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Chromatography-Free Wittig Reactions Using a Bifunctional Polymeric Reagent

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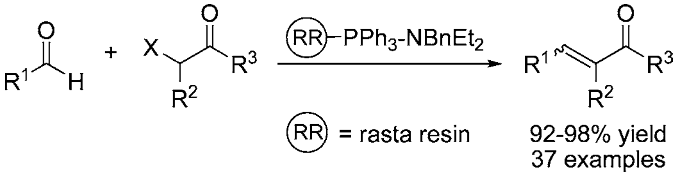
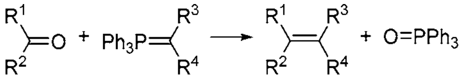
ABSTRACT



The first example of a polystyrene bearing two distinct reagent groups has been prepared. This phosphine and amine functionalized material was used in one-pot Wittig reactions with an aldehyde and either an α-halo-ester, -ketone, or -amide. Due to the heterogeneous nature of the polymer, the desired alkene product of these reactions could be isolated in excellent yield in essentially pure form after only filtration and solvent removal.

The Wittig reaction, first reported over half a century ago,[1] has a long and illustrious history. It is a widely used method for the conversion of the carbon−oxygen double bond of an aldehyde or a ketone into a carbon−carbon double bond by the use of a phosphorane reagent (eq 1). It unfortunately suffers from the fact that an equivalent of $PPh_3{=}O$ is formed as a byproduct, and thus the desired alkene product can be difficult to purify.[2] Thus, the Wittig reaction is neither atom economical nor environmentally friendly. Therefore much research has been directed toward developing versions of it that are either catalytic in the required phosphorus reagent[3,4] or that use a reagent that is easy to separate from the reaction mixture. In the later context, the use of both soluble[5] and insoluble[6] polymer-supported phosphines has been reported over the years. However, these previously described materials and methodologies all suffer from drawbacks, such as inefficient reactions or lengthy reagent synthesis, and are not widely used. For example, one of the more recent reports in this context describes the use of cross-linked polystyrene-supported PPh_3 with microwave heating, where the desired Wittig reaction products were obtained in between 0 and 95% after preparative reverse-phase HPLC.[7]



$$R^1R^2C{=}O + Ph_3P{=}CR^3R^4 \longrightarrow R^1R^2C{=}CR^3R^4 + O{=}PPh_3 \quad (1)$$

We have been studying various polymer supports[8] and the synthesis and use of numerous polymer-supported phos-

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phines.[9] Most recently we reported the use of the rasta resin architecture[10] to prepare **1** (Figure 1) that afforded nearly quantitative yields in one-pot Wittig reactions when it was mixed with an α -halo carbonyl compound, Et_3N and an aldehyde.[11,12] The improved efficiency of **1** compared to other heterogeneous polymer-supported phosphines in Wittig reactions was attributed to the fact that the phosphine reagent groups were attached to the flexible grafts of the polymer that are readily solvent accessible. Thus, **1** is not dependent upon swelling in the reaction medium as are the other previously reported or commercially available cross-linked phosphine functionalized polymers. Additionally, we have investigated the concept of attaching multiple different catalytic groups to a single polymer backbone and have reported examples of such materials bearing combinations of phosphine and phenol groups.[13] Herein we report the merging of these two areas of research and describe what is to our knowledge the first example of a bifunctional polymer bearing two distinct reagent groups and its use in one-pot Wittig reactions.

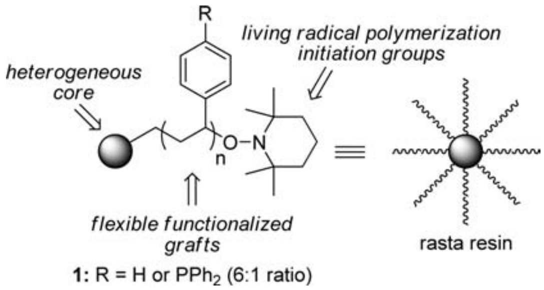
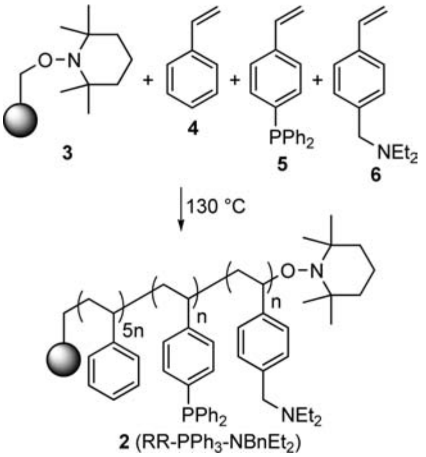
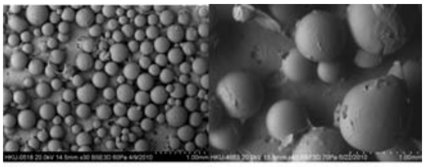


Figure 1. Rasta resin concept.

To synthesize a bifunctional rasta resin possessing both phosphine and amine groups, the synthesis of **1** was modified to incorporate an amine monomer (Scheme 1). Thus, the heterogeneous core **3** was prepared as reported,[11] and was then subjected to living polymerization with a 5:1:1 molar mixture of styrene (**4**), phosphine monomer **5**,[9a] and amine monomer **6**[14] to afford **2**. **4** was added to impart flexibility in the grafts. Elemental analysis was used to determine the loading level of **2** to be 1.05 mmol g^{-1} in phosphine and 1.06 mmol g^{-1} in amine, and gel-phase ^{31}P NMR analysis indicated that no oxidation of the phosphine groups occurred. Scanning electron miscroscopy was performed and both core **3** (Figure 2A) and **2** (Figure 2B) were spherical in shape, with the later, not surprisingly, being generally larger in diameter.

Scheme 1. Synthesis of **2**





(A) **3** (B) **2**

Figure 2. SEM images.

After **2** was prepared, its use in one-pot Wittig reactions of aldehydes **A**−**L** with α-halo carbonyl compounds **a**−**c** was examined (Table 1). It was envisioned that the phosphine groups of **2** would react with **a**−**c** to form the corresponding phosphonium salts and that these in turn would be deprotonated intramolecularly by the amine groups to form the reactive phosphorane moieties (Scheme 2). These reactions were setup using the aldehyde substrate as the limiting reagent and **2** as the reagent most in excess. In this way, the excess of **a**−**c**, compared to **A**−**L**, would be completely reacted with **2** and not contaminate the desired products at the end of the reactions, allowing **Aa**−**Lc** to be isolated in pure form as a mixture of stereoisomers after only filtration and solvent removal. Thus, a series of aryl aldehydes (entries 1−9), an allylic aldehyde (entry 10), and a pair of aliphatic aldehydes (entries 11 and 12) were converted into the corresponding alkenes by a mixture of **2** and **a**−**c** in excellent yields with stereoselectivities similar to what has been

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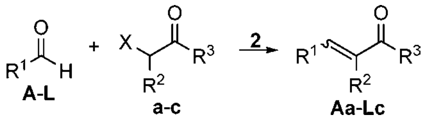
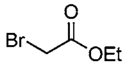
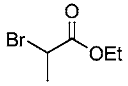
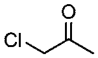
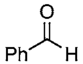
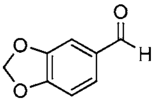
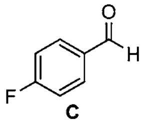
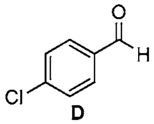
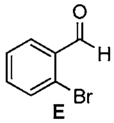
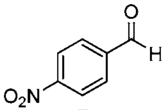
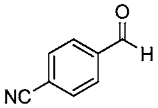
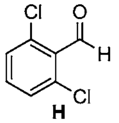
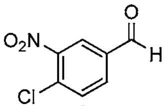
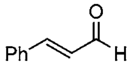
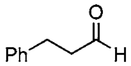
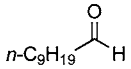
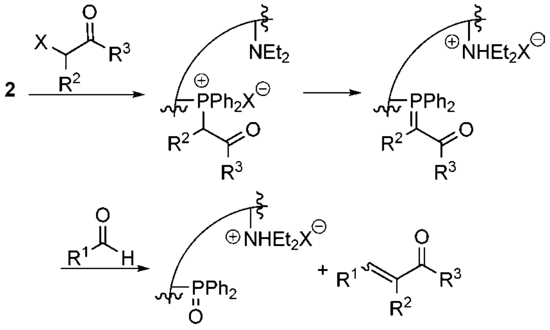
Table 1. One-Pot Wittig Reactions Using **2**



		 **a**		 **b**		 **c**	
entry	aldehyde	yield (%)[a]	*E*:*Z*[d]	yield (%)[b]	*E*:*Z*[d]	yield (%)[c]	*E*:*Z*[d]
1	 **A**	**Aa**, 92	97:3	**Ab**, 93	90:10	**Ac**, 94	94:6
2	 **B**	**Ba**, 97	90:10	**Bb**, 92	90:10	**Bc**, 94	99:1
3	 **C**	**Ca**, 97	94:6	**Cb**, 95	96:4	**Cc**, 95	99:1
4	 **D**	**Da**, 98	93:7	**Db**, 94	90:10	**Dc**, 96	99:1
5	 **E**	**Ea**, 98	83:17	**Eb**, 93	93:7	**Ec**, 96	86:14
6	 **F**	**Fa**, 98	95:5	**Fb**, 96	93:7	**Fc**, 93	98:2
7	 **G**	**Ga**, 96	94:6	**Gb**, 95	96:4	**Gc**, 96	99:1
8	 **H**	**Ha**, 95	81:19	**Hb**, 95	96:4	**Hc**, 93	98:2
9	 **I**	**Ia**, 96	93:7	**Ib**, 92	93:7	**Ic**, 94	83:17
10	 **J**	**Ja**, 94	92:8	**Jb**, 95	98:2	**Jc**, 94	98:2
11	 **K**	**Ka**, 95	93:7	**Kb**, 93	98:2	**Kc**, 92	99:1
12	 **L**	**La**, 96	92:8	**Lb**, 94	90:10	**Lc**, 93	99:1

[a] Isolated yield of reactions using 0.5 mmol of **A**−**L**, 0.9 mmol of **a** and 1.0 mmol of **2** in 5 mL of CH_2Cl_2 stirring at room temperature for 24 h. [b] Isolated yield of reactions using 0.5 mmol of **A**−**L**, 0.9 mmol of **b** and 1.0 mmol of **2** in 5 mL of CH_2Cl_2 stirring at 50 °C for 48 h. [c] Isolated yield of reactions using 0.5 mmol of **A**−**L**, 0.9 mmol of **c** and 1.0 mmol of **2** in 5 mL of CH_2Cl_2 stirring at 50 °C for 48 h. [d] Determined by ^1H NMR analysis.

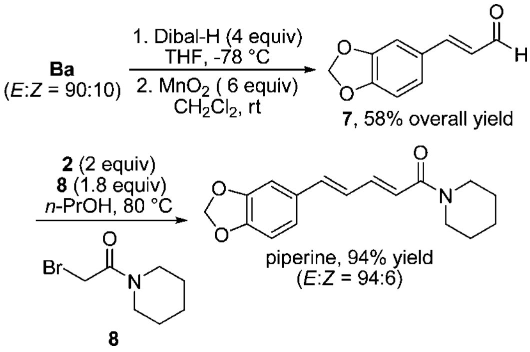
Scheme 2. Schematic of Wittig Reactions Using **2**



reported for similar one-pot Wittig reactions,[12] using a very simple process (mix, stir, filter, and concentrate) that is readily amenable to automation and use in high-throughput parallel synthesis.

After demonstrating that **2** is useful in one-pot Wittig reactions where isolation of a pure product is simple and fast, we sought to use it in a new route for the synthesis of piperine, one of the major flavor components of black pepper (Scheme 3).[16,17] Thus, **Ba** was converted to the corresponding aldehyde **7** in a 2-step reduction−oxidation sequence in 58% overall yield. Purification of **7** allowed for the removal of most of the *Z*-isomer that resulted from using **Ba** as a mixture of stereoisomers. Finally, piperine was prepared in 94% yield from **7** using a second one-pot Wittig reaction using **8** as the α-halo carbonyl reagent. LC−MS analysis of our synthetic piperine indicated that we obtained a 94:6 ratio of 2*E*,4*E*- to 2*Z*,4*E*-piperine. A trace of a compound with a slightly longer retention time and the same mass was also detected, and this is assumed to be 2*E*,4*Z*-piperine.

Scheme 3. Synthesis of Piperine



In conclusion, we have synthesized the first example of a bifunctional polymeric reagent and successfully used this material in a wide range of one-pot Wittig reactions. In all cases examined, only filtration and solvent removal were required to obtain a pure mixture of alkene product isomers. Studies focusing on regenerating **2** using recently reported reduction methodologies[17] are currently underway as are attempts to utilize the phosphine oxide groups of the recovered spent polymer to catalyze tandem reactions of the Wittig reaction products.[18]

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Supporting Information Available: Experimental details and characterization data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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