

# Organic Polymer Supports for Synthesis and for Reagent and Catalyst Immobilization

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## 1. Introduction

Merrifield first reported the concept of solid-phase peptide synthesis using heterogeneous chloromethylated polystyrene that was lightly cross-linked by divinylbenzene (Merrifield resin, Figure 1) nearly half a century ago,<sup>1</sup> and since then the use of polymers in various ways to facilitate synthesis and product purification has become widespread. While heterogeneous polystyrene such as Merrifield resin remains a workhorse in the field of polymer-assisted synthesis as a support for not only solid-phase synthesis but also reagent and catalyst immobilization as well, many other macromolecular materials have also been used. Perhaps the motivation for the ongoing examination of a broad array of polymers with different structures and properties for use in synthesis was best stated by the noted combinatorial chemistry pioneer Czarnik in his commentary "Solid-phase synthesis resins are like solvents",<sup>2</sup> since they can be viewed as constituting a significant portion of the

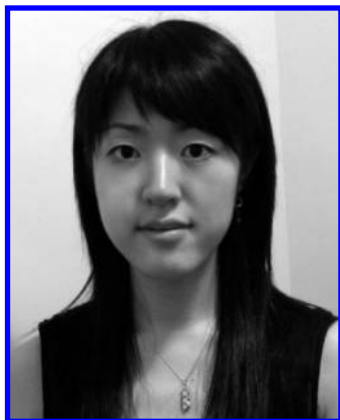
reaction environment. Therefore, just as there is no universally used solvent, it is reasonable to expect that since the structure of a polymer and its properties can impact different chemical reactions in various ways,<sup>3</sup> no single polymer structure would be optimal for every imaginable synthetic application.

In fact, this notion was recognized early on in the field of solid-phase peptide synthesis because Merrifield resin is only poorly compatible with the highly polar solvents commonly used in traditional peptide synthesis, such as DMF.<sup>4</sup> The poor solvent absorbing and swelling properties of Merrifield resin and its derivatives in polar solvents led Bayer to use soluble poly(ethylene glycol) (PEG, Figure 1) as the support in what he referred to as liquid-phase synthesis<sup>5</sup> and to add PEG grafts to the cross-linked polystyrene core of Merrifield resin.<sup>6</sup> While the use of PEG as a support for peptide synthesis is no longer common, the polystyrene–PEG composite material he introduced is widely used today and is known as Tentagel (Figure 1). This material has an advantage over Merrifield resin in that the point of synthesis is moved away from the nonpolar polystyrene backbone of the resin bead to the ends of the polyether grafts, and because of this, the need for the resin swelling is reduced.

Many others also made significant early contributions to this field and studied a large number of additional polymers in various formats for use not only as platforms for peptide synthesis but also both for organic molecule synthesis in general and as carriers of reagents and catalysts for reacting with unanchored synthetic substrates. This pioneering work, up to early 1999, is nicely summarized in a pair of "Perspective" articles that are collections of personal accounts by the main researchers in the field.<sup>7</sup> Contributors to these articles include Merrifield, Sheppard, Sparrow, Arshady, Meldal, Sherrington, Letsinger, Gletting, Barany, Rapp, the team of Gooding, Labadie, and Porco, Andrus, Buettner, Adams, Hoeplich, Rodda, Zhao, Lebl, and Daniels, who discuss their own research regarding the use various macromolecular materials, such as polyalkenes, polyethers, cotton, glass, etc., in numerous formats, including beads, surfaces, membranes, etc, for facilitating synthesis. Additionally, the range of soluble polymers used in this context has been reviewed by both Bergbreiter<sup>8</sup> and Janda.<sup>9</sup> These reviews include extensive discussions regarding the use of PEG, non-cross-linked polystyrene, polyethylene, and poly(acrylic acid) derivatives. A separate comprehensive review of the use of non-cross-linked polystyrene in organic synthesis has also recently appeared.<sup>10</sup>

The present survey of the literature focuses predominantly on the more recent work in the field of developing versatile polymer supports for organic synthesis that was not covered in the previous reviews,<sup>11</sup> and is somewhat arbitrarily limited to the discussion of organic polymers composed of the

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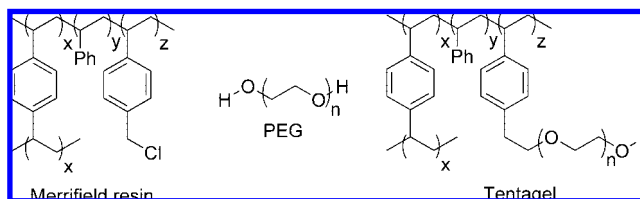


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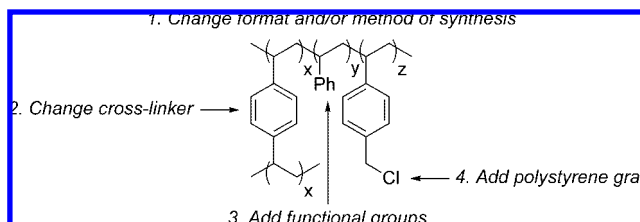


Patrick H. Toy received a B.S. degree in chemistry from The Ohio State University in 1990. He began his doctoral studies at the University of Minnesota under the direction of the late Prof. Paul G. Gassman and Prof. Hung-Wen (Ben) Liu. He was awarded a Ph.D. degree in 1998 with Prof. Martin Newcomb at Wayne State University. After 2 years of postdoctoral research with Prof. Kim D. Janda at the Scripps Research Institute, he worked in the combinatorial chemistry department at Wyeth in Pearl River, New York. In October 2001, he took a position as Assistant Professor in the chemistry department at the University of Hong Kong, where he was promoted to the rank of Associate Professor in June 2007. His research interests include organocatalysis and the use of polymers to facilitate organic synthesis.

elements carbon, nitrogen, and oxygen, which have been used to support synthetic substrates, reagents, or catalysts. Therefore, although they have been used successfully in synthesis, heterogeneous silica materials<sup>12</sup> and polysiloxanes (both homogeneous<sup>13</sup> and heterogeneous<sup>14</sup>) are not covered here. This review also does not discuss the use of dendrimers<sup>15</sup> and molecularly imprinted polymers<sup>16</sup> in synthesis, since the former are traditionally synthesized in a stepwise manner rather than by a chain reaction, and the latter are generally designed for a single specific application rather than general utility. For this same reason, self-supported polymeric catalysts<sup>17</sup> and related polymeric ligands are also omitted. For an up to date and extensive discussion regarding the use of soluble dendrimers in organic synthesis, see the contribution by Bergbreiter et al. to this collection of review articles. The organization of this review is based on the structure of the polymer backbones and the type of monomer used to prepare them, rather than on the physical or chemical properties of the materials or the types of compounds



**Figure 1.** Structures of Merrifield resin, PEG, and Tentagel.



**Figure 2.** Potential modifications for improved performance of heterogeneous polystyrene.

attached to them. Hybrid materials such as Tentagel that are combinations of two different polymers grafted together are discussed alongside the unanchored polymer that corresponds to the graft where the synthetic substrate, reagent, or catalyst is attached, rather than the polymer used to anchor the graft, since it is the polymer closer to the action and presumably exerts greater influence on the chemistry being performed. Thus, all of the grafted PEG polymers are presented together in section 3.1.

## 2. Polyalkenes

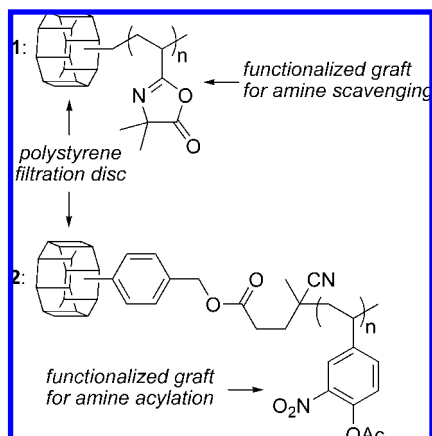
Polyalkene polymers have been the most widely used class of macromolecules in organic synthesis. This is probably due to the combination of their easy synthesis, relative inertness, and low cost. Since heterogeneous divinylbenzene cross-linked polystyrene is widely commercially available in various forms, such as lightly cross-linked and swelling microporous resin and highly cross-linked and nonswelling macroporous resin varieties, and derivatized with many different functional groups, it has probably been used more often than any other polymer in the context of organic synthesis. However, recent years have seen the use of new variations of polystyrene as well as other polyalkenes, such as polyisobutylene, polynorbornene, poly(styrene-*co*-maleic anhydride), and polyacrylamides.

### 2.1. Polystyrene

In seeking to improve the performance of polystyrene in organic synthesis applications, several strategies have been examined (Figure 2): (1) using heterogeneous cross-linked polystyrene in different formats or preparing the polymer in such a way that the functional groups are concentrated toward the surface of the resin, (2) using a cross-linker other than divinylbenzene to heterogenize polystyrene in order to modulate the physical and chemical properties of the resin, (3) adding functional groups to the polystyrene backbone that provide desired properties, and (4) grafting polystyrene onto a heterogeneous support and the use of the graft as the point of substrate/reagent/catalyst attachment in order to reduce the importance of resin swelling.

#### 2.1.1. New Formats and Preparation Procedures

Heterogeneous cross-linked polystyrene is generally used in bead form that is 100–400 mesh (inch<sup>-1</sup>) in diameter.



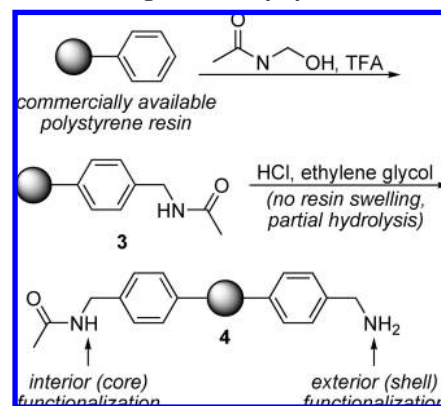
**Figure 3.** Functionalized polystyrene monoliths for reactive filtration.

Recently, Zhu has described the use of the ascension polymerization technique for the preparation of large uniform beads with diameters in excess of 1 mm.<sup>18</sup> This technique involves the injection of a hydrophobic monomer mixture at the bottom of a heated column containing a hydrophilic phase. The difference in densities of the phases causes the monomer droplets to slowly rise to the top of the column as polymerization proceeds. The size of the beads formed is controlled by both the diameter of the injection needle and the rate of monomer injection, while their porosity is controlled by the choice of porogen. Such large beads should be useful for the synthesis of compound libraries where each bead is functionalized with a unique compound, since they would provide more of each compound for biological screening than smaller beads could.

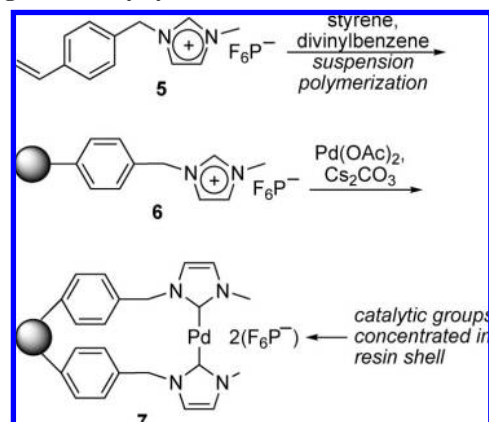
Also, cross-linked polystyrene can be prepared in virtually any desired form, and efforts to use it in monolithic form<sup>19</sup> have been reported. Fréchet coined the term “reactive filtration” when he reported the attachment of 2,2-dimethylazlactone groups to polystyrene discs **1** (Figure 3) cut from a rod of the polymer, and the use of this material to rather efficiently scavenge excess amines from reaction mixtures in a filtration process.<sup>20</sup> He later described the use of discs **2** to perform acylation reactions in a flow-through operation.<sup>21</sup> Janda has extended this concept further by using the shape of the monolith as an encoding element to record the synthetic history of the compounds attached to them.<sup>22</sup> Shapes such as circles, triangles, and squares were prepared and used for the solid-phase synthesis of a library of ureas.

As mentioned previously, one of the primary concerns when using a heterogeneous polymer such as Merrifield resin in organic synthesis is the ability of the resin to absorb the reaction solvent and swell. This is due to the fact that the polymers are generally randomly functionalized and that the majority of the functional groups are located on the interior of the bead. If the solvent cannot access these sites, neither can the dissolved reagents, catalysts, or substrates with which they are meant to react. Lee has addressed this issue by developing a new method for functionalizing cross-linked polystyrene beads in such a way that the majority of the resulting functional groups are located close to the exterior of the beads. He refers to such materials as core-shell resins, where the core is relatively unfunctionalized and the shell is highly derivatized. An aminomethyl polystyrene resin was the first reported example of this concept and was prepared from commercially available preformed polystyrene beads by aminomethylation to form

### Scheme 1. Synthesis of Core-Shell Aminomethyl Functionalized Heterogeneous Polystyrene



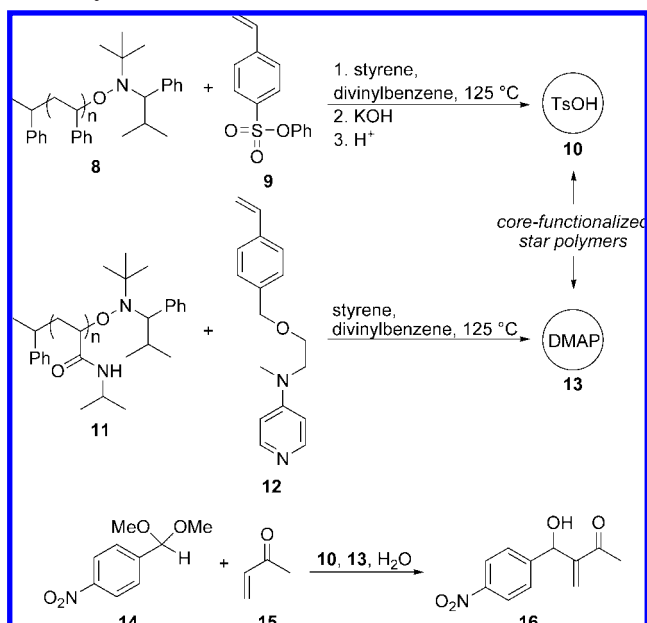
### Scheme 2. Synthesis of Core-Shell NHC Functionalized Heterogeneous Polystyrene



protected **3**, followed by the use of the polar solvent ethylene glycol in the amine deprotection step to form **4** (Scheme 1).<sup>23</sup> Since the polystyrene resin did not swell in the solvent, only the amine groups close to the surface of the bead were deprotected. The concentration of the resulting aminomethyl groups in the outer shell of the beads was confirmed by fluorescence microscopy, and **4** was used successfully for solid-phase peptide synthesis with the residual amide groups in the core of the resin being inconsequential.<sup>24</sup> It should be emphasized that since only the exterior portion the beads are functionalized with amine groups, the loading level of resins prepared in this way must be lower than that for resin beads of the same size that possess the desired functionalization throughout their interiors. In this case, **4** possessed a loading level of 0.92 mmol  $\text{-NH}_2 \text{ g}^{-1}$ , compared to typical commercially available aminomethyl resin loading levels of greater than 1.1 mmol  $\text{-NH}_2 \text{ g}^{-1}$ .

Lee reported another method for ensuring that the functional groups, in this case *N*-heterocyclic carbene (NHC) ligands, were located in the shell of a resin bead, thereby reducing the need for resin swelling (Scheme 2). In this case, monomer **5**, which is immiscible in both the styrene and aqueous phases of a suspension polymerization reaction, was used.<sup>25</sup> It was found that the ionic liquid nature of **5** allowed it to be located at the interface between the two phases during polymerization, and therefore, the NHC groups were incorporated on the surface of **6** as the beads formed. Confocal laser scanning microscopy of a fluorescent dye functionalized resin bead confirmed this notion, and **6** was converted into heterogeneous NHC functionalized polymer **7** (loading = 0.11 mmol Pd  $\text{g}^{-1}$ ). Energy dispersive X-ray (EDX) analysis

### Scheme 3. Synthesis and Use of Internally Functionalized Star Polymers



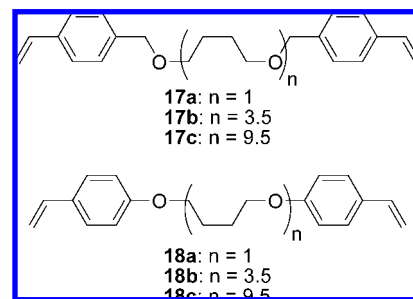
and IR spectroscopy indicated that the palladium was immobilized at the imidazolium groups of **7**, and it was used effectively to catalyze Suzuki,<sup>26</sup> Heck,<sup>27</sup> and Sonogashira<sup>28</sup> reactions in which DMF or a DMF/water mixture was used as the reaction solvent.

Hawker and Fréchet reported the complimentary strategy of concentrating the functional groups attached to a polystyrene in the interior of a soluble star polymer matrix so that the catalytic groups are core-confined due to the use of low molecular weight macroinitiators that form the surface of the final polymer.<sup>29</sup> This strategy allows for the simultaneous use of fundamentally incompatible reagents, such as acids and bases, since they are physically isolated from one another (Scheme 3). For example, such core-functionalized star polymers could be prepared by polymerizing polymer **8** with monomer **9** and divinylbenzene to form sulfonic acid core functionalized **10**, or by polymerizing polymer **11** with monomer **12** and divinylbenzene to afford 4-(dialkylamino)pyridine core functionalized **13**. It was found that **10** and **13** could be used together in a one-pot acetal hydrolysis/Morita-Baylis-Hillman reaction sequence with substrates **14** and **15** to efficiently form product **16**. They later applied this same concept to an iminium/enamine reaction cascade where the use of two differently functionalized star polymers allowed for the simultaneous use of four catalysts that normally could not all exist together.<sup>30</sup>

#### 2.1.2. Non-Divinylbenzene Cross-Linkers

It was demonstrated several years ago that changing the cross-linker of polystyrene resins from relatively small and rigid divinylbenzene to larger and more flexible compounds generally increases their mechanical stability and allows them to absorb more solvent.<sup>31</sup> Furthermore, when the cross-linker is based on an oligo(ethylene glycol) group, the polymer becomes more compatible with polar solvents and can function better as a support for solid-phase peptide synthesis than does Merrifield resin.<sup>31,32</sup>

In contrast to most of the early research in this area that centered on the use of highly polar oligo(ethylene glycol) groups to cross-link polystyrene to prepare polymer supports



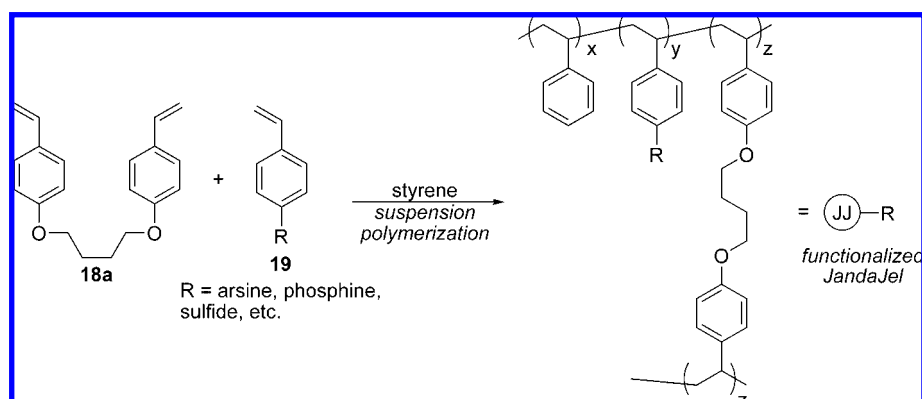
**Figure 4.** Polytetrahydrofuran-based compounds used to cross-link polystyrene.

for peptide synthesis, Janda used polytetrahydrofuran-based cross-linkers **17a-c** and **18a-c** in the suspension polymerization of styrene to prepare polymers for general organic synthesis (Figure 4).<sup>33</sup> The idea behind this concept was the maxim “like dissolves like” and that since THF is a good solvent for many organic reactions, incorporating a related polyether into a polystyrene resin should increase polymer swelling in this solvent. Somewhat surprisingly, it was observed that the swelling of resins prepared with such cross-linkers in THF was universally greater than that for analogous divinylbenzene cross-linked polymers and virtually independent of the length or structure of the polytetrahydrofuran cross-linker. Therefore, **18a**, which could be easily prepared in one pot on a large scale from inexpensive commercially available starting materials, was settled on for the preparation of what is now known as JandaJel.<sup>34</sup>

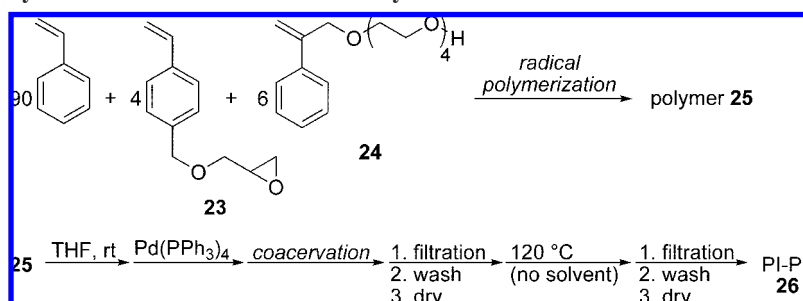
This polymer has been prepared with pendant arsines,<sup>35</sup> phosphines,<sup>36</sup> and other reagents,<sup>37</sup> using functionalized styrene monomers **19** in the suspension polymerization reaction (Scheme 4), and in all cases, the supported reagents showed good swelling in the solvents in which they were used. Interestingly, JandaJel was used for the solid-phase synthesis of the classically difficult to synthesize ACP(65-74) peptide sequence, with better results in terms of overall yield and product purity than was achieved using Merrifield resin.<sup>38</sup> Solid-phase synthesis of small drug-link organic molecules is also efficient using JandaJel as the support,<sup>39</sup> and as an illustration of the value of the large degree of swelling that JandaJel exhibits, it was successfully used in multipolymer reactions where a separate homogeneous polymer-supported reagent was reacted with it.<sup>40</sup> In one such example, JandaJel functionalized with phosphine groups was able to react with a separate soluble polymer-supported azo reagent to effect Mitsunobu reactions, whereas a divinylbenzene cross-linked polystyrene-supported phosphine reagent was unreactive.<sup>41</sup> Further evidence for the benefit of increased resin swelling was shown by several research groups that immobilized chiral catalysts and ligands such as **20-22** (Figure 5) onto JandaJel and obtained excellent results in terms of enantioselectivity of product formation when these heterogeneous materials were used.<sup>42-44</sup> Finally, the JandaJel cross-linker **18a** has also been used to prepare polystyrene microgels that are soluble polymers with lower viscosity than that of the corresponding linear polymers.<sup>45</sup> Such microgels can be used effectively as supports for both synthesis and reagent immobilization.<sup>46</sup>

Kobayashi has extended his work regarding the microencapsulation of metal catalysts in polystyrene and developed the concept he refers to as polymer incarceration, using oligo(ethylene glycol) groups to cross-link polystyrene. In this methodology, polymer cross-linking is performed after entrapment of the metal through coacervation with a linear

## Scheme 4. Synthesis of Functionalized JandaJels



## Scheme 5. Synthesis of Polymer-Incarcerated Palladium Catalysts



polystyrene functionalized with both oligo(ethylene glycol) and epoxide group groups that can react with each other upon heating. For example, copolymerization of styrene, **23**, and **24** afforded polymer **25**, which was used to generate one of the first examples of an incarcerated palladium catalyst, PI-Pd **26** (Scheme 5).<sup>47</sup> It should be noted that the details of the cross-linking reaction have not been reported and a proposed structure for the obtained cross-linked polymer has never been published in the chemical literature. Regardless of the ambiguity surrounding the cross-linking in these materials, numerous polymer incarcerated metal catalysts have been used with excellent results in a broad range of reactions and are highly reusable. The initial reports involved the entrapping of palladium to generate catalysts such as **26** for catalysis of alkene hydrogenation and allylation reactions using allylic carbonates.<sup>47,48</sup> These catalysts were subsequently used in Suzuki–Miyaura,<sup>49,50</sup> Heck,<sup>50,51</sup> aminocarbonylation,<sup>52</sup> and amidation<sup>53</sup> reactions. Polymer incarcerated scandium triflate,<sup>54</sup> ruthenium,<sup>55</sup> platinum,<sup>56</sup> and gold<sup>57</sup> catalysts have also been reported and used to perform Mukaiyama aldol, alcohol, and sulfide oxidation, hydrogenation,

and indole synthesis reactions, respectively. Significantly, in all reported applications of these polymer incarcerated metal catalysts, no significant metal leaching into the desired synthesis product was observed. Thus, they should be useful in synthetic applications where this issue is a concern, such as pharmaceutical manufacturing.

A limitation in some of the previous reactions catalyzed by **26** and its analogues was the need to add an external phosphine ligand. This issue was addressed in a second generation methodology using polymers functionalized with phosphine groups prepared by adding one of the monomers **27–31** (Figure 6) to the polymerization reaction. Use of the polymers thus prepared for palladium incarceration eliminated the need to add external phosphine for performing Suzuki–Miyaura,<sup>58</sup> hydrogenation,<sup>59</sup> amination,<sup>60</sup> and Sonogashira<sup>61</sup> reactions. Finally, polymer incarceration has been used to immobilize a lipase enzyme, but it required the addition of tris(2-aminoethyl)amine in the cross-linking

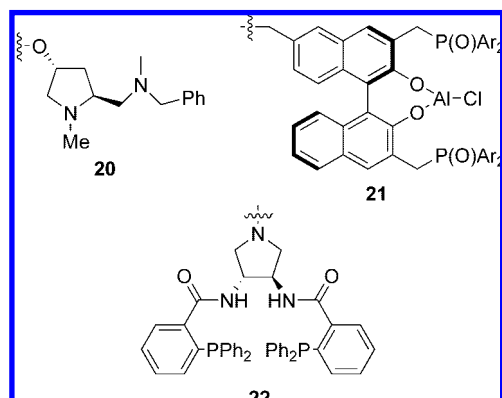


Figure 5. Chiral catalysts and ligands immobilized on JandaJel.

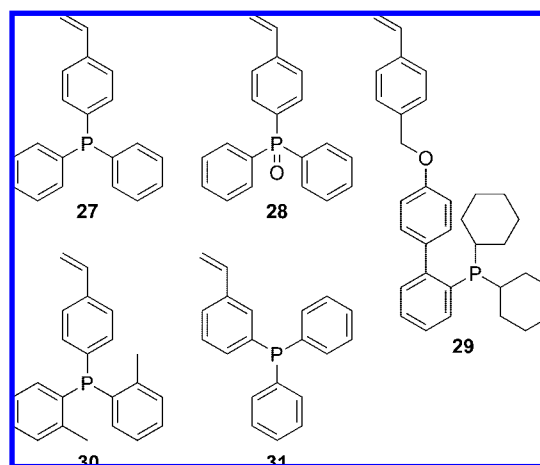
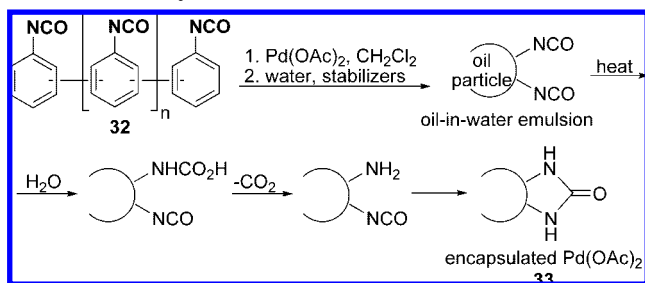


Figure 6. Phosphine monomers used in palladium incarceration.

### Scheme 6. Synthesis of Urea Cross-Linked Encapsulated Palladium Catalysts



step.<sup>62</sup> Incarceration in the heterogeneous polymer rendered the enzyme easily recyclable without attenuating its natural enantioselectivity.

A method for metal catalyst microencapsulation with polymethylene polyphenylene diisocyanate was reported by Ley that utilized urea groups to cross-link the polymer.<sup>63</sup> In this method, polyisocyanate polymer **32** is mixed with the catalyst to be encapsulated in  $\text{CH}_2\text{Cl}_2$  (Scheme 6). This is added to an aqueous stabilizer solution to generate an oil in water emulsion. Heating of this emulsion initiates urea formation with concomitant loss of carbon dioxide that links the original isocyanate groups of **32** and encapsulates the catalyst. The first example of this technique involved the encapsulation of  $\text{Pd}(\text{OAc})_2$  to generate heterogeneous catalyst **33** for Suzuki–Miyaura reactions.<sup>64</sup> This catalyst could also be used to catalyze a number of different reactions effectively in supercritical carbon dioxide<sup>65</sup> and several hydrogenation reactions.<sup>66</sup> Variations of this microencapsulated palladium catalyst are now commonly referred to as Pd-EnCat and have been used in a large number of variations of Suzuki–Miyaura<sup>67</sup> and hydrogenation<sup>68</sup> reactions from which the catalyst could be recovered and reused with no appreciable decrease in catalytic efficiency, in some cases up to 10 times. Additionally, an analogous microencapsulated osmium tetroxide catalyst has been reported for use in alkene dihydroxylation reactions.<sup>69</sup> The porosity of such polymer encapsulated catalysts has been studied,<sup>70</sup> and Jones has used Pd-EnCat together with poly(4-vinylpyridine) to suggest that when this catalyst is used in Heck reactions, catalysis occurs outside of the polyurea matrix by a soluble palladium species.<sup>71</sup>

Chiral cross-linkers have also been used to prepare heterogeneous polystyrene resins where the chiral moiety is used as a ligand in asymmetric catalysis (Figure 7). For example, Hoveyda and Schrock have used **34** to prepare a recyclable chiral molybdenum olefin metathesis catalyst that was used in enantioselective ring-opening and ring-closing metathesis reactions where the products were isolated with only slightly lower enantiomeric excess than when the corresponding small molecule catalyst was used.<sup>72</sup> Similarly, Seebach has used compounds such as **35** to prepare a variety of polystyrene beads with embedded  $\alpha,\alpha,\alpha,\alpha$ -tetraaryl-1,3-dioxolane-4,5-dimethanol (TADDOL) groups that were used to prepare recyclable chiral titanium Lewis acid catalysts for addition of  $\text{Bu}_2\text{Zn}$  to  $\text{PhCHO}$ .<sup>73</sup> This later report also describes the use of a number of cross-linkers where the tetraaryl groups possess polymerizable carbon–carbon double bonds. Luis has used a similar strategy to prepare supported bis(oxazolines) with **36**<sup>74</sup> for chiral copper cyclopropanation catalysts, as did Itsuno in his synthesis of a polymer-supported chiral 1,2-diamine from cross-linker **37** for use in an enantioselective ruthenium transfer hydrogenation catalyst for the reduction of aromatic ketones.<sup>75</sup> Interestingly, in all

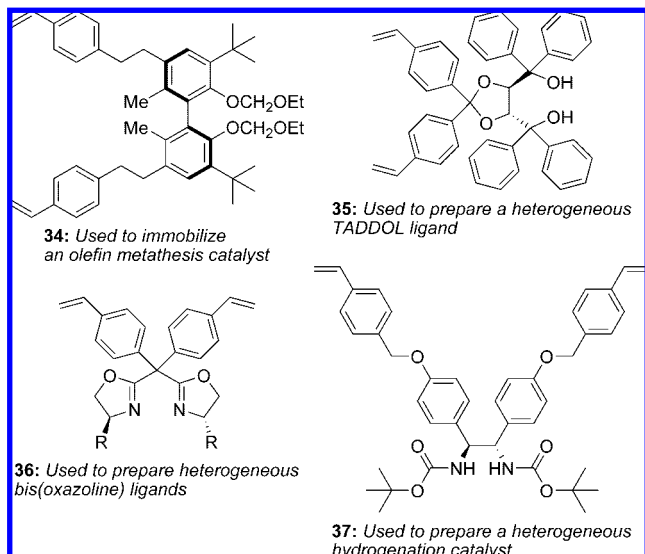
of these reports, the original symmetry of the unsupported ligand group was maintained in the supported version by the addition of two equivalent styrene groups and the use of these to incorporate the ligand into the heterogeneous polymer. Thus, it can be imagined that this strategy should be useful for immobilizing any chiral group where such symmetry is important to its performance. Furthermore, the catalysts formed from these polymer-supported ligand groups generally showed similar or only slightly reduced enantioselectivity in the reactions studied compared to the corresponding unsupported small molecule catalysts.

### 2.1.3. Functionalized Polystyrene

As discussed in the previous section, the use of PEG derivatives to cross-link polystyrene led to resins that performed well in solid-phase peptide synthesis, presumably due in part to their good swelling in the required solvents. This inspired Bradley to develop a complimentary strategy and add short oligo(ethylene glycol) groups to the backbone of divinylbenzene cross-linked polystyrene to make the resin beads more compatible with polar solvents.<sup>76</sup> Specifically, monomer **38** was used in the preparation of resin **39** by copolymerization with 4-vinylbenzyl chloride, styrene, and divinylbenzene (Scheme 7). The key difference between this strategy and Bayer's design of PEG-based Tentagel is that, in the latter, the PEG groups act as spacers to separate the polystyrene backbone from the point of synthesis, whereas, in the former, the PEG groups are merely spectators added to modulate the physical properties of the polymer. The validity of this concept and the utility of **39** were demonstrated by using this material to support efficient solid-phase peptide synthesis. For example, the tripeptide Ala-Val-Phe- $\text{NH}_2$  was prepared in slightly higher yield with similar purity (80% yield, 94% purity) using **39**, compared to when commercially available aminomethyl polystyrene resin was used (56–72% yield, 95% purity).

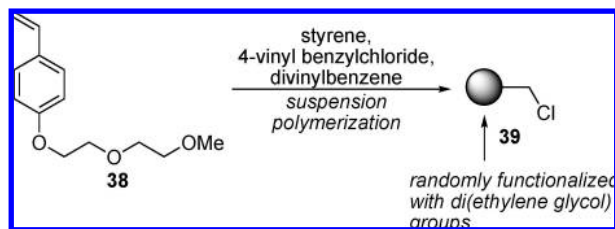
Toy later reported results similar to Bradley's in a study of polymer-supported phosphine catalysts for Morita–Baylis–Hillman (MBH) reactions.<sup>77</sup> Functional groups such as acetoxy, methoxy, hydroxyl, and nitrile groups were incorporated onto the polystyrene backbone by copolymerization of monomers **40–45** (Figure 8) with **27** and cross-linker **18a** in the process outlined in Scheme 4, and it was found that the addition of the methoxy groups from **44** afforded the best swelling catalyst in THF. This high swelling resin also proved to be the most efficient catalyst in all of the MBH reactions of *N*-tosyl arylimines with the various Michael acceptors studied. Interestingly, incorporation of hydroxyl groups into the polymer using **40** resulted in a resin that did not swell appreciably in THF but that was still a modestly effective catalyst. This observation led to the notion of cooperative catalysis by the hydrogen bond donating hydroxyl groups and the nucleophilic phosphine groups in the reactions.<sup>78</sup>

Similarly, for the generation of water compatible cross-linked polystyrene resin for use in asymmetric transfer hydrogenation reactions, Itsuno used monomer **46** (Figure 8) containing pendant sulfate groups.<sup>79</sup> The resulting polymer-supported chiral sulfonamide ligand proved to be even better at asymmetric induction than did the corresponding unsupported ligand! Apparently some synergy occurs between the two different functional groups in this material. This strategy was also applied to linear non-cross-linked polystyrene.



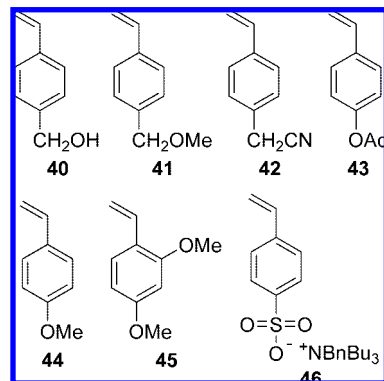
**Figure 7.** Structure of chiral cross-linkers used to prepare heterogeneous polystyrene.

### Scheme 7. Synthesis of Oligo(ethylene glycol) Functionalized Heterogeneous Polystyrene for Solid-Phase Peptide Synthesis

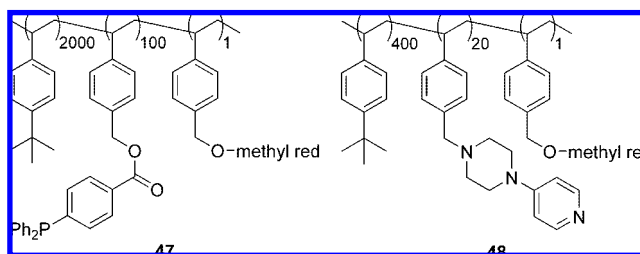


More recently, Bergbreiter has shown that poly(4-*tert*-butylstyrene) is hydrophobic enough to be selectively soluble in a nonpolar organic solvent so that its quantitative removal is achievable using biphasic polar liquid/nonpolar liquid separation.<sup>80</sup> For example, poly(4-*tert*-butylstyrene) functionalized with both a visualization dye such as methyl red and a catalytic phosphine (**47**) or amine group (**48**) could be used to effect desired reactions homogeneously in a mixed polar/nonpolar solvent system such as heptane/ethanol (Figure 9).<sup>81</sup> Upon completion of the reaction, water was added to form a biphasic mixture in which one layer is composed of the polymer containing nonpolar solvent and the other layer is a mixture of the polar solvent, water, and the reaction product. The nonpolar phase could then be reused with new substrate and additional polar solvent. Reactions performed using this methodology included phosphine catalyzed Michael addition of 2-nitropropane to methyl acrylate and amine catalyzed carbonate formation. The dye was used to monitor the efficiency of the phase separation and facilitate recovery of the polymers. Interestingly, it was observed that the isolated product yield increased with increasing reaction cycle number due to saturation of the heptane phase with product, and the yield reached a maximum that was comparable to what was obtained using a nonsupported catalyst after five reaction cycles.

Plenio almost simultaneously reported a similar strategy using poly(4-methylstyrene) to support phosphine ligands for use in palladium catalyzed Sonogashira and Suzuki coupling reactions.<sup>82</sup> This polymer was used in a cyclohexane/DMSO solvent mixture for the former and a cyclohexane/nitromethane solvent mixture for the later. In these reactions the cyclohexane catalyst containing phase could easily be



**Figure 8.** Polar monomers used to synthesize heterogeneous polystyrenes.



**Figure 9.** Bifunctional poly(*tert*-butylstyrene)s.

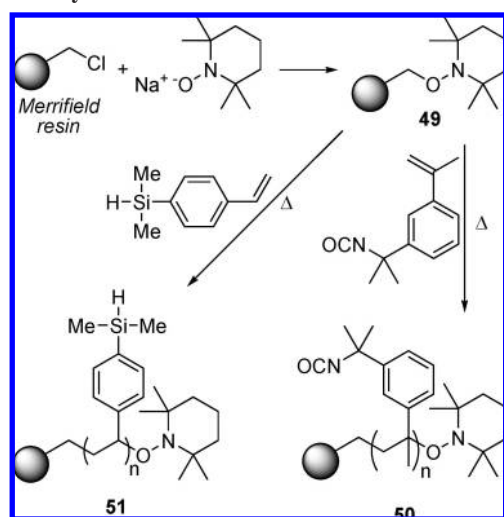
separated from the polar product containing phase upon reaction completion, with the catalyst phase being ready for reuse. NMR analysis of the product phase indicated that the desired products were not contaminated by any polymeric material. Furthermore, total reflection XRF and UV spectrophotometry were used to determine that more than 99.8% of the catalyst remained in the cyclohexane layer of these reactions. In a subsequent report this polymer was applied in a continuous Sonogashira reaction process in a fixed bed reactor.<sup>83</sup> Passing the polar substrate containing DMSO phase through the nonpolar catalyst containing cyclohexane or heptane phase led to virtually quantitative conversion for the coupling of various aryl bromides with phenylacetylene using 0.6 mol % of catalyst.

#### 2.1.4. Grafted Polystyrene

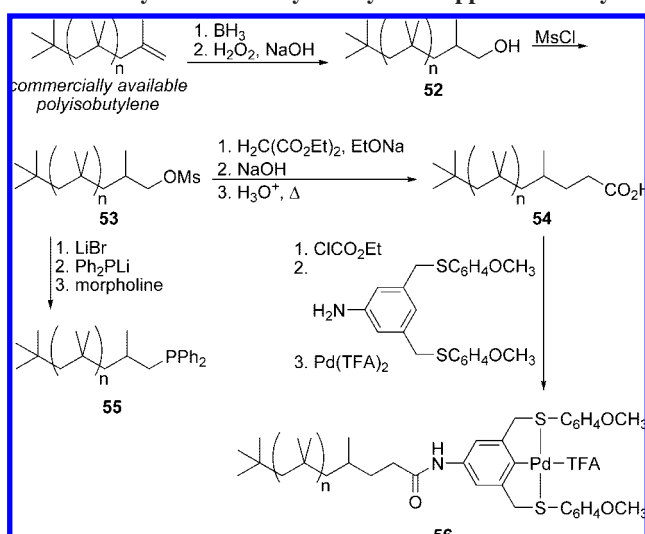
In the introductory section it was described how Bayer grafted PEG onto heterogeneous polystyrene resin in order to move the point of peptide synthesis away from the interior of the beads and reduce the need for resin swelling. Linear polystyrene has been applied in a related strategy with the advantage that there can be multiple sites of functionalization on each flexible polystyrene graft whereas PEG only provides a single terminal functional site. The first example of this was reported by Zhao and involved the radiolytic grafting of polystyrene onto the surface of fluoropolymer tubes.<sup>84</sup> This was accomplished by immersing the tubes in a styrene, MeOH, and H<sub>2</sub>SO<sub>4</sub> mixture and then  $\gamma$ -irradiating with a Co<sup>60</sup> source. The polystyrene grafts thus formed on the tubes were then aminomethylated and used as surfaces for solid-phase nitrile oxide and Diels–Alder cycloaddition reactions.

Hodges later reported the use of living free radical polymerization to graft polystyrene onto heterogeneous polystyrene resin to form what he referred to as Rasta resin.<sup>85</sup> This methodology was reported to be useful for the addition of grafts functionalized by electrophilic groups that might be incompatible with traditional suspension polymerization techniques. Merrifield resin was first functionalized with

Scheme 8. Synthesis of Rasta Resins



Scheme 9. Synthesis of Polyisobutylene-Supported Catalysts

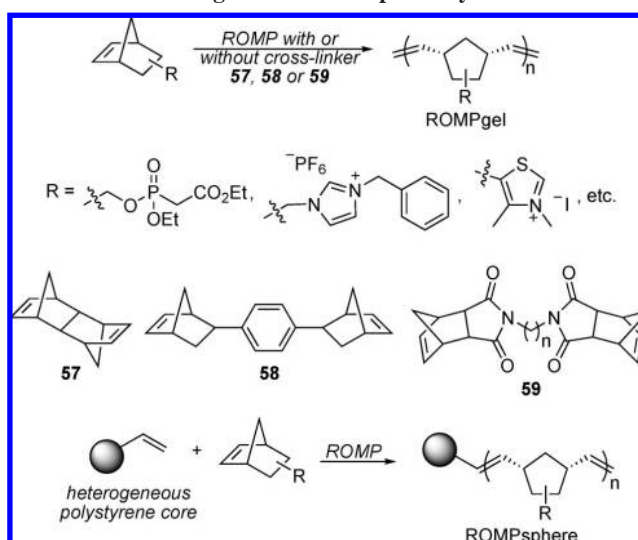


reduced TEMPO to generate the resin core **49** that was ready for living free radical polymerization of various styrene monomers (Scheme 8). Use of a rhodamine dye confirmed that the grafts and associated functional groups were concentrated on the exterior of the resulting beads.<sup>86</sup> For example poly(3-isopropenyl- $\alpha,\alpha$ -dimethylbenzyl isocyanate) grafts were added to **49**, and the resulting resin **50** (loading level 1.4–2.3 mmol g<sup>-1</sup>) was found to react quantitatively with primary and secondary amines in solution but not with 3-bromoaniline. Alternatively the polystyrene grafts could be functionalized with silane groups, as in **51**, for use as linkers in solid-phase synthesis.<sup>87</sup> More recently it was found that such resins could be prepared efficiently using microwave-initiated polymerization,<sup>88</sup> and Fontaine has extended this concept by using atom transfer radical polymerization (ATRP) initiators to attach poly(2-vinyl-4,4-dimethyl-5-oxazoline) grafts that are efficient at nucleophile scavenging<sup>89</sup> or that can serve as the platform for a densely functionalized basic amine resin.<sup>90</sup>

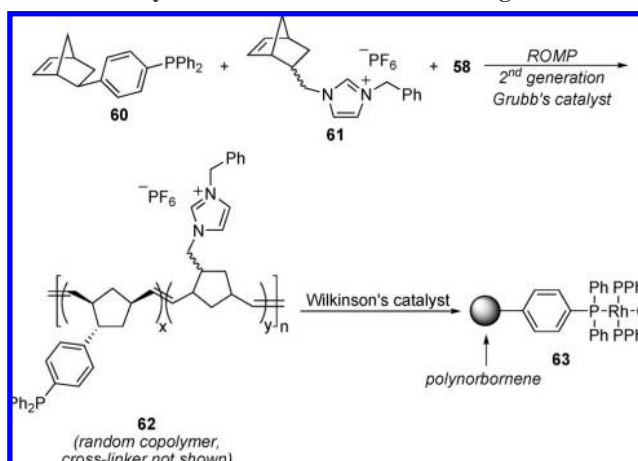
## 2.2. Polyisobutylene

Lately Bergbreiter has focused much of his attention to applying polyisobutylene as a soluble, nonpolar hydrocarbon analogue of PEG. This polymer is a terminal alkene that is commercially available with an average molecular weight

Scheme 10. ROMPgel and ROMPsphere Synthesis



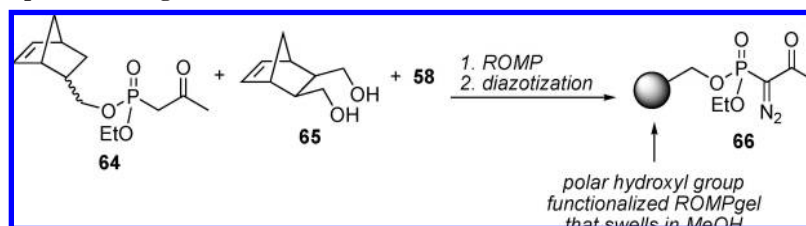
Scheme 11. Synthesis of a Bifunctional ROMPgel



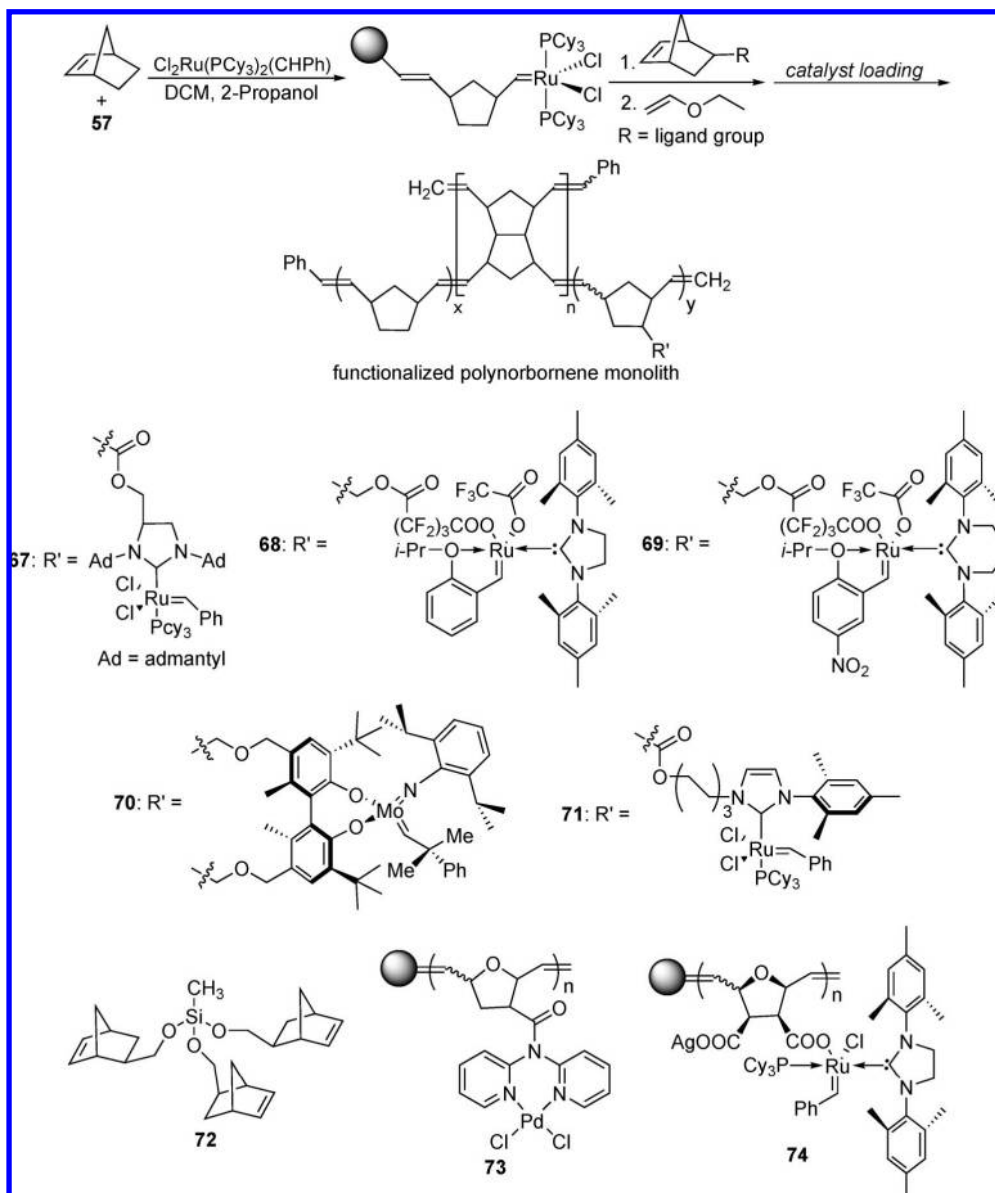
of 1000 or 2300 Da. It is reported that a major advantage of polyisobutylene over previously studied terminally functionalized polyethylene is that the former is readily soluble in a variety of nonpolar solvents whereas the latter is only soluble in such solvents at >75 °C.<sup>80,91</sup> Similar to the previously mentioned poly(4-*tert*-butylstyrene), polyisobutylene is very selectively soluble in nonpolar solvents such as heptane. Its carbon–carbon double bond can be transformed by the standard reactions of alkenes into more useful groups for attaching catalyst or reagent groups, such as hydroboration to form primary alcohol **52** (Scheme 9). This alcohol can then be converted to a mesylate leaving group in **53**, which can be displaced by a range of nucleophiles. For example, carboxylic acid **54** and phosphine **55** have been prepared, and all of these compounds are easily analyzed by <sup>1</sup>H NMR.<sup>91,92</sup> The first reported use of polyisobutylene as a catalyst support involved anchoring a sulfur–carbon–sulfur Pd(II) species to **53**. The resulting catalyst **56** was used to perform Heck, Sonogashira, and allylic substitution reactions with good recyclability.<sup>91</sup> More recently polyisobutylene has been used to support chiral bisoxazoline ligands for copper catalyzed cyclopropanation reactions,<sup>93</sup> as well as to serve as the basis for a self-separating atom transfer radical polymerization catalyst.<sup>94</sup> A polyisobutylene-supported RCM catalyst<sup>95</sup> and a chromium-based polycarbonate polymerization catalyst have also been reported.<sup>96</sup> All of these supported catalysts exhibited similar activity to their unan-



Scheme 12. Synthesis of a polar ROMPgel



Scheme 13. Polynorbornene Monolith-Supported Catalysts

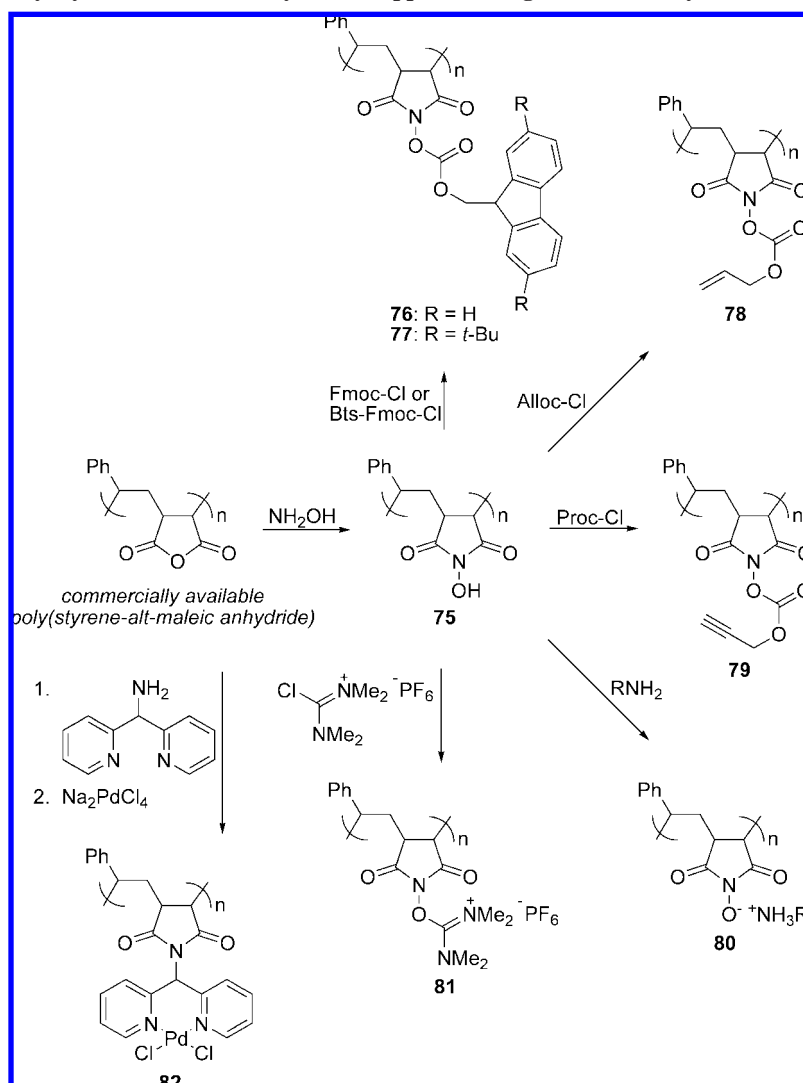


chored counterparts, and they were easily recovered and reused without appreciable loss of activity.

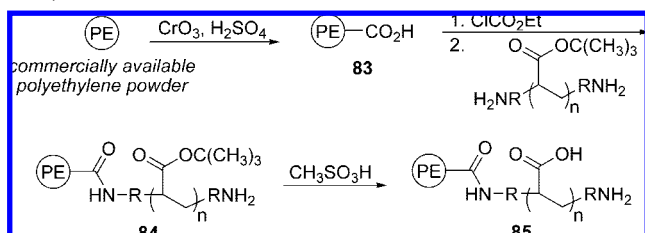
### 2.3. Polynorbornenes

The use of ring-opening metathesis polymerization (ROMP) to prepare polynorbornene derivatives amenable for use in synthesis has been widely studied. Perhaps the main motivations for using such polymers are that ROMP is generally compatible with many functional groups, and with proper monomer design, the polymers can be very densely functionalized. Much of the early work in applying

polynorbornenes has been reviewed by both of the pioneers in this field, Barrett<sup>97</sup> and Hanson.<sup>98</sup> Early on, Barrett referred to polynorbornenes, both with or without a norbornene-based cross-linker (57–59), as ROMPgel<sup>99</sup> and polystyrene resin grafted with polynorbornene as ROMP-sphere,<sup>100</sup> and we will use this nomenclature here (Scheme 10). A significant advancement in the preparation of cross-linked ROMPgels was Janda's reported methodology for application of the technique of suspension polymerization to their synthesis.<sup>101</sup> Using this technology a large number of norbornene-based cross-linkers could be used to prepare ROMPgels as heterogeneous resin beads.

Scheme 14. Synthesis of Poly(styrene-*alt*-maleic anhydride)-Supported Reagents and Catalysts

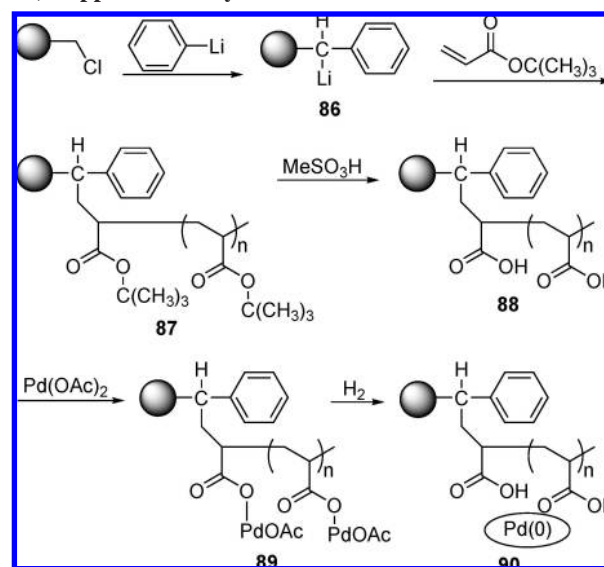
Scheme 15. Synthesis of Polyethylene Grafted Poly(acrylic acid)



Recent applications of polynorbornenes as a reagent support include the report by Toy and Hanson that a combination of non-cross-linked ROMPgels functionalized with phosphine groups and diethyl azodicarboxylate can react together in two-polymer Mitsunobu reactions in which the desired product was isolated in a highly pure state after filtration to remove all of the polymeric materials.<sup>41</sup>

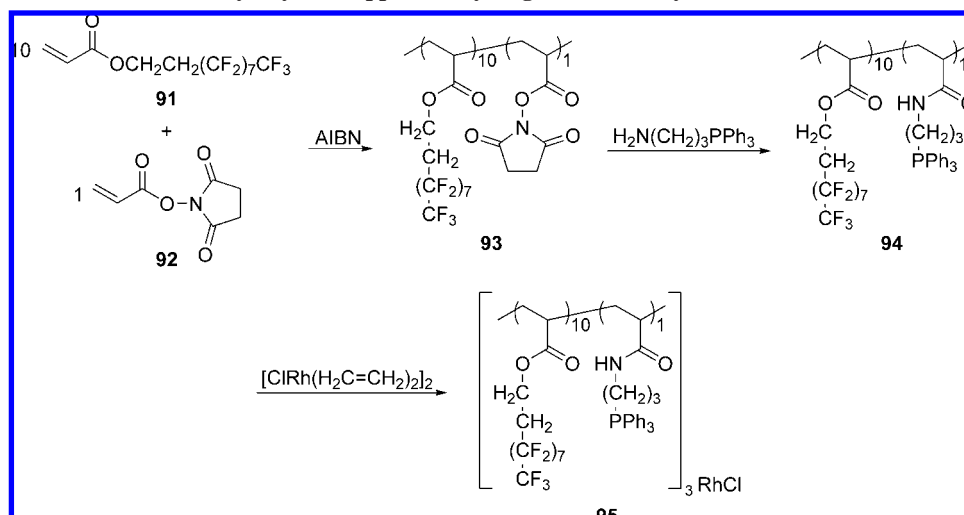
Other recent reports regarding the development and use of ROMPgels include the synthesis of a bifunctional version for the immobilization of Wilkinson's catalyst.<sup>102</sup> For this, Barrett copolymerized a phosphine monomer **60** together with imidazolium hexafluorophosphate monomer **61** and cross-linker **58** to form bifunctional ROMPgel **62** (Scheme 11). Heating **62** in the presence of Wilkinson's catalyst allowed for immobilization of the metal through a ligand

Scheme 16. Synthesis of Polystyrene Grafted Poly(acrylic acid)-Supported Catalysts

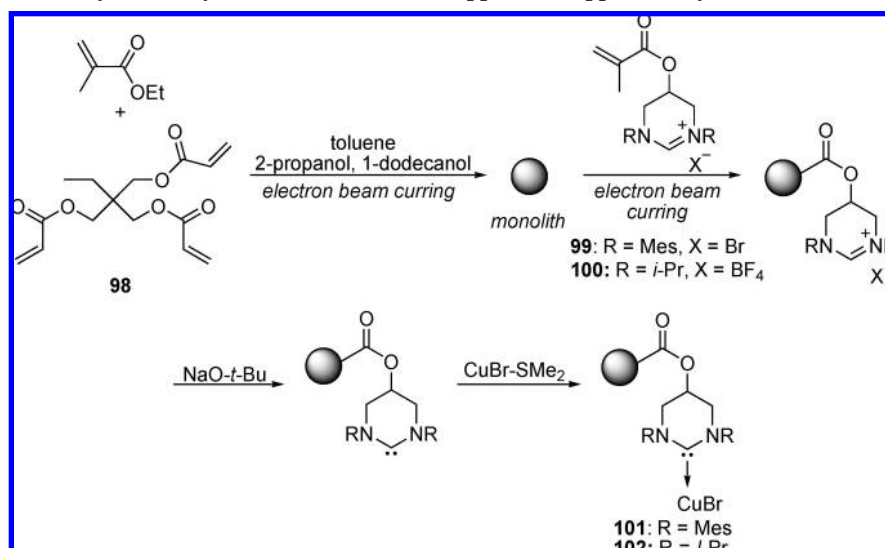


displacement process to form the desired supported catalyst **63** (loading level  $0.66 \text{ mmol Rh g}^{-1}$ ). The role of the imidazolium hexafluorophosphate groups in this catalyst is

## Scheme 17. Synthesis of a Fluorous Polyacrylate-Supported Hydrogenation Catalyst



## Scheme 18. Synthesis of a Poly(methacrylate)-Based Monolith-Supported Copper Catalyst



not clear, but good results were obtained in a series of parallel hydrogenation reactions.

This concept of using two different functionalized monomers in the polymerization reaction was extended to the copolymerization of **64**, **65** and cross-linker **58** to eventually form polar diol containing ROMPgel **66** that, due to presence of the hydroxyl groups, exhibited excellent swelling in polar solvents such as methanol (Scheme 12).<sup>103</sup> Polymer **66** was effective in the transformation of a series of aldehydes into the corresponding alkynes in methanol.

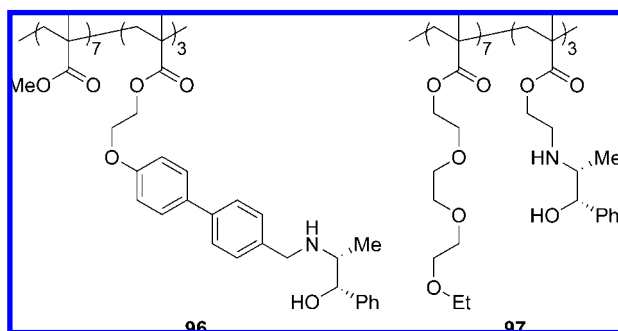


Figure 10. Soluble polymethacrylate-supported hydrogenation catalysts.

In addition to the ROMPgel and ROMPsphere formats described above, polynorbornene has also been prepared in monolithic form by Buchmeiser for use as a catalyst support. The monolithic support was prepared by copolymerization of norbornene and **57** in the presence of  $\text{CH}_2\text{Cl}_2$  and 2-propanol within a borosilicate column using  $\text{Cl}_2\text{Ru}(\text{PCy}_3)_2(\text{CHPh})$  as the ROMP catalyst (Scheme 13).<sup>104</sup> Functionalization of the thus formed polymer monolith with a ligand group bearing norbornene monomer was followed by capping

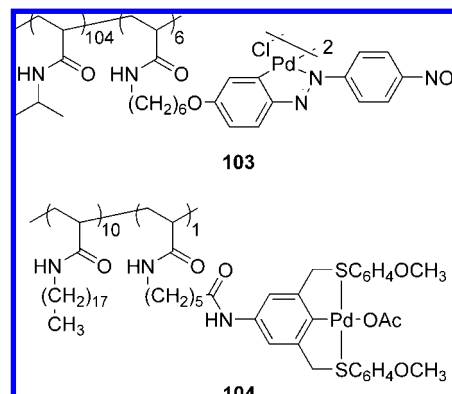
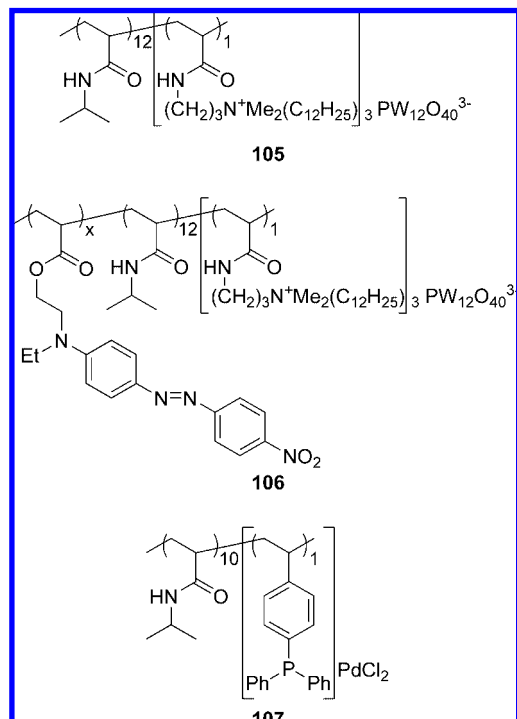


Figure 11. Soluble polyacrylamide-supported catalysts.



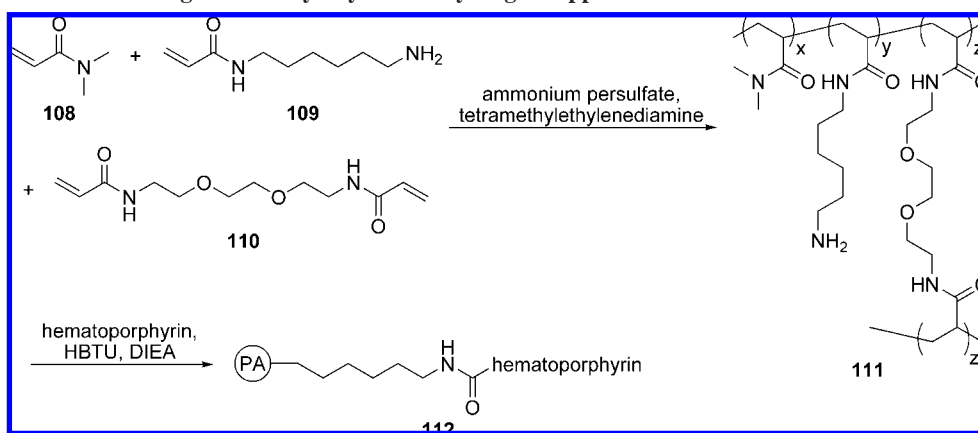
**Figure 12.** Insoluble polyacrylamide-supported catalysts.

with ethyl vinyl ether, carbene generation with DMAP, and catalyst loading to afford **67** (1.4 mmol Ru g<sup>-1</sup>). The combination of good and poor solvents used in the polymerization process ensured formation of the desired monolith microstructure with sufficient macroporosity. Catalyst **67** was found to be highly active in flow-through ROMP and RCM reactions, leading to Ru free products. Using the same polynorbornene structure and catalyst immobilization strategy, supported modified Grubbs–Hoveyda catalysts **68**<sup>105</sup> and **69**,<sup>106</sup> chiral Schrock catalyst **70**,<sup>107</sup> and Grubbs-type catalyst **71**<sup>108</sup> have also been developed and successfully

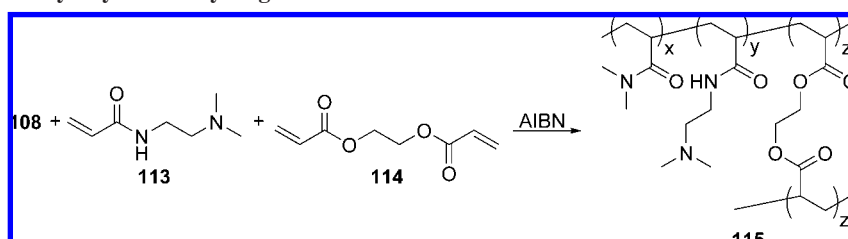
employed in numerous metathesis reactions. Monoliths prepared by copolymerization of norbornene with cross-linker **72** have also been reported that were functionalized as Pd catalyst **73** for Heck reactions<sup>109</sup> and as Grubbs–Hermann-type metathesis catalyst **74**.<sup>110</sup>

Other recent applications of polynorbornene supports include Barrett's use of ROMPgel to support a thiazolium organic catalyst for use in Stetter reactions,<sup>111</sup> and both ROMPgel and ROMPsphere have served as platforms for coupling reagents used in peptide synthesis<sup>112</sup> and a photo-oxygenation catalyst.<sup>113</sup> Hanson has reported ROMPgel functionalized with phosphonyl dichloride groups for amine scavenging<sup>114</sup> and monoamine hydrochloride groups for scavenging electrophiles.<sup>115</sup> ROMPgel was also used to support benzenesulfonyl azide groups used in diazo-transfer reactions,<sup>116</sup> benzylium salts in benzylation reactions,<sup>117</sup> carbodiimide groups for coupling reactions,<sup>118</sup> phosphine groups for cross-coupling reactions,<sup>119</sup> TEMPO in alcohol oxidation reactions,<sup>120</sup> pincer Pd(II) complexes as precatalysts in Heck reactions,<sup>121</sup> and salen complexes for a variety of applications.<sup>122</sup> Most recently Polo has used the ROMPgel norbornene monomer framework to display 2 cyclopentadiene or indene groups in the proper orientation for use as zirconium “self-immobilizing” precatalysts.<sup>123</sup> Exposure of the prepared biscyclopentadienyl and bisindenyl zirconocenes to methylaluminumoxane resulted in the expected polymerization to form immobilized catalysts that could be reactivated and used effectively in ethylene polymerization. Nomura has shown that monofunctionalized polynorbornene can serve as a phase tag, since it precipitates in methanol.<sup>124</sup> For example polynorbornene terminally functionalized with various pyridine groups can be used as a ligand in hydrogenation reactions. Upon completion of the reactions, methanol can be added to precipitate the polymer–metal complex for easy separation and reuse.

### Scheme 19. Synthesis of a Heterogeneous Polyacrylamide Hydrogel-Supported Photosensitizer



### Scheme 20. Synthesis of Polyacrylamide Hydrogels



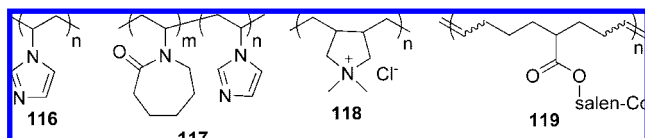


Figure 13. Miscellaneous polyalkene supports.

## 2.4. Poly(styrene-*co*-maleic anhydride)

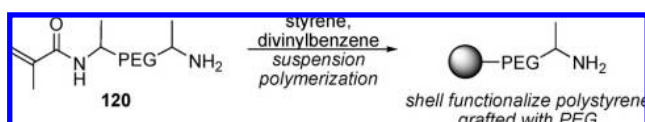
The alternating copolymer of styrene and maleic anhydride, poly(styrene-*alt*-maleic anhydride), can be precipitated from hexanes and is commercially available with an average molecular weight of approximately 550000 Da, containing 10–15% monomethyl ester. The high concentration and reactivity of the cyclic anhydride groups of this polymer make it ideal for use as a reagent support. Nájera first reported treatment of this polymer with hydroxylamine to afford polymer-supported *N*-hydroxysuccinimide **75** for use in peptide coupling reactions that exhibited very low levels of racemization (Scheme 14).<sup>125</sup> At the end of the reactions hexanes was added so that the polymeric material could be removed by filtration. Polymer-supported reagent **75** was then treated with either 9-fluorenylmethoxycarbonyl chloride (Fmoc-Cl)<sup>126</sup> or (2,7-di-*tert*-butyl-9-fluorenyl)methyl chloroformate (Bts-Fmoc-Cl)<sup>127</sup> to form reagents **76** and **77**, respectively, that were useful for amino acid protection. Alternatively **75** could be reacted with allyl chloroformate (Alloc-Cl) or propargyl chloroformate (Proc-Cl) to form the corresponding amino group protecting reagents **78** and **79**.<sup>128</sup> On the other hand, **75** could be reacted with ammonia or a primary amine to form ammonium salts **80**, which can react with a carboxylic acid in the presence of a coupling reagent to form amides<sup>129</sup> or functionalized as a uranium salt for use as polymer-supported peptide coupling reagent **81**.<sup>130</sup> In order to showcase the utility of the polymer in nonpeptide synthesis applications, they reacted poly(styrene-*alt*-maleic anhydride) with di(2-pyridyl)methylamine in order to generate recoverable palladium catalyst **82** for cross-coupling reactions that could take place in water.<sup>131</sup>

## 2.5. Poly(acrylic acid) Derivatives

### 2.5.1. Poly(acrylic acid)

Poly(acrylic acid) has been grafted onto both polyethylene and polystyrene by Bergbreiter. For the former, high density polyethylene powder was subjected to a chromic acid etching process, which resulted in the formation of a low concentration of carboxylic acid groups on **83** that were ready for further modification, such as the addition of preformed poly(*tert*-butyl acrylate) grafts to form **84** that were subsequently hydrolyzed to generate **85** (Scheme 15).<sup>132</sup> On the other hand, chloromethylated polystyrene such as Merrifield resin could be treated with excess phenyl lithium to generate lithiated polystyrene **86** that could initiate *tert*-butyl acrylate polymerization (Scheme 16).<sup>133</sup> Ester hydrolysis of **87** afforded poly(acrylic acid) functionalized polystyrene **88**, which was used to immobilize Pd(II) (**89**) as a catalyst for hydrogenation reactions. Catalyst **89** could be reduced with

Scheme 21. Macromonomer-Based Synthesis of Polystyrene Grafted with PEG



H<sub>2</sub> to form **90**, which was an active catalyst for allylic substitution and Heck reactions.<sup>134</sup>

### 2.5.2. Polyacrylates

Several polyacrylates have been reported as soluble supports for homogeneous catalysts where the ester groups are used to control the solubility of the polymer. For example Bergbreiter reported the use of a fluoroacrylate monomer to prepare polyacrylates selectively soluble in fluoruous solvents using a mixture of monomers **91** and **92** to synthesize polymer **93** (Scheme 17).<sup>135</sup> Reaction of **93** with a primary amine afforded phosphine functionalized polymer **94**, which was in turn converted into rhodium hydrogenation catalyst **95**. The fluoruous nature of **95** allowed it to be readily recovered from alkene hydrogenation reactions and reused without loss of activity by liquid/liquid separation. Akgerman and Fackler have further extensively studied this catalyst in a variety of hydrogenation and hydroformylation reactions under numerous conditions,<sup>136</sup> and Yao has reported a catalyst for RCM based on the same fluoruous polyacrylate polymer.<sup>137</sup>

Wills later described a similar strategy using methyl methacrylate and an ethyl PEG ester methacrylate to synthesize polymer-supported hydrogenation catalysts **96** and **97**, respectively, which were soluble in organic solvents and used as ligands for asymmetric transfer hydrogenation reactions (Figure 10).<sup>138</sup>

Finally, Buchmeiser has reported poly(methacrylate)-based polymer monoliths prepared by copolymerizing ethyl methacrylate and cross-linker **98** (Scheme 18).<sup>139</sup> In this work, the synthesized monoliths were functionalized using electron beam triggered free radical graft polymerization of ligand functionalized monomer **99** or **100**. This was followed by the generation of the corresponding carbenes, and subsequent copper immobilization afforded lightly loaded supported Cu(I)–NHC complexes **101** and **102**, approximately 20–25 μmol Cu g<sup>-1</sup> each, which were used to catalyze arylaldehyde cyanosilylation and hydrosilylation reactions in a continuous flow setup.

### 2.5.3. Polyacrylamides

The use of poly(*N*-isopropylacrylamide) (PNIPAM) as a support in organic synthesis has been extensively studied, especially by Bergbreiter,<sup>140</sup> and much of this work has been summarized in previous reviews.<sup>8</sup> In this section some of the more recent applications of such materials are presented. Also he has extended his dye labeling concept<sup>80</sup> to PNIPAM and used an azo dye attached to the polymer as a ligand to form catalyst **103** for Heck reactions (Figure 11).<sup>141</sup> Recently he has performed more in-depth studies of the role of the amide group on polymer solubility using libraries of polymers possessing various *N*-substituents,<sup>142</sup> and he has used poly(*N*-octadecylacrylamide) (PNODAM) as a support for a sulfur–carbon–sulfur Pd(II) species (**104**) in mechanistic studies of the Heck reaction.<sup>143</sup> In reactions using any of the polyacrylamide catalysts such as **103** and **104**, the product is separated from the catalyst by a liquid/liquid biphasic separation with the catalyst containing liquid phase ready for direct reuse.

Ikegami reported adding ammonium groups to PNIPAM to generate a polymer that could be used to immobilize phosphotungstic acid (Figure 12).<sup>144</sup> This immobilized acid **105** was found to be insoluble in water and most typical

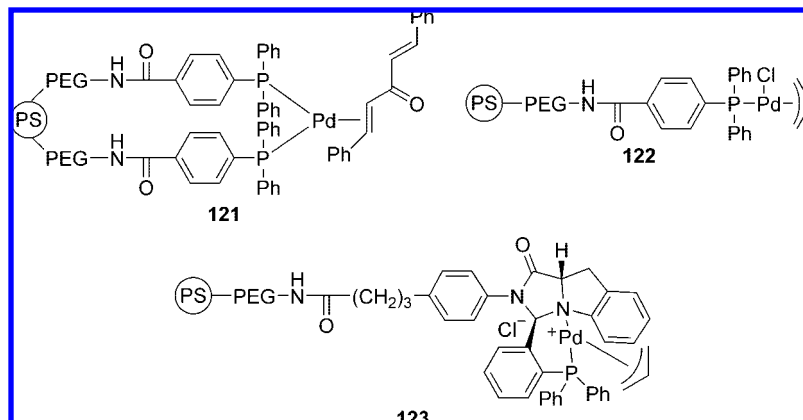
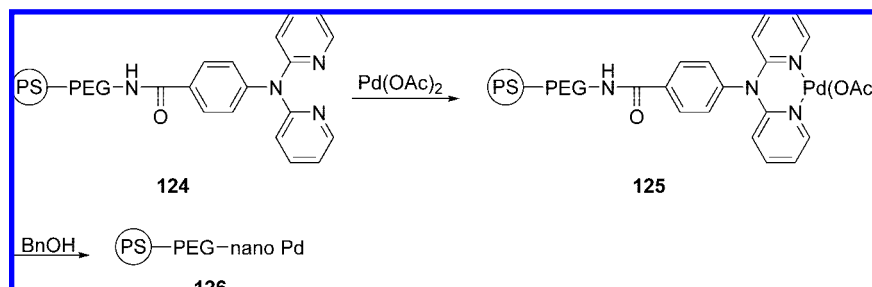
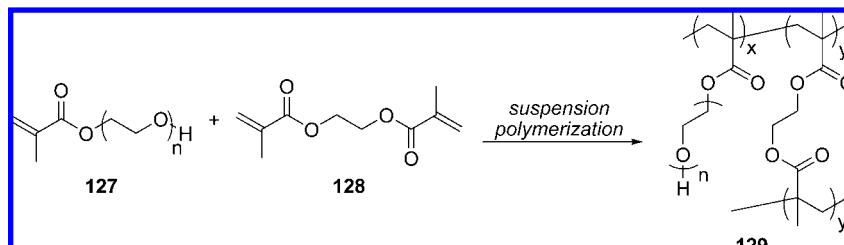


Figure 14. PEG-based Tentagel-supported palladium catalysts.

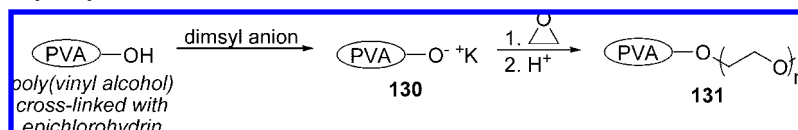
### Scheme 22. Synthesis of PEG-Based Tentagel-Supported Palladium Nanoparticles



### Scheme 23. Synthesis of Poly(ethylene glycol) Methacrylate Polymer Beads



### Scheme 24. Synthesis of Poly(vinyl alcohol) Beads Grafted with PEG



organic solvents such as methanol, ethyl acetate,  $\text{CH}_2\text{Cl}_2$ , etc., and it was used effectively as a heterogeneous catalyst for allylic alcohol, amine, and sulfide oxidation with hydrogen peroxide as the penultimate oxidant.<sup>145</sup> A visualization dye, disperse red, was added to second generation polymeric catalyst **106** to aid separation.<sup>146</sup> Ikegami later developed a copolymer of *N*-isopropyl acrylamide and 4-vinyltriphenylphosphine (**107**) that could likewise be used as a heterogeneous ligand for palladium in Suzuki–Miyaura<sup>147</sup> and Heck reactions.<sup>148</sup> The heterogeneity of **105**–**107**, as opposed to the homogeneity of **103** and **104**, is most likely due to the bonding of the tungsten and palladium centers of these catalysts to multiple positions of the polymer backbone, thereby creating cross-links.

Janda has reported the synthesis of a poly(*N,N*-dimethyl acrylamide) cross-linked hydrogel.<sup>149</sup> This polymer was initially used to encapsulate various proteins; however, it was later found to be useful as a water compatible anchor for the photosensitizer hematoporphyrin.<sup>150</sup> A mixture of mono-

mers **106** and **108** with cross-linker **110** was polymerized to afford **111**, which was functionalized with hematoporphyrin to generate supported photosensitizer **112** (Scheme 19). Upon exposure to light, an aqueous suspension of **112** efficiently generated singlet oxygen for reaction with anthracene.

Biffis subsequently described the use of a related polyacrylamide in microgel form that was soluble in a range of organic solvents to stabilize metal nanoclusters.<sup>151</sup> These microgels were prepared from various proportions of monomers **108**, and **113** and cross-linker **114** to afford polymers with the general structure of **115** (Scheme 20). Polymer **115** was used to prepare nanoclusters of palladium, platinum, and gold that were studied as catalysts in aerobic alcohol oxidation reactions.

## 2.6. Miscellaneous Polyalkenes

Several other polyalkenes have been used as supports for catalysts. Beletskaya has shown that poly(*N*-vinylimidazole)

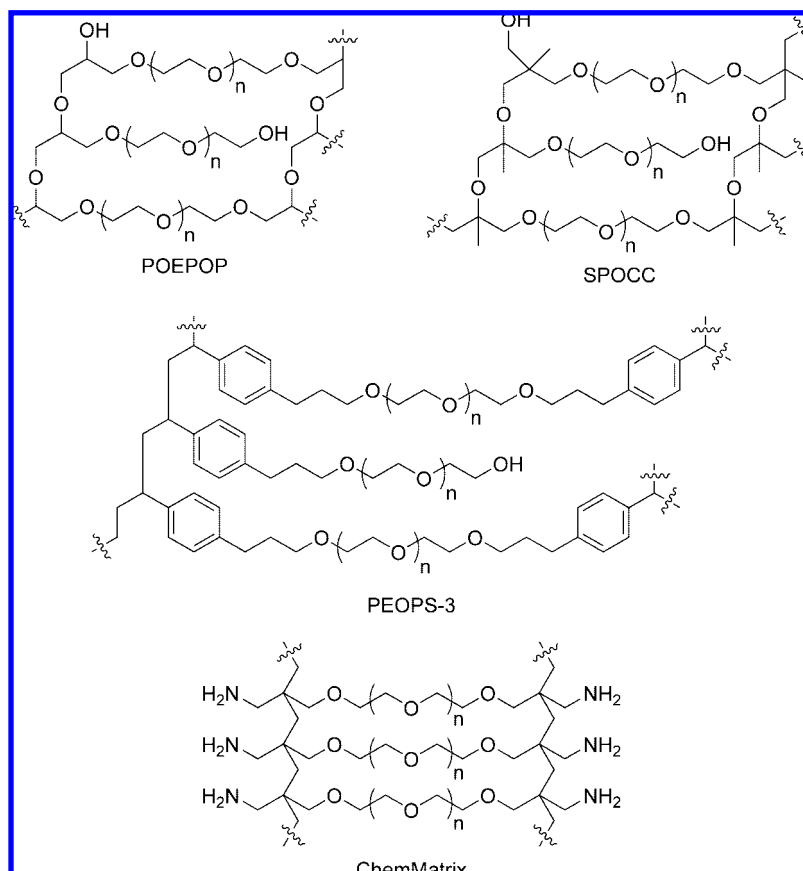
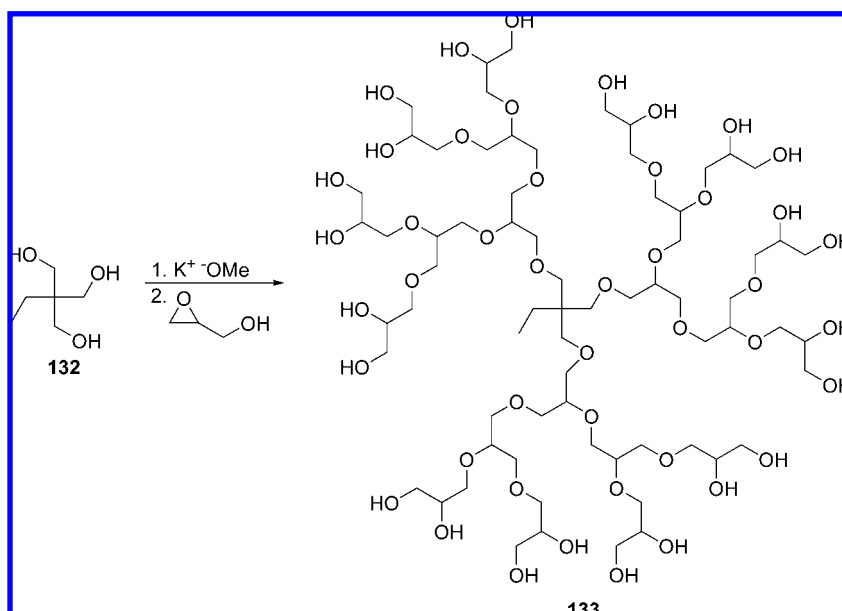


Figure 15. Cross-linked PEG resins.

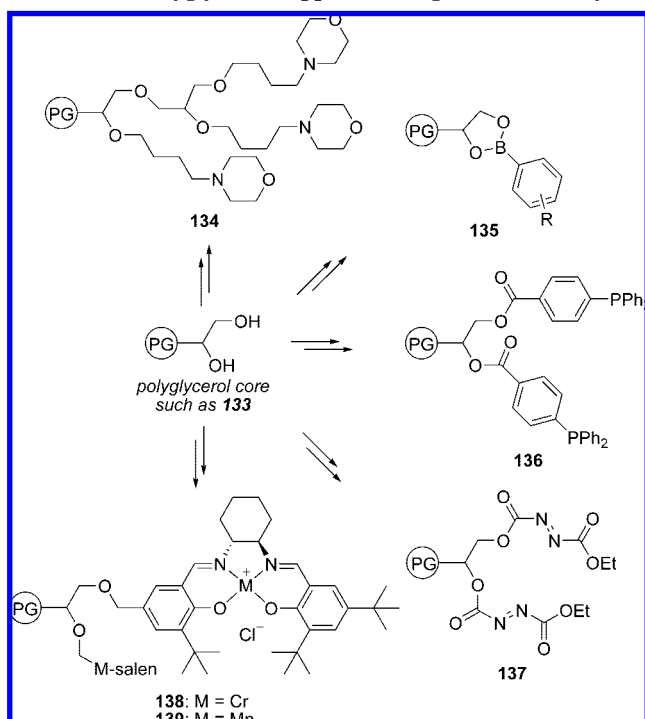
#### Scheme 25. Synthesis of Polyglycerol



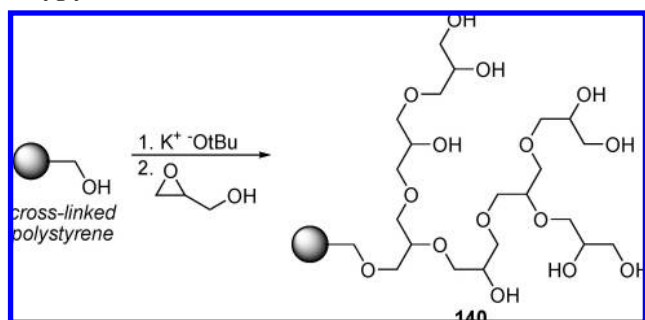
(**116**) can be used as a recyclable catalyst for the addition of thiols to Michael acceptors in water/ethanol solvent mixtures (Figure 13).<sup>152</sup> In this application **116** can be viewed as a perfunctionalized polyethylene derivative with pendant imidazole groups. Beletskaya has also reported the synthesis of poly(*N*-vinylimidazole-*co*-*N*-vinylcaprolactam) (**117**) and the use of both **116** and **117** to immobilize palladium for Heck reaction catalysis.<sup>153</sup> Such reactions were found to be more

efficient with **117** than with **116**. Additionally, Vankelecom reported the use of ionic poly(diallyldimethylammonium chloride) (**118**) in a method for supporting both an ionic liquid and Wilkinson's catalyst in hydrogenation reactions,<sup>154</sup> and Jones and Weck have used linear ring-opened polycyclooctene, as well as some cyclic oligomeric analogues, to support a cobalt–Salen complex (**119**), as well as some cyclic oligomeric analogues, for epoxide kinetic resolution reactions.<sup>155</sup>

Scheme 26. Polyglycerol-Supported Reagents and Catalysts



Scheme 27. Synthesis of Polystyrene Beads Grafted with Polyglycidol



### 3. Polyethers

#### 3.1. Poly(ethylene glycol)

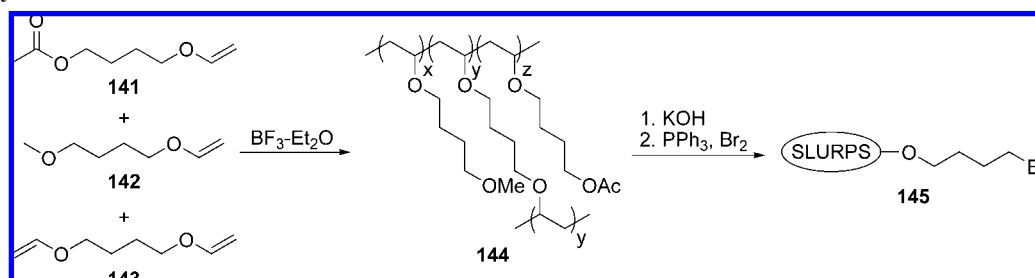
PEG is a water soluble linear polymer that is also compatible with a variety of polar organic solvents and can be precipitated from either 2-propanol or diethyl ether.<sup>9</sup> As mentioned previously, Bayer used this polymer as the support for liquid-phase peptide synthesis<sup>5</sup> and later grafted it onto heterogeneous polystyrene for use in solid-phase peptide synthesis.<sup>6</sup> Nowadays this composite polystyrene–PEG material comes in many forms from a variety of vendors with various trade names.<sup>156</sup> For example, Lee has used a

variation of his core–shell polymer synthesis concept to prepare PEG grafted polystyrene by using Jeffamine derived macromonomer **120** (Scheme 21).<sup>157</sup> Macromonomer **120** serves to stabilize the suspension polymerization system, and thus, the terminal amine groups are concentrated on the exterior shell of the formed resin beads. However, polystyrene grafted with PEG is still probably best known as Tentagel, and it remains widely used for solid-phase synthesis with initial loading levels of approximately 0.2 mmol g<sup>-1</sup>.

More recently the water compatibility of PEG-based Tentagel has been exploited and it has been used as a heterogeneous support for metal catalysts applied in aqueous media. Uozumi has pioneered much of this work and used Tentagel as a support for a variety of palladium catalysts. For example, supported Pd(dba)<sub>3</sub>(triarylphosphine)<sub>2</sub> catalyst **121** was easily prepared by reaction of commercially available Tentagel-supported phosphine with Pd<sub>2</sub>(dba)<sub>3</sub>·CHCl<sub>3</sub> in toluene, and used to catalyze cycloisomerization reactions of 1,6-enynes in water (Figure 14).<sup>158</sup> The hydrophobic substrates of these reactions diffused into the polystyrene portion of the resin, where the reactions occurred and the products remained. Upon completion of the reactions, the polymer was filtered and washed with supercritical carbon dioxide to remove the reaction product and the catalyst could be reused without a decrease in activity. A similar supported palladium–phosphine complex (**122**) was prepared and used to catalyze Suzuki–Miyaura reactions<sup>159</sup> and allylic aziridination<sup>160</sup> reactions in water. This strategy has also been applied to asymmetric catalysis using supported chiral phosphine **123**. With this catalyst, racemic allyl carbonates were converted to the corresponding allylic aryl ethers (84–94% ee),<sup>161</sup> alkylated with nitromethane (70–98% ee),<sup>162</sup> or underwent sulfonylation (33–81% ee).<sup>163</sup> A combinatorial library of Tentagel-supported chiral phosphine–palladium complexes with amino acid spacers between the PEG chain and the phosphine group has also been studied in allylic substitution reactions.<sup>164</sup>

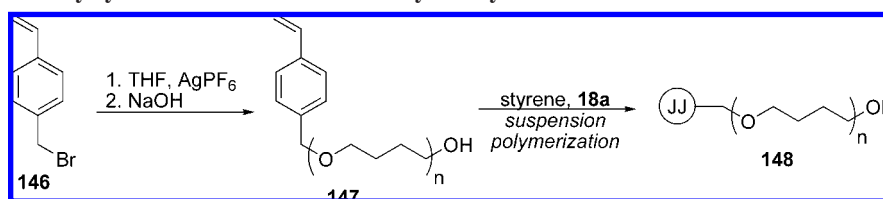
Tentagel has also recently been used to support palladium nanoparticles for aqueous applications.<sup>165</sup> Supported bispyridine ligand **124** was coordinated to Pd(OAc)<sub>2</sub>, and the resulting complex **125** was reduced with benzyl alcohol (Scheme 22). Reduction of the Pd(II) complex resulted in Pd(0) nanoparticles being formed that remained dispersed in the polymer support (**126**). Transmission electron microscopy indicated that the palladium particles had a mean diameter of 9.1 nm and narrow size distribution. Aqueous aerobic alcohol oxidation,<sup>166</sup> and hydrogenation and dehalogenation<sup>156</sup> reactions could be catalyzed using this catalyst. Furthermore similar methodology has been used to prepare Tentagel-supported platinum nanoparticles that were also used to catalyze aqueous aerobic alcohol oxidation reactions.<sup>167</sup>

Scheme 28. Synthesis of SLURPS

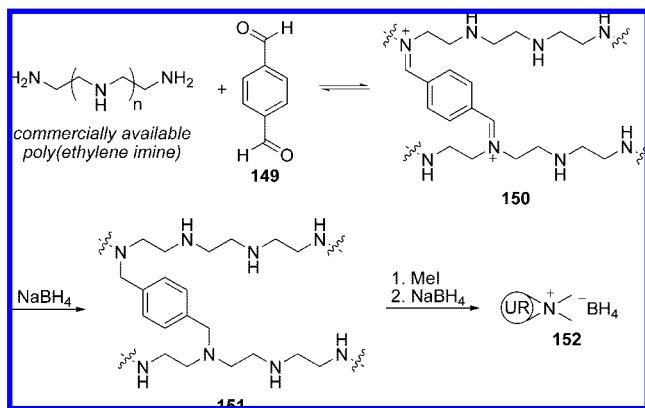




## Scheme 29. Synthesis of Polystyrene Beads Grafted with Polytetrahydrofuran



## Scheme 30. Synthesis of Poly(ethylene imine)-Based Ultra Resin



In addition to polystyrene, other polymers have been used to anchor PEG in order to render it heterogeneous. For example, Fréchet used methacrylate esters of ethylene glycol oligomers **127** in a suspension polymerization process with cross-linker **128** to synthesize hydroxyl group functionalized beads **129** that swell well in a variety of polar solvents that had relatively high loading values (1.2–1.8 mmol g<sup>-1</sup>) (Scheme 23).<sup>168</sup> The utility of **129** as a solid-phase synthesis support was demonstrated by their use in the synthesis of a hydantoin library.

More recently Zhu has used epichlorohydrin cross-linked poly(vinyl alcohol) beads prepared by a reverse suspension polymerization process,<sup>169</sup> which themselves have utility in organic synthesis,<sup>170</sup> as the starting material for anionic grafting of PEG in order to prepare a resin with higher loading than typical PEG-based Tentagel.<sup>171</sup> Treatment of the starting hydroxyl group functionalized polymer with dimsyl anion generated alkoxide groups (**130**) that reacted with ethylene oxide to form the grafted PEG chains of **131** with a loading level of approximately 2.0 mmol g<sup>-1</sup> (Scheme 24). The terminal hydroxyl groups of **131** were subsequently converted to aldehyde, carboxylic acid, and isocyanate functional groups for use in scavenging processes. Additionally resin **131** was used in solid-phase peptide synthesis and as a support for TEMPO catalysis.<sup>172</sup>

Rather than merely attaching PEG grafts to a polymeric backbone, Meldal has had a long-term interest in preparing resins for solid-phase organic chemistry that are composed almost entirely of PEG and has reported what are known as PEOPOP, SPOCC, and POEPS-3 resins with PEG components of various molecular weights (Figure 15).<sup>173</sup> Such polymers can be prepared by both cationic and anionic ring-opening suspension polymerization in silicon oil.<sup>174</sup> These resins all exhibit good mechanical properties and excellent swelling in polar solvents. When tetraethylene glycol is used as the PEG starting material, the resulting SPOCC-194 resin has a high loading capacity of 0.9–1.2 mmol g<sup>-1</sup> that can be used in a variety of solid-phase synthesis applications<sup>175</sup>

and, interestingly, even as a functionalizable optical fiber cladding material.<sup>176</sup>

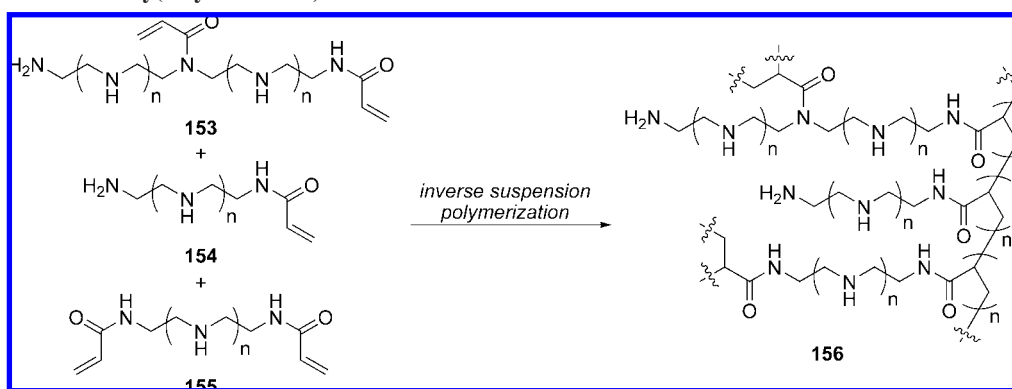
Similarly, Albericio has described the use of ChemMatrix resin (Figure 15) that is cross-linked by PEG as a support for solid-phase peptide synthesis.<sup>177</sup> This polymer is notable in that it only contains primary ether bonds and is therefore highly chemically stable. Amazingly, when it was used as the support for the linear solid-phase synthesis of the  $\beta$ -amyloid (1–42) peptide sequence, the crude product was obtained with 91% purity. It is proposed that the great utility of the resin is due to its ability to prevent peptide aggregation.

## 3.2. Polyglycerol

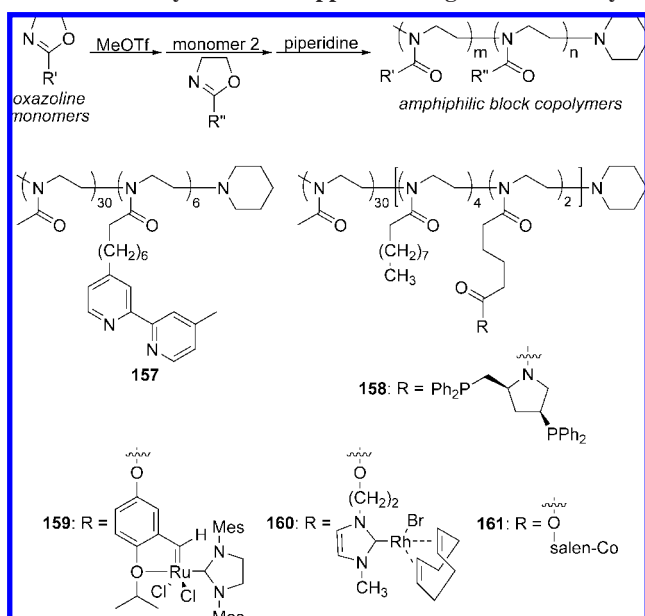
One of the major drawbacks to PEG as a support for organic chemistry is that it can only be terminally functionalized and thus its loading level is inversely proportional to its molecular weight. To overcome this limitation while maintaining the general polyether structure of PEG, polyglycerol has been studied. Reaction of an alcohol such as **132** with a base and excess glycidol results in ring-opening polymerization to form a soluble, hyperbranched polymer with both primary and secondary alcohol groups on the periphery, such as in **133** (Scheme 25).<sup>178</sup> It should be noted that structure **133** represents only three rounds of glycidol addition to core **132** in a symmetrical manner. The true structures of such polymers undoubtedly increase in complexity with increasing molecular weight. The physical properties of numerous polyglycerol derivatives have been extensively studied,<sup>179</sup> and they have been found to be biocompatible in numerous life sciences applications.<sup>180</sup> In the context of organic chemistry, polyglycerol has been used both as a synthesis platform and as a support for reagents and catalysts. For example, a multistep synthesis of a series of  $\gamma$ -aminobutyric acid lactam analogues using polyglycerol with a molecular weight of 8000 Da and a hydroxyl group loading level of 13.5 mmol g<sup>-1</sup> as the support has been reported.<sup>181</sup> At the end of each synthetic reaction, the polymer-supported product was isolated by dialysis with an appropriate membrane.

In terms of using polyglycerol as a reagent support, a procedure for the conversion of hydroxyl groups of polyglycerol into morpholine groups (**134**) has been reported (Scheme 26).<sup>182</sup> Alternatively, the hydroxyl groups can be used to immobilize boronic acids (**135**) for use in Suzuki–Miyaura reactions.<sup>183</sup> In this application, product purification was achieved by precipitation and ultrafiltration. Similar to the report by Toy and Hanson regarding the simultaneous use of 2 polynorbornene-supported reagents for performing Mitsunobu reactions, Haag has shown that polyglycerol-supported phosphine (**136**) and azo (**137**) reagents can also be used in this manner.<sup>184</sup> Perhaps most significantly Haag and Liese have shown that polyglycerol-supported Salen complexes of chromium (**138**) and manganese (**139**) can be used in a membrane reactor for homogeneous asymmetric

Scheme 31. Synthesis of Poly(ethylene imine)-Based ULTRAMINE Resin



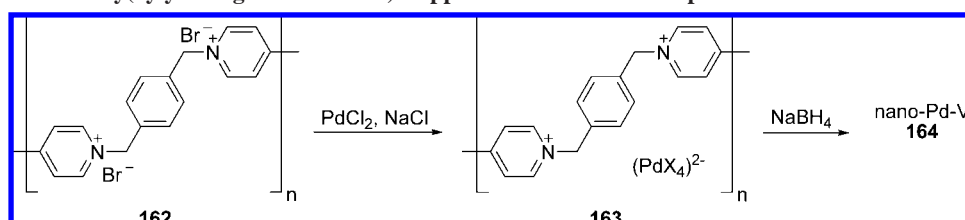
Scheme 32. Polyoxazoline-Supported Reagents and Catalysts



catalysis of Diels–Alder,<sup>185</sup> epoxidation,<sup>186</sup> and epoxide kinetic resolution reactions.<sup>187</sup>

As mentioned previously, polyglycerol is soluble in many solvents and has been used as a homogeneous support in organic chemistry. Thus, separation of the polymer from a reaction mixture requires either dialysis or precipitation and filtration. In order to simplify and speed up polymer separation, polyglycerol has been grafted onto polystyrene resin to form a heterogeneous support (**140**) using a heterogeneous alcohol core (Scheme 27).<sup>188</sup> Polystyrene-graft-polyglycerol **140** has similar properties to Tentagel in terms of swelling but has the key advantage of having a much higher loading capacity, up to 4.3 mmol g<sup>-1</sup> compared to less than 1.0 mmol g<sup>-1</sup>. However one potential drawback of **140**, and **133** as well, is that it is functionalized with nonequivalent alcohol groups.

Scheme 33. Synthesis of Poly(xylylviologen Dibromide)-Supported Palladium Nanoparticles



### 3.3. Miscellaneous Polyethers

Another non-PEG polyether resin with the name SLURPS (superior liquid uptake resin for polymer-supported synthesis) has been reported by Steinke.<sup>189</sup> The starting material for SLURPS is 1,4-butanediol derivative **141**, and while its preparation is based on polymerization of mixtures of enol ether monomers, it is included in this section because of its polyether structure. Mixtures of **141**, **142**, and cross-linker **143** (2 mol %) were cationically polymerized with BF<sub>3</sub>–Et<sub>2</sub>O to afford the polymer **144** that swelled exceptionally well in a variety of polar solvents and contained loading levels of up to 8.5 mmol g<sup>-1</sup> (Scheme 28). Conversion of the acetate groups to bromides (**145**) allowed for installation of various linker groups so that solid-phase peptide synthesis could be performed.<sup>190</sup> It should be noted that the great swelling of this resin allowed for reactions to be easily monitored by gel-phase NMR and FTIR spectroscopy.

Janda has reported an analogue of Tentagel where the PEG grafts are replaced by polytetrahydrofuran (Scheme 29).<sup>191</sup> Several alkyl halides such as **146** were used to prepare macromonomers such as **147**, by cationic ring-opening polymerization of THF, and these were suspension copolymerized with styrene and the JandaJel cross-linker **18a** to afford the grafted resins, such as **148**. All of the prepared resins showed good swelling in a wide range of organic solvents and had loading levels of approximately 0.6 mmol g<sup>-1</sup>. The utility of this new resin type was established by the solid-phase synthesis of 3-methyl-1-phenyl-2-pyrazolin-5-one using standard acylation, and imine formation reactions.

### 4. Poly(ethylene imine)

A completely different strategy for the generation of solid-phase synthesis resins with very high loading levels based on a polyamine structure was reported by Rademann.<sup>192</sup> Commercially, poly(ethylene imine) was condensed with small quantities of terephthalic dialdehyde (**149**) to form a cross-linked polyimine network (**150**) (Scheme 30). The imine groups were subsequently reduced to produce poly-

Table 1.

polymer support	format	loading level (mmol g <sup>-1</sup> )	applications	comments
polystyrene	insoluble large uniform beads	1.0–1.5	solid-phase synthesis	used for preparing large quantities of compound per bead
polystyrene	insoluble polymer monolith	0.3–1.0	scavenger reagent immobilization	used in reactive filtration for product purification
polystyrene	insoluble core–shell polymer prepared by partial hydrolysis	0.9	solid-phase synthesis	synthesis sites are concentrated in the exterior shell of the bead
polystyrene	insoluble core–shell polymer prepared using an ionic monomer	0.1	Pd catalyst immobilization	catalyst used in a variety of cross-coupling reactions
polystyrene	insoluble internally functionalized star polymer	0.35–0.45	site isolated catalyst immobilization	incompatible functional groups can be used simultaneously
polystyrene	insoluble JandaJel	1.0–4.0	solid-phase synthesis, and reagent and catalyst immobilization	prepared with a wide range of functional groups.
polystyrene	soluble microgel	0.5	solid-phase synthesis and reagent immobilization	low viscosity solutions
polystyrene	insoluble oligo(ethylene glycol) cross-linked	0.1	metal catalyst immobilization	negligible metal leaching and good recyclability
polyphenylene	insoluble urea cross-linked	0.4	metal catalyst immobilization	negligible metal leaching with good recyclability and similar utility as preceding polystyrene support
polystyrene	insoluble cross-linked with a chiral ligand group	0.1–0.5	metal catalyst immobilization	strategy for immobilizing chiral ligand groups with symmetry
polystyrene	insoluble befunctional	0.5–1.5	solid-phase synthesis and organocatalyst immobilization	additional functional group increases resin swelling
polystyrene	soluble bifunctional	0.3	metal catalyst and organocatalyst immobilization	additional functional group facilitates separation or participates in catalysis
polystyrene	insoluble grafted onto fluoropolymer tubes	30–35 μmol/tube	solid-phase synthesis	used for reactions with nonpolar or aromatic solvents at elevated temperatures
polystyrene	insoluble rasta resin	1.0–4.0	solid-phase synthesis and scavenger reagent immobilization	functional groups are on flexible grafts
polyisobutylene	soluble	0.2–0.5	metal catalyst immobilization	readily recycled by liquid/liquid biphasic separation
polynorbornene	soluble non-cross-linked ROMPgel	2.6	reagent and catalyst immobilization	used in a wide range of reactions
polynorbornene	insoluble cross-linked ROMPsphere resin	0.6–9.0	reagent and catalyst immobilization	more convenient to use than soluble ROMPgel but perhaps more difficult to prepare
polynorbornene	insoluble monolith	0.7–1.5	metal catalyst immobilization	used in continuous flow reactions
poly(styrene- <i>co</i> -maleic anhydride)	soluble	1.0–1.5	solid-phase synthesis and catalyst immobilization	precipitated using hexanes
poly(acrylic acid)	insoluble	5.0	Pd catalyst immobilization	relatively high loading level
polyacrylate	soluble	0.2–0.5	catalyst immobilization	readily recovered and reused by liquid/liquid biphasic separation
polymethacrylate	insoluble monolith	2.5 × 10 <sup>-5</sup>	Cu catalyst immobilization	better substrate accessibility than functionalized monolith
polyacrylamide	linear	0.2	Pd catalyst and organocatalyst immobilization	copolymerized monolith soluble in cold water and polar organic solvents but insoluble in hot water and nonpolar organic solvents
polyacrylamide	insoluble cross-linked	0.1	catalyst immobilization	macroporous structure via self-assembly
polyacrylamide	insoluble hydrogel	1.5	biomolecule immobilization and solid-phase synthesis	proposed drug delivery platform
poly-( <i>N</i> -vinylimidazole)	soluble	10.6	Pd catalyst immobilization	soluble in aqueous and aqueous-alcohol solvents

Table 1. continued

polymer support	format	loading level (mmol g <sup>-1</sup> )	applications	comments
poly( <i>N</i> -vinylimidazole- <i>co</i> - <i>N</i> -vinylcaprolactam)	soluble	6.2	Pd catalyst immobilization	higher activity than the poly- <i>N</i> -vinylimidazole homopolymer
poly(diallyldimethylammonium chloride)	soluble	not mentioned	metal catalyst immobilization	soluble in water and polar protic solvent
polycyclooctene	soluble	1.4	Co catalyst immobilization	less reactive catalyst than oligomeric cyclooctene-supported analogue
poly(ethylene glycol)	insoluble core-shell type polymer grafted onto polystyrene	0.1–0.4	solid-phase peptide synthesis	synthesis sites are concentrated in the exterior shell of the bead
poly(ethylene glycol)	insoluble Tentagel resin	0.1–0.5	metal catalyst immobilization	suitable for reactions in aqueous solvents
poly(ethylene glycol)	insoluble poly(ethylene glycol) methacrylate polymer	1.2–1.8	solid-phase synthesis	higher loading than other PEG type polymers
poly(ethylene glycol)	insoluble grafted onto poly(vinyl alcohol)	1.5–5.0	solid-phase synthesis and scavenger immobilization	high loading resin with excellent swelling properties, good mechanical and chemical stability
poly(ethylene glycol)	insoluble cross-linked	0.3–1.2	solid-phase synthesis	good swelling properties and reactions are readily monitored by NMR spectroscopy
polyglycerol	soluble	5.0–14.0	catalyst immobilization	high loading resin easily prepared on a kilogram scale
polyglycerol	insoluble grafted onto polystyrene	2.7–4.3	solid-phase synthesis	good swelling in various solvents with easier recovery than soluble polyglycerol
SLURPS	insoluble	3.6–8.6	solid-phase peptide synthesis	good swelling in highly polar solvents
poly tetrahydrofuran	insoluble grafted onto polystyrene	0.2–0.7	solid-phase synthesis	good swelling in nonpolar solvents at low temperatures
poly(ethylene imine)	insoluble Ultra resin	10.0–14.0	reagent immobilization	very high loading level that is similar to ULTRAMINE resin
poly(ethylene imine)	insoluble ULTRAMINE resin	16.0–21.0	scavenger immobilization	very high loading level that is similar to Ultra resin
poly(2-oxazoline)	insoluble	0.5–1.0	metal catalyst and phosphine group immobilization	amphiphilic block copolymer used in aqueous reactions
poly(xylylviologen dibromide)	insoluble	0.2–5.0	Pd catalyst immobilization	new strategy for preparing heterogeneous metal catalyst via self-assembly

(ethylene imine)-based ULTRA resin **151**, in which all of the secondary amine nitrogen atoms were available for derivatization and a loading level up to 14.0 mmol g<sup>-1</sup> was achieved. This resin was found to swell well in both polar and nonpolar solvents, and its utility in peptide and organic synthesis was demonstrated. More recently **151** was used as a heterogeneous support for borohydride.<sup>193</sup> This required quarternization of the secondary amine groups with methyl iodide followed by reaction with sodium borohydride to form the heterogeneous reagent **152** (loading level = 12.0 mmol g<sup>-1</sup>), which was used in aldehyde, ketone, and nitroolefin reduction and reductive amination reactions.

Meldal subsequently reported a very similar concept where the poly(ethylene imine) was first reacted with acryloyl chloride to generate macromonomers such as **153–155**, that could be polymerized using the inverse suspension polymerization technique to form polymers such as **156**, which he referred to as ULTRAMINE resin (Scheme 31).<sup>194</sup> Since some of the macromonomers contained multiple acrylamide groups, the resulting polymers were cross-linked and het-

erogeneous. Furthermore the amine group concentration could be increased by exhaustive reduction of the amide groups of **156** so that the resulting resin could function as an acid scavenger.

Additionally, Neumann reported the use of poly(ethylene imine) alkylated with iodomethane and 1-iodododecane to immobilize polyanionic polyoxometalates to generate a catalyst for aqueous oxidation reactions using H<sub>2</sub>O<sub>2</sub>,<sup>195</sup> which is conceptually similar to what was previously described by Ikegami.<sup>144–146</sup>

### 5. Poly(2-oxazoline)

A class of amphiphilic polymers for use as supports in organic synthesis that was prepared by cationic polymerization of 2-oxazoline monomers was reported by Weberskirch (Scheme 32). The living nature of the polymerization process allowed for block copolymers to be synthesized in which one block was water compatible and the other block was hydrophobic. The first example of such a polymer

contained 2,2'-bipyridine groups (**157**) in the hydrophobic portion and was useful as a macroligand in the atom-transfer radical polymerization of methyl methacrylate in water.<sup>196</sup> Subsequent versions contained pendant carboxylic acid groups that could be functionalized with a chiral phosphine group (**158**) for use in aqueous asymmetric hydrogenation reactions,<sup>197</sup> Hoveyda–Grubbs-type catalyst (**159**) for RCM in water,<sup>198</sup> a rhodium carbene complex (**160**) for aqueous two-phase hydroformylation reactions,<sup>199</sup> or a chiral cobalt–salen complex (**161**) for hydrolytic kinetic resolution reactions.<sup>200</sup> Furthermore, other variations of this theme include a related polymer-supported palladium carbene complex for coupling reactions in water<sup>201</sup> and a triphenylphosphine for aqueous two-phase hydroformylation reactions.<sup>202</sup>

## 6. Poly(xylylviologen dibromide)

Poly(xylylviologen dibromide) (**162**) has been known for quite some time,<sup>203</sup> but only recently has Uozumi shown that it can be used to support palladium nanoparticles.<sup>204</sup> Such supported catalysts were prepared by reacting **162** with PdCl<sub>2</sub> and a large excess of NaCl in water to form **163** (Scheme 33). This was followed by reduction of **163** with NaBH<sub>4</sub> to afford what is referred to as nano–Pd–V (**164**). The structure of this material was studied by scanning electron microscopy and other techniques to establish the existence of palladium nanoparticles. Heterogeneous **164** was used to catalyze  $\alpha$ -alkylation of ketones with primary alcohols,<sup>204</sup> and ring-opening alkylation of cyclic 1,3-diketones with primary alcohols,<sup>205</sup> and was readily recycled. A related supported phosphotungstate catalyst has also been reported.<sup>206</sup>

## 7. Summary Table

See Table 1 for a summary of the information presented in this review.

## 8. Conclusions

A wide range of organic polymers have been used as supports in organic chemistry in order to facilitate separation of a synthesis product from reagents or catalysts used to prepare it. Some of the main considerations when choosing which polymer to use in a particular application include solvent compatibility and loading level, and much research has been done to address these issues. Generally, higher loading is preferred, since this reduces the amount of both polymer and solvent needed. Nowadays a diverse range of polymers is available to choose from with loading capacities ranging from below 1 mmol g<sup>-1</sup> up to more than 20 mmol g<sup>-1</sup>, and possessing various solvent compatibilities to meet the desired needs. With regard to polymer loading level, it should be kept in mind that the maximum value for any polymer-supported reagent or catalyst is inversely proportional to the sum of the molecular weights of the reagent/catalyst group and the monomer used to prepare the polymer. For example, a loading level of 20 mmol g<sup>-1</sup> corresponds to a total molecular weight of only 50 g mol<sup>-1</sup> for both the immobilized group and the repeating unit of the polymer used to support it, and this represents the approximate upper attainable limit.

Some of the greatest advancements in this field include the development of materials for heterogeneous metal catalyst encapsulation with which leaching of less than a part per million of the entrapped species is often observed. Also the

historical preference for heterogeneous polymer supports that are directly filterable over homogeneous ones that require additional processing for their removal is being put to rest. Work summarized here shows that polymers with desirable solubility profiles can be easily and quantitatively removed and reused using liquid/liquid biphasic separation methodologies, and it is anticipated that such materials will find increasing utility in the future. However, what is mostly absent from the literature, though greatly needed, are studies that directly compare and contrast the performance of the newer polymers presented here. While such comparative studies of Merrifield resin and Tentagel were reported long ago, the performance of similar polymers such as terminally functionalized polynorbornenes and polyisobutylene, or Ultra and ULTRAMINE resins, has not been compared. It seems that when a new polymer is introduced these days, its utility in a broad range of applications is established and the question of whether or not it has performance advantages over other reported materials goes unasked.

Future developments in this field undoubtedly will take advantage of some of the recent advances in polymer synthesis technology such as inverse suspension polymerization, which broadens the range of monomers that can be used to prepare heterogeneous resins, and atom transfer radical polymerization, which allows for polymers with narrow molecular weight distributions and unique block structures to be prepared. How such methodologies are applied and what polymers they are used to synthesize is limited only by one's imagination. Undoubtedly as novel applications of polymer supports in organic synthesis are envisioned, new materials will be designed to meet the expected requirements.

## 9. Acknowledgments

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