



Title	Reengineering Classic Organic Reactions Using Polymeric Tools
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on the matrix. However, this heterogeneity should promote the migration of the additive into the network and hence modify its FR efficiency. The chosen biobased resource is a model molecule of the biophenol really targeted. So far, the phloroglucinol is produced by bacterial fermentation of glucose and has a limited availability. However, some biobased phenolic compounds such as gallic acid are more available than the phloroglucinol and could be used from the same synthesis pathway for a possible development as new biobased FR.

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Conference paper

Patrick H. Toy*

Reengineering classic organic reactions using polymeric tools

Abstract: Many of the most widely used reactions in organic synthesis suffer from drawbacks that can hamper their use. For example, the Mitsunobu, Wittig and Appel reactions all result in the formation of a full equivalent of triphenylphosphine oxide, which can be similar in polarity to the desired product, and thus be difficult to remove. Other reactions such as the Suzuki-Miyaura and Mizoroki-Heck reactions require the addition of numerous reagents, ligands and catalysts that can be laborious to separate from the targeted cross-coupled product. This review summarizes our recent work to address these issues by developing polymeric tools designed to simplify product isolation from these transformations.

Keywords: Appel reactions; Mitsunobu reactions; Mizoroki-Heck reactions; POC-2014; polymer-supported catalysts; polymer-supported reagents; Suzuki-Miyaura reactions; Wittig reactions.

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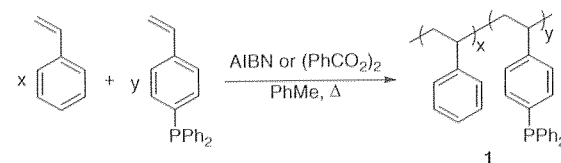
Introduction

As the field of synthetic organic chemistry has advanced in recent years, it seems that its main challenge has shifted from whether or not a particular compound can be synthesized to how to synthesize it in the most efficient and environmentally benign manner possible. Thus, many of the classic reactions that are very commonly used in organic synthesis are currently being re-examined in order to attempt to reduce or eliminate their drawbacks and inefficiencies [1]. For example, the Mitsunobu [2, 3], Wittig [4], and Appel [5] reactions all result in the formation of 1 molecule of $\text{Ph}_3\text{P}=\text{O}$ for every molecule of desired product formed, and this by-product can be difficult to remove. Therefore, new methods for performing these transformations that result in easier product purification may potentially be of broad interest and great utility. In this regard we have been developing polymeric tools for such applications, and describe herein our recent research.

We have had a long-term interest in studying organic polymers for use as reagent and catalyst supports with the aim of developing tools to simplify product isolation from reaction mixtures in which they are used [6, 7]. For example, since Ph_3P is widely used as a reagent, catalyst and ligand in organic chemistry we studied methods for the preparation of various polystyrenes functionalized with such groups [8], and used polymers such as **1** as organocatalysts for Morita-Baylis-Hillman [9–12] and alkyne to 1,3-diene isomerization reactions (Scheme 1) [13, 14]. Non-cross-linked **1** is soluble in organic solvents such as dichloromethane, dimethyl formamide and tetrahydrofuran, but insoluble in methanol and water. Thus, after it was used as a homogeneous organocatalyst, it could be precipitated and separated from the reaction product by addition of the concentrated reaction mixture to methanol followed by filtration.

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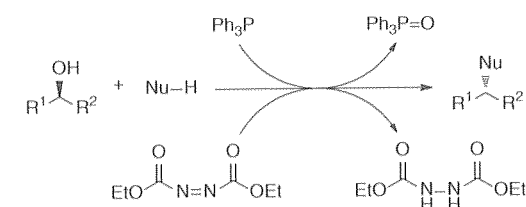
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Scheme 1 Synthesis of non-cross-linked polystyrenes **1** functionalized with phosphine groups.

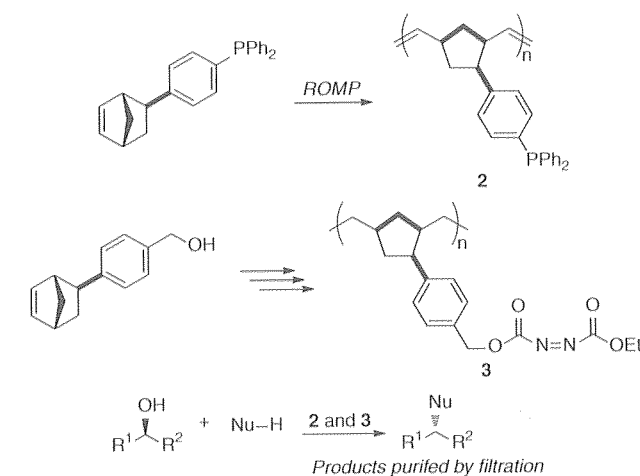
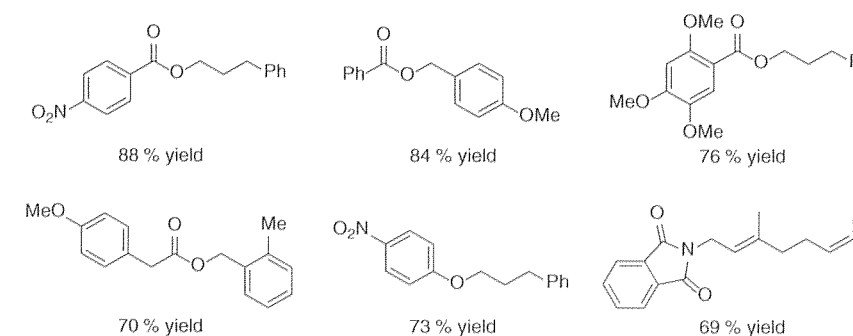
Polymeric reagents

Inspired by our work with polymers such as **1** we became interested in the concept of performing Mitsunobu reactions using two different soluble polymeric reagents, one functionalized with phosphine groups and the other with dialkyl azodicarboxylate moieties, since these reactions require both a phosphine and an azo reagent that produce a phosphine oxide and a hydriazide by-product, respectively (Scheme 2). Thus, while Mitsunobu reactions are highly efficient and stereoselective reactions between alcohol and pro-nucleophile substrates, they often result in very complex reaction mixtures from which it can be difficult and time consuming to isolate the desired product.

Our idea was to perform Mitsunobu reactions using two different polymeric reagents simultaneously so that their by-products could be removed by filtration. For this project we collaborated with Prof. Paul R. Hanson (Univ. of Kansas), who has used ring-opening metathesis polymerization to prepare numerous polymer-supported reagents, and prepared phosphine-functionalized polymer **2** and azo-functionalized polymer **3** (Scheme 3) [15]. As can be seen from the representative products from such reactions shown, the multipolymer Mitsunobu reactions proved to be versatile and work with a range of alcohol and pro-nucleophile



Scheme 2 The Mitsunobu reaction.

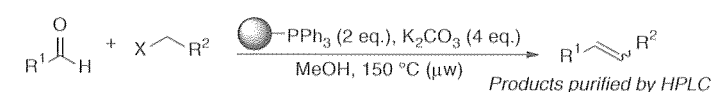
Scheme 3 Polymeric reagents **2** and **3** and their use in multipolymer Mitsunobu reactions.Fig. 1 Representative products synthesized using **2** and **3**.

substrates (Fig. 1). Importantly, it was gratifying to find that the desired products could be separated from the by-products by filtration to remove the polymeric materials.

Having established that multipolymer Mitsunobu reactions are indeed possible using our polymers and result in facile product purification, we next moved on to study Wittig reaction, which also produces $\text{Ph}_3\text{P}=\text{O}$ as a by-product. Our interest was driven primarily by the report from Westman in which he described the use of a commercially available polymer-supported Ph_3P reagent that was based on the Merrifield resin architecture (polystyrene cross-linked with divinylbenzene) that has the majority of the phosphine groups located on the interior to the resin bead [16]. The reactions he performed were one-pot Wittig reactions in which an aldehyde and an activated alkyl halide were mixed together with the phosphine reagent and a base to produce the desired alkene products via sequential in situ formation of a phosphonium salt and a phosphorane (Scheme 4). We were surprised that even though a polymer-supported phosphine was used that could be removed at the end of the reactions by filtration, preparative HPLC was required to purify the alkene products. Furthermore, the isolated product yields were generally rather low, ranging from 11 to 95%.

We speculated that the widely varying reaction yields reported by Westman were perhaps due to the fact that the alkyl halide and/or aldehyde molecules could not effectively diffuse into the interior of the functionalized polymer beads to react with the phosphine groups located there, which had long ago been reported to be an issue by Ford and co-workers [17, 18]. Thus, we chose to use the rasta resin architecture as the basis for polymer-supported phosphines for Wittig reactions since the reagent groups would be located on solvent accessible grafts attached to a cross-linked heterogeneous core (Fig. 2) [19–27].

The heterogeneous rasta resin core can be prepared from a Merrifield resin analogue [19], and this was heated in the presence of a mixture of styrene and a phosphine functionalized monomer to afford rasta resin **4** (Scheme 5) [28]. Elemental analysis was used to determine the phosphorous content of **4**, and thus its loading



Scheme 4 One-pot Wittig reactions reported by Westman.

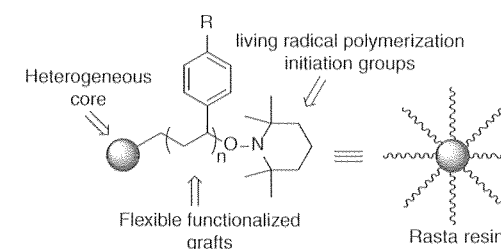
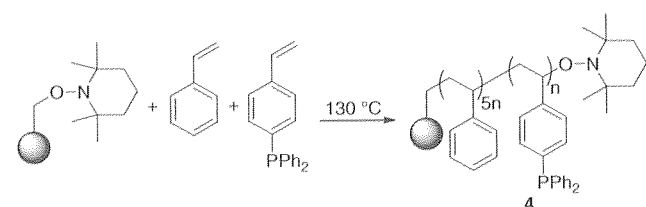


Fig. 2 The rasta resin concept.



Scheme 5 Synthesis of rasta resin 4.

level, and gel-phase ^{31}P NMR analysis indicated that the phosphine groups were not oxidized. Gratifyingly, when aldehydes, activated alkyl halides, and **4** were mixed together in chloroform with Et_3N as the base, the one-pot Wittig reactions proceeded to completion, and the expected 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. The activated alkyl halides used in these reactions included ethyl bromoacetate, ethyl 2-bromopropionate, chloroacetone, 2-bromoacetophenone and an alpha-bromo amide, and both aromatic and aliphatic aldehydes were successful as substrates [Fig. 3].

After reporting our results regarding the use of **4** in one-pot Wittig reactions, it occurred to us that if we could prepare a rasta resin functionalized with amine groups in addition to phosphine groups, it would be unnecessary to add a base to the reactions, and thus performing such reactions would be further simplified. Thus, second generation rasta resin **5** was prepared by the addition of an amine functionalized monomer to the graft polymerization process, and again elemental analysis was used to determine the loading levels of the amine and phosphine groups, and gel-phase ^{31}P NMR analysis indicated that the phosphine groups were not oxidized (Scheme 6) [29]. When the one-pot Wittig reactions were performed by mixing the aldehydes, activated alkyl halides, and **5** in chloroform in a 1.0:1.8:2.0 ratio, the reactions proceeded to completion, and again the alkene products could be isolated in very high yields as essentially pure mixtures of stereoisomers after only filtration to remove the polymer and solvent removal. The activated alkyl halides used in these reactions included ethyl bromoacetate, ethyl 2-bromopropionate and chloroacetone, and both aromatic and aliphatic aldehydes worked well as substrates [Fig. 4].

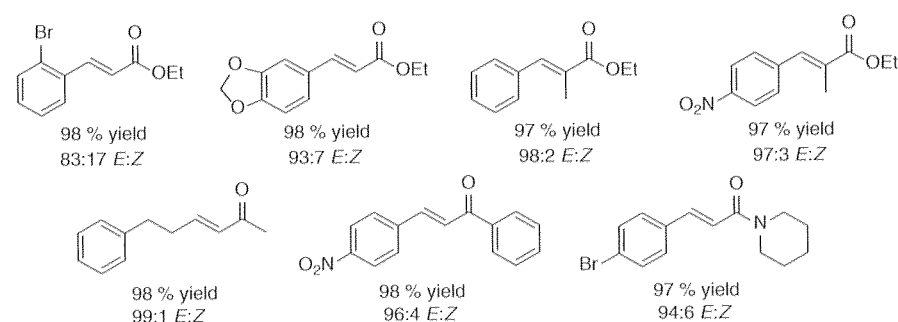
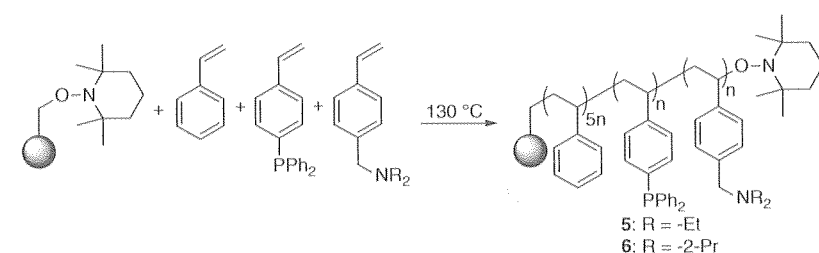


Fig. 3 Representative alkenes synthesized using 4.



Scheme 6 Synthesis of bifunctional rasta resins 5 and 6.

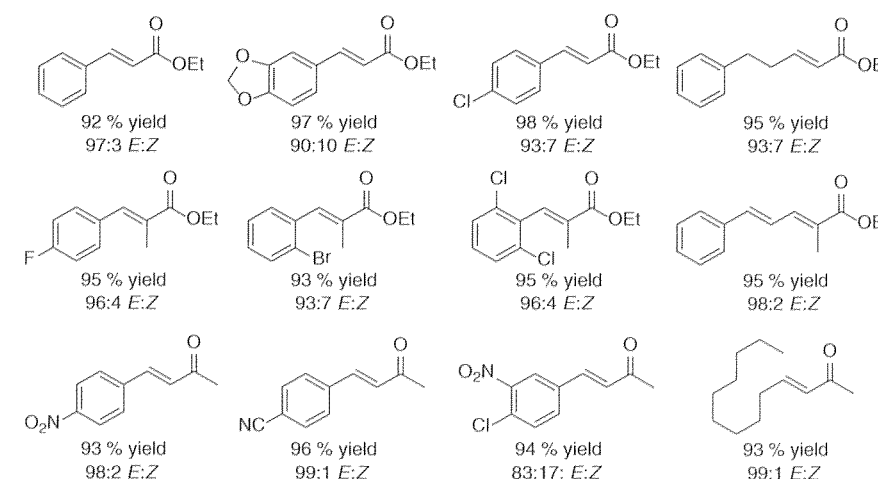


Fig. 4 Representative alkenes synthesized using 5.

While polymer **5** was indeed effective in mediating the one-pot Wittig reactions studied, it suffered from the significant drawback that 2.0 equivalents of it needed to be used compared to the aldehyde substrate in order for the reactions to proceed to completion in a reasonable amount of time. Since the synthesis of **5** requires several steps, this inefficiency increases the costs associated with its use and significantly 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 **5** was that some of the amine groups were competing with the phosphine groups to react with some of the excess alkyl halide, and thereby wasting some of the polymer [30]. Therefore, we prepared **6** in which the ethyl groups of **5** 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 6) [31]. Gratifyingly, under similar reaction conditions as those originally used for **5**, only 1.1 equivalents of **6** compared to aldehyde substrate was necessary in order to achieve similar results (Fig. 5).

To further explore the utility of our third generation polymeric reagent **6**, we followed the lead of the work reported by Nakajima et al. [32], and Zhou and co-workers [33, 34] 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 could be the waste from a Wittig reaction, respectively. We envisioned that our contribution would be to use **6** to perform these conjugate reduction and reductive aldol reactions in tandem with a one-pot Wittig reaction whereby the waste phosphine oxide groups of the first reaction would be put to use as the catalyst for the second one (Scheme 7).

We first validated the feasibility of the concept of tandem one-pot Wittig/reductive aldol reaction reactions using triphenylphosphine and diisopropylethylamine, and obtained good results [35]. Therefore, we were encouraged to use **6** 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 7. Using this methodology we were able to efficiently synthesize a range of ketone products in excellent overall yields (Fig. 6), and successfully obtain reductive aldol products using either a single aldehyde substrate (Fig. 7) or a pair of different ones (Fig. 8). The overall yields in these reductive aldol reactions were very good considering the number of steps involved in product formation. Thus, our strategy allows for the rapid combination of simple alkyl halide and

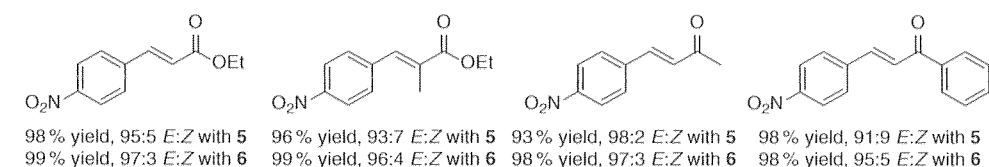
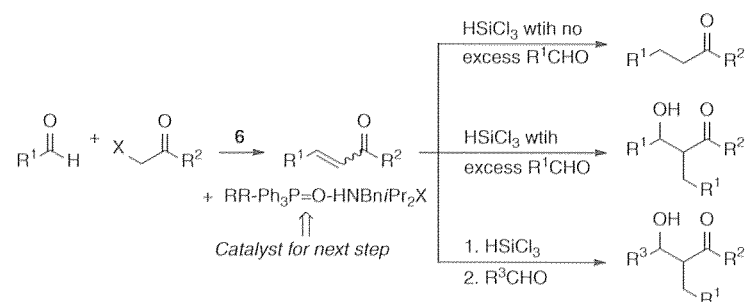


Fig. 5 Comparison of polymers 5 and 6 in one-pot Wittig reactions.



Scheme 7 One-pot Wittig/reduction reaction cascades using 6.

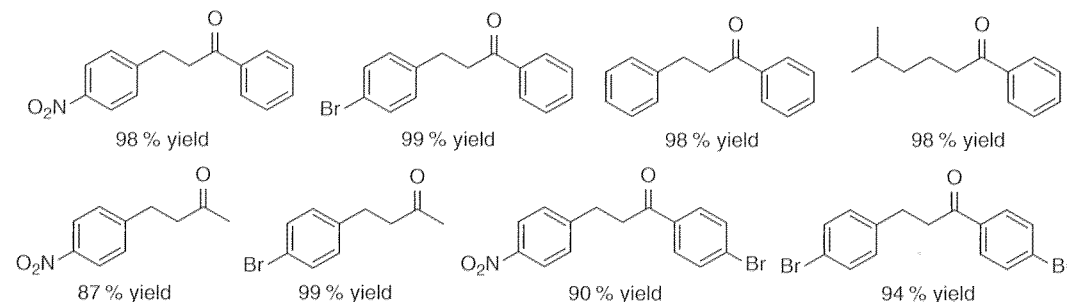


Fig. 6 Ketones synthesized from the corresponding alkyl halides and aldehydes using 6.

aldehyde building blocks to form more complex molecules in a one-pot procedure that is greatly facilitated by using a polymeric reagent. It should be noted that we were able to recover and regenerate polymer 6 after the one-pot Wittig/conjugate reduction reactions and reuse it in several reaction cycles before a significant decrease in its reactivity was observed.

The final $\text{Ph}_3\text{P}=\text{O}$ generating transformation we have examined is the Appel reaction for converting alcohols into corresponding alkyl halides. While the original version of this reaction involves the use of combination Ph_3P and CCl_4 and results in the formation of alkyl chlorides [5], nowadays reactions that use Ph_3PCl_2 or Ph_3PBr_2 to convert alcohols into alkyl chlorides or alkyl bromides, respectively, are also generally referred to as Appel reactions (Scheme 8).

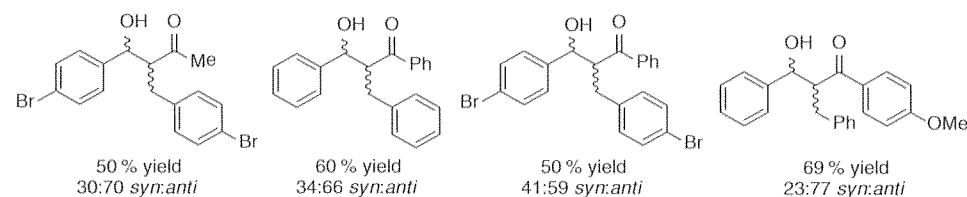


Fig. 7 Reductive aldol reaction products synthesized using 6 and excess aldehyde.

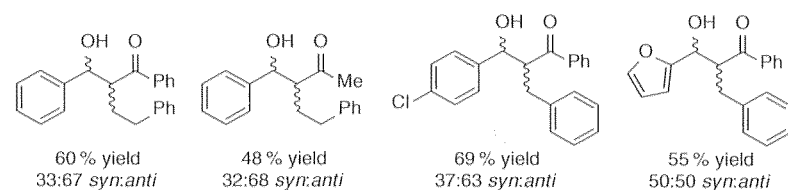
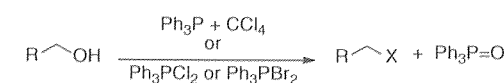


Fig. 8 Reductive aldol reaction products synthesized using 6 and a second aldehyde.



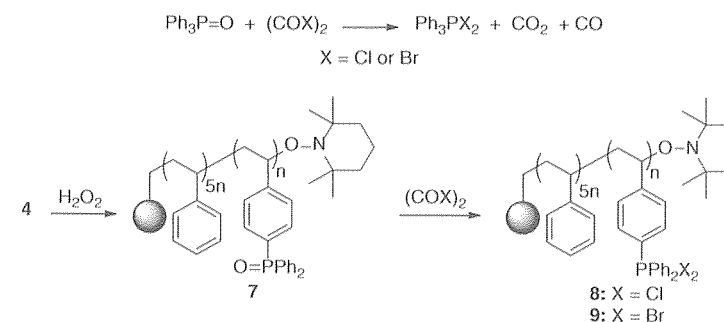
Scheme 8 Appel reactions.

This being the case, we were inspired to use the reaction reported by Masaki and Fukui in which $\text{Ph}_3\text{P}=\text{O}$ reacts with oxallyl chloride (or bromide) to produce Ph_3PCl_2 (or Ph_3PBr_2) plus CO and CO_2 (Scheme 9) [36–42]. Our thinking was that we could oxidize rasta resin 4 to the corresponding phosphine oxide functionalized polymer 7, and this could in turn be used as a heterogeneous reagent precursor to halogenated rasta resins 8 and 9 [43]. In all of these reactions, including the recycling experiments, the desired alkyl halide product was isolated in a pure state after only filtration and solvent removal.

As can be seen in Fig. 9, we were able to successfully use 8 and 9 to convert a broad range of alcohols into the corresponding alkyl halides in high yields, and since 7 was the polymeric by-product from these reactions, we were able to recover it and reuse it effectively in numerous reaction cycles. Additionally, we were able to use 8 and 9 in halogenation reactions of aziridines and aryl aldehydes to generate halogenated amines and 1,1-dihaloalkanes, respectively [Fig. 10]. While the reactions of aziridines went to completion and allowed for the products to be obtained in pure form after only filtration and solvent removal, the reactions of aldehydes did not proceed to completion and the products of these reactions required chromatographic purification. In general, bromination reactions of aldehydes afforded higher yields than did the corresponding chlorination reactions.

Polymeric catalysts

Early on in our research regarding non-cross-linked phosphine functionalized polystyrenes 1, we realized that the functional groups could serve as ligands for catalytic metals. Around the time of our work the use



Scheme 9 The Masaki-Fukui reaction and the synthesis of rasta resins 7–9.

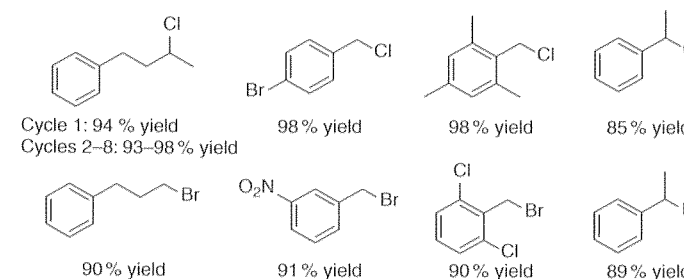


Fig. 9 Representative alkyl halides prepared from the corresponding alcohols using 8 and 9.

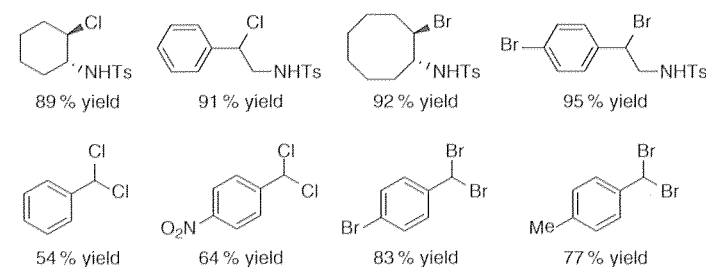
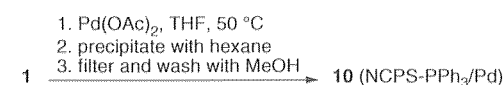


Fig. 10 Representative halogenated amines prepared from the corresponding aziridines and 1,1-dihaloalkanes prepared from the corresponding aldehydes using 8 and 9.

of unfunctionalized non-cross-linked polystyrene to microencapsulate metals such as Pd had become an area of interest in the catalysis community, and we realized using functionalized polymers such as 1 as the microencapsulating material would eliminate the need to add ligand molecules in order to generate active catalysts. We validated this concept and reported the use of 1 ($x = 7$, $y = 1$) to prepare Pd catalyst 10 for use in Suzuki-Miyaura reactions [44] (Scheme 10). Catalyst 10 was found to be an efficient heterogeneous catalyst for the cross-coupling of a wide variety of aryl boronic acids and aryl halides in *i*-PrOH or H_2O (or a mixture of these 2 solvents), and could be recovered and reused numerous times with moderate activity (Fig. 11). For the products shown in Fig. 11, the aryl group on the left was derived from an aryl halide and the aryl group on the right was derived from an arylboronic acid. Notably, the products of the Suzuki-Miyaura reactions were not contaminated by any phosphine or phosphine oxide, and Pd leaching from the catalyst was very low (0.2 % or less).

Although 10 can be used as a heterogeneous catalyst in polar protic solvents, we have also used the rasta resin platform to prepare a catalyst for Suzuki-Miyaura reactions that is insoluble in all solvents. Rasta resin 11 was prepared as outlined in Scheme 11, and was found to be an efficient catalyst when used in conjunction



Scheme 10 Preparation of catalyst 10.

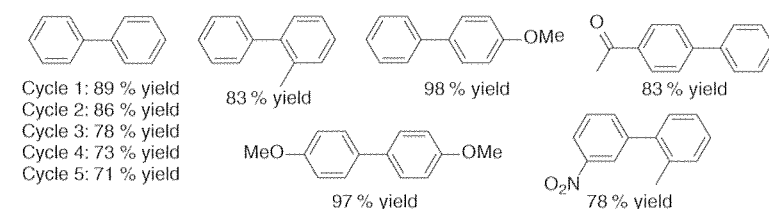
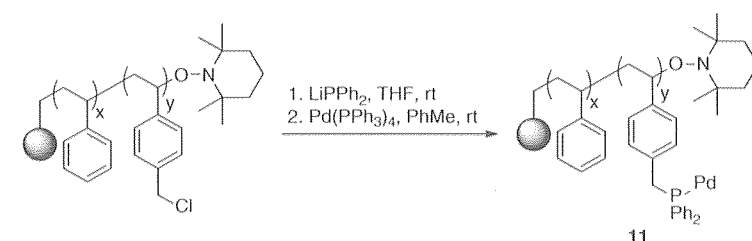


Fig. 11 Representative biaryls synthesized from aryl iodides using catalyst 10.



Scheme 11 Preparation of catalyst 11.

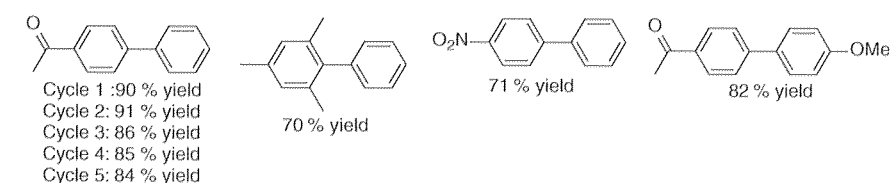
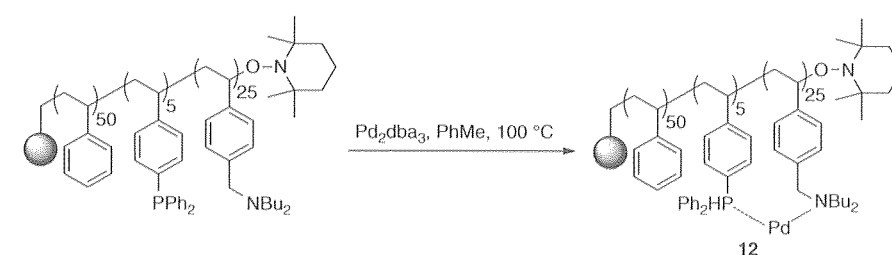


Fig. 12 Representative biaryls synthesized from aryl bromides using catalyst 11.

with K_3PO_4 as the base in a toluene/water solvent mixture (Fig. 12) [45]. For the products shown in Fig. 12, the aryl group on the left was derived from an aryl halide and the aryl group on the right was derived from an arylboronic acid. Importantly, 11 was found to have somewhat better recyclability than 10.

As mentioned above, the use of catalyst 11 in cross-coupling reactions necessitated the addition of the base K_3PO_4 for the reactions to proceed. Since tertiary amines are also capable of serving as the base in such transformations, we have more recently prepared bifunctional rasta resin 12 that is structurally similar to 5 and 6, but with dibutyl amine groups since Bu_3N was found by our collaborator Prof. Jean-Michel Becht (Univ. Haute Alsace) to be better than Et_3N or iPr_2EtN in such reactions (Scheme 12) [46]. This time we used our catalyst in Mizoroki-Heck reactions and found that cross-coupling reactions between aryl halides and methyl acrylate were efficiently catalyzed by heterogeneous 12 (Fig. 13). As was the case with 11, we found that 12 could be recycled several times with minimal metal leaching.

While catalysts 10–12 were able to effectively and efficiently catalyze cross-coupling reactions, they are somewhat limited by their relatively low loading levels due to the incorporation of large proportions of unfunctionalized styrene monomer in their synthesis. Their low loading levels means that large quantities of them (and solvent) are required. When we attempted to increase their loading by reducing the amount of styrene in the polymerization reactions, the product materials were difficult to handle or the reaction yields were unacceptably low. Thus, we have recently begun to examine the concept of using highly functionalized self-supported ligand polymers as platforms for generating catalysts. For example, we have synthesized a self-supported oxime polymer, and used it to generate catalyst 13 (Scheme 13) [47]. Although 13 is not functionalized with basic groups and required the addition of an external base (Cs_2CO_3) when it was used to catalyze Suzuki-Miyaura reactions, good yields of biaryls could be obtained in reactions between aryl bromides and aryl boronic acids (Fig. 14). For the products shown in Fig. 14, the aryl group on the left was derived from



Scheme 12 Preparation of catalyst 12.

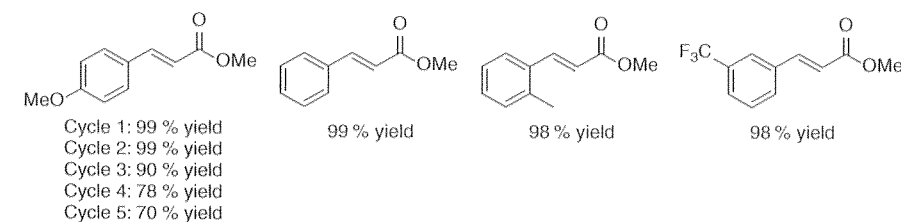
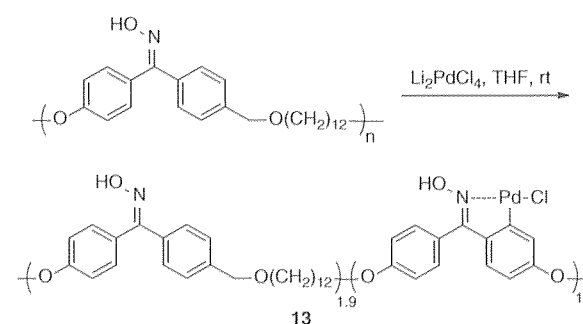


Fig. 13 Representative cinnamates synthesized from aryl iodides using catalyst 12.



Scheme 13 Preparation of catalyst 13.

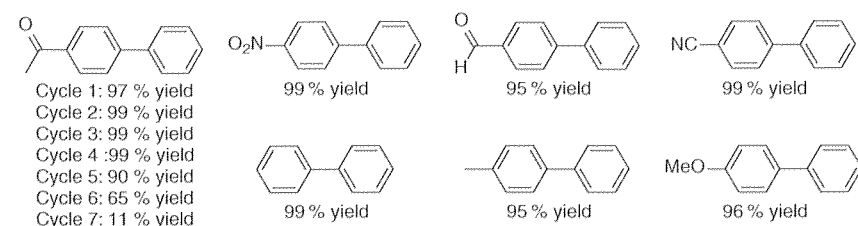


Fig. 14 Representative biaryls synthesized from aryl bromides using catalyst 13.

an aryl halide and the aryl group on the right was derived from an arylboronic acid. As with **11** and **12**, catalyst **13** was moderately recyclable, and we are currently working on extending this concept by developing bifunctional polymers that bear self-supported base groups in addition to ligand groups.

Conclusions

Herein we have described our recent research regarding the development of polymeric tools for more easily performing some of the classic reactions in organic synthesis that exhibit high efficiency and selectivity, yet present some operational challenges when they are used. Initially we were interested in developing more efficient polymer-supported phosphine reagents that would allow for its corresponding phosphine oxide by-product to be easily separated by filtration. This led us from multipolymer Mitsunobu reactions, to one-pot Wittig reaction-based reaction cascades, and finally to Appel and other halogenation reactions in which the same polymer can be reused over and over again since it is both the starting material and by-product of these transformations. Additionally, we have also applied some of our polymeric tools to simplify the set-up and product purification of some palladium-catalyzed cross-coupling reactions. In the future we hope to extend the utility of our polymeric tools by preparing ones with more and different functional groups so that they might be used as single reagents and/or catalysts for long reaction cascades that efficiently assemble simple building blocks into complex chemical structures.

While the polymers described in this report are not commercially available at this time, we would be happy to assist any interested parties in preparing and using them, and perhaps even supplying samples if they are available.

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