Development and Application of a Poly(ethylene glycol)-Supported Triarylphosphine Reagent: Expanding the Sphere of Liquid-Phase Organic Synthesis

Frank Sieber, Paul Wentworth Jr.,*,[†] Jonathan D. Toker, Anita D. Wentworth,
William A. Metz,[§] Neal N. Reed, and Kim D. Janda*,[‡]

*Department of Chemistry, The Scripps Research Institute and the Skaggs Institute for Chemical Biology,
10550 North Torrey Pines Road, La Jolla, California 92037*

Continuing studies into the utility of poly(ethylene glycol) (PEG)-supported triarylphosphines as functional polymer reagents in liquid-phase organic synthesis (LPOS) are being pursued. This report describes the synthesis and NMR characterization of an aryl−alkyl ether-linked PEG-triarylphosphine derivative (**2**) and its subsequent application in LPOS. The utility of **2** as a mild stoichiometric reagent for ozonide reduction has been demonstrated, and a direct comparison between **2**, a Merrifield resin-bound triarylphosphine derivative, and a solution-phase triphenylphosphine reagent revealed that the highest observed yields occur under liquid-phase conditions. Transformation of phosphine **2** into a phosphonium salt (**3**) then allowed the inherent aqueous solubility of PEG-functionalized moieties to be exploited by enabling a Wittig reaction, between a range of aldehydes and **3**, to occur under mildly basic aqueous conditions. This led to the generation of substituted stilbenes in good to excellent yields. Finally, regeneration of **2** was achieved by reduction of the PEG-supported triphenylphosphine oxide byproduct **4** with alane (100% conversion, 75% yield). This combination of reaction, recovery, and regeneration expands the utility of PEG-supported triarylphosphine reagents across the spectra of both organic chemistry and solution-phase combinatorial strategies.

Introduction

For many years functionalized polymers have been employed as stoichiometric reagents and catalysts, and also for reaction purification. However, their development and application in organic synthesis is undergoing a tremendous renaissance at present and is undoubtedly being fueled by the special requirements of both combinatorial and "green" chemistry.[1,2] There are a number of key advantages which link functionalized polymers to synthetic chemistry, including ease of product isolation, the ability to use an excess of reagents to drive a reaction to completion, and the fact that they can, in certain cases, be recycled for repeated use. In addition, solution-phase combinatorial chemistry is demanding an ever expanding "tool box" of polymer-supported reagents and catalysts to sustain the plethora of chemistries being probed for both library construction and purification.[3,4]

At present, the vast majority of available functionalized polymers are insoluble, being polystyrene based and possessing either low (Merrifield resin) or high (macroporous resins) degrees of cross-linking.[1,2] However, emerging problems associated with the use of insoluble polymeric derivatives under heterogeneous conditions, low-

ered reactivities, site−site interactions, extended reaction times, diffusion-limited reactivity, and reagent leaching, have meant that soluble matrixes[5] such as poly(ethylene glycol) (PEG),[6] fluorous supports,[7] linear poly(styrenes),[8−10] and poly(ethylenes)[11] are receiving increasing attention both for combinatorial synthesis and as supports for heterogeneous catalysts.

Our group recently communicated an extension of PEG-supported chemistry into the field of functionalized polymers as reagent supports.[12−14] We prepared a novel triarylphosphine derivative of PEG (**1**) and showed that, when compared to a heterogeneous commercially available counterpart, it possesses favorable reaction kinetics in both the Staudinger and Mitsunobu etherification reactions. The present study expands on those preliminary investigations in the following ways. The synthesis and NMR characterization of the more stable (ether-linked) PEG−triarylphosphine derivative **2** is reported. The application of **2** is then studied in the context of LPOS for a redox reaction involving ozonide decomposition. In parallel, a comparison of the soluble polymer-supported phosphine **2** with a solid-phase triarylphos-

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[†] Telephone: (619) 784-2476. Fax: (619) 784-2590. E-mail: paulw@scripps.edu.
[‡] Telephone (619) 784−2515. Fax: (619) 784−2595. E-mail: kdjanda@scripps.edu.
[§] On sabbatical leave from Hoechst-Marrion Roussel, New Jersey.
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phine reagent and a solution-phase reagent is undertaken. Subsequent transformation of **2** into polymer-supported phosphonium salt **3** then facilitates the first example of polymer-supported Wittig reactions *in aqua*. Finally, with the concept of economy firmly entrenched in our strategy, the regeneration of the oxidized phosphine **4** is examined, such that reagent **2** can be facilely recycled for continued use.
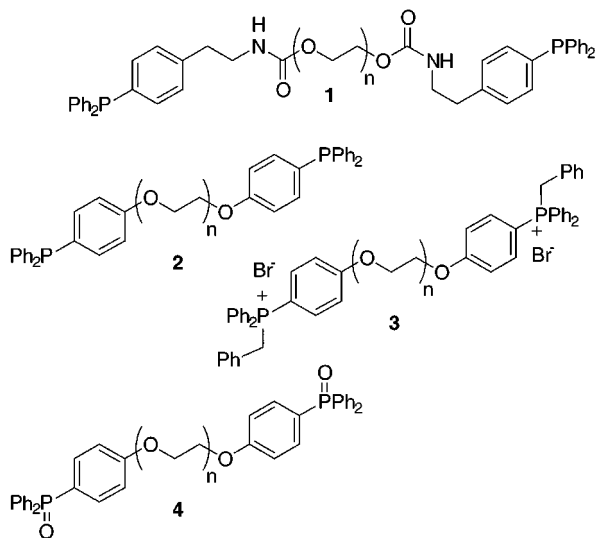

Results and Discussion

Synthesis of Liquid-Phase Phosphine Reagent 2. For a successful functional polymer-supported reagent strategy, two features have to be optimal: loading and stability across a broad range of reaction conditions. When choosing a soluble polymer for liquid-phase synthesis, a compromise has to be reached between loading capacity and solubility profile. In the original report, dihydroxy-PEG of molecular weight 3400 (PEG$_{3400}$, equivalent to a loading of ca. 0.5 mmol g^{-1}) was found to be the lowest molecular weight PEG that when functionalized as reagent **1** would reproducibly maintain its physical properties: soluble in H$_2$O, DMSO, DMF, dichloromethane (CH$_2$Cl$_2$), toluene, benzene, and warm THF but insoluble in diethyl ether, *t*-Bu ether, and *i*-Pr alcohol. For this study, therefore, dihydroxy-PEG$_{3400}$ was again selected as the matrix of choice. A concern with the original reagent (**1**) was the carbamate ester moiety incorporated as a linker between the triarylphosphine and the PEG support. The known base and acid sensitivity of the urethane linkage, coupled with worries about its lability in the presence of Lewis acids and metalating reagents, linked any further exploitation of PEG-supported tri-arylphosphines to an immediate replacement of this carbamate ester group. An aryl−alkyl ether moiety was chosen as the replacement linker, the chemical stability of which is comparable to that of the poly(ethylene oxide) backbone; therefore reagent **2** became the functionalized polymer of choice. Reported herewith is the primary high-yielding synthesis, isolation, and characterization of pure P(III) bistriphenylphosphine terminated poly(ethylene glycol) **2** (Scheme 1).[15]

(15) A recent report attempts the synthesis of **2** for use as a macroinitiator in block copolymer synthesis (Choi, Y. K.; Bae, Y. H.; Kim, S. W. *Macromolecules* **1995**, *28*, 8419−8421). However, the authors observed significant oxidation of the phosphine end groups during its isolation which they did not isolate in pure form.

Scheme 1
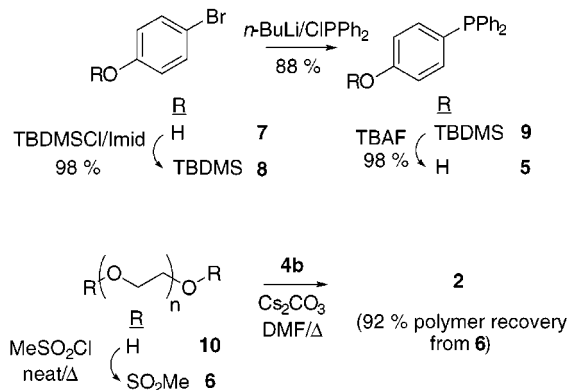
The synthetic strategy involves an initial concise preparation of the key hydroxyphosphine **5**,[16] followed by its attachment to PEG *via* the dimesylate **6**.[17] *p*-Bromophenol **7** was protected as the TBDMS ether **8**, which was then phosphinylated under standard conditions[18] to give the triarylphosphine **9**. The silyl ether was removed and the resultant hydroxyphosphine **5** was obtained in 85% yield for the three steps. Mesylate **6** was obtained by heating (50 °C) a neat solution of PEG$_{3400}$ **10** in methanesulfonyl chloride. No base was required under these conditions, which had the benefit that the purification of **6** was simplified from its original preparation.[17] Etherification between **6** and **5** was performed in rigorously degassed DMF. Phosphine **2** was then isolated by addition of the reaction mixture into degassed diethyl ether, followed by filtration and sequential washing of the polymeric precipitate with *i*-Pr alcohol (to remove salts) followed by diethyl ether to give reagent **2** in 92% yield, based on the weight of polymer isolated. ^{31}P NMR confirmed that the oxidation state of the phosphine termini of **2** were P(III) (δ −6.4 ppm) with little detectable P(V) (δ 28 ppm) contamination (<2%) (Figure 1,a and b). ^{1}H NMR of **2** also confirms the oxidation state of the phosphine termini, with the chemical shift of the aromatic ring protons clearly being dependent on the presence or absence of the phosphinyl oxygen bond. The oxidation state of the phosphine termini of **2** was routinely quantified by ^{31}P NMR after certain periods of storage. This revealed that even after prolonged exposure to air (2−3 weeks), little oxidation to the phosphine oxide (<5%) occurs.

The derivatization level of the polymer is also determined by inspection of the ^{1}H NMR of **2**. The chemical shift of α-methylene protons of PEG and its derivatives is a function of the moiety attached to the termini hydroxyl groups. For underivatized PEG$_{3400}$ the chemical shift of these α-protons is δ 3.8 ppm, for PEG−mesylate **6** this changes to δ 4.35 ppm (also detectable are the β-methylene protons δ 3.74 ppm), and for the phosphine-terminated polymer **2** this changes to δ 4.16 ppm (β-methylene protons δ 3.64 ppm). Inspection of the ^{1}H NMR

(16) A recent report descibes a one-step route to phosphine **5** in moderate yield (63% yield) [Herd, H.; Hessler, A.; Hingst, W.; Tepper, M.; Stelzer, O. *J. Organomet. Chem.* **1996**, *522*, 69−76]. However, in our hands the obtained yields were even lower (38%). Therefore, we adopted a three-step approach to **5**, with the overall yield being 85% (Scheme 1).

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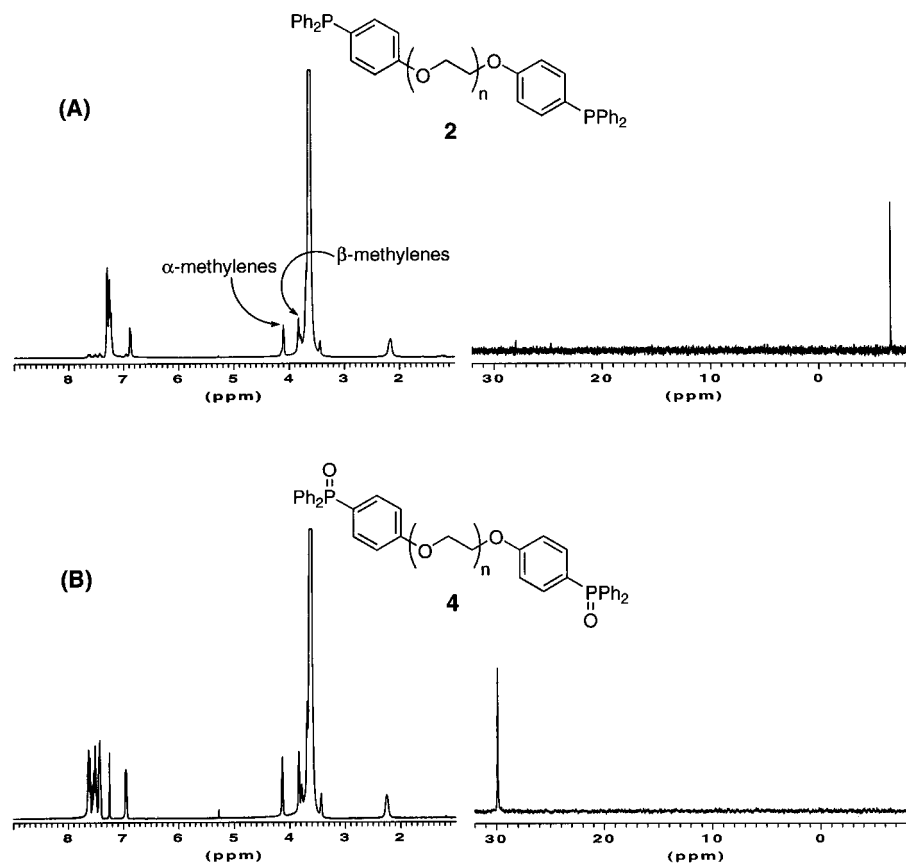
Figure 1. (A) ^{1}H and ^{31}P NMR spectra of PEG-supported triarylphosphine **2**. (B) ^{1}H and ^{31}P NMR spectra of PEG-supported triarylphosphine **4**.

of **2** shows that no mesylate **6** remains. However, potential side reactions during the workup procedure, following the etherification reaction, to generate **2** could invoke alternative routes of hydrolysis of the methanesulfonate ester of **6**. Washing of the isolated precipitate from the etherification reaction with *i*-Pr alcohol containing traces of water could conceivably lead to contamination with either polymer bound *i*-Pr ether or free hydroxyl termini. However, the ^{1}H NMR of **2** reveals no signals to support such a conclusion; therefore there is high confidence that the polymeric phosphine **2** is quantitatively substituted with terminal triarylphosphine residues (ca. 0.5 mmol g^{-1}).

The ease of NMR characterization of soluble polymer reagent **2** offers a considerable advantage over its solid-phase homologue which, to determine the oxidation state of the phosphine center, must involve either gel- or solid-phase NMR or single-bead FTIR techniques.[19]

Liquid-Phase Ozonide Reduction. As an entry level into the utility of **2** in organic chemistry, the mild chemical decomposition of ozonides was selected. Ozonolysis of alkenes has a broad scope of application in organic chemistry, and the range of methods for destruction of the intermediary ozonides is equally broad. However, the two major methods of choice, Zn/acetic acid or dimethyl sulfide, have limitations, a result of potential chemical substituent sensitivity in the former case or noxious reagents and high-boiling-point byproducts in the latter. For these reasons PPh$_3$ is an excellent alternative.[20] It has received only limited use in solution-phase

chemistry, however, because of the problems of removing both the excess PPh$_3$ and reaction byproduct, triphenylphosphine oxide, from the reaction mixture. The use of polystyrene-supported PPh$_3$ as a stoichiometric reagent for this reaction has been reported as an alternative and gives good to excellent yields of aldehydes.[21] Therefore, an important part of this study was a direct comparison between this new liquid-phase approach with **2** and a solid-phase approach with commercially available PPh$_3$.

A range of alkenes **11a–e** were treated with ozone at −78 °C in CH$_2$Cl$_2$ until a blue reaction mixture persisted. At this point the excess ozone was removed by purging with N$_2$. The incipient ozonides were then decomposed into the product aldehydes (**12a–e**) by addition of one of three reagents: PPh$_3$, polystyrene-supported PPh$_3$, or PEG-supported PPh$_3$ (**2**). The results are tabulated in Table 1.

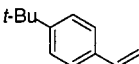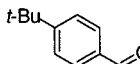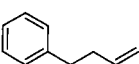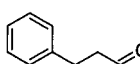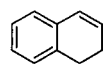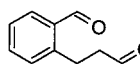The isolation procedure for the PEG-supported reagent involved a simple precipitation of the spent reagent into ether and concentration. This consistently removed >99% of the polymer byproduct. P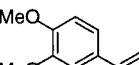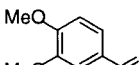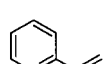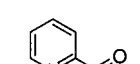assage of the ether concentrate through a short silica pad completely removed the remaining polymer traces, giving the product aldehydes in analytically pure form. The solid-phase reagent was separated from the reaction mixture by filtration. The product was isolated by then washing the resin with volumes of CH$_2$Cl$_2$. The solution-phase reactions were

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Table 1. Direct Comparison of Ozonide Hydrolysis between Solution-Phase, Solid-Phase, and Liquid-Phase Triphenylphosphine

entry	alkene	product	yield,[a] %		
			PPh_3[b]	⬤PPh_3[c]	**2**
1	11a	12a	94	58	98
2	11b	12b	80	73	92
3	11c	12c	84[d]	60[d]	97[d]
4	11d	12d	51	56	77
5	11e	12e	72	62	63

[a] Reaction conditions: the respective triphenylphosphine (2 equiv) was added to the ozonide (1 equiv) of the alkene in CH_2Cl_2 and left to stir for 2 h. Yields are based on HPLC comparison to authentic product standards. [b] Commercially available PPh_3 (Aldrich). [c] Commercially available polystyrene−PPh_3 resin (Aldrich). [d] Isolated yield.

purified by silica gel chromatography to remove the excess PPh_3 and the byproduct PPh_3O.

Generally, it is considered that liquid-phase chemistry can be wasteful in terms of the volumes of solvents required to precipitate the polymer support at the end of the reaction (in relation to solid-phase methods). When one is working with functionalized resins, however, the product is present in solution; therefore the resin has to be washed copiously to obtain the product in optimal yield. In our hands, the volumes of CH_2Cl_2 required to completely wash out the aldehyde products from the Merrifield resin were comparable to that of the diethyl ether necessary to precipitate the spent PEG reagent.

In all cases studied, the yields of aldehyde were highest with the soluble polymer-supported reagent **2**, and with the exception of **12d** the soluble reagent gave higher yields than the solid-phase reagent. This result may be a composite of three factors: increased reducing power of the soluble polymer-supported phosphine **2** when compared to both the solid- and solution-phase reagents, a result of the *p*-ethoxy ether functionality which links the reagent to the soluble polymer support, the homogeneous nature of the ensuing chemical process when compared to the hetereogeneous resin reagent, and the ease of isolation and purification of the products when compared with solution-phase strategy.

Liquid-Phase Wittig Reactions *in Aqua*. Organic chemistry in water has been the focus of considerable efforts in recent years.[22−24] There are isolated examples of Wittig reactions in water: nitrostyrenes,[25] *p*-carboxystyrene,[26] and vitamin A acetate[27] have all been synthesized in water *via* aqueous formaldehyde and their respective ylides. However, Wittig reactions with less reactive aldehydes resulted in hydrolysis of the phosphonium salts.[28] Wittig reactions and Horner−Wadsworth−Emmons reactions when conducted in the presence of water generally occur under biphasic conditions with a phase transfer catalyst, undoubtedly due to the limitations imposed by the solubility and stability of the phosphonium salts and/or the component aldehydes and ketones.[29−33]

The Wittig olefination reaction has been much studied throughout the evolution of cross-linked polymer-supported reagents, and considerable success has been achieved.[34−39] Bernard and Ford[39] noted an inverse correlation between the yield of alkene obtained from polymer-supported Wittig reagents with aldehydes and ketones in solution and the degree of divinylbenzene (DVB) cross-linking in the resin. Progressing from 0.5 to 20% DVB cross-linking, i.e., from gel to macroporous resins, can result in a fall of 20% in the yield of alkenes. These results suggested that a soluble polymer-supported phosphonium salt may give excellent yields in the Wittig reaction.

The physical properties of the PEG backbone are such that a PEG-supported phosphonium salt would be eminently water soluble and offer the tantalizing prospect of facilitating the first soluble polymer-supported Wittig olefination reactions *in aqua*. Treatment of PEG-supported phosphine **2** with benzyl bromide followed by precipitation into diethyl ether yielded the soluble polymer-supported benzyltriarylphosphonium salt **3** in 81% yield (based on the weight of polymer obtained). This polymeric phosphonium salt (**3**) is completely soluble in water at pH 7. The reaction of this novel Wittig salt (**3**) was then studied with a range of aldehydes (**12a** and **13a−d**) in aqueous sodium hydroxide solution (Scheme 2). The results are tabulated in Table 2.

The isolated yields of the alkenes **14a−e** by this method were good to excellent, proving that the rate of reaction of the ylide with the substrate aldehydes is indeed much faster than decomposition to **4**. Isolation of the stilbenes (**14a−e**) was achieved by partitioning the reaction mixture with CH_2Cl_2, followed by removal of the

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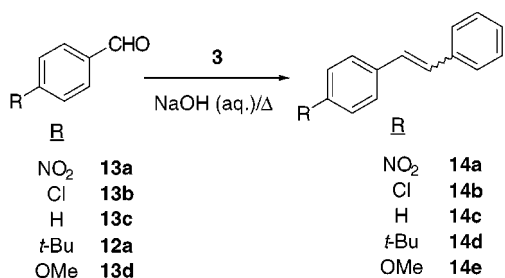(37) Clarke, S. D.; Harrison, C. R.; Hodge, P. *Tetrahedron Lett.* **1980**, *21*, 1375−1378.
(38) Hodge, P.; Waterhouse, J. *Polymer* **1981**, *22*, 1153−1154.
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Scheme 2

R			R	
NO$_2$	**13a**		NO$_2$	**14a**
Cl	**13b**		Cl	**14b**
H	**13c**		H	**14c**
t-Bu	**12a**		*t*-Bu	**14d**
OMe	**13d**		OMe	**14e**

Table 2. Aqueous Wittig Reactions between PEG-Supported Phosphonium Salt 3 and Aldehydes (12a and 13a−d)

entry	aldehyde	conditions	yield, %[a] (*E/Z* ratio)[b]
1	**13a**	1 N NaOH, rt	65 (56:44)
2		1 N NaOH, 90 °C	62 (75:25)
3	**13b**	1 N NaOH, rt	80 (46:54)
4		1 N NaOH, 90 °C	78 (75:25)
5	**13c**	1 N NaOH, rt	95 (48:52)
6	**12a**	1 N NaOH, rt	38 (49:51)
7		1 N NaOH, 90 °C	49 (47:53)
8	**13d**	1 N NaOH, rt	63 (54:46)

[a] All yields are isolated stilbenes (**14a−e**). [b] Determined by ^{1}H NMR of the crude mixture.

water by addition of anhydrous magnesium sulfate and then precipitation of the polymer-supported triphenylphosphine oxide byproduct **4** into diethyl ether and concentration of the etheric solution to dryness.

In a recent report describing Wittig reactions in basic aqueous media with base soluble phosphonium salts, the authors noted that the *E:Z* ratio, under certain conditions, was skewed during the product isolation process which involved filtration of the reaction mixture.[40] The liquid-phase strategy with **3** which involves partitioning is much more powerful, because it allows full extraction of both isomeric stilbenes without having to worry about contamination with the byproduct phosphine oxide which is removed by a simple precipitation.

To explore the scope of this reaction, two components were varied: base strength and temperature. Increasing the base strength (from 1 to 2 N NaOH) neither affected the yield of stilbenes (**14a−e**) nor the *E:Z* isomer distribution. However, elevating the temperature (up to 90 °C) resulted in improved yields of **14d** and as to be expected an increase in the *E:Z* ratio for all the stilbene products.

Regeneration of Spent Reagent 4. A number of standard methods were employed to regenerate the oxidized polymer-supported phosphine **4** (Table 3). Only poor to moderate reduction of **4** to **2** occurred with polymethylhydrosiloxane (PMHS)[41] using various conditions. The reason is perhaps due to unfavorable polymer−

Table 3. Regeneration of PEG-Supported Triarylphosphine 2

entry	reagent	conditions	P(V) to P(III),[a] %
1	PMHS,[b] CH$_2$Cl$_2$	CH$_2$Cl$_2$/rt	20
2	PMHS	benzene/reflux 20 h	33
3	PMHS	THF/reflux 20 h	40
4	HSiCl$_3$[c]	benzene/reflux 20 h	56
5	AlH$_3$·THF	THF/rt 30 min	100

[a] Measured by ^{31}P NMR of the reaction mixtures. [b] Polymethylhydrosiloxane. [c] With triethylamine.

polymer interactions between the polymeric reductant and the PEG backbone. Trichlorosilane,[42,43] while leading to a significant reduction of the phosphine group (56%), completely cleaved the terminal phosphine from the polymer. However, quantitative reduction of **4** was achieved with freshly prepared alane (AlH$_3$)[44] in THF as determined by ^{31}P NMR *vide supra*. The polymer was isolated in 75% yield following the usual precipitation into degassed ether. The incomplete polymer recovery is attributed to problems associated with the byproduct aluminum salts either complexing to the polymer support and thus preventing precipitation or polymer-backbone hydrolysis during the reduction process.

In conclusion, we have generated stable PEG−triarylphosphine derivative **2** as a stoichiometric reagent for a number of key chemical reactions. The broad nature of triphenylphosphine as a reagent in organic chemistry means that the potential scope of **2** is very wide. A direct comparison of the utility of this reagent (**2**) with a Merrifield-bound reagent and triphenylphosphine in solution has revealed that the observed yields for ozonide reduction are greatest under the liquid-phase conditions. In addition, the conferred water solubility of phosphonium salt **3** has facilitated high-yielding Wittig reactions under aqueous condition, a reaction inconceivable with Merrifield-supported triphenylphosphine. The utility of this reagent was made complete by its facile regeneration by quantitative reduction with alane and reisolation in 75% yield.

Insoluble polymer-supported strategies for organic chemistry and solution-phase combinatorial strategies are in a rapid phase of expansion at the moment. Soluble polymer supported strategies are developing in parallel and offer unique potentials, both in terms of the reactions available and the solvents in which they can be conducted. This report pushes back the boundary of soluble polymers as supports for stoichiometric reagents showing the broad solvent breadth that may be exploited and highlighting the regeneration of the reagent for recycling.

Supporting Information Available: Full experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

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