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 alkenic 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. 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. 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 that allow the waste to be removed simply by filtration. 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, 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). Since we were interested in performing one-pot Wittig reactions 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. 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.

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, Figure 2) that is highly loaded with both amine and phosphine groups. In fact, due to its high density of amine groups, PEI has previously been used as a platform in various forms for polymer-supported synthesis and reagents. For example, both Ultraseres (5) and ULTRAMINE (6) have been described in the literature, and most recently 7 has been prepared and used as a catalyst for Henry reactions. 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 NaBH3CN 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. Additionally, 8 exhibited only a single resonance in its 31P NMR spectrum at -6.1 ppm, representing the triarylphosphine moieties. Polymer 8 was found to be soluble in CH2Cl2, CHCl3, 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 1 Phosphine functionalized rasta resins 1-3
Figure 2 PEI and various derivatives

Scheme 1 Synthesis of 8 and its application in one-pot Wittig reactions
Finally these phosphorane groups react with the aldehyde substrate to form polymeric by-product and the desired alkene products. It is noteworthy that the by-product ammonium salt and phosphine oxide 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>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>Yield (%)</th>
<th>E/Z</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>18Aa</td>
<td>94</td>
<td>89/11</td>
</tr>
<tr>
<td>2</td>
<td>18Ba</td>
<td>92</td>
<td>95/5</td>
</tr>
</tbody>
</table>

Table 1  
One-Pot Wittig Reactions Using α-Bromoesters

We next used α-bromoamide 13c12a (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 reductant. In these reactions, 13d was used as the substrate to react with 16A and 16F (Table 4). The α, β-unsaturated alkenes generated in the Wittig reactions (20Ad and 20Fd, respectively) were treated in situ with Cl3SiH. 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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>Yield (%)</th>
<th>E/Z</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>19Cc</td>
<td>93</td>
<td>96/4</td>
</tr>
<tr>
<td>2</td>
<td>19De</td>
<td>98</td>
<td>94/6</td>
</tr>
<tr>
<td>3</td>
<td>19Fe</td>
<td>94</td>
<td>96/4</td>
</tr>
<tr>
<td>4</td>
<td>19He</td>
<td>100</td>
<td>94/6</td>
</tr>
<tr>
<td>5</td>
<td>19Jc</td>
<td>94</td>
<td>97/3</td>
</tr>
<tr>
<td>6</td>
<td>19Me</td>
<td>98</td>
<td>97/3</td>
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<tr>
<td>7</td>
<td>19Oc</td>
<td>95</td>
<td>81/19</td>
</tr>
<tr>
<td>8</td>
<td>19Pc</td>
<td>95</td>
<td>84/16</td>
</tr>
<tr>
<td>9</td>
<td>19Qc</td>
<td>96</td>
<td>92/8</td>
</tr>
<tr>
<td>10</td>
<td>19Re</td>
<td>87</td>
<td>95/5</td>
</tr>
<tr>
<td>11</td>
<td>19Sc</td>
<td>95</td>
<td>96/4</td>
</tr>
</tbody>
</table>

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

**Table 4** Tandem One-Pot Wittig/Conjugate Reduction Reactions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>21Ad</td>
<td>85</td>
</tr>
<tr>
<td>2</td>
<td>21Fd</td>
<td>90</td>
</tr>
</tbody>
</table>

* Reaction conditions: 16 (0.2 mmol), 13d (0.3 mmol), 8 (0.4 mmol), CHCl3 (1 mL), 65 °C, followed by HSiCl3 (0.4 mmol), 0 °C-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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References and Notes

(13) For the use of the oxides of 1 and 3 as a reagent precursors in a wide range of halogenation reactions, see: Xia, X.; Toy, P. H. Beilstein J. Org. Chem. 2014, 10, 1397.
(14) Various structures have been used to represent 4 in various publications. Since we used 4 purchased from the Aldrich Chemical Co., we use the structure shown in its catalog.
See Supporting Information.

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 °C 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 EtO (10 mL) and hexane (30 mL) in a beaker. The reaction mixture was stirred at 50 °C for 20 min before it was filtered through a short pad of diatomaceous earth, using additional EtO (2 x 10 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 = 16.0 Hz, 1H), 4.22 (q, J = 16.0 Hz, 1H), 2.42 (s, 3H), 2.16 (s, 3H), 1.24 (t, J = 7.2 Hz, 3H), 1.0 (s, 3H). 

**Elemental Analysis** Caled for C11H10O2: C 76.66, H 6.95. Found: C 76.71, H 6.92.


**General Procedure for Tandem Wittig/Conjugate Reduction Reactions**

The Wittig reaction was conducted as before, but when it was determined to be complete, it was cooled to 0 °C in an ice-water bath, and HSiCl3 (0.4 mmol) was added. The reaction mixture was stirred for 2 h at 0 °C 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). The mixture was stirred for 30 min, and then the aqueous phase was separated and washed with CH2Cl2 (3 x 15 mL). The com-

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bined organic layer was dried over MgSO₄ and concentrated under reduced pressure to afford the desired product in an essentially pure state based on ¹H NMR analysis.

1-(4-Bromophenyl)-3-phenylpropan-1-one (21Ad)

¹H NMR (400 MHz, CDCl₃) 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). ¹³C NMR (100 MHz, CDCl₃) 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 C₁₅H₁₃BrO: calc 288.0, found 288.2.
Graphical Abstract: