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Soluble Polymer-Supported Organic Synthesis

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ABSTRACT

Soluble polymers have been used as supports for reagent/catalyst immobilization and synthesis. Two polymers are commonly used in this context, linear polystyrene and poly(ethylene glycol). The complementary solubility properties of these polymers allow access to a wide range of chemistries. Parallel and combinatorial libraries of small molecules have been prepared using these polymers, and reagents/catalysts that are easily recovered and recycled have been immobilized on them. To develop soluble polymers with novel properties, bifunctional polymerization initiators have been used in a parallel combinatorial methodology to prepare block copolymers that exhibit unique solubility profiles.

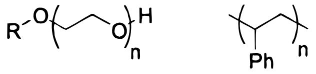
1. Introduction

Recent advances in the high-throughput screening of compounds for efficacy in biological assays have revolutionized the drug discovery process. The major effect of these new screening methods has been the shifting of the bottleneck of the process to the production of compounds for testing. This demand for large numbers of new compounds has, in turn, caused chemists to look for ways to simplify, expedite, and automate the process of small organic molecule synthesis. To this end, organic chemists have borrowed techniques from the peptide chemistry community in which polymers are used as supports for either substrate or reagent immobilization. The primary advantages of the attachment of one reaction component to a polymer are that (1) substrate removal from the reaction mixture is easily accomplished and (2) the bulk properties of the polymer carriers make them well suited for use with automation equipment.

Traditionally, insoluble polymer resins have been used as supports, and much organic chemistry has been performed with them.[1−3] Insoluble polymers have been most commonly used since they can easily be isolated by filtration and washed by passing solvent over them. Unfortunately, the heterogeneous reaction conditions that insoluble polymers dictate often complicate the transfer of traditional solution-phase chemical methodologies to solid-phase synthesis. Reaction kinetics can be nonlinear, and it is difficult to assess the completeness of reactions and the purity of the immobilized substrate being synthesized. In an attempt to make polymer-supported chemistry more solution-like, soluble polymers and fluorous systems have been utilized.[4−7] The use of soluble polymers has the potential to combine the best aspects of both solid-phase chemistry and solution-phase chemistry. The soluble polymers afford more normal reaction kinetics, facilitate compound characterization, and allow for polymer/compound isolation and purification through precipitation and filtration. We have focused our studies regarding high-throughput organic synthesis on the development of soluble polymer-based strategies and techniques, and our most recent work is described herein.

2. Soluble Polymer-Supported Small Organic Molecule Synthesis

Many polymers exist which are soluble in common organic solvents and suitable as supports for small organic molecule synthesis.[8] Our group has explored the scope of the utility of poly(ethylene glycol) (PEG) and linear polystyrene (LPS) in such applications. We have chosen these two polymers because (1) PEG is available commercially in a wide range of molecular weights in monomethyl ether (MPEG) and diol (PEG) form and (2) LPS is simple to prepare with a wide variety of functional groups and is compatible with a broad spectrum of chemistries. Furthermore, the polar nature of hydrophilic PEG and the nonpolar hydrophobic nature of LPS are complementary and should therefore allow access to a wide array of compound types.



PEG: R = H
MPEG: R = Me

LPS

A. PEG-Supported Synthesis. Prior to our entry into the field of soluble polymer-supported organic chemistry, PEG was used as a support for the synthesis of oligopeptides,[9] oligonucleotides,[10] and oligosaccharides.[11−14] Our first work in this area involved the use of PEG as a support for the combinatorial and parallel synthesis of pentapeptide and sulfonamide libraries, respectively.[15] This was the first report of the use of PEG in small organic molecule synthesis, and the pentapeptide library preparation was the first application of this polymer in a combinatorial sense. Members of the library were found to be ligands for a monoclonal antibody elicited against β-endorphin, and the identities of the ligands were determined through a recursive deconvolution strategy which was previously

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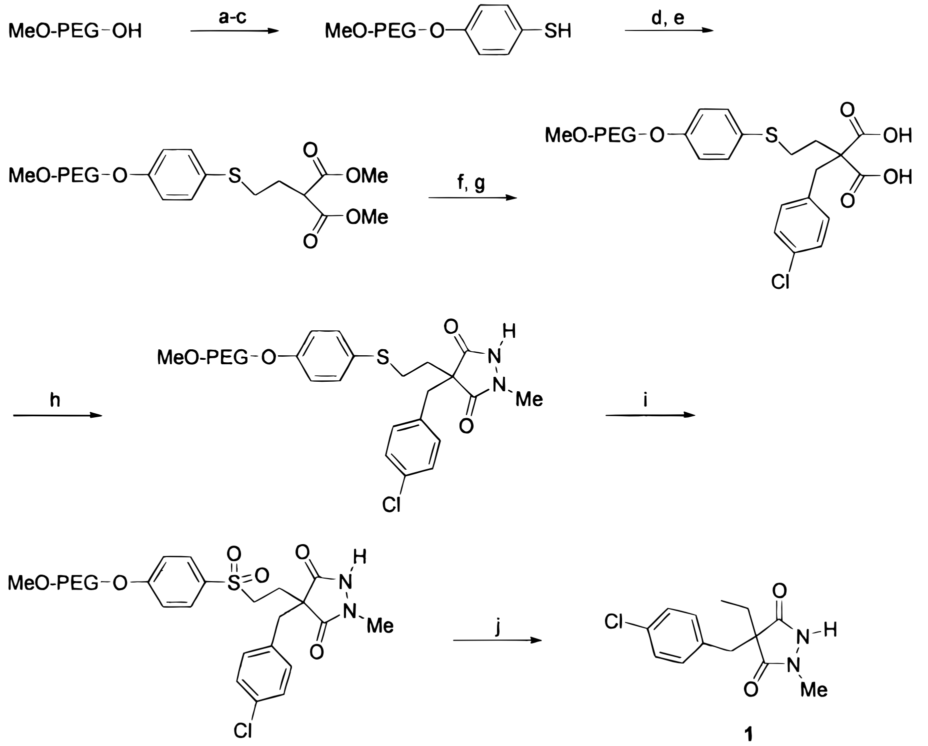
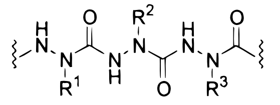


FIGURE 1. PEG-supported synthesis of 3,5-pyrazolidinediones. Conditions: (a) MsCl, Et_3N, CH_2Cl_2, room temperature, 12 h; (b) 4-HO-C_6H_4-S)$_2$, Cs_2CO_3, DMF, 65 °C, 6 h; (c) DTT, H_2O, reflux, 3 h; (d) $BrCH_2CH_2Br$, Cs_2CO_3, DMF, room temperature, 14 h; (e) $CH_2(CO_2Me)_2$, Cs_2CO_3, DMF, room temperature, 17 h; (f) 4-Cl-$C_6H_4CH_2Cl$, Cs_2CO_3, DMF, room temperature, 17 h; (g) (*i*) NaOH, H_2O, room temperature, 5 h, (*ii*) Amberlite IR-120 (H^+), 1 h; (h) CH_3NHNH_2, PyBOP, *i*Pr_2EtN, DMF, room temperature, 43 h; (i) $KHSO_5$, H_2O, room temperature; (j) 5% Na/Hg, Na_2HPO_4, MeOH/DMF (1/8), room temperature, 18 h.

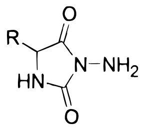
developed by our group.[16] Methodology similar to that used in the generation of the pentapetide library was also used to synthesize a new class of peptidomimetics, azatides, which are constructed of "α-aza-amino acids".[17]



Azatides

We next developed traceless linker systems for the formation of aliphatic C−H bonds that are based on the reduction of aryl sulfides and sulfones.[18−21] The sulfone version of the linker system was used to prepare alkylated malonates[22] and 3,5-pyrazolidinediones **1** (Figure 1),[23] a class of compounds which are used to treat rheumatoid arthritis and other diseases. A key observation made during the synthesis of compounds **1** was that isopropyl alcohol (IPA) is effective in precipitating PEG. Traditionally, diethyl ether and *tert*-butyl methyl ether have been used for this purpose. Since diethyl ether is relatively nonpolar, polar impurities are often associated with polymers precipitated from it, and the use of *tert*-butyl methyl ether to dissolve these impurities is undesirable due to it being environmentally unfriendly. The use of IPA overcomes these problems and affords more pure polymer-bound synthetic intermediates.

We have used an intramolecular cyclization cleavage strategy in the synthesis of 3-aminoimidazoline-2,4-diones (**2**).[24] Prior to our report, the syntheses and structural assignments of such structures were confusing and inefficient. Compound **2** is isomeric with hexahydro-1,2,4-triazine-3,6-dione (**3**), and the planned synthesis of one of these classes of compounds often resulted in the formation of the other class along with racemization of the product. Our synthesis was the first controlled method for preparing compounds **2** that maintained the stereochemistry of the starting materials (Figure 2).



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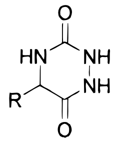

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Palladium-catalyzed cross-coupling of organotin reagents with organic electrophiles has become a versatile and common technique for the synthesis of conjugated systems.[25] We have explored the scope of such chemistry with PEG-immobilized aryl iodides with tributyl stannanes to form compounds **6**.[26] It was observed that the use of $Pd(PPh_3)_2Cl_2$ as the catalyst in DMF at 80 °C in the presence of LiCl was optimal for the formation of the desired products (Figure 3).

B. LPS-Supported Synthesis. The insolubility of PEG in tetrahydrofuran at low temperature and its potential to complex metal cations preclude its use as a support for much standard organometallic and anion chemistry. An alternative polymer that does not exhibit such limita-

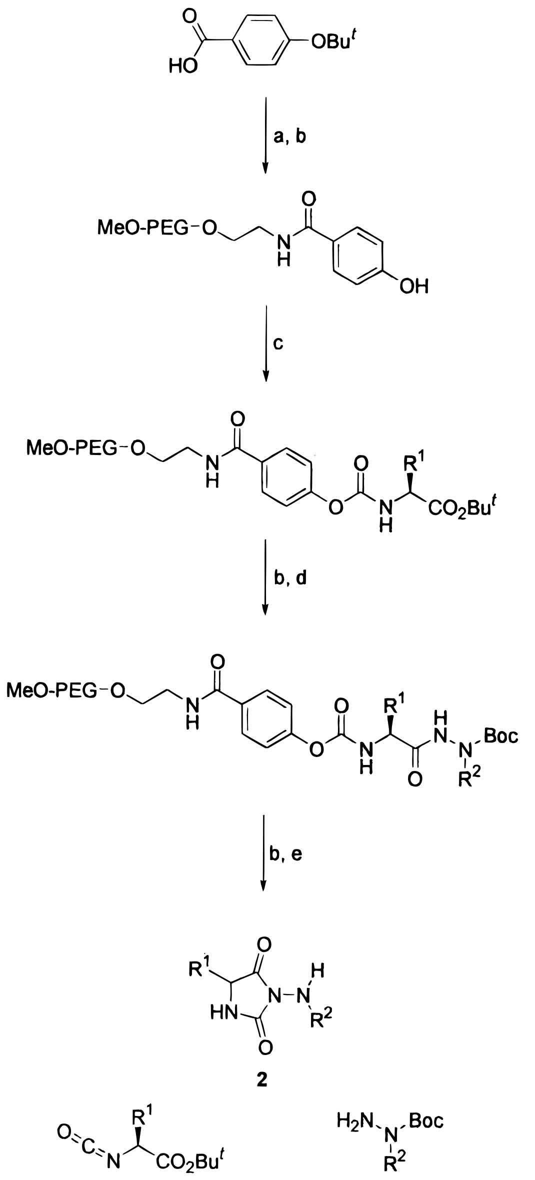


FIGURE 2. PEG-supported synthesis of 3-aminoimidazoline-2,4-diones. Conditions: (a) MeO-PEG-CH$_2$CH$_2$-NH$_2$, DCC, DMAP; (b) TFA/CH$_2$Cl$_2$ (1/1, v/v); (c) **4**; (d) **5**, DCC; (e) dilution, *i*Pr$_2$EtN (1.1 equiv).

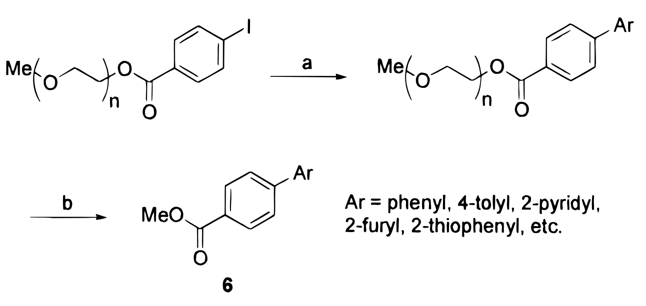
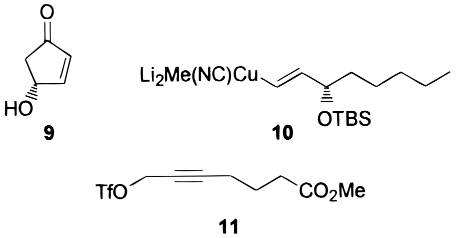


FIGURE 3. PEG-supported Stille cross-coupling reaction of an aryl iodide and tributyl stannanes: (a) ArSnBu$_3$, Pd(PPh$_3$)$_2$Cl$_2$, LiCl, DMF, 80 °C, 24 h; (b) KCN, MeOH, room temperature, 24 h.

tions is LPS. Previously, LPS had been used as a support for the synthesis of polypeptides.[27−29] An additional advantage of LPS is that the loading level of the polymer is not limited to twice the inverse of its molecular weight, as it is with PEG. The linear nature of PEG dictates that a maximum of two molecules can be attached to each polymer molecule, one at each terminus. Since a molecular weight of at least 2000 Da is necessary for PEG to have the desired precipitation properties, the maximum loading level is 1 mmol/g. The loading level of LPS can be adjusted as desired by changing the ratio of monomers used in the polymerization reaction and can approach the theoretical maximum of unfunctionalized polystyrene (9.6 mmol/g). When the LPS is functionalized with chloromethyl groups, it is essentially a soluble form of Merrifield resin (theoretical maximum loading of 6.6 mmol/g), and all chemistry performed with this resin could, therefore, in principle, be done under homogeneous reaction conditions. However, a caveat to the issue of loading is that, at a point when loading is too high or the molecules attached are too large, the polymer begins to exhibit the solubility properties of the attached molecules and may not precipitate properly. Furthermore, if there are many molecules attached closely on the polymer, they may interact with one another in undesirable ways.

To test the utility of LPS for low-temperature organometallic/anion chemistry, we have used chloromethyl-LPS as a support for the synthesis of prostaglandin E$_2$ methyl ester (**7**) and prostaglandin F$_{2\alpha}$ (**8**) (Figure 4).[30,31] In choosing these targets, we envisioned using a three-component (**9**−**11**) coupling strategy that would require the use of organocuprate and alkyllithium reagents.



Furthermore, such a LPS-supported synthesis would allow easy access to combinatorial or parallel libraries of analogues, through the variation of **9**−**11**, that could be tested for potential therapeutic use.

In the synthesis of **7** and **8**, we used the dihydropyran linker group introduced by Thompson and Ellman,[32] and (*R*)-**9** was attached through this onto the polymer to provide the prostaglandin core on which to append the α- and ω-chains (Figure 4). In the synthesis of **7**, a vinylstannane was used as the precursor to vinylcuprate **10** that installed the ω-chain. Conjugate addition of **10** and subsequent trapping of the resulting enolate as the corresponding trimethylsilyl ether, rather than direct quenching with an electrophilic α-chain equivalent, makes the synthesis useful for split-pool combinatorial library generation by allowing the combining of different reactive intermediates. The enolate was regenerated from the silyl enol ether by treatment with methyllithium and quenched with propargylic triflate **11** to install the α-chain. Selective reduction of the triple bond and cleavage from the polymer afforded **7** in 37% yield after purification.[30] Since hydrostannylation of the triple bond to form the cuprate

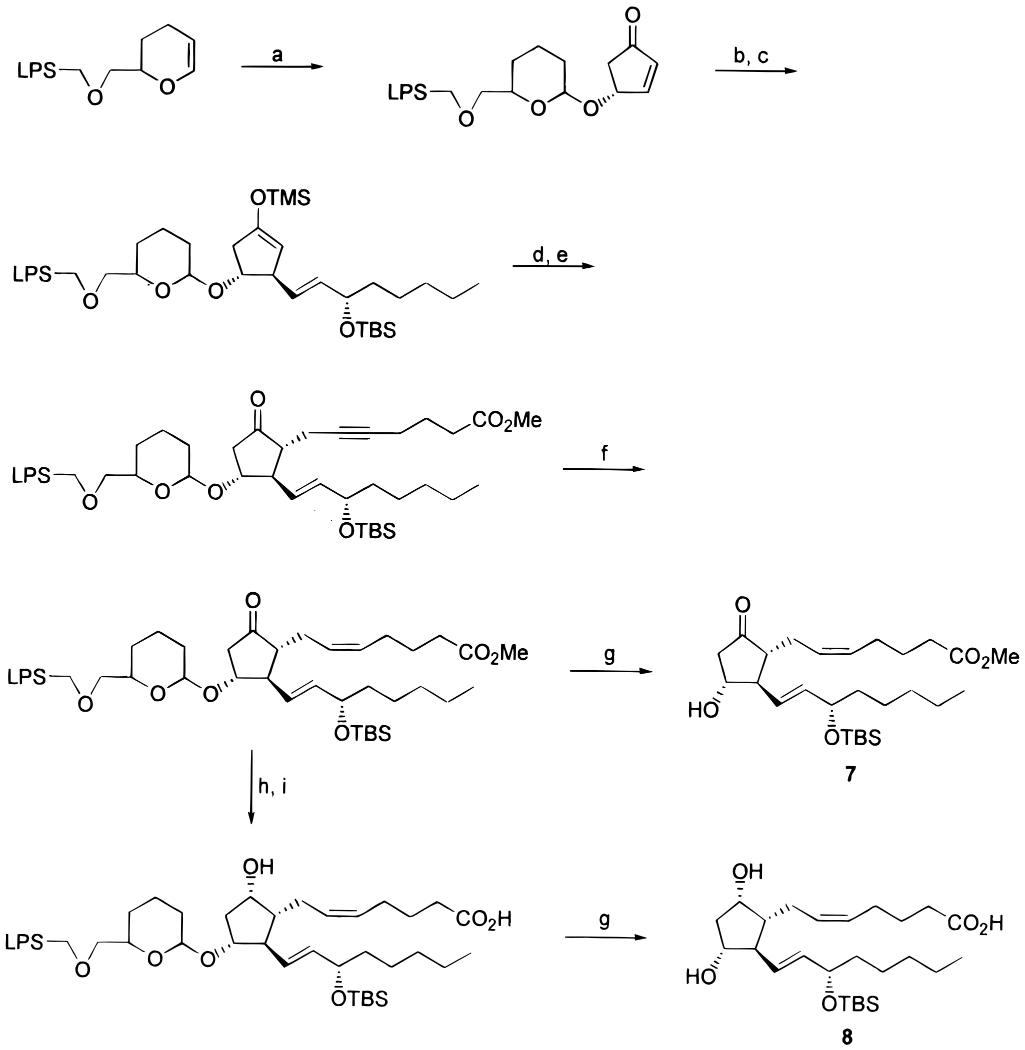


FIGURE 4. LPS-supported synthesis of prostaglandin E_2 methyl ester and prostaglandin $F_{2\alpha}$. Conditions: (a) **9**, PPTS, CH_2Cl_2, room temperature, 24 h; (b) **10**, THF, −78 °C, 15 min; (c) (*i*) TMSCl, −78 °C, 30 min, (*ii*) Et_3N 0 °C, 15 min; (d) MeLi, THF −23 °C, 20 min; (e) **11**, −78 °C, 10 min then −23 °C, 30 min; (f) H_2, 5% Pd−$BaSO_4$, quinoline, benzene/cyclohexane (1:1), room temperature, 48 h; (g) 48% aqueous HF/THF (3:20, v/v), 45 °C, 6 h; (h) L-Selectride, THF, −78 °C, 1 h; (i) 3 N LiOH, THF, MeOH, room temperature, 48 h.

precursor was neither stereospecific nor regiospecific, we used hydrozirconation by the Schwartz reagent to cleanly generate a *trans*-vinylcuprate precursor for the subsequent synthesis of **8**. Selective reduction of the ketone group with L-Selectride and saponification of the methyl ester prior to cleavage from the polymer afforded **8** in 30% overall yield.[31] The saponification of the methyl ester highlights one potential advantage of LPS over divinylbenzene cross-linked polystyrene resins. Such resins are notorious for their lack of swelling in alcohols and water, and the use of such solvents often results in long reaction times and poor conversions. When an appropriate cosolvent is used, LPS can be dissolved in the presence of protic solvents, and standard reaction kinetics can be observed.

As stated vide supra, the prostaglandins were chosen as synthetic targets because they can be assembled by the three-component coupling strategy and each of the components can be considered a point of diversity. Variation of each of these components can lead to combinatorial or parallel libraries from which biological activity can be identified and optimized. Our first effort toward this end was to vary both the α- and ω-chains and analyze the resulting prostanoid library for inhibition of cytomegalovirus (CMV).[33] By using four different α- and ω-chain precursors, we were able to prepare a 16-member library using what we term a “parallel-pool” strategy (Figure 5).

The four different ω-chain precursors **12a**−**d** were added individually to the previously described polymer-bound cyclopent-2-en-1-one (Figure 5, step a). These adducts were mixed together in equal amounts, and the mixture was then divided into four portions. Each portion was treated with one of the α-chain precursors **13a**−**d** (Figure 5, step b). This process resulted in four mixtures containing four compounds each. Reduction of the triple bonds and release from the polymers afforded mixtures **14a**−**d**, **15a**−**d**, **16a**−**d**, and **17a**−**d**. These mixtures were tested for inhibition of murine CMV growth in NIH 3T3 cells, and it was found that the mixture of **14a**−**d** produced the desired inhibition. Through parallel syn-

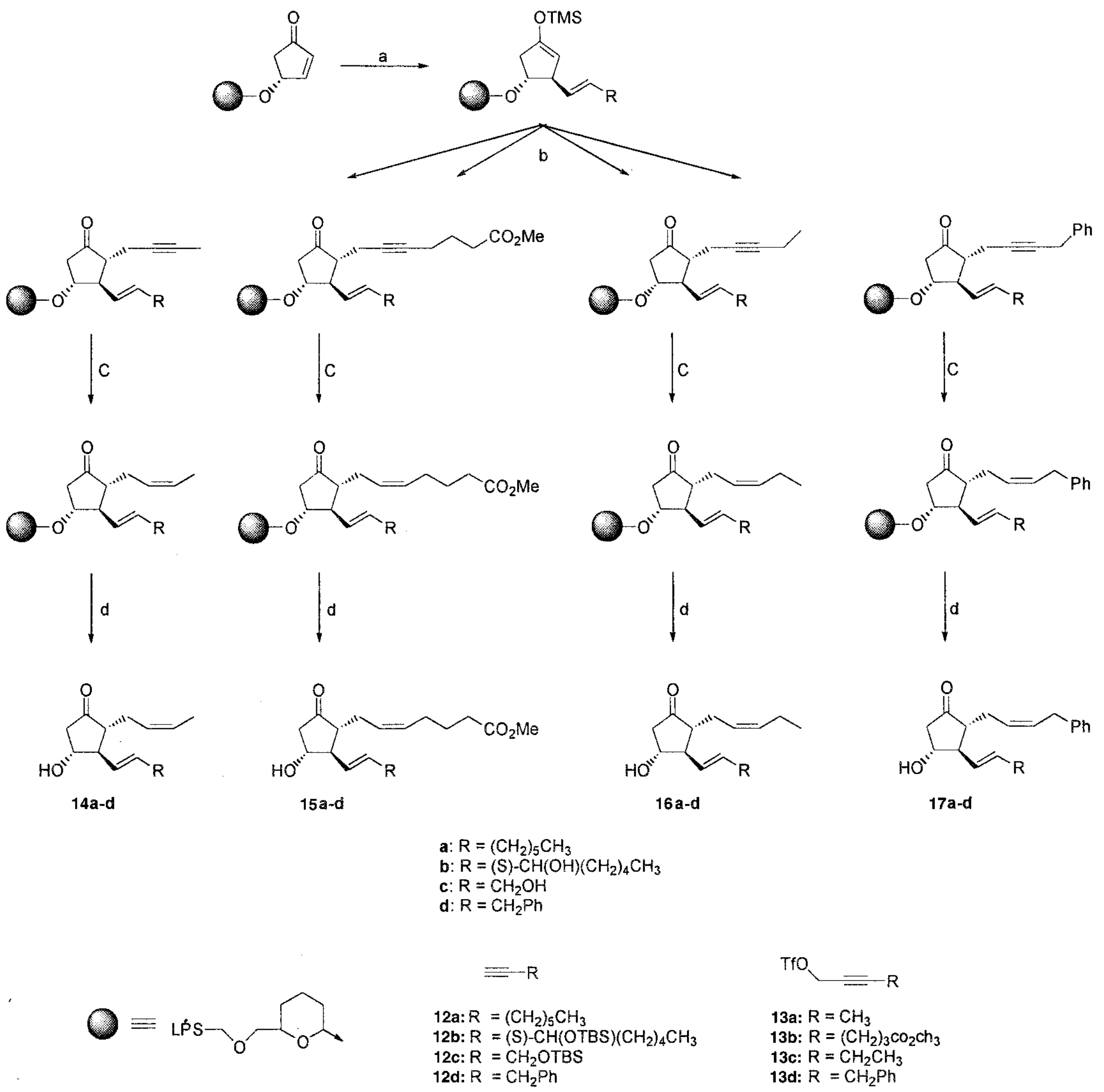
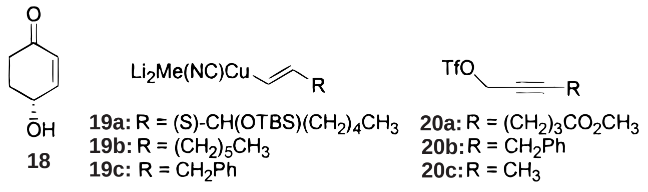
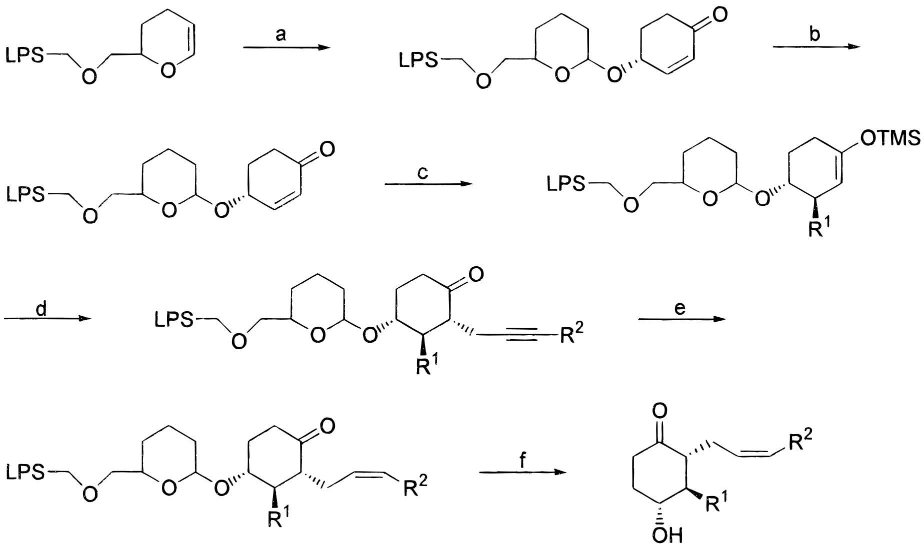


FIGURE 5. LPS-supported combinatorial synthesis of a prostanoid library. Conditions: (a) (*i*) **12a**, **12b**, **12c**, or **12d** (5 equiv), Cp$_2$Zr(H)Cl (5 equiv), THF, room temperature, 30 min, (*ii*) MeLi (10 equiv), −50 °C, 10 min, then CuCN (5 equiv), −50 °C, 15 min, (*iii*) MeLi (5 equiv), −50 °C, (*iv*) TMSCl (25 equiv), −50 °C, 40 min, then NEt$_3$ (50 equiv), −50 °C, 15 min; (b) (*i*) MeLi (4 equiv), THF, −23 °C, 40 min, (*ii*) **13a**, **13b**, **13c**, or **13d** (18 equiv), THF, −78 °C, 10 min, then −23 °C, 40 min; (c) H$_2$, 5% Pd/BaSO$_4$, quinoline, benzene/cyclohexane (1/1), 45 °C, 49 h; (d) 48% aqueous HF, THF, 45 °C, 6 h.

thesis of **14a**−**d** as single compounds, it was determined that **14a** was the component of the mixture responsible for the inhibition. These observations are significant since there are few antiviral drug therapies clinically available for CMV infection.[34]

To increase the diversity of our prostanoid library and to further study structure−activity relationships between CMV and our compounds, we have also changed the scaffold from a five- to a six-membered ring.[35] It was surprising to find that despite the enormous amount of work studying the biological activity of five-membered ring prostanoids and the many synthetic techniques used to prepare them, there were no reports in the literature describing general methods for the preparation of diverse six-membered-ring prostanoids. Thus, we first optimized the three-component coupling procedure using traditional solution-phase techniques and then applied it to the LPS-supported synthesis. Our synthetic approach mirrored that which we used previously for the five-membered-ring compounds (Figure 6): (a) immobilization of the cyclohex-2-en-1-one (**18**) on the polymer via an acetal linkage; (b) addition of the ω-chain through the conjugate addition of a vinylcuprate (**19a**−**c**); (c) trapping of the resulting enolate as a silyl ether; (d) regeneration of the enolate and addition of the α-chain by trapping with a propargyl triflate (**20a**−**c**); (e) reduction of the alkyne to an alkene;





21a: R^1 = (S)-CH(OH)$(CH_2)_4CH_3$, R^2 = $(CH_2)_3CO_2CH_3$
21b: R^1 = $(CH_2)_5CH_3$, R^2 = $(CH_2)_3CO_2CH_3$
21c: R^1 = $(CH_2)_5CH_3$, R^2 = CH_2Ph
21d: R^1 = $(CH_2)_5CH_3$, R^2 = CH_3
21e: R^1 = CH_2Ph, R^2 = $(CH_2)_3CO_2CH_3$

FIGURE 6. LPS-supported synthesis of six-membered-ring prostanoids. Conditions: (a) **18**, PPTS; (b) **19a**, **19b**, or **19c**; (c) TMSCl, NEt_3; (d) (*i*) MeLi, (*ii*) **20a**, **20b**, or **20c**; (e) H_2, 5% Pd/$BaSO_4$, quinoline; (f) 48% aqueous HF.

and (f) removal of the compound from the polymer. We have used this methodology to make a small set of six-membered-ring-containing prostanoids (**21a**–**e**). Importantly, the overall yields from the liquid- and solution-phase syntheses were comparable. The *trans,trans* stereochemical relationships between the side chains and the hydroxyl group of **21a**–**e** were determined through ^1H NMR studies.[35] We are currently working to increase the size of the library by increasing the diversity of the side chains.

3. Soluble Polymer-Supported Reagents and Catalysts

Traditional polymer-assisted synthesis has involved construction of a molecule on a polymer support. An alternative concept that has emerged over the past several years is the immobilization of reagents and catalysts on insoluble and soluble polymer supports for use in solution-phase synthesis.[36–38] Reagents can be used in excess to drive reactions to completion. The excess and polymer-bound byproducts can be removed by filtration, resulting in products that do not require further purification. Polymer-bound catalysts can likewise easily be removed from the reaction mixture and recycled.

A. PEG-Supported Cinchona Ligands. An example of this concept is the use of polymers to support expensive chiral ligands for asymmetric catalysis so that they can be recovered and reused. We have reported the immobilization of cinchona alkaloid ligands on PEG and their use in the Sharpless asymmetric dihydroxylation reaction.[39–41] These ligands, **22** and **23**, afford enantioselectivities that mirror those of the original Sharpless ligands for olefinic substrates. Ligand **22** was recovered and reused five times for the dihydroxylation of *trans*-stilbene, with no apparent decrease in yield or enantioselectivity. Ligands **22** and **23** have also been used in a multipolymer dihydroxylation system in which the olefinic substrates were attached to insoluble polystyrene resins (Figure 7).[41]

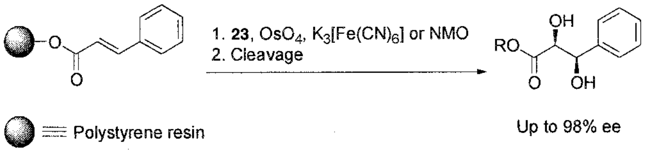
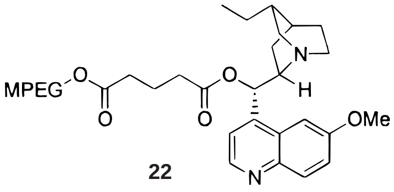


FIGURE 7. Multipolymer Sharpless asymmetric dihydroxylation system.



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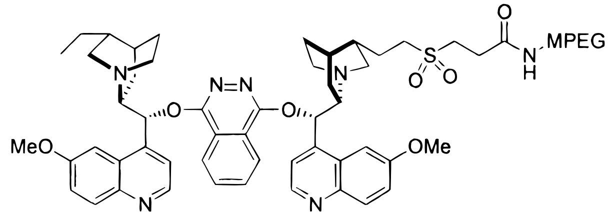

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B. PEG-Supported Reagents. Triphenylphosphine is a very versatile regent in organic synthesis. It is used in Wittig, Mitsunobu, Staudinger, and reduction reactions.

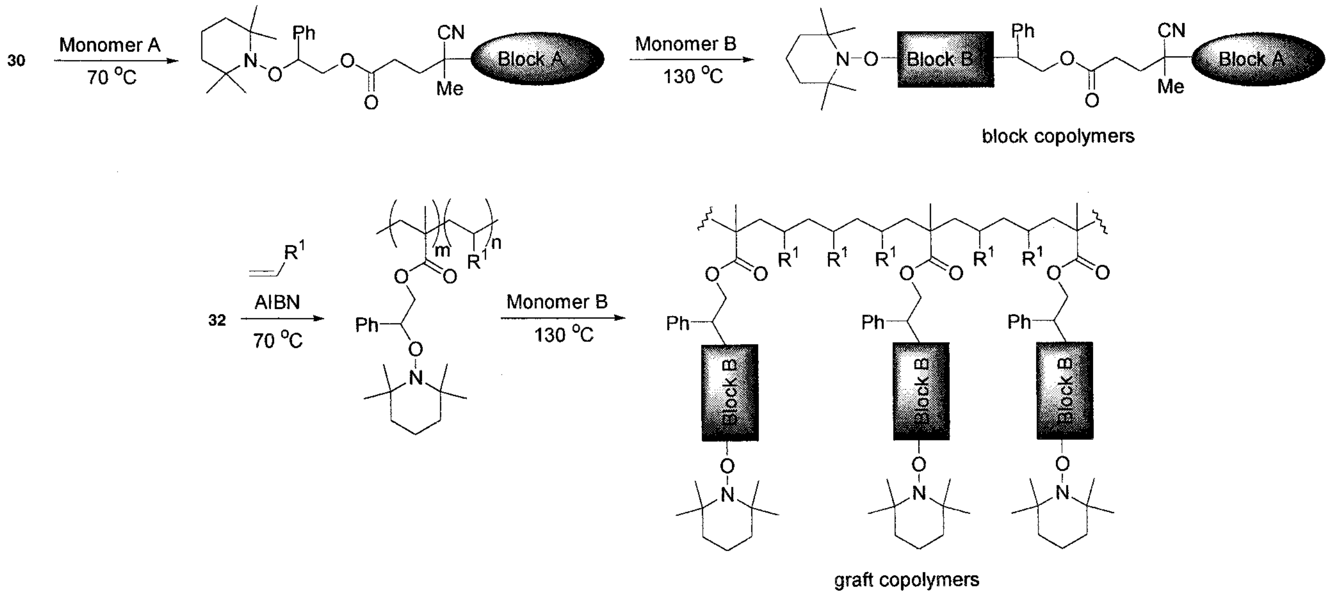
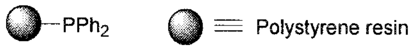


FIGURE 8. Block and graft copolymers prepared from initiators **30** and **32**.

Unfortunately, its byproduct in these reactions, triphenylphosphine oxide, is a polar material that is often difficult to remove from the reaction mixture. Because of these factors, PEG-bound triphenylphosphine reagents have been prepared, and their utility and efficiency compared to those of polystyrene resin-supported triphenylphosphine (**24**) has been explored. The first-generation reagent **25** was linked to the PEG by a carbamate linkage.[42] Its reactivity was found to be enhanced compared to that of the resin-bound reagent **24** in Staudinger and Mitsunobu reactions. In some cases, **25** afforded product when **24** did not, such as in aryl ether fromation from benzyl alcohol. The second-generation reagent **26** contains a phenyl ether linkage which should broaden the scope of chemistry with which it is compatible.[43] It has been applied in the quenching of ozonolysis reactions and as a support for phosphonium salts in aqueous Wittig reactions. Furthermore, we have found that the phosphine product from these reactions, the oxide of **26**, can easily be reduced with alane to regenerate **26**.



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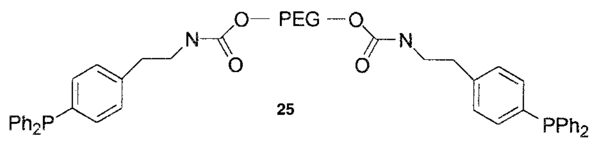

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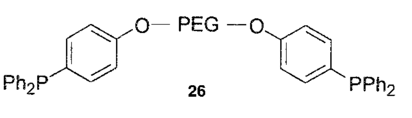

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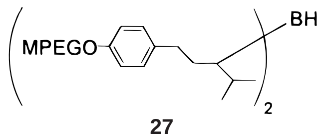
Reagents that selectively but reversibly react with reaction products can be used to isolate compounds from reaction mixtures by the "fishing out" principle.[44,45] We have demonstrated that this principle can be used with PEG-bound dialkylborane reagent **27** to isolate β-amino alcohols.[46] In this work, amines were used to open epoxides to afford β-amino alcohols that were isolated by addition of the PEG-bound reagent. Precipitation of the PEG-bound reagent from the reaction mixture with diethyl ether was followed by treatment with methanolic HCl to release the β-amino alcohol.



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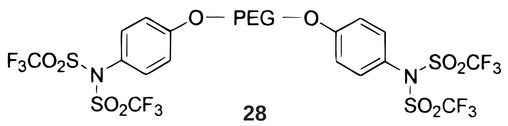
Vinyl and aryl triflates are synthetically useful compounds in metal-catalyzed cross-coupling reactions for the formation of carbon–carbon and carbon–heteroatom bonds. Unfortunately, their reactive nature often complicates their preparation and purification since they are prone to hydrolysis. We have developed PEG-bound triflimide **28** that simplifies the purification process by eliminating the need for an aqueous extraction of the reaction mixture to remove byproducts.[47] The triflimide byproducts are removed by simple precipitation with diethyl ether, and the salt byproducts are removed by filtration through silica gel. Yields of triflate formation with **28** were found to be comparable to those obtained using the traditional solution-phase reagent **29**.



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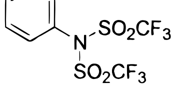

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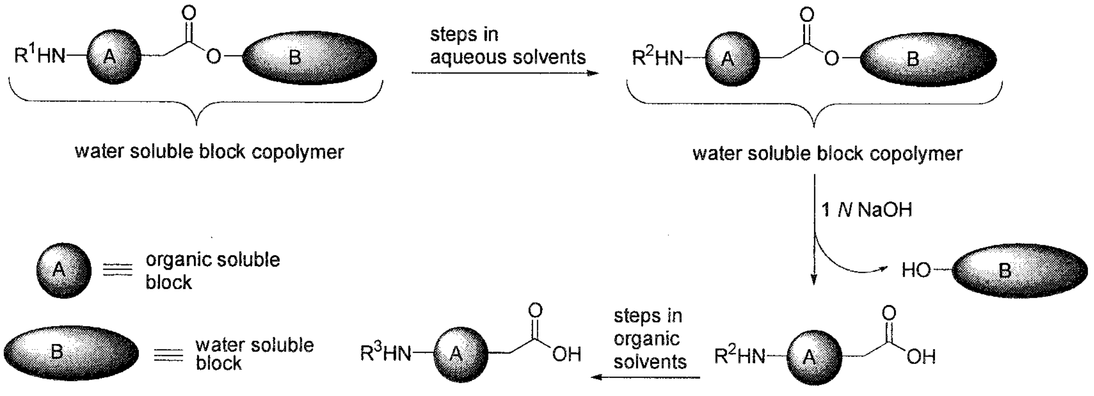
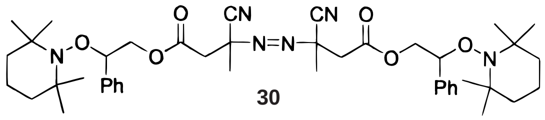
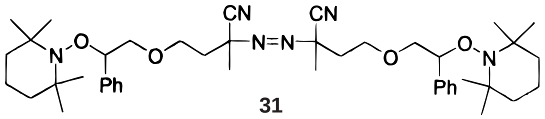


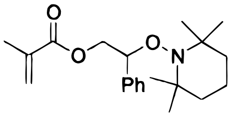
FIGURE 9. Oscillating solubility of liquid-phase polymer supports.

4. Parallel/Combinatorial Synthesis of New Polymer Supports for Liquid-Phase Chemistry

In addition to our use of common and commercially available polymers, we have a program in our laboratory aimed at developing new polymers with improved solubility properties for organic synthesis. Along these lines, we have developed bifunctional free radical polymerization initiators **30**−**32** that allow for the preparation of non-cross-linked block and graft (comb) copolymers that could be used as liquid-phase supports (Figure 8).[48,49] The bifunctional nature of **30** and **31** is based on the different thermal stability of their diazene and TEMPO moieties. Initiation of polymerization of one monomer at 70 °C afforded homopolymers containing TEMPO moieties. To alter the solubility properties of the resulting polymers, the TEMPO moieties could then be used to initiate polymerization of a second monomer at 130 °C to form block copolymers (Figure 8). Radical polymerization of initiator **32** in the presence of another monomer allows for preparation of graft (comb) copolymers since the TEMPO moiety is unchanged in the first polymerization. Initiation of polymerization of a second monomer at 130 °C produces the grafts.


30


31


32

Initiator **31** was used to prepare a library of 20 block copolymers from styrene, 4-*tert*-butylstyrene, 3,4-dimethoxystyrene, *N*-vinylpyrrolidinone, and *N*-isopropylacrylamide.[49] The solubility profiles of these copolymers were studied, and some of the copolymers were found to exhibit unique solubility properties not observed with either of the homopolymer polymers prepared from the individual monomers. For example, poly-*tert*-butylstyrene−poly-3,4-dimethoxystyrene (polyBS−DS) was found to be soluble in tetrahydrofuran and diethyl ether but insoluble in water. Interestingly, the solubility profiles of some of the block copolymers differed slightly between the two polymers derived from the same monomers but polymerized in the opposite order. These differences may be attributable to differences in block lengths. The utility of polyBS−DS as a catalyst support was demonstrated by the attachment of a chiral phosphine ligand to it for use in an asymmetric reduction reaction. Initiator **32** was used to prepare a library of seven graft copolymers from the same set of monomers (vide supra), and their solubility profiles were also examined and found to be different from those of the block copolymers prepared from **31**.[49] Initiator **30** contains ester moieties that are incorporated into the block copolymers prepared from it. Using this initiator, we prepared polymers via a two-dimensional polymerization that could oscillate between organic and aqueous phases upon ester cleavage (Figure 9).[49] Shown is the oscillation between water solubility and organic solubility, but the reverse is also possible.

5. Conclusion

The past decade has seen a renewal in interest in polymer-supported chemistry, and the vast majority of this work has used insoluble polymer resins in heterogeneous reaction conditions. We have demonstrated that, in many applications, soluble polymers can serve as superior alternatives due to the homogeneous reaction conditions they impart. Not only can soluble polymers be used as platforms for organic synthesis, but they can also serve as reagent supports that allow for simple purification of solution-phase products.

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References

(1) Brown, A. R.; Hermkens, P. H. H.; Ottenheijm, H. C. J.; Rees, D. C. Solid-Phase Synthesis. *Synlett* **1998**, *6*, 817−827.
(2) Dolle, R. E.; Nelson, K. H., Jr. Comprehensive Survey of Combinatorial Library Synthesis: 1998. *J. Comb. Chem.* **1999**, *1*, 235−282.
(3) Brown, R. C. D. Recent Developments in Solid-Phase Organic Synthesis. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3293−3320.
(4) Gravert, D. J.; Janda, K. D. Organic Synthesis on Soluble Polymer Supports: Liquid-Phase Methodologies. *Chem. Rev.* **1997**, *97*, 489−509.
(5) Harwig, C. W.; Gravert, D. J.; Janda, K. D. Soluble Polymers: New Options in Both Traditional and Combinatorial Synthesis. *Chemtracts* **1999**, *12*, 1−26.
(6) Wentworth, P., Jr.; Janda, K. D. Liquid-Phase Chemistry: Recent Advances in Soluble Polymer-Supported Catalysts, Reagents and Synthesis. *Chem. Commun.* **1999**, 1917−1924.
(7) Curran, D. P. Parallel Synthesis with Fluorous Reagents and Reactants. *Med. Res. Rev.* **1999**, *19*, 432−438.
(8) Bergbreiter, D. E. Alternative Polymer Supports for Organic Chemistry. *Med. Res. Rev.* **1999**, *19*, 439−450.
(9) Bayer, E.; Mutter, M. Liquid-Phase Synthesis of Peptides. *Nature (London)* **1972**, *237*, 512−513.
(10) Bonora, G. M.; Scremin, C. L.; Colonna, F. P.; Garbesi, A. HELP (High Efficiency Liquid Phase) New Oligonucleotide Synthesis on Soluble Polymeric Support. *Nucleic Acids Res.* **1990**, *18*, 3155−3159.
(11) Chiu, S.-H. L.; Anderson, L. Oligosaccharide Synthesis by the Thioglycoside Scheme on Soluble and Insoluble Polystyrene Supports. *Carbohydr. Res.* **1976**, *50*, 227−238.
(12) Douglas, S. P.; Whitfield, D. M.; Krepinsky, J. J. Polymer-Supported Solution Synthesis of Oligosaccharides. *J. Am. Chem. Soc.* **1991**, *113*, 5095−5097.
(13) Verduyn, R.; van der Klein, P. A. M.; van der Marel, G. A.; van Boom, J. H. Polymer-Supported Solution Synthesis of a Heptaglucoside Having Phytoalexin Elicitor Activity. *Recl. Trav. Chim. Pays-Bas.* **1993**, *112*, 464−466.
(14) Douglas, S. P.; Whitfield, D. M.; Krepinsky, J. J. Polymer-Supported Solution Synthesis of Oligosaccharides Using a Novel Versatile Linker for the Synthesis of D-Mannopentaose, a Structural Unit of D-Mannans of Pathogenic Yeasts. *J. Am. Chem. Soc.* **1995**, *117*, 2116−2117.
(15) Han, H.; Wolfe, M. M.; Brenner, S.; Janda, K. D. Liquid-Phase Combinatorial Synthesis. *Proc. Natl. Acad. Sci. U.S.A.* **1995**, *92*, 6419−6423.
(16) Erb, E.; Janda, K. D.; Brenner, S. Recursive Deconvolution of Combinatorial Chemical Libraries. *Proc. Natl. Acad. Sci. U.S.A.* **1994**, *91*, 11422−11426.
(17) Han, H.; Janda, K. D. Azatides: Solution and Liquid-Phase Syntheses of a New Peptidomimetic. *J. Am. Chem. Soc.* **1996**, *118*, 2539−2544.
(18) Jung, K. W.; Zhao, X.-Y.; Janda, K. D. A Linker that Allows Efficient Formation of Aliphatic C−H Bonds on Polymeric Supports. *Tetrahedron Lett.* **1996**, *37*, 6491−6494.
(19) Zhao, X.-Y.; Jung, K. W.; Janda, K. D. Soluble Polymer Synthesis: An Improved Traceless Linker Methodology for Aliphatic C−H Bond Formation. *Tetrahedron Lett.* **1997**, *38*, 977−980.
(20) Jung, K. W.; Zhao, X.-Y.; Janda, K. D. Development of New Linkers for the Formation of Aliphatic C−H Bonds on Polymeric Supports. *Tetrahedron* **1997**, *53*, 6645−6652.
(21) Zhao, X.-Y.; Janda, K. D. Soluble Polymer Traceless Linker Investigations: Solvent Effects on the Desulfonylation of Polyethylene Glycol (PEG) Substituted Aryl Alkyl Sulfones with Sodium Amalgam. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2439−2442.
(22) Zhao, X.-Y.; Janda, K. D. Syntheses of Alkylated Malonates on a Traceless Linker Derived Soluble Polymer Support. *Tetrahedron Lett.* **1997**, *38*, 5437−5440.
(23) Zhao, X.-Y.; Metz, W. A.; Sieber, F.; Janda, K. D. Expanding on the Purification Methodology of Polyethylene Glycol (PEG) Bound Molecules: The Synthesis of 3,5-Pyrazolidinediones. *Tetrahedron Lett.* **1998**, *39*, 8433−8436.
(24) Yoon, J.; Cho, C.-W.; Han, H.; Janda, K. D. Solution and Soluble Polymer Syntheses of 3-Aminoimidazoline-2-4-diones. *Chem. Commun.* **1998**, 2703−2704.
(25) Farina, V. New Perspectives in the Cross-Coupling Reactions of Organostannanes. *Pure Appl. Chem.* **1996**, *68*, 73−78.
(26) Sieber, F.; Wentworth, P., Jr.; Janda, K. D. Exploring the Scope of Poly(ethylene glycol) (PEG) as a Soluble Polymer Matrix for the Stille Cross-Coupling Reaction. *J. Comb. Chem.* **1999**, *1*, 540−546.
(27) Shemyakin, M. M.; Ovchinnikov, Y. A.; Kivyushkin, A. A.; Kozhevnikoya, I. V. Synthesis of Peptides in Solution on a Polymeric Support: Synthesis of Glycylglycyl-L-leucylglycine. *Tetrahedron Lett.* **1965**, *6*, 2323−2327.
(28) Maher, J. J.; Furey, M. E.; Greenberg, L. J. Improved Solid-Phase Peptide Synthesis on Non-Crosslinked Resins. *Tetrahedron Lett.* **1971**, *12*, 27−28.
(29) Narita, M.; Hirata, M.; Kusano, K.; Itsuno, S.-I.; Ue, M.; Okawara, M. Preparation of Soluble Polymer Supports for Peptide Synthesis by Copolymerization and Their Utilization for Sequential Polypeptide Synthesis by Fragment Condensation. *Pept. Chem.* **1980**, *17*, 107−112.
(30) Chen, S.; Janda, K. D. Synthesis of Prostaglandin E_2 Methyl Ester on a Soluble-Polymer Support for the Construction of Prostanoid Libraries. *J. Am. Chem. Soc.* **1997**, *119*, 8724−8725.
(31) Chen, S.; Janda, K. D. Total Synthesis of Naturally Occurring Prostaglandin $F_{2\alpha}$ on a Non-Crosslinked Polystyrene Support. *Tetrahedron Lett.* **1998**, *39*, 3943−3946.
(32) Although the use of a tetrahydropyran moiety as a linking group causes diastereomeric mixtures to be formed, this did not complicate the synthesis. Thompson, L. A.; Ellman, J. A. Straightforward and General Method for Coupling Alcohols to Solid Supports. *Tetrahedron Lett.* **1994**, *35*, 9333−9336.
(33) Lee, K. J.; Angulo, A.; Ghazal, P.; Janda, K. D. Soluble-Polymer Supported Synthesis of a Prostanoid Library: Identification of Antiviral Activity. *Org. Lett.* **1999**, *1*, 1859−1862.
(34) King, S. M. Immune Globulin Versus Antivirals Versus Combination for Prevention of Cytomegalovirus Disease in Transplant Recipients. *Antiviral Res.* **1999**, *40*, 115−137.
(35) Lopez-Pelegrin, J. A.; Janda, K. D. Solution and Polymer-Supported Asymmetric Three-Component Coupling Synthesis of Six-Membered Ring Prostanoids. *Chem. Eur. J.* In press.
(36) Booth, R. J.; Hodges, J. C. Solid-Supported Reagent Strategies for Rapid Purification of Combinatorial Synthesis Products. *Acc. Chem. Res.* **1999**, *32*, 18−26.
(37) Flynn, D. L. Phase-Trafficking Reagents and Phase-Switching Strategies for Parallel Synthesis. *Med. Res. Rev.* **1999**, *19*, 408−431.
(38) Parlow, J. J.; Devraj, R. V.; South, M. S. Solution-Phase Chemical Library Synthesis Using Polymer-Assisted Purification Techniques. *Curr. Opin. Chem. Biol.* **1999**, *3*, 320−336.
(39) Han, H.; Janda, K. D. Soluble Polymer-Bound Ligand-Accelerated Catalysis: Asymmetric Dihydroxylation. *J. Am. Chem. Soc.* **1996**, *118*, 7632−7633.
(40) Han, H.; Janda, K. D. A Soluble Polymer-Bound Approach to the Sharpless Catalytic Asymmetric Dihydroxylation (AD) Reaction: Preparation and Application of a [(DHQD)$_2$PHAL-PEG-OMe] Ligand. *Tetrahedron Lett.* **1997**, *38*, 1527−1530.
(41) Han, H.; Janda, K. D. Multipolymer-Supported Substrate and Ligand Approach to the Sharpless Asymmetric Dihydroxylation. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1731−1733.
(42) Wentworth, P., Jr.; Vandersteen, A. M.; Janda, K. D. Poly(Ethylene Glycol) (PEG) as a Reagent Support: the Preparation and Utility of a PEG-Triarylphosphine Conjugate in Liquid-Phase Organic Synthesis (LPOS). *Chem. Commun.* **1997**, 759−760.
(43) Sieber, F.; Wentworth, P., Jr.; Toker, J. D.; Wentworth, A. D.; Metz, W. A.; Reed, N. N.; Janda, K. D. Development and Application of a Poly(ethylene glycol)-Supported Triarylphosphine Reagent: Expanding the Sphere of Liquid-Phase Organic Synthesis. *J. Org. Chem.* **1999**, *64*, 5188−5192.
(44) Seymour, E.; Frechet, J. M. J. Use of Polymers as Protecting Groups in Organic Synthesis. IV. Applications of a Polystyrylboronic Acid Resin to the Selective Functionalization of Some Glycosides. *Tetrahedron Lett.* **1976**, *17*, 1149−1152.
(45) Hodge, P.; Waterhouse, J. Preparation of a Polymer-Supported Diol and its use in Isolating Aldehydes and Ketones from Mixtures and as a Protecting Group for Aldehydes and Ketones. *J. Chem. Soc., Perkin Trans. 1* **1983**, 2319−2323.
(46) Hori, M.; Janda, K. D. A Soluble Polymer Approach to the "Fishing Out" Principle: Synthesis and Purification of β-Amino Alcohols. *J. Org. Chem.* **1998**, *63*, 889−894.
(47) Wentworth, A. D.; Wentworth, P., Jr.; Mansoor, U. F.; Janda, K. D. A Soluble Polymer-Supported Triflating Reagent: A High-Throughput Synthetic Approach to Aryl and Enol Triflates. *Org. Lett.* **2000**, *2*, 477−480.
(48) Gravert, D. J.; Janda, K. D. Bifunctional Initiators for Free-Radical Polymerization of Non-Crosslinked Block Copolymers. *Tetrahedron Lett.* **1998**, *39*, 1513−1516.
(49) Gravert, D. J.; Datta, A.; Wentworth, P., Jr.; Janda, K. D. Soluble Supports Tailored for Organic Synthesis via Sequential Normal/Living Free Radical Processes. *J. Am. Chem. Soc.* **1998**, *120*, 9481−9495.

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