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

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Received: 25.03.2015 Accepted after revision: 20.04.2015 Published online: 18.06.2015 DOI: 10.1055/s-0034-1380810; Art ID: st-2015-w0209-l

**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 the desired products after simple purification procedures. The approach also served efficiently in tandem reaction sequences involving a one-pot Wittig reaction followed by conjugate reduction of the newly formed alkene product in situ. 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-oxvgen double bond of an aldehyde or ketone into a carboncarbon double bond.<sup>1,2</sup> While they are generally very efficient and can be highly stereoselective, Wittig reactions suffer from the drawback that an equivalent of a phosphine oxide byproduct 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 sound.<sup>3</sup> To address this issue, much research has been directed towards developing solutions to the problem of byproduct separation, including the use of polymer-supported phosphines<sup>4</sup> that allow the waste to be removed simply by filtration.<sup>5-7</sup> 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 and that can be easily removed from the desired product after the reaction could be of significant general interest.

We have been developing new organic polymers for use as reagents and catalyst supports,<sup>8,9</sup> and we 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).<sup>10</sup> We were interested in performing one-pot Wittig reactions<sup>11</sup> in which the required phosphorane reagent was formed in situ by deprotonation of a phosphonium salt: therefore, 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**, which were functionalized with tertiary amine groups in addition to the phosphine groups.<sup>12,13</sup> Although these polymer-supported reagents were easily synthesized and more reactive than traditional heterogeneous polymersupported phosphines, they suffered from low loading levels (ca. 1 mmol/g amine and phosphine) because of the polystyrene platform on which they were based.

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)<sup>14</sup> that is highly loaded with both amine and phosphine groups. In fact, because of its high density of amine groups, **4** has previously been used as a platform in various forms for polymer-supported synthesis and reagents.<sup>15</sup> For example, both Ultraresin (**5**)<sup>16</sup> and ULTRAMINE (**6**)<sup>17</sup> have been described in the literature, and, Syn lett

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most recently, **7** has been prepared and used as a catalyst for Henry reactions.<sup>18</sup> 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 afforded high yields of the pure products after simple separation of the polymeric byproduct. 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)<sub>2</sub> 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<sub>3</sub>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<sup>-1</sup>) were converted into tertiary amine groups in **8**.<sup>19</sup> Additionally, **8** exhibited only a single resonance in its <sup>31</sup>P NMR spectrum at  $\delta$  = -6.1 ppm, representing the triarylphosphine moieties. Polymer **8** 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 and 1.9 mmol/g, respectively.

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**. The amine groups then 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 byproduct **17** and the desired alkene



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products **18–20**. It is noteworthy that the byproduct 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 onepot Wittig reactions with aldehydes **16A–Q**. These reactions were performed homogeneously using conditions similar to those we have used before<sup>12</sup> (CHCl<sub>3</sub> at 65 °C; Table 1).<sup>20</sup> At the end of each reaction, the cooled reaction mixture was poured into 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 <sup>1</sup>H 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 **18Cb**, **18Fb**, and **18Ob**, and these products were also highly pure after precipitation of **17**, filtration, and solvent removal.



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Entry	Product		Yield (%)	E/Z <sup>b</sup>
10	CI OEt	18ja	92	91:9
11	O <sub>2</sub> N CI	18Ka	100	93:7
12	O <sub>2</sub> N Cl	18La	98	92:8
13	OEt	18Ma	97	92:8
14	OEt	18Na	95	90:10
15	OEt	180a	98	91:9
16	n-C <sub>7</sub> H <sub>15</sub> OEt	18Pa	97	91:9
17	OEt	18Qa	95	87:13
18	MeO	18СЬ	98	93:7
19	Br	18Fb	99	95:5
20	OEt	18Ob	95	>99:1
<sup>a</sup> Reaction conditions: <b>16</b> (0.2 mmol) <b>13</b> or <b>13b</b> (0.3 mmol) <b>8</b> (0.4 mmol)				

 <sup>a</sup> Reaction conditions: 16 (0.2 mmol), 13a or 13b CHCl<sub>3</sub> (1 mL), 65 °C.
 <sup>b</sup> Determined by <sup>1</sup>H NMR spectroscopic analysis. 0.2 mmol), **13a** (0.3 mmol), **8** (0.4 mmol),

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We then used  $\alpha$ -bromo amide  $13c^{12a}$  (Table 2) and  $\alpha$ bromo ketones 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 from 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 product was obtained after only precipitation of 17, filtration, and solvent removal.



Table 2 (continued)



<sup>a</sup> Reaction conditions: **16** (0.2 mmol), **13c** (0.3 mmol), **8** (0.4 mmol), CHCl<sub>3</sub> (1 mL), 65 °C.

<sup>b</sup> Determined by <sup>1</sup>H NMR spectroscopic analysis.

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.<sup>21–23</sup> In these reactions, **13d** was used as the substrate to react with **16A** and **16F** (Table 4).<sup>24</sup> The  $\alpha$ , $\beta$ -unsaturated alkenes generated in the Wittig reactions (**20Ad** and **20Fd**, respectively) were treated with SiCl<sub>3</sub> in situ. Activation of this reductant by the 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 that was obtained directly from the reaction mixture was essentially pure.

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 an advantage compared to our previously reported bifunctional polymeric reagents **2** and **3** because 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 heteroge-

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neous reagent so the precipitation step can be eliminated and recycling might be possible. The results of these studies will be reported shortly.





6 20Me 99 92:8

7 200e 94 92:8  
8 
$$n - C_7 H_{15}$$
 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 °C.

<sup>b</sup> Determined by <sup>1</sup>H NMR spectroscopic analysis.





 $^a$  Reaction conditions:  ${\bf 16}$  (0.2 mmol),  ${\bf 13d}$  (0.3 mmol),  ${\bf 8}$  (0.4 mmol), CHCl\_3 (1 mL), 65 °C, followed by HSiCl\_3 (0.4 mmol), 0 °C to r.t.

### Acknowledgment

This research was supported financially by the University of Hong Kong and the Research Grants Council of the Hong Kong S. A. R, P. R. of China (Project No. HKU 705510P).

#### **Supporting Information**

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1380810.

#### **References and Notes**

- (1) Wittig, G.; Geissler, G. Justus Liebigs Ann. Chem. 1953, 580, 44.
- (2) For selected recent reviews regarding the Wittig reaction, see:
  (a) Parvatkar, P. T.; Torney, P. S.; Tilve, S. G. Curr. Org. Synth.
  2013, 10, 288. (b) Byrne, P. A.; Gilheany, D. G. Chem. Soc. Rev.
  2013, 42, 6670.
- (3) Constable, D. J. C.; Dunn, P. J.; Hayler, J. D.; Humphrey, G. R.; Leazer, J. L. Jr.; Linderman, R. J.; Lorenz, K.; Manley, J.; Pearlman, B. A.; Wells, A.; Zaks, A.; Zhang, T. Y. *Green Chem.* **2007**, 9, 411.
- (4) For reviews of polymer-supported phosphines and their uses, see: (a) Guino, M.; Hii, K. K. *Chem. Soc. Rev.* 2007, 36, 608.
  (b) Bergbreiter, D. E.; Yang, Y.-C.; Hobbs, C. E. J. Org. Chem. 2011, 76, 6912.
- (5) (a) Camps, F.; Castells, J.; Font, J.; Vela, F. Tetrahedron Lett. 1971, 1715. (b) McKinley, S. V.; Rakshys, J. W. J. Chem. Soc., Chem. Commun. 1972, 134. (c) Heitz, W.; Michels, R. Angew. Chem., Int. Ed. Engl. 1972, 11, 298. (d) Clarke, S. D.; Harrison, C. R.; Hodge, P. Tetrahedron Lett. 1980, 21, 1375. (e) Akelah, A. Eur. Polym. J. 1982, 18, 559. (f) Bernard, M.; Ford, W. T. J. Org. Chem. 1983, 48,

98:2

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326. (g) Bernard, M.; Ford, W. T.; Nelson, E. C. J. Org. Chem. **1983**, 48, 3164. (h) Sieber, F.; Wentworth, P. Jr.; Toker, J. D.; Wentworth, A. D.; Metz, W. A.; Reed, N. N.; Janda, K. D. J. Org. Chem. **1999**, 64, 5188. (i) Westman, J. Org. Lett. **2001**, 3, 3745. (j) Shearouse, W. C.; Mack, J. Green Chem. **2012**, 14, 2771.

- (6) For examples of the use of ion-supported phosphines in Wittig reactions, see: (a) Shimojuh, N.; Imura, Y.; Moriyama, K.; Togo, H. *Tetrahedron* **2011**, *67*, 951. (b) Lebel, H.; Davi, M.; Roy, M.-N.; Zeghida, W.; Charette, A. B. *Synthesis* **2011**, 2275.
- (7) For an example of the conversion of Ph<sub>3</sub>PO waste from Wittig reactions into a filterable salt for easy removal, see: Byrne, P. A.; Rajendran, K. V.; Muldoon, J.; Gilheany, D. G. Org. Biomol. Chem. 2012, 10, 3531.
- (8) For a review on organic polymer supports for organic chemistry, see: Lu, J.; Toy, P. H. Chem. Rev. 2009, 109, 815.
- (9) For recent examples of our research regarding polymer-supported reagents and catalysts, see: (a) Teng, Y.; Toy, P. H. Synlett 2011, 551. (b) Lu, J.; Toy, P. H. Synlett 2011, 659. (c) Lu, J.; Toy, P. H. Synlett 2011, 1723. (d) Lu, J.; Toy, P. H. Synlett 2011, 2985. (e) Diebold, C.; Becht, J.-M.; Lu, J.; Toy, P. H.; Le Drian, C. Eur. J. Org. Chem. 2012, 893. (f) Lu, J.; Toy, P. H. Pure Appl. Chem. 2013, 85, 543. (g) Yang, Y.-C.; Leung, D. Y. C.; Toy, P. H. Synlett 2013, 24, 1870. (h) Yang, Y.-C.; Toy, P. H. Synlett 2014, 25, 1319. (i) Toy, P. H. Pure Appl. Chem. 2014, 86, 1651. (j) Derible, A.; Yang, Y.-C.; Toy, P. H.; Becht, J.-M.; Le Drian, C. Tetrahedron Lett. 2014, 55, 4331. (k) Beaupérin, M.; Smaliy, R.; Cattey, H.; Meunier, P.; Ou, J.; Toy, P. H.; Hierso, J.-C. Chem. Commun. 2014, 50, 9505. (l) Beaupérin, M.; Smaliy, R.; Cattey, H.; Meunier, P.; Ou, J.; Toy, P. H.; Hierso, J.-C. ChemPlusChem 2015, 80, 119.
- (10) Leung, P. S.-W.; Teng, Y.; Toy, P. H. Synlett 2010, 1997.
- (11) (a) Wu, J.; Yue, C. Synth. Commun. 2006, 36, 2939; and references cited therein. (b) Choudary, B. M.; Mahendar, K.; Kantam, M. L.; Ranganath, K. V. S.; Athar, T. Adv. Synth. Catal. 2006, 348, 1977. (c) El-Batta, A.; Jiang, C.; Zhao, W.; Anness, R.; Cooksy, A. L.; Bergdahl, M. J. Org. Chem. 2007, 72, 5244.
- (12) (a) Leung, P. S.-W.; Teng, Y.; Toy, P. H. Org. Lett. 2010, 12, 4996.
  (b) Teng, Y.; Lu, J.; Toy, P. H. Chem. Asian J. 2012, 7, 351.
- (13) For the use of the oxides of 1 and 3 as 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 a range of publications. Since we used 4 purchased from the Aldrich Chemical Co., we use the structure shown in its catalogue.
- (15) Haimov, A.; Cohen, H.; Neumann, R. J. Am. Chem. Soc. **2004**, 126, 11762.
- (16) (a) Rademann, J.; Barth, M. Angew. Chem. Int. Ed. 2002, 41, 2975.
  (b) Barth, M.; Rademann, J. J. Comb. Chem. 2004, 6, 340.
  (c) Barth, M.; Tasadaque, S.; Shah, A.; Rademann, J. Tetrahedron 2004, 60, 8703. (d) Barth, M.; Fischer, R.; Brock, R.; Rademann, J. Angew. Chem. Int. Ed. 2005, 44, 1560.
- (17) Roice, M.; Christensen, S. F.; Meldal, M. *Chem. Eur. J.* **2004**, *10*, 4407.
- (18) Ganesan, S. S.; Ganesan, A.; Kothandapani, J. Synlett **2014**, 25, 1847.

- (19) See the Supporting Information.
- (20) **General Procedure for One-Pot Wittig Reactions:** Polymer **8** (0.2 g, 0.4 mmol phosphine) was dissolved in CHCl<sub>3</sub> (1 mL) in a 10-mL round-bottomed flask equipped with a magnetic stirrer and a reflux condenser, and **13** (0.3 mmol) and **16** (0.2 mmol) were added. The mixture was stirred at 65 °C until the reaction was determined to be complete by TLC or <sup>1</sup>H NMR analysis. The reaction mixture was then cooled to r.t. and poured into a mixture of Et<sub>2</sub>O (10 mL) and hexane (30 mL) in a beaker. The flask was rinsed with additional Et<sub>2</sub>O (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 Et<sub>2</sub>O (2 × 10 mL) for rinsing. The filtrate was concentrated under reduced pressure to afford the desired product in an essentially pure state based on <sup>1</sup>H NMR analysis.
  - **Ethyl Cinnamate (8Aa):** <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 7.79 (d, J = 16.0 Hz, 1 H), 7.53–7.51 (m, 2 H), 7.38–7.37 (m, 3 H), 6.44 (d, J = 16.0 Hz, 1 H), 4.26 (q, J = 7.1 Hz, 2 H), 1.34 (t, J = 7.1 Hz, 3 H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ = 167.1, 144.7, 134.6, 130.3, 129.0, 128.2, 118.4, 60.6, 14.4. MS: m/z calcd for C<sub>11</sub>H<sub>12</sub>O<sub>2</sub>: 176.1; found: 176.1.
- (21) Lu, J.; Toy, P. H. Chem. Asian J. 2011, 6, 2251.
- (22) For similar reactions studied by others and the inspiration for our research in this area, see: (a) Sugiura, M.; Sato, N.; Kotani, S.; Nakajima, M. *Chem. Commun.* **2008**, 4309. (b) Cao, J.-J.; Zhou, F.; Zhou, J. *Angew. Chem. Int. Ed.* **2010**, *49*, 5096. (c) Chen, L.; Shi, T. D.; Zhou, J. *Chem. Asian J.* **2013**, *8*, 556. (d) Chen, L.; Du, Y.; Zeng, X.-P.; Shi, T.-D.; Zhou, F.; Zhou, J. Org. Lett. **2015**, *17*, 1557.
- (23) For a recent example of another reaction system in which a byproduct 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,<sup>[20]</sup> but when it was determined to be complete, the mixture was cooled to 0 °C in an ice-water bath, and HSiCl<sub>3</sub> (0.4 mmol) was added. The reaction mixture was stirred for 2 h at 0 °C and then warmed to room temperature. When the reaction was determined to be complete by TLC analysis, the excess HSiCl<sub>3</sub> and solvent were evaporated under reduced pressure. The resulting mixture was dissolved in CHCl<sub>3</sub> (20 mL) and then added to sat. ag Na<sub>2</sub>CO<sub>2</sub> (20 mL). The mixture was stirred for 30 min, then the aqueous phase was separated and washed with  $CH_2Cl_2$  (3 × 15 mL). The combined organic layer was dried over MgSO<sub>4</sub> and concentrated under reduced pressure to afford the desired product in an essentially pure state based on <sup>1</sup>H NMR analysis. 1-(4-Bromophenyl)-3-phenylpropan-1-one (21Ad): <sup>1</sup>H NMR  $(400 \text{ MHz}, \text{CDCl}_3)$ :  $\delta = 7.82 (d, J = 8.6 \text{ Hz}, 2 \text{ H}), 7.59 (d, J = 8.6 \text{ Hz}, 2 \text{ H})$ 2 H), 7.30–7.21 (m, 5 H), 3.26 (t, J = 7.5 Hz, 2 H), 3.06 (t, J = 7.5 Hz, 2 H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  = 198.3, 141.1, 135.6, 132.0, 129.6, 128.7, 128.5, 128.3, 126.3, 40.5, 30.1. MS: m/z calcd for C<sub>15</sub>H<sub>13</sub>BrO: 288.0; found 288.2.