Polyethyleneimine-Supported Triphenylphosphine and its Use as a Highly Loaded Bifunctional Polymeric Reagent in Chromatography-Free One-Pot Wittig Reactions

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Abstract: A polyethyleneimine-supported triphenylphosphine reagent has been synthesized and used as a highly loaded bifunctional homogeneous reagent in a range of one-pot Wittig reactions that afforded high yields of desired products after only simple purification procedures. Furthermore, it also served efficiently in tandem reaction sequences involving a one-pot Wittig reaction followed by in situ conjugate reduction of the newly formed alkene product. In these transformations the phosphine oxide groups generated in the Wittig reaction served as the catalyst for activating trichlorosilane in the subsequent reduction reaction.

Key words: conjugate reduction, polyethyleneimine, polymer supported reagents, triphenylphosphine, Wittig reactions

The classic Wittig reaction is one of the most versatile and widely used methods for converting the carbon-oxygen double bond of an aldehyde or ketone into a carbon-carbon double bond.[1,2] While they are generally very efficient and can be highly stereoselective, Wittig reactions suffer from the drawback that an equivalent of a phosphine oxide by-product is formed in conjunction with the desired product. Thus, even in high yielding reactions, the desired product generally requires extensive purification, and therefore, Wittig reactions are not considered to be environmentally friendly.[3] To address this issue, much research has been directed at developing solutions to the problem of by-product separation, including the use of polymer-supported phosphines[4] that allow the waste to be removed simply by filtration.[5-7] However, the polymer-supported phosphine reagents reported to date have limitations such as low phosphorous loading levels (typically 1 mmol/g), or low reactivity due to their heterogeneous nature. Therefore, the development of an easily synthesized polymer-supported phosphine reagent that is highly loaded and very reactive which can be easily removed from the desired product after a reaction could be of great general interest.

We have been developing new organic polymers for use as reagent and catalyst supports,[8,9] and recently reported the synthesis and application of several rasta resin triphenylphosphines in various Wittig reactions from which the desired products did not require chromatographic purification. Our initial polymer-supported reagent **1** was monofunctional, and only bore phosphine groups (Figure 1).[10] Since we were interested in performing one-pot Wittig reactions[11] in which the required phosphorane reagent was formed in situ by deprotonation of a phosphonium salt, a separate amine base had to be added to the reactions when **1** was used. Thus, we later developed bifunctional rasta resins **2** and **3** that were functionalized with tertiary amine groups in addition to the phosphine groups.[12,13] While these polymer-supported reagents were easily synthesized and more reactive than traditional heterogeneous polymer-supported phosphines, they suffered from low loading

levels (ca. 1 mmol/g amine and phosphine) due to the polystyrene platform on which they were based.
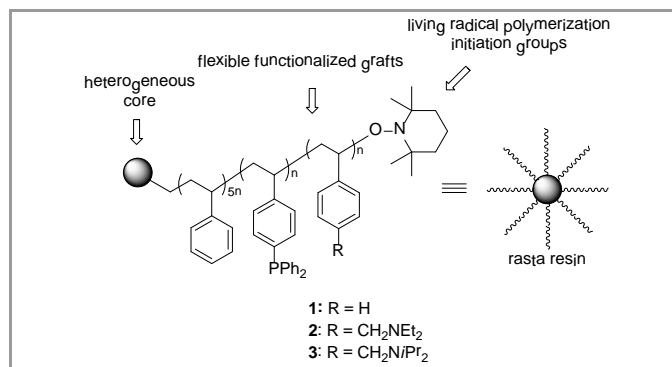

Figure 1 Phosphine functionalized rasta resins **1**-**3**

Therefore, in order to identify a more useful and practical bifunctional polymer-supported reagent for Wittig reactions, we sought to prepare a polymer based on commercially available polyethylene imine (PEI, **4**, Figure 2)[14] that is highly loaded with both amine and phosphine groups. In fact, due to its high density of amine groups, **4** has previously been used as a platform in various forms for polymer-supported synthesis and reagents.[15] For example, both Ultraresin (**5**)[16] and UL-TRAMINE (**6**)[17] have been described in the literature, and most recently **7** has been prepared and used as a catalyst for Henry reactions.[18] Herein we report the synthesis of bifunctional PEI-supported triphenylphosphine (PEI-TPP, **8**, Scheme 1), and its use in a wide range of one-pot Wittig reactions that afford high yields of the pure products after simple separation of the polymeric by-product.

The synthesis of **8** started with 4-bromobenzaldehyde (**9**), which was protected with ethylene glycol to form **10** (Scheme 1). This in turn was treated with *n*-BuLi followed by ClP(Ph)$_2$ to form triarylphosphine **11**. Acid-catalyzed hydrolytic deprotection of the aldehyde group of **11** generated **12**, which was reacted with **4** (mw = ca. 25,000) together with acetaldehyde and NaBH$_3$CN to afford **8**. At this stage IR spectroscopy was used to verify that the original primary and secondary amine groups of **4** (3277 cm^{-1}) were converted into tertiary amine groups in **8**.[19] Additionally, **8** exhibited only a single resonance in its ^{31}P NMR spectrum at -6.1 ppm, representing the triarylphosphine moieties. Polymer **8** was found to be soluble in CH$_2$Cl$_2$, CHCl$_3$, and THF, but insoluble in diethyl ether, MeOH, and hexanes. The loading levels of the amine and phosphine groups of **8** were determined by elemental analysis to be 7.5 mmol/g and 1.9 mmol/g, respectively.
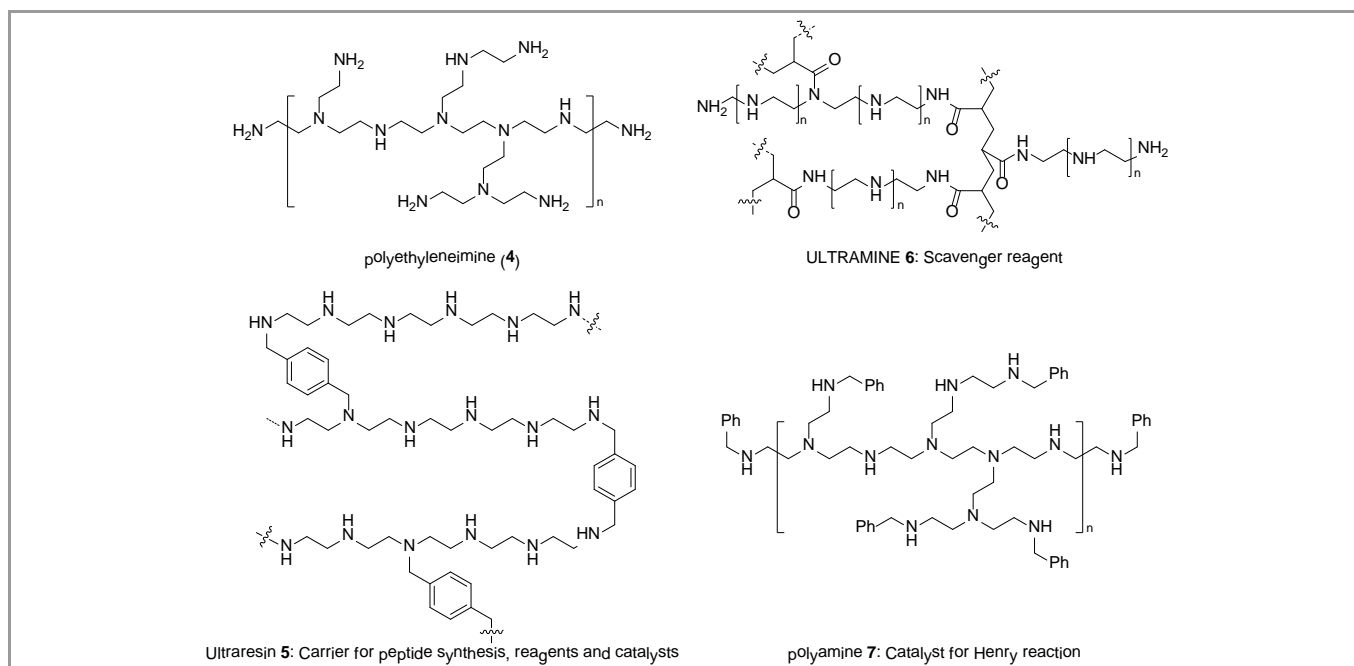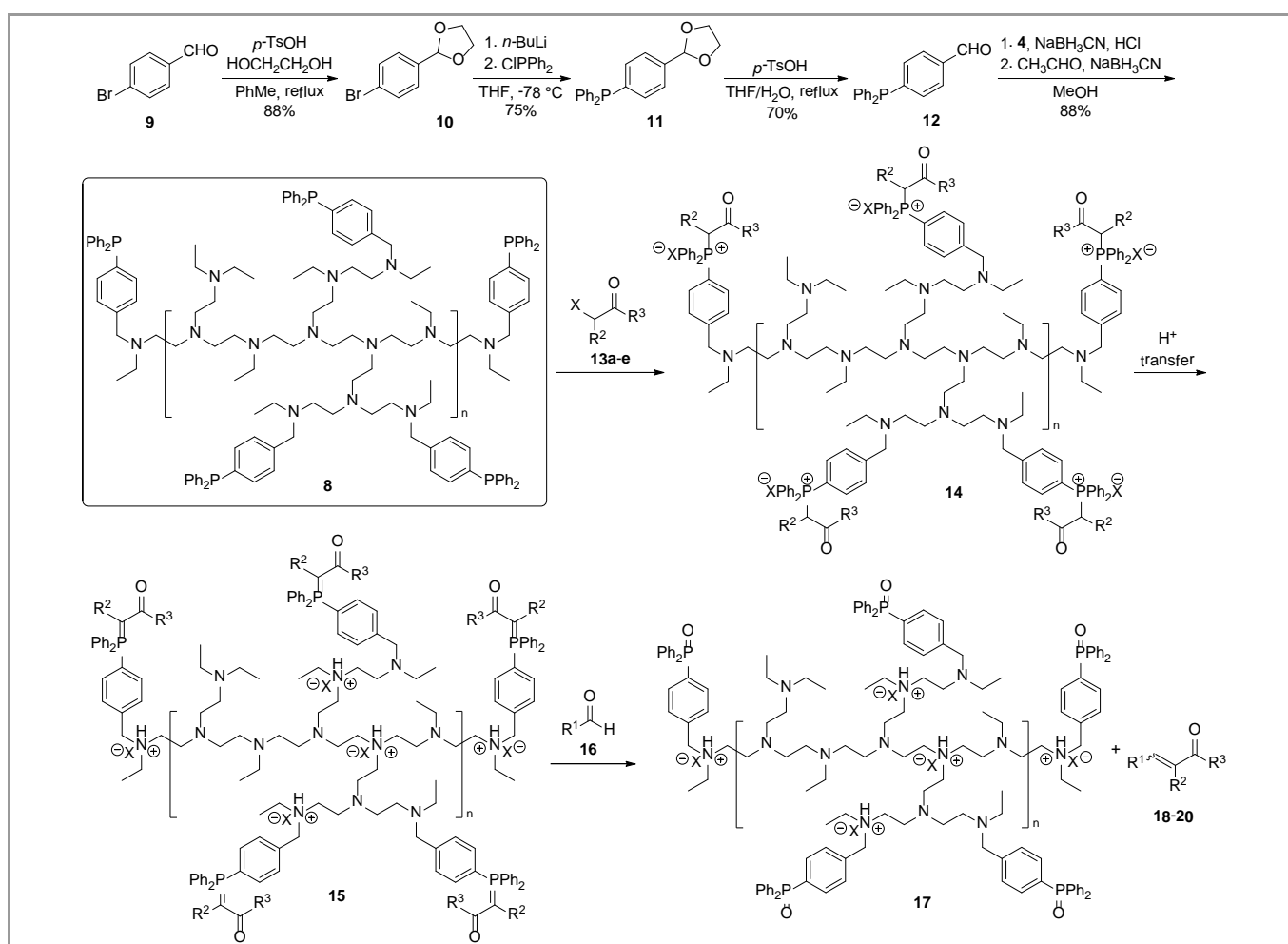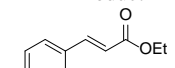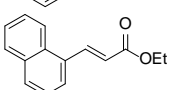
Figure 2 PEI and various derivatives

Scheme 1 Synthesis of **8** and its application in one-pot Wittig reactions
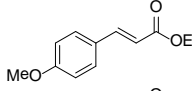
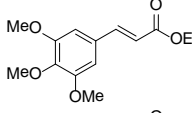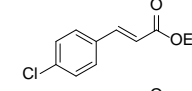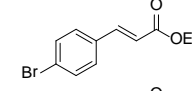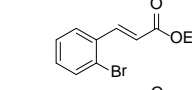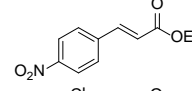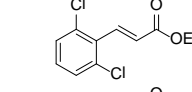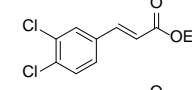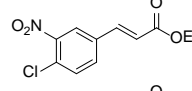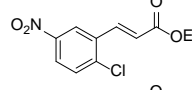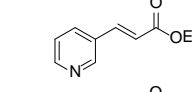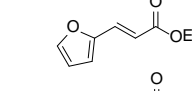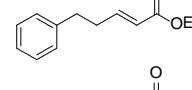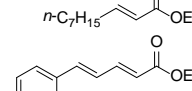With **8** in hand, we next examined its use as a bifunctional reagent in one-pot Wittig reactions. As illustrated in Scheme 1, in these reactions the phosphine moieties of **8** react with activated alkyl halides **13** to form phosphonium salt **14**. Next, the amine groups deprotonate the phosphonium salt groups to form the ylide groups of **15**. Finally these phosphorane groups react with the aldehyde substrate **16** to form polymeric by-product **17** and the desired alkene products **18**-**20**. It is noteworthy that the by-product ammonium salt and phosphine oxide groups are both immobilized on the polymer support, and thus should be separable from the desired alkene product by a simple filtration operation, eliminating the need for an aqueous workup and chromatographic purification.

We first used ethyl bromoacetate (**13a**) and ethyl 2-bromopropionate (**13b**) as the activated alkyl halides in one-pot Wittig reactions with aldehydes **16A**-**Q**. These reactions were performed homogeneously using conditions similar to what we have used before,[12] CHCl₃ at 65 °C (Table 1).[20] At the end of each reaction, the cooled reaction mixture was poured in a mixture of diethyl ether and hexane to induce precipitation of **17**. After filtration and solvent evaporation, the desired product was obtained as the expected mixture of *E* and *Z* isomers. When **13a** was used, **18Aa**-**Qa** were all obtained in excellent yields with typical *E*:*Z* ratios. Importantly, all products were found to be essentially pure diastereomeric mixtures according to ¹H NMR analysis, and did not require any additional purification. As can be seen in Table 1, unsubstituted aromatic aldehydes (entries 1 and 2), electron-rich aromatic aldehydes (entries 3 and 4), electron-poor aromatic aldehydes (entries 5-12), heteroaromatic aldehydes (entries 13 and 14), alkyl aldehydes (entries 15 and 16), and even cinnamaldehyde (entry 17) all worked very well in these reactions. Similarly, ester **13b** was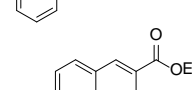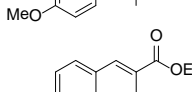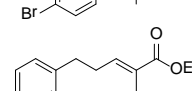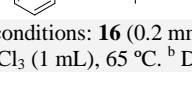 used to synthesize trisubstituted alkenes **19Cb**, **19Fb**, and **19Ob**, and these products were also highly pure after precipitation of **17**, filtration and solvent removal.

Table 1 One-Pot Wittig Reactions Using α-Bromoesters[a]

Entry	Product		Yield (%)	*E*/*Z*[b]
1		**18Aa**	94	89/11
2		**18Ba**	92	95/5
3		**18Ca**	92	80/20
4		**18Da**	86	91/9
5		**18Ea**	95	93/7
6		**18Fa**	95	87/13
7		**18Ga**	97	74/26
8		**18Ha**	100	96/4
9		**18Ia**	97	>99/1
10		**18Ja**	92	91/9
11		**18Ka**	100	93/7
12		**18La**	98	92/8
13		**18Ma**	97	92/8
14		**18Na**	95	90/10
15		**18Oa**	98	91/9
16		**18Pa**	97	91/9
17		**18Qa**	95	87/13
18		**18Cb**	98	93/7
19		**18Fb**	99	95/5
20		**18Ob**	95	>99/1

[a] Reaction conditions: **16** (0.2 mmol), **13a** or **13b** (0.3 mmol), **8** (0.4 mmol), CHCl₃ (1 mL), 65 °C. [b] Determined by ¹H NMR spectroscopy.

We next used α-bromoamide **13c**[12a] (Table 2) and α-bromoketones **13d** and **13e** (Table 3) as the alkyl halide to perform the one-pot Wittig reactions. For the reactions using **13c**-e, we chose a random sample of the aldehydes used in Table 1. Additionally, for reactions with **13c** we also used aldehydes **16R** and **16S** (Table 2, entries 10 and 11). Regardless of which alkyl halide and aldehyde combination we studied, in all cases excellent yield of highly pure desired product was obtained after only precipitation of **17**, filtration and solvent removal.

Finally, since our group has an interest in studying tandem reactions in which the waste of an initial reaction catalyzes a subsequent transformation, we were also interested in evaluating the reactivity of **8** in one-pot

Wittig reactions that were followed immediately by conjugate reduction reactions catalyzed by the phosphine oxide waste.[21-23] In these reactions, **13d** was used as the substrate to react with **16A** and **16F** (Table 4).[24] The α, β-unsaturated alkenes generated in the Wittig reactions (**20Ad** and **20Fd**, respectively) were treated in situ with Cl$_3$SiH. Activation of this reductant by phosphine oxide groups of **17** effected conjugate reduction to afford the final ketone products **21Ad** and **21Fd**. Gratifyingly excellent yield was obtained in both cases and the product obtained directly from the reaction mixture was essentially pure.

Table 2　One-Pot Wittig Reactions Using an α–Haloamide[a]

Entry	Product		Yield (%)	E/Z[b]
1		**19Cc**	93	96/4
2		**19Dc**	98	94/6
3		**19Fc**	94	96/4
4		**19Hc**	100	94/6
5		**19Jc**	94	97/3
6		**19Mc**	98	97/3
7		**19Oc**	95	81/19
8		**19Pc**	95	84/16
9		**19Qc**	96	92/8
10		**19Rc**	87	95/5
11		**19Sc**	95	96/4

[a] Reaction conditions: **16** (0.2 mmol), **13c** (0.3 mmol), **8** (0.4 mmol), CHCl$_3$ (1 mL), 65 ºC. [b] Determined by ^{1}H NMR spectroscopy.

Table 3　One-Pot Wittig Reactions Using α–Haloketones[a]

Entry	Product		Yield (%)	E/Z[b]
1		**20Ad**	95	>99/1
2		**20Fd**	93	>99/1
3		**20Hd**	96	92/8
4		**20Pd**	95	95/5
5		**20Fe**	99	98/2
6		**20Me**	99	92/8
7		**20Oe**	94	92/8
8		**20Pe**	97	97/3

[a] Reaction conditions: **16** (0.2 mmol), **13d** or **13e** (0.3 mmol), **8** (0.4 mmol), CHCl$_3$ (1 mL), 65 ºC. [b] Determined by ^{1}H NMR spectroscopy.

Table 4　Tandem One-Pot Wittig/Conjugate Reduction Reactions.[a]

Entry	Product		Yield (%)
1		**21Ad**	85
2		**21Fd**	90

[a] Reaction conditions: **16** (0.2 mmol), **13d** (0.3 mmol), **8** (0.4 mmol), CHCl$_3$ (1 mL), 65 ºC, followed by HSiCl$_3$ (0.4 mmol), 0 ºC-rt.

In conclusion, we have used commercially available polymer **4** to prepare bifunctional reagent **8** bearing both phosphine and tertiary amine groups, and successfully applied this material in a wide range of one-pot Wittig reactions from which the desired product could be obtained in high yield and purity after only precipitation of the waste, filtration and solvent removal. Reagent **8** has the advantage compared to our previously reported bifunctional polymeric reagents **2** and **3** since it is much more densely functionalized, and thus reactions involving it require less reagent and solvent. We are currently studying the application of **8** in other reactions, and the possibility of preparing a cross-linked version of it that can function as a heterogeneous reagent so the precipitation step can be eliminated and recycling might be possible. The results of these studies will be reported shortly.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

Acknowledgement

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(19) See Supporting Information.

(20) **General Procedure for one-pot Wittig Reactions**
Polymer **8** (0.2 g, 0.4 mmol phosphine) was dissolved in CHCl₃ (1 mL) in a 10-mL round-bottomed flask equipped with a magnetic stirrer and a reflux condenser, followed by **13** (0.3 mmol) and **16** (0.2 mmol). The mixture stirred at 65 ºC until the reaction was determined to be complete by TLC or ¹H NMR analysis. The reaction mixture was then cooled to rt and poured into a mixture of Et₂O (10 mL) and hexane (30 mL) in a beaker. The flask was rinsed with additional Et₂O (10 mL), and the combined organic solution was allowed to stand for 10 min before it was filtered through a short pad of diatomaceous earth, using additional Et₂O (2 x10 mL) for rinsing. The filtrate was concentrated under reduced pressure to afford the desired product in an essentially pure state based on ¹H NMR analysis.
Ethyl cinnamate (8Aa)
¹H NMR (400 MHz, CDCl₃) δ 7.79 (d, *J* = 16.0 Hz, 1H), 7.53-7.51 (m, 2H), 7.38-7.37 (m, 3H), 6.44 (d, *J* = 16.0 Hz, 1H), 4.26 (q, *J* = 7.1 Hz, 2H), 1.34 (t, *J* = 7.1 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 167.1, 144.7, 134.6, 130.3, 129.0, 128.2, 118.4, 60.6, 14.4. MS for $C_{11}H_{12}O_2$: calc 176.1, found 176.1.

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(23) For a recent example of another reaction system in which a by-product of one reaction catalyzes a subsequent transformation, see: Zhu, F.; Xu, P.-W.; Zhou, F.; Wang, C.-H.; Zhou, J. *Org. Lett.* **2015**, *17*, 972.

(24) **General Procedure for Tandem Wittig/Conjugate Reduction Reactions**
The Wittig reaction was conducted as before,[20] but when it was determined to be complete, it was cooled to 0 ºC in an ice-water bath, and HSiCl₃ (0.4 mmol) was added. The reaction mixture was stirred for 2 h at 0 ºC and then warmed to room temperature. After the reaction was determined to be complete by TLC analysis the excess HSiCl₃ and solvent were evaporated under reduced pressure. The resulting mixture was dissolved in CHCl₃ (20 mL) and then added to saturated aq. Na₂CO₃ (20 mL). This was stirred for 30 min, and then the aqueous phase was separated and washed with CH₂Cl₂ (3 x 15 mL). The com-

bined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure to afford the desired product in an essentially pure state based on ^{1}H NMR analysis.

1-(4-Bromophenyl)-3-phenylpropan-1-one (21Ad)
^{1}H NMR (400 MHz, CDCl$_3$) δ 7.82 (d, J = 8.6 Hz, 2H), 7.59 (d, J = 8.6 Hz, 2H), 7.30-7.21 (m, 5H), 3.26 (t, J = 7.5 Hz, 2H), 3.06 (t, J = 7.5 Hz, 2H). ^{13}C NMR (100 MHz, CDCl$_3$) δ 198.3, 141.1, 135.6, 132.0, 129.6, 128.7, 128.5, 128.3, 126.3, 40.5, 30.1. MS for $C_{15}H_{13}BrO$: calc 288.0, found 288.2.

Graphical Abstract:

PEI-TPP