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Solid-phase synthesis has developed rapidly in recent years. It is widely used in the pharmaceutical industry for the syntheses of biooligomeric molecules, some small molecules, and combinatorial chemistry as well. Polymeric reagents are currently playing an important role in solid-phase synthesis.

A polymeric reagent, polymer-supported diphenylphosphoryl azide (DPPA), was prepared from phenol resin. The conversion from phenol resin to polymer-supported DPPA is about 80% efficient. This polymer-supported version of DPPA is useful due to its lower toxicity, moisture tolerance and ease of workup after reaction.

The synthetic application of this solid-phase reagent was explored by conversion of a variety of carboxylic acids to urethanes and ureas through Curtius rearrangement reactions. Carboxylic acids bearing different functional groups (aromatic, aliphatic and heterocyclic carboxylic acids) were subjected to the reactions. The corresponding products were isolated with satisfactory yields. By using this polymer-supported DPPA, oxazolidinone, imidazolidinone and thiazolidinone derivatives were also successfully prepared from carboxylic acids with different reactive functional groups in the β position, such as alcohols, thiols and primary or secondary
amines. The desired compounds were obtained in good yields via Curtius rearrangement and subsequent intramolecular cyclization.

This polymer-supported DPPA was further used in the divergent syntheses of polyurethane dendrimers. Purification became easier in the synthesis because a simple filtration could remove DPPA and all other phosphorous derivatives. Four molecules with different sizes, branching numbers and polarity were used as core molecules. Solvent selection was also considered in the synthesis. All the molecular weights of these polyurethane dendrimers were determined by MALDI-TOF Mass Spectra, which established the formation of the dendrimers. The diameters of all polyurethane dendrimers were calculated using Chem3D Ultra based on PM3 (semi-empirical level) optimized structures.

Other solid-phase reagents were studied as well. Polymer-bound organosilicon reagents, such as silyl ketene, silyl azide and silyl cyanide, were converted from a polymer-boundtrialkylsilyl chloride. Applications of these organosilicon reagents were carried out using classical organic reactions. Solid phases were compared between polystyrene resin, Si-dimethylsilyl derivatized silica gel and TentaGel-S-Br. The feasibility of further development of these reagents was established.
POLYMERIC REAGENTS IN SOLID-PHASE SYNTHESSES OF SMALL MOLECULES AND DENDRIMERS

A DISSERTATION

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<td>( t )-Butoxycarbonyl</td>
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<tr>
<td>CBZ</td>
<td>Carbobenzyloxy</td>
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<td>DCC</td>
<td>Dicyclohexylcarbodiimide</td>
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<tr>
<td>DCL</td>
<td>Dichloroacetic acid</td>
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<td>DMT</td>
<td>Dimethoxytrityl</td>
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<td>DPPA</td>
<td>Diphenylphosphoryl azide</td>
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<td>DVB</td>
<td>Divinylbenzene</td>
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<td>FmOH</td>
<td>9-Fluorenemethanol</td>
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<td>FT-IR</td>
<td>Fourier Transform-Infrared spectroscopy</td>
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<td>HPLC</td>
<td>High-performance liquid chromatography</td>
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<td>LCT</td>
<td>Electrospray time-of flight</td>
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<td>MALDI-TOF</td>
<td>Matrix-assisted laser desorption/ionization-time of flight</td>
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<td>MAS NMR</td>
<td>Magic angle spinning NMR</td>
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<td>NMP</td>
<td>( N )-Methylpyrrolidinone</td>
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<td>NMR</td>
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<td>Pip.</td>
<td>Piperidine</td>
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<td>PS</td>
<td>Polystyrene</td>
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<tr>
<td>TLC</td>
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Chapter I. Solid-phase synthesis and reagents

Chemical reactions can be divided into two main classes: one is the homogeneous reaction, which takes place in a single phase; the other is the heterogeneous reaction, which happens at the interface of two phases. There is a specific family of heterogeneous reactions in which the reagents are linked to various solid supports via different chemical functionalities. Multistep reactions then take place on the solid phase which cause the conversion from starting materials to the target compounds. Finally the cleavage of the target molecules from the solid phase completes the reactions. This technique is commonly referred to as solid-phase synthesis.¹

Solid-phase reagents are currently enjoying a renaissance in organic chemistry and play an important role in solid-phase synthesis. Because of the attachment of the chemical reagents to an insoluble polymer matrix, an excess of the polymer-supported reagent can be added into the reaction, allowing more efficient reactions of the reactants. After reaction, a simple filtration process can provide the new product in both high yield and purity. Sometimes the spent polymer-supported reagents can be recovered, which also leads to the potential for its recycling, thus meeting the requirements of modern environmentally friendly chemistry. Although solid phase reagents haven’t been well-developed, the power and elegance of this approach has been demonstrated by S. V. Ley, who reported the first total syntheses of three natural products using a sequence of polymer-supported reagents.²
1-1. Background

Solid-phase synthesis was first introduced in 1963 by R. B. Merrifield for the efficient preparation of a tetrapeptide on a polymer support that remains insoluble throughout the synthesis (Figure 1). It involved the stepwise addition of N-protected amino acids and the deprotection to a polypeptide chain which was bound by a covalent bond to the solid support. This provided a procedure in which reagents and by-products were removed by filtration, and the purification of the intermediates was eliminated. The desired peptide was eventually removed from the solid support by cleavage of the ester linkage and isolation by filtration.

![Figure 1. Merrifield’s synthesis of an oligopeptide.](image)

One of the important reasons for the development of solid-phase methodology was to overcome the technical difficulties associated with the solubility and purification of growing peptide chains in solution. The advantages of solid-phase synthesis were speed and simplicity of operation. On the solid phase, purification can be simply operated by washing the resin with a variety of
solvents, allowing any unbound impurities to be dissolved and washed away. After cleavage of the final products, the solid supports can be removed by filtration. Therefore, the development of improved solid-phase syntheses focuses on chemical reactions of substrates attached to solid supports, including methods for attachment and detachment from supports.

Solid-phase synthesis has rapidly become a standard technology for the preparation of oligopeptides and other polymer syntheses, such as polynucleotides and oligosaccharides. In 1985, M. H. Caruthers described the solid-phase synthesis of a dinucleotide (Figure 2), using a deoxynucleoside covalently joined to silica gel through an amide bond. The amount of deoxynucleoside that can be immobilized on silica is convenient for synthesizing both the minimal quantities of DNA required for biological studies and the large amounts required for biophysical research.

![Caruthers’ solid-phase synthesis of a dinucleotide.](image)

In 1993, S. J. Danishefsky and his coworkers developed a strategy for the solid-phase synthesis of oligosaccharides (Figure 3). Among the three major classes of biooligomers, the synthesis of polysaccharides has proven to be the most difficult. In the syntheses of polypeptides and poly(2-
deoxynucleotides), there is no stereochemistry in the amide and the phosphate bonds. In contrast, each glycosidic bond makes the chemistry of this class more challenging due to problems of regio- and chemoselectivity as well as availability of suitable building blocks and overall complexity. Even today, this class is underexploited.

![Figure 3. Danishefsky’s synthesis of oligosaccharides with polymer-bound glycals.](image)

In all these biooligomer syntheses, there are only two reactions, bond formation and deprotection, that need to be optimized. The solid-phase organic synthesis of nonoligomeric small organic molecules is quite different. In organic reactions (even a short synthesis), different reaction conditions and workup procedures may be required for each step. Therefore, solid-phase organic synthesis of non-oligomeric molecules has received less attention until the recent emergence of combinatorial chemistry, which synthesizes large collections of diverse molecules in parallel. J. G. Breitenbucher and H. C. Hui reported the solid-phase synthesis of a medium-large discrete library of 8448 benzopyrans using the reductive amination cocktail formed from
titanium isopropoxide and sodium triacetoxyborohydride (Figure 4). The benzopyran scaffold is present in a number of biologically active compounds, and this library was tested in several biological assays.

**Figure 4.** Solid-phase synthesis of the benzopyran library.
Combinatorial technology appeared and developed very recently; however, it has rapidly attracted great interest among an enormous number of research workers. The advent of high throughput and automated techniques has facilitated the synthesis of large collections of different compounds, related by a structure type, rapidly and efficiently. In combinatorial chemistry, reaction conditions should be chosen carefully to decrease by-product formation. With the additional use of solid-phase synthesis, combinatorial methodologies allow for the products to be automatically separated from all other residues in the solution by attachment to the resin, facilitating the removal of reagents and by-products by a simple filtration step. Moreover, A. Furka et al applied “mix and split” solid-phase protocol, by which the problem of differences in reagent reactivity can be overcome. Solid-phase synthesis for the preparation of small molecules has been a crucial step in the development of combinatorial synthesis, which has wide applications in the pharmaceutical industry and other fields (Figure 5). It seems inevitable that
the attention and development of solid-phase organic synthesis will continue to expand rapidly over the next decade as researchers explore the scope of this technique.

1-2. Significance and limitations of solid-phase organic synthesis

Many of the advantages of solid phase synthesis and reagents have been exploited. The convenience of purification by filtration is the most important, since it simplifies the processing of organic reactions. Meanwhile, excesses of solution-phase reagents can often be used in solid-phase synthesis since they can easily be removed, meaning that reactions can often be driven to completion with higher yields. Compared to solution-phase reactions, solid-phase reactions have the ability to isolate product molecules present in low concentrations from excesses of starting materials, since the products are attached on the solid support. Furthermore, the ease of automation is synthetically useful and meaningful in both research labs and industry.

The use of polymer supports in solid phase organic synthesis inevitably has its limitations. Since the reaction conditions required are generally different from those of classical solution-phase chemistry, solid-phase synthesis can not be applied in all kinds of reactions, even theoretically. Classic heterogeneous reactions, such as heterogeneous catalysis, have not been easily used on a solid support. Moreover, traditional methods of analysis are limited in identifying the products on a solid phase matrix due to the presence of the solid support, although improvements are being made (e.g. MAS gel phase NMR). The small quantity of bound molecules on the solid support is another limitation restricting the wide application of solid-phase organic synthesis. More methodology suitable for solid-phase synthesis is needed.
1-3. Basic principles of solid-phase organic synthesis and reagents

The main differences between solid-phase synthesis and organic synthesis in solution focus on four parts, including (i) the types of solid supports, (ii) the linkers used to anchor compounds to the supports, (iii) monitoring reactions on solid phase, and (iv) purity and yield determination of solid-phase reactions.¹

1-3-1. Solid supports

The most commonly used solid supports in solid-phase synthesis are hydrophobic polystyrene (PS) resins, which consist of PS with 1-2% divinylbenzene (DVB) as crosslinking agent.¹³ One important factor in the reactivity on solid supports is the swelling of the resins. Swelling heavily depends on the solvent and the percentage of crosslinking of the resin. PS resins swell in most solvents, especially in apolar solvents, and behave as gels; thus the reaction with reagents in solution is facilitated by access to the inner sites of the resin, improving the reactivity. PS resins are cheap and commercially available with many different functional groups at a good loading level (in the range of 1 mmol/g).

PS resins swell poorly in polar protic solvents. To overcome this drawback, a polyethylene glycol (PEG) chain grafted to the PS resin was developed.¹⁴ This hybrid solid support provides the applications of solid-phase synthesis in hydrophilic solvents. Recently, a family of nonswelling macroporous resins was introduced for solid-phase synthesis, allowing many
different experimental conditions to be used. In addition, gel-like soluble supports and high-loading dendrimer supports are also being used more and more.

1-3-2. Linkers

A linker is required to connect the target molecule to the solid support in solid-phase synthesis. A good linker should be easy to prepare and to cleave from the target molecules. It should be stable to all the reaction conditions in the synthesis, but specifically sensitive to cleavage reagents and conditions. A good linker should not bring any troublesome by-product into reactions. And ideally, a good linker should release different product with different cleavage reagents and conditions are used.

Many families of solid-phase linkers are currently used in solid-phase synthesis and solid-phase reagents, which can be classified according to reaction conditions used for their cleavage, such as acid- and base-labile linkers, photolabile linkers, safety-catch linkers and so on. A major drawback to all of these linkers is a functional group will be brought onto the solid phase, which may have a negative effect on some biological or chemical activities of the target molecule. Recently traceless cleavage has become a major area of interest in solid-phase linker chemistry, in which a functional group is excised leaving behind no trace or “memory” of the solid-phase synthesis. The most widely exploited class of traceless linkers are those based on silicon chemistry. In 1995, the first two linkers of this variety were developed independently by M. J. Plunkett and J. A. Ellman and B. Chenera et al (Figure 6). Later, a traceless linker as a silyl ether was developed by T. L. Boehm and H. D. H. Showalter who utilized a mild fluoride-
mediated desilylation as a cleavage mechanism. More recently, polymer-supported rhodium carbenoids, derived from α-diazo-carbonyl compounds, were used for the traceless synthesis of furans by cycloreversion chemistry. A so-called cyclative cleavage, in which the last solid-phase synthesis step simultaneously cyclizes and cleaves the final compound from the solid support, was also developed. A large number of additional examples of cyclative cleavage approaches to a wide panel of isolated and condensed ring systems were summarized in a recent review.

![Figure 6. Traceless linkers based on silyl chemistry.](image)

**Figure 6.** Traceless linkers based on silyl chemistry.

### 1-3-3. Reaction monitoring

In organic synthesis, reaction monitoring is very important in order to optimize the yields of target molecules and minimize by-products. The traditional monitoring methods in solution phase reactions are thin-layer chromatography (TLC), high-performance liquid chromatography
(HPLC) or gas chromatography (GC), which are used to monitor the disappearance of the starting materials. However, these methods do not work very well in solid-phase synthesis, because excess reagents are always used in solid-phase synthesis. Alternative methods used for monitoring the reactions on solid supports are divided into off-bead and on-bead methods.

Off-bead methods are those usually used in classical organic chemistry. It is an accurate way to monitor the reactions, where the polymer-bound reaction products are cleaved from the support with subsequent analysis of the cleavage solution. However, the cleavage may take too much time, lose compounds, or introduce misinterpretation of the reaction outcome. Therefore, these limitations encouraged the development of fast, reliable and sensitive on-bead monitoring methods.

There are several on-bead methods. Colorimetric/Fluorescence detection uses colored reagents to detect the appearance or the disappearance of a functional group on solid support. Infrared Spectroscopy (IR) is the most frequent reaction monitoring technique to detect the change of a functional group. Nuclear Magnetic Resonance Spectroscopy (NMR), especially gel-phase NMR techniques, has specific applications in the determination of structure and the measurement of purity and yields of the target molecules in solid-phase synthesis. Finally, Mass Spectrometry (MS), which has recently become possible through the use of Matrix-Assisted Laser Desorption/Ionization-Time of Flight (MALDI-TOF) mass spectrometry, allows in situ cleavage of a small number of resin beads.
1-3-4. Purity and yield determination

The determination of the reaction yields carried out in the solid-phase synthesis and the structures and purity of the products is an essential component of the process of solid-phase synthesis. Usually the same analytical methods for reaction monitoring are used, but their usefulness for qualitative analysis may vary. It seems that the use of MAS NMR-related analytical techniques for quantitative solid-phase synthesis analysis will become more widespread in the future.\(^3\)

1-4. The future of solid-phase synthesis and solid-phase reagents

Solid-phase synthesis attracted the attention of pharmaceutical companies as a strategy for increasing synthetic throughput. Empirical evidence of interest of solid-phase synthesis is shown in Figure 7. From 1995 to 1999, the number of references to solid-phase synthesis increased 5-fold. During the same period, references to total synthesis remained consistent while the number of citations to asymmetric synthesis declined dramatically. Since 1999, the number of solid-phase synthesis references has declined slightly, suggesting that interest in this area has reached a plateau. More significant are the reports from numerous pharmaceutical companies that solid-phase synthesis has largely been replaced by solution-phase parallel synthesis as the technique of choice for library construction.\(^3\)
Figure 7. Reference counts in CAS for the keywords ‘total synthesis’, ‘solid phase synthesis’ and ‘asymmetric synthesis’ over the period 1990 to 2001.

Solid-phase synthesis looked set to revolutionize small molecule synthesis, but this early promise has not reached fruition. What factors will affect the future of solid-phase synthesis and solid-phase reagents? There are two contexts: ‘macroscopic’ (relating to organizational, infrastructure and skill set issues) and ‘microscopic’ (relating to solid-phase chemistry). These two issues need to be addressed before solid-phase synthesis can achieve its full potential in drug discovery.
References


Chapter II. Preparation and applications of polymer-supported diphenylphosphoryl azide (DPPA)

2-1. Introduction

During the period of 1885-1900, the study of isocyanates started. Soon after, their use in industrial applications was recognized. A great number of methods for the preparation of isocyanates has been reported in the literature. The most common method of preparing isocyanates involves the reaction between an amine or its salt and phosgene. Curtius, Hofmann, or Lossen rearrangements and double decomposition reactions are widely used as well.\(^1\)

2-1-1. Curtius rearrangement

The decomposition of acyl azides to isocyanates and nitrogen is known as the Curtius rearrangement. The reaction is a preparative method for isocyanates and for compounds derivable from isocyanates, such as urethanes, ureas, amides and amines. The method was first developed to a considerable extent by Schroeter, who prepared several isocyanates by treating an acid chloride with sodium azide and warming the resulting product in benzene solution. Curtius has used the method for the preparation of substituted ethylene diisocyanates. The intermediate diazide can be prepared by treating substituted succinic hydrazides with nitrous acid. Yields from the reaction are usually good, as in the case of undecyl isocyanate, which was obtained in 81-86% yield. A complete survey of such preparations reported in the literature was given by Smith (Figure 8).\(^2\)
Carboxylic acids and their derivatives can be converted to amines through Curtius rearrangement. In 1972, S. Yamada and coworkers used diethylphosphoryl azide to replace sodium azide as a modified azide to conduct Curtius reactions under mild reaction conditions. In 1974, diphenylphosphoryl azide (DPPA) was used to make the Curtius reaction more efficient (Figure 9).
**2-1-2. Solid-phase Curtius rearrangement**

The use of polymers to assist the Curtius reaction recently became popular in drug delivery and combinatorial chemistry. Several reports of polymer-bound carboxylic acids undergoing rearrangement to polymer-bound isocyanates have appeared which led to a large number of small molecule libraries (Figure 10). Papers describing polymer-bound nucleophiles scavenging isocyanate intermediates generated by the Curtius reaction were published as well.

![Figure 10. Polymer-bound isocyanates to form small molecule libraries.](image)

**2-1-3. Diphenylphosphoryl azide (DPPA)**

DPPA is a useful and versatile reagent in organic synthesis. It has been used for racemization-free peptide syntheses, thiol ester synthesis, a modified Curtius reaction, C-acylation of active methylene compounds, esterification of an α-substituted carboxylic acid, formation of diketopiperazines, an alkyl azide synthesis, phosphorylation of alcohols and amines, and polymerization of amino acids and peptides. Furthermore, DPPA acts as a nitrene source and as a
1,3-dipole. The ring contraction of cyclic ketones to form cycloalkanecarboxylic acid was also completed using DPPA.\(^8\)

However, toxicity considerations limit the usage of DPPA and cause environmental problems. The high boiling point of DPPA creates additional difficulties in workup and purification after reactions. The relative sensitivity of DPPA to moisture and oxidizing agents also adds the requirement of careful storage. Recent technological advancements in polymer-supported reagents provide solutions to these problems.\(^9\)

2-2. Preparation of polymer-supported diphenylphosphoryl azide (DPPA)

To solve the problems brought by DPPA in organic synthesis, polymer-supported DPPA was synthesized (Figure 11). Phenol resin (1.5 mmol/g, Advanced ChemTech) was first swelled in CH\(_2\)Cl\(_2\) under a nitrogen atmosphere for 5 minutes, then 5.0 equivalents of phenyl dichlorophosphate was added at room temperature and the mixture was stirred for 8 hours.\(^10\)

After removal of excess phenyl dichlorophosphate by a simple wash with CH\(_2\)Cl\(_2\) under nitrogen atmosphere, the polymer-bound phosphoryl chloride resin (1) was converted to polymer-supported DPPA (2) by treatment with 3.0 equivalents of NaN\(_3\) and 3.0 equivalents of crown ether (15-crown-5) in CH\(_2\)Cl\(_2\) and refluxing for 24 hours.\(^11\) The crown ether was a necessary phase-transfer reagent to provide maximum reaction efficiency. The excess NaN\(_3\) and crown ether were removed by filtration and washing with CH\(_2\)Cl\(_2\) and a small amount of distilled water. After drying under vacuum overnight, the polymer-supported DPPA was ready to use. In comparison to phenol resin, the FT-IR spectrum of polymer-supported DPPA shows a strong
azide absorption peak at 2168 cm\textsuperscript{-1}, which is identical to that of DPPA. This polymer-supported DPPA is quite stable at room temperature. There is no obvious change observed in the IR spectrum after one month of storage in air.\textsuperscript{12}

![Figure 11. Synthesis of polymer-supported DPPA.](image)

## 2-3. Applications of polymer-supported DPPA

The synthetic use of polymer-supported DPPA was explored by converting a variety of carboxylic acids to urethanes or ureas through Curtius reaction under standard reaction conditions. Furthermore, polymer-supported DPPA was used in preparations of oxazolidinone, imidazolidinone and thiazolidinone derivatives.

### 2-3-1. Preparation of urethanes and ureas

The preparation of urethanes and ureas was started from the swelling of polymer-supported DPPA (1.0 eq, based on fully azide-loaded resin) in benzene under a nitrogen atmosphere. To this suspension, 1.2 equivalents of carboxylic acid and 1.4 equivalents of Et\textsubscript{3}N were added. The mixture was heated to reflux for 30 minutes to form an isocyanate. 1.7 equivalents of alcohol was then added and the reaction was heated at reflux for 24 hours. After cooling to room temperature, the solid phase, including unreacted DPPA and phosphorous derivatives still linked
to the resin, was removed by filtration and washing. The combined filtrates were washed and
dried to afford the desired product (Figure 12). Carboxylic acids bearing different functional
groups (aromatic, aliphatic and heterocyclic carboxylic acids) were subjected to intermolecular
Curtius reactions with polymer-supported DPPA, and the corresponding urethanes and ureas
were obtained. The results of Curtius rearrangements with polymer-supported DPPA on aromatic
carboxylic acids are listed in Table 1. Since the reaction conditions haven’t been individually
optimized, the current overall yields after two steps (synthesis of polymer-supported DPPA and
preparation of urethane or urea) are satisfactory. (yield: 36% – 80%). Table 2 shows the results
of Curtius rearrangement with polymer-supported DPPA on aliphatic carboxylic acids. The
percentage yields of the aliphatic products are a little lower than those on aromatic carboxylic
acids. This is reasonable because Curtius rearrangements on aliphatic acids are known to be not
as efficient as these on aromatic acids. In conclusion, either aromatic or aliphatic carboxylic
acids with different functional groups react with polymer-supported DPPA readily and
subsequently undergo Curtius rearrangements to produce urethanes and ureas.

![Figure 12. Preparation of urethanes and ureas through intermolecular Curtius rearrangement with polymer-supported DPPA.](image)
<table>
<thead>
<tr>
<th>Entry</th>
<th>RCOOH</th>
<th>R’OH (or R”OH)</th>
<th>Product</th>
<th>Yield $^{a,b}$ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Benzoic acid</td>
<td>EtOH</td>
<td>![Image]</td>
<td>53$^{13}$</td>
</tr>
<tr>
<td>2</td>
<td>$o$-Anisic acid</td>
<td>EtOH</td>
<td>![Image]</td>
<td>72$^{13}$</td>
</tr>
<tr>
<td>3</td>
<td>$p$-Nitrobenzoic acid</td>
<td>EtOH</td>
<td>![Image]</td>
<td>80$^{13}$</td>
</tr>
<tr>
<td>4</td>
<td>Picolinic acid</td>
<td>EtOH</td>
<td>![Image]</td>
<td>48$^{14}$</td>
</tr>
<tr>
<td>5</td>
<td>$o$-Anisic acid</td>
<td>Dodecanol</td>
<td>![Image]</td>
<td>52$^{12}$</td>
</tr>
<tr>
<td>6</td>
<td>Terephthalic acid $^c$</td>
<td>EtOH</td>
<td>![Image]</td>
<td>36$^{15}$</td>
</tr>
<tr>
<td>7</td>
<td>$p$-Nitrobenzoic acid</td>
<td>Octylamine</td>
<td>![Image]</td>
<td>41$^{16}$</td>
</tr>
</tbody>
</table>

$^a$ Isolated yields after column chromatography, based on fully azide loaded resin. An excess of carboxylic acid was used in the reactions to calculate the yields after two steps. $^b$ All the product exhibited physical and spectral (NMR, IR and MS) properties in accord with the assigned structures. $^c$ The ratio between polymer-supported DPPA and terephthalic acid is 2.2 : 1.
Table 2. Urethane or urea prepared from aliphatic carboxylic acids with polymer-supported DPPA

<table>
<thead>
<tr>
<th>Entry</th>
<th>RCOOH</th>
<th>R’OH (or R”OH)</th>
<th>Product</th>
<th>Yield a,b(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>p-Tolylacetic acid</td>
<td>EtOH</td>
<td><img src="image1.png" alt="Image" /></td>
<td>46 17</td>
</tr>
<tr>
<td>2</td>
<td>Butyric acid</td>
<td>Phenol</td>
<td><img src="image2.png" alt="Image" /></td>
<td>52 18</td>
</tr>
<tr>
<td>3</td>
<td>Decanoic acid</td>
<td>Benzyl alcohol</td>
<td><img src="image3.png" alt="Image" /></td>
<td>34 19</td>
</tr>
<tr>
<td>4</td>
<td>4-Acetylbutyric acid</td>
<td>2-Propanol</td>
<td><img src="image4.png" alt="Image" /></td>
<td>47 12</td>
</tr>
<tr>
<td>5</td>
<td>trans-Cinnamic acid</td>
<td>t-Butanol</td>
<td><img src="image5.png" alt="Image" /></td>
<td>54 5</td>
</tr>
<tr>
<td>6</td>
<td>Butyric acid</td>
<td>Aniline</td>
<td><img src="image6.png" alt="Image" /></td>
<td>45 20</td>
</tr>
</tbody>
</table>

a Isolated yields after column chromatography, based on fully azide loaded resin. An excess of carboxylic acid was used in the reactions to calculate the yields after two steps. b All the product exhibited physical and spectral (NMR, IR and MS) properties in accord with the assigned structures.

2-3-2. Preparation of N-heterocyclic rings

Syntheses of N-heterocyclic rings have been studied for some time. These sorts of compounds, including oxazolidinones, have received increased attention since they are known to be the core structural units of compounds with antibacterial, antiallergenic and immunosuppressant activities. In recent years, solid-phase supported synthesis has proven to be an efficient technique.
for the preparation of a large number of heterocyclic compounds, in response to increasing interest from the pharmaceutical industry in the generation of diverse libraries of heterocyclic compounds.\textsuperscript{24} Herein, polymer-supported DPPA was used to prepare a variety of heterocyclic compounds (Table 3).\textsuperscript{25}

Salicylic acid, anthranilic acid and their derivatives were the first candidates for evaluation of cyclization reactions with polymer-supported DPPA and Et\textsubscript{3}N in benzene (Figure 13, Entries 1-4 in Table 3). The two functional groups, a carboxylic acid and a hydroxyl (or amino) group in the ortho-position, are poised to form a five-membered ring following Curtius rearrangement. Since the azide loading on polymer beads was not normally assayed for each run, a slight excess of the acid was used. The reactions were heated to reflux for 24 hours. After workup, the crude products were obtained with acceptable quality (95% pure). Column chromatography was performed to obtain pure bicyclic oxazolidinone and imidazolidinone derivatives. The yields ranged from 53\% to 75\% after chromatography, based on the resin as the limiting reagent.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure13.png}
\caption{Preparation of oxazolidinone and imidazolidinone derivatives from salicylic acid, anthranilic acid and their derivatives with polymer-supported DPPA.}
\end{figure}

Encouraged by these results, further applications of polymer-supported DPPA were explored on various amino acids (Figure 14, Entries 5-7 in Table 3). \textit{L}-Serine, \textit{L}-threonine and \textit{L}-cysteine were selected because their structural characteristics led to the formation of five-membered
rings. The free amino acids were first protected as their BOC-derivatives by treating amino acids with di-tert-butyl dicarbonate in 10% solution of Et$_3$N in MeOH. BOC-protected amino acids were used because they offer better solubility than free amino acids in organic solvents. Additionally, the bulky BOC group also reduced the possibility of intermolecular reactions, and increased the possibility of intramolecular reactions to form desired five-membered rings. The BOC-protected amino acids were heated with polymer-supported DPPA and Et$_3$N at reflux in 1,4-dioxane for 24 hours. Following the general workup procedure, the crude products were obtained in 98% purity. Purification by column chromatography afforded the pure oxazolidinone and thiazolidinone derivatives with yields from 59% to 67%. Considering the mechanism of Curtius rearrangement, the chiral centers in these amino acids should be retained. While the cyclization products are optically active, their optical purity was not assessed. In the case of threonine (R = CH$_3$, X = O), the diastereomer with the indicated cis orientation of substituents is the only product observed by NMR spectroscopy, since the coupling constant is 7.3 Hz.

![Chemical reaction diagram](image)

$X = O, S; \quad R = H, Me$

**Figure 14.** Preparation of oxazolidinone and thiazolidinone derivatives from BOC-protected amino acids with polymer-supported DPPA.

While the trapping of isocyanate formed in the Curtius rearrangement usually makes use of alcohols and primary amines, we investigated a secondary amine in our reaction (Figure 15, Entry 8 in Table 3). 3-Benzylaminopropionic acid was prepared by the reaction between benzylamine and acrylic acid in THF. After filtration, the white solid was partitioned between
ether and NaOH solution. The separated aqueous phase was acidified with HCl to pH = 2. After vacuum evaporation, a mixture of 3-benzylaminopropionic acid and NaCl was obtained as white solid.\(^{28}\) This crude product was used directly in the subsequent reactions. Heating 3-benzylaminopropionic acid with polymer-supported DPPA and Et\(_3\)N in 1,4-dioxane for 24 hours followed by workup and column chromatography purification afforded pure 1-benzylimidazolidin-2-one in 53% yield.

![Figure 15. Preparation of 1-benzylimidazolidin-2-one by using polymer-supported DPPA.](image)

In addition, \(N\)-CBZ-\(\gamma\)-amino-\(n\)-butyric acid was used in an attempt to form the six-membered ring system. However, lactam formation through intramolecular cyclization was the major product (> 90% from \(^1\)H NMR spectrum, Figure 16, Entry 9 in Table 3). It would appear that trapping of the intermediate phosphoryl anhydride before rearrangement predominates when five-membered ring formation can occur. In the previous entries, such a process would afford a \(\beta\)-lactam, a clearly disfavored process.

![Figure 16. Competitive reactions between solid-phase reaction and solution-phase reaction.](image)
Table 3. N-Heterocyclic derivatives synthesized by polymer-supported DPPA

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reactant</th>
<th>Product</th>
<th>Yield $^{ab}$(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>COOH</td>
<td>OH</td>
<td>69$^{13}$</td>
</tr>
<tr>
<td></td>
<td>MeO-COOH</td>
<td>HN</td>
<td>53$^{29}$</td>
</tr>
<tr>
<td>3</td>
<td>COOH</td>
<td>NH$_2$</td>
<td>75$^{13}$</td>
</tr>
<tr>
<td>4</td>
<td>Cl-COOH</td>
<td>NH$_2$</td>
<td>64$^{30}$</td>
</tr>
<tr>
<td>5</td>
<td>HO-COOH</td>
<td>HN Boc</td>
<td>60$^{31}$</td>
</tr>
<tr>
<td>6</td>
<td>HO-COOH</td>
<td>HN Boc</td>
<td>59</td>
</tr>
<tr>
<td>7</td>
<td>HS-COOH</td>
<td>HN Boc</td>
<td>67</td>
</tr>
<tr>
<td>8</td>
<td>Ph-COOH</td>
<td></td>
<td>53$^{32}$</td>
</tr>
<tr>
<td>9</td>
<td>Ph$_2$CO-NH-COOH</td>
<td></td>
<td>&lt; 10$^c$</td>
</tr>
<tr>
<td></td>
<td>Ph$_2$CO-NH-</td>
<td></td>
<td>&gt; 90$^c$</td>
</tr>
</tbody>
</table>
The azide loading of polymer-supported DPPA is hard to analyze. Both on-bead and off-bead methods do not work very well, thus we have to select an original approach by using parallel reactions to estimate the azide loading. First, we chose a relatively efficient Curtius reaction ($p$-nitrobenzoic acid and $t$-BuOH) from S. Yamada’s paper as the model reaction, having a yield of 84%. We repeated this reaction with traditional liquid DPPA several times to confirm that the 84% yield of this reaction was reliable and repeatable. Then, we started 9 parallel reactions where a mixture of 0.25 g of polymer-supported DPPA, 1.5 mL of $t$-BuOH and 0.3 mL of Et$_3$N in benzene was refluxed with varying amount of $p$-nitrobenzoic acid (Table 4). The $p$-nitrobenzoic acid was progressively increased in amount from 0.05 to 1.00 mmol in these 9 parallel reactions. Following normal workup procedure, the amount of the carbamate was analyzed (Figure 17). From the curve in Figure 17, we know the yields of products increased until it reached a limiting value when the carboxylic acid was in excess. The starting phenol resin has a loading level at 1.3 mmol/g, so 0.25 g of polymer-supported DPPA should contain 0.325 mmol of DPPA. In the curve, the highest yield of the product was around 0.22 mmol. Because of the 84% normal yield, the estimated effective azide loading was determined to be 1.05 mmol/g and the conversion of phenol resin to polymer-supported DPPA was around 80%.
Table 4. Parallel reactions of azide loading analysis

![Chemical reaction diagram]

<table>
<thead>
<tr>
<th>Entry</th>
<th>4-Nitrobenzoic acid</th>
<th>(4-Nitro-phenyl)-carbamic acid tert-butyl ester</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mg</td>
<td>mmol</td>
</tr>
<tr>
<td></td>
<td>mg</td>
<td>mmol</td>
</tr>
<tr>
<td>1</td>
<td>8</td>
<td>0.05</td>
</tr>
<tr>
<td>2</td>
<td>17</td>
<td>0.10</td>
</tr>
<tr>
<td>3</td>
<td>25</td>
<td>0.15</td>
</tr>
<tr>
<td>4</td>
<td>33</td>
<td>0.20</td>
</tr>
<tr>
<td>5</td>
<td>50</td>
<td>0.30</td>
</tr>
<tr>
<td>6</td>
<td>67</td>
<td>0.40</td>
</tr>
<tr>
<td>7</td>
<td>84</td>
<td>0.50</td>
</tr>
<tr>
<td>8</td>
<td>100</td>
<td>0.60</td>
</tr>
<tr>
<td>9</td>
<td>167</td>
<td>1.00</td>
</tr>
</tbody>
</table>

Carbamate vs. Carboxylic acid

![Graph showing carbamate vs. carboxylic acid]

\[ y = 0.0039x + 0.2116 \]

Figure 17. Parallel reactions of azide loading analysis examining the effective loading of DPPA
2-5. Conclusions

A polymeric reagent, polymer-supported diphenylphosphoryl azide (DPPA), was prepared from phenol resin. This polymer-supported version of DPPA is useful due to its lower toxicity, moisture tolerance and ease of workup after reaction. Azide loading on the resin has been determined by parallel reactions, and the conversion from phenol resin to polymer-supported DPPA is around 80%.

The synthetic application of this solid-phase reagent was explored by conversion of a variety of carboxylic acids to urethanes and ureas through Curtius rearrangement reactions. Carboxylic acids bearing different functional groups (aromatic, aliphatic and heterocyclic carboxylic acids) were subjected to the reaction. The corresponding products were isolated with satisfactory yields.

By using polymer-supported DPPA, oxazolidinone, imidazolidinone and thiazolidinone derivatives were also successfully prepared from carboxylic acids bearing different reactive functional groups in the β position, such as alcohols, thiols, primary and secondary amines. The desired compounds were obtained in good yields via Curtius rearrangement and subsequent intramolecular cyclization.

This polymer-supported DPPA may be a useful synthetic organic reagent in the future.
2-6. Experimental section

General experimental information. All manipulations were performed in oven-dried glassware under a nitrogen atmosphere unless otherwise mentioned. All solvents and reagents were dried or purified using standard procedures and were distilled freshly before use. The standard workup included washing the reaction mixture with water followed by brine, then the separated organic phase was dried over magnesium sulfate, and concentrated in vacuo. Phenol resin was purchased from Advanced ChemTech (1.3 - 1.5 mmol/g loading). Column chromatography was performed on silica gel (Natland International Corp. 200 – 400 mesh) using the indicated solvents. TLC analyses were carried out using C4 silica gel plates (Silicycle Inc.). Melting points were determined with a Gallenkamp melting point apparatus and were uncorrected. \(^1\)H and \(^{13}\)C NMR spectra were recorded on a 200 or 300 MHz FT-NMR spectrometer (Bruker Avance) in CDCl\(_3\), DMSO-d\(_6\) or D\(_2\)O (Aldrich). IR spectra were determined as a neat film (using NaCl plate) or KBr pellet on a Perkin-Elmer 1600 FT-IR spectrophotometer. High-resolution MS spectra were performed on the Micromass LCT Electrospray mass spectrometer by the Mass Spectrometry and Proteomics Facility, The Ohio State University, Columbus, OH.

Synthesis and spectra data

\[
\text{OH} \xrightarrow{\text{dichlorophosphoryl chloride}} \text{O} \xrightarrow{\text{NaN}_3, \text{15-crown-5}} \text{OPh} \xrightarrow{\text{CH}_2\text{Cl}_2, \text{reflux, 24 h}} \text{O} \xrightarrow{\text{NaN}_3} \text{OPh} \xrightarrow{\text{CH}_2\text{Cl}_2, \text{rt, 8 h}} \text{OPh} \xrightarrow{\text{NaN}_3, \text{15-crown-5}} \text{OPh} \xrightarrow{\text{CH}_2\text{Cl}_2, \text{reflux, 24 h}} \text{OPh} \xrightarrow{\text{NaN}_3} \text{OPh}
\]
**Preparation of polymer-supported diphenylphosphoryl chloride (1) and polymer-supported diphenylphosphoryl azide (DPPA) (2).** Phenol resin (1.0 g, 1.5 mmol) was swelled in CH$_2$Cl$_2$ (10 mL) under nitrogen atmosphere for 5 minutes, then phenyl dichlorophosphate (1.1 mL, 7.5 mmol, 5.0 eq) was added at room temperature and stirred for 8 hours. After filtration, the polymer-supported diphenylphosphoryl chloride resin was washed with anhydrous CH$_2$Cl$_2$ (20 mL $\times$ 3) under nitrogen atmosphere. The polymer-supported diphenylphosphoryl chloride resin was swelled in CH$_2$Cl$_2$ (10 mL), then NaN$_3$ (0.29 g, 4.5 mmol, 3.0 eq) and 15-crown-5 (0.99 g, 4.5 mmol, 3.0 eq) were added at room temperature, followed by heating to reflux for 24 hours. After cooling to room temperature, the mixture was filtered and the resin was washed with distilled water (10 mL $\times$ 3) and CH$_2$Cl$_2$ (30 mL $\times$ 3). After drying under vacuum overnight, polymer-supported diphenylphosphoryl azide was obtained. FT-IR (cm$^{-1}$): 3398, 3026, 2922, 2168, 1601, 1492, 1452, 1162, 966, 755, 696.

**General procedure for preparation of carbamate and urea derivatives.** Polymer-supported DPPA (1.0 eq, based on fully azide-loaded resin) was swelled in benzene (10 mL) under a nitrogen atmosphere for 5 minutes. To this suspension were added carboxylic acid (1.2 eq) and Et$_3$N (1.4 eq) at room temperature. The mixture was heated to reflux for 30 minutes. The alcohol or amine (1.7 eq) was then added and reaction was heated at reflux for 24 hours. After cooling to room temperature, the resin was removed by filtration and washed with EtOAc (100 mL). The combined filtrates were washed with aqueous NaOH solution (1 M, 30 mL $\times$ 3), distilled water (30 mL $\times$ 3) and brine (30 mL). After drying over MgSO$_4$, solvent was removed under vacuum to afford the crude product.
Preparation of N-phenylcarbamic acid ethyl ester (Table 1, Entry 1). The general procedure was followed using polymer-supported DPPA (1.0 g, ~1.5 mmol), benzoic acid (0.22 g, 1.8 mmol), Et₃N (0.21 g, 2.1 mmol) and EtOH (0.15 mL, 2.5 mmol). Purification was performed by silica-gel column chromatography (5:1 petroleum ether/diethyl ether) to give pure phenylcarbamic acid ethyl ester as a colorless liquid (0.13 g, 53% yield): ¹H NMR (CDCl₃, 300 MHz) δ 1.29 (t, J = 7.1 Hz, 3H), 4.21 (q, J = 7.1 Hz, 2H), 6.62 (br, 1H), 7.01-7.06 (m, 1H), 7.24-7.38 (m, 4H). ¹³C NMR (CDCl₃, 75 MHz) δ 14.53, 61.19, 118.66, 123.33, 129.01, 137.94, 153.60. The spectral data were identical to those reported in the literature.¹³

Preparation of N-(2-methoxyphenyl)carbamic acid ethyl ester (Table 1, Entry 2). The general procedure was followed using polymer-supported DPPA (1.0 g, ~1.5 mmol), o-anisic acid (0.27 g, 1.8 mmol), Et₃N (0.21 g, 2.1 mmol) and EtOH (0.15 mL, 2.5 mmol). Purification was performed by silica-gel column chromatography (10:1 petroleum ether/diethyl ether) to give pure N-(2-methoxyphenyl)carbamic acid ethyl ester as a colorless liquid (0.21 g, 72% yield): ¹H NMR (CDCl₃, 300 MHz) δ 1.30 (t, J = 7.1 Hz, 3H), 3.84 (s, 3H), 4.21 (q, J = 7.1 Hz, 2H), 6.82-6.98 (m, 3H), 7.19 (br, 1H), 8.05 (m, 1H). ¹³C NMR (CDCl₃, 75 MHz) δ 14.57, 55.64, 61.06, 109.96, 118.17, 121.12, 122.61, 127.76, 147.56, 153.54. The spectral data were identical to those reported in the literature.¹³
Preparation of *N*-(4-nitrophenyl)carbamic acid ethyl ester (Table 1, Entry 3). The general procedure was followed using polymer-supported DPPA (1.0 g, ~1.5 mmol), *p*-nitrobenzoic acid (0.30 g, 1.8 mmol), Et₃N (0.21 g, 2.1 mmol) and EtOH (0.15 mL, 2.5 mmol). Purification was performed by silica-gel column chromatography (1:1 petroleum ether/diethyl ether) to give pure *N*-(4-nitrophenyl)carbamic acid ethyl ester as a yellow solid (0.25 g, 80% yield): $^1$H NMR (CDCl₃, 300 MHz) δ 1.31 (t, $J = 7.1$ Hz, 3H), 4.25 (q, $J = 7.1$ Hz, 2H), 6.94 (br, 1H), 7.53 (dd, $J = 7.1$, 2.1 Hz, 2H), 8.18 (dd, $J = 7.1$, 2.1 Hz, 2H). $^{13}$C NMR (CDCl₃, 75 MHz) δ 14.42, 62.02, 117.66, 125.24, 143.00, 143.96, 152.80. The spectral data were identical to those reported in the literature.$^{13}$

Preparation of *N*-pyridin-2-ylcarbamic acid ethyl ester (Table 1, Entry 4). The general procedure was followed using polymer-supported DPPA (1.0 g, ~1.5 mmol), picolinic acid (0.22 g, 1.8 mmol), Et₃N (0.21 g, 2.1 mmol) and EtOH (0.15 mL, 2.5 mmol). Purification was performed by silica-gel column chromatography (1:1 petroleum ether/diethyl ether) to give pure *N*-pyridin-2-ylcarbamic acid ethyl ester as a white solid (0.12 g, 48% yield): $^1$H NMR (CDCl₃, 300 MHz) δ 1.31 (t, $J = 7.1$ Hz, 3H), 4.23 (q, $J = 7.1$ Hz, 2H), 6.97 (m, 1H), 7.67 (m, 2H), 7.96 (d, $J = 8.4$ Hz, 1H), 8.23 (d, $J = 4.1$ Hz, 1H). $^{13}$C NMR (CDCl₃, 75 MHz) δ 18.38, 58.41, 113.01, 118.24, 138.34, 147.30, 152.34, 153.06. The spectral data were identical to those reported in the literature.$^{14}$
Preparation of \(N\)-(2-methoxyphenyl)carbamic acid dodecyl ester (Table 1, Entry 5). The general procedure was followed using polymer-supported DPPA (1.0 g, \(~1.5\) mmol), \(o\)-anisic acid (0.27 g, 1.8 mmol), \(\text{Et}_3\text{N}\) (0.21 g, 2.1 mmol) and 1-dodecanol (0.46 g, 2.5 mmol). Purification was performed by silica-gel column chromatography (10:1 petroleum ether/diethyl ether) to give pure \(N\)-(2-methoxyphenyl)carbamic acid dodecyl ester as a colorless wax (0.26 g, 52% yield): \(^1\)H NMR (CDCl\(_3\), 300 MHz) \(\delta\) 0.86 (t, \(J = 6.9\) Hz, 3H), 1.24 (m, 18H), 1.66 (m, 2H), 3.85 (s, 3H), 4.14 (t, \(J = 6.7\) Hz, 2H), 6.82 (m, 1H), 6.96 (m, 2H), 7.2 (m, 1H), 8.1 (br, 1H). \(^{13}\)C NMR (CDCl\(_3\), 75 MHz) \(\delta\) 14.08, 22.66, 25.86, 28.96, 29.28, 29.32, 29.52, 29.56, 29.60, 29.62, 31.89, 55.61, 65.30, 109.93, 118.13, 121.11, 122.56, 127.77, 147.52, 153.63. FT-IR (cm\(^{-1}\)): 3436, 2924, 2853, 1736, 1604, 1531, 1461, 1207, 1130.\(^{12}\)

Preparation of \(N\)-(4-ethoxycarbonylaminophenyl)carbamic acid ethyl ester (Table 1, Entry 6). Polymer-supported DPPA (1.8 g, \(~2.7\) mmol, 2.1 eq, based on fully azide-loaded resin) was swelled in benzene (30 mL) under a nitrogen atmosphere for 5 minutes. To this suspension was added terephthalic acid (0.22 g, 1.3 mmol, 1.0 eq) and \(\text{Et}_3\text{N}\) (0.33 g, 3.2 mmol, 2.5 eq) at room temperature. The mixture was heated to reflux for 30 minutes. \(\text{EtOH}\) (0.19 mL, 3.2 mmol, 2.5 eq) was then added and reaction was heated at reflux for 24 hours. Workup followed the general procedure. Purification was performed by silica-gel column chromatography (1:1 petroleum
ether/diethyl ether) to give pure N-(4-ethoxycarbonylaminophenyl)carbamic acid ethyl ester as a white wax (0.12 g, 36% yield): $^1$H NMR (CDCl$_3$, 200 MHz) $\delta$ 1.28 (t, $J = 7.1$ Hz, 6H), 4.19 (q, $J = 7.1$ Hz, 4H), 6.48 (br, 2H), 7.29 (s, 4H). The spectral data were identical to those reported in the literature.$^{15}$

\[ \text{Preparation of } N\text{-}(4\text{-nitrophenyl})\text{-}N'\text{-}(1\text{-octyl)urea (Table 1, Entry 7).} \]

The general procedure was followed using polymer-supported DPPA (1.0 g, ~1.5 mmol), p-nitrobenzoic acid (0.30 g, 1.8 mmol), Et$_3$N (0.21 g, 2.1 mmol) and octylamine (0.32 g, 2.5 mmol). Purification was performed by silica-gel column chromatography (1:1 petroleum ether/diethyl ether) to give pure $N\text{-}(4\text{-nitrophenyl})\text{-}N'\text{-}(1\text{-octyl)urea as a yellow solid (0.18 g, 41% yield):} \]

$^1$H NMR (acetone-d$_6$, 300 MHz) $\delta$ 0.86 (t, $J = 6.9$ Hz, 3H), 1.28 (m, 10H), 1.47-1.54 (m, 2H), 3.21 (m, 2H), 6.07 (br, 1H), 7.72 (dd, $J = 7.2$, 1.9 Hz, 2H), 8.13 (dd, $J = 7.2$, 1.9 Hz, 2H), 8.58 (br, 1H). $^{13}$C NMR (CDCl$_3$, 75 MHz) $\delta$ 14.06, 22.61, 26.87, 29.20, 29.24, 29.96, 31.77, 40.53, 117.69, 125.26, 142.21, 145.48, 154.22. The spectral data were identical to those reported in the literature.$^{16}$

\[ \text{Preparation of } N\text{-}(4\text{-methylbenzyl)carbamic acid ethyl ester (Table 2, Entry 1).} \]

The general procedure was followed using polymer-supported DPPA (1.0 g, ~1.5 mmol), $p$-tolylacetic acid (0.27 g, 1.8 mmol), Et$_3$N (0.21 g, 2.1 mmol) and EtOH (0.15 mL, 2.5 mmol). Purification was performed by silica-gel column chromatography (5:1 petroleum ether/diethyl ether) to give pure
N-(4-methylbenzyl)carbamic acid ethyl ester as white crystals (0.13 g, 46% yield): \(^1\)H NMR (CDCl\(_3\), 300 MHz) \(\delta\) 1.23 (t, \(J = 7.1\) Hz, 3H), 2.31 (s, 3H), 4.12 (q, \(J = 7.0\) Hz, 2H), 4.30 (d, \(J = 5.8\) Hz, 2H), 4.91 (br, 1H), 7.10-7.18 (m, 4H). \(^{13}\)C NMR (CDCl\(_3\), 75 MHz) \(\delta\) 14.62, 21.05, 44.78, 60.89, 127.50, 129.29, 135.56, 137.11, 156.61. The spectral data were identical to those reported in the literature.\(^{17}\)

Preparation of \(N\)-propylcarbamic acid phenyl ester (Table 2, Entry 2). The general procedure was followed using polymer-supported DPPA (1.0 g, ~1.5 mmol), butyric acid (0.16 g, 1.8 mmol), Et\(_3\)N (0.21 g, 2.1 mmol) and phenol (0.24 g, 2.5 mmol). Purification was performed by silica-gel column chromatography (1:1 petroleum ether/diethyl ether) to give pure \(N\)-propylcarbamic acid phenyl ester as a colorless liquid (0.14 g, 52% yield): \(^1\)H NMR (acetone-d\(_6\), 200 MHz) \(\delta\) 0.93 (t, \(J = 7.4\) Hz, 3H), 1.48-1.66 (m, 2H), 3.15 (q, \(J = 6.1\) Hz, 2H), 6.77 (br, 1H), 7.07-7.19 (m, 3H), 7.30-7.38 (m, 2H). The spectral data were identical to those reported in the literature.\(^{18}\)

\(n\)-CH\(_3\)(CH\(_2\))\(_8\)COOH + phenol \xrightarrow{\text{polymer-supported DPPA, Et\(_3\)N, benzene, reflux, 24 h}} \text{CHCHJ(CH\(_2\))\(_8\)} \(O\)N

Preparation of \(N\)-nonylcarbamic acid benzyl ester (Table 2, Entry 3). The general procedure was followed using polymer-supported DPPA (1.0 g, ~1.5 mmol), decanoic acid (0.31 g, 1.8 mmol), Et\(_3\)N (0.21 g, 2.1 mmol) and benzyl alcohol (0.27 g, 2.5 mmol). Purification was performed by silica-gel column chromatography (5:1 petroleum ether/diethyl ether) to give pure
N-nonyl-carbamic acid benzyl ester as a white solid (0.14 g, 34% yield): \(^1\)H NMR (CDCl\(_3\), 300 MHz) \(\delta\) 0.86 \((t, J = 7.0\) Hz, 3H), 1.23 \((m, 12H)\), 1.44 \((m, 2H)\), 3.16 \((q, J = 6.6\) Hz, 2H), 4.69 \((br, 1H)\), 5.07 \((s, 2H)\), 7.29-7.35 \((m, 5H)\). \(^{13}\)C NMR (CDCl\(_3\), 75 MHz) \(\delta\) 14.07, 22.63, 26.71, 29.20, 29.34, 29.68, 29.95, 31.90, 41.11, 66.56, 128.05, 128.09, 128.49, 136.67, 156.35. The spectral data were identical to those reported in the literature.\(^{19}\)

\[
\begin{array}{c}
\text{H} \quad \text{N} \\
\text{O} \quad \text{O} \\
\text{O} \quad \text{OH} \\
\text{OH}
\end{array}
\quad \xrightarrow{\text{polymer-supported DPPA}}
\quad \begin{array}{c}
\text{O} \quad \text{N} \\
\text{O} \quad \text{O} \\
\text{O} \quad \text{OH}
\end{array}
\]

**Preparation of N-(4-oxopentyl)carbamic acid isopropyl ester (Table 2, Entry 4).** The general procedure was followed using polymer-supported DPPA (1.0 g, ~1.5 mmol), 4-acetylbutyric acid (0.23 g, 1.8 mmol), Et\(_3\)N (0.21 g, 2.1 mmol) and 2-propanol (0.19 mL, 2.5 mmol). Purification was performed by silica-gel column chromatography (1:1 petroleum ether/diethyl ether) to give pure N-(4-oxopentyl)carbamic acid isopropyl ester as a colorless oil (0.13 g, 47% yield): \(^1\)H NMR (CDCl\(_3\), 300 MHz) \(\delta\) 1.19 \((d, J = 6.2\) Hz, 6H), 1.72 \((m, 2H)\), 2.13 \((s, 3H)\), 2.47 \((t, J = 7.1\) Hz, 2H), 3.14 \((q, J = 6.5\) Hz, 2H), 4.65 \((br, 1H)\), 4.86 \((m, 1H)\). \(^{13}\)C NMR (CDCl\(_3\), 50 MHz) \(\delta\) 22.13, 23.96, 29.98, 40.23, 40.69, 67.96, 156.40, 208.42. FT-IR (cm\(^{-1}\)): 2923, 1710, 1528, 1252, 1112.\(^{12}\)

\[
\begin{array}{c}
\text{H} \quad \text{N} \\
\text{O} \quad \text{O} \\
\text{O} \quad \text{OH}
\end{array}
\quad \xrightarrow{\text{polymer-supported DPPA}}
\quad \begin{array}{c}
\text{H} \quad \text{N} \\
\text{O} \quad \text{O} \\
\text{O} \quad \text{OH}
\end{array}
\]

**Preparation of N-styrylcarbamic acid tert-butyl ester (Table 2, Entry 5).** The general procedure was followed using polymer-supported DPPA (1.0 g, ~1.5 mmol), trans-cinnamic acid (0.27 g, 1.8 mmol), Et\(_3\)N (0.21 g, 2.1 mmol) and t-BuOH (0.23 mL, 2.5 mmol). Purification was
performed by silica-gel column chromatography (5:1 petroleum ether/diethyl ether) to give a mixture of geometrical (cis- and trans-) isomers of N-styrylcarbamic acid tert-butyl ester as white crystals (0.18 g, 54% yield): $^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 1.51 (s, 9H), 5.92 (d, $J$ = 14.5 Hz, 1H), 6.44 (d, $J$ = 8.0 Hz, 1H), 7.12-7.19 (m, 1H), 7.24-7.28 (m, 5H). $^{13}$C NMR (CDCl$_3$, 75 MHz) $\delta$ 28.24, 80.90, 109.63, 124.26, 125.14, 126.05, 128.37, 128.58, 128.94, 128.98, 136.53, 152.60. The spectral data were identical to those reported in the literature.$^5$

Preparation of N-phenyl-N’-propylurea (Table 2, Entry 6). General procedure was followed using polymer-supported DPPA (1.0 g, ~1.5 mmol), butyric acid (0.16 g, 1.8 mmol), Et$_3$N (0.21 g, 2.1 mmol) and aniline (0.23 g, 2.5 mmol). Purification was performed by silica-gel column chromatography (1:1 petroleum ether/diethyl ether) to give pure N-phenyl-N’-propylurea as a yellow solid (0.12 g, 45% yield) $\delta$ $^1$H NMR (acetone-d$_6$, 300 MHz): 0.91 (t, $J$ = 7.4 Hz, 3H), 1.46-1.58 (m, 2H), 3.16 (q, $J$ = 6.0 Hz, 2H), 5.79 (br, 1H), 6.90 (t, $J$ = 7.4 Hz, 1H), 7.18-7.24 (m, 2H), 7.48 (dd, $J$ = 8.7, 1.0 Hz, 2H), 7.86 (br, 1H). The spectral data were identical to those reported in the literature.$^{20}$

General procedure for preparation of five-membered cyclic urethane and urea derivatives.

Polymer-supported DPPA (1.0 eq, based on fully azide loaded resin), carboxylic acid derivatives (1.2 eq) and Et$_3$N (1.3 eq) were mixed in a round-bottom flask with benzene or 1,4-dioxane (10 mL). The mixture was heated to reflux under a nitrogen atmosphere for 24 hours. After cooling to room temperature, the resin was removed by filtration and washed with EtOAc (100 mL). The
combined filtrates were washed with aqueous NaOH solution (1 M, 30 mL × 3), distilled water (30 mL × 3) and brine (30 mL). After drying over magnesium sulfate, solvent was removed under vacuum to afford the crude product.

![Reaction Diagram]

**Preparation of 3H-benzoaxazol-2-one (Table 3, Entry 1).** The general procedure was followed using polymer-supported DPPA (1.00 g, ~1.5 mmol, assume 100% loading), salicylic acid (0.25 g, 1.8 mmol) and Et₃N (0.20 g, 2.0 mmol) in benzene. Purification was performed by silica-gel column chromatography (1:1 petroleum ether/diethyl ether) to give pure 3H-benzoaxazol-2-one as a yellow solid (0.14 g, 69% yield): ¹H NMR (CDCl₃, 300 MHz) δ 7.07-7.21 (m, 4H), 9.95 (br, 1H); ¹³C NMR (CDCl₃, 75 MHz) δ 110.11, 110.24, 122.71, 124.20, 129.40, 143.86, 156.34. The spectral data were identical to the reported data.¹³

![Reaction Diagram]

**Preparation of 5-methoxy-3H-benzoaxazol-2-one (Table 3, Entry 2).** The general procedure was followed using polymer-supported DPPA (1.00 g, ~1.5 mmol), 5-methoxysalicylic acid (0.30 g, 1.8 mmol) and Et₃N (0.20 g, 2.0 mmol) in benzene. Purification was performed by silica-gel column chromatography (1:1 petroleum ether/diethyl ether) to give pure 5-methoxy-3H-benzoaxazol-2-one as a white solid (0.13 g, 53% yield): ¹H NMR (CDCl₃, 300 MHz) δ 3.78 (s, 3H), 6.62 (dd, J = 8.7, 2.6 Hz, 1H), 6.67 (d, J = 2.6 Hz, 1H), 7.08 (d, J = 8.7 Hz, 1H), 9.33
(br, 1H); $^{13}$C NMR (CDCl$_3$, 75 MHz) $\delta$ 55.94, 96.75, 107.85, 110.45, 129.97, 138.00, 156.35, 156.85. The spectral data were identical to the literature data.$^{29}$

**Preparation of 1,3-dihydrobenzoimidazol-2-one (Table 3, Entry 3).** The general procedure was followed using polymer-supported DPPA (1.00 g, ~1.5 mmol), anthranilic acid (0.25 g, 1.8 mmol) and Et$_3$N (0.20 g, 2.0 mmol) in benzene. Purification was performed by silica-gel column chromatography (1:2 petroleum ether/diethyl ether) to give pure 1,3-dihydrobenzoimidazol-2-one as a white solid (0.15 g, 75% yield): $^1$H NMR (DMSO-d$_6$, 300 MHz) $\delta$ 6.90 (s, 4H), 10.56 (s, 2H); $^{13}$C NMR (DMSO-d$_6$, 75 MHz) $\delta$ 108.44, 120.37, 129.66, 155.24. The spectral data were identical to the literature data.$^{13}$

**Preparation of 1,3-dihydro-benzimidazol-2-one (Table 3, Entry 4).** The general procedure was followed using polymer-supported DPPA (1.00 g, ~1.5 mmol), 5-chloroanthranilic acid (0.31 g, 1.8 mmol) and Et$_3$N (0.20 g, 2.0 mmol) in benzene. Purification was performed by silica-gel column chromatography (1:2 petroleum ether/diethyl ether) to give pure 1,3-dihydrobenzoimidazol-2-one as a white solid (0.16 g, 64% yield): $^1$H NMR (DMSO-d$_6$, 300 MHz) $\delta$ 6.88-6.99 (m, 3H), 10.76 (s, 2H); $^{13}$C NMR (DMSO-d$_6$, 75 MHz) $\delta$ 108.38, 109.52, 120.11,
The spectral data were identical to those reported in the literature.\textsuperscript{30}

\[
\begin{align*}
\text{H}_2\text{N} & \quad \text{COOH} \quad \overset{\text{Boc}_2\text{O}, \text{Et}_3\text{N}}{\text{MeOH, 50°C, 1 h}} \quad \text{BOC}^+\text{H} & \quad \text{COOH} \\
\text{MeOH, 50°C, 1 h} & \quad \overset{\text{polymer-supported DPPA}}{\text{Et}_3\text{N, 1,4-dioxane, reflux, 24 h}} \quad \text{BOC}^+\text{H} & \quad \text{N} & \quad \text{O} & \quad \text{O}
\end{align*}
\]

**Preparation of N-(2-oxooxazolidin-4-yl)carbamic acid tert-butyl ester (Table 3, Entry 5).** *L*-Serine (0.21 g, 2.0 mmol) was reacted with di-tert-butyl dicarbonate (0.52 g, 2.4 mmol) in 10% solution (20 mL) of Et\textsubscript{3}N in MeOH and heated to 50 °C for 1 hour. After cooling, the solvent was then evaporated under reduced pressure, and the residue was stirred for 10 minutes with ice-cold dilute HCl (pH ≈ 2) and extracted immediately with EtOAc. The combined organic extract was dried with MgSO\textsubscript{4}, then filtered and evaporated. The pure BOC-protected serine was crystallized from ether.\textsuperscript{26} The general procedure was followed using polymer-supported DPPA (1.00 g, ~1.5 mmol), BOC-protected serine (0.37 g, 1.8 mmol) and Et\textsubscript{3}N (0.20 g, 2.0 mmol) in 1,4-dioxane. Purification was performed by silica-gel column chromatography (1:1 petroleum ether/diethyl ether) to give pure N-(2-oxooxazolidin-4-yl)carbamic acid tert-butyl ester as a white solid (0.18 g, 60% yield): \textsuperscript{1}H NMR (DMSO-d\textsubscript{6}, 300 MHz) \(\delta\) 1.38 (s, 9H), 3.97 (dd, \(J\) = 9.2, 3.7 Hz, 1H), 4.43 (t, \(J\) = 8.8 Hz, 1H), 5.29 (m, 1H), 7.81 (d, \(J\) = 8.7 Hz, 1H), 8.22 (s, 1H); \textsuperscript{13}C NMR (DMSO-d\textsubscript{6}, 75 MHz) \(\delta\) 28.16, 59.62, 68.98, 78.60, 154.65, 157.87. The spectral data were identical to those reported in the literature.\textsuperscript{31}
Preparation of \(N\)-(5-methyl-2-oxooxazolidin-4-yl)carbamic acid tert-butyl ester (Table 3, Entry 6). \(L\)-Threonine (0.24 g, 2.0 mmol) was reacted with di-\(\text{tert}\)-butyl dicarbonate (0.52 g, 2.4 mmol) in 10% solution (20 mL) of triethylamine in MeOH, then heated to reflux for 1 hour. After cooling, the solvent was then evaporated under reduced pressure, and the residue was stirred for 10 minutes with ice-cold dilute HCl (\(pH \approx 2\)) and extracted immediately with EtOAc. The combined organic extract was dried with MgSO\(_4\), then filtered and evaporated. The pure BOC-protected threonine was crystallized from ether.\(^{26}\) The general procedure was followed using polymer-supported DPPA (1.00 g, \(~\)1.5 mmol), BOC-protected serine (0.39 g, 1.8 mmol) and Et\(_3\)N (0.20 g, 2.0 mmol) in 1,4-dioxane. Purification was performed by silica-gel column chromatography (1:1 petroleum ether/diethyl ether) to give pure \(N\)-(5-methyl-2-oxooxazolidin-4-yl)carbamic acid tert-butyl ester as a white solid (0.19 g, 59% yield): \(^1\)H NMR (DMSO-\(d_6\), 300 MHz) \(\delta\) 1.16 (d, \(J = 6.4\) Hz, 3H), 1.38 (s, 9H), 4.68 (quint, \(J = 6.6\) Hz, 1H), 5.22 (dd, \(J = 9.3, 7.3\) Hz, 1H), 7.70 (d, \(J = 9.6\) Hz, 1H), 8.02 (s, 1H); \(^{13}\)C NMR (DMSO-\(d_6\), 75 MHz) \(\delta\) 14.00, 24.14, 62.32, 75.00, 78.40, 154.77, 157.63; FT-IR (cm\(^{-1}\)) \(\nu_{\text{max}}\) 3346, 2938, 1752, 1715, 1681, 1514, 1385, 1231, 1161, 1101, 1074, 974, 877; HRMS (electrospray) m/z [M+Na\(^+\)] calcd. for C\(_9\)H\(_{16}\)N\(_2\)O\(_4\)Na\(^+\): 239.1008, found 239.0996.

Preparation of \(N\)-(2-oxothiazolidin-4-yl)carbamic acid tert-butyl ester (Table 3, Entry 7). \(L\)-Cysteine (0.24 g, 2.0 mmol) was reacted with di-\(\text{tert}\)-butyl dicarbonate (0.52 g, 2.4 mmol) in
10% solution (20 mL) of Et₃N in MeOH, then heated to reflux for 1 hour. After cooling, the solvent was then evaporated under reduced pressure, and the residue was stirred for 10 minutes with ice-cold dilute HCl (pH ≈ 2) and extracted immediately with EtOAc. The combined organic extract was dried with MgSO₄, then filtered and evaporated. The pure BOC-protected cysteine was crystallized from ether. The general procedure was followed using polymer-supported DPPA (1.00 g, ~1.5 mmol), BOC-protected serine (0.40 g, 1.8 mmol) and Et₃N (0.20 g, 2.0 mmol) in 1,4-dioxane. Purification was performed by silica-gel column chromatography (2:1 to 1:1 petroleum ether/diethyl ether) to give pure N-(2-oxothiazolidin-4-yl)carbamic acid tert-butyl ester as a pale yellow solid (0.22 g, 67%): ¹H NMR (DMSO-d₆, 300 MHz) δ 1.39 (s, 9H), 3.11 (dd, J = 11.5, 3.9 Hz, 1H), 3.67 (dd, J = 11.5, 7.3 Hz, 1H), 5.34 (m, 1H), 7.88 (d, J = 7.7 Hz, 1H), 8.55 (s, 1H); ¹³C NMR (DMSO-d₆, 75 MHz) δ 28.16, 34.72, 61.94, 78.56, 154.47, 171.69; FT-IR (cm⁻¹) ν_max 3364, 3228, 2923, 1679, 1659, 1499, 1356, 1214, 1155, 1027, 958, 846; HRMS (electrospray) m/z [M+Na⁺] calcd. for C₈H₁₄N₂O₃SNa⁺: 241.0623, found 241.0607.

Preparation of 1-benzylimidazolidin-2-one (Table 3, Entry 8). Benzylamine (0.47 g, 4.4 mmol, 2.2 eq) and acrylic acid (0.14 g, 2.0 mmol, 1.0 eq) were added into THF (10 mL) and stirred at room temperature for 24 hours. A white solid formed during stirring. After filtration, the white solid was partitioned between ether (30 mL) and NaOH solution (1 M, 30 mL). After separation, the aqueous phase was acidified with HCl (1 M) to pH = 2. The water was removed by rotary evaporation and dried under vacuum (0.1 mmHg) overnight. A mixture of 3-(benzylamino)propionic acid and NaCl was obtained as white solid. This crude product was good
enough for the subsequent reactions. $^1$H NMR (D$_2$O, 300 MHz) $\delta$ 2.67 (t, $J$ = 6.7 Hz, 2H), 3.20 (t, $J$ = 6.6 Hz, 2H), 4.14 (s, 2H), 7.36 (s, 5H); $^{13}$C NMR (D$_2$O, 75 MHz) $\delta$ 30.58, 42.75, 51.56, 129.70, 130.14, 130.20, 130.85, 174.75.

The general procedure was then followed using polymer-supported DPPA (1.00 g, $\sim$1.5 mmol), 3-(benzylamino)propionic acid (obtained above) and Et$_3$N (0.20 g, 2.0 mmol) in 1,4-dioxane. Purification was performed by silica-gel column chromatography (diethyl ether) to give pure 1-benzylimidazolidin-2-one as a white solid (0.14 g, 53% yield): $^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 3.24-3.30 (m, 2H), 3.35-3.40 (m, 2H), 4.34 (s, 2H), 5.03 (br, 1H), 7.22-7.33 (m, 5H); $^{13}$C NMR (CDCl$_3$, 75 MHz) $\delta$ 38.03, 44.48, 47.62, 127.38, 128.01, 128.54, 137.08, 162.72. The spectral data were identical to those reported in the literature.$^{32}$

**Azide loading analysis.** In 9 round bottom flasks, 0.25 g of polymer-supported DPPA, 1.5 ml of $t$-BuOH, 0.3 mL of Et$_3$N and 2 mL of benzene were added individually, followed by a varying amount of $p$-nitrobenzoic acid and the reaction mixture was refluxed for 20 hours. In these 9 parallel reactions, the $p$-nitrobenzoic acid has gradually increased amount from 8 to 167 mg (0.05 to 1.00 mmol). After cooling to room temperature, the resin was removed by filtration and washed with EtOAc (20 mL). The combined filtrates were extracted with aqueous NaOH solution (1 M, 10 mL $\times$ 3), distilled water (10 mL $\times$ 3) and brine (10 mL). After drying over MgSO$_4$, solvent was removed under vacuum to afford the crude product. Purification was performed on silica-gel column chromatography (1:1 petroleum ether/diethyl ether) to give pure product. After vacuum drying overnight, the amount of product in each round bottom flask was measured carefully to further use for the azide loading curve (Figure 17).
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Chapter III. Divergent approach to synthesize polyurethane dendrimers by using polymer-supported diphenylphosphoryl azide (DPPA)

3-1. Introduction

3-1-1. Dendrimer

Dendrimers are symmetrical, highly-ordered monodisperse, tree-like macromolecules, which are synthesized from regular, highly-branched monomers.\(^1\) Their shape, size, and other physical properties, such as flexibility, polarity and solubility, are controlled by choices in the building block chosen for constructing the higher generations and functional groups selected for the periphery.\(^2\) The selection of various types of core molecules\(^2\) will also lead to the synthesis of dendrimers with a variety of shape, properties and applications.

Dendrimer synthesis is a relatively new field of polymer chemistry. In 1978, F. Vogtle and coworkers published the synthesis of polyamine dendritic molecules through a divergent approach.\(^4\) After this report, a variety of structural classes of dendritic macromolecules have been reported by a number of research groups such as R. Mulhaupt\(^5\), D. A. Tomalia\(^6\), G. R. Newkome\(^7\) and E. W. Meijer\(^8\). In 1990, J. M. J. Frechét and coworkers utilized a new convergent growth methodology in the synthesis of a number of dendritic polyether macromolecules.\(^9\) In 1994, G. Vankoten and coworkers modified silicon-based dendrimers with nickel complexes.\(^10\) D. N. Reinhoudt \textit{et al.} reported the synthesis of dendrimers with coordination centers throughout all the layers \textit{via} a divergent approach in 1996.\(^11\) Later, more and more papers were published on
various dendrimer syntheses. In 1997, M. Bradley et al. reported the solid-phase synthesis of polyamidoamine (PAMAM) dendrimers on Tenta-Gel resin-bound linker (Figure 18).
Dendrimers have some proven applications, and numerous potential applications. They have been used in the production of industrial adhesives. They are expected to serve as components in a variety of nanomachines. Dendrimers are of interest to researchers in medical technology, where they might help carry and deliver drugs in the body, or serve as replacements for plasma components. Dendrimers might also prove useful in the manufacture of nanoscale batteries and lubricants, catalysts, and herbicides.\textsuperscript{13}

3-1-2. **Dendrimer synthetic approaches**

There are two main defined approaches of dendrimer synthesis, divergent and convergent. Divergent approach is an “inside-out” approach. In the divergent approach, the molecule is assembled from the core to the periphery. Convergent approach is an “outside-in” approach. In the convergent approach, the dendrimer is synthesized beginning from the outside and terminating at the core (Figure 19). In either method the synthesis requires a stepwise process, attaching one generation to the last, purifying, and then changing functional groups for the next stage of reaction.
Divergent approach:

The divergent approach starts from a reactive core and branching units with protected points. After a generation growth, the periphery of the molecule is activated for reaction with more monomers. The two steps can be repeated to form dendrimers of higher generation. The divergent approach is successful for the production of large quantities of dendrimers since, in each generation-adding step, the molar mass of the dendrimer is enlarged dramatically. Very large dendrimers have been prepared in this way, but incomplete growth steps and side reactions lead to the isolation and characterization of slightly imperfect by-products. Divergently grown

Convergent approach:

The convergent approach starts from surface units. After a generation growth, the focal point is activated for reaction with more monomers. The two steps can be repeated to form dendrimers of higher generation. The convergent approach is successful for the production of large quantities of dendrimers since, in each generation-adding step, the molar mass of the dendrimer is enlarged dramatically. Very large dendrimers have been prepared in this way, but incomplete growth steps and side reactions lead to the isolation and characterization of slightly imperfect by-products. Convergently grown

Figure 19. Two dendrimer synthetic approaches: convergent and divergent.
dendrimers are virtually impossible to isolate pure from their side products. The synthetic chemist must rely on extremely efficient reactions in order to ensure low polydispersities.

Convergent growth\(^9\) begins at branching units which will be the surface of the dendrimer, and works inwards by gradually linking surface units together with more monomers. When the growing dendritic wedges are large enough, they are attached to a suitable core to give a complete dendrimer. The advantages of convergent approach over divergent approach are that only two simultaneous reactions are required for any generation-adding step. Most importantly, this protocol makes the purification of perfect dendrimers simple. There are also certain other advantages associated with convergent growth. The growth reactions do not have to be so stringently efficient, and it becomes possible to introduce subtle engineering into the dendritic structure. However, convergent syntheses are not without their own shortcomings. The number of steps required to build up a large structure is not reduced compared with the divergent approach, yet a great deal more starting material is required. The convergent methodology also suffers from low yields in the synthesis of large structures. Dendritic wedge of higher generations encounter serious steric problems in the reactions of their “focal point”.

There are several other dendrimer growth techniques. The use of “hypercores” and “branched monomers” facilitate the dendrimer synthesis in fewer steps or higher yields.\(^{15}\) Moreover, “double exponential” and “mixed” growth is more subtle than the ability to build large dendrimers in relatively few steps.\(^{16}\) In fact, double exponential growth is so fast that it can be repeated only two or perhaps three times before further growth becomes impossible. Other advances made in the area of fast dendrimer growth have been less versatile. Of particular
interest is the very elegant “two-step” approach developed by Frechêt. Recent advances in the synthesis of low polydispersity hyperbranched polymers have promoted interest in their dendrimer-like properties. Hyperbranched polymers are of considerable industrial interest as a consequence of the ease of their synthesis.

3-1-3. Polyurethane dendrimer and our previous work

Polyurethanes are one of the most versatile materials today. Their many uses range from flexible foam in upholstered furniture to rigid foams as insulation in walls and roofs to thermoplastic polyurethane use in medical devices and footwear to coatings, adhesives, sealants and elastomers used on floors and automotive interiors. Polyurethane dendrimers have special structures of alternative hydrophilic and hydrophobic layers in one molecule, which may carry or separate compounds with different polarity in molecular scale.

In the past decade, a few research groups have reported polyurethane dendritic macromolecules. Porphyrins were encapsulated into polyurethane dendrimers for study of their photochemical behavior, electrochemical properties, and use as regioselective catalysts. The constructing of dendrimer-porphyrin macromolecules had been reported employing ether, ether-amide, and ester as linkages. In 1998, our group reported a convergent synthesis of a polyurethane dendrimer-prophyrin containing long chain alkyl groups at the periphery (Figure 20).
In this convergent synthesis of polyurethane dendrimer, the outer units with the functionality in the periphery were determined in the first step, which can not be changed later in the synthesis. Various properties and applications can be adjusted if the outer units can be modified. Therefore, a divergent approach may often be better choice for the synthesis of polyurethane dendrimers,
even though in the divergent synthesis incomplete reaction at the periphery will lead to the occurrence of defects or imperfection in the next generation.

3-2. Synthetic strategies

3-2-1. Initial model

In the initial strategy (Figure 21), 1,3,5-benzenetricarboxylic acid was to be the core. 5-Hydroxyisophthalic acid was first protected by methylation, then converted into dimethyl 5-(3-hydroxypropoxy)benzene-1,3-dioate (A) through reaction with 3-bromo-1-propanol and K$_2$CO$_3$. Dimethyl 5-(3-hydroxypropoxy)benzene-1,3-dioate was thus formed, which reacted with polymer-supported DPPA, Et$_3$N and 1,3,5-benzenetricarboxylic acid, in refluxing benzene in an attempt to get the first generation of triply branched polyurethane dendrimer with six methyl esters on the surface. The first generation polyurethane dendrimer would then be hydrolyzed in a mixture of NaOH solution and THF to afford the first generation of polyurethane dendrimer with six carboxylate groups on the surface. This six carboxylate group compound would later be reacted with dimethyl 5-(3-hydroxypropoxy)benzene-1,3-dioate, polymer-supported DPPA and Et$_3$N to get the second generation of polyurethane dendrimer with methyl esters on the surface. The above procedures were to be repeated over and over again. Ultimately the polyurethane dendrimer with the desired generation and molecular weight would be prepared.
However, when we started this synthesis, we recovered substantial amounts of starting materials. We tried different alcohols (A) and solvents (Table 5); all of these reactions failed with the same phenomena. If we used normal liquid DPPA, the reaction took place smoothly. We attribute this difference to the observation that, in the Curtius reaction, the first step is to form a salt of 1,3,5-benzenetricarboxylic acid and Et₃N. This salt has very poor solubility in organic solvents, inhibiting the further reaction between the salt and the DPPA on solid phase. For this reason, we
chose another strategy of divergent approach to synthesize polyurethane dendrimers by using polymer-supported DPPA.

**Table 5.** Alcohols and solvents used to form polyurethane dendrimer in unsuccessful strategy.

<table>
<thead>
<tr>
<th>Alcohol (A)</th>
<th>Solvent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dodecyl alcohol</td>
<td>Benzene</td>
</tr>
<tr>
<td>Dodecyl alcohol</td>
<td>1,4-Dioxane</td>
</tr>
<tr>
<td>1,4-Dioxane/DMSO (4:1)</td>
<td>1,4-Dioxane/DMSO (4:1)</td>
</tr>
<tr>
<td>n-Butanol</td>
<td>n-Butanol</td>
</tr>
</tbody>
</table>

**3-2-2. Strategy**

To solve the problem of poor solubility of the salt of 1,3,5-benzenetricarboxylic acid and Et$_3$N in organic solvents, we chose compounds with multi hydroxyl groups as cores (Figure 22). Carboxylic acid with two protected hydroxyl groups was chosen as the branching unit. This carboxylic acid would react with polymer-supported DPPA and Et$_3$N to form an isocyanate compound with two protected hydroxyl groups. The isocyanate reacts with the polyhydroxylic core to get the first generation of polyurethane dendrimer with protected hydroxyl groups on the surface. After deprotection, the compound with more hydroxyl groups reacts with isocyanate to get the second generation of polyurethane dendrimer. Repeating these procedures, polyurethane dendrimers in higher generations can be formed. Finally, polyurethane dendrimers with hydroxyl
groups on the surface can be terminated by different functional groups to obtain different
dendrimers with different properties and applications.

**Figure 22.** New design of polyurethane dendrimer synthesis.
3-3. Divergent syntheses of polyurethane dendrimers

3-3-1. Synthesis of branching monomer

The synthesis of the branching monomer for polyurethane dendrimers was started from 3,5-dihydroxybenzoic acid methyl ester (Figure 23). The 3,5-dihydroxy-benzoic acid methyl ester was first reacted with 3-bromo-1-propanol and K$_2$CO$_3$ in acetone and refluxed overnight. The resulting 3,5-bis-(3-hydroxypropoxy)benzoic acid methyl ester (3) was then hydrolyzed in a mixture of NaOH solution and THF at 50 °C overnight to afford 3,5-bis-(3-hydroxypropoxy)benzoic acid (4). The 3,5-bis-(3-hydroxypropoxy)benzoic acid was reacted with acetic anhydride in pyridine at room temperature for 40 hours to obtain 3,5-bis-(3-}

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Figure 23. Synthesis of branching monomer.
acetoxypropoxy)benzoic acid (5) as the branching monomer for polyurethane dendrimer synthesis. After column chromatography, the overall yield of the product in the whole synthesis is 94%. The pure 3,5-bis-(3-acetoxypropoxy)benzoic acid crystallizes as a white solid.

3-3-2. Synthesis of polyurethane dendrimers

The branching monomer, 3,5-bis-(3-acetoxypropoxy)benzoic acid, was reacted with Et₃N and polymer-supported DPPA in benzene for 3 hours, then heated to reflux to form the isocyanate intermediate (B) (Figure 24). A multi hydroxyl group compound (6a-6d) was added to the mixture to reflux 24 hours to get the first generation of polyurethane dendrimer with ester groups on the surface (7a-7d). After column chromatography, the compound was hydrolyzed to afford the polyurethane dendrimer with hydroxyl groups on the surface. The compound with the additional hydroxyl groups was subjected to further reactions with isocyanate intermediate to obtained the second generation of polyurethane dendrimers (8a-8d). Repeating the hydrolysis and Curtius rearrangement steps, finally led to the third generation of polyurethane dendrimers (9a-9d) (Figure 25).

Figure 24. Synthesis of isocyanate intermediate.
Figure 25. Synthesis of polyurethane dendrimers.
$^1$H-NMR and $^{13}$C NMR were used to analyze the polyurethane dendrimers formed, however the NMR spectra did not give enough information to characterize the differences between generations. The chemical shifts of the different generations in the NMR spectra are very similar; only the integrals in $^1$H NMR are different. However, in the higher generation dendrimers, the integrals are very big and it is hard to determine precise integral ratios. At the same time, NMR spectra of polymers always have broad peaks, and coupling constants could not always be detected. Therefore, NMR spectra for polymers are not fully interpretable. With MALDI-TOF MS, the molecular weights of polyurethane dendrimers in different generations can be measured.$^{26}$ (Table 6)

Table 6. Yields and MALDI-TOF MS of polyurethane dendrimers

<table>
<thead>
<tr>
<th>Core</th>
<th>Generation</th>
<th>First generation (7)</th>
<th>Second generation (8)</th>
<th>Third generation (9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diethylene glycol (a)</td>
<td>Isolated Yields</td>
<td>100%</td>
<td>87%</td>
<td>64%</td>
</tr>
<tr>
<td></td>
<td>$\text{M}+\text{Na}^+$</td>
<td>831.32</td>
<td>831.35</td>
<td>2067.80</td>
</tr>
<tr>
<td></td>
<td>$\text{M}+\text{K}^+$</td>
<td>847.29</td>
<td>847.31</td>
<td>2083.78</td>
</tr>
<tr>
<td>Triethylene glycol (b)</td>
<td>Isolated Yields</td>
<td>87%</td>
<td>72%</td>
<td>60%</td>
</tr>
<tr>
<td></td>
<td>$\text{M}+\text{Na}^+$</td>
<td>875.34</td>
<td>875.43</td>
<td>2111.83</td>
</tr>
<tr>
<td></td>
<td>$\text{M}+\text{K}^+$</td>
<td>891.32</td>
<td>891.39</td>
<td>2127.80</td>
</tr>
<tr>
<td>(c)</td>
<td>Isolated Yields</td>
<td>83%</td>
<td>69%</td>
<td>57%</td>
</tr>
<tr>
<td></td>
<td>$\text{M}+\text{Na}^+$</td>
<td>1376.54</td>
<td>1376.45</td>
<td>3231.27</td>
</tr>
<tr>
<td></td>
<td>$\text{M}+\text{K}^+$</td>
<td>1392.52</td>
<td>1392.43</td>
<td>3247.24</td>
</tr>
<tr>
<td>(d)</td>
<td>Isolated Yields</td>
<td>75%</td>
<td>69%</td>
<td>54%</td>
</tr>
<tr>
<td></td>
<td>$\text{M}+\text{Na}^+$</td>
<td>951.37</td>
<td>951.51</td>
<td>2187.86</td>
</tr>
<tr>
<td></td>
<td>$\text{M}+\text{K}^+$</td>
<td>967.35</td>
<td>967.46</td>
<td>2203.83</td>
</tr>
</tbody>
</table>
3-3-3. Solvent effect\textsuperscript{27}

1,4-Dioxane was first used as solvent in the preparation of polyurethane dendrimers, because its polarity compared well with benzene. Instead of the anticipated polyurethane dendrimer, however, the major product was compound 10 (from \textsuperscript{1}H and \textsuperscript{13}C NMR), no matter what kind of compound we used as the core.

\[
\text{Acetic acid 3-(3-(3-acetoxypropoxy)-5-{3-[3,5-bis-(3-acetoxypropoxy)phenyl]ureido}phenoxy)propyl ester (10)}
\]

This compound 10 was a result of the reaction between isocyanate and another carboxylic acid molecule (Figure 26).\textsuperscript{28} The key step in Curtius rearrangement is the rate of decomposition reaction of acyl azide. 1,4-Dioxane and benzene are two common solvents for Curtius rearrangement. The major differences between these two solvents are polarity and boiling point. 1,4-Dioxane is the more polar solvent, which may have an effect on the carbonyl group so that the double bond character between N\textsubscript{a} and N\textsubscript{b} decreases. Therefore, the energy of activation needed for the decomposition reaction is decreased, and the reaction rate increases. At the mean time, the higher reflux temperature of 1,4-dioxane also increases the rate of decomposition. Because of these two factors, 1,4-dioxane will facilitate the azide decomposition and form isocyanate faster, compared to benzene. The unreacted carboxylic acid will react with the isocyanate directly, which leads to the formation of compound 10.
Figure 26. Mechanism of Curtius rearrangement.

3-3-4. Sizes of polyurethane dendrimers

To have some sense of the sizes of those polyurethane dendrimers, the diameters of all polyurethane dendrimers in different generations were calculated using Chem3D Ultra 8.0 based on PM3 (semi-empirical level) optimized structures. The diameters of polyurethane dendrimers are around 20 Å bigger when the generations of polyurethane dendrimers are one higher (Table 7). Calculations were attempted with Gaussian 98 to calculate their volumes in solvent, however, the dendrimers are too large for ab initio calculations. For those small dendrimers in first generation, the radii of dendrimers are around 7-11 Å.
Table 7. Diameters of polyurethane dendrimers

<table>
<thead>
<tr>
<th>Core</th>
<th>First generation (7)</th>
<th>Second generation (8)</th>
<th>Third generation (9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diethylene glycol (a)</td>
<td>30 Å</td>
<td>50 Å</td>
<td>70 Å</td>
</tr>
<tr>
<td>Triethylene glycol (b)</td>
<td>33 Å</td>
<td>53 Å</td>
<td>73 Å</td>
</tr>
<tr>
<td>(<a href="#">c</a>)</td>
<td>36 Å</td>
<td>56 Å</td>
<td>76 Å</td>
</tr>
<tr>
<td>(<a href="#">d</a>)</td>
<td>37 Å</td>
<td>57 Å</td>
<td>77 Å</td>
</tr>
</tbody>
</table>

3-4. Conclusions

Polymer-supported DPPA was used in the divergent syntheses of polyurethane dendrimers in different generations with different cores. Purification became easier in the synthesis because a simple filtration could remove DPPA and all other phosphorous derivatives.

Four molecules with different sizes, branching numbers or properties were used as core molecules. All of the molecular weights of these polyurethane dendrimers were determined by MALDI-TOF mass spectrum, which established the formation of the dendrimers, while NMR could not afford enough information on the characterization of the dendrimers. The diameters of all polyurethane dendrimers were calculated using Chem3D Ultra based on PM3 (semi-empirical level) optimized structures.
Solvents selection was also considered in the synthesis. Compared to 1,4-dioxane, benzene is better solvent in the divergent synthesis of polyurethane dendrimers with polymer-supported DPPA.

3-5. Experimental section

**General Experimental Information.** All manipulations were performed in oven-dried glassware under a nitrogen atmosphere unless otherwise mentioned. All solvents and reagents were dried or purified using standard procedures and were distilled freshly before use. The standard workup included washing the reaction mixture with water followed by brine, then the separated organic phase was dried over magnesium sulfate, and concentrated in vacuo. Phenol resin was purchased from Advanced ChemTech (1.3 - 1.5 mmol/g loading). Column chromatography was performed on silica gel (Natland International Corp. 200 – 400 mesh) using the indicated solvents. TLC analyses were carried out using C4 silica gel plates (Silicycle Inc.). Melting points were determined with a Gallenkamp melting point apparatus and were uncorrected. $^1$H and $^{13}$C NMR spectra were recorded on a 200 or 300 MHz FT-NMR spectrometer (Bruker Avance) in CDCl$_3$, acetone-d$_6$, methanol-d$_4$ or DMSO-d$_6$ (Aldrich). IR spectra were determined as a neat film (using NaCl plate) or KBr pellet on a Perkin-Elmer 1600 FT-IR spectrophotometer. MALDI-TOF MS spectra were performed on a Bruker Reflex III TOF mass spectrometer (Bruker, Billerica, MA) equipped with a nitrogen laser ($\lambda$ 337 nm, Laser Science, Franklin, MA).
Synthesis and spectra data

Preparation of 3,5-bis-(3-hydroxypropoxy)benzoic acid methyl ester (3). In a 100 mL round bottom flask, methyl 3,5-dihydroxybenzoate (1.68 g, 10 mmol, 1.0 eq), K₂CO₃ (3.30 g, 24 mmol, 2.4 eq), 3-bromo-1-propanol (2.78 g, 20 mmol, 2.0 eq) and acetone (50 mL) were placed. The reaction mixture was refluxed overnight under nitrogen. The mixture was concentrated with a rotary evaporator to afford a thick slurry. The slurry was then washed with distilled water (100 mL) and ether (100 mL) to afford crude 3,5-bis-(3-hydroxypropoxy)benzoic acid methyl ester as a white solid: ¹H NMR (acetone-d₆, 300 MHz) δ 1.96 (quint, J = 6.3 Hz, 4H), 3.71 (m, 4H), 3.85 (s, 3H), 3.87 (br, 2H), 4.12 (t, J = 6.3 Hz, 4H), 6.73 (t, J = 2.2 Hz, 1H), 7.11 (d, J = 2.3 Hz, 2H); ¹³C NMR (acetone-d₆, 75 MHz) δ 33.13, 52.41, 58.89, 66.02, 106.71, 108.35, 132.90, 161.23, 167.05.

Preparation of 3,5-bis-(3-hydroxypropoxy)benzoic acid (4). The crude 3,5-bis-(3-hydroxypropoxy)benzoic acid methyl ester was dissolved in THF (20 mL) without further purification, then NaOH solution (2.5 M, 30 mL) was added. The mixture was heated to 60 °C and stirred overnight. After cooling to room temperature, THF and aqueous layers were
separated. The aqueous layer was acidified by HCl to pH < 7, and evaporated to afford a white solid with crude product and NaCl. Acetone (50 mL) was then added to the white solid and stirred overnight. After filtration, the white solid was washed carefully with acetone (100 mL). The combined filtrates were evaporated to afford a white solid, which was further vacuum evaporated overnight to remove water completely. The crude 3,5-bis-(3-hydroxypropoxy)benzoic acid was ready for the next step without further purification. \(^1\)H NMR (DMSO-d\(_6\), 300 MHz) \(\delta\) 1.84 (quint, \(J = 6.2\) Hz, 4H), 3.53 (t, \(J = 5.8\) Hz, 4H), 4.04 (t, \(J = 6.3\) Hz, 4H), 4.55 (br, 2H), 6.70 (m, 1H), 7.02 (d, \(J = 2.1\) Hz, 2H), 12.98 (br, 1H); \(^{13}\)C NMR (DMSO-d\(_6\), 75 MHz) \(\delta\) 32.03, 57.24, 64.98, 105.70, 107.32, 132.79, 159.79, 166.99.

**Preparation of 3,5-bis-(3-acetoxypropoxy)benzoic acid (5).** 3,5-Bis-(3-hydroxypropoxy)benzoic acid was dissolved in a mixture of pyridine and acetic anhydride (20 mL, 20 mol% of acetic anhydride). The mixture was stirred at room temperature under nitrogen for 40 hours, then quenched with distilled water (20 mL). Concentrated HCl solution was added to acidify the solution to pH \(\approx\) 2. The solution was extracted with EtOAc (30 mL \(\times\) 3). The combined organic layers were washed with HCl solution (1 M, 30 mL), distilled water (30 mL (3) and brine (30 mL), then evaporated. Purification was performed by silica-gel column chromatography (1:1 petroleum ether/diethyl ether with 0.5 % AcOH) to give pure 3.5-bis-(3-acetoxypropoxy)benzoic acid as a white solid (3.33 g, 94% overall yield from methyl 3,5-dihydroxybenzoate): 1H NMR (CDCl\(_3\), 300 MHz) \(\delta\) 2.03 (s, 6H), 2.08 (quint, \(J = 6.0\) Hz, 4H),
4.03 (t, J = 6.1 Hz, 4H), 4.22 (t, J = 6.2 Hz, 4H), 6.63 (t, J = 2.3 Hz, 1H), 7.19 (d, J = 2.3 Hz, 2H), 10.80 (br, 1H); 13C NMR (DMSO-d6, 75 MHz) (20.82, 28.33, 61.09, 64.54, 107.34, 108.13, 131.07, 159.70, 171.17, 171.19; IR (neat film) νmax 2965 (br), 1738, 1594, 1447, 1371, 1246, 1171, 1055, 836, 772 cm⁻¹.

Preparation of 3-[3,5-bis-(3-hydroxypropoxy)phenoxy]propan-1-ol (6c). In a 100 mL round bottom flask, benzene-1,3,5-triol (0.63 g, 5 mmol, 1.0 eq), K₂CO₃ (2.50 g, 18 mmol, 3.6 eq), 3-bromo-1-propanol (2.10 g, 15 mmol, 3.0 eq) and acetone (40 mL) were placed. The reaction mixture was refluxed overnight under nitrogen. The mixture was concentrated with a rotary evaporator to afford a thick slurry which was then partitioned between distilled water and ether. The aqueous layer was then evaporated to get a white solid with crude product, KBr and K₂CO₃. Acetone (50 mL) was added to the white solid and stirred overnight. After filtration, the white solid was washed carefully with acetone (100mL). The combined filtrates were evaporated to get a white solid, which was further vacuum evaporated overnight to remove water completely. The product, 3-[3,5-bis-(3-hydroxypropoxy)phenoxy]propan-1-ol (1.16 g, 77% yield), was pure enough for the further reaction: ¹H NMR (DMSO-d₆, 300 MHz) δ 1.81 (quint, J = 6.3 Hz, 6H), 3.51 (t, J = 5.8 Hz, 6H), 3.96 (t, J = 6.4 Hz, 6H), 4.51 (br, 3H), 6.04 (s, 3H); ¹³C NMR (DMSO-d₆, 75 MHz) δ 32.12, 57.34, 64.59, 93.66, 160.52.
Preparation of 3-[4-(hydroxypropoxy)phenoxy]propan-1-ol (6d). In a 100 mL round bottom flask, benzene-1,4-diol (0.55 g, 5 mmol, 1.0 eq), K$_2$CO$_3$ (1.66 g, 12 mmol, 2.4 eq), 3-bromo-1-propanol (1.53 g, 11 mmol, 2.2 eq) and acetone (40 mL) were placed. The reaction mixture was refluxed overnight under nitrogen. The mixture was concentrated with a rotary evaporator to afford a thick slurry which was then partitioned between distilled water and ether. The aqueous layer was then evaporated to get a white solid with crude product, KBr and K$_2$CO$_3$. Acetone (50 mL) was added to the white solid and stirred overnight. After filtration, the white solid was washed carefully by acetone (100mL). The combined filtrates were evaporated to get a white solid, which was further vacuum evaporated overnight to remove water completely. The obtained 3-[4-(hydroxyl-propoxy)-phenoxy]-propan-1-ol (0.78 g, 69% yield) was pure enough for further reaction: $^1$H NMR (acetone-d$_6$, 300 MHz) δ 1.91 (quint, $J = 6.3$ Hz, 4H) 3.70 (t, $J = 6.2$ Hz, 4H), 4.01 (t, $J = 6.4$ Hz, 4H), 6.83 (s, 4H); $^{13}$C NMR (acetone-d$_6$, 75 MHz) δ 33.40, 59.07, 65.97, 116.03, 154.09.

General procedure I for syntheses of polyurethane dendrimers with acetoxyl groups on the periphery. 3.5-Bis-(3-acetoxypropoxy)benzoic acid, polymer-supported DPPA and triethylamine were mixed in a round bottom flask with benzene under a nitrogen atmosphere. The mixture was stirred for 3 hours, and then core compounds or polyurethane dendrimers with hydroxyl groups on the periphery in the last generation was added. The mixture was further heated to reflux. After cooling to room temperature, the resin was removed by filtration and washed with EtOAc (60 mL). The combined filtrates were washed with aqueous NaOH solution
(1 M, 20 mL × 3), distilled water (20 mL × 3) and brine (20 mL). After drying over MgSO₄, solvent was removed under vacuum to afford the crude product.

**General procedure II for hydrolysis of polyurethane dendrimers with acetoxy groups on the periphery into polyurethane dendrimers with hydroxyl groups on the periphery.** The polyurethane dendrimers with acetoxy groups on the periphery obtained above were dissolved in a solution of 5 mol% of K₂CO₃ in a mixture of MeOH and distilled water (2:1) (50 mL) and stirred for 2 hours. The mixture was vacuum evaporated to afford a white solid. Acetone (50 mL) was added into the round bottom flask with the white solid and stirred overnight. After filtration and washing with more acetone (100 mL), the combined filtrates were vacuum evaporated to afford crude product. After purification and vacuum evaporation overnight, the formed polyurethane dendrimers with hydroxyl groups on the periphery were used as the starting material in the next step.

**Preparation of diethylene glycol cored first generation - OAc (DEG-FG-OAc) (7a).** The general procedure I was followed using 3,5-bis-(3-acetoxypropoxy)benzoic acid (177 mg, 0.5 mmol, 2.5 eq), polymer-supported DPPA (0.6 g, ~0.72 mmol, 3.6 eq) and Et₃N (120 mg, 1.2 mmol, 6.0 eq) with benzene (10 mL). Diethylene glycol (21 mg, 0.2 mmol, 1.0 eq) was then added and the mixture refluxed for 24 h. Purification was performed by silica-gel column chromatography (1:1 to 1:2 hexanes/EtOAc) to give pure diethylene glycol cored first generation – OAc (DEG-FG-OAc) as colorless oil (0.17 g, 100% yield): ¹H NMR (CDCl₃, 300 MHz) δ 2.02 (m, 20H), 3.71 (t, \( J = 4.2 \) Hz, 4H), 3.94 (t, \( J = 6.1 \) Hz, 8H), 4.18 (t, \( J = 6.3 \) Hz, 8H), 4.27 (t, \( J = 4.5 \) Hz, 4H), 6.11 (t, \( J = 2.0 \) Hz, 2H), 6.56 (d, \( J = 2.0 \) Hz, 4H), 7.08 (br, 2H); ¹³C
Preparation of diethylene glycol cored first generation - OH (DEG-FG-OH). The general procedure II was carried out on diethylene glycol cored first generation – OAc (DEG-FG-OAc) obtained above. Purification was performed by silica-gel column chromatography (10:1 CHCl₃/MeOH) to give diethylene glycol cored first generation - OH (DEG-FG-OH) as colorless oil (0.13 g, 100% yield): ¹H NMR (acetone-d₆, 300 MHz) δ 1.93 (quint, J = 6.2 Hz, 8H), 3.71 (m, J = 5.0 Hz, 16H), 4.04 (t, J = 6.3 Hz, 8H), 4.23 (m, 4H), 6.18 (t, J = 2.1 Hz, 2H), 6.81 (d, J = 2.2 Hz, 4H), 8.63 (br, 2H); ¹³C NMR (acetone-d₆, 75 MHz) δ 32.94, 58.71, 64.26, 65.19, 69.55, 96.08, 97.76, 141.39, 153.91, 161.18; IR (neat film) νₘₐₓ 3322 (br), 2954, 2885, 1732, 1715, 1614, 1557, 1445, 1261, 1163, 1064, 832 cm⁻¹.

Preparation of diethylene glycol cored second generation - OAc (DEG-SG-OAc) (8a). The general procedure I was followed using 3,5-bis-(3-acetoxypropoxy)benzoic acid (177 mg, 0.5 mmol, 5.0 eq), polymer-supported DPPA (1.0 g, ~1.2 mmol, 12.0 eq) and Et₃N (182 mg, 1.8 mmol, 18.0 eq) with benzene (10 mL). A solution of diethylene glycol cored first generation - OH (DEG-FG-OH) (64 mg, 0.1 mmol, 1.0 eq) in acetone (1 mL) was added and heated to reflux for 36 h. Purification was performed by silica-gel column chromatography (1:1, 1:2 to 2:5 hexanes/EtOAc) to give pure diethylene glycol cored second generation - OAc (DEG-SG-OAc) as a white viscous solid (0.18 g, 87% yield): ¹H NMR (CDCl₃, 300 MHz) δ 2.02 (m, 48H), 3.74
(m, 4H), 3.96 (t, $J = 6.0$ Hz, 24H), 4.20 (t, $J = 6.3$ Hz, 24H), 4.27 (m, 4H), 6.14 (t, $J = 2.1$ Hz, 6H), 6.56 (m, 4H), 6.62 (d, $J = 1.6$ Hz, 8H), 6.99 (br, 2H) 7.13 (br, 4H); $^{13}$C NMR (CDCl$_3$, 75 MHz) $\delta$ 20.92, 28.50, 28.72, 61.23, 61.74, 64.37, 69.23, 96.63, 97.39, 97.60, 139.52, 139.85, 153.39, 160.24, 171.08; MALDI-TOF MS $m/z$ [M+Na$^+$] calcd for C$_{98}$H$_{128}$N$_6$O$_{41}$Na$^+$ 2067.80, found 2067.47 and [M+K$^+$] calcd for C$_{98}$H$_{128}$N$_6$O$_{41}$K$^+$ 2083.78, found 2083.63.

**Preparation of diethylene glycol cored second generation - OH (DEG-SG-OH).** The general procedure II was carried out on diethylene glycol cored second generation – OAc (DEG-SG-OAc) obtained above. Purification was performed by silica-gel column chromatography (10:1 CHCl$_3$/MeOH) to give pure diethylene glycol cored second generation - OH (DEG-SG-OH) as a white viscous solid (0.15 g, 100% yield): $^1$H NMR (acetone-d$_6$, 300 MHz) $\delta$ 1.92 (m, 16H), 2.08 (m, 8H), 2.85 (br, 8H), 3.70 (m, 20H), 4.03 (m, 24H), 4.26 (m, 12H), 6.17 (m, 6H), 6.79 (m, 8H), 6.83 (m, 4H), 8.63 (m, 6H); $^{13}$C NMR (acetone-d$_6$, 75 MHz) $\delta$ 26.63, 33.26, 59.03, 62.10, 64.63, 65.16, 65.54, 69.85, 96.42, 96.66, 98.08, 98.26, 141.76, 154.24, 161.27, 161.47.

**Preparation of diethylene glycol cored third generation - OAc (DEG-TG-OAc) (9a).** The general procedure I was followed using 3,5-bis-(3-acetoxypropoxy)benzoic acid (177 mg, 0.5 mmol, 10.0 eq), polymer-supported DPPA (1.0 g, ~1.2 mmol, 24.0 eq) and Et$_3$N (182 mg, 1.8 mmol, 36.0 eq) with benzene (10 mL). A solution of diethylene glycol cored second generation - OH (DEG-SG-OH) (86 mg, 0.05 mmol, 1.0 eq) in acetone (1 mL) was added and the mixture refluxed reflux for 48 h. Purification was performed by silica-gel column chromatography (1:1, 1:2 to 1:4 hexanes/EtOAc) to give pure diethylene glycol cored third generation - OAc (DEG-TG-OAc) as a white viscous solid (0.14 g, 64% yield): MALDI-TOF MS $m/z$ [M+Na$^+$] calcd for
Preparation of triethylene glycol cored first generation – OAc (TEG-FG-OAc) (7b). The general procedure I was followed using 3,5-bis-(3-acetoxypropoxy)benzoic acid (177 mg, 0.5 mmol, 2.5 eq), polymer-supported DPPA (0.6 g, ~0.72 mmol, 3.6 eq) and Et₃N (120 mg, 1.2 mmol, 6.0 eq) with benzene (10 mL). Triethylene glycol (30 mg, 0.2 mmol, 1.0 eq) was added and the mixture refluxed for 24 h. Purification was performed by silica-gel column chromatography (1:1 to 1:2 hexanes/EtOAc) to give pure triethylene glycol cored first generation – OAc (TEG-FG-OAc) as colorless oil (0.15 g, 87% yield): ¹H NMR (CDCl₃, 300 MHz) δ 2.02 (m, 20H), 3.67 (s, 4H), 3.73 (t, J = 5.9 Hz, 4H), 3.95 (t, J = 6.0 Hz, 8H), 4.19 (t, J = 6.2 Hz, 8H), 4.30 (t, J = 4.5 Hz, 4H), 6.13 (m, 2H), 6.60 (d, J = 1.0 Hz, 4H), 7.03 (br, 2H); ¹³C NMR (CDCl₃, 75 MHz) δ 20.91, 28.50, 61.21, 64.35, 69.51, 70.79, 96.73, 97.54, 139.68, 153.34, 160.27, 171.03; MALDI-TOF MS m/z [M+Na⁺] calcd for C₄₀H₅₆N₂O₁₈Na⁺ 875.34, found 875.43 and [M+K⁺] calcd for C₄₀H₅₆N₂O₁₈K⁺ 891.32, found 891.39.

Preparation of triethylene glycol cored first generation – OH (TEG-FG-OH). The general procedure II was carried out on triethylene glycol cored first generation – OAc (TEG-FG-OAc) obtained above. Purification was performed by silica-gel column chromatography (10:1 CHCl₃/MeOH) to give triethylene glycol cored first generation - OH (TEG-FG-OH) as a colorless oil (0.12 g, 100% yield): ¹H NMR (acetone-d₆, 300 MHz) δ 1.92 (quint, J = 6.2 Hz, 8H), 3.61 (s, 4H), 3.70 (m, 16H), 4.04 (t, J = 6.3 Hz, 8H), 4.22 (t, J = 4.7 Hz, 4H), 6.18 (t, J =
2.2 Hz, 2H), 6.82 (d, J = 2.1 Hz, 4H), 8.63 (br, 2H); $^{13}$C NMR (acetone-d$_6$, 75 MHz) δ 33.28, 59.03, 64.65, 65.53, 69.99, 71.20, 96.45, 98.12, 141.74, 154.28, 161.48.

**Preparation of triethylene glycol cored second generation – OAc (TEG-SG-OAc) (8b).** The general procedure I was followed using 3,5-bis-(3-acetoxypropoxy)benzoic acid (177 mg, 0.5 mmol, 5.0 eq), polymer-supported DPPA (1.0 g, ~1.2 mmol, 12.0 eq) and Et$_3$N (182 mg, 1.8 mmol, 18.0 eq) with benzene (10 mL). A solution of triethylene glycol cored first generation - OH (TEG-FG-OH) (69 mg, 0.1 mmol, 1.0 eq) in acetone (1 mL) was added and the mixture refluxed for 36 h. Purification was performed by silica-gel column chromatography (1:1 to 1:4 hexanes/EtOAc) to give pure triethylene glycol cored second generation – OAc (TEG-SG-OAc) as a white viscous solid (0.15 g, 72% yield): $^1$H NMR (CDCl$_3$, 300 MHz) δ 2.02 (m, 48H), 3.67 (s, 4H), 3.74 (m, 4H), 3.94 (m, 24H), 4.24 (m, 28H) 6.13 (m, 6H), 6.64 (m, 12H), 7.21 (br, 6H); $^{13}$C NMR (CDCl$_3$, 75 MHz) δ 20.89, 28.47, 28.70, 60.07, 61.21, 61.68, 64.33, 64.55, 69.44, 70.93, 96.59, 97.52, 139.69, 139.87, 153.43, 160.21, 171.06; MALDI-TOF MS m/z [M+Na$^+$] calcd for C$_{100}$H$_{132}$N$_6$O$_{42}$Na$^+$ 2111.83, found 2111.80 and [M+K$^+$] calcd for C$_{100}$H$_{132}$N$_6$O$_{42}$K$^+$ 2127.80, found 2127.77.

**Preparation of triethylene glycol cored second generation – OH (TEG-SG-OH).** The general procedure II was carried out on triethylene glycol cored second generation – OAc (TEG-SG-OAc) obtained above. Purification was performed by silica-gel column chromatography (30:1 CHCl$_3$/MeOH) to give pure triethylene glycol cored second generation - OH (TEG-SG-OH) as a white viscous solid (0.15 g, 100% yield): $^1$H NMR (acetone-d$_6$, 300 MHz) δ 1.93 (m, 24H), 3.72 (m, 32 H), 4.04 (m, 32H), 4.28 (t, J = 6.5 Hz, 4H), 6.18 (m, 6H), 6.80 (m, 12H), 8.55 (m, 6H).
Preparation of triethylene glycol cored third generation – OAc (TEG-TG-OAc) (9b). The general procedure I was followed using 3,5-bis-(3-acetoxypropoxy)benzoic acid (177 mg, 0.5 mmol, 10.0 eq), polymer-supported DPPA (1.0 g, ~1.2 mmol, 24.0 eq) and triethylamine (182 mg, 1.8 mmol, 36.0 eq) with benzene (10 mL). A solution of triethylene glycol cored second generation - OH (TEG-SG-OH) (86 mg, 0.05 mmol, 1.0 eq) in acetone (1 mL) was added to reflux for 48 h. Purification was performed by silica-gel column chromatography (1:1 to 1:4 hexanes/EtOAc) to give pure triethylene glycol cored third generation - OAc (TEG-TG-OAc) as a white viscous solid (0.14 g, 60% yield): MALDI-TOF MS m/z [M+Na\(^+\)] calcd for C\(_{220}\)H\(_{284}\)N\(_{14}\)O\(_{90}\)Na\(^+\) 4584.80, found 4584.41 and [M+K\(^+\)] calcd for C\(_{220}\)H\(_{284}\)N\(_{14}\)O\(_{90}\)K\(^+\) 4600.77, found 4600.35.

Preparation of 3-[3,5-bis-(3-hydroxypropoxy)phenoxy]propan-1-ol cored first generation – OAc (THB-FG-OAc) (7c). The general procedure I was followed using 3,5-bis-(3-acetoxypropoxy)benzoic acid (283 mg, 0.8 mmol, 4.0 eq), polymer-supported DPPA (1.0 g, ~1.2 mmol, 6.0 eq) and Et\(_3\)N (180 mg, 1.8 mmol, 9.0 eq) with benzene (10 mL). A solution of 3-[3,5-bis-(3-hydroxypropoxy)phenoxy]propan-1-ol (60 mg, 0.2 mmol, 1.0 eq) in acetone (1 mL) was added and the mixture refluxed for 24 h. Purification was performed by silica-gel column chromatography (2:1, 1:1 to 1:2 hexanes/EtOAc) to give pure 3-[3,5-bis-(3-hydroxypropoxy)phenoxy]propan-1-ol cored first generation – OAc (THB-FG-OAc) as a white viscous solid (0.22 g, 83% yield): \(^1\)H NMR (CDCl\(_3\), 300 MHz) \(\delta\) 2.03 (m, 36H), 3.98 (t, \(J = 6.0\) Hz, 18H), 4.21 (t, \(J = 6.2\) Hz, 12H), 4.31 (t, \(J = 6.0\) Hz, 6H), 6.04 (s, 3H), 6.14 (m, 3H), 6.59 (m, 6H), 6.69 (br, 3H); \(^{13}\)C NMR (CDCl\(_3\), 75 MHz) \(\delta\) 20.93, 28.49, 28.80, 61.21, 62.04, 64.38, 94.10, 96.71, 97.50, 139.65, 153.22, 160.28, 160.60, 171.06; MALDI-TOF MS m/z [M+Na\(^+\)] calcd for
Preparation of 3-[3,5-bis-(3-hydroxypropoxy)phenoxy]propan-1-ol cored first generation – OH (THB-FG-OH). The general procedure II was followed using 3-[3,5-bis-(3-hydroxypropoxy)phenoxy]propan-1-ol cored first generation – OAc (THB-FG-OAc) obtained above. Purification was performed by silica-gel column chromatography (10:1 to 5:1 CHCl₃/MeOH) to give pure 3-[3,5-bis-(3-hydroxypropoxy)phenoxy]propan-1-ol cored first generation – OH (THB-FG-OH) as a white solid (0.18 g, 100% yield): ¹H NMR (acetone-d₆, 300 MHz) δ 1.92 (quint, J = 6.2 Hz, 12H), 2.07 (quint, J = 6.0 Hz, 6H), 3.70 (m, 18H), 4.03 (t, J = 6.3 Hz, 18H), 4.26 (t, J = 6.2 Hz, 6H), 6.10 (s, 3H), 6.18 (t, J = 2.1 Hz, 3H), 6.80 (d, J = 2.1 Hz, 6H), 8.63 (br, 3H); ¹³C NMR (acetone-d₆, 75 MHz) δ 29.63, 33.26, 58.90, 59.03, 65.23, 65.54, 94.80, 96.39, 98.06, 141.77, 154.22, 161.48, 161.72.

Preparation of 3-[3,5-bis-(3-hydroxypropoxy)phenoxy]propan-1-ol cored second generation – OAc (THB-SG-OAc) (8c). The general procedure I was followed using 3,5-bis-(3-acetoxypropoxy)benzoic acid (283 mg, 0.8 mmol, 8.0 eq), polymer-supported DPPA (1.3 g, ~1.6 mmol, 16.0 eq) and Et₃N (200 mg, 2.0 mmol, 20.0 eq) with benzene (10 mL). A solution of 3-[3,5-bis-(3-hydroxypropoxy)phenoxy]propan-1-ol cored first generation – OH (THB-FG-OH) (110 mg, 0.1 mmol, 1.0 eq) in acetone (1 mL) was added and the mixture refluxed for 36 h. Purification was performed by silica-gel column chromatography (1:1 to 1:3 hexanes/EtOAc) to give pure 3-[3,5-bis-(3-hydroxypropoxy)phenoxy]propan-1-ol cored second generation – OAc (THB-SG-OAc) as a white solid (0.22 g, 69% yield): ¹H NMR (CDCl₃, 300 MHz) δ 2.02 (m,
Preparation of 3-[3,5-bis-(3-hydroxypropoxy)phenoxy]propan-1-ol cored second generation – OH (THB-SG-OH). The general procedure II was followed using 3-[3,5-bis-(3-hydroxypropoxy)phenoxy]propan-1-ol cored second generation – OAc (THB-SG-OAc) obtained above. Purification was performed by silica-gel column chromatography (10:1 to 5:1 CHCl₃/MeOH) to give pure 3-[3,5-bis-(3-hydroxypropoxy)phenoxy]propan-1-ol cored second generation – OH (THB-SG-OH) as a white viscous solid (0.19 g, 100% yield): ¹H NMR (methanol-d₄, 300 MHz) δ 1.96 (m, 42H), 3.74 (m, 42H), 4.01 (t, J = 6.2 Hz, 24H), 4.10 (t, J = 6.3 Hz, 18 H), 6.08 (s, 3H), 6.14 (m, 9H), 6.65 (m, 18) 7.89 (s, 9H).

Preparation of 3-[3,5-bis-(3-hydroxypropoxy)phenoxy]propan-1-ol cored third generation – OAc (THB-TG-OAc) (9c). The general procedure I was followed using 3,5-bis-(3-acetoxypropoxy)benzoic acid (283 mg, 0.8 mmol, 16.0 eq), polymer-supported DPPA (1.5 g, ~1.8 mmol, 36.0 eq) and Et₃N (212 mg, 2.1 mmol, 42.0 eq) with benzene (10 mL). A solution of 3-[3,5-bis-(3-hydroxypropoxy)phenoxy]propan-1-ol cored second generation – OH (THB-SG-OH) (135 mg, 0.05 mmol, 1.0 eq) in acetone (1 mL) was added and the mixture refluxed for 48 h. Purification was performed by silica-gel column chromatography (1:1 to 1:4 hexanes/EtOAc) to give pure 3-[3,5-bis-(3-hydroxypropoxy)phenoxy]propan-1-ol cored third generation – OAc.
(THB-TG-OAc) as a white viscous solid (0.20 g, 57% yield): MALDI-TOF MS m/z [M+Na$^+$] calcd for C$_{336}$H$_{429}$N$_{21}$O$_{135}$Na$^+$ 6940.72, found 6940.70 and [M+K$^+$] calcd for C$_{336}$H$_{429}$N$_{21}$O$_{135}$K$^+$ 6956.70, found 6957.19.

Preparation of 3-[4-(3-hydroxypropoxy)phenoxy]propan-1-ol cored first generation – OAc (DHB-FG-OAc) (7d). The general procedure I was followed using 3,5-bis-(3-acetoxypropoxy)benzoic acid (177 mg, 0.5 mmol, 2.5 eq), polymer-supported DPPA (0.6 g, ~0.72 mmol, 3.6 eq) and Et$_3$N (120 mg, 1.2 mmol, 6.0 eq) with benzene (10 mL). A solution of 3-[4-(3-hydroxypropoxy)phenoxy]propan-1-ol (45 mg, 0.2 mmol, 1.0 eq) in acetone (1 mL) was added and the mixture refluxed for 24 h. Purification was performed by silica-gel column chromatography (1:1 to 1:2 hexanes/EtOAc) to give pure 3-[4-(3-hydroxypropoxy)phenoxy]propan-1-ol cored first generation – OAc (DHB-FG-OAc) as a white solid (0.14 g, 75% yield): $^1$H NMR (CDCl$_3$, 300 MHz) δ 2.03 (m, 24H), 3.99 (m, 12H), 4.21 (t, J = 6.3 Hz, 8H), 4.33 (t, J = 6.2 Hz, 4H), 6.15 (t, J = 2.0 Hz, 2H), 6.56 (m, 4H), 6.81 (s, 4H); $^{13}$C NMR (CDCl$_3$, 75 MHz) δ 20.92, 28.51, 28.98, 61.20, 62.15, 64.38, 96.77, 97.53, 115.46, 139.60, 153.04, 153.22, 160.30, 171.03; MALDI-TOF MS m/z [M+Na$^+$] calcd for C$_{46}$H$_{60}$N$_2$O$_{18}$Na$^+$ 951.37, found 951.51 and [M+K$^+$] calcd for C$_{46}$H$_{60}$N$_2$O$_{18}$K$^+$ 967.35, found 967.46.

Preparation of 3-[4-(3-hydroxypropoxy)phenoxy]propan-1-ol cored first generation – OH (DHB-FG-OH). The general procedure II was followed using 3-[4-(3-hydroxypropoxy)phenoxy]propan-1-ol cored first generation – OAc (DHB-FG-OAc) obtained above. Purification was performed by silica-gel column chromatography (10:1 CHCl$_3$/MeOH) to give pure 3-[4-(3-hydroxypropoxy)phenoxy]propan-1-ol cored first generation – OH (DHB-FG-
OH) as a white solid (0.11 g, 100% yield): $^1$H NMR (acetone-$d_6$, 300 MHz) δ 1.92 (m, 12H), 3.70 (m, 12H), 4.04 (t, $J = 6.4$ Hz, 12H), 4.28 (t, $J = 6.3$ Hz, 4H), 6.18 (t, $J = 2.2$ Hz, 2H), 6.79 (d, $J = 2.1$ Hz, 4H), 6.86 (s, 4H), 8.01 (s, 2H); $^{13}$C NMR (acetone-$d_6$, 75 MHz) δ 32.56, 33.27, 59.02, 62.13, 65.64, 68.00, 96.40, 98.08, 116.23, 139.40, 152.13, 154.06, 161.47.

**Preparation of 3-[4-(3-hydroxypropoxy)phenoxy]propan-1-ol cored second generation – OAc (DHB-SG-OAc) (8d).** The general procedure I was followed using 3,5-bis-(3-acetoxypropoxy)benzoic acid (177 mg, 0.5 mmol, 5.0 eq), polymer-supported DPPA (1.0 g, ~1.2 mmol, 12.0 eq) and Et$_3$N (182 mg, 1.8 mmol, 18.0 eq) with benzene (10 mL). A solution of 3-[4-(3-hydroxypropoxy)phenoxy]propan-1-ol cored first generation – OH (DHB-FG-OH) (76 mg, 0.1 mmol, 1.0 eq) in acetone (1 mL) was added and the mixture refluxed for 36 h. Purification was performed by silica-gel column chromatography (1:1 to 2:3 hexanes/EtOAc) to give pure 3-[4-(3-hydroxypropoxy)phenoxy]propan-1-ol cored second generation – OAc (DHB-SG-OAc) as a white viscous solid (0.15 g, 69% yield): $^1$H NMR (CDCl$_3$, 300 MHz) δ 2.04 (m, 52H), 3.96-4.11 (m, 28H), 4.20-4.26 (m, 28H), 6.13-6.18 (m, 6H), 6.57-6.63 (m, 12H), 6.91 (m, 4H); $^{13}$C NMR (CDCl$_3$, 75 MHz) δ 20.92, 28.51, 29.67, 61.06, 61.13, 64.42, 97.12, 98.32, 115.08, 140.35, 156.06, 160.14, 160.46, 171.06; MALDI-TOF MS $m/z$ [M+Na$^+$] calcd for C$_{106}$H$_{136}$N$_6$O$_{42}$Na$^+$ 2187.86, found 2187.60 and [M+K$^+$] calcd for C$_{106}$H$_{136}$N$_6$O$_{42}$K$^+$ 2203.83, found 2203.60.

**Preparation of 3-[4-(3-hydroxypropoxy)phenoxy]propan-1-ol cored second generation – OH (DHB-SG-OH).** The general procedure II was followed using 3-[4-(3-hydroxypropoxy)phenoxy]propan-1-ol cored second generation – OAc (DHB-SG-OAc) obtained above. Purification was performed by silica-gel column chromatography (10:1 CHCl$_3$/MeOH) to
give pure 3-[4-(3-hydroxypropoxy)phenoxy]propan-1-ol cored second generation – OH (DHB-SG-OH) as a white viscous solid (0.13 g, 100% yield): $^1$H NMR (methanol-d$_4$, 300 MHz) $\delta$ 1.97 (m, 28H), 3.71 (m, 28H), 4.01 (t, $J$ = 6.2 Hz, 16H), 4.10 (t, $J$ = 6.2 Hz, 12H), 6.14 (t, $J$ = 2.2 Hz, 6H), 6.58 (m, 12H), 7.01 (s, 4H), 7.90 (s, 6H).

**Preparation of 3-[4-(3-hydroxypropoxy)phenoxy]propan-1-ol cored third generation – OAc (DHB-TG-OAc) (9d).** The general procedure I was followed using 3,5-bis-(3-acetoxypropoxy)benzoic acid (177 mg, 0.5 mmol, 10.0 eq), polymer-supported DPPA (1.0 g, ~1.2 mmol, 24.0 eq) and Et$_3$N (182 mg, 1.8 mmol, 36.0 eq) with benzene (10 mL). A solution of 3-[4-(3-hydroxypropoxy)phenoxy]propan-1-ol cored second generation – OH (DHB-SG-OH) (91 mg, 0.05 mmol, 1.0 eq) in acetone (1 mL) was added and the mixture refluxed for 48 h. Purification was performed by silica-gel column chromatography (1:1 to 1:4 hexanes/EtOAc) to give pure 3-[4-(3-hydroxypropoxy)phenoxy]propan-1-ol cored third generation – OAc (DHB-TG-OAc) as a white viscous solid (0.13 g, 54% yield): MALDI-TOF MS $m/z$ [M+Na$^+$] calcd for C$_{226}$H$_{288}$N$_{14}$O$_{90}$Na$^+$ 4660.83, found 4660.75 and [M+K$^+$] calcd for C$_{226}$H$_{288}$N$_{14}$O$_{90}$K$^+$ 4676.80, found 4676.76.

**Formation of acetic acid 3-(3-(3-acetoxypropoxy)-5-{3-[3,5-bis-(3-acetoxypropoxy)phenyl]ureido}phenoxy)propyl ester (10).** The general procedure I was followed using 3,5-bis-(3-acetoxy-propoxy)-benzoic acid, polymer-supported DPPA and Et$_3$N with 1,4-dioxane, then a
compound with multiple hydroxyl groups was added and the mixture refluxed. Desired polyurethane dendrimer products could not be detected by TLC chromatography. Purification was performed by silica-gel column chromatography (1:5 petroleum ether/diethyl ether). Desired products could not be isolated and detected by NMR spectroscopy. The predominant product after purification is acetic acid 3-(3-(3-acetoxypropoxy)-5-{3-[3,5-bis-(3-acetoxypropoxy)phenyl]ureido}phenoxy)propyl ester, obtained as a white solid: $^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 2.02 (m, 22H), 3.92 (t, $J = 6.01$ Hz, 8H), 4.18 (t, $J = 6.3$ Hz, 8H), 6.11 (t, $J = 1.9$ Hz, 2H), 6.55 (d, $J = 2.0$ Hz, 4H), 7.38 (br, 2H); $^{13}$C NMR (CDCl$_3$, 75 MHz) $\delta$ 20.90, 28.44, 61.25, 64.28, 96.62, 98.84, 140.13, 152.99, 160.24, 171.23.
References


13. [http://whatis.techtarget.com/definition/0,,sid9_gci515363,00.html](http://whatis.techtarget.com/definition/0,,sid9_gci515363,00.html)


Chapter IV. Polymer-bound organosilicon reagents

4-1. Introduction

Silicon is the second most abundant element in the earth’s crust. Traditionally, silicon was used in its most common inorganic form, that is, as silica, silicate and aluminosilicates. Organosilicon compounds are defined as those species which possess carbon-silicon bonds.¹ The study of organosilicon chemistry is over 100 years old. Since no organosilicon compound is known to occur naturally and the production of organosilicon compounds from the naturally occurring forms of silicon is both difficult and expensive, it has only become an important branch of chemistry during the last 40 years.² Organosilicon compounds were first prepared using the Friedel and Crafts dialkylzinc reaction.³ It was not until the unique properties of silicons were discovered that organosilicon derivatives became readily accessible to researchers.

4-1-1. Properties and applications of organosilicon compounds

Both silicon and carbon are members of Group IV of the periodic table. In spite of this close relationship, there are not only similarities but also striking differences between these elements. Silicon’s utility in organic synthesis depends upon three main factors: its relative bond strengths to other elements, its relative electronegativity, and the involvement or lack of involvement of its empty low-energy d-orbitals.
The physical properties of organosilicon compound are very similar to those of carbon analogues with comparable molecular weight, indicating that organosilicon compounds are quite stable. For their chemical properties, the silicon-carbon bond (360 kJ) is thermodynamically nearly as strong as a single C-C bond. Meanwhile, silicon (1.64) always appears less electronegative than carbon (2.35), resulting in strong polarization of C-Si bonds and in a tendency for the site of greatest reactivity at silicon. Therefore, a carbon-silicon bond is relatively stable towards homolytic fission, but is more readily cleaved by ionic reagents, either by nucleophilic attack at silicon or electrophilic attack at carbon.

Organosilicon derivatives have various applications in industry, synthesis and medicine. Its industrial applications mainly include organosilicon polymers with different properties, such as stationary phases of chromatographic columns. Organosilicon reagents have been applied to organic synthesis at an increasingly rapid rate, especially for the protection of alcohol groups and carbonyl groups. Organosilicon compounds also have some physiology, toxicology and medicinal applications.

4-1-2. Polymer-bound organosilicon chemistry

The unique nature and chemistry of organosilicon compounds is well-suited to solid-phase reactions because of the stability of the compounds and the predictability of the reaction processes and mechanisms. Unlike the more electropositive organometallic compounds, silicon reagents can be treated and stored much like their carbon analogs, because the hyperconjugation-like effect of carbon-silicon bonds can stabilize electron deficient $p$-orbitals in the $\beta$ position.
Moreover, the silicon-oxygen (531 kJ) and silicon-fluorine (807 kJ) bonds have high bond strength, making the protection and deprotection of silyl reactions simple with a good degree of stereocontrol.  

Polymer-bound organosilicon compounds are known and mostly used as linkers and protecting groups. The availability of solid-phase organosilanes could allow one to make a far fuller use of these valuable compounds. The products of solid-phase reactions afford useful arrays of functional groups that should be of value in the synthesis of diverse libraries and combinatorial chemistry.

4-2. Target and significance

A solid-phase silane was expected to be readily converted into a polymer-bound trialkylsilyl chloride. From this unstable silyl chloride intermediate, it was envisioned that further transformations would lead to polymer-bound silyl ketene, silyl azide and silyl cyanide species (Figure 27), and potentially silyl nitronates and silyldiazomethane as well.

![Figure 27. Polymer-bound organosilicon reagents](image-url)
The most significant contributions of incorporating these reagents into the solid phase are obvious. From the silyl chloride, several points of diversity can be accessed in a single step. The silyl group tends to stabilize reactive intermediates that are not normally isolable. As a result, product formation with these reagents affords fewer reaction by-products, so that purification are made easier. In addition, removal of the silyl group is facile and it involves chemistry which is compatible with most functional groups. Therefore, polymer-bound organosilicon intermediate would provide powerful new tools for the creation of new, useful libraries.

4-3. Solid supports

In solid-phase reactions, the choice of solid supports is very important. There has been a great deal of recent activities focusing on the solid phase.\(^9\)

4-3-1. Polystyrene resin

Most of the current solid phases are crosslinked polystyrene and their derivatives. However, when using polystyrene resin as a solid support, the loading of the functional groups is hard to analyze. In the reaction, poor swelling of the resin can prevent the solvent and reagents from accessing the interior of the beads, therefore, the solvent needs to be carefully chosen to optimize the solvent-solid phase compatibility and minimize rate effects arising from phase transfer considerations. Because of these issues, two other resins were selected for trials with organosilicon reagents.
4-3-2. Si-dimethylsilyl derivatized silica gel

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\text{Si-} \quad \text{Si-H}
\]

Si-dimethylsilyl derivatized silica gel is commercially available. Since this is a silica gel based resin, it will neither swell nor shrink in organic solvents, and is compatible with all kinds of organic solvents. While Si-dimethylsilyl derivatized silica gel is only surface functionalized, it has a high loading capacity of functional groups.\(^{10}\) Normally, the silane loading on the Si-dimethylsilyl derivatized silica gel is 1.5 mmol/g, while most polystyrene resin have loading at about 1.0 mmol/g.

Silica gel based silane resins have great advantages in application, but it also brings a drawback. Since silica has a huge absorption in the entire range of the IR spectrum, all the peaks of functional groups are overlapped and no meaningful information can observed. This leads to difficulties in analyzing the reaction processes.

4-3-3. TentaGel S Br

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\text{TG-} \quad \text{O} \quad \text{Br}
\]

Another potential resin is TentaGel-S-Br. It is a grafted copolymer consisting of polyethylene glycol on low crosslinked polystyrene. Because of the polyethylene glycol long chains, this resin has flexible linker spaces and is more compatible with polar solvents. The properties of this resin are highly dominated by polyethylene glycol.\(^{11}\)
4-4. Results

In preliminary studies, polymer-bound organosilicon reagents were prepared on chloromethylated polystyrene. The reactions did not work very well with very low yields of products. Therefore, Si-dimethylsilyl derivatized silica gel and TentaGel-S-Br were used for the rest of this study.

4-4-1. Si-dimethylsilyl derivatized silica gel

4-4-1-1. Preparation of coumarin from polymer-bound silyl ketene (Figure 28)

Si-dimethylsilyl derivatized silica gel was reacted with 6.0 equivalents of 1,3-dichloro-5,5-dimethylhydantoin to form polymer-bound silyl chloride resin (11).\(^\text{12}\) Since this resin is a moisture-sensitive intermediate, it must be handled in a nitrogen atmosphere and used for the next step immediately. This unstable silyl chloride intermediate was then reacted with 5.0 equivalents of a mixture of ethoxyacetylene and \(n\)-BuLi in THF to provide polymer-bound silyl ethoxyacetylene resin (12). The polymer-bound silyl ethoxyacetylene resin was swelled in freshly distilled DMF and warmed to 120 °C to complete a rearrangement and provide polymer-bound silyl ketene resin (13).\(^\text{13}\)

The polymer-bound silyl ketene resin was reacted with 5.0 equivalents of a mixture of salicylaldehyde and NaH in freshly distilled DMF through cyclization-elimination.\(^\text{14}\) After the reaction, the formed coumarin (14, 81% yield) was cleaved from the solid phase and stayed in the solution, so the separation from silyl derivatives was easy by a simple filtration.
4-4-1-2. Preparation of cyanohydrin from polymer-bound silyl cyanide (Figure 29)

The preparation of a polymer-bound silyl cyanide resin attracted attention because it could allow a safer transfer of the cyanide group, with a concomitant trapping action of the supported silicon atom. The chlorine of polymer-bound silyl chloride resin described above was exchanged with a large excess of TMSCN at 80 °C to form easily the polymer-bound silyl cyanide resin (15). After complete removal of the remaining TMSCN by washing with CH₂Cl₂, polymer-bound silyl cyanide was isolated.

To prove the synthetic utility of polymer-bound silyl cyanide resin, we attempted in the solid phase the well-known solution synthesis of cyanohydrin using TMSCN. A large excess of
benzaldehyde was added to polymer-bound silyl cyanide resin and heated to form 2-hydroxy-2-phenylacetonitrile (16) with 76 % yield.

\[
\begin{align*}
\text{Me}_3\text{SiCN} & \quad 80 \degree C, 36 \text{ h} \\
\text{Me}_3\text{SiCN} & \quad 90 \degree C, 24 \text{ h}
\end{align*}
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Figure 29. Preparation of cyanohydrin from polymer-bound silyl cyanide

4-4-1-3. Preparation of 3\textit{H}-1,3-oxazine-2,6-dione from polymer-bound silyl azide (Figure 30)

It is known that a halogen-azide exchange occurs in solution when reacting a high boiling silyl chloride with TMS-N\textsubscript{3}. The polymer-bound silyl chloride resin was exchanged with a large excess of TMS-N\textsubscript{3} at 85 °C to form polymer-bound silyl azide resin (17).\textsuperscript{15} After filtration and washing, 1.0 equivalent of maleic anhydride in benzene was added and the mixture was refluxed to provide 3\textit{H}-1,3-oxazine-2,6-dione (18, 62% yield).\textsuperscript{17}

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\begin{align*}
\text{Me}_3\text{SiN}_3 & \quad 85 \degree C, 72 \text{ h} \\
\text{Me}_3\text{SiN}_3 & \quad \text{benzene, reflux, 24 h}
\end{align*}
\]

Figure 30. Preparation of 3\textit{H}-1,3-oxazine-2,6-dione from polymer-bound silyl azide
4-4-2. TentaGel S Br

Because of the drawbacks described previously in using Si-dimethylsilyl derivatized silica gel, another potential solid phase that was examined for use in organosilicon chemistry is TentaGel-S-Br resin. Ten equivalents of a mixture of allyl alcohol and NaH was reacted with TentaGel-S-Br resin to provide TentaGel allyl ether resin (19). TentaGel allyl ether resin was coupled with Et$_2$SiH$_2$, catalyzed by Wilkinson’s catalyst, to form TentaGel silane resin (20). The peak observed at 2096 cm$^{-1}$ indicates the presence of Si-H bond. (Figure 31)

The TentaGel silane resin can be further converted to TentaGel silyl chloride resin, following the hydantoin reaction as described before. This TentaGel silyl chloride intermediate may be useful in the preparation of organosilicon reagents also.

**Figure 31.** Formation of TentaGel based polymer-bound silane
4-5. Conclusions

Polymer-bound organosilicon reagents, silyl ketene, silyl azide and silyl cyanide, were prepared from a polymer-bound trialkylsilyl chloride. Applications of these organosilicon reagents were surveyed using classical organic reactions. Solid phases compared included polystyrene resin, Si-dimethylsilyl derivatized silica gel and TentaGel-S-Br. The products of these solid-phase reactions afforded useful arrays of functional groups that should be of value in the synthesis of diverse libraries. The above organosilicon resins are, primarily, scaffolds for the assembly of solid phase compounds that are easily released and reagents for their use in solution phase combinatorial chemistry. The feasibility of further development of these reagents was proven.

4-6. Experimental data

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\text{Si}\quad\text{Si}\quad\text{Si}\quad\text{Si}\quad\text{Cl} \quad \xrightarrow{1,3\text{-dichloro-5,5-dimethylhydantoin}} \quad \text{CH}_2\text{Cl}_2, \quad 12\text{~h, r.t.} \quad \begin{array}{c} \text{Si}\quad\text{Si}\quad\text{Cl} \end{array}
\]

Preparation of polymer-bound silyl chloride resin (11). To a 10 mL round bottom flask under nitrogen was added silica gel based silane resin (200 mg, 0.30 mmol) and 1,3-dichloro-5,5-dimethylhydantoin (0.35 g, 1.80 mmol, 6.0 eq) in dry CH$_2$Cl$_2$ (4 mL). After stirring 6 hours, the mixture was filtered and washed with dry CH$_2$Cl$_2$ (5 mL × 3) and dry THF (5 mL × 3) under nitrogen. The obtained polymer-bound silyl chloride resin was used for subsequent reactions immediately after washing.
Preparation of polymer-bound silyl ethoxyacetylene resin (12). $n$-BuLi (1.2 mL of 1.4 M in hexane, 1.65 mmol, 5.5 eq) was added dropwise via syringe to a cooled (0 °C) solution of ethoxyacetylene (0.21 g of 50 % in hexane, 1.50 mmol, 5.0 eq) in anhydrous THF (8 mL). After stirring an additional 0.5 hour at 0 °C, the solution was transferred into a round bottom flask with polymer-bound silyl chloride resin under nitrogen and the mixture was stirred overnight at room temperature. The mixture was then filtered and the precipitate was washed well with dry MeOH and dry THF. The polymer-bound silyl ethoxyacetylene resin was red-brown.

Preparation of polymer-bound silyl ketene resin (13). Freshly distilled DMF (5 mL) was added into the round bottom flask with polymer-bound silyl ethoxyacetylene resin, and the mixture was heated to 120 °C for 2 hours. After cooling, the polymer-bound silyl ketene resin was ready for use.

Synthesis of coumarin from polymer-bound silyl ketene resin (14). NaH (40 mg, 1.65 mmol, 5.5 eq) and freshly distilled DMF (5 mL) were placed in a dry 10 mL round bottom flask under
nitrogen. Salicylaldehyde (0.18 g, 1.50 mmol, 5.0 eq) was added and the mixture was stirred under nitrogen at room temperature for 20 min until hydrogen evolution had ceased. The mixture was then transferred into a round bottom flask with polymer-bound silyl ketene and stirred overnight. The reaction was quenched with water and the mixture was filtered to remove the solid phase. The solution was poured into distilled water (100 mL) and extracted with ether (40 mL × 3). The combined organic layers were washed with saturated NaHCO₃ solution (30 mL × 3), distilled water (30 mL × 3), brine (30 mL) and dried with MgSO₄. Purification was performed by silica-gel column chromatography (4:1 hexanes/EtOAc) to give pure coumarin as a white solid (35 mg, 81% yield): ¹H NMR (DMSO-d₆, 300 MHz) δ 6.46 (d, J = 9.6 Hz, 1H), 7.29-7.37 (m, 2H), 7.55-7.61 (m, 1H), 7.68 (dd, J = 7.7, 1.5 Hz, 1H), 8.03 (d, J = 9.5 Hz, 1H). ¹³C NMR (DMSO-d₆, 75 MHz) δ 116.21, 116.27, 118.73, 124.48, 128.44, 131.94, 144.21, 153.49, 159.94. GC-MS m/z [M⁺] 146. The spectral data were identical to those reported in the literature.¹⁴

Preparation of polymer-bound silyl cyanide resin (15). Polymer-bound silyl chloride resin (200 mg, 0.3 mmol) was placed in a round bottom flask fitted with a reflux condenser under nitrogen. TMSCN (2 mL) was added as a single portion and the reaction mixture was gently stirred at 80 °C for 36 hours, cooled to room temperature, filtered under a positive nitrogen pressure and rinsed with CH₂Cl₂ (10 mL × 5) to give polymer-bound silyl cyanide resin.
Preparation of 2-hydroxy-2-phenylacetonitrile (16). To the round bottom flask with polymer-bound silyl cyanide resin, freshly distilled benzaldehyde (2 mL) was added under nitrogen. The mixture was heated at 90 °C for 24 hours, filtered and rinsed with CH$_2$Cl$_2$ (10 mL × 5). The filtrate was evaporated to dryness and the crude was purified by flash column chromatography, eluting with 4:1 hexanes/EtOAc to yield 30 mg (76% yield) of pure 2-hydroxy-2-phenylacetonitrile: $^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 5.49 (s, 1H), 7.37-7.43 (m, 3H), 7.44-7.48 (m, 2H). $^{13}$C NMR (CDCl$_3$, 75 MHz) $\delta$ 63.62, 119.14, 126.31, 128.89, 129.30, 136.21. GC-MS m/z [M$^+$] 133. The spectral data were identical to those reported in the literature.$^{16b}$

Preparation of polymer-bound silyl azide resin (17). Polymer-bound silyl chloride resin (200 mg, 0.3 mmol) was placed in a round bottom flask fitted with a reflux condenser under nitrogen. TMS-N$_3$ (2 mL) was added as a single portion and the reaction mixture was gently stirred at 85 °C for 72 hours, cooled to room temperature, filtered under a positive nitrogen pressure and rinsed with CH$_2$Cl$_2$ (10 mL × 5) to give polymer-bound silyl azide resin.
Preparation of 3H-1,3-oxazine-2,6-dione (18). To a round bottom flask with polymer-bound silyl azide resin, maleic anhydride (30 mg, 0.3 mmol, 1.0 eq) and freshly distilled benzene (3 mL) were added under nitrogen. The mixture was warmed to 50 °C for 20 hours, and the color of the solution turned from white to yellow, and then red. The red solution was chilled to 5 °C, then filtered and washed with cool benzene (2 mL × 2). Evaporation of the filtrate caused separation of a red-brown wax which was taken up in dry ether. Addition of n-hexanes caused the precipitation of 21 mg of 3H-1,3-oxazine-2,6-dione (62% yield): $^1$H NMR (DMSO-d$_6$, 300 MHz) $\delta$ 5.60 (d, $J$ = 7.3 Hz, 1H), 7.64 (dd, $J$ = 7.4, 5.5 Hz, 1H). $^{13}$C NMR (DMSO-d$_6$, 75 MHz) $\delta$ 94.85, 137.29, 146.67, 165.67. GC-MS m/z [M$^+$] 113. The spectral data were identical to those reported in the literature.$^{17}$

Preparation of TentaGel allyl ether resin (19). Allyl alcohol (200 mg, 3.5 mmol, 10.0 eq) was dropwise added into a dry round bottom flask with NaH (96 mg, 4.0 mmol, 11.4 eq) in freshly distilled DMF (5 mL) at 0 °C under nitrogen. The mixture was warmed to room temperature and stirred for 2 hours, then transferred into another round bottom flask with TentaGel-S-Br resin (1.0 g, 0.35 mmol) in freshly distilled DMF (5 mL) under nitrogen. The mixture was warmed to 50 °C and stirred for 24 hours. After cooling, the mixture was filtered and washed with dry
MeOH (20 mL × 5) and dry THF (20 mL × 5). After vacuum evaporation, the TentaGel allyl ether was obtained. FT-IR (cm⁻¹): 2870, 1638, 1453, 1350, 1105, 701.

Preparation of TentaGel silane resin (20). TentaGel allyl ether resin obtained above was placed in a dry round bottom flask and purged with nitrogen for 5 min. Then the flask was charged with 10 mL of a toluene solution of RhCl(PPh₃)₃ (3.5 mg, 0.0035 mmol, 1.0 mol %) and stirred for several minutes to swell the resin. Et₂SiH₂ (92 mg, 1.05 mmol, 3.0 eq) was added dropwise with a syringe at room temperature, and the reaction mixture was stirred for 6 hours. After filtration, the resin was washed with toluene (20 mL × 5) and THF (20 mL × 5), then dried under vacuum to provide TentaGel silane resin. FT-IR (cm⁻¹): 2874, 2096, 1453, 1351, 1109, 700.
References


