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Rasta Resin-PPh₃ and Its Use in Chromatography-Free Wittig Reactions

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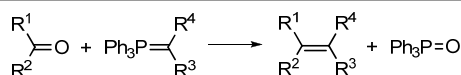
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Abstract: Rasta resin-PPh₃ (**RR-PPh₃**), a new heterogeneous polystyrene-based phosphine, has been synthesized and used in one-pot Wittig olefination reactions of aldehydes. In these reactions an excess of **RR-PPh₃** was used for the *in situ* generation of the phosphorane reactant, and allowed for isolation of a high yield of very pure alkene product after only filtration and solvent removal. The excellent results obtained in this study are attributed to the flexible nature of the rasta resin structure, which makes it less dependant upon swelling than other heterogeneous polystyrene materials previously used to support phosphine reagents in Wittig reactions.

Key words: polymer-supported reagent, polystyrene, phosphine, phosphorane, Wittig reaction

Carbon-carbon double bonds constitute one of the central functional groups in organic chemistry, and an important method for synthesizing such bonds is the Wittig reaction. This transformation involves the use of phosphorane reagent to transfer an alkylidene group to an aldehyde or ketone group, with concurrent transfer of the original carbonyl oxygen to phosphorous (Scheme 1).¹ Usually the phosphorane is prepared by reaction of a tertiary phosphine, typically PPh₃, with an alkyl halide followed by deprotonation of the thus formed phosphonium salt with an appropriate base.



Scheme 1 The Wittig reaction

While the Wittig reaction is very reliable and predictable, one of its shortcomings is the fact that a stoichiometric amount of a phosphine oxide byproduct is formed that must be separated from the desired alkene product. This drawback and the associated costs of product purification in terms of manpower, solvent and waste generated, limits the use of the Wittig reaction in industrial applications, and thus, more environmentally benign methods for performing this transformation are highly desirable.² One strategy that has been examined to address this issue and to make the Wittig reaction less polluting involves changing the role of the phosphine reagent, or a surrogate for it, to that of a catalyst.^{3,4} Another approach has been to use a heterogeneous supported phosphine reagent so that the oxide byproduct can be removed from the desired product simply by filtration, and this is the focus of the current research.

There have been numerous reports in the literature regarding the use of heterogeneous polystyrene-supported PPh₃ reagents in Wittig reactions.⁵ However, despite the fact that such phosphines are commercially available

from numerous sources, this methodology has not been widely used. This is perhaps due to the wide range of results reported in the literature. For example, the most recent detailed study of such polymer-assisted reactions was reported by Westman.⁶ He performed one-pot reactions in which the aldehyde substrate was mixed together with the reagents required for the *in situ* generation of the phosphorane reagent,⁷ with microwave heating, and reported isolated yields of pure product ranging from 0 to 95% (15 examples) after preparative reverse-phase HPLC (Scheme 2).



Scheme 2 One-pot Wittig reactions

We have synthesized and studied numerous polymer-supported phosphines,^{8,9} and based on our observation that the presence of polar groups reduces the ability of cross-linked polystyrene to swell,¹⁰ agreed with the notion that the poor results reported in the literature were most likely due to the structure of the polymer-supported phosphines used and their need to be swollen so that substrate molecules can access all of the phosphorane groups.¹¹ Therefore, in order to avoid the issue of decreased polymer swelling caused by the presence of a high concentration of phosphorane groups, we wanted to prepare a heterogeneous polymer-supported phosphine for which substrate accessibility is not dependant upon swelling, and use it in Wittig reactions. While numerous organic polymer structures have been used to support reagents for organic synthesis,¹² we were drawn to the rasta resin architecture that has functional group bearing grafts attached to a cross-linked polystyrene core, since the location of the reagent groups on flexible and solvent-accessible “hairs” should reduce or eliminate the need for resin swelling (Figure 1).¹³

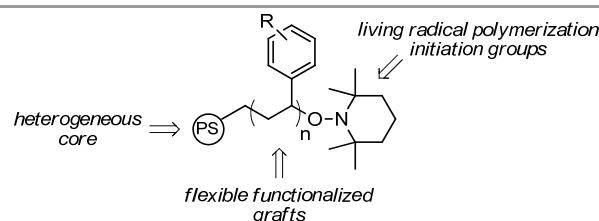
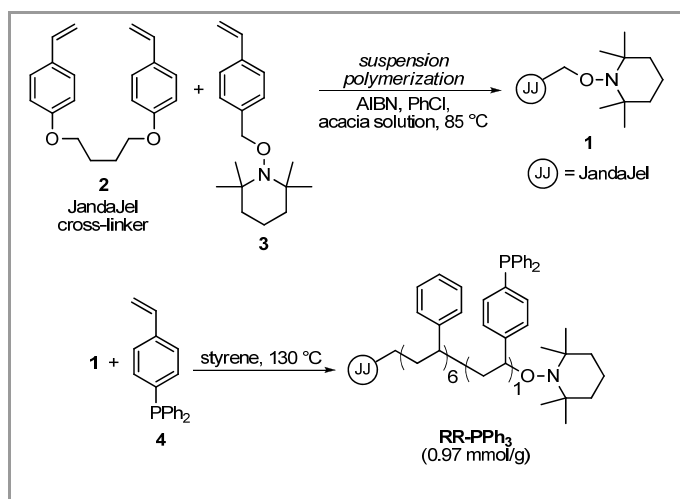


Figure 1 The rasta resin concept

In order to prepare rasta resin-PPh₃ (**RR-PPh₃**), we first synthesized the heterogeneous core **1**, which bears living radical polymerization initiator groups (Scheme 3). This

was achieved by suspension co-polymerization of the JandaJel cross-linker (**2**),¹⁴ chosen over more typically used divinylbenzene due to its increased flexibility, with the ether formed between reduced TEMPO and 4-vinylbenzyl chloride (**3**).¹⁵ It should be noted, however, that in principle any cross-linker, including divinylbenzene, should work with the rasta resin concept. Core **1** was then subjected to co-polymerization of phosphine bearing monomer **4**^{8a} and styrene (for additional flexibility) to afford **RR-PPh₃**. This material was characterized by elemental analysis to determine the phosphine loading level (0.97 mmol/g), and ³¹P NMR analysis was performed to confirm the oxidation state of the phosphine groups.¹⁵ Finally, SEM analysis was conducted to compare the size and morphology of **1** and **RR-PPh₃**. As can be seen in Figure 2 (scale: 1 cm = 1 mm) both **1** and **RR-PPh₃** are generally spherical in shape, and the latter grew to be much larger in diameter than its precursor.



Scheme 3 Synthesis of **RR-PPh₃**

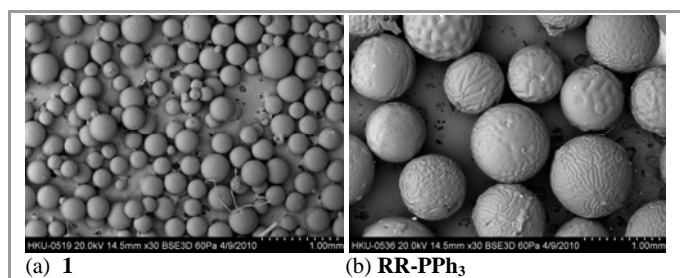


Figure 2 SEM images

After scaling up the synthesis and preparing 10's of grams of **RR-PPh₃**, we examined its use in one-pot Wittig reactions with a range of aldehyde substrates and alkyl halide reagents (Table 1). For these reactions we used Et₃N as the base for the deprotonation of the *in situ* formed phosphonium salt, and a larger excess of **RR-PPh₃** (2.0 equivalents) compared to the alkyl halide (1.5 equivalents) so that the latter would completely react with the polymer-bound phosphine groups, and not be mixed with the desired product at the end of the reaction.¹⁶ Furthermore, it was anticipated that the triethylammonium salt formed could be removed by filtration through

silica gel, and that the excess Et₃N used would be volatile. Thus, only minimal product purification would be required. As can be seen in Table 1, reaction conditions were optimized for each alkyl halide, since some were less reactive than others, and from our observations, formation of the phosphonium salt was generally rate-limiting in the reaction sequence. Some representative literature results using PPh₃ in corresponding reactions are included for comparison.

The alkyl halides studied in these reactions included a primary α -halo ester (entries 1-4), a secondary α -halo ester (entries 5-8), a pair of α -halo ketones (entries 9-13), and a α -halo amide (entries 14 and 15). The aldehydes examined included various benzaldehydes (both electron-rich and -poor), and an aliphatic (3-phenylpropanal) and an allylic (*trans*-cinnamaldehyde) aldehyde. These reactants were combined randomly to test the versatility and generality of our methodology. Gratifyingly, conditions were found that allowed for very high yield of all desired products to be formed. The fact that these reactions work well with both CH₂Cl₂ (entries 1-13) and 1-PrOH (entries 14 and 15) as the solvent highlights the versatility of **RR-PPh₃**, and demonstrates that resin swelling is not mandatory. Regardless of the exact conditions used, essentially quantitative yield of the expected mixture of *E*- and *Z*-stereoisomers of the alkene product was recovered after only filtration of the reaction mixture through a plug of silica gel, washing of the polymer and removal of the solvent. Significantly, in all cases the product was highly pure and no trace of contamination by phosphine or amine by-products was detected by ¹H NMR. Finally, the ratios of *E*- to *Z*-stereoisomers were similar to what has been reported in the literature for similar reactions using PPh₃.^{7,15} Thus, these reactions were simple to perform, and isolation of pure products produced much less waste than is normally the case with typical Wittig reactions.

In conclusion, we have applied the rasta resin architecture in the synthesis of a novel heterogeneous polystyrene-based phosphine, **RR-PPh₃**, and used this material as a reagent in a wide range of one-pot Wittig reactions. In all cases studied, the product from these reactions did not require purification beyond filtration, and was isolated in essentially quantitative yield. The high yields obtained in this study are significantly better than what has been previously reported using other heterogeneous polymer-supported PPh₃ reagents. Encouraged by these findings, we are currently examining the use of **RR-PPh₃** to prepare preformed phosphoranes, and the application of these with microwave heating in order to improve the Wittig reaction methodology we describe here by shortening the required reaction time. Furthermore we are investigating the recycling of the oxidized **RR-PPh₃** recovered at the end of the reactions using the mild conditions recently reported by Tanaka and co-workers.¹⁷ The results of these studies will be reported in due course.





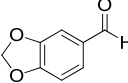

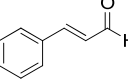



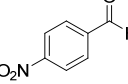

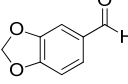

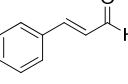



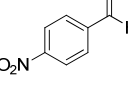

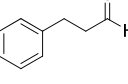


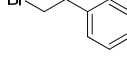
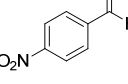
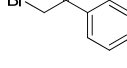

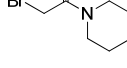
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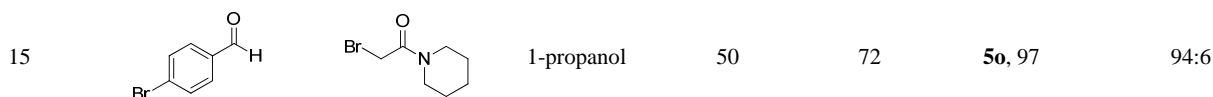
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Table 1 Wittig reactions using **RR-PPh₃**¹⁶

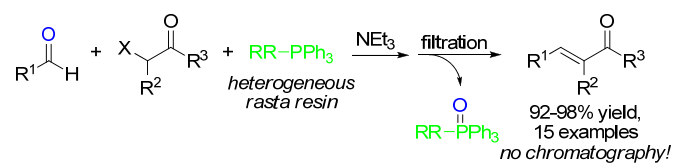
Entry	Aldehyde	Alkyl halide	Solvent	Temperature (°C)	Time (h)	Yield (%) ^a	E:Z ^b
	$\text{R}^1\text{CHO} + \text{X-CH(R}^2\text{)-CO-R}^3 \xrightarrow[\text{solvent}]{\text{RR-PPh}_3, \text{NEt}_3} \text{R}^1\text{-CH=C(R}^2\text{)-CO-R}^3$ <p style="text-align: center;">X = Cl or Br 5 (major isomer)</p>						
1			CH ₂ Cl ₂	25	12	5a , 92 (96) ^c (93) ^d	96:4 (99:1) ^c (93:7) ^d
2			CH ₂ Cl ₂	25	12	5b , 98	83:17
3			CH ₂ Cl ₂	25	72	5c , 98	93:7
4			CH ₂ Cl ₂	25	72	5d , 96 (82) ^c	90:10 (99:1) ^c
5			CH ₂ Cl ₂	50	36	5e , 97	98:2
6			CH ₂ Cl ₂	50	30	5f , 98	97:3
7			CH ₂ Cl ₂	50	72	5g , 98	97:3
8			CH ₂ Cl ₂	50	72	5h , 94	92:8
9			CH ₂ Cl ₂	50	36	5i , 96	99:1
10			CH ₂ Cl ₂	50	24	5j , 98	99:1
11			CH ₂ Cl ₂	50	60	5k , 98	99:1
12			CH ₂ Cl ₂	50	72	5l , 98 (91) ^d	96:4 (90:10) ^d
13			CH ₂ Cl ₂	50	22	5m , 98 (93) ^d	96:4 (93:7) ^d
14			1-propanol	50	36	5n , 98	96:4



^aIsolated yield of reactions using 0.5 mmol of aldehyde. ^bDetermined by ¹H-NMR analysis. ^cTaken from reference 7b. ^dTaken from reference 7c.

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- (15) See Supporting Information for details.
- (16) **General Procedure for Wittig Reactions:**
To a solution of the aldehyde (0.5 mmol) and the alkyl halide (0.75 mmol) in the appropriate solvent (5 mL), was added **RR-PPh₃** (1.0 mmol), followed by NEt₃ (1.0 mmol). The reaction mixture was stirred at the indicated temperature until TLC analysis indicated that the aldehyde was completely consumed, and then filtered through a plug of silica gel. After washing the polymer with CH₂Cl₂ (2 × 50 mL) the combined filtrate was concentrated *in vacuo* to afford pure product. All alkene products were characterized by ¹H- and ¹³C-NMR spectroscopy. Stereoisomeric ratios were determined by ¹H-NMR spectroscopy.
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Rasta Resin-PPh₃ and Its Use in Chromatography-Free Wittig Reactions