ARTICLE

OBC
www.rsc.org/obc

Novel polymer-supported coupling/dehydrating reagents for use in organic synthesis †

Kathryn E. Fairfull-Smith (née Elson),[a] Ian D. Jenkins*[b] and Wendy A. Loughlin[a]
[a] *School of Science, Griffith University, Nathan, Brisbane, QLD, 4111, Australia*
[b] *Natural Product Discovery, Griffith University, Nathan, Brisbane, QLD, 4111, Australia. E-mail: I.Jenkins@griffith.edu.au*

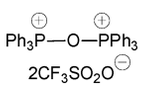
Received 5th May 2004, Accepted 1st June 2004
First published as an Advance Article on the web 29th June 2004

Two novel dehydrating reagents **3** and **4**, based on a phosphonium anhydride and an oxyphosphonium triflate respectively, were prepared by reaction of the corresponding polymer-supported phosphine oxides with triflic anhydride. Reagent **3**, based on the novel phosphorus heterocycle 1,1,3,3-tetraphenyl-2-oxa-1,3-diphospholanium bis(trifluoromethanesulfonate), was found to be a useful reagent for ester and amide formation. A wide range ofcoupling/dehydration-type reactions, such as ester, amide, anhydride, peptide, ether and nitrile formation, were performed in high yield using the more readily prepared polymer-supported triphenylphosphine ditriflate **4**, which was easily recovered and re-used several times without loss of efficiency. With primary alcohols, both reagents **3** and **4** provide an alternative to the Mitsunobu reaction, where the use of azodicarboxylates and chromatography to remove the phosphine oxide by-product can be avoided. The use of 4-dimethylaminopyridine allowed the esterification of secondary alcohols with **4** to proceed in high yield but with retention of configuration.

Introduction

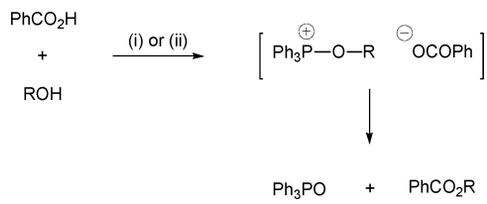
The Mitsunobu reaction[1–4] has found widespread use in synthetic organic chemistry, particularly for the inversion of configuration of an alcohol. The reaction proceeds under mild, essentially neutral conditions and has been well documented for a variety of substrates. However, it does generate both phosphine oxide and dialkyl hydrazinedicarboxylate by-products, which usually require separation by chromatography in order to isolate the desired product. Another drawback with large-scale applications is the explosive nature and/or cost of most azodicarboxylate reagents.[5]

In the search for an alternative protocol for the Mitsunobu reaction which would simplify the purification procedure and avoid the use of azodicarboxylates, we considered the Hendrickson 'POP' reagent **1**.[6,7]This reagent, triphenylphosphonium anhydride trifluoromethanesulfonate **1**, brings about dehydrations in a similar manner to the Mitsunobu reaction through what appears to be the same intermediate (an alkoxyphosphonium salt) (Scheme 1).



1

Our initial work on reagent **1** revealed that although it gave excellent results in a wide range of dehydration-type reactions and S_N2 displacements on primary alcohols, it gave mainly elimination rather than the expected S_N2 substitution when reacted with secondary alcohols.[8] Surprisingly, both the Hendrickson and Mitsunobu reactions proceed through the same alkoxyphosphonium ion intermediate as judged by ^{31}P NMR. We have demonstrated that when **1** is used as a reagent, the presence of trialkylammonium triflate salts favours elimination over substitution.[8]



Scheme 1

One disadvantage with using the Hendrickson reagent **1** is that *two* moles of triphenylphosphine oxide are liberated per dehydration reaction compared with only one mole in the Mitsunobu reaction. This exacerbates the problem of separation of the product by chromatography. Our approach to solving this problem was to prepare a polymer-supported version of **1** in which the two phosphine oxide moieties were tethered, such that after reaction, both would remain attached to the polymer support. The advantages of such a reagent are considerable: (a) removal of the phosphine oxide is achieved simply by filtration of the polymer beads; (b) the recovered phosphine oxide can be readily converted back into the phosphonium anhydride by treatment with triflic anhydride; (c) azodicarboxylates are not required; (d) competing Mitsunobu-type side reactions such as alkylation of the hydrazine dicarboxylate are eliminated. Thus, we pursued a series of five-, six- and seven-membered cyclic analogues of **1** as possible Mitsunobu alternatives[9] and from this work, the five-membered cyclic compound, 1,1,3,3-tetraphenyl-2-oxa-1,3-diphospholanium bis(trifluoromethanesulfonate) **2**, was identified as a potential candidate for polymer attachment.

2

Herein we report the synthesis and use in ester and amide formation of the polymer-supported five-membered cyclic 'POP' derivative **3**. In addition, we describe the synthesis and

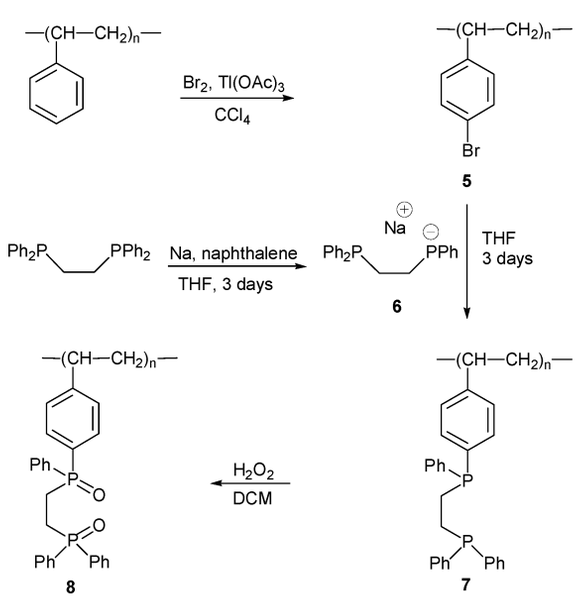
† Electronic supplementary information (ESI) available: (1) gel-phase ^{31}P NMR spectrum of polymer-supported 1,2-bis(diphenylphosphinyl)-ethane **8**; (2) gel-phase ^{31}P and ^{19}F NMR spectra of polymer-supported 1,1,3,3-tetraphenyl-2-oxa-1,3-phospholanium bis(trifluoromethanesulfonate) **3**; (3) stacked gel-phase ^{31}P spectra of polymer-supported triphenylphosphine oxide with (a) 0 equiv. triflic anhydride, (b) 0.5 equiv. triflic anhydride, (c) 1.0 equiv. triflic anhydride; (4) gel-phase ^{19}F NMR spectra of polymer-supported triphenylphosphine ditriflate **4**; (5) ^{1}H and ^{13}C NMR spectra of *N*-benzyl-*N*-(4-nitrobenzoyl)-4-nitrobenzamide. See http://www.rsc.org/suppdata/ob/b4/b406770c/

DOI: 10.1039/b406770c

use of the more readily prepared polymer-supported triphenylphosphine ditriflate **4** in a variety of dehydration-type transformations. A preliminary account of some of our results with the latter reagent has appeared.[10] We also re-visit the solution-phase Hendrickson reagent **1** and report a method for the formation of esters (with retention of configuration) from secondary alcohols.

Results and discussion

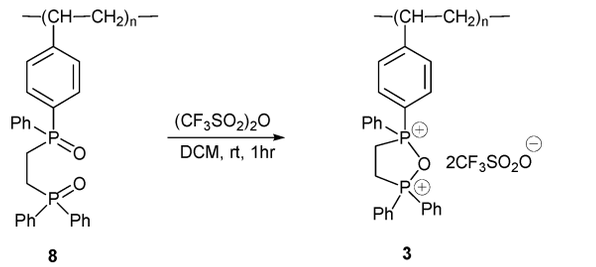
Initially, we sought to attach 1,2-bis(diphenylphosphino)ethane to a brominated poly(styrene-co-divinylbenzene) resin such that upon oxidation and subsequent treatment with triflic anhydride, the polymer-supported reagent **3** could be obtained. Brominated poly(styrene-co-divinylbenzene) resin **5** was prepared by treatment of a solution of poly(styrene-co-divinylbenzene) resin and thallium(III) acetate in carbon tetrachloride with bromine (Scheme 2) according to the procedure of Farrall and Fréchet.[11] The incorporation of bromine was found to be 3.53 mmol g^{-1} (28.21%) by elemental analysis. Treatment of 1,2-bis(diphenylphosphino)ethane with a solution of the radical anion of naphthalene (preformed *in situ* from a mixture of naphthalene and sodium in tetrahydrofuran [THF]),[12] formed the corresponding phosphinyl species **6**. The reaction of **6** with a slurry of the brominated poly(styrene-co-divinylbenzene) resin **5** afforded polymer-supported 1,2-bis(diphenylphosphino)ethane **7**. Subsequent oxidation with hydrogen peroxide gave the desired polymer-supported reagent **8** (Scheme 2) and the incorporation of phosphorus was found to be 1.9 mmol g^{-1} (5.89%) by elemental analysis. Gel-phase ^{31}P NMR analysis of the polymer-supported reagent **8** also confirmed the presence of the phosphine oxide (δ 33.3 ppm).



Scheme 2

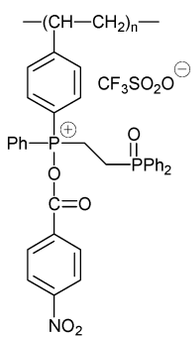
Addition of triflic anhydride to a dichloromethane (DCM) slurry of **8** generated the polymer-supported reagent **3** (Scheme 3). This was confirmed by gel-phase ^{31}P NMR, where a shift from the bis-phosphine oxide (δ 33.3 ppm) to the cyclic 'POP' species **3** was observed (δ 57.0 ppm). These results are consistent with the ^{31}P NMR data obtained for the non-polymeric five-membered cyclic 'POP' species **2** (δ 58.6 ppm).[9]

The use of the polymer-supported reagent **3** was examined for the esterification of a primary alcohol and the formation of an amide from a primary amine. Consecutive addition of 4-nitrobenzyl alcohol, 4-nitrobenzoic acid and diisopropylethylamine to a stirred solution of **3** in DCM generated 4-nitrobenzyl 4-nitrobenzoate in high yield (96%) after stirring for 2 h at room temperature. The product was obtained cleanly



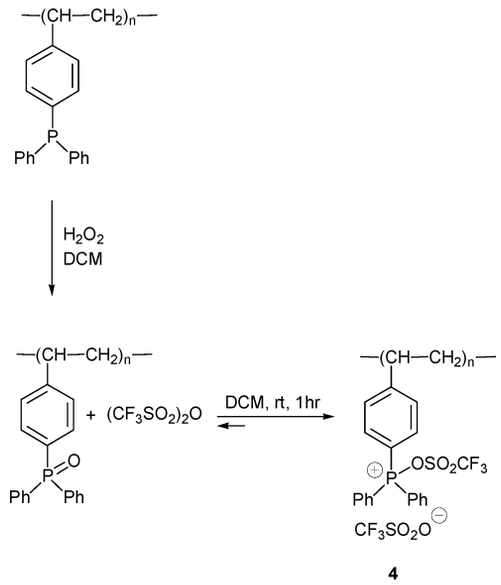
Scheme 3

after filtration and a sodium hydrogen carbonate wash of the filtrate to remove the diisopropylethylammonium triflate. Similarly, *N*-benzyl 4-nitrobenzamide was formed in good yield (93%) by treatment of **3** with 4-nitrobenzoic acid, followed by addition of benzylamine and diisopropylethylamine and stirring for 2 h at room temperature. It was necessary in this case to preform the activated species **9** (by addition of 4-nitrobenzoic acid to **3** in DCM and stirring for 2 h at room temperature) before addition of the benzylamine to avoid the formation of the (unreactive) polymer-supported benzylaminophosphonium triflate **10**.[9] Thus, the polymer-supported cyclic 'POP' species **3** is a useful reagent for the formation of esters from primary alcohols and amides from primary amines, as it does not require chromotography for product purification and avoids the use of azodicarboxylates.



9

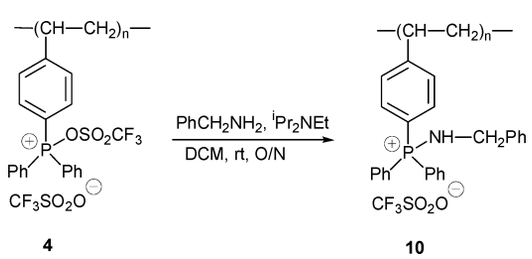
The use of **3** was not explored further because during the course of this work, a reagent formed from the reaction of polymer-supported triphenylphosphine oxide and triflic anhydride was shown to work just as well and was easier to prepare. This reagent, polymer-supported triphenylphosphine ditriflate **4**, facilitates dehydrations in the same manner as polymer-supported cyclic 'POP' species **3**, and is formed from commercially available polymer-supported triphenylphosphine (polystyrene crossed-linked with 2% divinylbenzene). Polymer-supported triphenylphosphine ditriflate **4** was easily prepared by treatment of a swelled solution of polymer-supported triphenylphosphine oxide (formed by oxidation of the corresponding phosphine with excess hydrogen peroxide) in DCM with triflic anhydride (Scheme 4). Characterisation of **4** proved difficult due to its extreme sensitivity to moisture. Addition of one equivalent of triflic anhydride to an NMR tube of swollen polymer-supported triphenylphosphine oxide in CD_2Cl_2 under nitrogen showed a downfield shift in the gel-phase ^{31}P NMR signal from δ 27.9 ppm to δ 53.3 ppm. Addition of only 0.5 equivalents of triflic anhydride generated a ^{31}P NMR signal at δ 42.7 ppm. This is most readily explained by a rapid equilibrium (on the ^{31}P NMR timescale) between the phosphine oxide moiety, triflic anhydride and the phosphine ditriflate **4**, with the equilibrium lying very much towards the ditriflate **4** (Scheme 4). Analysis of **4** by gel-phase ^{19}F NMR revealed a broad singlet at δ −80.1 ppm, which is further upfield and significantly broader than that observed for triflic anhydride (δ −73.6 ppm) or triflic acid (δ −78.3 ppm) in the presence of poly(styrene-co-divinylbenzene). Treatment of a slurry of



Scheme 4

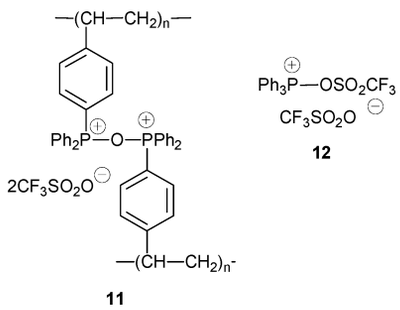
polymer-supported triphenylphosphine oxide in CD_2Cl_2 with triflic acid gave the protonated phosphine oxide with similar ^{31}P NMR (δ 52.1 ppm) and ^{19}F NMR (δ −80.3 ppm) shifts to **4**. However, an attempt to form 4-toluic anhydride from its corresponding acid in the presence of the polymer-supported protonated phosphine oxide and diisopropylethylamine yielded unreacted acid, thus confirming that the structure of **4** was not simply a protonated phosphine oxide. By comparison, tetrabutylammonium triflate has a ^{19}F NMR shift at δ − 80.6 ppm. A time-averaged ^{19}F NMR shift of δ −80.3 ppm, which is between that of triflic acid (δ −78.3 ppm) and free triflate ion (δ −80.6 ppm), does not seem unreasonable for structure **4**. Equilibration of the fluorines could be achieved *via* the rapid equilibrium shown in Scheme 4, or *via* a (transient) symmetrical phosphorane intermediate in equilibrium with **4**.

The species **4** was also characterised as its more stable benzylaminophosphonium triflate **10**, following reaction with benzylamine in the presence of diisopropylethylamine (Scheme 5). Two peaks were observed by gel-phase ^{31}P NMR at δ 39.8 ppm (compound **10**) and δ 30.0 ppm (polymer-supported triphenylphosphine oxide) in a ratio of 9 : 1. The non-polymeric benzylaminotriphenylphosphonium triflate had a ^{31}P NMR signal at δ 39.4 ppm.[9] The 9 : 1 ratio may be due to reaction with adventitious water during the addition of the benzylamine, however, it is also consistent with the equilibrium shown in Scheme 4 (*i.e.*, 1 : 9 ratio of the phosphine oxide to the ditriflate **4**).



Scheme 5

These characterisation methods all reveal the structure of the reagent to most likely be polymer-supported triphenylphosphine ditriflate **4**. If two polymer chains were to join together to form the 'POP' bond linkage (as illustrated by **11**), one would expect a gel-phase ^{31}P NMR signal closer to that of the solution-phase Hendrickson reagent **1** (δ 75.6 ppm).[13] Moreover, the formation of the polymer-supported aminophosphonium triflate would show a 1 : 1 ratio of the oxide to the aminophosphonium triflate **10**, which was not observed. It is interesting to note in this regard, that the original structure proposed by Hendrickson[14] for **1** was 'triphenylphosphine ditriflate' **12**, *i.e.* a structure analogous to **4**. It was only later that a Norwegian group[15] showed that this structure was incorrect and that the product formed upon treatment of triphenylphosphine oxide with triflic anhydride is in fact **1** (recently confirmed by X-ray crystallography).[16] The phosphonium ditriflate **12** is almost certainly formed first, but is then rapidly attacked by a second molecule of triphenylphosphine oxide to form the phosphonium anhydride **1**. In the case of polymer-supported triphenylphosphine oxide, once the ditriflate **4** has been formed, unless there is a second phosphine oxide moiety in close proximity on another (or the same) polymer chain (which is highly unlikely), phosphonium anhydride formation cannot occur.



Next, a range of dehydration reactions was carried out using polymer-supported triphenylphosphine ditriflate **4** to demonstrate its versatility. In all cases, a small excess of the polymer-supported phosphine oxide was employed as excess triflic anhydride could react with the alcohol to form the triflate ester, the amide to form a triflamide, or the carboxylic acid to form the corresponding anhydride. Initially, the ester 4-nitrobenzyl 4-nitrobenzoate was formed in high yield (95%) after treatment of **4** with 4-nitrobenzyl alcohol, 4-nitrobenzoic acid and diisopropylethylamine for 2 h at room temperature (Table 1, entry 1). The product was obtained cleanly following filtration and washing of the filtrate with sodium hydrogen carbonate to remove the diisopropylethylammonium triflate. The reagent **4** was very sensitive to moisture as attempts to isolate it by filtration before re-suspension in DCM and subsequent addition of 4-nitrobenzyl alcohol, 4-nitrobenzoic acid and diisopropylethylamine, gave none of the desired ester, 4-nitrobenzyl 4-nitrobenzoate. Thus, **4** appears to be best prepared and used directly *in situ*.

Polymer-supported triphenylphosphine ditriflate **4** is a useful reagent for the formation of amides. In a similar manner to the use of the polymer-supported five-membered cyclic 'POP' **3**, the acyloxyphosphonium salt was preformed by addition of 4-nitrobenzoic acid to **4** in DCM. Subsequent addition of benzylamine and diisopropylethylamine formed *N*-benzyl 4-nitrobenzamide (Table 1, entry 2) in good yield (96%) after 2 h at room temperature. Repeated recycling of the recovered polymer gave reproducible yields in the synthesis of *N*-benzyl 4-nitrobenzamide (recycled three times). *N*-Benzyl-4-methoxybenzamide (entry 3) was obtained in a similar fashion in high yield *via* dehydration with **4**. Interestingly, the use of two equivalents of 4-nitrobenzoic acid with **4**, benzylamine and diisopropylethylamine furnished *N*-benzyl-*N*-(4-nitrobenzoyl)-4-nitrobenzamide (entry 4) in high yield (90%). A large number of the amides prepared by dehydration with **4** (entries 5–11) were obtained in reasonable yields (71–90%), but required longer reaction times (overnight at room temperature) to reach completion. The combination of 4-nitrobenzoic acid and 4-nitroaniline (entry 12) was particularly sluggish, requiring one week at room temperature to reach completion. This is presumably associated with having electron-withdrawing NO_2 groups on

Table 1 Useful synthetic transformations using polymer-supported triphenylphosphine ditriflate **4**

Entry[a,b]	Substrate	Nucleophile	Product	Yield (%) (mp/°C)	Lit. mp/°C
1	$4\text{-}NO_2C_6H_4CH_2OH$	$4\text{-}NO_2C_6H_4COOH$	4-Nitrobenzyl 4-nitrobenzoate	95 (165–167)	168[20]
2	$4\text{-}NO_2C_6H_4COOH$	$C_6H_5CH_2NH_2$	*N*-Benzyl-4-nitrobenzamide	96 (140–143)	141.5–143[21]
3	$4\text{-}MeOC_6H_4COOH$	$C_6H_5CH_2NH_2$	*N*-Benzyl-4-methoxybenzamide	88 (124–126)	127–129[21]
4	$4\text{-}NO_2C_6H_4COOH$[c]	$C_6H_5CH_2NH_2$	*N*-Benzyl-*N*-(4-nitrobenzoyl)-4-nitrobenzamide	90 (165–167)	—
5	$4\text{-}MeOC_6H_4COOH$	$4\text{-}NO_2C_6H_4NH_2$	*N*-(4-Nitrophenyl)-4-methoxybenzamide	83 (178–180)	184–185[22]
6	$4\text{-}NO_2C_6H_4COOH$	$4\text{-}MeOC_6H_4NH_2$	*N*-(4-Methoxyphenyl)-4-nitrobenzamide	72 (193–196)	199–202[23]
7	$4\text{-}MeOC_6H_4COOH$	$4\text{-}MeOC_6H_4NH_2$	*N*-(4-Methoxyphenyl)-4-methoxybenzamide	71 (206–208)	202–203[24]
8	$4\text{-}NO_2C_6H_4COOH$	$C_5H_{10}NH$	*N*-(4-Nitrobenzoyl)-piperidine	84 (114–116)	120[25]
9	$4\text{-}MeOC_6H_4COOH$	$C_5H_{10}NH$	*N*-(4-Methoxybenzoyl)piperidine	90 (oil)	—
10	$4\text{-}NO_2C_6H_4COOH$	$^iPr_2NH$	*N*,*N*-Diisopropyl-4-nitrobenzamide	86 (136–138)	141.5–142[26]
11	$4\text{-}MeOC_6H_4COOH$	$^iPr_2NH$	*N*,*N*-Diisopropyl-4-methoxybenzamide	77 (oil)	—
12	$4\text{-}NO_2C_6H_4COOH$	$4\text{-}NO_2C_6H_4NH_2$	*N*-(4-Nitrophenyl)-4-nitrobenzamide	63 (264–266)	260–263[27]
13	C_6H_5COOH	$C_6H_5SO_2NH_2$[d]	*N*-Benzoylbenzenesulfonamide	71 (145–146)	148–149[28]
14[e,f]	Z–Gly–Phe–OH	H–Val–OMe·HCl	L,L-Z–Gly–Phe–Val–OMe	65 (95–97)	98[17]
15	$C_6H_5C(O)NH_2$	—	Benzonitrile	88 (oil)	—
16	*meso*-$C_6H_5CH(OH)CH(OH)C_6H_5$	—	(*E*)-Stilbene oxide	85 (64–66)	69[29]
17	$C_6H_5CH_2OH$	$C_6H_5CH_2OH$	Dibenzyl ether	73 (oil)	—
18	$4\text{-}NO_2C_6H_4CH_2OH$	$4\text{-}NO_2C_6H_4CH_2OH$	Bis(4-nitrobenzyl) ether	42 (94–96)	97–98[30]
19	$4\text{-}NO_2C_6H_4CH_2OH$	$MeOC_6H_4OH$	O-(4-Nitrobenzyl)-4-methoxyphenol	88 (88–90)	85–87[31]
20	$CH_3C_6H_4COOH$	$CH_3C_6H_4COOH$	4-Toluic anhydride	95 (87–89)	93[7b]
21	$4\text{-}ClC_6H_4CH_2OH$	NaN_3[g]	4-Chlorobenzyl azide	89 (oil)	—
22	$4\text{-}ClC_6H_4CH_2OH$	$CH_3C(O)SH$	4-Chlorobenzyl thioacetate	91 (oil)	—
23[h]	$4\text{-}NO_2C_6H_4COOH$	Cyclohexanol	*O*-(4-Nitrobenzoyl)-cyclohexanol	85 (49–51)	47–48[32]
24[i]	$4\text{-}NO_2C_6H_4COOH$	(−)-Menthol	*O*-(4-Nitrobenzoyl)-(−)-menthol	84 (60–62)	—[j]

[a] Reaction conditions: polymer-supported triphenylphosphine oxide (1.35 equiv.), triflic anhydride (1.0 equiv.), substrate (1.0 equiv.), nucleophile (1.0 equiv.), diisopropylethylamine (3.5 equiv.), DCM (10 mL). [b] Reaction times: entries 1–3 (2 h, rt), entries 4–11, 13–17 and 19–24 (overnight, rt), entries 12 and 18 (1 week, rt). [c] Acid (2.0 equiv.) was used. [d] Prepared according to Vogel (mp 148–149 °C, lit.,[33] 150–152 °C). [e] Anteunis' test for racemisation.[17] [f] 1-Hydroxybenzotriazole (HOBT) (1.0 equiv.) and excess diisopropylethylamine (5.5 equiv.) were used. [g] Added as a suspension in dimethylformamide (1 mL). [h] DMAP (1.0 equiv.) was used. [i] 4-Nitrobenzoic acid (1.2 equiv.) and DMAP (1.2 equiv.) were used. [j] ^{1}H NMR data in agreement with the literature.[18]

both reactants, though it is not clear why this should inhibit the reaction.

Acylation of sulfonamides was readily achieved: *N*-benzoylbenzenesulfonamide (entry 13) was formed by the coupling of benzoic acid and benzenesulfonamide with **4**.

The use of **4** for peptide bond formation also was investigated. The extent of racemization was examined using Arteunis' test[17] (the coupling of Z–Gly–Phe–OH and Val–OMe·HCl). Initially, the reaction was carried out in the standard manner by consecutive addition of Val–OMe·HCl and diisopropylethylamine to a slurry of the activated acid (preformed by stirring Z-Gly-Phe-OH and **4** at room temperature in DCM for 2 h), however the Z protecting group was not stable under these reaction conditions. Thus, the order of addition was altered and the activated acid generated in the presence of base (diisopropylethylamine). Addition of Val–OMe·HCl formed the desired tripeptide Z–Gly–Phe–Val–OMe after stirring at room temperature overnight, yet a 1 : 1 mixture of epimers was detected by ^{1}H NMR, with characteristic peaks of the L,L-epimer (δ 0.74, 2 × d, $(CH_3)_2CH$ and δ 3.65, s, CH_3O) and D,L-epimer (δ 0.82 + 0.85, 2 × d, $(CH_3)_2CH$ and δ 3.64, s, CH_3O) consistent with those in the literature.[17] However, the use of racemization-suppressing agent 1-hydroxybenzotriazole (HOBT) did allow Z–Gly–Phe–Val–OMe (entry 14) to be synthesised cleanly from **4** as a single epimer (L,L) (none of the D,L-epimer was observed by ^{1}H NMR) in reasonable (65%) yield.

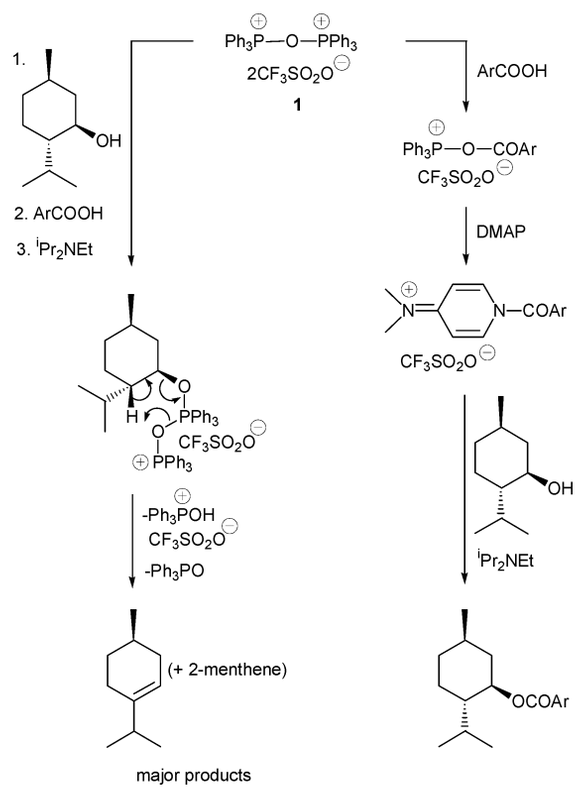
Dehydration of benzamide to benzonitrile (entry 15) was achieved by refluxing with **4** and diisopropylethylamine in DCM overnight. Similarly, the epoxide (*E*)-stilbene oxide (entry 16) was obtained in good yield (85%) by dehydration of *meso*-hydrobenzoin with **4** and diisopropylethylamine at room temperature overnight. Unlike the Mitsunobu reaction, the reagent **4** can be used to convert (primary) alcohols into acyclic ethers. For example, addition of two equivalents of benzyl alcohol to **4** and diisopropylethylamine generated the symmetrical ether, dibenzyl ether (entry 17), in reasonable yield (73%) after stirring at room temperature overnight in DCM. The formation of bis(4-nitrobenzyl)ether (entry 18) from 4-nitrobenzyl alcohol and **4**, occurred in 42% yield after stirring for one week at room temperature. The presence of electron withdrawing NO_2 groups on both reactants may again be the reason for the slow reaction observed. As expected, alkyl aryl ethers are readily formed. Thus, coupling of 4-nitrobenzyl alcohol and 4-methoxyphenol, yielded *O*-(4-nitrobenzyl)-4-methoxyphenol (entry 19) in high yield (88%).

Dehydration of carboxylic acids to give anhydrides was readily achieved. For example, 4-toluic anhydride (entry 20) was formed in good yield (95%), following the reaction of 2 equivalents of 4-toluic acid with **4** and diisopropylethylamine in DCM.

Alcohols do not react with sodium azide under Mitsunobu conditions.[8] By contrast, consecutive addition of sodium azide (as a suspension in dimethylformamide) and diisopropylethylamine to a slurry of **4** and 4-chlorobenzyl alcohol in DCM generated 4-chlorobenzyl azide (entry 21) after stirring at room temperature overnight. 4-Chlorobenzyl thioacetate (entry 22) was obtained by treatment of a mixture of **4** and 4-chlorobenzyl alcohol in DCM with thioacetic acid and diisopropylethylamine.

The use of polymer-supported triphenylphosphine ditriflate **4** for esterification of secondary alcohols was also examined. Previous work from this laboratory[8] has shown that secondary alcohols undergo competitive *syn* elimination rather than S_N2 substitution in the presence of the Hendrickson reagent **1**, a nucleophile and base. This unexpected result was due to the presence of trialkylammonium triflate salts, which are not present in Mitsunobu S_N2-type esterifications. Accordingly, when a solution of **4** was refluxed overnight with (−)-menthol, 4-nitrobenzoic acid and diisopropylethylamine, the presence of 2- and 3-menthenes, (−)-menthol and neomenthyl 4-nitrobenzoate (ratio 79 : 16 : 5) were identified following GC/MS analysis.

In order to avoid competing elimination, the order of addition was changed and the activating agent 4-dimethylaminopyridine (DMAP) was employed. The new reaction conditions were initially trialled on the solution-phase Hendrickson reagent **1**. Addition of 4-nitrobenzoic acid to a solution of **1** in DCM formed the corresponding acyloxyphosphonium salt. Subsequent treatment with DMAP gave the activated ester, which underwent nucleophilic displacement after the addition of cyclohexanol and diisopropylethylamine. *O*-(4-Nitrobenzoyl)-cyclohexanol was obtained after stirring at room temperature for 15 min in 96% yield, following chromatography to remove the phosphine oxide. In a similar fashion, O-(4-nitrobenzoyl)-(−)-menthol was obtained in good yield (92%) after stirring (−)-menthol with **1**, 4-nitrobenzoic acid and DMAP in DCM overnight. A significantly faster reaction was observed when a slight excess (1.2 equiv.) of both 4-nitrobenzoic acid and DMAP were employed (with 1.0 equiv. of both 4-nitrobenzoic acid and DMAP, 38% unreacted (−)-menthol remained after stirring at room temperature overnight). It should be noted that retention of configuration was observed with the use of an optically active alcohol (the ^{1}H NMR shift of H1 of *O*-(4-nitrobenzoyl)-(−)-menthol at δ 4.98 ppm was in agreement with the literature).[18] Importantly, very little (<5%) or no elimination was observed (by GC/MS or ^{1}H NMR spectroscopy) in both cases as the change in order of addition and use of DMAP precluded the formation of the mixed phosphorane/phosphonium salt of the alcohol, an intermediate required for elimination (Scheme 6).



Scheme 6

In a similar fashion, the use of **4** for esterification of secondary alcohols was examined. The activated ester of 4-nitrobenzoic acid was generated by addition of DMAP to the polymer-supported acyloxyphosphonium salt (preformed by addition of 4-nitrobenzoic acid to **4** in DCM). Subsequent treatment with cyclohexanol and diisopropylethylamine gave *O*-(4-nitrobenzoyl)cyclohexanol in good yield (85%) after stirring at room temperature overnight (Table 1, entry 23). The product was obtained cleanly after a sodium hydrogen carbonate wash to remove the DMAP and diisopropylethylammonium ditriflate by-products. The use of a catalytic amount of DMAP (0.1 equiv.) gave predominately cyclohexene (68%) by GC/MS analysis, implying competitive attack on **4** by cyclohexanol and thus indicating that at least one equivalent of DMAP is required to prevent elimination. After stirring (−)-menthol with the activated ester of 4-nitrobenzoic acid (preformed from **4**, 4-nitrobenzoic acid and DMAP) in DCM overnight, *O*-(4-nitrobenzoyl)-(−)-menthol was also obtained in good yield (84%) (entry 24). Again, retention of configuration was observed.

Conclusion

Polymer-supported 1,2-bis(diphenylphosphinyl)ethane **8** was synthesised from brominated poly(styrene-co-divinylbenzene) in two steps. The reaction of **8** with triflic anhydride yielded the polymer-supported cyclic 'POP' species **3**, a useful reagent for the synthesis of esters and amides. Another novel dehydrating reagent, polymer-supported triphenylphosphine ditriflate **4**, was more conveniently synthesised from the oxidised form of commercially available polymer-supported triphenylphosphine with triflic anhydride. The versatility of **4** as a general dehydrating-type reagent was demonstrated by the synthesis of a range of simple amides, esters (from primary and secondary alcohols), and ethers, a tripeptide, a nitrile, an epoxide, an anhydride, an azide and a thioacetate. In the presence of DMAP, secondary alcohols were esterified successfully with retention of configuration, however the order of addition of reagents was important. The beauty of both the polymer-supported triphenylphosphine ditriflate **4** and the polymer-supported cyclic 'POP' species **3** lies in the fact that the main by-product, the phosphine oxide, remains attached to the polymer-support. All products can be cleanly obtained following filtration of the polymer beads and a sodium hydrogen carbonate wash of the filtrate to remove the diisopropylethylammonium triflate. An additional advantage of these polymeric reagents **3** and **4** is that after reaction, the polymer is again obtained as its oxide, ready for recycling. The re-use of **4** several times showed no loss of activity. Thus, **3** and **4** are effective dehydrating reagents which avoid the use of azodicarboxylates and chromatography to remove the phosphine oxide.

Experimental

General methods

General experimental procedures are described elsewhere.[8] In order to remove surface impurities, all resins were washed[11] before use by stirring for 40 min with each of the following solutions: 1 M NaOH 60 °C, 1 M HCl 60 °C, 1 M NaOH 60 °C, 1 M HCl 60 °C, H_2O 25 °C, DMF 40 °C, 1 M HCl 60 °C, H_2O 60 °C, MeOH 25 °C, DCM–MeOH (2 : 3) 25 °C, DCM–MeOH (3 : 1) 25 °C, DCM–MeOH (9 : 1) 25 °C, DCM 25 °C. The resin beads were then dried at 125 °C for 48 h at 100 mmHg (house vacuum) on a Kugelrohr apparatus. ^{19}F NMR spectra were recorded at 376 MHz, using an external reference of hexafluorobenzene in CD_2Cl_2 (δ −164.9 ppm).

Bromination of poly(styrene-co-divinylbenzene)

Brominated poly(styrene-co-divinylbenzene) was prepared from poly(styrene-co-divinylbenzene) (10 g, 0.096 mol) using thallium(III) acetate (0.6 g, 1.6 mmol) and bromine (6.72 g, 2.16 mL, 0.042 mol) as reported by Farrall and Fréchet.[11] Elemental analysis found 28.21% Br, corresponding to 3.53 mmol Br/g resin (51% of phenyl rings brominated).

Synthesis of polymer-supported 1,2-bis(diphenylphosphino)-ethane 7

Diphenyl[2-(phenylphosphino)ethyl]phosphine, sodium salt **6** was prepared from sodium (3.33 g, 0.145 mol), naphthalene

(15.5 g, 0.12 mol) and 1,2-bis(diphenylphosphino)ethane (1.7 g, 0.043 mol) according to Chou *et al.*[12] Attachment of **6** to the poly(styrene-co-divinylbenzene) resin was performed *via* the method of Pitman and Hirao[19] using brominated poly(styrene-co-divinylbenzene) resin **5** (4 g, 0.014 mol) to yield polymer-supported 1,2-bis(diphenylphosphino)ethane **7** as brown coloured beads. δ_P (162 MHz, $CDCl_3$, gel-phase) −12.3 (br s).

Synthesis of polymer-supported 1,2-bis(diphenylphosphinyl)-ethane 8 from polymer-supported 1,2-bis(diphenylphosphino)-ethane 7

Polymer-supported 1,2-bis(diphenylphosphino)ethane (2 g) was placed in DCM (25 mL) and hydrogen peroxide (15 mL, 30% wt solution in water) added. The slurry was left to stir overnight at room temperature and the resulting beads collected by filtration and washed with DCM (60 mL). The beads were dried at 125 °C at 10 mmHg for 48 h. Polymer-supported 1,2-bis(diphenylphosphinyl)ethane **8** was obtained as light yellow beads. Elemental analysis for P found 5.88%, corresponding to 1.9 mmol P/g resin (30% of phenyl rings contain a bound $P(O)(C_6H_5)CH_2CH_2P(O)(C_6H_5)_2$). ν_{max} (KBr)/cm^{-1} 1180 (P=O). δ_P (162 MHz, $CDCl_3$, gel-phase) 33.3 (br s).

Synthesis of polymer-supported 1,1,3,3-tetraphenyl-2-oxa-1,3-phospholanium bis(trifluoromethanesulfonate) 3

Polymer-supported 1,2-bis(diphenylphosphinyl)ethane **8** (0.1 g, 0.19 mmol, 1.9 mmol g^{-1}) was swollen in CD_2Cl_2 (0.75 mL) in a 5 mm NMR tube under nitrogen. Triflic anhydride (16.5 μL, 0.095 mmol) was added and the slurry mixed thoroughly by vortex to give polymer-supported 1,1,3,3-tetraphenyl-2-oxa-1,3-phospholanium bis(trifluoromethanesulfonate) **3**. δ_P (162 MHz, CD_2Cl_2, gel-phase) 57.0 (br s).

Synthesis of 4-nitrobenzyl 4-nitrobenzoate using polymer-supported 1,1,3,3-tetraphenyl-2-oxa-1,3-phospholanium bis(trifluoromethanesulfonate) 3

Polymer-supported 1,2-bis(diphenylphosphinyl)ethane **8** (0.8 g, 1.52 mmol, 1.9 mmol/g) was stirred gently in DCM (15 mL) for 30 min under nitrogen. Triflic anhydride (0.13 mL, 0.75 mmol) was then added and the slurry stirred for 1 h at room temperature. Subsequent treatment with 4-nitrobenzyl alcohol (0.12 g, 0.75 mmol), 4-nitrobenzoic acid (0.13 g, 0.75 mmol) and diisopropylethylamine (0.36 mL, 2 mmol) formed a yellow slurry which was left to stir for 2 h at room temperature. The polymer beads were removed by filtration, washed with DCM (50 mL) and the filtrate washed with sodium hydrogen carbonate (3 × 30 mL, saturated aqueous solution). The organic phase was concentrated *in vacuo* and dried under high vacuum to yield 4-nitrobenzyl 4-nitrobenzoate as a yellow solid (0.22 g, 96%). Mp 165–167 °C, (lit.,[20] 168 °C).

Synthesis of *N*-benzyl 4-nitrobenzamide using polymer-supported 1,1,3,3-tetraphenyl-2-oxa-1,3-phospholanium bis(trifluoromethanesulfonate) 3

A slurry of **3** was prepared as detailed above from polymer-supported 1,2-bis(diphenylphodphinyl)ethane **8** (0.4 g, 0.76 mmol, 1.9 mmol g^{-1}) and triflic anhydride (65 μL, 0.38 mmol). 4-Nitrobenzoic acid (0.13 g, 0.75 mmol) was added and the mixture stirred for 2 h at room temperature. Addition of benzylamine (63 μL, 0.75 mmol) and diisopropylethylamine (0.36 mL, 2 mmol) generated a yellow slurry which was allowed to stir at room temperature for 2 h. The polymer beads were removed by filtration, washed with DCM (50 mL) and the filtrate washed with sodium hydrogen carbonate (3 × 30 mL, 5% aqueous solution). The organic phase was concentrated *in vacuo* and dried under high vacuum to yield *N*-benzyl 4-nitrobenzamide as a light yellow solid (0.18 g, 93%). Mp 138–140 °C, (lit.,[21] 141.5–143 °C).

Oxidation of polymer-supported triphenylphosphine

Polymer supported triphenylphosphine (polystyrene polymer cross-linked with 2% divinylbenzene, 3 mmol g^{-1}) (2 g, 9 mmol) was placed in DCM (50 mL). Hydrogen peroxide (20 mL, 30% wt solution in water) was added and the slurry left to stir overnight at room temperature. The resulting yellow beads were collected by filtration, washed with DCM (60 mL) and dried under high vacuum. δ_P (162 MHz, $CDCl_3$, gel-phase) 30.0 (br s).

Synthesis of polymer-supported triphenylphosphine ditriflate 4 (polymer-supported trifluoromethanesulfonyloxy triphenyl-phosphonium trifluoromethanesulfonate)

In a 5 mm NMR tube, a gel-phase sample of polymer-supported triphenylphosphine oxide (0.075 g, 0.23 mmol, 3 mmol g^{-1}) was prepared in CD_2Cl_2 (0.75 mL) under nitrogen. Triflic anhydride (19.5 μL, 0.11 mmol) was added and the slurry mixed by vortex. A ^{31}P NMR spectrum was recorded. The addition of triflic anhydride (19.5 μL, 0.11 mmol) was repeated and following mixing, ^{31}P and ^{19}F NMR spectra recorded. With 0.5 equiv. triflic anhydride: δ_P (162 MHz, CD_2Cl_2, gel-phase) 42.7 (br s); with 1.0 equiv. triflic anhydride: δ_P (162 MHz, CD_2Cl_2, gel-phase) 53.3 (br s), δ_F (376 MHz, CD_2Cl_2, gel-phase) −80.1 (br s).

Synthesis of polymer-supported benzylaminotriphenylphos-phonium trifluoromethanesulfonate 10

Polymer-supported triphenylphosphine oxide (0.3 g, 0.9 mmol, 3 mmol/g) was swollen in DCM (10 mL) under nitrogen. Triflic anhydride (0.17 mL, 1 mmol) was added and the slurry stirred for 1 h at room temperature. Following treatment with benzylamine (0.13 mL, 1.2 mmol) and diisopropylethylamine (0.4 mL, 2.3 mmol), the mixture was allowed to stir at room temperature overnight. The beads were then collected by filtration, washed with DCM (60 mL) and dried under high vacuum. The resulting dark brown beads were shown to contain a mixture of polymer-supported benzylaminotriphenylphosphonium trifluoromethanesulfonate **10** and polymer-supported triphenylphosphine oxide in a 9 : 1 ratio by ^{31}P NMR. δ_P (162 MHz, $CDCl_3$, gel-phase) 30.0 (br s), 39.9 (br s), ratio 1 : 9.

Representative example for the use of polymer-supported triphenylphosphine ditriflate 4 for amide formation: synthesis of *N*-benzyl-4-nitrobenzamide

Polymer-supported triphenylphosphine oxide (0.3 g, 0.9 mmol, 3 mmol g^{-1}) was stirred gently in dry DCM (10 mL) for 30 min under nitrogen. Addition of triflic anhydride (0.12 mL, 0.66 mmol) generated a dark brown slurry which was left to stir for 1 h. 4-Nitrobenzoic acid (0.11 g, 0.66 mmol) was then added and the solution stirred at room temperature for 2 h. Consecutive addition of benzylamine (72 μL, 0.66 mmol) and diisopropylethylamine (0.4 mL, 2.3 mmol) produced a light brown slurry which was stirred at room temperature for 2 h. The polymer beads were collected on a filter and washed with DCM (60 mL). The yellow filtrate was washed with sodium hydrogen carbonate (3 × 50 mL, 5% aqueous solution) and the combined DCM layers concentrated *in vacuo*. The resulting yellow oil was dried under high vacuum to yield *N*-benzyl-4-nitrobenzamide as a light yellow solid (0.16 g, 96%). Mp 140–143 °C, (lit.,[21] 141.5–143 °C).

Formation of *N*-benzyl-*N*-(4-nitrobenzoyl)-4-nitrobenzamide using polymer-supported triphenylphosphine ditriflate 4

Polymer-supported triphenylphosphine ditriflate **4** was prepared as above from polymer-supported triphenylphosphine oxide (0.3 g, 0.9 mmol, 3 mmol g^{-1}) and triflic anhydride (0.12 mL, 0.72 mmol). 4-Nitrobenzoic acid (0.11 g, 0.66 mmol)

was then added and the solution stirred at room temperature for 2 h. Consecutive addition of benzylamine (36 μL, 0.33 mmol) and diisopropylethylamine (0.4 mL, 2.26 mmol) produced a light brown slurry which was stirred at room temperature overnight. The polymer beads were collected on a filter and washed with DCM (60 mL). The yellow filtrate was washed with sodium hydrogen carbonate (3 × 50 mL, 5% aqueous solution) and the combined DCM layers concentrated *in vacuo*. Purification by flash chromatography (DCM) yielded *N*-benzyl-*N*-(4-nitrobenzoyl)-4-nitrobenzamide as a pale yellow solid (0.12 g, 90%). Mp 165–167 °C (Found: C, 62.23; H, 3.80; N, 10.21. Calc. for $C_{21}H_{15}N_3O_6$: C, 62.22; H, 3.73; N, 10.37%); ν_{max}(KBr)/cm^{-1} 1350 (s, NO_2), 1526 (s, NO_2), 1603 (m, C(O)N), 1691 (s, C(O)N); δ_H (400 MHz, $CDCl_3$) 5.23 (s, 2H, CH_2), 7.2–7.4 (m, 5H, Ar–H), 7.57 (d, J = 9.0 Hz, 4H, Ar–H), 8.07 (d, J = 9.0 Hz, 4H, Ar–H); δ_C (100 MHz, $CDCl_3$) 50.6, 123.8, 128.3, 128.5, 128.9, 129.5, 136.0, 141.1, 149.5, 171.6; (ESMS−) *m*/*z* 405 (MH^-, 10%), 255 (M − [$C(O)C_6H_4NO_2$], 30%), 166 ($NC(O)C_6H_4NO_2$, 100%).

Synthesis of L,L-Z–Gly–Phe–Val–OMe using polymer-supported triphenylphosphine ditriflate 4 and HOBT

Polymer-supported triphenylphosphine ditriflate **4** was prepared as above from polymer-supported triphenylphosphine oxide (0.15 g, 0.45 mmol, 3 mmol g^{-1}) and triflic anhydride (57.5 μL, 0.33 mmol). Diisopropylethylamine (0.32 mL, 1.82 mmol), 1-hydroxybenzotriazole (0.045 g, 0.33 mmol) and Z–Gly–Phe–OH (0.118 g, 0.33 mmol) were then added and the solution stirred at room temperature for 2 h. Addition of H–Val–OMe·HCl (0.0435 g, 0.33 mmol) produced a yellow slurry which was stirred at room temperature overnight. The polymer beads were collected on a filter and washed with DCM (60 mL). The yellow filtrate was washed with sodium hydrogen carbonate (3 × 50 mL, 5% aqueous solution) and water (5 × 50 mL) and the combined DCM layers concentrated *in vacuo* then dried under high vacuum to remove the remaining traces of diisopropylethylamine. The single isomer of L,L-Z–Gly–Phe–Val–OMe was obtained as a light orange solid (0.1 g, 66%). Mp 95–97 °C, (lit.,[17] 98 °C).

Representative example for the use of polymer-supported triphenylphosphine ditriflate 4 for general dehydrations: synthesis of 4-nitrobenzyl 4-nitrobenzoate

Polymer-supported triphenylphosphine ditriflate **4** was prepared as above from polymer-supported triphenylphosphine oxide (0.3 g, 0.9 mmol, 3 mmol g^{-1}) and triflic anhydride (0.12 mL, 0.72 mmol). 4-Nitrobenzyl alcohol (0.1 g, 0.66 mmol), 4-nitrobenzoic acid (0.11 g, 0.66 mmol) and diisopropylethylamine (0.4 mL, 2.3 mmol) were then added and the reaction left to stir overnight at room temperature. The polymer beads were removed by filtration, washed with DCM (50 mL) and the filtrate washed with sodium hydrogen carbonate (3 × 30 mL, saturated aqueous solution). The organic phase was concentrated *in vacuo* and dried under high vacuum to yield 4-nitrobenzyl 4-nitrobenzoate as a yellow solid (0.19 g, 95%). Mp 165–167 °C, (lit.,[20] 168 °C).

Attempted preparation of neomenthyl 4-nitrobenzoate [(1*S*,2*S*,5*R*)-5-methyl-2-(1-methylethyl)cyclohexyl 4-nitrobenzoate] using polymer-supported triphenylphosphine ditriflate 4

Polymer-supported triphenylphosphine ditriflate **4** was prepared as above from polymer-supported triphenylphosphine oxide (0.3 g, 0.9 mmol, 3 mmol g^{-1}) and triflic anhydride (0.12 mL, 0.72 mmol). (1*R*,2*S*,5*R*)-(−)-Menthol (0.103 g, 0.66 mmol), 4-nitrobenzoic acid (0.11 g, 0.66 mmol) and diisopropylethylamine (0.4 mL, 2.3 mmol) were then added and the mixture heated to reflux overnight. The polymer beads were separated by filtration and an aliquot of the filtrate analysed by GC/MS, which showed 2- and 3-menthenes: (1*R*,2*S*,5*R*)-(−)-menthol : neomenthyl 4-nitrobenzoate = 79 : 16 : 5. The identity of the products generated was confirmed by ^{1}H NMR spectroscopy.[8]

Representative example for the esterification of secondary alcohols using the Hendrickson reagent 1 and DMAP: synthesis of *O*-(4-nitrobenzoyl)-(−)-menthol [(1*R*,2*S*,5*R*)-5-methyl-2-(1-methylethyl)cyclohexyl 4-nitrobenzoate]

A solution of triphenylphosphine oxide (2 g, 7.2 mmol) in DCM (10 mL) under nitrogen was cooled on ice. Triflic anhydride (0.5 mL, 3 mmol) was added and the solution stirred for 30 min. Addition of 4-nitrobenzoic acid (0.6 g, 3.6 mmol) to the resulting white precipitate formed a clear solution after stirring for 15 min at room temperature. DMAP (0.44 g, 3.6 mmol) was added and after 5 min, the solution treated with (1*R*,2*S*,5*R*)-(−)-menthol (0.46 g, 3 mmol) and diisopropylethylamine (1.15 mL, 6.6 mmol). After stirring at room temperature for 15 min, the solution was washed with sodium hydrogen carbonate (3 × 20 mL, saturated aqueous solution) and water (2 × 20 mL). The DCM layers were combined, dried (anhydrous $MgSO_4$) and concentrated *in vacuo*. The resulting yellow residue was submitted to flash chromatography (DCM) to afford O-(4-nitrobenzoyl)-(−)-menthol as a pale yellow solid (0.84 g, 92%). Mp 60–62 °C. The ^{1}H NMR data obtained was identical to that previously reported.[18]

Attempted preparation of *O*-(4-nitrobenzoyl)cyclohexanol using polymer-supported triphenylphosphine ditriflate 4 and catalytic DMAP

Polymer-supported triphenylphosphine ditriflate **4** was prepared as above from polymer-supported triphenylphosphine oxide (0.3 g, 0.9 mmol, 3 mmol g^{-1}) and triflic anhydride (0.12 mL, 0.72 mmol). 4-Nitrobenzoic acid (0.11 g, 0.66 mmol) was added and the solution stirred for 15 min at room temperature. The slurry was then treated with DMAP (8 mg, 0.066 mmol) and after 5 min, cyclohexanol (70 μL, 0.66 mmol) and diisopropylethylamine (0.4 mL, 2.3 mmol) added. After stirring at room temperature overnight, analysis of the reaction mixture by GC/MS showed cyclohexene : *O*-(4-nitrobenzoyl)cyclohexanol : cyclohexanol = 68 : 18 : 14. The identity of the products generated was confirmed by ^{1}H NMR spectroscopy.

Representative example for the esterification of secondary alcohols using polymer-supported triphenylphosphine ditriflate 4 and DMAP: synthesis of *O*-(4-nitrobenzoyl)-(−)-menthol [(1*R*,2*S*,5*R*)-5-methyl-2-(1-methylethyl)cyclohexyl 4-nitrobenzoate]

Polymer-supported triphenylphosphine ditriflate **4** was prepared as above from polymer-supported triphenylphosphine oxide (0.3 g, 0.9 mmol, 3 mmol g^{-1}) and triflic anhydride (0.12 mL, 0.72 mmol). 4-Nitrobenzoic acid (0.13 g, 0.8 mmol) was added and the solution stirred for 15 min at room temperature. The slurry was then treated with DMAP (0.1 g, 0.8 mmol) and after 5 min (1*R*,2*S*,5*R*)-(−)-menthol (0.104 g, 0.66 mmol) and diisopropylethylamine (0.4 mL, 2.3 mmol) added. After stirring at room temperature overnight, analysis of the reaction mixture by GC/MS showed *O*-(4-nitrobenzoyl)-(−)-menthol : 2- and 3-menthenes = 97 : 3. The polymer beads were then collected on a filter and washed with DCM (60 mL). The combined filtrates were extracted with sodium hydrogen carbonate (3 × 50 mL, saturated aqueous solution) and water (2 × 50 mL) and the DCM layers dried (anhydrous $MgSO_4$) and concentrated *in vacuo*. The resulting pale yellow oil was dried under high vacuum to afford *O*-(4-nitrobenzoyl)-(−)-menthol as a pale yellow oil which solidified upon standing (0.17 g, 84%). Mp 60–62 °C, identical to that obtained using the Hendrickson reagent **1**.

Acknowledgements

We gratefully acknowledge financial support for this work from Griffith University, Natural Product Discovery and AstraZeneca. We also thank Dr Sue E. Boyd for assistance with the ^{19}F NMR work.

References

1 O. Mitsunobu, *Synthesis*, 1981, 1–28.
2 D. L. Hughes, *Org. React.*, 1992, **42**, 335–656.
3 I. D. Jenkins and O. Mitsunobu, in *Encyclopaedia of Reagents for Organic Synthesis*, ed. L. A. Paquette, Wiley, 1995, vol. 8, pp. 5379–5390.
4 D. L. Hughes, *Org. Prep. Proc. Int.*, 1996, **28**, 127–164.
5 J. C. Kauer, *Org. Synth.*, 1963, **Coll. vol. IV**, 411–415.
6 J. B. Hendrickson, in *Encyclopaedia of Reagents for Organic Synthesis*, ed. L. A. Paquette, Wiley, 1995, vol. 8, pp. 5404–5407.
7 (*a*) J. B. Hendrickson and M. S. Hussoin, *J. Org. Chem.*, 1987, **52**, 4137–4139; (*b*) J. B. Hendrickson and M. S. Hussoin, *J. Org. Chem.*, 1989, **54**, 1144–1149.
8 K. E. Elson, I. D. Jenkins and W. A. Loughlin, *Org. Biomol. Chem.*, 2003, **1**, 2958–2965.
9 K. E. Elson, I. D. Jenkins and W. A. Loughlin, *Aust. J. Chem.*, 2004, **57**, 371–376.
10 K. E. Elson, I. D. Jenkins and W. A. Loughlin, *Tetrahedron Lett.*, 2004, **45**, 2491–2493.
11 M. J. Farrall and J. M. J. Fréchet, *J. Org. Chem.*, 1976, **41**, 3877–3882.
12 T. Chou, C. Tsao and S. Hung, *J. Organomet. Chem.*, 1986, **312**, 53–58.
13 D. Crich and H. Dyker, *Tetrahedron Lett.*, 1989, 475–476.
14 J. B. Hendrickson and S. M. Schwartzman, *Tetrahedron Lett.*, 1975, 277–280.
15 A. Aaberg, T. Gramstad and S. Husebye, *Tetrahedron Lett.*, 1979, 2263–2264.
16 S.-L. You, H. Razavi and J. F. Kelly, *Angew. Chem., Int. Ed.*, 2003, **42**, 83–85.
17 C. van der Auwera, S. van Damme and M. J. O. Anteunis, *Int. J. Peptide Res.*, 1987, **29**, 464–471.
18 J. A. Gomez-vidal, M. T. Forrester and R. B. Silverman, *Org. Lett.*, 2001, **3**, 2477–2479.
19 C. U. Pitman Jr and A. Hirao, *J. Org. Chem.*, 1978, **43**, 640–646.
20 E. Lyons and E. Reid, *J. Am. Chem. Soc.*, 1917, **37**, 1727–1735.
21 G. W. Cline and S. B. Hanna, *J. Am. Chem. Soc.*, 1987, **109**, 3087–3091.
22 P. E. Verkade, B. M. Wepster and P. H. Witjens, *Recl. Trav. Chim. Pays-Bas Belg.*, 1951, **70**, 127–141.
23 D. F. Shi, T. D. Bradshaw, S. Wrigley, C. J. McCall, P. Levieveld, I. Fichtner and M. F. G. Stevens, *J. Med. Chem.*, 1996, **37**, 3375–3384.
24 S. Ikenoya, M. Masui, H. Ohmori and H. Sayo, *J. Chem. Soc., Perkin Trans. 2*, 1974, **6**, 571–576.
25 E. Buhleier, W. Wehnew and F. Vogel, *Chem. Ber.*, 1979, **112**, 559–566.
26 M. Goulet, T. F. Walsh, M. J. Ujjainwalla and M. J. Wyrratt, Jr., *US Pat.*, 2000, US 6156772, CAN 134:29307.
27 J. F. Dezern, *J. Polym. Sci., Part A: Polym. Chem.*, 1988, **26**, 2157–2169.
28 N. Shangguan, S. Katukajvala, R. Greenberg and L. J. Williams, *J. Am. Chem. Soc.*, 2003, **125**, 7754–7755.
29 V. K. Aggarwal, M. Kalomiri and A. P. Thomas, *Tetrahedron: Asymmetry*, 1994, **5**, 723–730.
30 N. Tamaoki, S. Yoshimura and T. Yamaoka, *Bull. Chem. Soc. Jpn.*, 1991, **64**, 2011–2012.
31 M. R. Pitts, J. R. Harrison and C. J. Moody, *J. Chem. Soc., Perkin Trans. 1*, 2001, **9**, 955–977.
32 C. J. O'Connor, A. S. H. Mitha and P. Walde, *Aust. J. Chem.*, 1986, **39**, 249–257.
33 A. I. Vogel, *Vogel's Textbook of Practical Organic Chemistry, including Qualitative Organic Analysis*, Longman: London, 4th edn., 1978.