzyl bromide	80
3	3-Phenylpropan-1-o1	(3-Bromopropyl)benzene	81
4	4-Phenylbutan-1-o1	(4-Bromobutyl)benzene	82
5	4,4,4-Triphenylbutan-1-o1	(4-Bromobutane-1,1,1-triyl)tribenzene	73
6	Undec-10-en-1-o1	11-Bromoundec-1-ene	89
7	Cinnamyl alcohol	Cinnamyl bromide	89
8	Octan-2-o1	2-Bromooctane	76
9	Adamantanol	1-Bromoadamantane	97
10	Trinorbornan-*endo*-2-ol	Trinorbornan-*exo*-2-yl bromide	89
11	(−)-Bornan-2-ol	Bornan-*exo*-2-yl bromide	71

[a] Reagents and conditions: 2.2 : 1.1 : 1 molar ratios of PS-TPP : CBr$_4$: alcohol, CHCl$_3$; entries 1–8 (RT, 5–40 min); entries 9–11 (61 °C, 16 h).
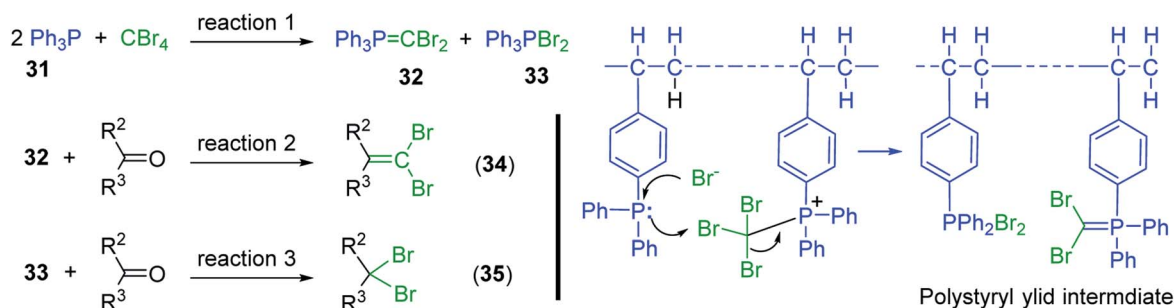
Scheme 8 Synthesis of dibromoalkenes and *gem*-dibromides from carbonyl compounds with PS-TPP/CBr$_4$ reagent system.

dibromide (**33**) produced in the first step (reaction 1) to produce *gem*-dibromides **35** (reaction 3). Hodge investigated the synthesis of 1,1-dihaloalkenes by reacting carbonyl compounds with PS-TPP and carbon tetrahalides (CBr$_4$ and CCl$_4$).[39] The reactions with carbon tetrachloride required harsh conditions and generally produced inseparable mixtures of dichloroalkene and *gem*-dichloride. However, the reaction with CBr$_4$ proceeded at 20 °C and in most cases afforded dibromoalkenes (**34**) in

good and consistent yields (87–98%) with minimal formation of *gem*-dibromides **35** (3–13%). Mechanistically, the olefination reactions using the PS-TPP/CBr$_4$ reagent system proceeds through the polystyryl ylide intermediate shown in Scheme 8.

3.2.8. Conversion of epoxides to halohydrins. Polystyryldiphenylphosphine–halogen complexes (PS-TPP–X$_2$) comprise convenient reagents for the conversion of epoxides to halohydrins under very mild and non-acidic conditions.[40] They

Table 9 Conversion of epoxides to halohydrins using PS-TPP–X$_2$ complexes[a]

Entry	Epoxide	Halohydrin	Yield (%)
1			X = I: 97 X = Br: 95 X = Cl: 96
2			X = I: 95 X = Br: 96 X = Cl: 98
3			X = I: 95 X = Br: 96 X = Cl: 97
4			X = I: 95 X = Cl: 97
5			95

[a] Reagents and conditions: 1.2 : 1 molar ratio of PS-TPP–X$_2$: epoxide, CH$_2$Cl$_2$, RT, 10 min.

Table 10 Esterification of carboxylic acids using PS-TPP–I_2 complexes[a]

Entry	Carboxylic acid	Alcohol	Yield (%) of ester
1	CH_3CO_2H	5α-Cholestan-3β-ol	96
2	CH_3CO_2H	5α-Cholestan-3α-ol	85
3	$PhCO_2H$	CH_3OH	90
4	$PhCO_2H$	5α-Cholestan-3β-ol	85
5	$CH_3(CH_2)_6CO_2H$	5α-Cholestan-3β-ol	93
6	$CH_3(CH_2)_{14}CO_2H$	CH_3OH	98
7	$CH_3(CH_2)_{14}CO_2H$	5α-Cholestan-3β-ol	92
8	$CH_3(CH_2)_{16}CO_2H$	CH_3CH_2OH	95
9	$CH_3(CH_2)_{16}CO_2H$	5α-Cholestan-3β-ol	94
10	Linoleic acid	CH_3OH	87
11	Linoleic acid	5α-Cholestan-3β-ol	84

[a] Reagents and conditions: 1.1 : 1.1 : 1 molar ratio of PS-TPP–I_2 : carboxylic acid : alcohol, CH_2Cl_2, 40–50 °C, 1–3 h.

are semi-crystalline solids which are easy to handle, stable at room temperature, and amenable to storage for weeks. However, they undergo rapid decomposition if they are exposed to moisture giving the corresponding hydrogen halide and phosphine oxide. The halogen complexes were prepared by treating PS-TPP with an equimolar amount of bromine (1 M) or iodine (1 M) solution, or by bubbling gently gaseous chlorine through the suspended polymer resin in CH_2Cl_2. The halogens got consumed immediately and the formation of the complexes was almost instantaneous. Epoxide-ring opening reactions proceeded in high yields (Table 9) and maintained regio- and stereo-selectivity when compared to the same transformation carried out with $Ph_3P–X_2$ complexes.

Table 11 Synthesis of alkyl halides from alcohols[a]

Entry	Alcohol	Product	Yield (%)
1	Benzyl alcohol	Benzyl iodide	93
2	4-Methoxy-benzyl alcohol	4-Methoxy-benzyl iodide	96
3	3,4-Dimethoxy-benzyl alcohol	3,4-Dimethoxy-benzyl iodide	89
4	4-Nitro-benzyl alcohol	4-Nitro-benzyl iodide	96
5	3-Chloro-benzyl alcohol	3-Chloro-benzyl iodide	95
6	4-Chloro-benzyl alcohol	4-Chloro-benzyl bromide	91
7	4-Bromo-benzyl alcohol	4-Bromo-benzyl bromide	92
8	3-Phenylpropan-1-ol	(3-Bromopropyl)benzene	81
9	Octan-1-ol	1-Iodooctane	92
10	3-Methylbut-2-en-1-ol	1-Iodo-3-methylbut-2-ene	87
11	Cyclohexanol	Iodocyclohexane	76
12	Diphenylmethanol	(Iodomethylene)dibenzene	85
13			79
14	n = 2-8, 10	n = 2-8, 10	88–93

[a] Reagents and conditions: 1 : 1.2 : 1 molar ratio of alcohol : PS-TPP : X_2 (X= I, Br), MW, 120 °C, CH_3CN, 3–7 min.

Table 12 Conversion of alcohols into formate esters by PS-TPP–I$_2$–dimethylformamide adducts[a]

Entry	Alcohol	Formate ester	Yield (%)
1			93
2			90
3			90
4			92
5			78
6			84
7			92

[a] Reagents and conditions: 2.3 : 2.3 : 2.4 : 1 molar ratios of PS-TPP : I$_2$: DMF : alcohol, RT, 30 min.

3.2.9. Esterification of carboxylic acids using poly-styryldiphenylphosphine–halogen complexes (PS-TPP–X$_2$). Caputo *et al.* also demonstrated the utility of polystyryldiphenylphosphine–halogen complexes (PS-TPP–X$_2$) in the condensation of carboxylic acids and alcohols to afford esters in high yields and under mild conditions (Table 10).[41] The
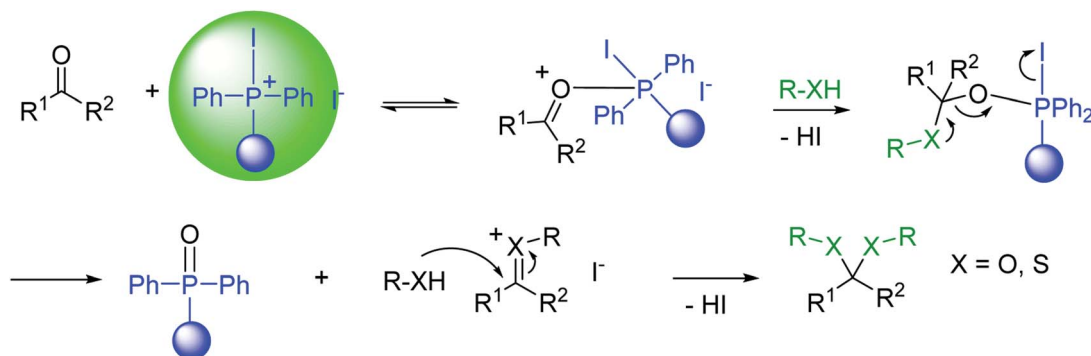
Scheme 9 Mechanism of acetalization of carbonyl compounds using PS-TPP–I$_2$.

Table 13 Acetalization reactions of ketones and aldehydes catalysed by PS-TPP–I$_2$ complex[a]

Entry	R^1	R^2	R^3	Yield (%)
1	Ph	Me	–O-(CH$_2$)$_2$-O–	80
2	Ph	Me	–S-(CH$_2$)$_2$-S–	98
3	Ph	Me	–S-(CH$_2$)$_2$-O–	92
4	Ph	Ph	–S-(CH$_2$)$_2$-S–	86
5	Ph	Ph	–S-(CH$_2$)$_2$-O–	88
6	Ph	H	–S-(CH$_2$)$_2$-S–	98
7	Ph	H	–S-(CH$_2$)$_2$-O–	85
8	n-C$_7$H$_{15}$	H	–O-(CH$_2$)$_2$-O–	84
9	n-C$_7$H$_{15}$	H	–S-(CH$_2$)$_2$-S–	98
10	n-C$_7$H$_{15}$	H	–S-(CH$_2$)$_2$-O–	85
11	–(CH$_2$)$_2$CH(t-C$_4$H$_9$)(CH$_2$)$_2$		n-C$_4$H$_9$S–	80
12	–(CH$_2$)$_2$CH(t-C$_4$H$_9$)(CH$_2$)$_2$		CH$_3$O–	92

[a] Reagents and conditions: 1.2 : 1 : 4 molar ratio of PS-TPP–I$_2$: carbonyl compound : protecting reagent, Et$_3$N (for entries 1, 3, 8 and 12), MeCN, RT, 40 min.

complexes were prepared as before[40] and the procedure involved adding the acid to an equimolar amount of the complex, followed by stirring at room temperature for 10–15 min. Subsequent addition of the alcohol and warming up to 40–50 °C gave the desired ester in high yield within 1–3 h. The halogen complexes act both as condensating agents and acid catalysts. The reaction was assumed to involve protonated acyl halides as the key intermediates that react with the added alcohol. The advantage of this protocol include rapid ester formation, directly from the acid, broad range of alcohol and carboxylic acid substrates, and simple workup. The iodine complex (PS-TPP–I$_2$) was most practical, among the three halogen complexes, as the formation of esters with PS-TPP–Cl$_2$ was slow, whereas the use of PS-TPP–Br$_2$ resulted in some bromination of double bonds for unsaturated substrates.

3.2.10. Microwave assisted conversion of alcohols to alkyl halides with PS-TPP–X$_2$ complexes. Microwave assisted organic synthesis has been implemented as a technology in organic
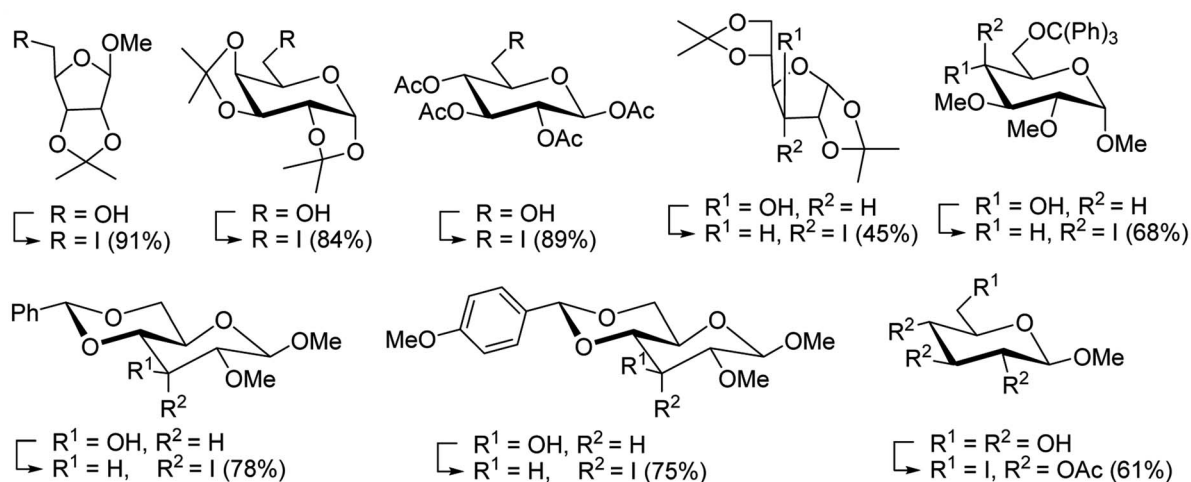
Scheme 10 Conversion of alcohols into alkyl iodides with PS-TPP–I$_2$ complex. Reagents and conditions: 3 : 1.3 : 3 : 1 molar ratios of PS-TPP : I$_2$: imidazole : alcohol, toluene, 50–120 °C, 3–8 h.

chemistry since the mid-1980's.[42] Recently, a microwave assisted procedure for the conversion of allylic, benzylic and aliphatic alcohols to the corresponding alkyl bromides and iodides using polymer-supported triphenylphosphine and iodine or bromine was described by Rokhum et al.[43] The iodination and bromination reactions were complete within 7 minutes under microwave irradiation conditions and gave alkyl halides in yields ranging from 76–96% (Table 11). Primary alcohols converted to the corresponding halides at a faster rate than secondary alcohols and preference of secondary over tertiary substitution was observed with unsymmetrical diols (entry 13). In case of symmetrical diols (entry 14), the mono-iodinated products were obtained in very high yields (88–93%). The methodology features high chemo- and regio-selectivity behaviour, short reaction times, product isolation requiring only filtration and solvent removal.

3.2.11. Formylation of primary and secondary alcohols using PS-TPP and iodine. The conversion of alcohols into formic acid esters is a well known protection strategy.[44] Unfortunately, many of the methods used to prepared formate esters use drastic conditions and suffer from serious limitations which include heating the alcohol in 85% formic acid or employing uncommon reagents. Palumbo et al. exploited PS-TPP–halogen complexes in the synthesis of formic acid esters from various primary and secondary alcohols (Table 12).[45] It is noted that tertiary alcohols under the same conditions failed to give the desired formate esters and instead afforded the alkyl halides. Both iodine and chlorine complexes (PS-TPP–I$_2$ and PS-TPP–Cl$_2$) were suitable, whereas the bromine complex (PS-TPP–Br$_2$) was not tolerated at least with unsaturated alcohols due the co-occurrence of a side reaction involving

Table 14 Synthesis of (E)-nitroalkenes from aldehydes and nitroalkanes[a]

Entry	Aldehyde	R^2	Nitroalkene product	Yield (%)
1		H		93
2		CH$_3$		89
3		H		84
4		H		93
5		CH$_3$		89
6		CH$_3$		89
7		H		81
8		H		55
9		CH$_3$		58

[a] Reagents and conditions: 1 : 1.5 : 1.5 : 1.5 : 2 molar ratios of aldehyde : nitroalkane : PS-TPP : iodine : imidazole, RT, CH$_2$Cl$_2$, 1–3 h.

Table 15 Synthesis of *N*-protected β-iodoamines using PS-TPP–I$_2$ complex[a]
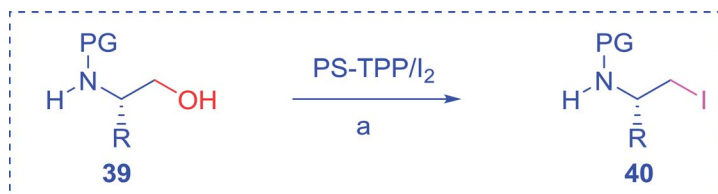
Entry	PG	R	Yield (%)
1	Cbz	Me	89
2	Cbz	Bn	90
3	Boc	CH(CH$_3$)$_3$	90
4	Boc	CH$_2$COOBn	82
5	Boc	Ph	95
6	Fmoc	Me	92
7	Fmoc	Bn	94
8	Fmoc	CH$_2$CH(CH$_3$)$_3$	94

[a] Reagents and conditions: 2.2 : 2.5 : 1 molar ratios of PS-TPP/I$_2$: imidazole : alcohol, CH$_2$Cl$_2$, reflux, 1 h.

some bromination of double bonds. The iodine complex was the most convenient considering the ease of handling compared with chlorine.

3.2.12. Acetalization of carbonyl compounds with PS-TPP–I$_2$ complex. Cyclic and acyclic acetals, dithioacetals, and oxathioacetals are very common groups used to protect the

Table 16 Preparation of dipeptides with polymeric triphenylphosphine and I$_2$[a]

Entry	*N*-Protected α-AA	*O*-Protected α-AA	Dipeptide	Yield (%)
1				99
2				98
3				95
4				95
5				95

[a] Reagents and conditions: 2.2 : 2 : 1 : 1 : 2.5 molar ratios of PS-TPP : I$_2$: *N*-protected α-amino acid : *O*-protected α-amino acid : imidazole, CH$_2$Cl$_2$, RT, 30 min.
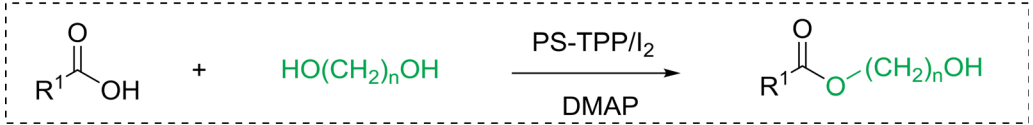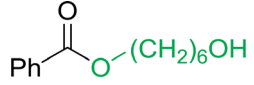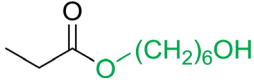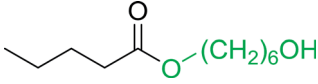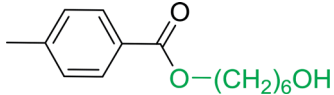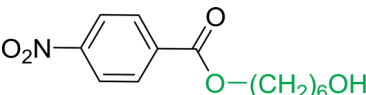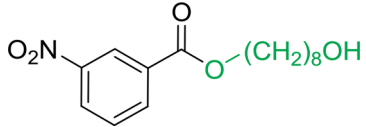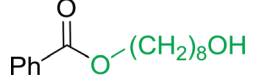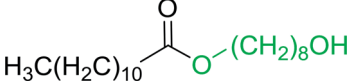
carbonyl function of aldehydes and ketones.[46] One drawback of acetalization, besides using alcoholic media and Brønsted acid catalysts, is the generation of water during the reaction and the need to remove it by physical or chemical means to drive the equilibrium forward. Thus, a strategy to prepare acetals from carbonyl compounds and alcohol, diols, dithiols, or hydroxythiols under anhydrous conditions and devoid of water formation has been described using the combination of PS-TPP and I_2.[47] In this approach, the carbonyl compound in anhydrous acetonitrile is treated with a pre-formed PS-TPP–I_2 complex, followed by the desired protecting reagent. An adduct is formed between the positively charged phosphorus atom and carbonyl oxygen, thus activating the carbonyl carbon center for nucleophilic addition by a molecule of the protecting reagent (Scheme 9). A subsequent non-equilibrium step involves the elimination of PS-TPPO and generation of an oxygen-stabilized carbocation which undergoes further reaction with a second reagent

molecule or a tethered nucleophile on the same reagent to afford the final product.

The devised procedure for acetalization tolerates aliphatic and aromatic aldehydes and ketones, as shown in Table 13. It is noted that in order to avoid acidic medium for certain substrates, anhydrous Et_3N was added in portions throughout the reaction.

3.2.13. Polymer-supported triphenylphosphine dibromide (PS-TPP–Br_2–imiH) and diiodide (PS-TPP–I_2–imiH): conversion of alcohols into alkyl iodides. Building on Hodge's earlier work regarding the use of polymer-supported triphenylphosphine dibromide (PS-TPP–Br_2) in the conversion of alcohols into alkyl bromides,[36] Classon prepared a similar polymer-supported phosphine–halogen complex using iodine in combination with imidazole (PS-TPP–I_2–imiH).[48] The addition of imidazole enhanced reactivity and neutralized liberated HI, resolving reactivity and yield issues encountered earlier by Hodge et al. in

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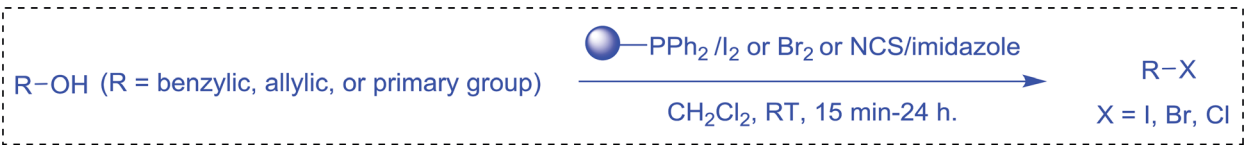
Table 17 Preparation of monoesters from diols using PS-TPP and iodine[a]

Entry	Alcohol	Carboxylic acid	Product	Yield (%)
1	$HO(CH_2)_6OH$	Benzoic acid		88
2		Propanoic acid		91
3		Pentanoic acid		87
4		4-Methylbenzoic acid		84
5		4-Nitrobenzoic acid		92
6	$HO(CH_2)_8OH$	3-Nitrobenzoic acid		84
7		Benzoic acid		85
8		Lauric acid		91

[a] Reagents and conditions: 1.5 : 1.5 : 1 : 1 : 3 molar ratios of PS-TPP/I_2 : alcohol : carboxylic acid : DMAP, THF/CH_2Cl_2 (1 : 3 v/v), RT, 18–22 h.

Table 18 Halogenation of alcohols[a]

R–OH (R = benzylic, allylic, or primary group) →[PPh₂/I₂ or Br₂ or NCS/imidazole, CH₂Cl₂, RT, 15 min–24 h.] R–X (X = I, Br, Cl)

Entry	Alcohol	Alkyl halide	Yield (%)
1	Benzyl alcohol	Benzyl iodide	97
2	o-Tolylmethanol	1-(Iodomethyl)-2-methylbenzene	95
3	(2-Bromophenyl)methanol	1-Bromo-2-(iodomethyl)benzene	95
4	(2-Methoxyphenyl)methanol	1-(Iodomethyl)-2-methoxybenzene	96
5	3-(Hydroxymethyl)benzonitrile	3-(Iodomethyl)benzonitrile	98
6	(3-Nitrophenyl)methanol	1-(Iodomethyl)-3-nitrobenzene	98
7	(4-Methoxyphenyl)methanol	1-(Iodomethyl)-4-methoxybenzene	92
8	(2,4-Dichlorophenyl)methanol	1-(Iodomethyl)-2,4-dichlorobenzene	97
9	(2,4-Dimethoxyphenyl)methanol	1-(Iodomethyl)-2,4-dimethoxybenzene	95
10	(E)-3-Phenylprop-2-en-1-ol	(E)-(3-Iodoprop-1-en-1-yl)benzene	95
11	(Z)-3,7-Dimethylocta-2,6-dien-1-ol	(Z)-1-Iodo-3,7-dimethylocta-2,6-diene	91
12	(E)-3,7-Dimethylocta-2,6-dien-1-ol	(E)-1-Iodo-3,7-dimethylocta-2,6-diene	88
13	p-Tolylmethanol	1-(Bromomethyl)-4-methylbenzene	96
14	p-Tolylmethanol	1-(Chloromethyl)-4-methylbenzene	90
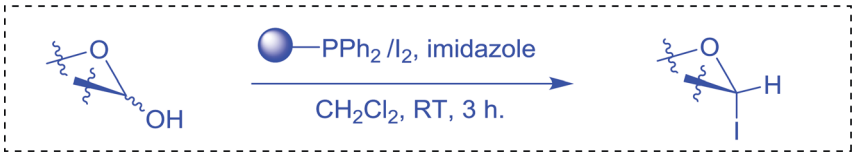
[a] Reagents and conditions: entries 1–12; 1.3 : 1.3 : 1.3 : 1 molar ratios of PS-TPP : I₂ : imidazole : alcohol, CH₂Cl₂, RT, 15–120 min; entry 13; same conditions except Br₂ was used; entry 14; same conditions except NCS was used and the reaction was stirred for 24 h.

the bromination of alcohols using the related PS-TPP–Br₂ complex.[36] Other bases such as pyridine or Et₃N were examined, although much lower yields were generally obtained. The halogenation reactions were performed in heated toluene which provided a two phase liquid–liquid reaction system and promoted faster reactivity than other solvents because the non-polar character of the solvent appears to destabilize the charged phosphonium halide intermediate and drive decomposition to the uncharged alkyl iodide and phosphine oxide byproduct. The iodinations examined involved the synthesis of iodides from alcohols, using various carbohydrates as substrates. Acid-

sensitive groups such as acetals, glycosidic linkages, and triphenylmethyl ethers remained intact under reaction conditions (Scheme 10). However unprotected polyhydroxy sugars were unsuitable as substrates and gave complicated reaction mixtures.

3.2.14. Synthesis of (E)-nitroalkenes from aldehydes and nitroalkanes PS-TPP and I₂. Bez et al. described the first solid phase one-pot procedure for the synthesis of (E)-nitroalkenes **38** (ref. 49) by reacting diverse aromatic, aliphatic, and α,β-unsaturated aldehydes (**36**) with nitroalkanes (**37**) in the presence of polymer-bound triphenylphosphine, iodine and imidazole

Table 19 Preparation of glycosyl iodides from protected sugars[a]

[structure OH] →[PPh₂/I₂, imidazole, CH₂Cl₂, RT, 3 h.] [structure with H and I]

Entry	Carbohydrate	Protection group	Yield (%)
1	D-Glucopyranose	2,3,4,6-Tetra-O-acetyl	97
2	D-Glucopyranose	2,3,4,6-Tetra-O-benzyl	95
3	D-Galactopyranose	2,3,4,6-Tetra-O-acetyl	95
4	D-Galactopyranose	2,3,4,6-Tetra-O-benzyl	92
5	D-Mannopyranose	2,3,4,6-Tetra-O-acetyl	95
6	D-Mannopyranose	2,3,4,6-Tetra-O-benzyl	94
7	D-Mannofuranose	2,3,5,6-Di-O-isopropylidene	98

[a] Reagents and conditions: 1.9 : 1.9 : 3.5 : 1 Molar ratios of PS-TPP : I₂ : imidazole : sugar.

(Table 14). Although the same transformation proceeded with similar efficiency using triphenylphosphine instead of its polymer-bound analogue, easy removal of the unwanted polymer-bound triphenylphosphine oxide provided the edge for practical application of the protocol. The reaction generally gave good yields except with less electrophilic aldehydes such as 3,4-dimethoxybenzaldehyde (entry 8) and 3,4-methylenedioxybenzaldehyde (entry 9) which also required longer reaction time (3 h) for complete conversion.

3.2.15. Preparation of *N*-protected β-iodoamines from β-amino alcohols using PS-TPP–I₂ complex. Enantiomerically pure *N*-protected β-iodoamines are important synthetic precursors used for the preparation of D- or L-β-amino acids, which themselves represent challenging synthetic targets.[50] One approach to the preparation of β-amino acids consists of homologating the requisite α-aminoacid, whereby the α-carboxyl group gets converted into an alkyl halide in preparation for the subsequent homologation step. Longobardo *et al.* developed a general synthesis of chiral *N*-protected β-iodoamines **40**, possessing either D- or L-configuration, by treating the precursor chiral *N*-protected β-aminols **39** with PS-TPP–I₂ complex.[51] The β-aminoalcohols were accessed from *N*-protected α-aminoacid or commercial β-aminols. As shown in Table 15, the conversion was effective for β-aminols protected with the most frequently used *N*-protecting groups (Cbz, Boc, Fmoc) without any detectable racemization of the stereocenter. The utility of this methodology was later demonstrated by Longobardo *et al.* in the synthesis of enantiopure *N*- and *C*-protected *homo*-β-amino acids by direct homologation of α-aminoacid.[52] The devised process involved reducing the carboxyl group of *N*-protected α-amino acids and converting the resulting *N*-protected β-amino alcohols into the corresponding β-iodoamines with PS-TPP–I₂, which represented the key step of the strategy. Subsequent cyanation and acidic hydrolysis of the β-amino cyanides afforded enantiopure *homo*-β-amino acids.

3.2.16. Peptide synthesis using PS-TPP–I₂ complex. The utility of the polystyryl diphenylphosphine–iodine complex (PS-TPP–I₂) has also been showcased in peptide synthesis.[53] The action of the complex involves converting the free carboxylic acid group of a *N*-protected α-amino acid into an acyl donor intermediate, followed by nucleophilic substitution by the amino function of a second, *C*-protected α-amino acid, affording fully protected dipeptides. Using this approach, Longobardo and coworkers were able to couple various *N*-protected α-amino acid with α-aminoacyl esters, by using PS-TPP–I₂, in high yields and without detectable racemization of the reacting substrates (Table 16).[53] Neutral reaction conditions were secured by the addition of excess imidazole to neutralize the released hydrogen iodide. Thus, the process was effective for substrates carrying the common *N*-protecting groups (Fmoc, Boc, Cbz) and tolerated acid sensitive *S*- and *O*-protecting groups like the trityl (entry 3), methyl (entries 2 and 3), *tert*-butyl (entry 4), and benzyl groups (entry 5).

3.2.17. Monoesterification of symmetric diols using PS-TPP–I₂ complex. The preparation of carboxylic acid esters from di- or polyhydroxylated substrates is a challenging synthetic task and the introduction of reliable strategies towards the selective monoesterification of such alcohols is useful.[54] Rokhum and Pathak reported the use of PS-TPP/iodine in coupling reactions between carboxylic acids and alcohols or amines to produce esters and amides, respectively.[55] More importantly, the PS-TPP–I₂ reagent has been shown to affect the monoesterification of symmetrical diols without resorting to high dilution or slow addition conditions. As shown in Table 17, the monoesterification of 1,6-hexanediol (entries 1–5) and 1,8-hexanediol (entries 6–8) with various carboxylic acids was achieved in high yields (84–92%) in the presence of DMAP and preformed PS-TPP–I₂ complex.

3.2.18. Iodination, bromination, and chlorination of alcohols with PS-TPP/X₂ and PS-TPP/NCS imidazole systems.

Table 20 Esterification of alkylphosphonic acids[a]

Entry	R¹	R²	Product	Yield (%)
1	CH₃	CH₃	*O,O′*-Dimethyl methylphosphonate	85
2	CH₃	C₃H₇	*O,O′*-Dipropyl methylphosphonate	90
3	CH₃	C₅H₁₁	*O,O′*-Dipentyl methylphosphonate	94
4	CH₃	C₁₀H₂₁	*O,O′*-Didecyl methylphosphonate	82
5	C₂H₅	C₂H₅	*O,O′*-Diethyl ethylphosphonate	90
6	C₂H₅	C₅H₁₁	*O,O′*-Dipentyl ethylphosphonate	92
7	C₂H₅	C₁₀H₂₁	*O,O′*-Didecyl ethylphosphonate	84
8	C₃H₇	CH₃	*O,O′*-Dimethyl propylphosphonate	87
9	C₃H₇	C₅H₁₁	*O,O′*-Dipentyl propylphosphonate	92
10	C₃H₇	C₁₀H₂₁	*O,O′*-Didecyl propylphosphonate	83

[a] Reagents and conditions: 1 : 3 : 6.6 : 3 : 2.5 molar ratios of alkyl phosphonic acid : iodine : imidazole : PS-TPP : alcohol, 45–50 °C, CH₂Cl₂, 2 h.

Building on the previous reports describing the use of PS-TPP and iodine for the conversion of α-amino acids and sugars into the corresponding iodides,[48,52,56] Kita et al. extended the methodology to the halogenation of alcohols under new conditions.[57] The reagent system was prepared by treating a suspension of PS-TPP in CH_2Cl_2 at room temperature with imidazole and iodine, bromine, or N-chlorosuccinimide (NCS). Subsequent addition of various allylic, benzylic, and primary alcohols gave the halogenated products in very high yields (88–98%) (Table 18). The reactions worked well with ortho, meta, para-, and multisubstituted benzylic alcohols (entries 2–9), as well as allylic (entries 10–12) and simple alcohols (entries 1, 13 and 14). While the iodination and bromination reactions were complete within 2 h in all cases, the chlorination reaction (entry 14) required 24 h for complete conversion. Finally, when the reagent system was tested on secondary alcohols, the reaction was very slow and unpractical for such systems.

3.2.19. Synthesis of glycosyl iodides. A new and stereo-selective synthesis of α-D-glycosyl iodides obtained by the replacement of the free anomeric hydroxyl functional group of fully protected sugars using PS-TPP–iodine complex was reported by Caputo and co-workers.[56] Thus, the addition of various protected sugars to a mixture of PS-TPP, iodine, and imidazole, at room temperature, resulted in the rapid conversion to the α-glycosyl iodide anomer (Table 19). No traces of the β-anomers were observed in any of the examples, suggesting that the process is thermodynamically controlled.

3.2.20. Esterification of alkylphosphonic acids. Alkylphosphonates have many synthetic and pharmaceutical applications.[58] In addition, methyl, ethyl, i-propyl and n-propyl esters of alkyl phosphonic acids are registered chemical warfare agents (CWAs).[59] The related O,O′-dialkyl alkylphosphonates (DAPs) are very useful reference chemicals that have been used as markers of nerve agents.[60] However, since they are also classified as CWAs, they are not available commercially and access to this class of compounds becomes inevitable during verification analysis. Dubey et al. reported a procedure for the preparation of DAPs by esterification of alkylphosphonic acids using primary alcohols, iodine, imidazole, and PS-TPP (Table 20).[61] Pure phosphonate esters were obtained by vacuum distillation in 83–94% yield following removal of PS-TPP oxide and imidazolium iodide by filtration.

3.2.21. Acetonation of sugars (protection of diols) with triphenylphosphine polymer-bound/iodine complex. The triphenylphosphine polymer-bound/iodine complex is a strong Lewis acid and a dehydrating agent as shown by the many transformations presented thus far.[62] Palumbo et al. exploited this feature to prepare O-isopropylidene derivatives of various sugars by condensing the sugar with acetone.[63] The isopropylidene function has been widely used in carbohydrate chemistry to protect diols and in certain cases sugar derivatives incorporating such a group have shown antipyretic and anti-inflammatory activities.[64] The synthesis of the reagent complex involved adding a solution of iodine to an equimolar amount of polystyryl diphenylphosphine suspension at room temperature under dry N_2 atmosphere and dark conditions. Subsequent addition of an acetone solution of the sugar to the

suspension then afforded the thermodynamically more stable acetonides within 30 minutes in very high purity and yields (Table 21).

3.2.22. Conversion of alcohols to alkyl halides with catalytic amounts of PS-TPP. As shown earlier, Kita et al.[57] had already reported a convenient method of iodination of alcohols using PS-TPP/iodine/imidazole reagent system. Rokhum reported a modification of Kita's method, switching imidazole with DMAP.[65] However in both approaches the catalyst (imidazole/DMAP) was used in excess and the recovery and reuse of the reagent system was not possible. A major drawback of using equimolar amounts of PS-TPP for the halogenation of alcohols is the formation of polymer-supported triphenylphosphine oxide byproduct as the end of the reaction, which in principle may be recycled using reducing conditions.[66,67] However, in order to avoid the inconvenience associated with recovering and recycling the polymer through reduction,

Table 21 Preparation of O-isopropylidene sugar derivatives[a]

Entry	Sugar	O-Isopropylidene derivatives	Yield (%)
1	D-Glucose		95
2	D-Ribose		95
3	D-Mannose		95
4	L-Arabinose		95
5	D-Galactose		97

[a] Reagents and conditions: 2 : 2 : 1 molar ratios of PS-TPP : I_2 : sugar, acetone, RT, 45 min.
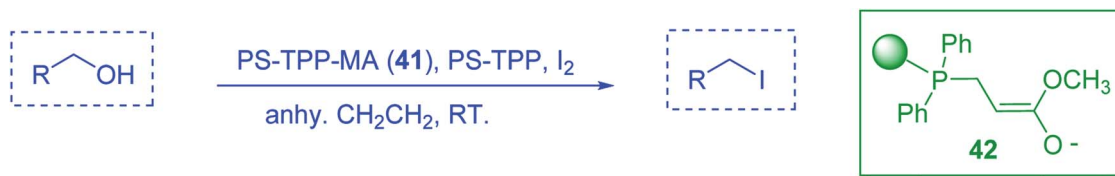
Scheme 11 Solid phase conversion of alcohols to iodides using PS-TPP–MA and soluble Ph$_3$P.

Rokhum described a clever approach to the selective halogenation of alcohols using catalytic amounts of polymer-supported triphenylphosphine–methylacrylate complex **41**.[68] The protocol involves reactions of PS-TPP and methylacrylate in dichloromethane (10 mL) at room temperature for two minutes to generate *in situ* the triphenylphosphine–methylacrylate complex **42** (40 mol%). Subsequent addition of iodine and polymer supported triphenylphosphine, followed by the alcohol afforded the desired iodide products in 78–93% yields. The procedure was successful with primary aliphatic alcohols, as well as secondary and tertiary ones, although the latter took longer time from complete conversion. Allyl alcohols were also converted into the corresponding iodides without affecting the olefinic bonds. Direct bromination using the reported reaction conditions proceeded as well to afford the desired bromides in high yields (87–91%) (Scheme 11).

3.3. Application of polymer-supported phosphonium salts derived from PS-TPP as traceless linkers for solid phase synthesis of alkenyl, alkyl and heterocyclic products

Solid-phase synthesis of small organic molecule libraries for drug discovery programs has been one of the key driving forces responsible for the rapidly expanding field of combinatorial chemistry.[69] Consequently, a large number of polymeric supports have been devised to immobilise compounds *via* polar functional groups such as alcohols, amides, and carboxylic

acids.[69] With the growing need to access a diverse range of small molecules, additional linker groups were required to meet the demand. One particular type, termed "traceless" linkers, leave no remnants in the cleaved product of the functionality utilized to tether the substrate to its support. Hughes showcased the utility of polymer-bound phosphonium salts derived from PS-TPP as traceless linkers for the solid-phase synthesis of small molecules.[70] Thus, as shown in Scheme 12, the phosphonium salt **44** was prepared from 2-nitrobenzyl bromide (**43**) and PS-TPP, followed by reduction of the nitro group to generate the polymer-bound aniline **45**. Finally, the aniline was acylated with 4-methoxybenzoyl chloride to afford anilide **46**. The polymer-supported substrate **46** was elaborated and cleaved, *via* hydrolysis or an intramolecular Wittig/cyclization reaction in a traceless manner, to afford alkenyl, heteroaryl, and alkyl products (**47–49**) in 78–82% yield.

3.4. Staudinger reaction

3.4.1. Reduction of nucleoside azides to amines. Functionalization of nucleosides by converting the sugar moiety into an aminosugar has been extensively studied.[71,72] Reducing an azido function attached to the carbohydrate part represents one of the most convenient means for the preparation of the amine group.[72] Building on this early work, Holletz and Cech described the reduction of nucleoside azides to amines under mild conditions and good yields using PS-TPP (Table 22).[73] The
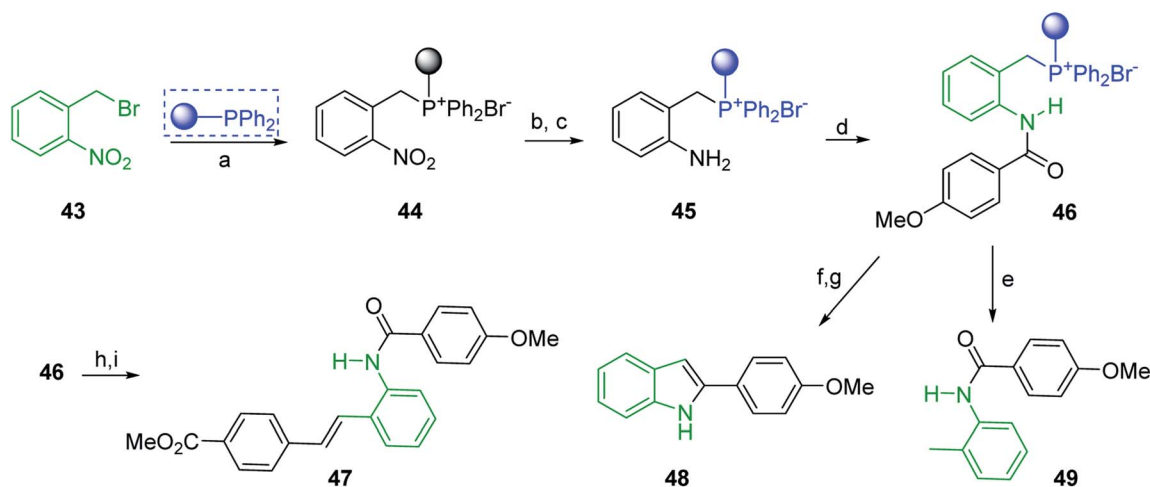
Scheme 12 Solid-phase synthesis polymer-supported phosphonium salts derived from PS-TPP. Reagents and conditions: (a) DMF, 70 °C, 48 h; (b) Na$_2$S$_2$O$_4$, EtOH, reflux, 90 min; (c) HBr, MeOH, dioxane; (d) 4-methoxybenzoyl chloride, pyridine, CH$_2$Cl$_2$, 5 h; (e) NaOMe, MeOH, reflux, 4 h, 81%; (f) toluene, DMF, distill; (g) KOtBu, reflux, 45 min, 78% for both steps; (h) methyl 4-formylbenzoate (2 eq.), NaOMe (2 equiv.), MeOH, reflux, 2 h; (i) Girard's Reagent T (3 equiv.), AcOH, 18 h, **5** was produced in 82% overall yield as a 3 : 1 mixture of *E/Z* isomers.

reaction was executed in two steps using pyridine or dioxane as solvents. In the first step, reaction of PS-TPP with the azido nucleoside afforded an iminophosphorane, which upon subsequent hydrolysis in the second step with water or concentrated ammonia, led to the formation of the amine. While water hydrolysis left the base protecting group intact (entries 1, 2 and 3), ammonia was used in cases where simultaneous hydrolysis and N-deprotection was desired (entries 5 and 6). The reaction workup required only filtration of the suspended PS-TPPO and evaporation of the filtrate *in vacuo* to afford pure products in nearly quantitative yields (89–100%).

Table 22 Reduction of azido nucleoside to amines using PS-TPP[a]

Entry	Azido nucleoside	Amine product	Yield (%)
1			98
2			100
3			100
4			89

Table 22   (*Contd.*)

$$R^1-N=N=N \xrightarrow{a} R^1-NH_2$$

Entry	Azido nucleoside	Amine product	Yield (%)
5			93
6			94

a Reagents and conditions: entries 1 and 2; 5 : 1 molar ratio of PS-TPP : azido nucleoside, dioxane, RT, 2 h, then H_2O, 2 h; entry 4; molar ratio of PS-TPP : azido nucleoside, pyridine, RT, 3 h, then NH_3 (32%), 5 h; entries 3, 5 and 6; 5 : 1 molar ratio of PS-TPP : azido nucleoside, dioxane, RT, 2 h, then NH_3 (32%), overnight.

3.4.2.   Conversion of sugar azides to sugar isothiocyanates. Isothiocyanates are very useful synthetic intermediates in carbohydrate chemistry,[74] and have been utilized in the synthesis of various functional groups as well as heterocyclic rings.[75] Azides comprise convenient precursors as means to introduce the isothiocyanate group to sugars *via* a tandem Staudinger–aza-Wittig reaction of the azide with Ph_3P and carbon disulfide.[75] Fernández *et al.* demonstrated the utility of PS-TPP *in lieu* of Ph_3P in the one-step preparation of non-anomeric sugar isothiocyanates from primary and secondary sugar azides (Table 23).[76] While primary azidodeoxy sugars afforded the corresponding primary deoxyisothiocyanato in high yields (entries 1–3), secondary azides, especially those with the azide group located at an endocyclic carbon atom, gave much lower yields (entries 5 and 6). Mono- and disaccharides, including pyranose and furanose derivatives, protected with a variety of labile and sensitive *O*-protecting groups underwent successful functional group interconversion, illustrating the scope of the method. This strategy was not successful with glycosyl azides because of the higher reactivity of the anomeric isothiocyanate. Prior to the work of Fernández *et al.*, a similar reduction reaction of a 3′-azidonucleoside using PS-TPP was reported by Cech and Zehl as a technical improvement to the preparation of isothiocyanato derivatives.[77] The proposed mechanism of these reactions involve initial formation of a polymer-supported iminophosphorane intermediate, followed by a cyclization reaction with carbon disulfide to give a four-membered ring, and subsequent cycloreversion of the ring to afford the isothiocyanate.

3.4.3.   A one-pot aza-Wittig based polymer supported route to primary and secondary amines. Azides have been employed as the nitrogen source for the preparation of primary amines by converting the azide into an iminophosphorane (the Staudinger reaction), followed by hydrolysis.[78] This approach, however, can not be used to access secondary amines because imine intermediates are not involved. Hemming and co-workers disclosed a study describing the conversion of azides **50** into α-unsubstituted primary amines **51** or α-branched secondary amines **52** *via* the intermediacy of polymer-supported iminophosphoranes and imines (Table 24).[79] Their strategy involved a Staudinger reaction between PS-TPP and various azides (R^1-N_3), affording polymer-supported iminophosphoranes. Subsequent *in situ*

aza-Wittig reaction of the resulting iminophosphorane with aromatic or alkyl aldehydes (R²CHO) gave imine intermediates, which were either reduced *in situ* to the corresponding α-unsubstituted primary amines (path a), or functionalized *via* 1,2-addition of organometallic reagents (R³MgX or R³Li) to afford α-branched secondary amines (path b). The use of trimethylsilyl azides (R¹ = TMS, entries 11–13) permitted synthesis of primary amines following *in situ* N-desilylation, whilst using benzyl azides allowed access to N-benzyl protected amines (entry 1, 6, 9 and 10). On the other hand, the wide range of suitable organometallic reagents allowed the preparation of synthetically useful homoallylic amines (entries 10 and 11). The

yields ranged from 52–99% for most substrates except when the hindered pivalaldehyde was used (entry 6).
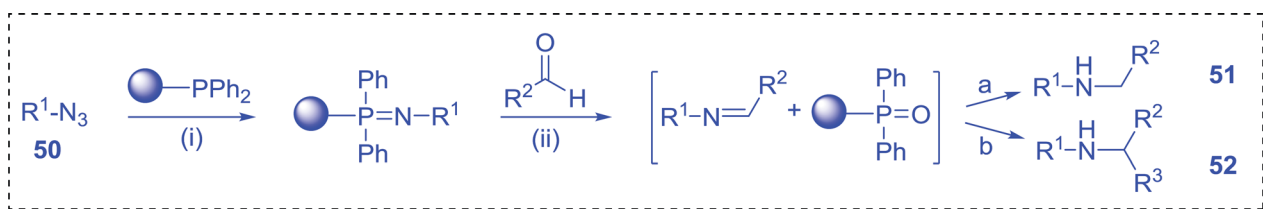
3.4.4. Aza Wittig synthesis of pyrido[1,2-*c*]pyrimidine heterocycles. Pyrido[1,2-*c*] pyrimidines comprise a promising class of heterocycles which may potentially provide novel superoxide scavengers and anti-inflammatory agents.[80] Molina and co-workers designed a solid-phase synthesis of these fused azaheterocycles *via* an aza Wittig reaction under mild reaction conditions. Their strategy for the synthesis of pyrido[1,2-*c*] pyrimidines **55** and **56** is outlined in Scheme 13. Staudinger reaction between PS-TPP (**1**) and ethyl α-azido-β-(2-pyridyl) acrylate (**53**) in dry CH₂Cl₂ at room temperature gave the polymer-bound iminophosphorane **54**. Subsequent reaction of

Table 23 Synthesis of deoxyisothiocyanato sugars from azidodeoxy sugars[a]

Entry	Azide	Isothiocyanates	Yield (%)
1			95
2			97
3			86
4			73
5			24
6			18

[a] Reagents and conditions: 1.2 : 1 : 10–25 molar ratios of PS-TPP : azidodeoxy sugars : CS₂, dioxane, RT, 16–48 h.

Table 24 Synthesis of primary and secondary amines from azides and aldehydes using PS-TPP[a]

Entry	R^1	R^2	R^3	Yield (%)
1	Bn	Ph	H	99
2	Ph	p-F-C$_6$H$_4$	H	69
3	Ph	n-Pr	H	71
4	Ph	Me	H	52
5	p-MeO-C$_6$H$_4$	Ph	H	91
6	Bn	t-Bu	H	17
7	Ph	PhCH=CH	n-Bu	96
8	Ph	Ph	n-Bu	99
9	Bn	Ph	n-Bu	83
10	Bn	Ph	H$_2$C=CHCH$_2$	91
11	TMS	Ph	H$_2$C=CHCH$_2$	79
12	TMS	p-MeO-C$_6$H$_4$	n-Bu	69
13	TMS	Ph	Ph	59

[a] Reagents and conditions: (i) 4 : 1 molar ratio of PS-TPP : azide, THF, RT, 2–3 h. (ii) Aldehyde (1.5 molar equivalent), THF, reflux, 3 h; entries 1–6, path a, NaBH$_3$CN or NaBH$_4$ or BH$_3$-THF (1.5 molar equivalent), MeOH, NH$_4$Cl (aq), RT, 1 h; entries 7–13, path b, R^{3}MgX or RLi, NH$_4$Cl (aq), RT, 1 h.

54 with carbon dioxide or carbon disulfide at 90 °C afforded pyrido[1,2-c]pyrimidines 55a and 55b in 83% and 93% yield, respectively. On the other hand, aza Wittig reaction of imino-phosphorane 54 with aromatic isocyanates produced the carbodiimides 58 through the intermediacy of species 57. The former (58) underwent regioselective electrocyclization to give the corresponding pyrido[1,2-c]pyrimidines 56 in yields ranging from 82% to 90%.
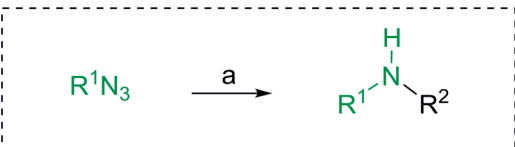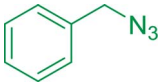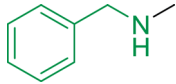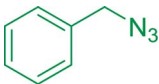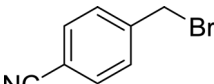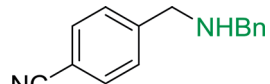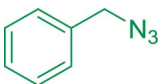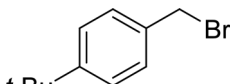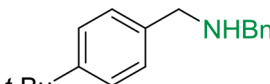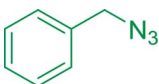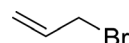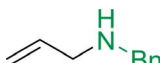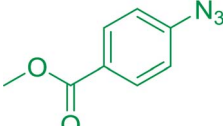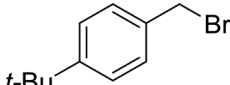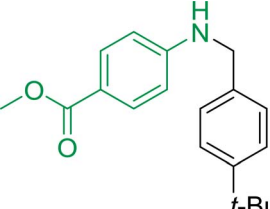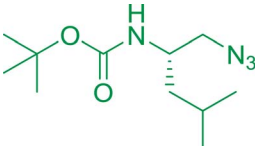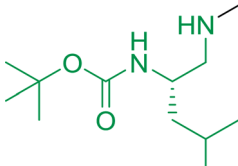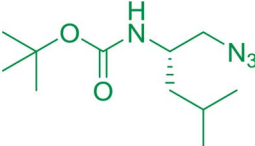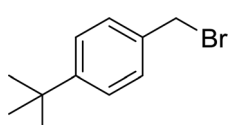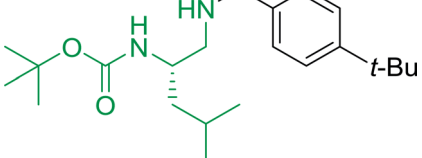
3.4.5. Synthesis of secondary amines from alkyl azides and alkyl halides. The most popular methods for the synthesis of

secondary amines use either reductive aminations or alkylation procedures on primary amines. However, overalkylation leading to the formation of the corresponding tertiary or quaternary ammonium salts is difficult to avoid. Classon et al. described a one-pot, two-step procedure that delivers only secondary amines from the corresponding azides and reactive alkyl halides using polymer-bound, triphenylphosphine-supported synthesis (Table 25).[81] The solid-phase method involves a Staudinger reaction between PS-TPP (1) and the azide to afford the corresponding phosphoazide which rapidly eliminates nitrogen
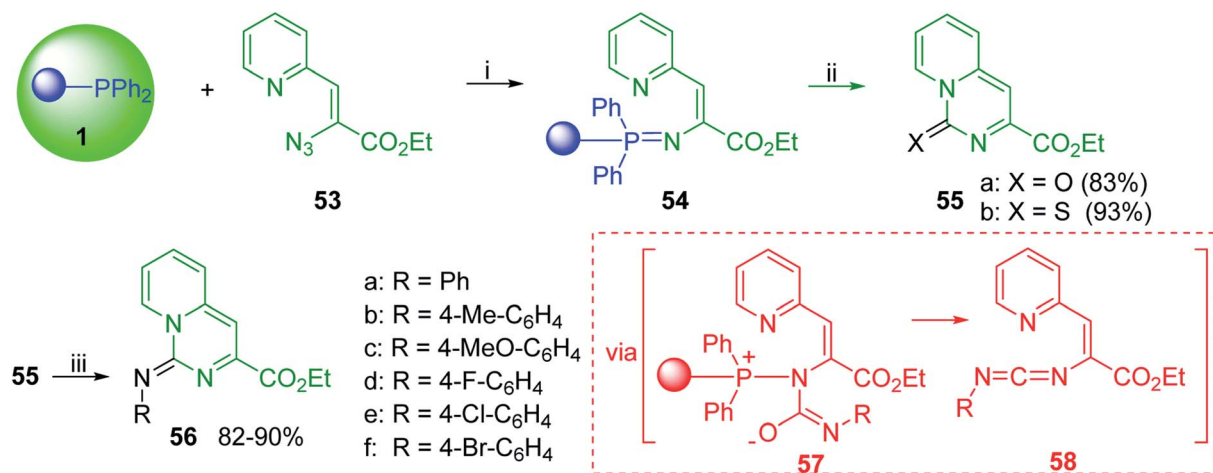
Scheme 13 Preparation of pyrido[1,2-c]pyrimidines. Reagents and conditions: (i) CH$_2$Cl$_2$, RT; (ii) solid CO$_2$ or CS$_2$, toluene, sealed tube, 90 °C; (iii) Ar-NCO, CH$_2$Cl$_2$, RT.

Table 25 Synthesis of secondary amines[a]

Entry	Azide	Alkyl halide	Product	Yield (%)
1		MeI		81
2				82
3				87
4				78
5				21
6		MeI		85
7				82

[a] Reagents and conditions: (i) PS-TPP, THF, 5 min. RT.; (ii) azide, THF, 4 h, RT.; (iii) alkyl halide, THF, 16 h, RT; (iv) KOH–MeOH, 4 h, 65 °C; 2 : 1 : 3 : 10 molar ratios of PS-TPP : azide : alkyl halide : KOH–MeOH.
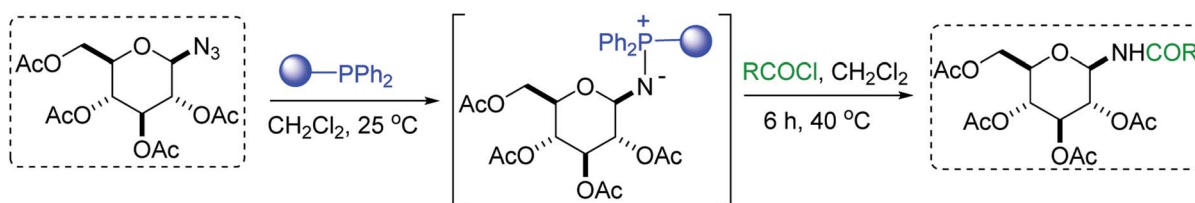
Scheme 14 Synthetic strategy towards the synthesis of glucopyranosyl amides using PS-TPP. Reagents and conditions: 1.3 : 1 : 2 molar ratios of PS-TPP : azide : acid chloride, CH$_2$Cl$_2$, 40 °C, 6 h.

to give an iminophosphorane intermediate. Subsequent alkylation with alkyl (entries 1 and 6), allyl (entry 4), or benzyl (entries, 2, 3, 5 and 7) halides produced the corresponding resin-bound disubstituted aminophosphonium salts. Finally, the secondary amines were freed from the solid support by hydrolytic cleavage using methanolic KOH. The yields obtained were good in all examples (78–87%) except when phenylazide was used (21%) (entry 5). The low yield was attributed to its reduction to the corresponding aniline.

3.4.6. Synthesis of glucopyranosyl amides using PS-TPP. The presence of the glycosyl amide motif in naturally occurring biomolecules like glycoproteins and nucleic acids has inspired interest in the synthesis of compounds containing such structural feature.[82] In particular, glycosyl amides have been synthetically targeted because they have been suggested as potential inhibitors of glycosyl hydrolases[83] and the binding of fibroblast growth factor (FGF-2) to heparin.[84] Norris *et al.* devised a method for the introduction of the glycosyl amide by way of a Staudinger process in which a glycosyl azide reacts with PS-TPP, followed by reaction of the resulting iminophosphorane with an acid chloride (Scheme 14).[85]
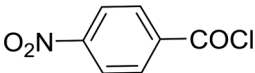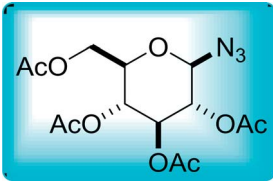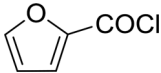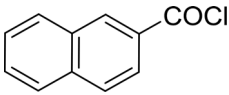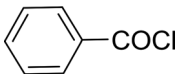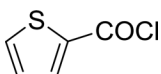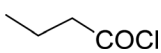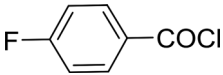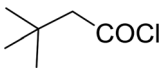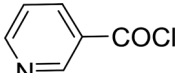
Norris *et al.* reacted 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl azide with PS-TPP and various acid chlorides (Table 26, entries 1–9) using a parallel synthesizer to prepare a small library of glucopyranosyl amides. The excess acid chloride was removed at the end of the reaction by treatment with polymer-supported

tris(2-aminoethyl) amine. Optimum yield was observed with *p*-nitrobenzoyl chloride, underscoring the preference of the polymer-bound iminophosphorane for highly electrophilic acid chlorides (entry 1). On the other hand, the highly hindered pivaloyl chloride inhibited the reaction between the iminophosphorane intermediate and acid chloride (entry 8).

3.5. The Mitsunobu reaction

3.5.1. Esterification using PS-TPP. The condensation of alcohols with carboxylic acids *via* triphenylphosphine-azodicarboxylate activation is one of the most reliable and common methods for esterification (the Mitsunobu reaction).[86] However, byproducts from the Mitsunobu reaction and excess reagents are non-volatile and soluble in organic solvents necessitating difficult chromatographic separation of the desired product almost always. PS-TPP was first utilized in the Mitsunobu reaction by Amos *et al.* in 1983 for the preparation of esters from alcohols and carboxylic acids (Table 27).[87] The use of PS-TPP conferred convenience in terms of purification of the ester product. The method worked well with aliphatic and aromatic acids and tolerated a variety of functional groups as shown in Table 27. The yield was unaffected in the series of benzoic acids substituted with electron-donating and electron-withdrawing groups (entries 1 and 4–7). As anticipated, secondary alcohols (entries 3, 4 and 11) gave consistently lower

Table 26 Synthesis of glucopyranosyl amides from carboxylic acids

Entry	Acid chloride	Azide	Glucopyranosyl amide yield (%)
1	O₂N—C₆H₄—COCl		93
2	furan-2-COCl		40
3	naphthalene-2-COCl		72
4	C₆H₅—COCl	AcO glucopyranosyl azide (N₃)	55
5	thiophene-2-COCl		56
6	CH₃CH₂CH₂COCl		61
7	F—C₆H₄—COCl		61
8	(CH₃)₃C—CH₂—COCl		—
9	pyridine-3-COCl		40

yields than primary alcohols (entries 1, 2 and 5–10) and tertiary alcohols were too hindered and remained unreacted. When an optically pure alcohol was used (entry 11), inversion of the chiral center was observed.
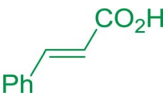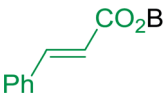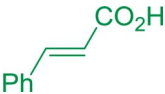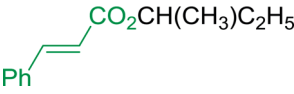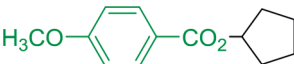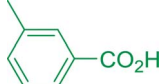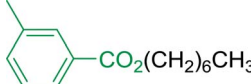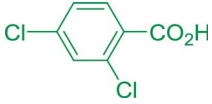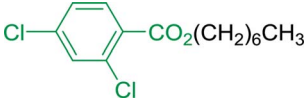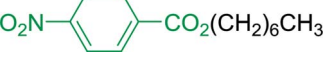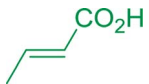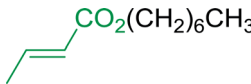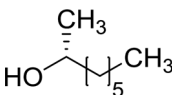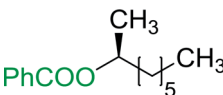
3.5.2. Synthesis of aryl ethers from phenols and alcohols.

Georg and co-workers[88] reported the first example of a Mitsunobu reaction[86] using PS-TPP in the synthesis of aryl ethers. The group prepared a library of aryl ethers from phenols with electron releasing and electron withdrawing groups and various alcohols (Table 28).[88] In a typical experiment, PS-TPP, diethyl azodicarboxylate (DEAD), the alcohol, and the phenol in dichloromethane were stirred at room temperature for 4–12 hours. Filtration of the resin, followed by evaporation of the solvent *in vacuo* and purification by column chromatography afforded pure aryl ethers in 59–94% yields. It is noted that presence of electron withdrawing substituents at the aromatic ring of the phenol (Cl and CN) accelerated the reaction rate,

whereas electron donating substituent (OMe) generally reduced the reaction rate, resulting in a slower reaction progress.

3.5.2.1. Stereochemical inversion of secondary alcohols. Georg *et al.* found that polymer-supported triphenylphosphine can replace triphenylphosphine in the Mitsunobu reaction to form stereochemically inverted secondary alcohols.[89] The procedure addresses the most significant drawback associated with the Mitsunobu reaction which includes removal of excess triphenylphosphine and its oxide by-product. The protocol is very comparable to the standard Mitsunobu reaction in regards to yield, stereochemical inversion, reaction time, and even inversion of sterically hindered secondary alcohols. As shown in Table 29, benzylic, alkyl, and cyclic secondary alcohols underwent successful inversion of configuration, although yields were slightly lower with the former two types of substrates (entries 3 and 5) and much lower for sterically hindered ones (entry 6). It is noted that no racemisation was observed for substrates bearing an acidic proton at the stereocenter (entries 2 and 4).

Table 27 Preparation of esters from alcohols and carboxylic acids using PS-TPP[a]

$$R^1\text{-OH} \quad + \quad R^2\text{-COOH} \quad \xrightarrow{a} \quad R^2\text{-COOR}^1$$

Entry	Alcohol	Carboxylic acid	Ester product	Yield (%)
1	PhCH$_2$OH	PhCO$_2$H	PhCO$_2$Bn	86
2	PhCH$_2$OH	Ph-CH=CH-CO$_2$H	Ph-CH=CH-CO$_2$Bn	86
3	C$_2$H$_5$CH(CH$_3$)OH	Ph-CH=CH-CO$_2$H	Ph-CH=CH-CO$_2$CH(CH$_3$)C$_2$H$_5$	64
4	Cyclopentanol	H$_3$CO–C$_6$H$_4$–CO$_2$H	H$_3$CO–C$_6$H$_4$–CO$_2$-cyclopentyl	75
5	1-Heptanol	(methylphenyl)-CO$_2$H	(methylphenyl)-CO$_2$(CH$_2$)$_6$CH$_3$	90
6	1-Heptanol	(dichlorophenyl)-CO$_2$H	(dichlorophenyl)-CO$_2$(CH$_2$)$_6$CH$_3$	89
7	1-Heptanol	O$_2$N–C$_6$H$_4$–CO$_2$H	O$_2$N–C$_6$H$_4$–CO$_2$(CH$_2$)$_6$CH$_3$	84
8	PhCH$_2$OH	(CH$_3$)$_3$CCO$_2$H	(CH$_3$)$_3$CCO$_2$Bn	99
9	EtOH	HO$_2$C(CH$_2$)$_4$CO$_2$H	EtO$_2$C(CH$_2$)$_4$CO$_2$Et	79
10	1-Heptanol	CH$_2$=CH-CH=CH-CO$_2$H	CH$_2$=CH-CH=CH-CO$_2$(CH$_2$)$_6$CH$_3$	92
11	HO-CH(CH$_3$)-(CH$_2$)$_5$-CH$_3$	PhCO$_2$H	PhCOO-CH(CH$_3$)-(CH$_2$)$_5$-CH$_3$	65

[a] Reagents and conditions: 1.8 : 1.4 : 1 : 1 molar ratios of PS-TPP : DEAD : carboxylic acid : alcohol, THF, 25 °C, 4 h.

The yields reported were in general comparable to those obtained when the inverted products were prepared using standard homogeneous Mitsunobu conditions, suggesting that the reactivity of PS-TPP is similar to its free form. Many of the inverted esters were hydrolyzed to the corresponding alcohols with LiOH which were isolated in 95–97% yields. Optical rotation analysis of the alcohols showed complete inversion of configuration when compared with the starting material.

3.5.3. Synthesis of aryl ethers from aminoalcohols. Building on the method of Georg *et al.* who described earlier the preparation of aryl–alkyl ethers from phenols and alcohols using a solution-based Mitsunobu coupling strategy with PS-TPP,[88] Shuttleworth *et al.* discovered an improvement to the etherification reaction and reported optimum conditions.[90] Thus, when Shuttleworth and co-workers treated a collection of phenols with *N*-protected aminoalcohols under Georg's conditions, poor conversion to the ether products was observed (16–49% yields). It was shown that the progress of this reaction could be significantly enhanced when a tertiary amine base is used and the order of reagent addition is modified. The improved procedure calls for the treatment of a slight excess of PS-TPP with DEAD at 0 °C for 5 min, followed by the addition a premixed solution of the aminoalcohol, phenol, and Et₃N. It was suggested that the base enhances the overall rate of reaction as it plays a role in the formation of the phenolate required for the S_N2 nucleophilic displacement of the alkoxyphosphonium salt derived from the aminoalcohols. The modified approach was successfully applied to the synthesis of a range of aryl ethers from phenols and *N*-protected aminoalcohols (Table 30).

3.5.4. Scavenging the hydrazinedicarboxylate ester byproduct in the Mitsunobu reaction with PS-TPP (solid phase scavenger). The Mitsunobu reaction is a four component process that utilizes an alcohol, nucleophile, phosphine, and azodicarboxylate ester. Furthermore, upon reaction completion, two side products, the hydrazinedicarboxylate ester and

phosphine oxide, are generated. In their quest for impurity annihilation and to add further improvement to the Mitsunobu process, Barrett *et al.* employed PS-TPP (**1**) and an olefinic azodicarboxylate (bis(5-norbornenyl-2-methyl) azodicarboxylate, DNAD, **59**) to obtain Mitsunobu products in 43–100% yields (86–96% purity) from alcohols and carboxylic acids or their nucleophilic equivalents (phthalimides, or *N*-hydroxyphthalimides).[91] Ring opening metathesis-polymerization (ROMP) of the hydrazine by-product (DNADH₂) using Grubbs catalyst (Cl₂(Cy₃P)₂Ru=CHPh) converted it to a poly(DNADH₂) solid which was conveniently removed by filtration alongside PS-TPPO. In addition to its role in the Mitsunobu reaction, PS-TPP was added during reaction work-up to form a complex with excess DNAD so it may be filtered out (Scheme 15).

3.5.5. The Mitsunobu reaction with PS-TPP and di-*t*-butylazodicarboxylate. Others groups have also described alternative methods to improved the Mitsunobu process by using PS-TPP with azodicarboxylates that can be destroyed *in situ*. Pelletier *et al.* reported a protocol in which PS-TPP and commercially available di-*t*-butylazodicarboxylate (DBAD, **60**) were used in the Mitsunobu reaction whereby the latter and its expected hydrazide byproduct **61** were destroyed *in situ* upon treatment with trifluoroacetic acid (TFA) at the completion of the reaction (Scheme 16).[92] Both of these compounds provide volatile gaseous byproducts (2-methylpropene) and water-soluble hydrazine ditrifluoroacetate. Filtration to remove the phosphine oxide resin and excess PS-TPP followed by standard aqueous work-up afforded products in high purity (>95%) in certain cases. This approach was employed to prepare a 3 × 5 parallel library which was free of phosphine and hydrazine impurities without recourse to chromatography. The methodology was successfully applied to the alkylation of a wide range of nucleophiles containing many representative and moderately acidic functional groups (sulphonamide, phenol, imide, hydantoin, and carboxylic acid) with a variety of alcohols

Table 28 Preparation of aryl ethers from alcohols and phenols using PS-TPP[a]

Entry	Phenol	Alcohol	Aryl ether	Product	Yield (%)
1	R¹ = CN	R² = heptyl	R¹ = CN	R² = heptyl	68
2	R¹ = CN	R² = benzyl	R¹ = CN	R² = benzyl	94
3	R¹ = CN	R² = furfuryl	R¹ = CN	R² = furfuryl	88
4	R¹ = Cl	R² = heptyl	R¹ = Cl	R² = heptyl	65
5	R¹ = Cl	R² = benzyl	R¹ = Cl	R² = benzyl	88
6	R¹ = Cl	R² = furfuryl	R¹ = Cl	R² = furfuryl	84
7	R¹ = OMe	R² = heptyl	R¹ = OMe	R² = heptyl	63
8	R¹ = OMe	R² = benzyl	R¹ = OMe	R² = benzyl	86
9	R¹ = OMe	R² = furfuryl	R¹ = OMe	R² = furfuryl	78

[a] Reagents and conditions: 1.5 : 1.5 : 1.5 : 1 molar ratios of PS-TPP : DEAD : alcohol : phenol.

(methanol, isopropanol, benzyl alcohol). A similar protocol using TFA for the destruction and removal of DBAD was used by Aberle *et al.* during PS-TPP-mediated esterification and inversion of carbinol stereochemistry of a tropane alkaloid.[93]

3.6. Conversion of carboxylic acids to amides

Buchstaller *et al.* reported a two-step procedure for the conversion of carboxylic acids into amides at ambient temperature under neutral conditions.[94] Initially, the acid was converted into
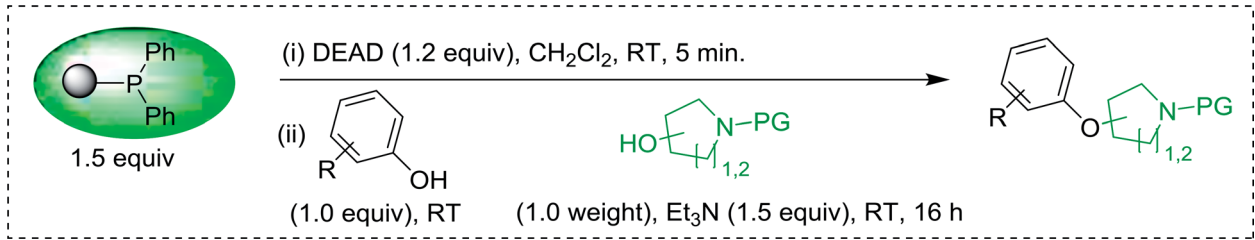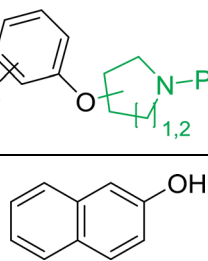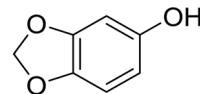
Table 29 Stereochemical inversion of secondary alcohols[a,b]

Entry	Alcohol	Inverted ester	Yield[c] (%)
1			98
2			74
3			65
4			76
5			71
6			25

[a] Reagents and conditions: 1 : 1.2 : 2 : 2 molar ratios of alcohol : R^{3}COOH (R^{3}COOH = 4-nitrobenzoic acid or chloroacetic acid) : DEAD : PS-TPP, THF, RT, 3–12 h. [b] Reagents and conditions: LiOH, H$_2$O/acetone, RT, 95–97% yield. [c] The yield shown is for step a.

Table 30 Preparation of aryl ethers from aminoalcohols

Entry		72% conv.	68% conv.	61% conv.	75% conv.
1		72% conv.	68% conv.	61% conv.	75% conv.
2		64% conv.	98% conv.	75% conv.	99% conv.

the acid chloride using PS-TPP and trichloroacetonitrile. The reaction was carried out in dichloromethane at room temperature for 3 h. Subsequent treatment with various types of amines (aromatic, benzylic, primary, and secondary) and polymer-bound morpholine as a base afforded the desired amides in 42–99% yields (Table 31).

3.7. Ultrasound-mediated esterification of carboxylic acids catalyzed by polymer-supported triphenylphosphine

Very recently, Pattarawarapan *et al.* described a sonochemical method for the methyl esterification of carboxylic acids catalyzed by polymer-supported triphenylphosphine.[95] Thus, using $1 : 2 : 0.1$ molar ratio of 2,4,6-trichloro-1,3,5-triazine (TCT)/Na_2CO_3/PS-Ph$_3$P, various carboxylic acids containing reactive hydroxyl groups as well as acid- and base-sensitive moieties were converted to methyl esters in one step without the need to pre-activate the acid (Table 32). The products were obtained in 70–99% yield within 10–30 minutes and in most cases did not require purification by column chromatography. It is noted that in the absence of PS-Ph$_3$P catalyst, the reaction gave complex

mixture of products containing only 27–35% of the corresponding ester. Therefore, a significant increase in both the reaction rate and product yield was observed by using catalytic quantities of PS-Ph$_3$P under ultrasonic irradiation conditions. The proposed mechanism of esterification involves formation of triazinephosphonium chloride, subsequent displacement with a carboxylate anion to give an acyloxytriazine, and an ensuing attack by methanol to afford the ester product with concomitant elimination of the hydroxyl derivative of TCT.

3.8. Reductive amination of aldehydes and ketones

Aldehydes and ketones have been shown to undergo indirect reductive amination using polymer-supported triphenylphosphine-palladium acetate complex PS-TPP–Pd(OAc)$_2$ (10 mol% loading) as a heterogeneous and recyclable catalyst and sodium formate as a reducing agent (Table 33).[96] The catalyst was easily prepared and isolated quantitatively as a yellowish solid by heating a mixture of PS-TPP and Pd(OAc)$_2$ (P/Pd ratio of $4 : 1$) in DMF to 45–50 °C for 4 h. The protocol involved two stages where the imine or iminium ion is first
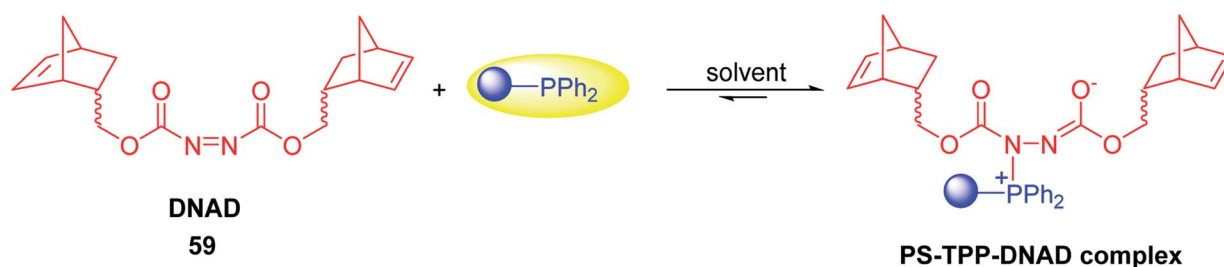
Scheme 15 Removal of excess DNAD from the Mitsunobu reaction with PS-TPP.
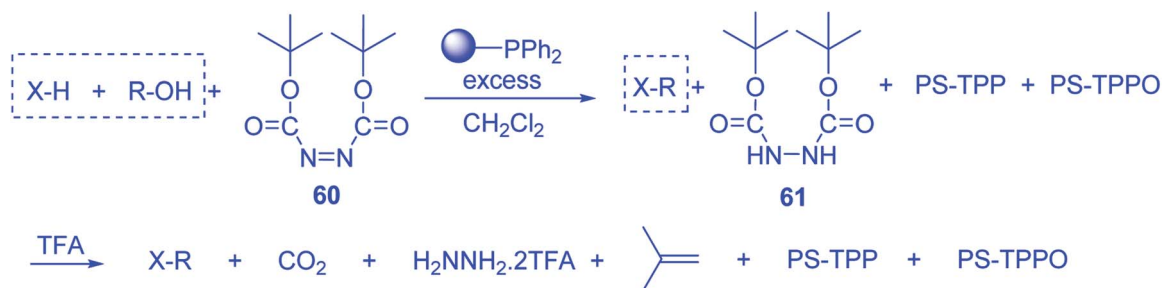
Scheme 16 Mitsunobu reaction with PS-TPP and removal of byproducts.

formed from the aldehyde or ketone, respectively, followed by PS-TPP–Pd(OAc)$_2$-mediated catalytic reduction with sodium formate. Aromatic aldehydes and ketones gave higher yields than the corresponding aliphatic substrates and the catalyst was reusable over four consecutive cycles without any profound loss of catalytic activity.

3.9. Synthesis of (E)-nitroalkenes by isomerisation of (E/Z)-nitro olefin mixtures

Treatment of (E/Z) mixture of nitroolefins with catalytic amounts of PS-TPP (0.1 equiv.) has been reported to produce pure (E)-nitroalkenes in a number of cases (Table 34).[97] The mechanism of isomerisation involves addition of nucleophilic

Table 31 Synthesis of various amides from carboxylic acids[a]

Entry	Product					
1	benzoic acid (COOH)	73	93	89	75	82
2	phenylacetic acid	77	96	95	86	73
3	phenoxyacetic acid	86	99	97	86	86
4	cinnamic acid	89	99	98	83	86
5	thiophene-2-acetic acid	71	87	99	73	83
6	propanoic acid	70	42	71	66	76

[a] Reagents and conditions: (i) PS-PPh$_3$, CCl$_3$CN, carboxylic acid, CH$_2$Cl$_2$, 3 h, RT.; (ii) amine, polymer-bound morpholine, CH$_2$Cl$_2$, 4 h, RT; 3 : 5 : 1 : 1 : 3 molar ratios of PS-TPP : CCl$_3$CN : carboxylic acid : amine : polymer-bound morpholine.

PS-TPP to the activated double bond, interconversion to the appropriate intermediate, and subsequent elimination reaction to afford the nitroalkene. The stereoselectivity of the E/Z-isomerisation was retained in all cases (entries 1–4) except when a phenyl group was introduced in α-position (entry 5) or a phenylthio group in the β-position (entry 6). In these examples, an E/Z-ratio of 90 : 10 and 65 : 35 was observed, respectively.

3.10.   Debromination of α-bromo ketones

An effective method for the debromination of various α-bromo ketones using PS-TPP was described by Salunkhe et al.[98] The debromination reaction proceeded in high yields (85–97%) in anhydrous benzene using equimolar amounts of the resin-bound polymer. Pure ketones were isolated (Table 35) following filtration of the polymeric phosphine oxide by-product and solvent removal in vacuo.

3.11.   Henry reaction of aldehydes with nitroalkanes

Polymer-supported triphenylphosphine was found to react with ethyl acrylate in a stoichiometric ratio to generate an ethyl acrylate conjugated polystyryldiphenylphosphine (PDPP–EA) complex in situ.[68] The complex was used to catalyze the synthesis of 2-nitroalcohols from the reaction of various nitroalkanes and aldehydes (Henry reaction) under solvent-free conditions (Table 36).[99] The catalyst was easily prepared in under 10 min by stirring an equimolar mixture of PS-TPP and ethyl acrylate. Although the ensuing Henry reaction proceeded well in a number of solvents, the highest yields were obtained without solvent and optimum efficiency of the method required 10 mol% of the catalyst. Resin-bound triphenylphosphine could be recovered from the reaction and reused up to five times without loss of activity. The reaction protocol was applied for the reaction of primary and secondary niroalkanes with aliphatic aldehydes and aromatic aldehydes bearing various electron-donating and electron-withdrawing substituents (Table 36). Good yields were observed with all types of

substrates, including those with some degree of steric hindrance (entry 5).

3.12.   Hydroperoxide reduction

Reduction of hydroperoxides into alcohols with PS-TPP represents a very mild approach to such a transformation especially in complex synthetic settings. Galal et al. described the reduction of hydroperoxide 62 using PS-TPP (Scheme 17).[100] The reaction was carried out rapidly (50 min) at room temperature and afforded the alcohol product 63 in 92% yield.

3.13.   Ozonide reduction

One of the most popular approaches for the preparation of carbonyl compounds from alkenes involves ozonolysis of a double bond, followed by reductive cleavage of the resulting ozonide with a reducing agent.[101] Santaniello et al. used PS-TPP to reduce ozonides to the corresponding carbonyl products (Table 37).[102] Various aldehydes and ketones were obtained in high yields (80–92%) and were virtually pure.

3.14.   Stereoselective isomerization of α,β-ynones to (E,E)-α,β-γ,δ-dienones using PS-TPP

PS-TPP has been successfully used as an organocatalyst for the stereoselective isomerization of α,β-ynones to (E,E)-α,β-γ,δ-dienones.[103] The amount of PS-TPP (20 mol%) and the reaction temperature (80 °C) were critical to the isomerization process. Thus, under these optimized conditions, the conversion of several ynones to the corresponding dienones was accomplished in moderate to good yields (Table 38). Ynones with aromatic and heteroaromatic substituents could be isomerized in good yields (entries 1–3) whilst aliphatic ynones showed lower yields (entries 4–6). The recovered PS-TPP was reused several times as it retained its catalytic activity, although the catalytic capacity was reduced significantly after repeated use as reflected by a steady decrease in product yield.

Table 32   Methyl esterification of carboxylic acids[a]

Entry	R^{1}CO$_2$H	Yield (%)	Entry	R^{1}CO$_2$H	Yield (%)
1	PhCOOH	90	8	4-HOC$_6$H$_4$COOH	70
2	3,4-(MeO)$_2$C$_6$H$_3$COOH	99	9	PhCH=CHCOOH	82
3	3-Me$_2$NC$_6$H$_4$COOH	85	10	Ph(CH$_2$)$_4$COOH	97
4	4-ClC$_6$H$_4$COOH	97	11	4-HOPhCH$_2$COOH	77
5	2-IC$_6$H$_4$COOH	92	12	Benzoylglycine	87
6	4-O$_2$NC$_6$H$_4$COOH	96	13	Boc-Gly-OH	80
7	Nicotinic acid	80	14	Fmoc-Gly-OH	85

[a] Reagents and conditions: R^{1}CO$_2$H/TCT/Na$_2$CO$_3$/PS-Ph$_3$P (1 : 1 : 2 : 0.1 molar ratio), MeOH, sonication, 50 °C, 10–30 min.
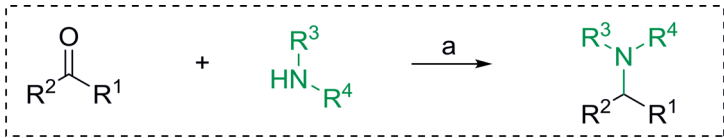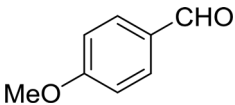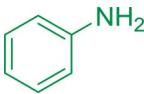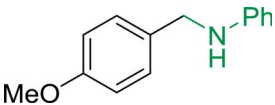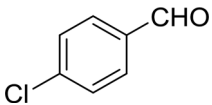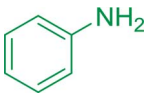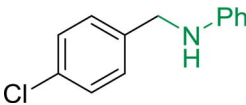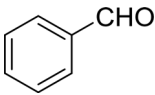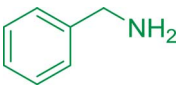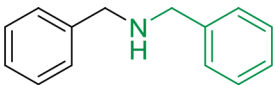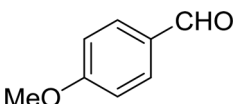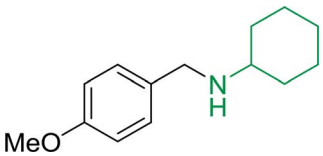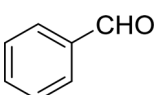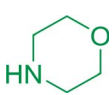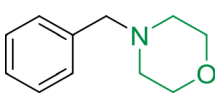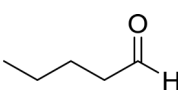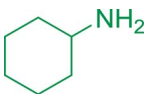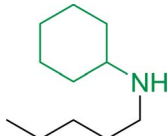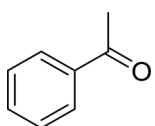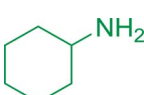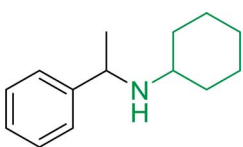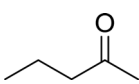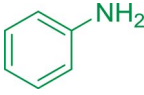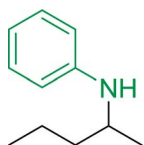
3.15. γ-Addition of pronucleophiles to alkynoate

Some years ago, Trost *et al.* discovered the ability of triphenylphosphine to redirect the conjugate addition of various carbon nucleophiles from the normal β-position to the γ-position of 2-alkynoates[104] and applied the new method to the construction of tetrahydrofuran and tetrahydropyran rings[105] which show widespread occurrence in many classes of natural products. Nitrogen pronucleophiles also underwent successful γ-addition reactions in the same manner to afford nitrogen-containing products.[106] In these transformations, the nucleophilic triphenylphosphine, which was used in catalytic amounts, first added to the triple bond of an α,β-unsaturated system and finally was eliminated from the reaction product after a series of transformations. As an improvement to the γ-addition reactions which require tertiary phosphine homogeneous catalysts, regarded as the major limitation of the methodology, Li *et al.* efficiently carried out Trost's γ-addition of various carbon pronucleophiles to methyl 2-butynoate catalyzed by PS-TPP.[107] The
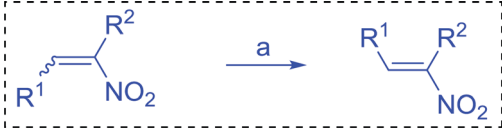
Table 33 Reductive amination of aldehydes and ketones[a]

Entry	Aldehyde/ketone	Amine	Product	Yield (%)
1				74
2				84
3				85
4				82
5				68
6				58
7				70
8				61

[a] Reagents and conditions: aldehyde or ketone (1 mmol), amine (1 mmol), molecular sieves 4Å (1 g), PS-TPP–Pd(OAc)$_2$ (10 mol%), sodium formate (3 mmol), heating for 6 h at 85 °C, DMF (5 mL).

Table 34 Isomerization of (E/Z)-nitroalkenes into pure (E)-nitroalkenes with PS-TPP[a]

Entry	R[1]	R[2]	(E/Z)-Nitroolefin mixture	Time (h)	Product (E/Z)
1	Me	Pr	55 : 45	20	100 : 0
2	Me	(CH$_2$)$_2$COOEt	90 : 10	20	100 : 0
3	Et	Pr	60 : 40	40	100 : 0
4	Me	Ph	80 : 20	20	100 : 0
5	Ph	Pr	80 : 20	20	90 : 10
6	Me	SPh	0 : 100	48	65 : 35

[a] Reagents and conditions: 1 : 0.1 molar ratio of nitroalkene : PS-TPP, RT, CH$_2$Cl$_2$, 100% yield.

reactions were run in aqueous media using water : toluene (5 : 1) under microwave irradiation conditions (Table 39) and conventional heating as well. The polymer catalyst was recovered and reused in subsequent reactions without loss of activity. In general, high yields were obtained with all pronucleophiles for which pK_a < 16, although increased steric hindrance or lowered kinetic acidity of the pronucleophile compromised the yield (entries 5 and 6).

4. Application of PS-TPP in heterocycle synthesis

4.1. Synthesis of 1,3,4-thiadiazole-2,5-dicarbonitrile and thiazole-2,4,5-tricarbonitrile

1,3,4-Thiadiazole-2,5-dicarbonitrile (**66**) shows interesting biological activity and is an excellent fungicide for *Aspergillus* (Scheme 18).[108] While **66** may be prepared in few steps from commercially available starting material, reactivity on silica gel and hydration of one of the nitrile groups (converting to the amide) during chromatography presents purification and isolation challenges.[109] Koutentis *et al.* showcased the utility of PS-TPP in the preparation of **66** and the novel analog, thiazole-2,4,5-tricarbonitrile (**67**), from the corresponding precursors 1,2-bis(4-chloro-5H-1,2,3-dithiazol-5-ylidene)hydrazine (**64**) and 2-(4-chloro-5H-1,2,3-dithiazol-5-ylidene)-2-(4-chloro-5H-1,2,3-dithiazol-5-ylideneamino)acetonitrile (**65**), respectively. Thus, treatment of dithiazole **64** with 6 molar equivalents of PS-TPP in dry CH$_2$Cl$_2$ and stirring for 1 h afforded **66** in 69% yield. Similarly, **67** was prepared in 76% yield under the same conditions, albeit lower amount of PS-TPP (5 equiv.) was used.
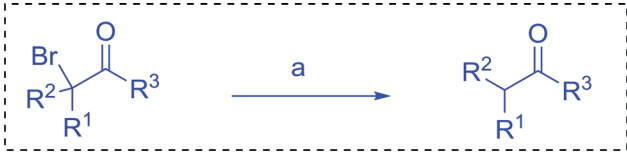
4.2. Synthesis of 3-aminoindole-2-carbonitriles

As a part of ongoing research into expanding the use of 1,2,3-dithiazoles in heterocyclic ring transformations, Koutentis and Michaelidou employed PS-TPP in the conversion of 2-(4-chloro-5H-1,2,3-dithiazolylideneamino)benzonitriles into 3-aminoindole-2-carbonitriles (Table 40).[110] Indoles exhibit a wide spectrum of biological activities and are important heteroarenes.[111] Moreover, substituted 3-aminoindole-2-carbonitriles are scant and strategies for their synthesis is necessary. In light of this, Koutentis undertook a detailed study where various substituted 2-(4-chloro-5H-1,2,3-dithiazolylideneamino)benzonitriles (**68**) reacted with PS-TPP (5 equiv.) in the presence of water (2 equiv.) to afford the desired 3-aminoindole-2-carbonitriles (**69**) together with anthranilonitriles as a side product.

4.3. Synthesis of substituted 2-phenylbenzothiazoles

Substituted 2-phenylbenzothiazoles are of tremendous importance to medicinal chemistry and are considered as privileged pharamacophore.[112] Several 2-phenylbenzothiazole derivatives have been shown to exhibit selective and potent biological activities, culminating in their clinical evaluation against certain types of tumours. For instance, 2-(4-amino-3-methylphenyl)-5-fluorobenzothiazole emerged as a lead compound against breast and ovarian cancer and had undergone phase 1 clinical trial in the U.K. in the form of its water soluble L-lysyl amide prodrug (Phortress).[113,114] 2-(3,4-Dimethoxyphenyl)-5-fluorobenzothiazole (PMX 610) is another clinical candidate with selective cytotoxicity profile reminiscent of the related 2-(4-aminophenyl)benzothiazole series.[115] In addition, the radioactive ^{11}C-labelled 6-hydroxy-4-(methylaminophenyl)benzothiazole known as Pittsburgh compound B has been developed for use in positron emission tomography (PET) scans to image beta-amyloid plaques in neuronal tissue as a non-invasive method of investigating Alzheimer's disease and other neurodegenerative conditions. 2-Phenylbenzothiazoles can be synthetically accessed *via* condensation of 2-aminophenol with benzaldehydes or benzoic acid derivatives, followed by oxidation of the resulting dihydrobenzothiazole. However, the synthesis of substituted 2-phenylbenzothiazoles is challenging because the requisite substituted 2-aminothiophenols are prone to oxidation.
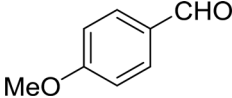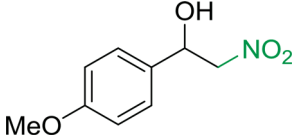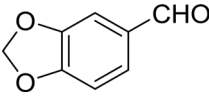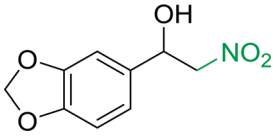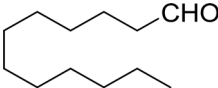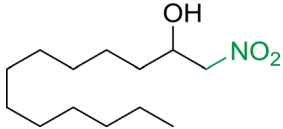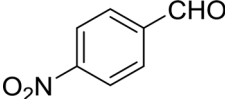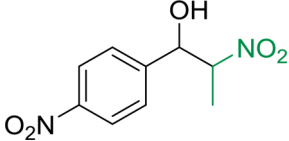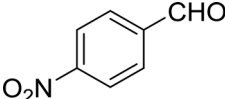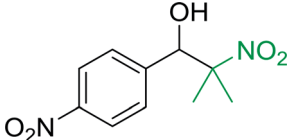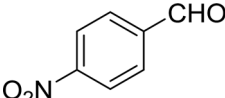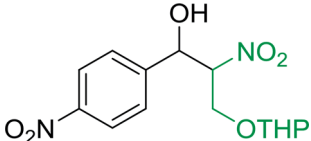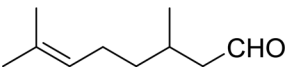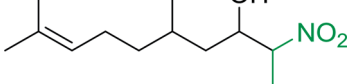
Table 35 Debromination of various α-bromo ketones [a]

Entry	α-Bromo ketone	Ketone product	Yield (%)
1	3-Bromocamphor	Camphor	97
2	2-Bromocyclohexanone	Cyclohexanone	89
3	p-Nitrophenacyl bromide	p-Nitroacetophenone	85
4	Phenacyl bromide	Acetophenone	96

[a] Reagents and conditions: α-bromo ketone, PS-TPP, benzene, RT, 30–50 min.

Table 36 Henry reaction of various aldehydes with nitroalkanes using 1 and ethyl acrylate[a]

$$R^1CHO \quad + \quad R^2R^3CHNO_2 \xrightarrow{a} \quad \underset{R^2}{\overset{OH}{\underset{R^1}{\mid}}} \underset{R^2}{\overset{NO_2}{\underset{R^3}}}$$

Entry	Aldehyde	Nitroalkane	Product	Yield (%)
1	MeO—C₆H₄—CHO	$H_3C{-}NO_2$		88
2	methylenedioxybenzaldehyde	$H_3C{-}NO_2$		88
3	long-chain alkyl CHO	$H_3C{-}NO_2$		86
4	O₂N—C₆H₄—CHO	$\diagup NO_2$		90
5	O₂N—C₆H₄—CHO	isopropyl NO₂		91
6	O₂N—C₆H₄—CHO	$O_2N{\diagdown}{\diagup}OTHP$		84
7	citronellal-type CHO	$\diagup NO_2$		88

[a] Reagents and conditions: 1 : 2 : 0.1 : 0.1 molar ratios of aldehyde : nitroalkane : PS-TPP : ethyl acrylate, solvent-free conditions, RT, 2–4 h.
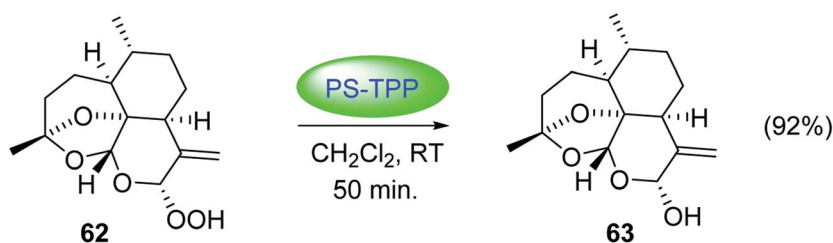
Scheme 17 Hydroperoxide reduction to alcohol with PS-TPP.

Table 37 Synthesis of carbonyl compounds from alkenes[a]

Entry	R^1	R^2	R^3	Yield (%)
1	Ph	H	H	80
2	Ph	H	H	86
3	C$_9$H$_{19}$	CH$_3$	H	92
4	C$_5$H$_{11}$	CH$_3$	H	88
5	C$_7$H$_{15}$	H	C$_7$H$_{15}$	91
6	Allyl-C(OH)-CH$_2$ CH$_3$	H	H	90

[a] Reagents and conditions: 1 : 1 molar ratio of PS-TPP : alkene.

Westwell *et al.* developed an approach to substituted 2-phenyl-benzothiazoles where PS-TPP and *p*-TSOH were used to promote a reaction between stable 2-aminothiophenol disulfides and benzaldehydes (Table 41).[116] The procedure features a variety of substituents on both the benzothiazole and phenyl rings with yields ranging between 80–97%.

4.4. Synthesis of 1,2,4-oxadiazoles

1,2,4-Oxadiazole are biologically interesting heterocycles that act as bioisosteres for amides or esters in medicinal chemistry.[117] These compounds comprise an important structural motif and have been incorporated into muscarinic[118] and benzodiazepine[119] receptor agonists, serotoninergic (5-HT3)

Table 38 Stereoselective conversion of α,β-ynones to (*E,E*)-α,β-γ,δ-dienones using PS-TPP[a]

Entry	Ynones	Dienones	Yield (%)
1			79
2			81
3			80
4			64
5			51
6			47

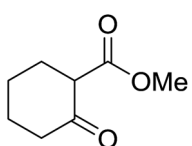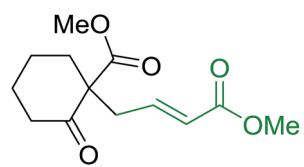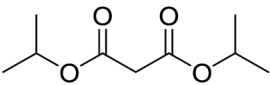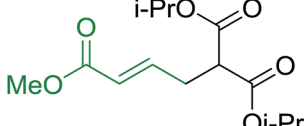[a] Reagents and conditions: PS-TPP (20 mol%), ynones (1 mmol), toluene, 80 °C, 18 h.
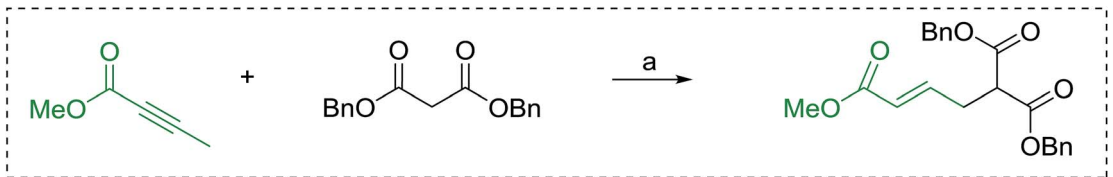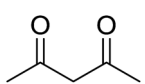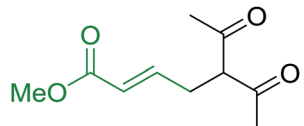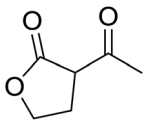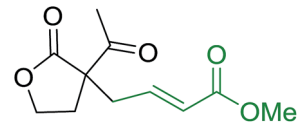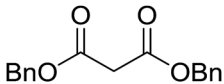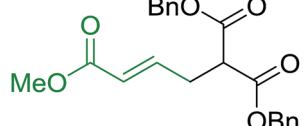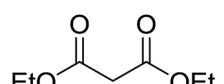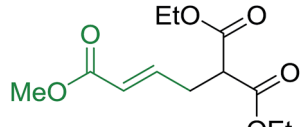
antagonists,[120] as well as antirhinovirals.[117] They have also found applications as peptide mimetics.[121] Because of their biological properties, Wang *et al.* developed a polymer-assisted solution phase reaction protocol for the synthesis of 1,2,4-oxadiazole in an expeditious manner.[122] They found that under microwave heating conditions at 100 °C for 5 min, various carboxylic acids are converted into the corresponding acid chlorides in nearly quantitative yields by treatment with trichloroacetonitrile and PS-PPh$_3$. Thus, in the first step, the preparation of 1,2,4-oxadiazoles involved generating the acid chlorides *in situ* from the corresponding carboxylic acids using PS-PPh$_3$/CCl$_3$CN. Subsequent addition of the amidoxime and DIEA in THF and heating in the microwave at 150 °C for 15 min

afforded the desired 1,2,4-oxadiazole in excellent yield (Table 42). It is noteworthy that the PS-PPh$_3$ resin from the first step did not interfere with the reaction in the second step, thereby allowing the transformation to be performed in on pot.

4.5. Synthesis of vinylthio-, vinylsulfinyl-, vinylsulfonyl- and vinylketo-benzofuroxans and benzofurazans

Vinylthio-, vinylsulfinyl and vinylsulfonyl-benzofuroxan heterocycles possess remarkable *in vitro* activities against different *Trypanosoma cruzi* strains,[123] which is a protozoan parasite responsible for causing Chagas' disease, a potentially life-threatening disease of the heart and gastrointestinal tract. The parasite infects a population of nearly 30 million yearly and

Table 39 PS-TPP-catalyzed γ-addition of pronucleophiles to methyl 2-butynoate[a]

Entry	Pronucleophile	Product	Yield (%)
1			97
2			96
3			82
4			83
5			61
6			67

[a] Reagents and conditions: 1 : 1 : 0.35 molar ratios of methyl 2-butynoate : pronucleophile : PS-TPP, H$_2$O/toluene (5 : 1), MW, 150 °C, 45–90 min.
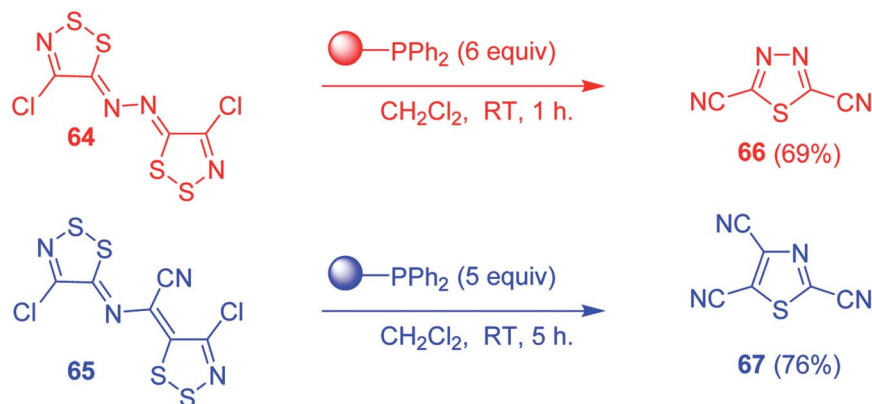
Scheme 18 Preparation of 1,3,4-thiadiazole-2,5-dicarbonitrile and thiazole-2,4,5-tricarbonitrile.

is transmitted to animals and people by insect vectors. Unfortunately, the emergence of *T. cruzi* parasite strains resistant to drugs used clinically and experimentally as anti-*T. cruzi* increased the urgency to design novel anti-trypanosomatid agents. On the basis of previous results[123] obtained by Castro *et al.* in regards to the trypanosomicidal properties of benzofuroxan derivatives, they developed a synthetic route to access these derivatives using a Wittig reaction performed under mild conditions with PS-TPP.[124] Attempted preparation of such compounds though classical aldolic conditions led to total decomposition of the starting formylbenzofuroxan or reduction the *N*-oxide moiety. As shown in Scheme 19, treatment of 2-bromoacetophenones (**70**) with PS-TPP yielded the corresponding phosphonium salts, which upon deprotonation with NaH and subsequent condensation with formylbenzofuroxan (**71**) and the concomitant elimination of polymer-supported triphenylphosphine oxide through Wittig reaction produced exclusively *E*-vinylketo-benzofuroxans (**72**). Similarly,

(bromomethyl)(phenyl)sulfane (**73**) were transformed in a similar manner to mixtures of separable *E/Z* vinylthio-benzofuroxan geometric isomers (**74**) (Scheme 19), which were further derivatized to the vinylsulfinyl- **75**, and vinylsulfonyl-**76** benzofuroxans by oxidation with *m*-CPBA and H_2O_2, respectively.

In addition, PS-TPP was used as a mild reducing agent to render benzofurozan derivatives **78** in excellent yields by deoxygenating a number of the benzofuroxan products **77** for the purpose of verifying the role played by the N-oxide group in the trypanosomicidal activity (Scheme 20).

4.6. Synthesis of β-lactams using PS-TPP

β-Lactams are the most prescribed antibacterial agents for the treatment of bacterial infections.[125,126] However, bacteria have developed mechanisms to resist the action of β-lactam drugs. Thus, the synthesis of β-lactams with new structural features is always useful. A simple and useful method for the generation of

Table 40 Preparation of 3-aminoindole-2-carbonitriles from 1,2,3-dithiazoles
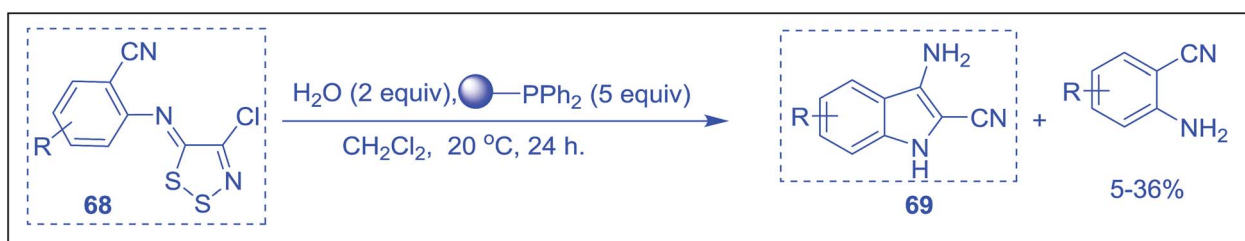
Entry	R	Yield (%) of **69**
1	H	26
2	5-NO$_2$	55
3	3-Br-5-NO$_2$	27
4	4-Cl	39
5	5-Cl	13
6	6-Me	17
7	4-MeO	29

β-lactams by reacting α-bromo carboxylic acids and imines was described by Kikuchi and Hashimoto[127] (Scheme 21). This coupling reaction was mediated by Ph$_3$P or PS-TPP to afford the β-lactams with high *trans*-selectivity and high yields in most cases.

5.   Peptide synthesis

5.1.   Peptide synthesis with polymeric triphenylphosphine/2,2′-dipyridyl disulfide

Horiki described the synthesis of dipeptides by the Mukaiyama procedure[128] using PS-TPP and 2,2′-dipyridyl disulfide (Scheme 22).[129] The procedure involved refluxing a mixture of PS-TPP, PySSPy, N-protected valine, ethyl glycinate, and Et$_3$N in CH$_2$Cl$_2$ for 1 d. Best results were obtained when 2 equiv. of PS-TPP and 1.5 equiv. PySSPy to each amino acid were employed.

5.2.   Synthesis of peptidyl ketones and peptidyl diketones from peptidyl phosphorane 4

El-Dahshan *et al.* demonstrated the utility of PS-TPP in the solid-phase synthesis of peptidyl ketones and peptidyl diketones by C-alkylations and C-acylations of peptidyl phosphorus ylide resins in which the substrate was eventually freed oxidative or by hydrolytic cleavage.[130] The starting point for the synthetic sequence was the preparation of polymer-supported triphenylphosphoranylidene acetate (79) from PS-TPP and 2-(trimethylsilyl)ethyl 2-bromoacetate or *t*-butyl 2-bromoacetate. Subsequent acylation of 79 with Fmoc-protected amino acids (79 → 80) (Scheme 23), followed by Fmoc cleavage of 80, peptide elongation, and acylation of the N-terminus of the

resulting peptidyl-phosphoranylidene acetate ester furnished resin 81. Deprotection of the ester group of 81 led to immediate decarboxylation to produce peptidyl phosphorane 82.

Next, methylation (entry 1) or benzylation (entry 2) of 82a (Table 43), followed by oxidative cleavage afforded the peptidal diketones (entries 1 and 2) in good yields. For the preparation of peptidyl ketones, 82b was directly hydrolyzed under basic conditions with NaHCO$_3$ in THF/water (entries 3 and 4) or under acidic conditions in the case of its methylated phosphorane 82a (entry 5).

6.   Application in total synthesis

6.1.   Synthesis of a small library of palmarumycin CP$_1$ analogs

Wipf and co-workers[132] utilized PS-TPP for the synthesis of a small library of palmarumycin CP$_1$ (83) analogs after developing an efficient synthetic approach for the preparation of palmarumycin CP$_1$, a natural product and an antifungal agent.[131] The library was obtained by a Mitsunobu coupling reaction of palmarumycin CP$_1$ with a total of 13 alcohols using PS-TPP (Table 44).[132] The reaction was performed on a very small scale (2–7 mg) to afford the ether products 84 in high purity and reasonable yields.

6.2.   Total synthesis of epothilone A

The epothilones[133,134] belong to a class of natural products that exhibit extraordinary cytotoxicity and are potential cancer drugs. As such, they prevent cancer cells from dividing by promoting GTP-independent tubulin polymerization, thus

Table 41   Synthesis of substituted 2-phenylbenzothiazoles[a]
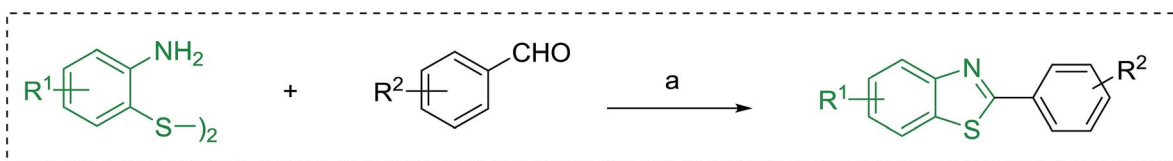
Entry	R^1	R^2	Yield (%)
1	H	4-OMe	97
2	H	4-OH	97
3	H	3-NO$_2$	94
4	H	4-Br	86
5	6-F	4-OMe	88
6	6-F	4-OH	87
7	6-F	4-NO$_2$	93
8	6-F	4-Br	92
9	6-F	4-CN	89
10	6-OEt	4-OMe	87
11	6-OEt	4-OH	94
12	6-OEt	4-NO$_2$	87
13	6-OEt	4-Br	80

[a] Reagents and conditions: 1 : 1 : 1 : 0.2 molar ratios of aldehyde : PS-TPP : substituted bis(2-aminophenyl)disulfide : *p*-TSOH, toluene/DMF (1 : 1), reflux, 2 h.

Table 42 Synthesis of 1,2,4-oxadiazoles from carboxylic acids and amidoximes[a]
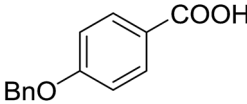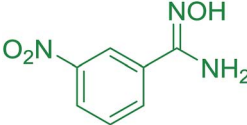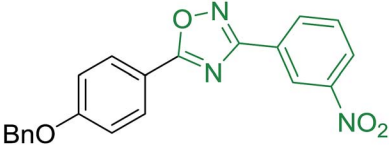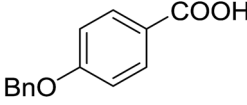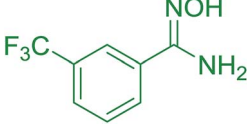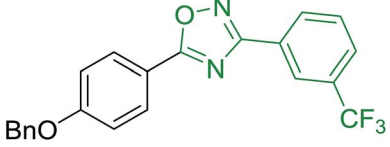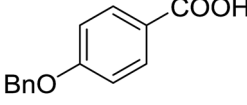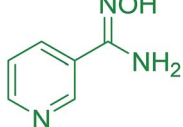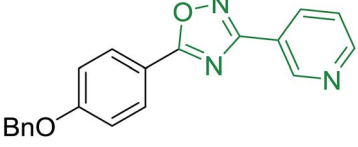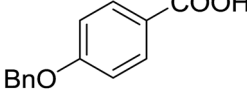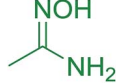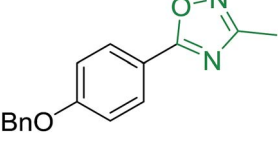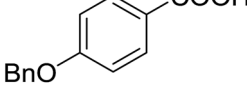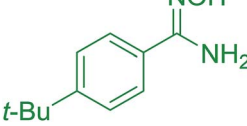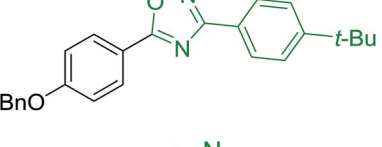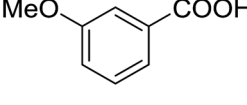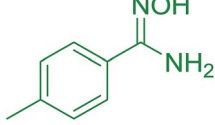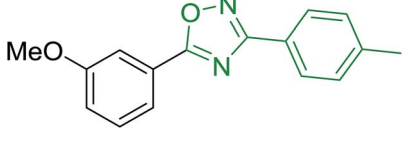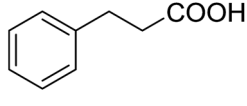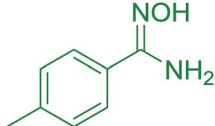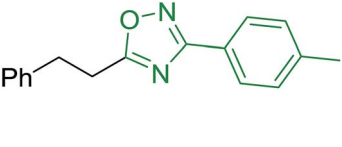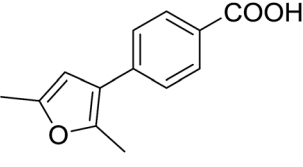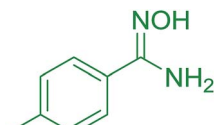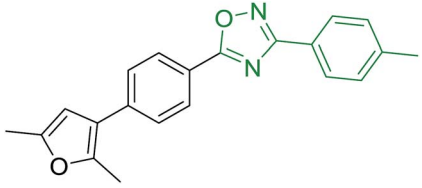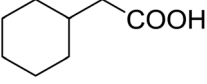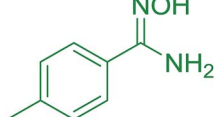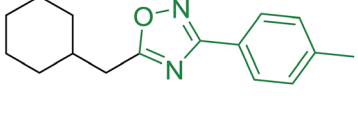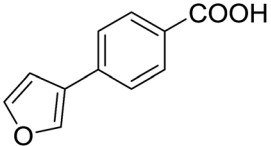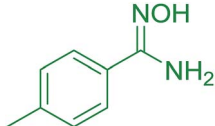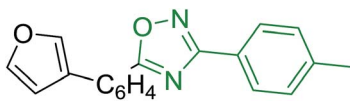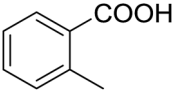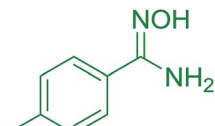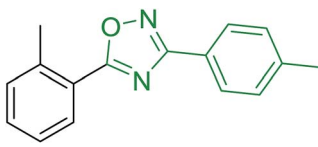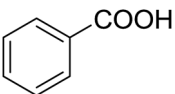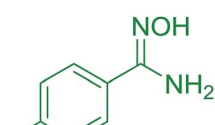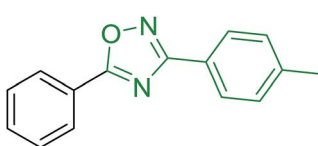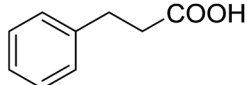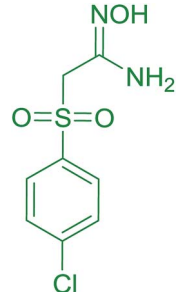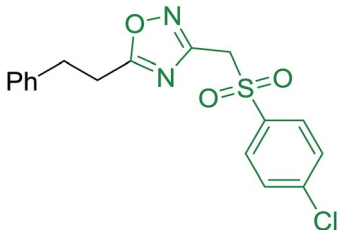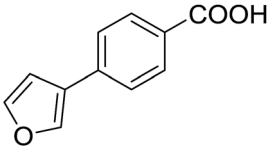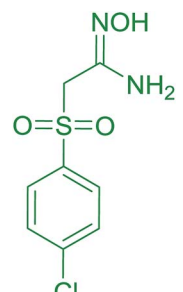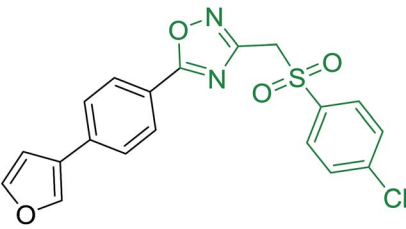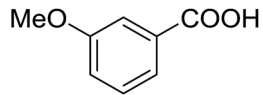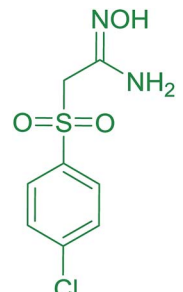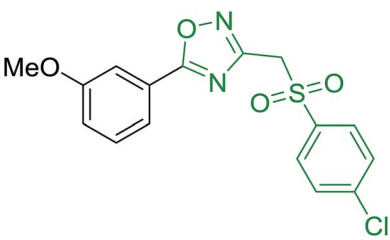

Entry	Carboxylic acid	Amidoxime	Product	Yield (%)
1				90
2				80
3				94
4				80
5				93
6				98
7				93
8				90
9				97

Table 42 (*Contd.*)

Entry	Carboxylic acid	Amidoxime	Product	Yield (%)
10				96
11				98
12				95
13				83
14				77
15				89

^a Reagents and conditions: (i) PS-TPP, CCl₃CN, carboxylic acid, THF, MW, 5 min, 100 °C; (ii) amidoxime, DIEA, THF, MW, 15 min, 150 °C; molar ratios of PS-TPP : CCl₃CN : carboxylic acid : amidoxime : DIEA 3 : 1.5 : 1 : 1 : 2.

inducing mitotic arrest and inhibiting tumor growth.[134] Mechanistic investigation into the mode of action showed that the epothilones bind competitively to the same sites in β-tubulin as taxol, although the former appear to have better efficacy, and milder adverse effects than taxol.[135] Moreover, certain epothilones exhibit cytotoxic biological activity against multiple-drug-resistant cells, and are relatively more soluble in water than the analogous taxanes, making them interesting synthetic drug targets. Ley et al. devised a synthetic approach employing immobilized reagents, including PS-TPP, in a multistep sequence leading to epothilones A (91) and C (90) (Scheme 24).[136,137] Their approach to the 16-membered macrocycles (90 and 91) involved a convergent stereoselective coupling of three fragments, one of which involved a Wittig reaction between the thiazole fragment 87 and the aldehyde fragment 88. Preparation of the key polymer-bound thiazole 87 involved conversion of primary alcohol 85 to iodide 86 with PS-TPP, iodine, and polymer-supported triethylamine. The resulting iodide 86 was converted to the supported phosphonium salt 87 by heating with PS-TPP in toluene. Subsequent treatment of salt 87 with NaHMDS, followed by washing with dry THF gave the salt-free ylide which was coupled via a Wittig reaction with aldehyde 88 to afford the required C12–C13 cis-alkene 89. Having this key compound in hand, the proposed synthetic strategy was successfully completed by desilylating the allylic and primary alcohols, oxidizing the latter to the carboxylic acid, followed by a Yamaguchi macrolactonisation to afford epothilones C (90). The analogue 91 was accessed through the epoxidation of 90.

7. PS-TPP–metal complexes and their application in synthesis

7.1. Cobalt immobilization on PS-TPP

The Pauson–Khand (P–K) reaction was first reported in 1971[138] and inspired many investigations in the ensuing years.[139] The reaction is used for the synthesis of cyclopentenones via a cobalt carbonyl-mediated cyclization of an alkene, an alkyne, and carbon monoxide. Challenges associated with handling the very labile $Co_2(CO)_8$ spurred the development of a PS-TPP cobalt carbonyl complex as a catalyst for the Pauson–Khand reaction.[140] The catalyst (92) was prepared by reacting equimolar amounts of PS-TPP and $Co_2(CO)_8$ in 1,4-dioxane at 75 °C and proved more stable than the latter. Thus, at 70 °C, 50 mbar overpressure of carbon monoxide, and 5 mol% of 92, the enynes 93 and 95 shown in Scheme 25 converted to the corresponding cyclopentanones 94 and 96 in 66 and 57% yield, respectively.

7.2. Immobilization of functionalized alkynes on PS-TPP

The PS-TPP cobalt carbonyl complex 92 developed by Comely et al. was also used as a traceless alkyne linker.[141] The temporary and reversible immobilisation of an alkyne functional group (Nicholas reaction) onto a polymeric support which leaves minimal remnant of the solid support upon decomplexation of the product is a very desirable property for solid-phase synthesis. Thus, treatment of resin 92 with hex-5-yn-ol (97) generated the polymer-bound alkyne complexes 98 and 99 (ratio; 3 : 7, respectively), which could be acetylated (70% yield)
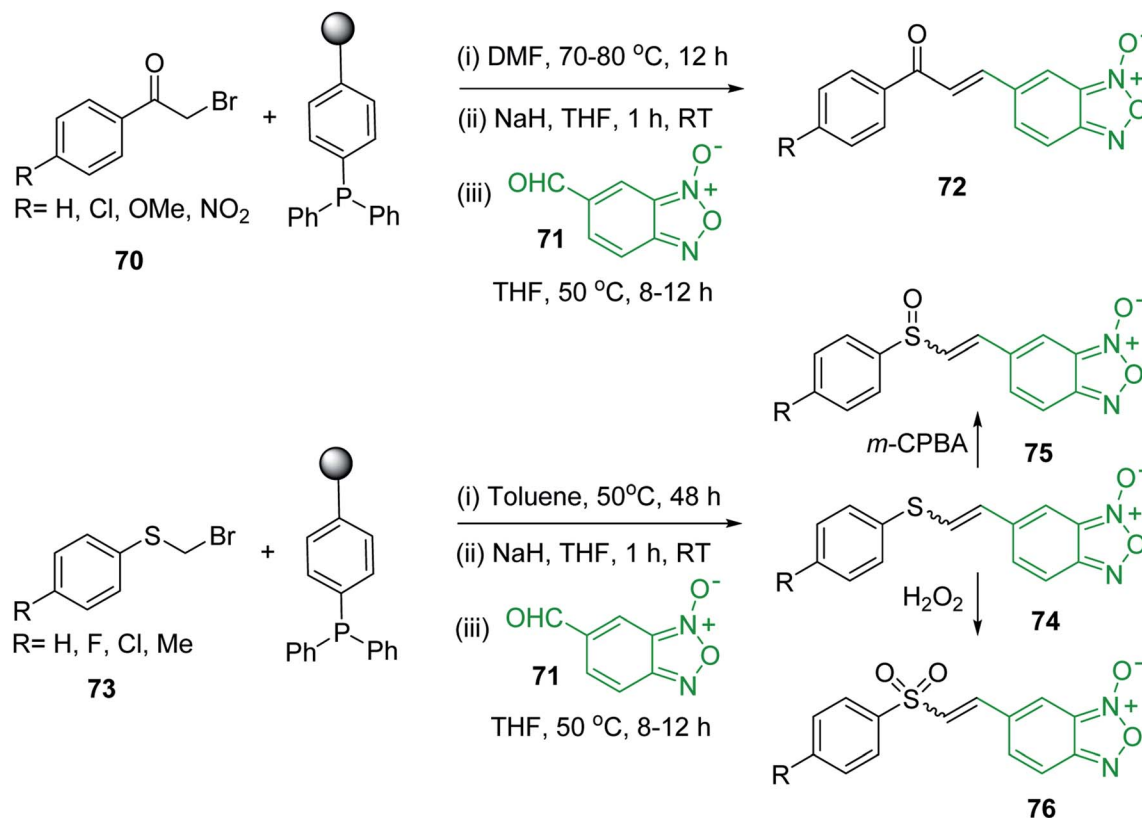
Scheme 19 Solid-phase synthesis of vinylketo-benzofuroxanyl compounds and their vinylthio, vinylsulfinyl, and vinylfulfonyl derivatives.
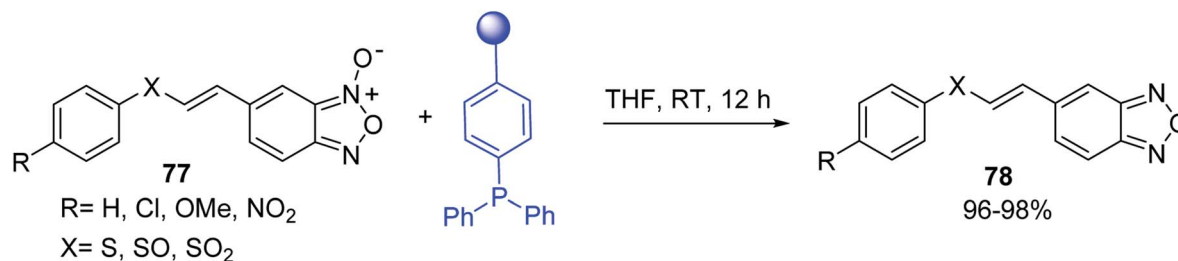
Scheme 20 Solid-phase synthesis of benzofurozan derivatives.

or converted to the aldehyde by the Parikh–Doering oxidation (17% yield) (Scheme 26). Decomplexation of the alkyne was possible with aerial oxidation in dichloromethane under white light for 72 h.

7.3. PS-TPP-supported rhodium catalyst for use in the synthesis of ketones from benzyl alcohols and 1-alkene

Jun *et al.* reported the reaction benzyl alcohol bearing various substituents with 1-alkene to generate the corresponding ketones by PS-TPP-supported rhodium catalyst formed *in situ*.[142] In a typical experiment, the alcohol reacted with an equimolar amount of 1-alkene in the presence of PS-TPP (15 mol%), Ph_3P (5 mol%), $RhCl_3 \cdot xH_2O$ (5 mol%), and 2-amino-4-picoline (100 mol%) as co-catalyst (Table 45) in toluene at 130 °C for 72 h. The catalytic activity of the recovered catalyst did not decrease after reusing it for four cycles and electron-withdrawing substituents (entries 2 and 4) afforded ketones in higher yields than electron-donating groups (entries 3 and 5). The yield was also negatively impacted with sterically hindered olefinic substrates (entries 6 and 7). This polymer-supported

Rh(I) catalyst could also be generated *in situ* from other Rh(I) complexes *via* a ligand exchange reaction.

7.4. PS-TPP-supported ruthenium catalyst for use in transfer hydrogenation and hydrocarbon oxidation

Chloro-ruthenium complexes such as $RuCl_2(PPh_3)_3$ (**100**) have been used frequently in metal-mediated transformations which include transfer hydrogenation and hydrocarbon oxidation.[143] Soluble phosphines have been widely used as ligands for catalysis employing heavy metals. Unfortunately, removal of soluble derivatives of heavy metals from organic reactions is challenging. Besides providing ease of separation from the product mixture at the end of the reaction, attaching a metal complex to a polymer lowers toxicity and air sensitivity of such species and precludes contamination of the product with heavy metals. Leadbeater reported an insoluble version of $RuCl_2(PPh_3)_3$ (**101**) and described its capabilities in transfer hydrogenation and hydrocarbon oxidation. Immobilization of the ruthenium complex was carried out by stirring an equimolar mixture of PS-TPP and $RuCl_2(PPh_3)_3$ in toluene at room
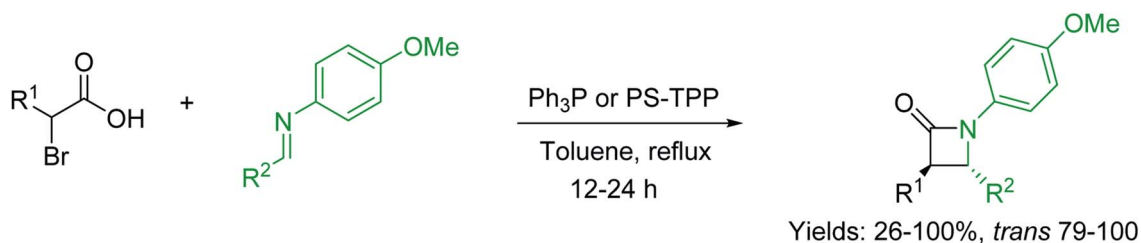
Scheme 21 Preparation of β-lactams. Reagents and conditions: 1 : 1.2 : 2.1 molar ratios of imine : acid : phosphine, toluene, reflux, 12–24 h.
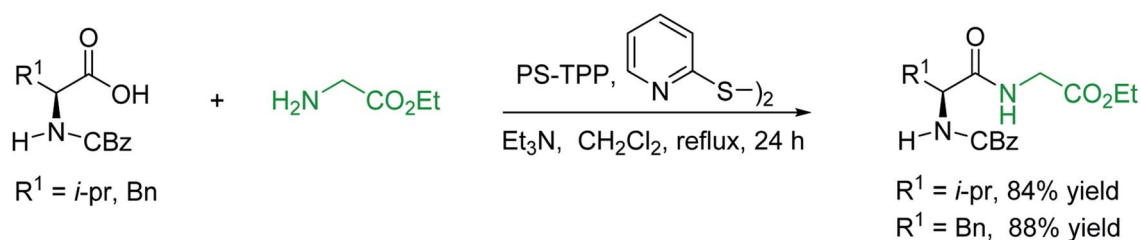
Scheme 22 Preparation of peptides with polymeric triphenylphosphine/2,2′-dipyridyl disulfide. Reagents and conditions: 2 : 1.5 : 1 : 1 : 1 molar ratios of PS-TPP : PySSPy : amino acid : ethyl glycinate : Et₃N, CH₂Cl₂, reflux, 1 d.
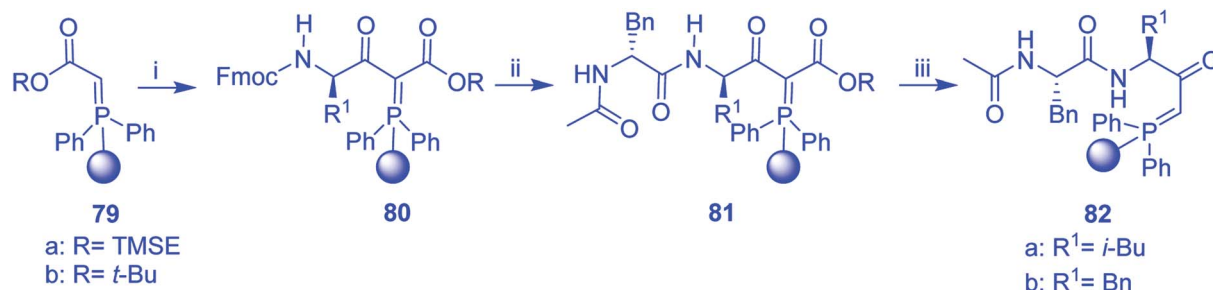
Scheme 23 Synthesis of peptidyl phosphoranes. Reagents and conditions: (i) Fmoc-AA-OH, MSNT/2,6-lutidine, 12 h, RT for **79a**; BTFFH, DIPEA, 12 h, RT for **79b**; (ii) 20% piperidine/DMF, 6 min; Fmoc-AA-OH, DIC, HOBT, DMF, 3 h; (iii) TAS-F, DMF, 1 h, RT for **81a** or 95% TFA, CH$_2$Cl$_2$, 15 h, RT for **81b**.

temperature overnight.[144] The resulting polymer-bound ruthenium complex, which was isolated by filtration, was stable in air and amenable to prolonged storage under an atmosphere of nitrogen. Using catalytic amount of the immobilized complex (0.15%), selective hydrogen transfer from 2-propanol to various ketones (Table 46, entries 1–4) occurred rapidly,

Table 43 Synthesis of peptidyl ketones and peptidyl diketones from phosphorane **82**[a]

Entry	Peptidyl phosphorane **82**	Alkylated phosphorane	Peptidyl ketones/diketones	Yield (%)
1				75
2				63
3		—		45
4				38
5		—		70

[a] Reagents and conditions: methylation of **82a** and **82b**: alkyl halide (3 equiv.), THF, 12 h, RT for **82a** or 70 °C for **82b**; oxidative cleavage conditions: 3–4 equiv. DMSO in acetone, CH$_2$Cl$_2$, 1 h, 0 °C; basic hydrolysis conditions: 5% NaHCO$_3$, THF/H$_2$O (4 : 1); acidic hydrolysis conditions: glacial acetic acid/THF/H$_2$O (1 : 4 : 1), 8 h, 50 °C.

Table 44 Preparation of palmarumycin analogs[a]
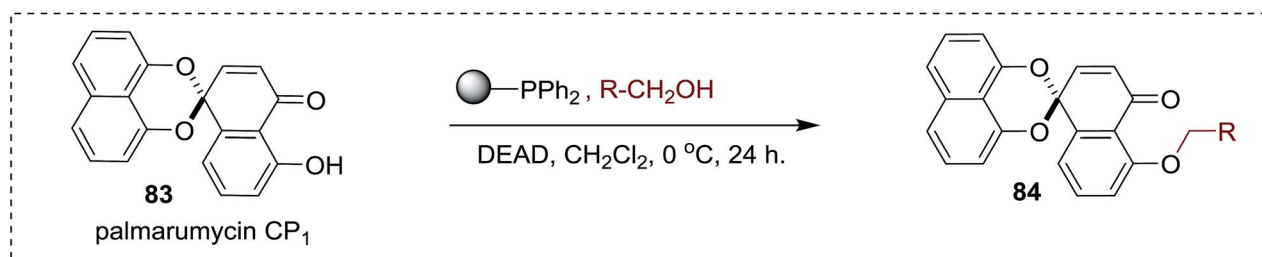
Entry	Phenol	R	Yield (%)
1	Palmarumycin CP$_1$	(E)-HC=CHPh	52
2		(E)-HC=CHMe	88
3		n-C$_5$H$_{11}$	50
4		(E)-CH$_2$HC=CHEt	43
5		m-MeOPh	67
6		Bn	33
7		2-Furyl	29
8		(E,E)-HC=C(Me)CH$_2$CH$_2$CH=CMe$_2$	83
9		3-Furyl	50
10		2-Pyridyl	43
11		3-Pyridyl	29
12		4-Pyridyl	17
13		HC=CH$_2$	71

[a] Reagents and conditions: 1 : 5 : 5 : 5 molar ratios of palmarumycin CP$_1$: PS-TPP : alcohol : DEAD, CH$_2$Cl$_2$, 0 °C, 24 h.

delivering the product alcohols in yields (40–83%) comparable to those obtained with the unsupported RuCl$_2$(PPh$_3$)$_3$ complex. Similarly, the oxidation of a range of alcohols

(entries 5 and 6) and hydrocarbons (entries 7–10) using a catalytic amount of the polymer-supported ruthenium complex and t-BuOOH gave the desired ketones in good
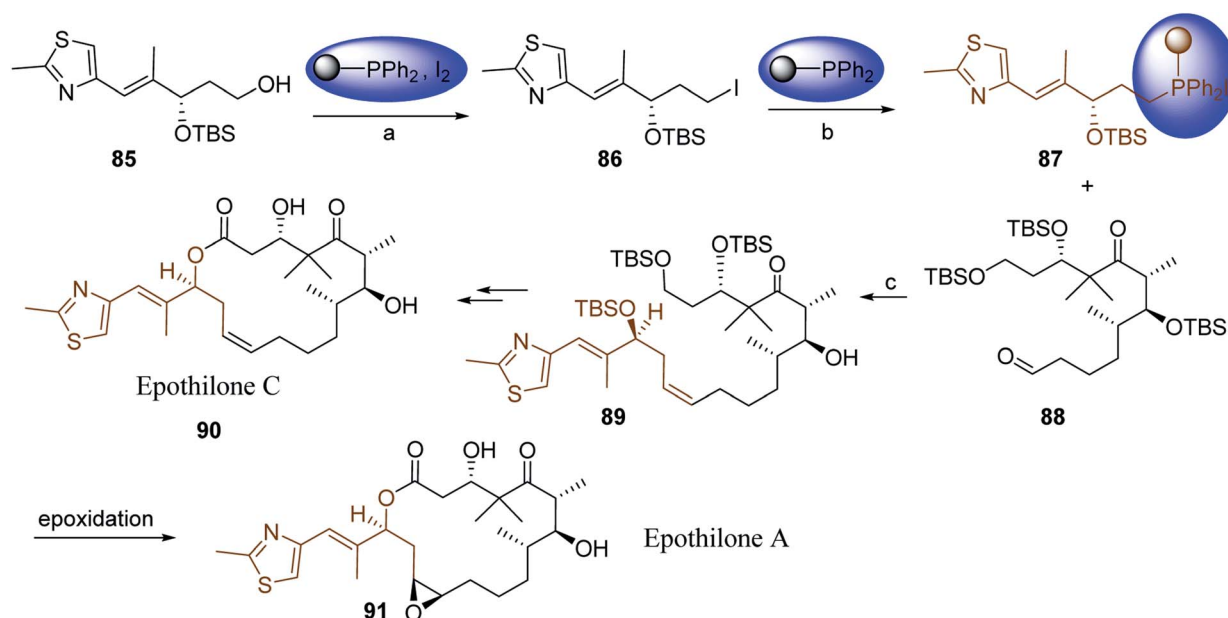
Scheme 24 Total synthesis of epothilones A and C. Reagents and conditions: (a) iodine (4.0 equiv.), PS-TPP (5.0 equiv., 3.3 mmol g^{-1}), imidazole (6.0 equiv.), MeCN/Et$_2$O (3 : 1), then diethylaminomethylpolystyrene (8.0 equiv., 3.2 mmol g^{-1}), Amberlite IRC-50 (13.0 equiv., ~5 mmol g^{-1}), toluene, RT, 105 min, 73%; (b) PS-TPP (1.0 equiv., 3.3 mmol g^{-1}), toluene, 90 °C, 18 h; (c) phosphonium salt 87 (2.5 equiv.), NaHMDS (10.0 equiv.), THF, RT, 15 min, then THF wash, then aldehyde 88 (1.0 equiv.), 78 °C → 40 °C, 15 min, 93%.
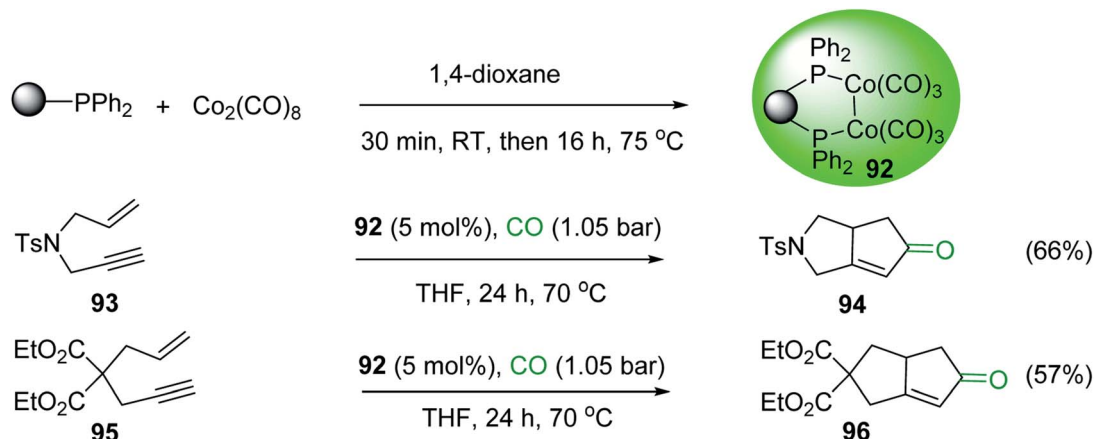
Scheme 25 Catalytic Pauson–Khand reaction.
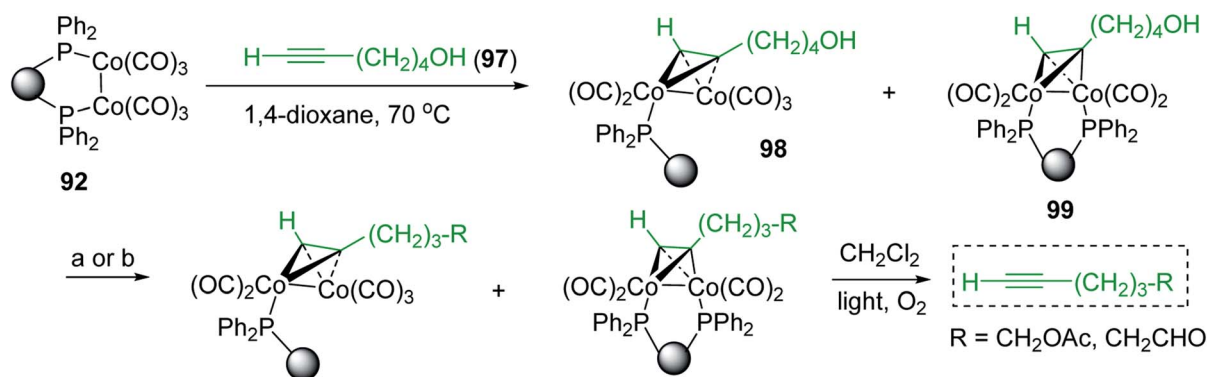
Scheme 26 Reactions and decomplexation of immobilised functionalized alkynes. Reagents and conditions: (a) acetic anhydride, Et_3N; (b) SO_3-py, DMSO, Et_3N.

yields (47–100%). It was shown that the catalyst could be recycled and reused a number of times without losing activity.

7.5. PS-TPP–arene-ruthenium complex for use in enol formate synthesis and the cyclopropanation of olefins

Arene-ruthenium complex **103** is another analog of a homogeneous metal complex that has been immobilized on PS-TPP by

Table 45 Preparation of ketones from benzyl alcohols and 1-alkene
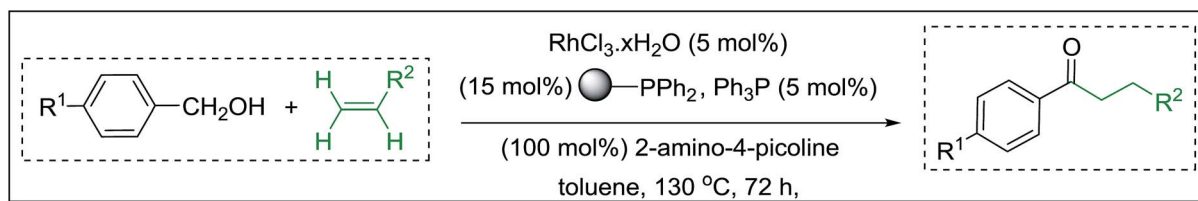
Entry	R^1	R^2	Yield (%)
1	H	$n\text{-}C_4H_9$	69
2	F	$n\text{-}C_4H_9$	75
3	CH_3	$n\text{-}C_4H_9$	67
4	CF_3	$n\text{-}C_4H_9$	70
5	CH_3O	$n\text{-}C_4H_9$	61
6	H	$t\text{-}C_4H_9$	50
7	F	$t\text{-}C_4H_9$	53

Leadbeater.[145] The free complex [Ru-(*p*-cumene)Cl$_2$(Ph$_3$P)] is among many other arene ruthenium catalysts that have been frequently used in a plethora of metal-mediated reactions such as enol formate synthesis[146] and cyclopropanation of alkenes.[147] The air-stable polymer-bound complex **103** was prepared *via* a thermolysis reaction of the dimer **102** with two molar equivalents of PS-TPP (**1**) in CH$_2$Cl$_2$ (Scheme 27).

The ruthenium polymer-supported complex **103** was used catalytically (1 mol%) for the regioselective addition of formic acid to terminal alkynes and diynes to generate the corresponding enol formates in 76–95% yields (Table 47, entries 1–

5). Reactions were conducted in toluene since it produced optimum yields even though resin swelling is not as marked as in other solvents. The catalyst was similarly active in alkene cyclopropanation reactions (entries 6 and 7).

7.6. Catalytic oxidation of benzylic and allylic alcohols and acid anhydride synthesis with PS-TPP–cobalt complex

PS-TPP has also been used by Leadbeater to attach the homogeneous transition metal catalyst CoCl$_2$(PPh$_3$)$_2$ (**104**) and assess its ability in the catalytic oxidation of alcohols to aldehydes and

Table 46 Transfer hydrogenation and hydrocarbon oxidation with PS-TPP–RuCl$_2$(PPh$_3$)$_2$ complex **101**[a]

Entry	Substrate	Product	Yield (%)	Entry	Substrate	Product	Yield (%)
1			83	6			64
2			62	7			45
3			61	8			80
4			40	9			70
5			85	10			89

[a] Reagents and conditions: (i) 1 : 1 molar ratio of PS-TPP : RuCl$_2$(PPh$_3$)$_3$, toluene, RT, overnight; entries 1–4, path a, 50 mg : 10 mL : 10 mmol reagent ratios for PS-TPP–RuCl$_2$(PPh$_3$)$_2$ complex : 2-propanol : ketone, 1,2-dichloroethane, reflux, 15 min, then NaOH (10 mg), 2-propanol, reflux, 1.5 h; entries 5–10, path b, 50 mg : 2 mmol : 6 mmol reagent ratios for PS-TPP–RuCl$_2$(PPh$_3$)$_2$ complex : hydrocarbon : 30% peracetic acid, 1,2-dichloroethane/EtOAc (7 : 1), reflux, 2 h.
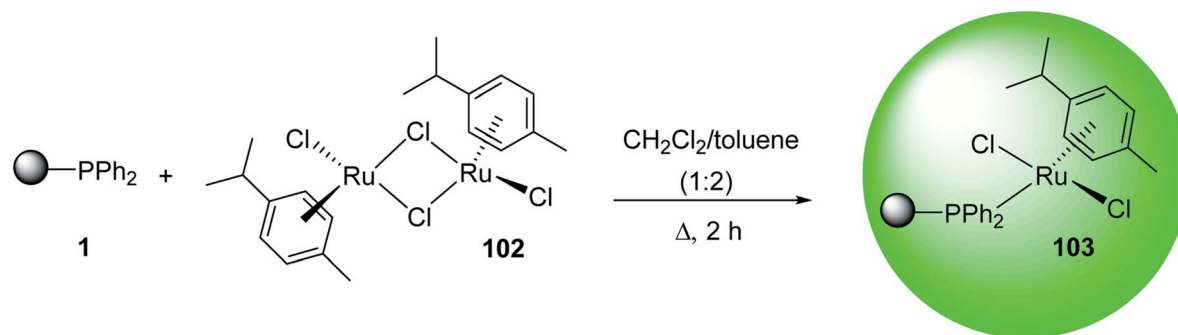
Scheme 27 Preparation of PS-TPP–arene-ruthenium complex **103**.

ketones and the synthesis of acid anhydrides (Table 48). Immobilization of the cobalt catalyst was achieved by agitating a mixture of $CoCl_2(PPh_3)_2$ and the functionalized phosphine resin **1** (1 : 1.7 molar ratio) in CH_2Cl_2 overnight.[148] The catalyst loading was estimated to be approximately 2.4 mmol g^{-1} of resin. The resulting complex **105** (1 mol%) was used to selectively oxidize primary and secondary benzylic alcohols as well as allylic alcohols using *tert*-butylhydroperoxide as oxidant (entries 1–4). Aliphatic alcohols remained unaffected under the reaction conditions. The group demonstrated that the polymeric support had little effect on the product yield compared to the

homogeneous cobalt complex. The supported catalyst was also investigated in the coupling of acid chlorides and carboxylic acids. Several asymmetrically substituted acid anhydrides were prepared in good yields (entries 5–7).

7.7. Polystyrene-bound triphenylphosphine gold(ɪ) catalysts; synthesis of furans, pyrroles, and oxazolidines

Cationic gold(ɪ) complexes exhibit significant affinity to carbon–carbon multiple bonds and have become particularly attractive catalysts because they are resistant to moisture and air.

Table 47 Enol formate synthesis and alkene cyclopropanation with [Ru-(*p*-cumene)Cl$_2$(PS-TPP)]^a

Entry	Substrate 1	Substrate 2	Product	Yield (%)
1	Ph≡H	HCO$_2$H		76
2	Bu≡H	HCO$_2$H		95
3	H≡(CH$_2$)$_4$≡H	HCO$_2$H		81
4	H≡(CH$_2$)$_4$≡H	MeCO$_2$H		82
5	H≡(CH$_2$)$_4$≡H	PhCO$_2$H		84
6	Ph (vinyl)	N$_2$=CHCO$_2$Et		71
7	(o-methylstyrene)	N$_2$=CHCO$_2$Et		82

^{a} Reagents and conditions: entries 1–5, 1 : 1.3 : 0.01 molar ratio of formic acid : alkyne : [Ru-(*p*-cumene)Cl$_2$(PS-TPP)], toluene, reflux, 15 h; entries 6 and 7, 1 : 1.3 : 0.01 molar ratio of ethyl diazoacetate : alkene : [Ru-(*p*-cumene)Cl$_2$(PS-TPP)], CH$_2$Cl$_2$, 60 °C, 4 h.

Table 48 Catalytic oxidation of alcohols and acid anhydride preparation[a]
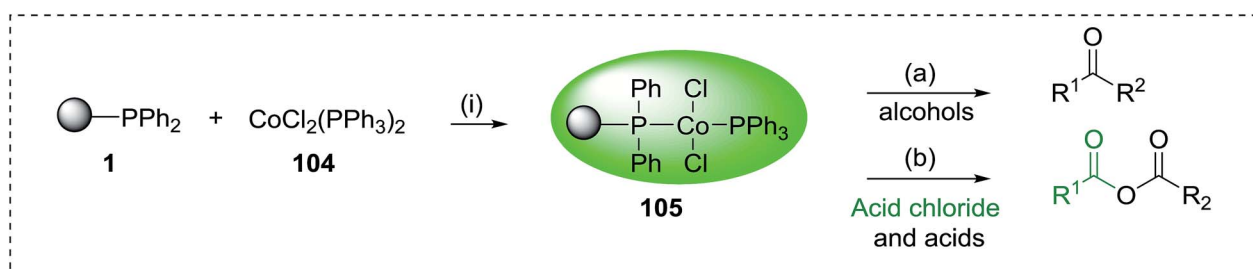
Entry	Substrate	Product	Yield (%)
1	BnOH	PhCHO	86
2	(1-phenylethanol, Ph–CH(OH)–CH₃)	(acetophenone, Ph–CO–CH₃)	91
3	(benzoin, HO–CH(Ph)–CO–Ph)	(benzil, Ph–CO–CO–Ph)	75
4	Ph–CH=CH–CH₂OH	Ph–CH=CH–CHO	70
5	PhCOCl + PhCOOH	PhCO–O–COPh	87
6	PhCOCl + EtCOOH	PhCO–O–COEt	78
7	iso-PrCOCl + iso-PrCOOH	(iso-Pr–CO–O–CO–iso-Pr)	86

[a] Reagents and conditions: (i) 1.7 : 1 molar ratio of PS-TPP : CoCl₂(PPh₃)₂, CH₂Cl₂, RT, overnight; entries 1–4, path a, 1 : 2 : 0.01 molar ratio of alcohol : *tert*-butylhydroperoxide : PS-TPP–CoCl₂(PPh₃), CH₂Cl₂, reflux, 4 h.; entries 5–7, path b, 1 : 1 : 0.01 molar ratio of acid chloride : carboxylic acid : PS-TPP–CoCl₂(PPh₃), CH₂Cl₂, 40 °C, 4 h.

Table 49 Synthesis of furans and pyrroles using PS-PPh₂Au⁺NTf⁻ complex[a]
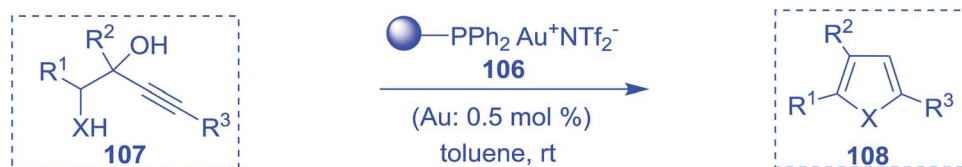
Entry	R^1	R^2	R^3	X	Yield (%)
1	H	Me	$(CH_2)_2Ph$	O	98
2	H	Me	2-Thienyl	O	88
3	$-(CH_2)_4-$		Ph	O	95
4	H	H	Ph	O	92
5	H	Me	$(CH_2)_2Ph$	NBoc	79

[a] Reagents and conditions: 1 : 0.005 molar ratio of PS-PPh₂Au⁺NTf⁻ : substrate, toluene, RT, 2 h.
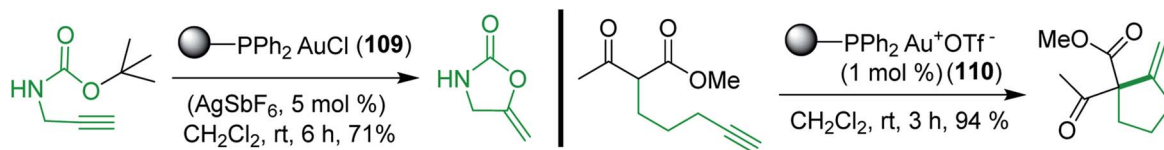
Scheme 28 Au-catalyzed carbocycle and oxazolidine-forming reactions.

Additionally, they display a high catalytic reactivity, often requiring a small loading to drive a wide range of transformations, such as nucleophilic reactions and intramolecular cyclizations.[149] Akai *et al.* described the synthesis of polystyrene-bound triphenylphosphine-gold(ı) cationic complexes by first treating PS-TPP with (Me₂S)AuCl (1 : 1) in CH₂Cl₂ at room temperature to give the immobilized gold compound PS-PPh₂-AuCl.[150] The polymer resin mesh size was critical where the most effective coordination was achieved with mesh size 100–200. Subsequent addition of 1 molar equivalent of AgOTf or AgNTf₂ to PS-PPh₂AuCl generated the cationic catalysts PS-PPh₂Au⁺OTf⁻ and PS-PPh₂Au⁺NTf⁻ (106), respectively. The two cationic catalysts were used in the rapid synthesis of furans and pyrroles 108 *via* the intramolecular cyclization of unsaturated 1,2-diols or 1,2-aminoalcohols 107. Table 49 shows some representative cyclization products obtained with catalyst 106, where similar yields were also observed when PS-PPh₂Au⁺OTf⁻ was used.

Other types of Au-catalyzed cyclizations such as carbocycle and oxazolidine-forming reactions also proceeded successfully

with PS-PPh₂Au⁺NTf⁻ (110) and the polymer-bound pre-catalyst PS-PPh₂AuCl (109) (Scheme 28).

7.8. Polymer-supported monodentate phosphine complexes

7.8.1. Trost's PS-PPh₂-Pd(PPh₃)₃ catalyst; allylic acetates substitution. Palladium complexes have been used as catalysts in cross coupling reactions to affect valuable C–C bond-forming transformations. Pittman *et al.* were first to attach palladium complexes to PS-TPP and use them in the oligomerization reaction of 1,3-butadiene to give mixture of products.[151] Keinan and Trost were the first to report the use of the polymer-supported analogue, 111, of the well-known palladium complex Pd(PPh₃)₄, in clean cross coupling reactions.[152] The protocol involves heating a solution of the latter parent metal complex with PS-PPh₂ (1) to generate complex 111 containing between 1.5–2 mol% Pd (Scheme 29). Since it was reported in the 1970's, 111 has found many useful applications in catalysis, although displaying differing selectivity in certain cases compared to the homogeneous analogue Pd(PPh₃)₄. For instance, when complex 111 was used as a catalyst for the reaction of the allylic acetate *cis*-3-acetoxy-5-carbomethoxy-1-
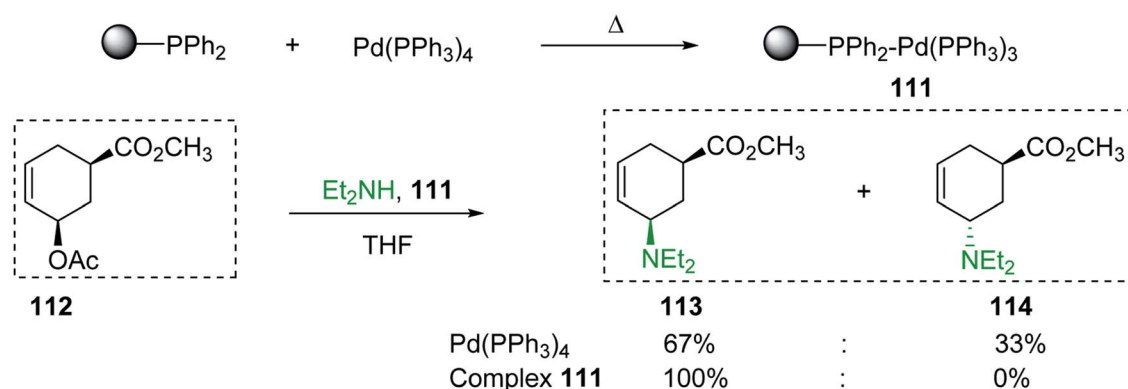
Scheme 29 Trost's PS-PPh₂-Pd(PPh₃)₃ catalyst; stereospecific amination of allyl acetates.
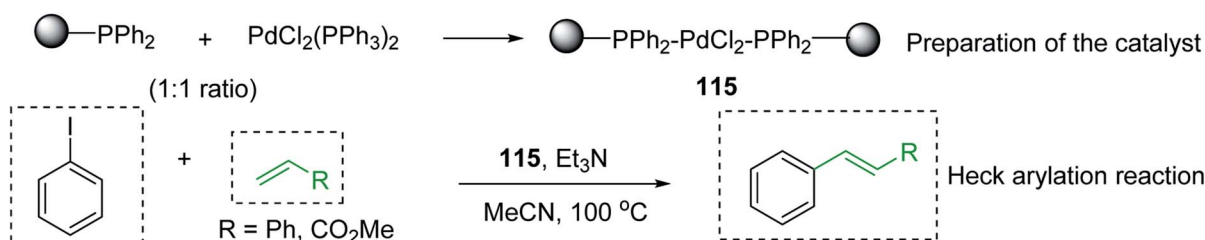
Scheme 30 Hallberg's PS-PPh₂-Pd(Cl)₂PPh₃ catalyst and its application in the Heck arylation.

cyclohexene (**112**) with Et$_2$NH, the *cis* substitution product **109** was produced with net retention of stereochemistry due to steric steering (Scheme 29). However, the use of non-supported Pd(PPh$_3$)$_4$ afforded a mixture of *cis*-3-diethylamino-5-carbomethoxy-L-cyclohexene (**113**) and its *trans* diastereomer **114** which had inverted configuration. Apparently, the pathway leading to

Table 50 Cyanation of aryl triflates and aryl halides[a]

Entry	Aryl triflate or halide	Aryl nitrile	Yield (%), microwave irradiation	Yield (%), thermal heating
1			X = OTf: 92 X = I: 99 X = Br: 95	X = OTf: 94 — —
2			X = I: 92 X = Br: 98	— —
3			92	—
4			96	98
5			94	93
6			92	92
7			94	93
8			89	93
9			90	91

[a] Reagents and conditions: PS-Ph$_3$P (3 mol%), Pd(OAc)$_2$ (7 mol%), Zn(CN)$_2$ (1 molar equivalent), DMF, microwave irradiation (2–3 min for aryl triflates; 30–50 min for aryl halides at 140 °C); thermal heating conditions (1.5–3 h).

inversion of configuration was not possible due to the inability of the amine nucleophile to co-ordinate to the polymer supported palladium complex **111**. Trost exploited the availability of this clean retention pathway for nitrogen nucleophiles for the development of a convenient isoquinuclidine synthesis.[152]

7.8.2. Hallberg 's PS-PPh₂-Pd(Cl)₂PPh₃ catalyst; Heck arylation. Hallberg and co-workers[153] have reported supported analogues of $PdCl_2(PPh_3)_2$ from PS-PPh₂ and $PdCl_2(PhCN)_2$ by reacting the two components (Scheme 30). Interestingly, the group prepared supported complexes with Pd : P ratios of 1 : 1, 1 : 2, 1 : 3 and 1 : 4 and discovered that coordination of the metal to the resin changes with metal loading, complex **115** being formed at low metal loading. The complexes were investigated in the Heck arylation of methyl acrylate and styrene with iodo- and bromobenzene (Scheme 30). The supported complex **115** with low PS-PPh₂ : Pd ratio was found to be most effective

for the arylation reactions of the aryl iodide substrates, whereas the complexes with high PS-PPh₂ : Pd ratios worked best with the aryl bromoanalogues. In general, the rates of reaction of the latter analogues were reported to be much slower than those obtained with homogeneous analogues, reaction durations being days rather than hours.

7.8.3. Palladium-catalyzed cyanation of aryl triflates and aryl halides using polymer-supported triphenylphosphine. A method for the expeditious cyanation of aryl triflates and aryl halides using a heterogeneous palladium catalyst prepared from PS-TPP as the ligand and palladium(ɪɪ) acetate has been demonstrated by Srivastava *et al.*[154,155] In this methodology, a variety of aryl triflates and aryl halides bearing both electron-withdrawing and electron-donating groups were successfully cross-coupled with zinc cyanide under microwave as well as under conventional heating conditions (Table 50). While both

Table 51 Allylation of carboxylic acids, alcohols, and amines[a]

Entry	Pronucleophiles	Allylated products	Yield (%)
1	2-amino benzonitrile (NH₂, CN)	N-cinnamyl 2-aminobenzonitrile (H–N, Ph, CN)	82
2	N-tosylaniline (NHTs)	N-cinnamyl-N-tosylaniline (Ts–N, Ph)	85
3	N-benzylaniline (NHBn)	N-benzyl-N-cinnamylaniline (Bn–N, Ph)	84
4	BnOH	cinnamyl benzyl ether (Bn–O, Ph)	82
5	1-phenylethanol (OH)	1-phenylethyl cinnamyl ether (O, Ph)	80
6	MeCOOH	cinnamyl acetate (Ph)	85
7	PhCOOH	cinnamyl benzoate (Ph–O, Ph)	92
8	cinnamic acid (COOH)	cinnamyl cinnamate (Ph)	95

[a] Reagents and conditions: 1 : 1.2 : 0.1 : 0.1 molar ratios of 1-phenyl-1-propyne : pronucleophile (amine, alcohol, carboxylic acid) : benzoic acid : PS-TPP (5 equiv. to Pd(OAc)), toluene, 110 °C, 6–18 h.

reaction conditions offered similar yields for aryl triflates (91–98%), microwave-induced cyanation required much shorter times (2–3 minutes) for the completion of reaction whereas thermal conditions needed 1.5–3 hours. On the other hand, aryl halides required relatively longer microwave heating (30–50 min) time for complete reaction. It is noted that complete conversion of the triflate to the corresponding nitrile product was possible with as little as 3 mol% of PS-TPP catalyst and 1 equivalent of $Zn(CN)_2$. This is noteworthy since similar transformations require much higher loading of both catalyst and cyanation reagent. By comparison, aryl halides required 7 mol% of PS-TPP catalyst.

7.8.4. Allylation of carboxylic acids, alcohols, and amines using PS-TPP–palladium complex. Allyl esters, allyl ethers, and allyl amines are useful functional groups with wide utility in organic synthesis.[156] Bhanage *et al.* reported an effective heterogeneous catalytic methodology for the allylation of various *N*- and *O*-pronucleophiles with 1-phenyl-1-propyne as the allylating agent and PS-TPP–Pd as the heterogeneous catalyst (Table 51).[157,158] Preparation of the PS-TPP–Pd complex involved refluxing a mixture of PS-TPP (5 molar equivalents) as the heterogeneous ligand and $Pd(OAc)_2$ as the catalyst precursor in toluene for 20 min. Various reaction parameters for the allylation reaction such as catalyst loading, time, temperature, solvent, and molar ratio of reagents were investigated and optimized. Highest yields were obtained when the allylating agent (1-phenyl-1-propyne), the pronucleophile (amine, alcohol, carboxylic acid), benzoic acid, and Pd(OAc)/PS-TPP were used in a 1 : 1.2 : 10 mol% : 10 mol% and refluxed for 6–18 h in toluene. As shown in Table 51, the allylation protocol was successful with various *N*- and *O*-pronucleophiles. Interestingly, carboxylic acids (entries 6–8) were more effective as substrates for the allylation reaction than alcohols (entries 4 and 5). Weaker *N*-pronucleophiles such as those containing electron deficient anilines (entries 1 and 2) or are sterically hindered (entry 3) were well tolerated giving the desired allyl amines in good to high yields.

8. Conclusion

Solid-phase synthesis continues to evolve as it offers important features such as removal of the product by filtration of the solid resin, easy handling, reduced side reactions, and recyclability of the solid matrix for repeated use. Although Ph_3P is ranked as one of the worst atom-economic reagents known, polymer-supported triphenylphosphine has found many applications. This is because the commonly encountered problems in solution-phase chemistry involving Ph_3P such as removal of excess Ph_3P, Ph_3P-complexes, and the by-product Ph_3PO can be easily avoided with PS-TPP. Moreover, the byproduct PS-TPPO can be reduced to PS-TPP by treatment with trichlorosilane. In the past few decades since its first preparation in 1971, PS-TPP (**1**) has demonstrated wide applicability and its many proven applications have been well documented. Surprisingly, no comprehensive review has been dedicated to the versatile reagent as it has been often briefly mentioned in reviews of wider scope. The reagent has since been successfully used in the

Mitsunobu reactions, the Staudinger reaction, and for the preparation of PS-TPP–halophosphorane complexes, Wittig reagents, and as a ligand for palladium, cobalt, ruthenium, gold, and rhodium complexes. The heavy metal catalysts proved more air stable and were utilized in transfer hydrogenation and hydrocarbon oxidation reactions, Pauson–Khand-, Nicholas-, and Heck reactions. Others have also used it for the mono-olefination of symmetrical dialdehydes, preparation of vinyl ethers, thioethers, isocyanates, dipeptides, acid chlorides, alkyl halides, amides, amines, dibromoalkenes, halohydrins, and esters. Furthermore, formylation of primary and secondary alcohols, as well as acetalization of carbonyl compounds has been demonstrated. The reagent has also been useful in the synthesis of heterocycles such as 2-phenylbenzothiazoles, 3-aminoindole-2-carbonitriles, 1,3,4-thiadiazole-2,5-dicarbonitrile, thiazole-2,4,5-tricarbonitrile, 1,2,4-oxadiazoles, vinylthio-, vinylsulfinyl-, vinylsulfonyl- and vinylketo-benzofuroxans and benzofurazans, and β-lactams. The reagent also has proven valuable for the reduction of steroidal ozonides, isomerization of *E/Z* mixtures of nitro olefins, and has been used occasionally as a linker for solid phase synthesis. Finally, the reagent was elegantly applied in the total synthesis of a small library of palmarumycin CP_1 analogs and the total synthesis of epothilone A. PS-TPP demonstrated high success in a wide range of reaction types and rendered the purification process much more facile because the liberated phosphine oxide byproduct remains attached to the resin. Based on its past performance, it is likely that the reagent will make its debut in yet to be seen novel transformations.

Conflicts of interest

There are no conflict of interest to declare.

Acknowledgements

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