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Multifunctional organic polymeric catalysts and reagents*

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Abstract: A series of polystyrenes bearing multiple different functional groups has been synthesized, and these materials have been used as catalysts and reagents in a variety of organic reactions. Polymers functionalized with various combinations of amine, phenol, phosphine, and thiourea groups have been prepared in both non-cross-linked (soluble) and cross-linked (insoluble) formats. Reactions catalyzed by these polymers include Morita–Baylis–Hillman (MBH), alkyne to 1,3-diene isomerization, and decarboxylative Doebner–Knoevenagel reactions. Furthermore, Wittig and tandem Wittig/reduction reactions have been performed using heterogeneous polymeric reagents possessing a combination of amine and phosphine groups.

Keywords: Doebner–Knoevenagel reactions; organocatalysis; polymer-supported catalysts; polymer-supported reagents; polystyrene; reductive aldol reactions; Wittig reactions.

INTRODUCTION

During the course of some studies regarding the use of polystyrene-supported phosphines as catalysts for variations of the Morita–Baylis–Hillman (MBH) reaction [1], we prepared a series of cross-linked polystyrenes possessing functional groups such as nitrile, ester, alcohol, or ether groups in addition to the catalytic nucleophilic phosphine moieties [2]. The purpose of these secondary functional groups was to see if they improved swelling of the resins, and thus the catalytic efficiency of the anchored phosphine groups. We were rather surprised to find that even though a polymer functionalized with both benzyl alcohol and triarylphosphine groups did not swell appreciably in most organic solvents examined, moderate-to-good product yields could be obtained from intermolecular aza-MBH reactions using it as the catalyst. Since it is commonly believed that the more a resin swells the more accessible the catalyst groups attached to it are to dissolved substrate molecules [3], and that a high degree of resin swelling is generally thought to be required for good results, we found our observation to be curious.

After considerable deliberation, we came to the conclusion that a plausible explanation for our finding was that the hydroxyl groups were cooperatively catalyzing the reactions by hydrogen-bond activation of the substrates, and this additional catalysis helped to overcome the reduced substrate accessibility to the catalytic groups due to the lack of polymer swelling. In order to find evidence or precedent for our belief, we undertook a thorough literature search that turned up only a few examples of multifunctional organic polymer-supported catalysts, especially where different organic groups immobilized on the same polymer work together to catalyze reactions. For example, Bergbreiter and co-workers attached unreactive dye groups to polymers that also supported a catalyst in order to visualize

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their location [4], and Sasai et al. added two different metal cations to 2,2'-dihydroxy-1,1'-binaphthalene (BINOL)-functionalized polymers to generate bifunctional catalysts [5]. To our knowledge, the only examples of organic polymers functionalized with two distinct reactive organic groups that may work together to cooperatively effect a reaction are the cross-linked polystyrene resin with both dimethylaminopyridine (DMAP) and pyridine groups reported by Fréchet et al. that was used in alcohol acylation reactions [6], and the series of polyolefins functionalized with both imidazole and weakly acidic groups, such as **1–3** (Fig. 1), described by Overberger and co-workers [7], that were used as catalysts for ester hydrolysis reactions. Considering our extensive experience in developing polymer-supported catalysts and reagents [8,9], and using combinations of these materials to perform organic reactions [10], we were interested to further study the scope and utility of such multifunctional organic polymeric catalysts.

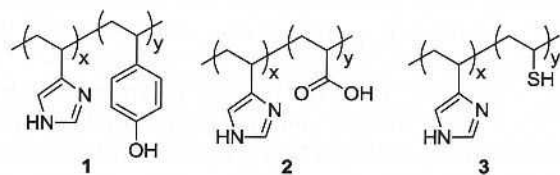
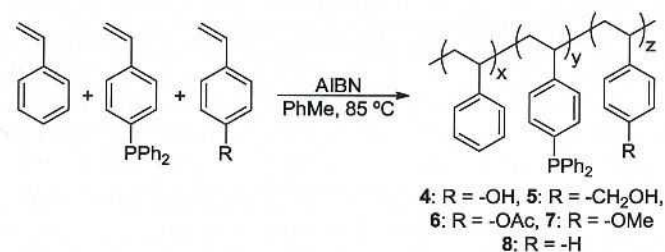


Fig. 1 Bifunctional organic polymeric catalysts for ester hydrolysis reported by Overberger.

BIFUNCTIONAL POLYMERIC CATALYSTS

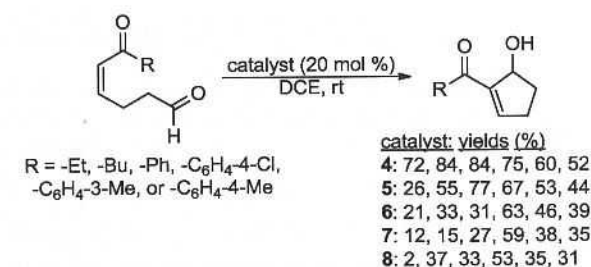
In order to eliminate the need for polymer swelling, we prepared a series of soluble non-cross-linked polystyrenes functionalized with both phosphine groups and either hydrogen bond donating or accepting groups (**4–7**) for use as catalysts in MBH reactions by polymerizing appropriate mixtures of monomers under free radical conditions (Scheme 1) [11]. For the synthesis of these polymers, as well as those described later, the functional monomers used were either commercially available or synthesized in 1–3 steps from easily available starting materials such as 4-bromostyrene or 4-vinylbenzyl chloride. Unfunctionalized styrene was added to these reactions in order to impart flexibility in the polymers, and to make them easy-to-handle powders in the dry state. The polymerization reactions were carried out under standard conditions and afforded moderate-to-good isolated yields (ca. 40–80 %) of the desired materials. All of the non-cross-linked polymers described in this report were characterized at least by ^1H NMR spectroscopy and elemental analysis, and were found to have loading levels similar to the theoretical values based on the ratio of monomers used in the polymerization reactions.



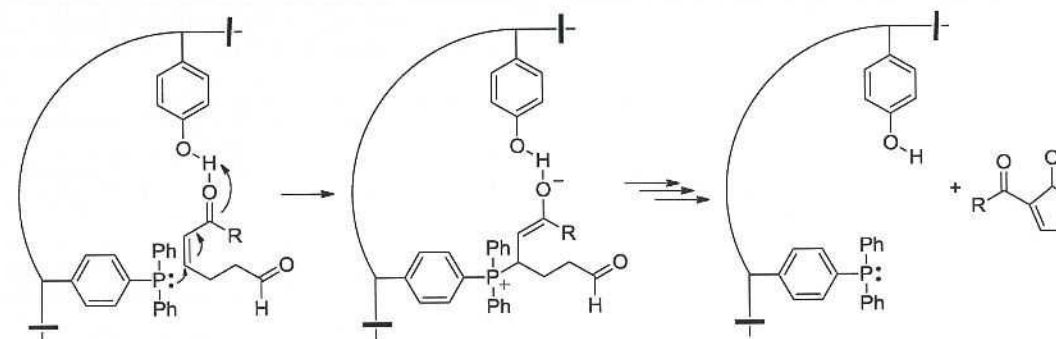
Scheme 1 Synthesis of non-cross-linked polymeric catalysts **4–8**.

Once synthesized, comparison of the catalytic efficiency of **4–7** and monofunctional **8**, which possessed only phosphine groups, was performed in a series of side-by-side intramolecular MBH reactions (Scheme 2). These experiments indicated that the best catalyst for all such reactions investigated

was **4**, which bore phenol groups in addition to the nucleophilic phosphine groups. Polymer **5**, with benzyl alcohol groups as the hydrogen bond donating groups, was less effective than **4**, but more efficient than **6** and **7**, with hydrogen bond accepting groups, and monofunctional **8** in all cases. Thus, it appears that the hydrogen bond donating groups of **4** and **5** can work together with the nucleophilic phosphine groups to cooperatively catalyze the reactions, possibly in a manner as outlined in Scheme 3. Since phenol groups are stronger hydrogen bond donors than alkyl alcohols, it seems reasonable that **4** should be a better catalyst than **5**. Furthermore, we also prepared a related series of polymeric catalysts analogous to **4–8** in which the phosphine groups were replaced by DMAP groups, and observed very similar results when these were used to catalyze a series of intermolecular MBH reactions involving methyl vinyl ketone, 2-cyclopenten-1-one, or 2-cyclohexen-1-one as the enone electrophile [11].

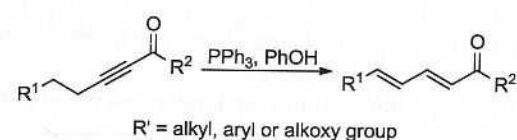


Scheme 2 MBH reactions catalyzed by **4–8**.

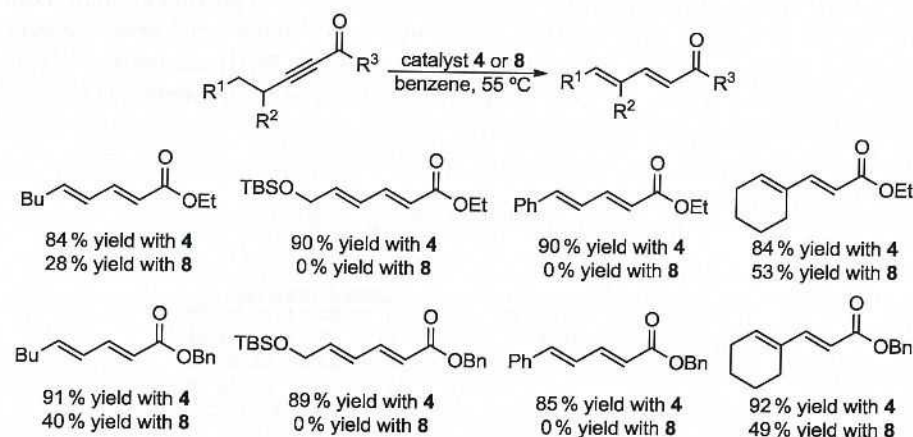


Scheme 3 Possible mechanism for MBH reactions catalyzed by **4**.

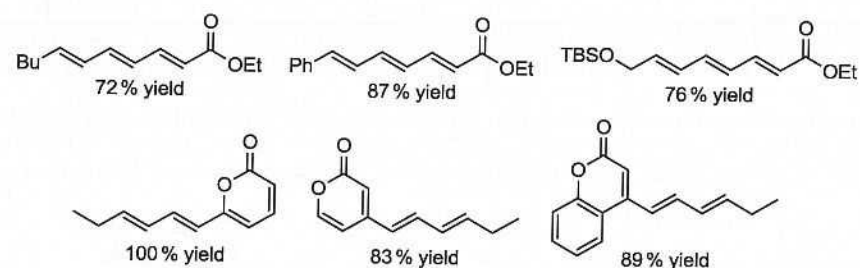
Having validated the superiority of bifunctional **4** as a catalyst in MBH reactions compared to monofunctional **8**, we next turned our attention to examining the utility of **4** as a catalyst for the phosphine-catalyzed isomerization of electron-withdrawing group activated alkynes to the corresponding (*E,E*)-dienes [12] that was simultaneously reported by Trost and Kazmaier [13], and Lu and Ma [14] some years ago. This reaction was of interest to us because Rychnovsky and Kim had reported that when phenol is used as a co-catalyst with triphenylphosphine, the substrate scope of this reaction can be effectively extended to ester activated alkynes (Scheme 4) [15]. Thus, we synthesized a series of alkynoate substrates and studied their isomerization using both **4** and **8** (Scheme 5) [16]. In agreement with the observations of Rychnovsky and Kim, when **8** was used as the catalyst either no or low yield of the expected diene was obtained. Gratifyingly, when bifunctional **4** was used as the catalyst, good-to-excellent yield of the corresponding (*E,E*)-diene product was isolated in all cases. Polymer **4** was also used to synthesize (*2E,4E,6E*)-trienoates from the corresponding conjugated alkyne starting materials, and to isomerize alkyne-substituted 2(*H*)-pyran-2-one derivatives (Fig. 2).



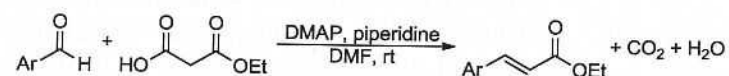
Scheme 4 Phosphine-catalyzed alkyne isomerization reactions.



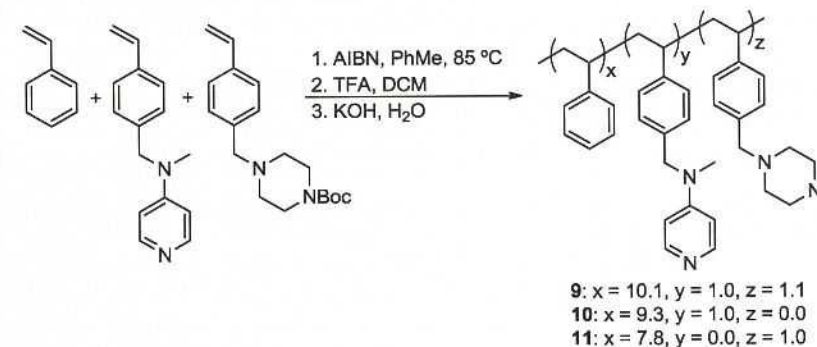
Scheme 5 Alkyne isomerization reactions catalyzed by 4 and 8.

Fig. 2 (2*E*,4*E*,6*E*)-Trienoates and 2(*H*)-pyran-2-one derivatives synthesized with 4.

Another reaction we have studied using a multifunctional organic polymeric catalyst is the decarboxylative Doebner–Knoevenagel reaction between a non-enolizable aldehyde and monoethyl malonate that was recently refined by List and co-workers [17]. They reported that a combination of piperidine and DMAP catalysts transformed non-enolizable aldehydes into the corresponding *E*-enoates upon reaction with a malonic acid monoester in what can be considered an organocatalytic and more atom-economical alternative to the Wittig reaction (Scheme 6). Thus, we prepared bifunctional polymer **9** as a macromolecular substitute for the combination of DMAP and piperidine, and monofunctional polymers **10** and **11** for the sake of comparison using standard methodology (Scheme 7) [18].

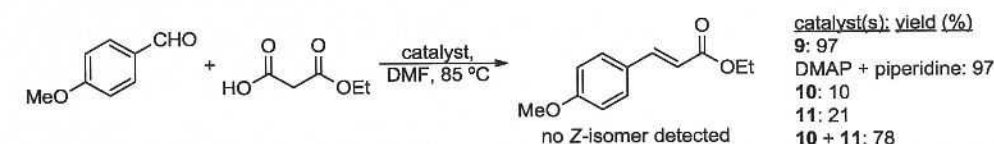


Scheme 6 Decarboxylative Doebner–Knoevenagel reactions.



Scheme 7 Synthesis of non-cross-linked polymeric catalysts 9–11.

When we used **9** to catalyze the reaction between monoethyl malonate and 4-methoxybenzaldehyde, the product ethyl 4-methoxycinnamate was obtained in 97% yield and with very high stereoselectivity (Scheme 8). The same results were obtained using the combination of piperidine and DMAP to catalyze the reaction, but when either **10** or **11** was used, only 10 and 21% yield of the product was obtained, respectively. Clearly, the presence of both the DMAP and cyclic secondary amine groups of **9** is required for efficient catalysis. Interestingly, when a combination of monofunctional **10** and **11** was used to catalyze the same reaction, lower product yield (78%) was obtained than when only bifunctional **9** was used under identical reaction conditions. Thus, there appears to be an advantage to co-immobilizing both functional groups on the same polymer in such reactions. A wide variety of aryl-aldehydes, including heteroaromatic examples and a dialdehyde, was successfully applied as the starting material using **9** as the catalyst, and high yield of the expected product was obtained in all cases except for very sterically hindered 2,6-dichlorobenzaldehyde (Fig. 3).



Scheme 8 Decarboxylative Doebner–Knoevenagel reactions catalyzed by 9–11.

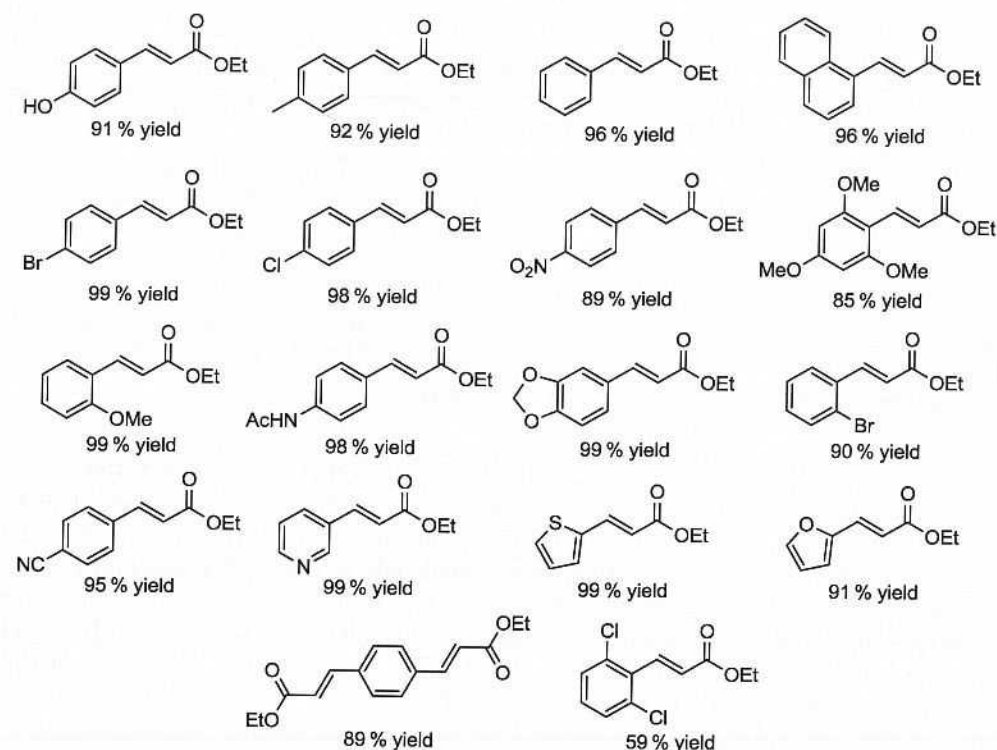
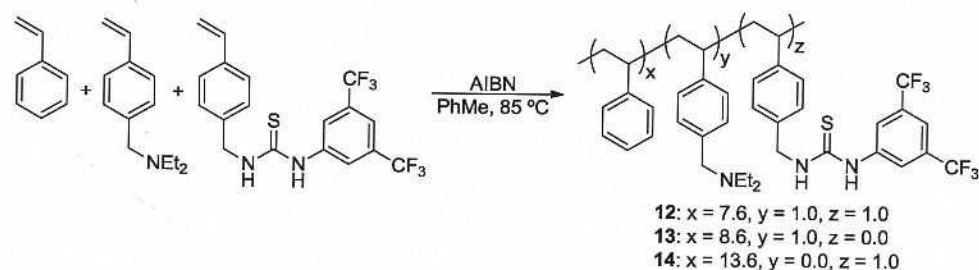


Fig. 3 Decarboxylative Doebner–Knoevenagel reaction products prepared using **9**.

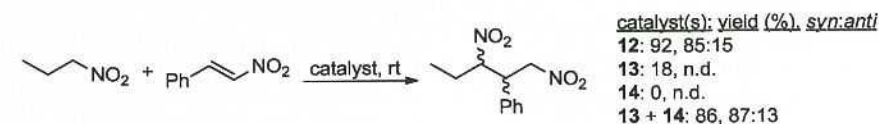
Next, we were inspired by the report of Wulff and Rabalakos describing a bifunctional chiral catalyst possessing both amine and thiourea groups for catalyzing the asymmetric addition of nitroalkenes to nitroalkenes [19]. We thought it would be interesting to test the ability of moderately basic groups and hydrogen bond donating groups to coexist on a single polymer backbone, and to cooperatively catalyze reactions. Thus, polymers **12–14** were synthesized as before, using a thiourea and an amine monomer that were both easily synthesized from 4-vinylbenzyl chloride (Scheme 9) [20].



Scheme 9 Synthesis of non-cross-linked polymeric catalysts **12–14**.

Reactions between excess nitropropane and *trans*- β -nitrostyrene using polymers **12–14** as catalyst were conducted without solvent (Scheme 10). When bifunctional **12** was used as the catalyst, the expected product was obtained in high yield and with good stereoselectivity. However, only low yield of the product was produced when amine-functionalized **13** was the catalyst, and no product was observed when thiourea-bearing **14** was used. Interestingly, when a combination of **13** and **14** was used

to catalyze the reaction, similar results in terms of yield and stereoselectivity were obtained as when **12** was used alone. Therefore, it seems that the presence of both basic amine and hydrogen bond donating thiourea groups is required for such reactions to proceed efficiently, and that polymer **12** is a suitable platform for delivering them. Using **12** as the catalyst, a variety of substituted *trans*- β -nitrostyrenes were successfully reacted with nitropropane in excellent yield and high stereoselectivity (Fig. 4).



Scheme 10 Nitropropane addition reactions catalyzed by **12–14**.

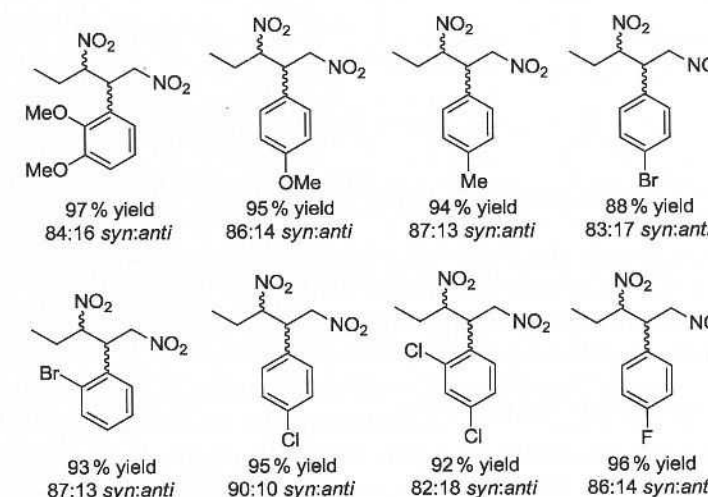
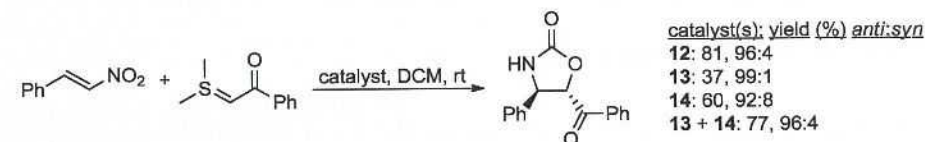


Fig. 4 Dinitro compounds synthesized using **12**.

Polymers **12–14** were then applied as catalysts in the cycloaddition reaction between a nitroalkene and a sulfur ylide recently reported by Xiao et al. [21], using *trans*- β -nitrostyrene as the substrate (Scheme 11) [20]. As we observed previously for the nitropropane addition reactions, bifunctional **12** proved to be an efficient catalyst. However, both monofunctional **13** and **14** were only moderately active catalysts when used individually under identical reaction conditions, but they worked well when used together as a pair. Other combinations of nitroalkene and sulfur ylide substrates were also examined, and they resulted in the highly stereoselective formation of the expected products in moderate-to-good yields (Fig. 5). These results are generally in line with what was previously reported in terms of product yield and stereoselectivity [21].



Scheme 11 Sulfur ylide cycloaddition reactions catalyzed by **12–14**.

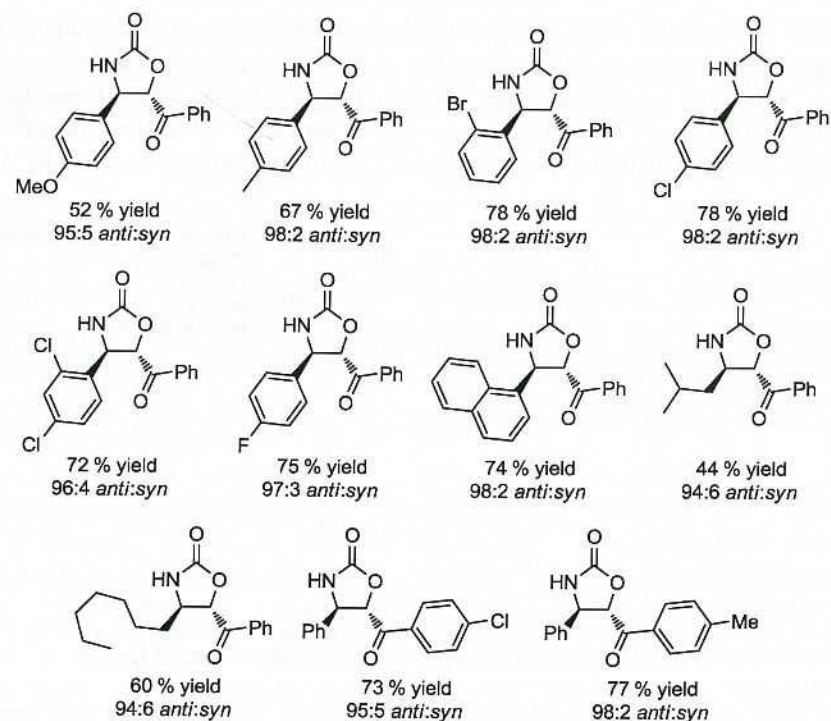
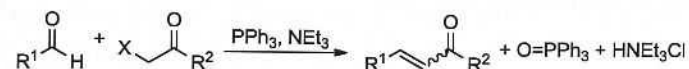


Fig. 5 Cycloaddition products synthesized using 12.

BIFUNCTIONAL POLYMERIC REAGENTS

Having established the generality of the concept of polystyrene-based multifunctional polymeric catalysts, at least in terms of amine, phosphine, phenol, and thiourea catalysis, we next moved on to apply the strategy of co-locating different functional groups on the same polymer backbone to polymeric reagents that might be useful in organic reactions that require a combination of different reagents to perform. The reaction we chose to study initially is the one-pot variation of the Wittig reaction in which an activated alkyl halide and an aldehyde substrate are mixed together with a combination of a phosphine reagent and an amine base. In such reactions, the alkyl halide first reacts with the phosphine reagent to form the corresponding phosphonium salt that in turn reacts with the amine base to generate the corresponding phosphorane. This reactive intermediate then reacts with the aldehyde to form an alkene product (Scheme 12). Our idea was that if we could prepare a heterogeneous amine-phosphine bifunctional polymeric reagent, the final alkene products from such reactions could be isolated in a pure state after only filtration and solvent removal.



Scheme 12 One-pot Wittig reactions.

As one might imagine, researchers have studied the use of heterogeneous polymer-supported phosphines in variations of the Wittig reaction since they were first introduced in the 1970s, and in fact a commercially available phosphine-functionalized cross-linked polystyrene reagent has been used in such one-pot Wittig reactions but with only limited success [22]. The widely varying reaction yields

reported in this work (0–95 %) were perhaps due to the fact that the alkyl halide and/or aldehyde molecules could not effectively diffuse into the interior of the polymer beads to react with the phosphine groups located there, as had been previously reported to be an issue by Ford and co-workers [23]. Thus, we chose to use the rasta resin polymer architecture for our bifunctional polymeric reagent since the reagent groups would be located on solvent accessible grafts attached to a cross-linked heterogeneous core (Fig. 6) [24,25].

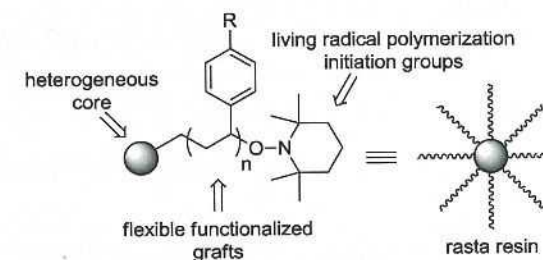
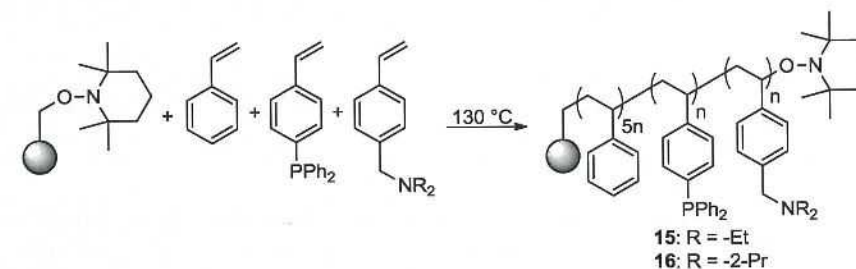


Fig. 6 The rasta resin concept.

The rasta resin core can be prepared from a Merrifield resin analogue [24a,25a], and this was heated in the presence of styrene, an amine monomer, and a phosphine monomer to afford **15** (Scheme 13). Elemental analysis was used to determine the loading level of the polymer, and ^{31}P NMR analysis indicated that the phosphine groups were not oxidized. Gratifyingly, when aldehydes, activated alkyl halides, and **15** were mixed together in chloroform in a 1.0:1.8:2.0 ratio, the one-pot Wittig reactions proceeded to completion and the alkene products could be isolated in very high yields as pure mixtures of the expected stereoisomers after only filtration to remove the polymer and solvent removal [26]. Activated alkyl halides used in these reactions included ethyl bromoacetate, ethyl 2-bromopropionate, and chloroacetone, and both aromatic and aliphatic aldehydes were successful as substrates (Fig. 7).



Scheme 13 Synthesis of polymers **15** and **16**.

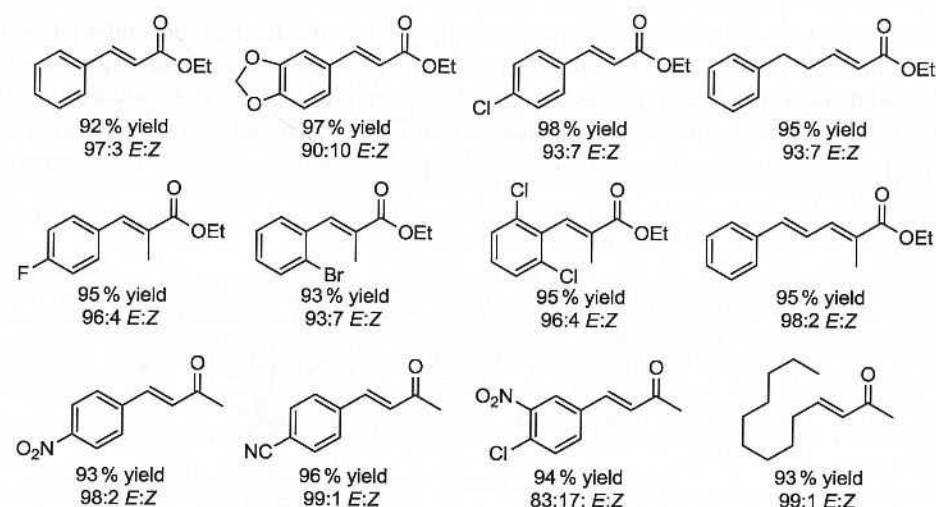


Fig. 7 Representative alkenes synthesized using **15** from the corresponding aldehydes.

While polymer **15** was indeed effective in mediating the one-pot Wittig reactions studied, it suffered from the significant drawback that 2.0 equiv of it needed to be used compared to the aldehyde substrate in order for the reactions to be proceed to completion in a reasonable amount of time. Since the synthesis of **15** requires several steps, this increases the costs associated with its use and seriously limits the applications for which it might be practical. One reason we felt that might be responsible for the need for such a large excess of **15** was that some of the amine groups were competing with the phosphine groups to react with some of the alkyl halide, and thereby wasting some of polymer [27]. Therefore, we prepared **16** in which the ethyl groups of **15** were replaced by 2-propyl groups, in the hopes that more sterically hindered amine groups would reduce unwanted side reactions so that a smaller excess of it could be used (Scheme 13) [28]. Happily, under similar reaction conditions as those used for **15**, only 1.1 equiv of **16** compared to aldehyde substrate was necessary in order to achieve similar results (Fig. 8).

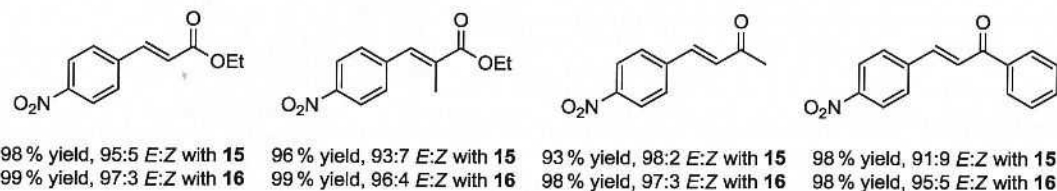
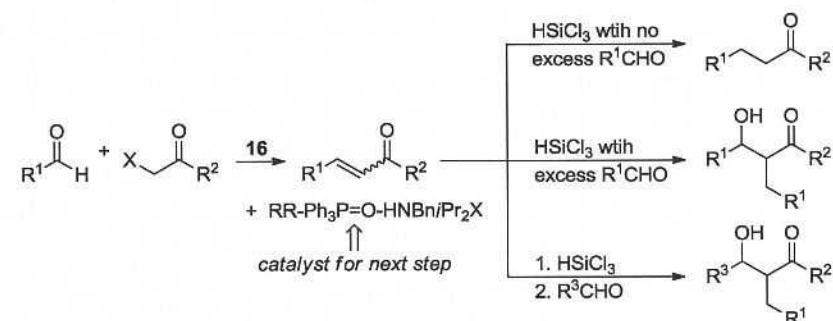


Fig. 8 Comparison of polymers **15** and **16** in one-pot Wittig reactions.

To further explore the utility of our second-generation polymeric reagent **16**, we followed the lead of the work by Nakajima et al. [29] and Zhou and Cao [30], who showed that phosphine oxides are capable of catalyzing the trichlorosilane-mediated conjugate reduction of enones and related reductive aldol reactions, and that the phosphine oxide catalyst for such reactions can be the waste from a Wittig reaction, respectively. Our angle was to use **16** to perform these conjugate reduction and reductive aldol reactions in tandem with a one-pot Wittig reaction whereby the waste phosphine oxide of the first reaction is put to use as the catalyst for the second one (Scheme 14).



Scheme 14 One-pot Wittig/reduction reaction cascades using **16**.

We first validated the feasibility of the concept of tandem one-pot Wittig/reductive aldol reactions using triphenylphosphine and diisopropylethylamine, and obtained good results [31]. Therefore, we were encouraged to use **16** in one-pot Wittig reactions followed immediately by conjugate reduction of the product, or using the product in a reductive aldol reaction with either another molecule of the same aldehyde starting material or with a molecule of a second aldehyde as outlined in Scheme 14. Using this methodology, we were able to efficiently synthesize a range of ketone products in excellent overall yield (Fig. 9), and successfully obtain reductive aldol products using either a single aldehyde substrate (Fig. 10) or a pair of different ones (Fig. 11) in good overall yield, especially considering the number of steps involved. Thus, our strategy allows for the rapid combination of simple alkyl halide and aldehyde building blocks to form more complex molecules in a one-pot procedure that is greatly facilitated by using a polymeric reagent.

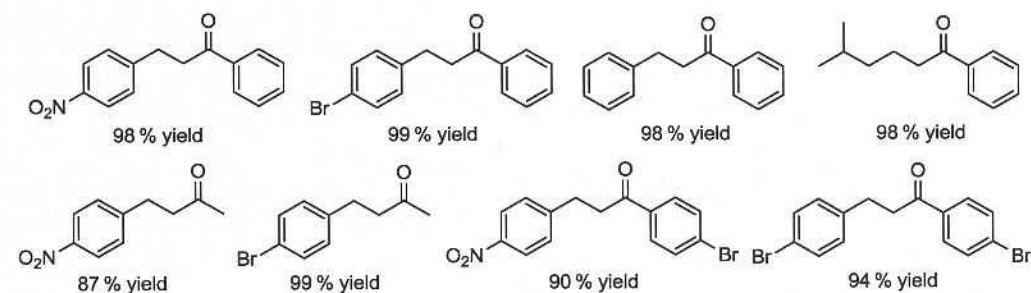


Fig. 9 Ketones synthesized from the corresponding alkyl halides and aldehydes using **16**.

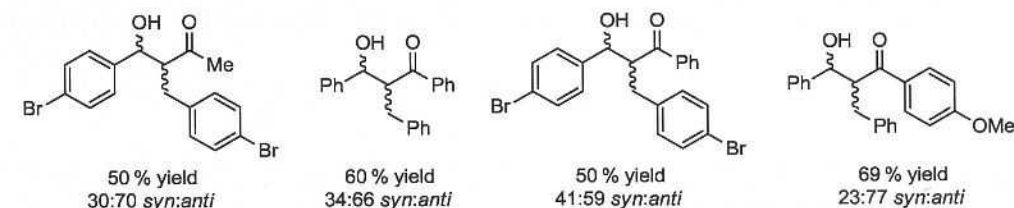


Fig. 10 Reductive aldol reaction products synthesized using **16** and excess aldehyde.

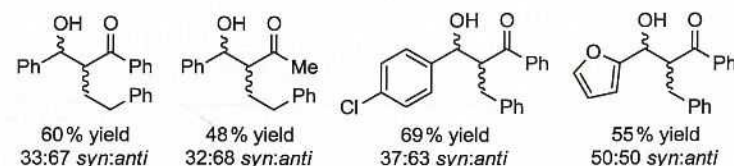


Fig. 11 Reductive aldol reaction products synthesized using **16** and a second aldehyde.

CONCLUSIONS

In summary, we have designed, efficiently synthesized, and successfully utilized a variety of multifunctional organic polymeric catalysts and reagents in a range of organic reactions from which product isolation is facilitated by the macromolecular nature of our materials. When the polymers were used as catalysts, we found in all cases that the presence of multiple different catalytic functional groups attached to the same polymer backbone provided more efficient catalysis than when a corresponding monofunctional polymer bearing only one of the two catalytic groups was used. Thus, it appears that synergy exists between the different catalytic groups, and that they are able to cooperatively catalyze the reactions studied.

Heterogeneous bifunctional amine-phosphine polymeric reagents based on the rasta resin architecture were also prepared, and found to be effective in mediating one-pot Wittig reactions from which the desired alkene products could be isolated in a highly pure state after only filtration and solvent removal. A second iteration of such a polymeric reagent was also successfully applied in reaction cascades in which one-pot Wittig reactions were followed by either a conjugate reduction or a reductive aldol reaction that was catalyzed by the phosphine oxide groups formed in the prior process. Thus, in these reaction cascades the role of the polymer changed from that of a reagent in the first reaction to serving as a catalyst in the second.

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Synthesis of multifunctional polymers by combination of controlled radical polymerization (CRP) and effective polymer analogous reactions*

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Abstract: The combination of controlled radical polymerization (CRP) reactions and click chemistry offers high potential for the preparation of multifunctional polymers and significantly broadens the application scope of functional soft matter materials. In order to demonstrate the strategies as well as the potential of this methodology combination, examples for end-group and side-chain modification of polymers produced by CRP methods and the use of the resulting materials in functional polymer films are given.

Keywords: click chemistry; controlled radical polymerization (CRP); multifunctionality; polymer chemistry; thin films.

INTRODUCTION

In the last decade, the combination of controlled radical polymerization (CRP) techniques (nitroxide-mediated radical polymerization (NMRP) [1], reversible addition-fragmentation chain transfer (RAFT) [2,3], atom-transfer radical polymerization (ATRP) [4]) and highly effective and selective organic reactions termed as the “click chemistry” [5] have been demonstrated to be a versatile tool for the specific construction of novel functional macromolecules [6]. The large number of reviews already published in the meantime and the impressive number of research groups active in this field underlines the importance of this methodology in polymer science [5–20].

In 2001, Sharpless et al. [5] introduced the term “click chemistry” with its famous representative, the cycloaddition of azides with alkynes under Cu catalysis [2]. He defined a “click reaction” with a set of criteria: “The reaction must be modular, wide in scope, give very high yields, generate only inoffensive byproducts that can be removed by nonchromatographic methods, and be stereospecific (but not necessarily enantioselective)” with further specifications for easy-to-realize reaction conditions and easy product isolation.

The most well-known reactions satisfying the philosophy of click chemistry are, besides the most popular 1,3-cycloaddition between azides and alkynes, thiol-ene, oxime, Diels–Alder, and pyridyl disulfide reactions as well as the Michael addition and activated ester coupling. Although Sharpless has seen the application of click chemistry mainly in the pharmaceutical area, very fast, click reactions were

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