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Reactive polymers: design considerations, novel preparations and selected applications in organic chemistry

Jean M.J. Fréchet*, Graham D. Darling, Shinichi Itsuno,
Pei-Zhi Lu, Marina Vivas de Meftahi, and Wesley A. Rolls, Jr.

Department of Chemistry, University of Ottawa, Ottawa,
Ontario, K1N-9B4, Canada.

Abstract - Crosslinked reactive polymers with novel structures have been prepared from the corresponding monomers or by newly developed chemical modification reactions. These include the preparation of polymers with two or three carbon spacer groups between backbone and functionality, the first preparation of a Grignard reagent on an insoluble polymer, and some new copper mediated chemical modification reactions resulting in C-C bond formation. Novel applications of these polymers in asymmetric syntheses, regenerable polymeric protecting groups, supernucleophilic catalysts, polymeric separation media for HPLC, as well as aids in the determination of reaction mechanisms, have been investigated. Microenvironment effects within the polymer beads are shown to be important when considering the use of an insoluble reactive polymer.

INTRODUCTION

The first synthetic reactive polymers of some significance were undoubtedly the ion-exchange resins [1] first prepared as early as 1935 [2] from phenol-formaldehyde condensates, then adapted in the early 1950's to the more suitable styrene-divinylbenzene structures [3,4] which are still in use today. Despite their great importance, the impact of ion-exchange resins on the specialized field of reactive polymers is overshadowed by Merrifield's development of the solid-phase method of synthesis in the early 1960's [5]. Merrifield's concept not only revolutionized [6] the field of peptide synthesis for which it had been developed, but also spread quickly to other areas of organic synthesis, catalysis, separation science, etc. Interestingly, the development of numerous new polymeric reagents, catalysts, and supports, has resulted in a better awareness of the fact that polymers could be designed to have special reactivities and this, in turn, has contributed to a new interest in reactive polymers for application in areas not directly related to synthesis, catalysis, or separation science.

This report will make no attempt to broad coverage of the field of reactive polymers; indeed, several books [7-9] and numerous other reviews have adequately covered most of the various synthetic or catalytic applications of the field. Instead this will focus mainly on the authors' own recent experiences and will present a limited and perhaps somewhat biased view of that part of the field of reactive polymers which is of closest interest to the synthetic organic or industrial chemist.

PREPARATION OF POLYMERIC REAGENTS, CATALYSTS, AND SUPPORTS

Although some very interesting results have been obtained in applications involving soluble polymers [10] the discussion below will focus almost exclusively on the preparation of crosslinked reactive resins, macroporous or gel-type. Gel-type polymers, such as the 1-2% crosslinked (chloromethyl)polystyrene used by Merrifield [5], have no permanent pores but swell extensively in some appropriately chosen solvents. Functional groups attached to these polymers have high reactivities, often comparable to those of analogous small molecules in solution. Similarly, as the chains have excellent mobilities in the swollen state, their ^{13}C-NMR spectra can be measured easily albeit with some line broadening, under conventional conditions [11]. In contrast, more highly crosslinked macroporous resins prepared by suspension polymerization in the presence of porogens [12,13] often have high porosities and high surface areas which make them more suitable in certain applications such as those involving flow-systems prevalent in the area of polymer-based separation media. A definite drawback of macroporous resins when compared to swellable gels, is their lower reactivity and relatively poor mechanical properties which often preclude their use.

Note * : address correspondence to this author at the Department of Chemistry, Cornell University, Ithaca, New York 14853-1301, U.S.A.

Preparation by chemical modification

The chemical modification route is particularly attractive with polystyrene based resins as their aromatic rings can be modified readily by electrophilic aromatic substitution or through other simple reactions. Thus the chloromethylation of polystyrene [3] was one of the important reactions used in the development of ion exchange resins and was also used as the key polymer functionalization reaction in Merrifield's original approach [5]. Other widely applicable functionalization reactions which have been studied extensively are the bromination [14-16] and the lithiation [14, 17-18] of crosslinked polystyrene. In fact, it is likely that well over half the reactive crosslinked resins prepared to date have been made through procedures involving either chloromethylated or lithiated polystyrene. This is due to the ease with which displacement or addition reactions (Fig. 1) can be carried out on (chloromethyl)polystyrene or on (lithio)polystyrene. These reactions which can be performed under classical conditions have been reviewed [19]; in the case of nucleophilic displacements on (chloromethyl)polystyrene the reactions can also be done using phase transfer catalysis [20].

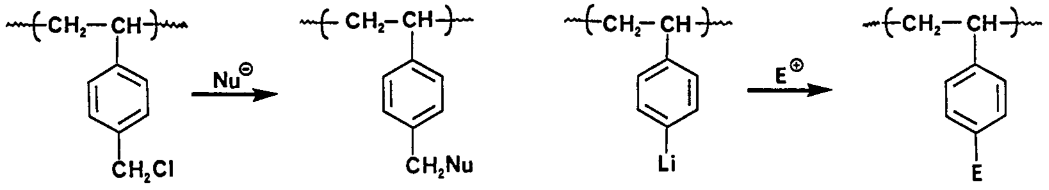

Fig. 1. Typical reactions involving (chloromethyl) or (lithio)polystyrene

Control of structure during chemical modification. Although the chemical modification approach has been extremely successful in its application to the preparation of resins having a great variety of structures, it is a route which should be considered with great care. For example, it is unwise to assume that a reaction which has been optimized for the preparation of a small molecule will be directly applicable to the chemical modification of a polymer. Indeed the reactive polymer literature is full of examples where the lack of reactivity, or the strange behavior of a particular functional polymer, is attributed to the deleterious effect of attachment to a polymer backbone, when in fact it is the chemical modification procedure which is at fault. The term "polymer-analogous reaction" may be a useful descriptor for a procedure in which a known reaction, optimized for the preparation of a small molecule, is applied to the modification of a polymer, but it should not lead to the complacent assumption that the reaction applied to a polymeric substrate will afford results which duplicate exactly those of the model reaction. In fact this terminology which may be seriously misleading should probably be avoided altogether.

Whenever chemical modification of a polymer is contemplated, it must be remembered that any side-reaction which occurs may result in the permanent attachment of undesired or even deleterious functionalities to the polymer backbone [21]. The same can be said of incomplete reactions which afford materials containing at least two clearly distinguishable reactive groups. These may have divergent reactivities which could potentially reduce the effectiveness of the final resin. Although attempts may be made to eliminate the potential harmful effects of undesired functionalities resulting from chemical modification processes [22], it is always best to optimize the process itself by developing procedures uniquely suited to the target resin [23-24]. At the same time, analytical controls must be established to confirm the quantitative nature of the functionalization reaction [23-24].

Consideration of microenvironment within a reactive polymer. This is an issue which is all too often forgotten in the design of reactive polymers. It should be remembered that whenever an insoluble polymer is used as a reactant or catalyst in a given reaction, the microenvironment of the reactive site is very different from that which prevails in classical solution chemistry. Thus, there exists within the reaction medium an uneven distribution of both the polymer-bound reactive species and also of the groups which make up the backbone of the polymer. For example, reactions carried out with a reactive styrene resin with a degree of functionalization of 0.1 may be affected by the fact all reactive ends are constantly surrounded by the styrenic moieties to which they are attached, these may provide a special non-polar microenvironment which is not normally obtained in the more usual solution reactions [25-27]. In addition, as the reactive sites are all attached to the insoluble polymer and are therefore not evenly distributed throughout the medium, high local concentrations leading to site-site interactions may occur. Such interactions of reactive sites which have been observed in numerous polymer-supported reactions [21, 28-31] are examples of other types of microenvironment effects which are also often seen in polymer-assisted chemistry. These microenvironment effects can be extremely important if they are harnessed to contribute positively to the ultimate design; they may also be harmful especially if they result from uncontrolled, and therefore sometimes undetected, side-reactions during synthesis. Attempts to design the microenvironment of reactive sites have been reported in the literature [24-26, 28, 31].

Use of polymethylene spacers on polystyrene substrates. Though a very large number of reactive polymers have been prepared satisfactorily by modification of (chloromethyl)polystyrene, it has become apparent that the benzylic linkage between reactive group and resin may not always provide the long-term stability which is desirable in reactive polymers. Hence, it is well known that benzylic quaternary onium salts are easily dealkylated [32] while benzylic amines, sulfides, esters and ethers may be susceptible to cleavage by acid or to hydrogenolysis [33]. It should be emphasized however, that it is this very lability of benzylic substituents which made (chloromethyl)polystyrene the support of choice in solid-phase synthesis [5] as controlled release of the finished peptide can be achieved readily. Nevertheless, there are numerous instances where reactive polymers have undergone unexplained cleavage side-reactions which have affected their ability to be regenerated and reused. Though, as was mentioned earlier, non-benzylic reactive polymers can be prepared from (lithio)polystyrene [14], it appeared useful to develop reactive polymers in which a short spacer group is introduced between the styrenic rings and the reactive groups. To this effect, a series of synthetic approaches have been developed for the introduction of a dimethylene spacer between functionality and aromatic ring [23-24] by sequential modifications of crosslinked polystyrene. The common feature of these modifications is that each was optimized to ensure that quantitative yields were obtained in each of the key modification steps. Though it is generally true that a dimethylene spacer may be subject to unwanted elimination reactions, it is possible in most cases to develop reaction conditions for which such eliminations are not possible, or structures in which the polymer-bound functionalities are poor leaving groups under basic conditions. This work on the introduction of dimethylene spacers is of particular interest as it demonstrates the frequent inadequacy of blindly applied "polymer-analogous" reactions: special reaction conditions are required to cope with the unusual environment which prevails within reactive polymers. For example, while model reactions suggest that (2-bromoethyl)polystyrene should be readily obtained from the corresponding 2-hydroxyethyl analog by reaction with lithium bromide and chlorotrimethylsilane in acetonitrile, it is found that this reaction only proceeds to 90% completion. This is likely due to the unique non-polar microenvironment within the polymer (styrenic residues held in proximity to the alcohol site) which allows the silylation of some of the reactive groups to occur in competition to the normal bromination which is usually quantitative in the polar acetonitrile medium. The choice of other optimized reaction conditions [23] affords the fully brominated polymer as shown in Fig. 2.

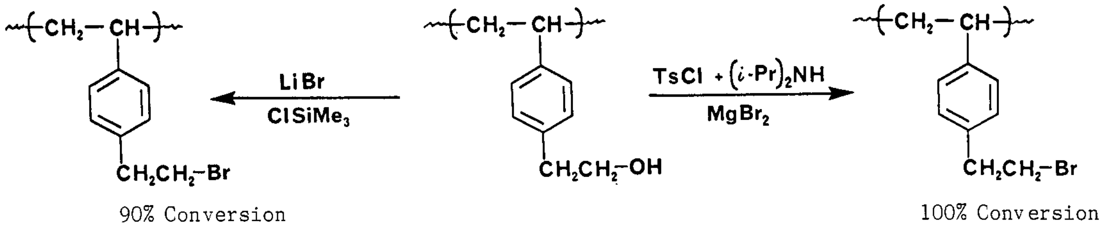

Fig. 2. Development of a quantitative bromination procedure for a hydroxylated resin.

Other spacer groups which may be even more suitable can also be used advantageously [26, 34-36] but the work on dimethylene spacers clearly demonstrates that chemical modification procedures need to be studied and optimized on the target polymers and not just taken from the organic literature without due consideration of the special requirements which apply to reactive polymers.

Chemical modification of glycidyl methacrylate resins. Although the previous discussion was focused entirely on crosslinked polystyrene resins, it is worth noting here that another reactive resin which has received much attention is crosslinked glycidyl methacrylate. Most of the work on this polymer has been carried out on macroporous resins [12, 37-38]. With few exceptions, the chemical modification of these resins is generally not quantitative but this has not overly affected their end use which has mainly been in the area of separation media.

New directions in chemical modification. It may be said that the reactivity of (lithio)polystyrene is complementary to that of (chloromethyl)polystyrene as the former can be used as a nucleophilic reagent while the latter has electrophilic properties. In theory, (chloromethyl)polystyrene itself could also be turned into a complementary nucleophilic reagent by transformation into the corresponding lithiated or organomagnesium reagent. Unfortunately attempts at lithiation of (chloromethyl)polystyrene under a variety of conditions all met with failure as the reagent couples instantly to yield biphenylic species thereby increasing the degree of crosslinking of the resin and destroying all desired functionality [24]. Similarly, synthesis of the polymer-supported Grignard reagent is made difficult by the fact both (chloromethyl)polystyrene and magnesium are solid insoluble reagents. Numerous attempts to prepare the Grignard reagent either directly or via reactive species such as magnesium bromide, or soluble Grignard reagents operating as magnesium "shuttles" failed to produce the desired polymeric Grignard [24]. We have recently been able to solve this problem satisfactorily [39] using magnesium anthracene-THF complex [40] as the metalating species (Fig. 3). Under these conditions excellent yields of the insoluble polymer-bound benzylic Grignard species are obtained; these reagents are currently being used in the development of several new and interesting reactive polymers.

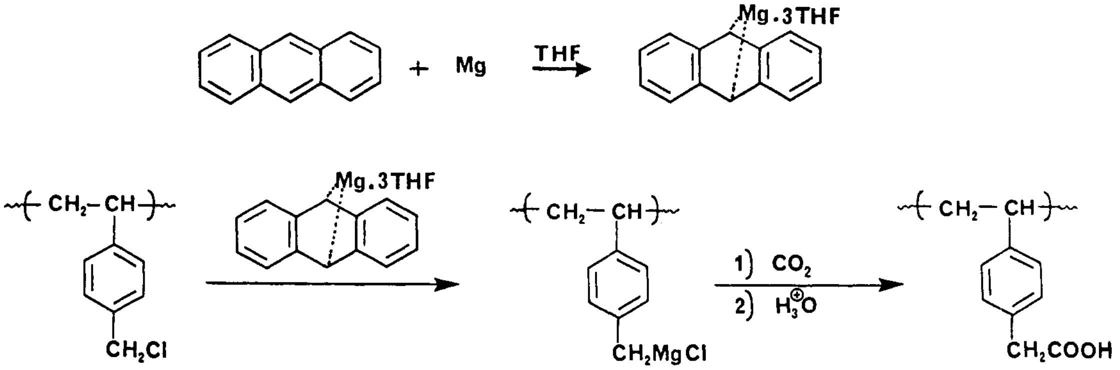

Fig. 3. Preparation and test reaction of an insoluble Grignard reagent

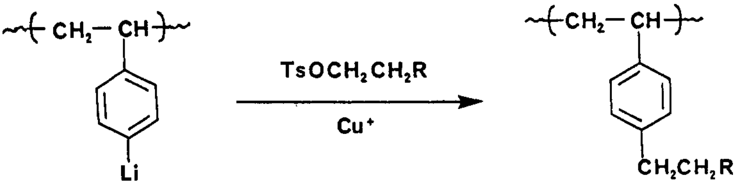

Fig. 4. Copper-mediated formation of C-C bonds on insoluble polymers.

Similarly, the development of polymer modification reactions in which linkage of reactive moieties to polystyrene is accomplished through carbon-carbon bonds only, as opposed to the carbon-heteroatom linkages which are usually obtained in the reaction of (chloromethyl)polystyrene with nucleophiles, has led us to develop organo-copper mediated reactions which can be carried out using crosslinked polystyrene resins as reactive substrates (Fig. 4). Such reactions promise to be useful in the preparation of certain polymeric catalysts [41].

Finally, our attempts to modify cleanly crosslinked polymers derived from 2-methyl-5-vinylpyridine through activation of the 2-methyl group (Fig. 5) were much less successful as we were not able to eliminate side reactions. The introduction of acetate, halogen, or dialkylamino functional groups, often via the N-oxide derivative were usually accompanied by undesired side-reactions such as additional crosslinking and also the incorporation of some uncontrolled functionalities into the reactive polymer [42]. Though the modified polymers may still be usable in some applications, these modification reactions cannot be compared to those described earlier in this report as optimization could not be carried out.

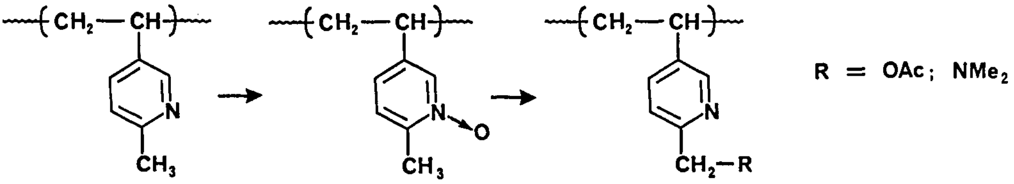

Fig. 5. Chemical modification of poly(2-methyl-5-vinylpyridine)

Preparation from reactive monomers

The preparation of useful crosslinked reactive resins from functional monomers has received much less sustained attention than the chemical modification approach described above. This is due in part to the limited availability of functional monomers and to the reluctance of many researchers to venture into the preparation of bead polymers with suitable physical as well as chemical characteristics.

The preparation of 1-2% crosslinked gel polymers by suspension polymerization is a relatively easy task provided a suitable crosslinking agent with a reactivity comparable to that of the functional monomer is available. In practice, divinylbenzene, ethylene dimethacrylate or bis-acrylamide are used most frequently, though specialty crosslinking agents such as divinylpyridine have also been used. Several procedures for the preparation of gel resins have been described in the literature [26, 42-44]. In contrast, it is relatively more difficult to prepare highly porous, high surface area, macroporous resins as numerous variables such as the nature and amount of porogenic agent, the stirring rate and reactor design, the relative proportions of the various components in the reaction mixture, etc., all have a significant effect on the characteristics of the final resins. Fortunately there exist several excellent accounts of procedures which are useful in the preparation of macroporous acrylic [12] or styrenic [13, 45] resins.

Figure 6 shows several relatively easily accessible substituted styrene monomers which are useful in the preparation of reactive polymers. While some of these monomers are commercially available, others, which are sometimes prepared for proprietary industrial applications, may be more difficult to obtain. Several other interesting and commerically available functional monomers such as glycidyl methacrylate, 2-hydroxyethyl methacrylate, and other acrylics have also been used extensively to prepare reactive polymers. It is expected that as the market for specialty polymers grows larger, other functional monomers will be added to the catalogs of chemical suppliers.

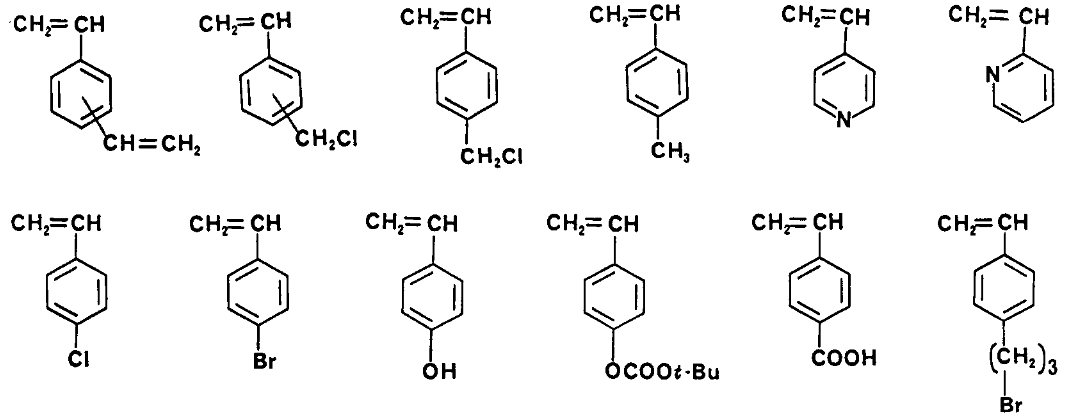

Fig. 6. Examples of functionalized styrene monomers.

Preparation of resins containing pendant phenolic groups. Crosslinked polystyrene resins containing pendant phenolic groups can be easily obtained by suspension copolymerization of protected p-hydroxystyrene with divinylbenzene. We have found that an extremely useful monomer for this preparation is 4-t-butyloxycarbonyloxystyrene [45-46]. This monomer co- or ter-polymerizes well with divinylbenzene and/or styrene and affords a t-BOC protected phenolic resin which can be easily de-protected by a variety of routes such as hydrolysis, acidolysis, or thermolysis. As will be seen below, the thermal deprotection reaction which only affords gaseous by-products , carbon dioxide and 2-methyl-propene (Fig. 7), is particularly well suited to the preparation of the very small porous beads of the type which is commonly used for HPLC packings.

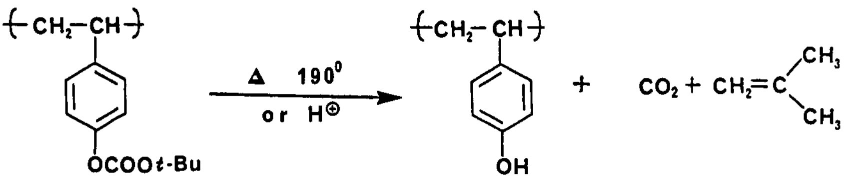

Fig. 7. Thermal removal of t-BOC protecting groups

Monomers containing a trimethylene spacer. A convenient alternative to chloromethylstyrene for the preparation of reactive monomers is the p-(3-bromopropyl)styrene which was originally developed by Hallensleben [34]. This monomer and others derived from it are particularly suitable for the preparation of reactive polymers in which the active sites are separated by a short spacer arm from the styrene residues. We have used p-(3-bromopropyl)styrene as the starting material in the preparation of several other more elaborated structures containing for example pendant activated silicon or a dialkylaminopyridine group as shown in Fig. 8. [26, 47]

Miscellaneous reactive monomers. Numerous other reactive monomers are being prepared for ultimate applications in polymer assisted chemistry. For example several chiral amino alcohol ligands have been attached to chloromethylstyrene (Fig. 9) for the preparation of polymeric reagents or catalysts used in asymmetric synthesis [28, 48-50]. Other interesting structures which may find varied applications include vinyl t-butyl carbonate [51] and numerous other carbonate substituted vinyl compounds.

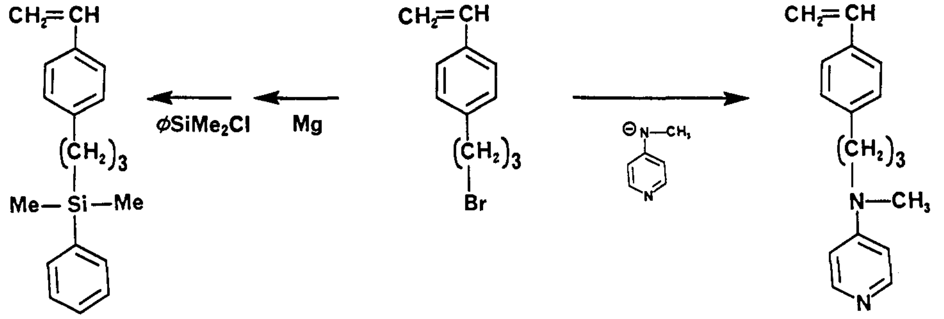

Fig. 8. Preparation of monomers having a trimethylene spacer group.

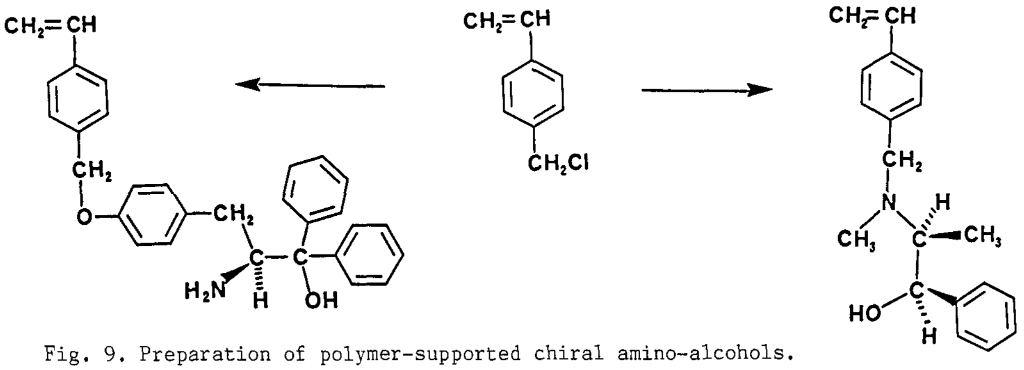

Fig. 9. Preparation of polymer-supported chiral amino-alcohols.

POLYMER-ASSISTED CHEMISTRY

As most of the organic applications of reactive polymers have been reviewed recently [7-9, 21], some will be mentioned briefly in the following paragraphs but detailed coverage will be limited to a small selection of newer examples, mainly from the authors' own laboratory, which provide a view of some of the directions in which the field is moving at the present time.

With the continued expansion of the field of biotechnology, immobilized enzymes and cells are still receiving a considerable amount of attention. Several industrial processes based on such immobilized species have been in operation for some time now [52-54] and others are likely to follow.

In the area of polymer-supported transition metal catalysts serious problems with the long-term stability of the functionalized supports have been encountered [55-56]. Future developments in this area will hinge on research into immobilizing systems of improved stability.

Some very imaginative uses of soluble polymeric reagents and catalysts have been described by Bergbreiter [10, 57] following the earlier successful application of soluble supports in the synthesis of polypeptides [58]. The polymeric photosensitizers of Neckers and coworkers [59-60] have now been studied in great detail and provide an interesting and unique alternative to the conventional photosensitizers. Outstanding work in the area of molecular recognition through the use of polymeric templates by Wulff and coworkers [61-62] continues to stimulate research towards polymeric enzyme models.

Polymer-assisted asymmetric synthesis

While most early work in the application of chiral polymers for asymmetric processes was directed towards materials useful in the chromatographic separation of enantiomers [62-64], several reports of the use of polymers as chiral auxiliaries in asymmetric syntheses have appeared. These include polymeric phase transfer catalysts [65] or chiral polymers used in asymmetric addition [66-69] or alkylation reactions [70-71]. More recently, much activity has been concentrated on polymer-assisted asymmetric reductions [28, 48-49].

The solid-phase approach seems to be ideally suited for numerous asymmetric reactions in which the chiral auxiliary remains unaffected in the overall process as chiral molecules are often valuable commodities for which recycling is a very practical requirement. Attachment of the chiral moieties to insoluble reactive polymers ensures that their recovery will be quantitative and may therefore facilitate their use. This reasoning had contributed to the development of a number of chiral polymers for asymmetric reductions. Early work on polymer-bound lithium aluminium hydride chiral complexes [73-75] having afforded results which were vastly inferior to those obtained with many low molecular weight complexes, we undertook a thorough study of the reaction [28]. The chiral auxiliary chosen for this study was cross-linked polystyrene containing (1R,2S)-ephedrine bound through nitrogen to some of its p-methylene-substituted aromatic rings. The chiral reagent is prepared by successive treatment of a solution of lithium aluminium hydride in ether with 2 molar equivalents of an achiral phenol and 1 equivalent of the polymer. The resulting complex is then used in the stoichiometric reduction of a prochiral ketone such as acetophenone (Fig.10).

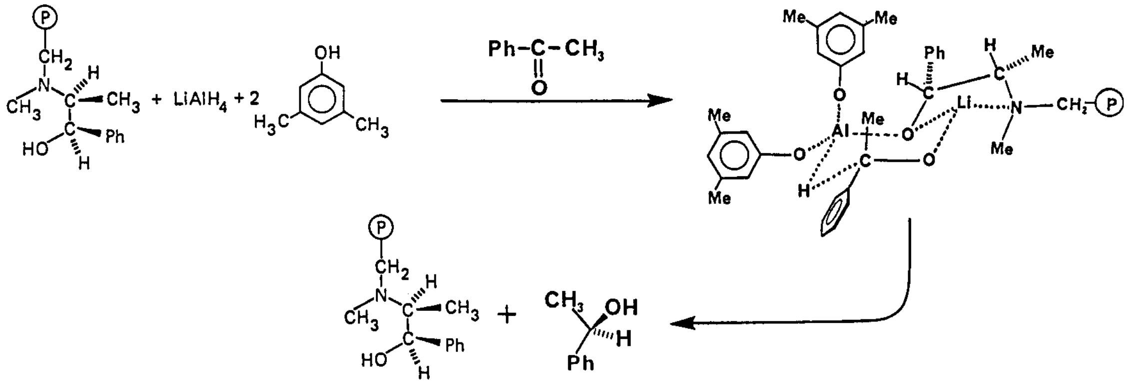

Fig. 10. Asymmetric hydride reduction using a polymeric chiral auxiliary.

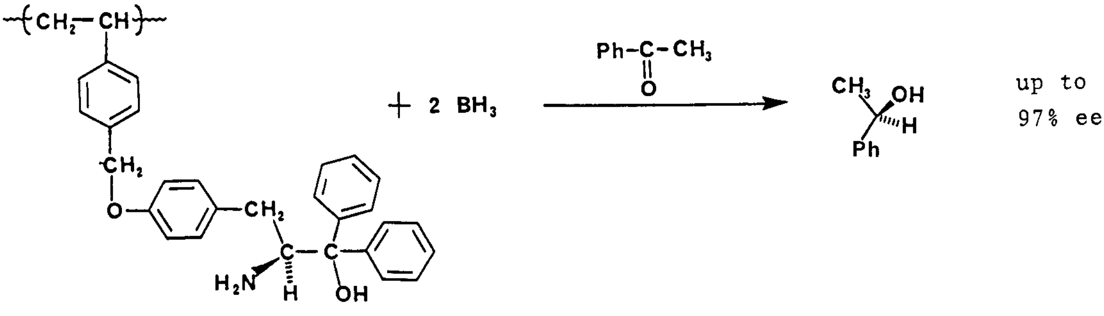

Fig. 11. Asymmetric reduction with a polymeric chiral borane complex.

A series of experiments with various polymers having different degrees of functionalization (DF) showed clearly that there existed an inverse relationship between polymer DF and enantioselectivity. This is due to the interaction of reactive sites in the higher capacity polymers for which selective formation of the desired chiral complex is not favored. This results in binding of the hydride to several rather than to a single chiral center, as well as in the formation of other fully achiral hydride moieties with a concommitant loss of selectivity. However, at lower degrees of functionalization, the polymer-bound species behave independently of one another as is the case with soluble complexes formed with N-benzyl-ephedrine and good selectivity is observed.

A better sytem for polymer-assisted asymmetric reductions has been studied extensively by Itsuno et al. [48]. In this work it was found that the asymmetric reduction of prochiral ketones with complexes formed from certain polymer-bound chiral amino alcohols and borane gave excellent results as the system is free from the type of multiple binding interactions which are prevalent with lithium aluminium hydride complexes. A typical reaction scheme (Fig. 11) involves the formation of an active complex by reaction of the chiral polymer with two molar equivalents of borane. This reagent can reduce aromatic ketones with optical yields approaching 100% [76-77]. An interesting extension of the method is its adaptation to a continuous flow system where borane and ketone are supplied continuously to a specially designed column filled with the chiral polymer which is constantly regenerated in the process [78]. The same polymer-bound borane complex can be used in the reduction of oxime ethers to optically active amines; here again optical yields approach 100%. Although the exact structures of the chiral complexes involved in the reduction of oxime ethers are not clear, the following observations [49, 79] provide some insight in the reaction:

- The reduction is much faster with the amino alcohol-borane than with borane alone.
- The product does not bind to the complex allowing the use of a flow system.
- The chiral complex need not be present in stoichiometric amount if a flow-system is

used, ratios of over 10:1 have produced satisfactory results.
These results are extremely encouraging and suggest that indeed chiral polymers may have a promising future as auxiliaries in asymmetric reaction. This is particularly true for reactions in which the product does not remain attached to the solid chiral complex as these may be adapted to flow systems.

Regenerability in the design of polymeric reagents or protecting groups

Regenerability is a very important consideration in the design of a reactive polymer used as reagent or protecting group in organic synthesis [21]. This is particularly important as, with a few notable exceptions such as the polyvinylpyridines [80-82] most polymeric reagents are not readily available. For example, several years ago, we had prepared a polymeric silylation reagent 4-(chlorodimethylsilyl)polystyrene by reaction of (lithio)polystyrene with an excess of dichlorodimethylsilane [14]. Though this reagent could be used effectively in the protection of alcohols our results were not reported as we found the polymeric reagent lacking in its ability to be regenerated. The main problem was the structural design of the reagent whereby silicon was bound directly to the aromatic rings of the styrenic backbone. As phenyl-silicon bonds are notoriously labile to electrophiles, regeneration of the reagent could not be carried out without observing a drastic lowering of the silicon content of the polymer. This problem can be remedied by using a different design for the reagent in which silicon is not either linked directly to a phenyl ring or placed in a labile benzylic position. This was accomplished [47] by preparing crosslinked beads of 4-[3-(phenyldimethylsilyl)propyl]polystyrene by suspension polymerization of the corresponding monomer with styrene and divinylbenzene the degree of functionalization of the final polymer being a function of the monomer feed ratio. In this case the lability of the phenyl-silicon bond of the pendant group is used to advantage in the subsequent creation of the active center by cleavage with acid to yield the desired silylation reagent. Though cleavage to yield a chlorodimethylpropyl pendant group is possible we opted for the novel trifluoroacetylsilyl group as silylating species. This affords a polymer which reacts well with alcohols and can be used for their temporary protection (Fig. 12). Recycling after cleavage of the alcohol is done easily and quantitatively through trifluoroacetylation or the more usual chlorination. In either case no loss of silicon is observed upon repeated recycling. This example is interesting as it illustrates a design where novel chemistry on a solid polymer was developed without the need for prior "analogous" solution experiments.

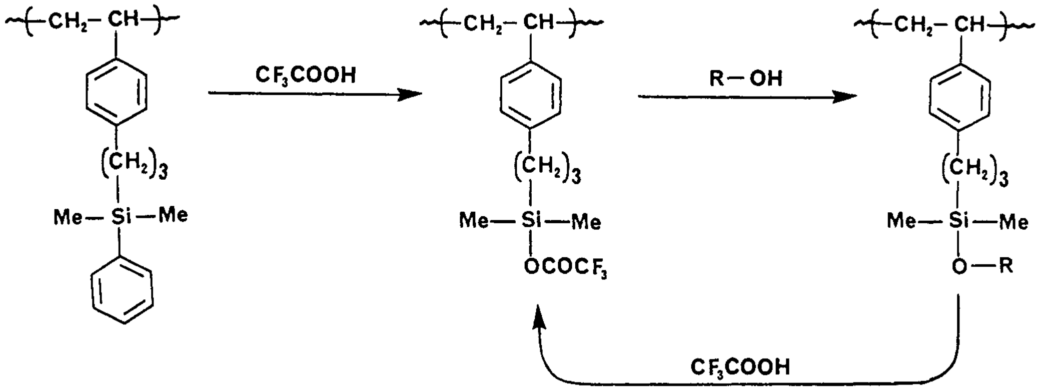

Fig. 12. Regenerable silicon-containing polymeric protecting group.

Use of reactive polymers in the determination of reaction mechanisms

As crosslinked polymers remain insoluble throughout the course of reactions in which they are involved, their confer their insolubility to any reactive species which becomes attached to them during reaction. This phenomenon can be useful in helping to determine the nature of certain reactive intermediates in complex chemical reactions. For example, several groups have used the "three-phase test" involving two reactive polymers suspended in the same medium to determine whether certain intermediates are free or bound in some chemical reactions [83-85].

In the course of our development of new polymer-bound catalysts for asymmetric addition reactions, we have used the insolubility of the polymeric catalyst to determine the mechanism of the addition reaction. The test reaction we studied was the addition of diethylzinc to benzaldehyde [86]; this reaction is catalyzed by a variety of alcohols and amines and we chose to test first the applicability of the polymer-bound ephedrine described earlier [28]. While our work was in progress, several reports from other laboratories on similar diethylzinc addition reactions using soluble catalysts appeared [87-88]. Our findings confirmed that the polymer-bound ephedrine as well as other polymer-bound amino alcohols could be used efficiently as catalysts in this asymmetric addition reaction but the mechanism proposed by others [88] did not match our observations with the insoluble catalyst. Here again, the insoluble nature of the catalyst facilitates the exploration of the reaction mechanism as the distinct phases which can be separated from the reaction mixture at different stages of the reaction provide excellent clues as to the nature of the overall process. In this case, our results show a two zinc species mechanism in which the initially formed polymer-bound zinc complex only acts to bind the aldehyde in a chiral environment while alkyl transfer occurs in enantioselective fashion from unbound diethylzinc.

Development of high activity polymeric supernucleophilic catalysts

The discovery of the remarkable acceleration of acylation reactions by N,N-dimethylaminopyridine catalysts [89] has led to the rapid development of numerous other catalysts with similar structures [90]. As these catalysts are relatively costly and are used in applications where their complete removal from reaction medium after reaction may be required, they are ideal candidates for attachment to insoluble polymer supports. Previous work by several groups [91-95] has confirmed the feasibility of this approach but the polymers which have been reported to-date often lacked in reactivity, stability, or physical properties. We have prepared and studied a number of new catalytic structures, both low molecular weight and polystyrene-based [24, 26-27] and succeeded in producing insoluble polymeric catalysts (Fig. 13) possessing both high reactivities and good chemical stability.

This study also confirms that the small but clearly detectable differences in reactivity behavior between the polymers and model catalysts in solution can be attributed directly to the microenvironment which exists within the polymeric catalysts. Even at moderate degrees of functionalization reactive sites are locally more concentrated in the polymer than would be the case in a homogenous solution. This increases the local polarity at the site of reaction, which, in turn, affects attack of the alcohol on the charged intermediate and causes a small but detectable drop in polymer catalytic activity when compared to the free models in solution. Similarly, in a less favorable polar reaction medium the polymer shows a relative enhancement in its activity when compared to the free catalyst as the local (styrenic) environment of the catalytic sites provides a 'polarity shield' which cannot be imitated in homogeneous medium. Overall, this study confirms the potential usefulness of polymeric acylation catalysts and the importance of spacer groups and microenvironment considerations in the structural design of the catalysts.

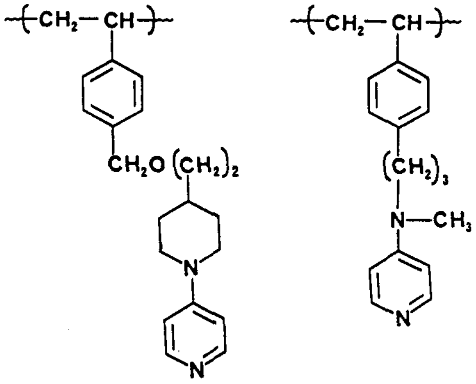

Fig. 13. Supernucleophilic catalyst resins

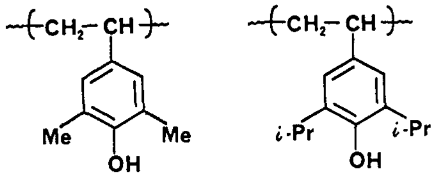

Fig. 14. New phenolic separation media

New reactive polymers as media for HPLC column packings

Though a large variety of sorbents for HPLC have been described in recent years, the vast majority of these are based on inorganic matrices such as silica. Numerous sorbents containing bound organic groups have been prepared [96] but all silica-based media suffer from the same limitation which is their lack of stability at high pH. This has led to the development of more chemically inert polymer-based sorbents such as the macroporous styrene-divinylbenzene resins [97], ion-exchange resins [98-99], or a variety of methacrylic resins [100-102]. With very few notable exceptions, little work has been done in the specific development of reactive resins suitable for HPLC though there may be significant advantages in their use for specialized separations as materials with very specific interactions and excellent chemical resistance could result.

We have undertaken [45] the development of macroporous resins based on styrene monomers containing free phenolic groups. These materials are expected to show interesting properties in their interactions with a variety of substrates of different acidities. In view of the complications which arise in the free-radical polymerization of vinyl-phenols, the monomers we chose all had their phenolic hydroxyls protected as the t-butyloxycarbonyl (t-BOC) derivative. As was seen above, this t-BOC protecting group is removed easily by acid or base hydrolysis or by thermolysis near 190°C. In general, purification of small 5-$10\mu m$ beads after their preparation by suspension polymerization or after their chemical modification (i.e. deprotection) is a very tedious operation. In this instance however, the use of a thermally labile protecting group facilitates greatly the preparation of HPLC-grade beads as no purification is required after removal of the t-BOC groups since all the by-products of the deprotection are gaseous. The variables which control the size, surface area, pore size, and pore size distribution for bead polymers have been explored in detail in an excellent study by Svec and coworkers [102] dealing with glycidyl methacrylate-ethylene dimethacrylate resins. Though not directly applicable to all monomer systems their findings are extremely useful and may be adapted in the determination of the relative proportions of the various components in the polymerization mixture, the choice of porogen, etc. Using such techniques and a variety of other t-BOC protected derivatives of 2,6-dialkyl-4-vinyl-phenols a number of new 5-10μm size higly porous polymeric adsorbents of various acidities (Fig.14) have been prepared and shown to be effective in HPLC separations.

Other developments in reactive polymers

Reactive polymers are increasingly finding new applications as specialty materials in a great variety of applications which cannot be discussed here. These include among others, new generations of membrane materials which show excellent chemical or size selectivity, polymer-assisted transport systems, specialty binder materials, photoresists and other imaging systems [103], photo- or electroconductive materials, etc. As these increase in importance the field of reactive polymers will continue to evolve and grow in many new directions.

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