Staudinger/aza-Wittig reactions utilizing a novel linear polymer-supported triphenylphosphine as a modified liquid-phase reagent

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ABSTRACT

A new triphenylphosphine reagent linked to a linear maleimide-styrene copolymer is synthesized and is found to be effective for the formation of a variety of imines via the Staudinger/aza-Wittig reaction. This linear polymer-supported triphenylphosphine has a unique solubility behavior and provides for a simple means of purifying the desired imine from the phosphine oxide by-product. The reactivity of this polymeric reagent is superior to that of the cross-linked polymer-supported phosphine reagent.

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With the advent of combinatorial chemistry and multiple parallel syntheses in drug discovery, there has been an increasing interest in new synthetic methods, which afford clean products without time consuming work-up and purification procedures.[1] Triphenylphosphine has been used extensively in various organic transformations, such as Mitsunobu,[2] Wittig,[3] and Staudinger[4,5] reactions. However, in all of these reactions, separation of the desired products from the triphenylphosphine oxide by-product can present difficulties, especially for small-scale reactions. The use of polymer supports[6] can circumvent this problem if the reaction site is readily accessible and if the polymeric reagent retains the reactivity of free triphenylphosphine.

There are a number of key advantages which link functionalized polymers to synthetic chemistry, including the ease of product isolation, minimization of side-reactions and, in certain cases, the ability to be recycled for repeated use.[7–10] Since the introduction of the Merrifield method for peptide synthesis,[11] insoluble polymer supports have been incorporated into numerous synthetic methodologies. Although highly successful, solid-phase synthesis still exhibits several shortcomings due to the heterogeneous reaction conditions, these include lower reactivity, site–site interactions, nonlinear kinetic behavior, unequal distribution and/or access to the chemical reaction, extended reaction times, diffusion-limited reactivity, and reagent leaching. Due to these problems, soluble matrices have received increasing attention in combinatorial synthesis[12] and as supports for heterogeneous catalysts,[13] however,

it is generally 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 this Letter, we report the synthesis and application of a novel versatile liquid-phase polymer-supported triphenylphosphine reagent as an efficient and modified liquid-phase supported reagent in the Staudinger/aza-Wittig reaction.

The liquid-phase polymeric reagent, poly(styrene-*co*-3-maleimido- phenyldiphenylphosphine) **2**, was synthesized in one step from triphenylphosphine oxide supported on non-cross-linked maleimide-styrene copolymer **1** (Scheme 1).

The copolymer **1** was synthesized from triphenylphosphine oxide according to our reported procedure.[14] Reduction of **1** with trichlorosilane and *N,N*-dimethylaniline at 110 °C gave the non-cross-linked copolymer-supported triphenylphosphine **2** in quantitative yield.[15] This was confirmed by ^{31}P NMR spectroscopy, where a shift from the copolymer **1** (δ 28.5) to the copolymer **2**
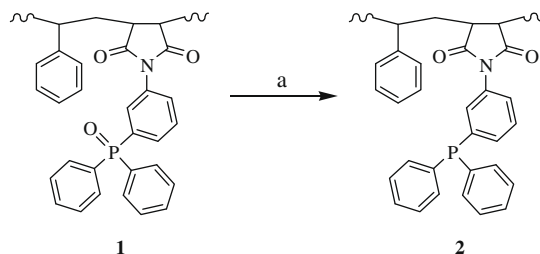

Scheme 1. Reagents and condition: (a) HSiCl$_3$, *N,N*-dimethylaniline, *p*-dioxane, 110 °C.

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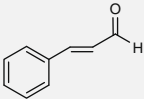*E-mail address:* hmahdavi@khayam.ut.ac.ir (H. Mahdavi).

Table 1
Solubility of the copolymers **1** and **2** (++, soluble at room temperature; +, soluble on heating; and −, insoluble)

Polymer	Solvent							
	DMSO	Toluene	*p*-Dioxane	CH$_2$Cl$_2$	CHCl$_3$	THF	EtOAc	MeOH
Copolymer **1**	++	−	+	++	++	−	−	−
Copolymer **2**	++	−	++	++	++	++	−	−

Scheme 2.
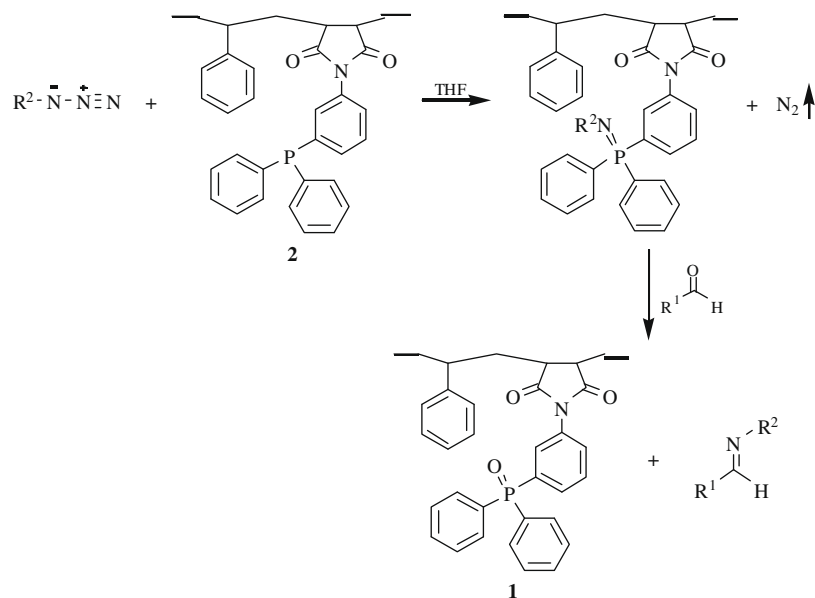
Table 2
Staudinger/aza-Wittig reaction with copolymer **2**

Entry[a,b]	Substrate	Azide[c]	Product[d]	Yield[e] (%)
1			**3**[17]	91
2			**4**[18]	94
3			**5**[19]	88
4			**6**[20]	96

Table 2 (continued)

Entry[a,b]	Substrate	Azide[c]	Product[d]	Yield[e] (%)
5			**7**[21]	89
6			**8**[22]	97
7			**9**[21]	97
8			**10**[17]	90
9			**11**[17]	91
10			**12**[23]	95
11			**13**[20]	91

[a] Reaction conditions: copolymer-supported triphenylphosphine **2** (1.0 equiv), aldehyde (1.0 equiv), azide (1.0 equiv), and THF (10 mL).
[b] Reaction times: entries 1–4, 8–11 (22 h, rt); 5–7 (43 h, rt).
[c] Benzyl azide,[24] 2-azidoethylbenzene,[25] 1-azido-4-methoxybenzene,[26] 3-azidomethyl-2-oxazolidone,[20] and azidobenzene[27] were prepared according to the reported procedures.
[d] All spectroscopic and physical properties were consistent with those reported in the literature.
[e] Isolated yield of analytically pure imine (¹H and ¹³C NMR).

was observed (δ −4.4). The capacity of copolymer **2** (loading of phosphorus) was determined by elemental analysis of phosphorus as 2.1 mmol/g of resin.

The solubility of the polymers **1** and **2** in various solvents was examined and the results are shown in Table 1. It was found that the solubility of polymer **2** was fairly good in common organic solvents, such as chloroform, tetrahydrofuran (THF), and dichloromethane, at room temperature but in THF, polymer **1** was insoluble. The utility of these solvents in Staudinger/aza-Wittig reaction using polymer **2** was then evaluated. A balance of high conversion and readily removable by-product (filtration) was achieved when THF was used as the solvent. In THF, the starting polymer **2** was soluble but became insoluble as the reaction proceeded, and at the end of the reaction it could be easily filtered off.

Copolymer-supported triphenylphosphine **2** was subsequently used in a series of Staudinger/aza-Wittig reactions to demonstrate its versatility (Scheme 2).

A preparative scale procedure involved adding an azide to a mixture of the aldehyde and copolymer **2** in THF.[16] Initially, the reaction conditions were optimized for the formation of *N*-benzylidenebenzylamine. Treatment of copolymer **2** with benzaldehyde and benzyl azide in THF for 22 h at room temperature afforded
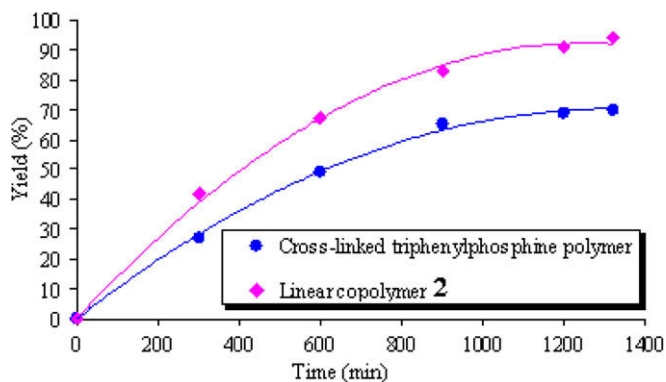
Figure 1. Imine formation using polymeric phosphine reagents.

N-benzylidenebenzylamine in high yield (91%). During the reaction, nitrogen evolution was quite rapid and the phosphine oxide by-product precipitated as the reaction proceeded. The product was obtained by filtration and evaporation of the solvent. Interestingly, there was no signal in the ^{31}P NMR spectrum of the THF solution related to the polymeric reagent. In a similar fashion, several other imines were produced in high yields (Table 2). Analysis by NMR and GC–MS indicated that the conversion was over 94% in all the reactions.

In parallel, a direct comparison between this new liquid-phase approach with **2** and a procedure involving the use of a solid-phase triphenylphosphine reagent was undertaken. The yields of the imines obtained after various reaction times using copolymer **2** in THF were compared with those obtained from analogous reactions using a cross-linked polymer-supported triphenylphosphine (Fig. 1). These data showed that the reactivity of the soluble reagent **2** was superior to that of the insoluble cross-linked polymer-supported phosphine.

In conclusion, a new linear copolymer-supported triphenylphosphine **2** has been synthesized and its utility as a reagent/activating agent in the Staudinger/aza-Wittig reaction is described. This copolymer has a reasonably high loading and allows stoichiometric reactions to take place between azides and aldehydes. The use of this novel liquid-phase reagent offers considerable advantages over solution-based methodologies. Although it is considered generally that soluble polymeric reagents are wasteful in terms of the volumes of solvents required to precipitate the polymer support at the end of the reaction, the side-product of this new soluble reagent, the corresponding triphenylphosphine oxide, precipitates spontaneously during the reaction and is removed by filtration.

Oxide **1** can be converted back to **2** and recycled at least for four times without loss of efficiency.

Acknowledgment

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15. *Procedure for the synthesis of poly(styrene-co-3-maleimidophenyldiphenyl phosphine)* **2**: In a 70 mL pressure tube, copolymer **1** (2 mmol, 1.1 g) was dissolved in anhydrous degassed *p*-dioxane (50 mL) under an argon atmosphere. To this solution were added *N,N*-dimethylaniline (2.5 mL, 20 mmol) and trichlorosilane (2.0 mL, 20 mmol) at room temperature. The reaction mixture was then stirred vigorously at 110 °C for 15 h. The solution was cooled to ambient temperature and then poured into MeOH (120 mL) with vigorous stirring to precipitate the copolymer. The copolymer suspension was filtered, rinsed with H$_2$O and MeOH and then placed in a vacuum oven at 70 °C for 20 h. Copolymer-supported triphenylphosphine **2** was obtained as a white solid (100% yield). IR (KBr) (ν_{max}, cm^{-1}): 1712, 1487, 1435, 1380, 1126, 725, 690, 545. ^{31}P NMR (202.4 MHz, CDCl$_3$): δ −4.44 (1P, s).
16. *Representative experimental procedure for the preparation of N-benzylidenebenzylamine* (**3**): To a stirred solution of copolymer **2** (184 mg, 0.38 mmol) in THF (10 mL) was added benzaldehyde (40 mg, 0.38 mmol). Next benzyl azide (50 mg, 0.38 mmol) was added and the reaction mixture was stirred at room temperature for 22 h (43 h for the cinnamyl derivatives). The copolymer became insoluble as the reaction proceeded, and at the end of the reaction, the copolymer beads were collected by filtration and washed with THF (60 mL). The solvent was evaporated to afford *N*-benzylidenebenzylamine (67 mg, 91%).[17] ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.38 (s, 1H), 7.77 (m, 2H), 7.19–741 (br s, 8H), 4.82 (s, 2H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 162.09, 139.25, 136.70, 130.84, 128.61, 128.51, 128.30, 128.04, 127.0, 65.1.
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