Graphical Abstract
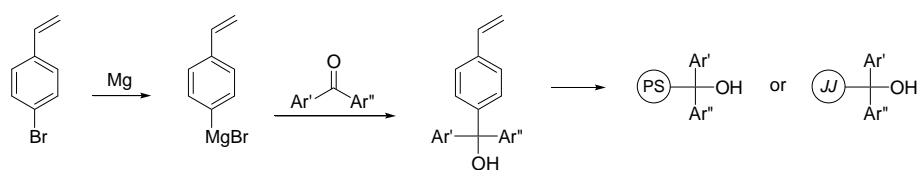
An improved and general synthesis of monomers for incorporating trityl linker groups into polystyrene synthesis supports

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Abstract—A straightforward and general synthesis of trityl alcohols in which one of the aryl rings is substituted with a vinyl group is presented. The synthesis of the alcohols involves the direct addition of the Grignard reagent prepared from 4-bromostyrene to substituted benzophenones. These compounds were used to incorporate trityl linker groups into polystyrene-based organic synthesis supports. Both non-cross-linked and cross-linked (*J*anda*J*el[TM]) polystyrene have been prepared using these monomers. © 2004 Elsevier Science. All rights reserved

1. Introduction

In polymer-supported synthesis, linker moieties are required for the attachment of the synthesis substrate to the polymer support. Commonly these linker groups are based on standard protecting groups used in traditional solution-phase synthesis.[1] Trityl groups[2] are often used in this context since they can be prepared with various subsituents on the aryl rings that modulate their cleavage and because they can serve as protecting groups for alcohols,[3] acids,[4] amides,[5] amines,[6] amino acids,[7] hydroxamic acids,[8] imidazoles,[9] nucleotides,[10] thiols,[11] and thioureas.[12] The most common trityl group functionalized polymers used in this regard are cross-linked unsubstituted trityl resin[13] and 2-chlorotrityl resin.[14]

The polymer bound trityl alcohol groups of such resins are usually introduced by one of three methods: (1) The sequence of lithiation of a halogentated phenyl group of a preformed polymer, followed by treatment with a benzophenone.[15] (2) The sequence of Friedal-Crafts acylation of a preformed polymer with a benzoyl chloride followed by the addition of an aryl Grignard reagent.[10,16] (3) Direct lithiation of cross-linked polystyrene using a 1:1 complex of *n*-BuLi and TMEDA, followed by reaction with a benzophenone.[17] However, a significant drawback of all of these methods is that since they derivatize preformed polymers, it is difficult to determine the final composition of the product polymer and to accurately control the its homogeneity and loading level.[18]

Therefore, in order to prepare better defined polymers with easily controllable levels of trityl group incorporation, the functional monomer, (4-ethenylphenyl)diphenyl methanol (**1a**) (Scheme 1), has been prepared and co-polymerized with styrene and divinylbenzene under suspension polymerization conditions to afford polystyrene trityl resin by Kurth et al.[19] Their first reported synthesis of **1a** involved the addition of *t*-BuLi to 4-bromostyrene followed by reaction of the thus formed aryl lithium species with benzophenone.[19a] The same authors also reported a procedure involving the use of potassium, potassium iodide and anhydrous magnesium chloride to activate 4-bromostyrene.[19b] Later, Rimmer et al. reported that the first synthesis of **1a** was not readily reproducible due to anionic polymerisation of the starting material, and that an inverse addition procedure (4-bromostyrene added to *t*-BuLi) afforded acceptable and reproducible yields of **1a**.[20] Most recently, Janda et al. have reported the only other method for the preparation of **1a** which involves a 4 step synthetic sequence starting with 4-vinylbenzyl alcohol.[21] While these reported syntheses do produce the desired product, they are less than optimal, especially when considering the reported difficulty in reproducing the results, the costs and hazards associated with using *t*-BuLi and potassium, and the length of the most recent synthesis. Furthermore, they have not been demonstrated to be general methods for the preparation of substituted trityl monomers, as they only report the synthesis of **1a**.

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We are interested in the preparation and applications of polymers that incorporate monomers derivatized with various functional groups[22] and have successfully used the Grignard reagent formed from 4-bromostyrene to prepare monomers containing sulfide[23] and phosphine[24] groups. Herein we report our results regarding using this reagent to prepare **1a** and derivatives of it and the incorporation of these into both cross-linked and, for the first time, non-cross-linked polystyrene polymers.

2. Results and discussion

Obviously, the most direct method for preparing compounds **1** is via the nucleophilic addition of a styrene equivalent to a substituted benzophenone. Hence this was the method used in the first reported synthesis of such compounds.[19a] However, the nucleophile used was an aryl lithium and such a strongly nucleophilic species readily initiates anionic polymerization of styrene molecules and makes this method low yielding and unreliable.[20] Therefore we chose to examine the addition of the relatively less nucleophilic styrene Grignard reagent, prepared simply from 4-bromostyrene and magnesium,[25] to a series of benzophenones (Scheme 1).
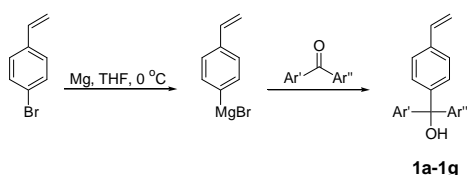
1a: Ar' = Ar" = Ph (65%)   **1b**: Ar' = Ph, Ar" = 4-Me-C_6H_4 (65%)

1c: Ar' = Ph, Ar" = 4-OMe-C_6H_4 (67%)   **1d**: Ar' = Ar" = 4-OMe-C_6H_4 (75%)

1e: Ar' = Ph, Ar" = 2-Cl-C_6H_4 (77%)   **1f**: Ar' = Ph, Ar" = 4-Cl-C_6H_4 (72%)

1g: Ar' = Ar" = 4-Cl-C_6H_4 (82%)

Scheme 1. Synthesis of monomers **1a-f**.

Gratifyingly, these reactions afforded good yields (65-82%) of the desired products (**1a-g**), even when the benzophenones were substituted with deactivating electron donating groups. As might be expected, the benzophenones substituted with electron withdrawing substituents afforded slightly higher yields (**1e-g**). In all of these reactions, 4-bromostyrene was used in excess of the benzophenone since any unreacted Grignard reagent was converted to easily removable styrene. When it was used as the limiting reagent, the excess benzophenone was more tedious to separate from the desired alcohol. It should be noted that the synthesis of only monomer **1a** has been previously reported and that monomer **1d** represents a new linker group. To our knowledge, no previously used trityl linker in solid-phase synthesis contained more than one electron donating group in addition to the alkyl group from the polystyrene backbone, to modulate the electron density at the incipient carbocation center.[26] Therefore the use of these types of more highly

substituted linkers may allow for the synthesis substrates to be more selectively or mildly cleaved from the polymers.

We next examined the use of our monomers in the preparation of both non-cross-linked and cross-linked polystyrenes (Scheme 2). Co-polymerization of **1a** with styrene in the presence of AIBN afforded soluble polymer **2a**, which is reported here for the first time. In order to determine the efficiency of incorporation of the functional monomers in this polymerization process, monomer **1c** was co-polymerized with styrene to afford **2b**. Analysis of **2b** by ^{1}H NMR shows that reaction of a 10:1 ratio of styrene:**1c** results in the observed incorporation of these monomers in a ratio of 8.8:1. This indicates that monomers with electron donating substituents are slightly more reactive than styrene in the polymerization process.

Suspension co-polymerization of **1a**, **1e** and **1f** with styrene and the *J*anda*J*el^{TM} cross-linker, 1,4-bis(4-vinylphenoxy)butane, afforded *JJ*-Tr-OH (**3a**), *JJ*-2-Cl-Tr-OH (**3b**), and *JJ*-4-Cl-Tr-OH (**3c**), respectively (Scheme 2).[27-29] It is important to note that the loading levels of **3b** and **3c**, based on elemental analysis of chlorine, are slightly lower than expected (theoretical 1.5 mmol/g loading each, observed 1.3 mmol/g (**3b**), and 1.1 mmol/g (**3c**)). This implies that, in contrast to **1c**, monomers **1e** and **1f** are incorporated somewhat more slowly than styrene is during polymerization process. These differences in reactivity must therefore be taken into account when preparing polymers with specific loading levels. In order to determine the rate of incorporation of **1a** into **3a**, we treated **3a** sequentially with TBDMSCl/DMSO[16c,30] and BnNH$_2$ to form **4** and **5**, respectively. Elemental analysis of both **4** (chlorine, 5.4%) and **5** (nitrogen, 2.1%) indicates that **3a** has a loading level close to the theoretical 1.5 mmol/g.

Scheme 2. Synthesis of polymers **2-5**.
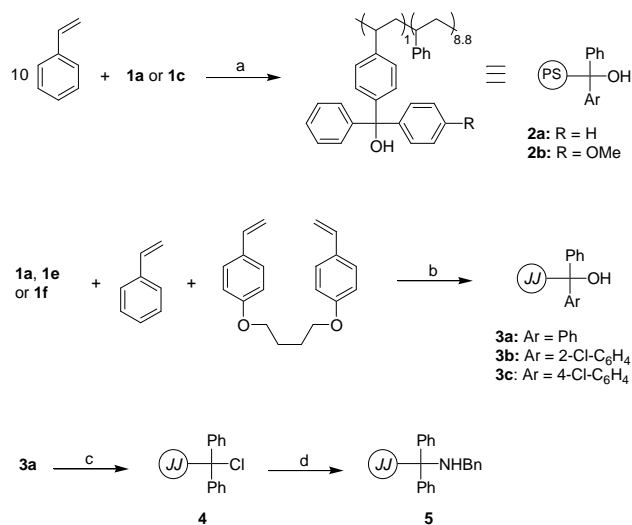
Reagents and condtions: (a) AIBN, toluene, 80 °C. (b) chlorobenzene, benzoyl peroxide, water, acacia gum, NaCl, 85 °C. (c) TBDMSCl, DMSO, CH$_2$Cl$_2$, rt. (d) BnNH$_2$, THF, rt.

3. Conclusions

In summary, we have developed an improved, general and reproducible method for the synthesis of a variety of substituted triphenyl methanols that contain a vinyl group. These compounds can be used to directly introduce trityl linker groups into both soluble and insoluble polystyrene polymers. Given the wide range of substituted benzophenones that are commercially available or easily synthesized, our methodology allows access to a great number of new trityl linkers having varying acid sensitivities, which should further enhance the applicability of such linkers. The utility of such linkers in the new non-cross-linked polymers **2a-b** in polymer-supported peptide/organic synthesis is currently being assessed.

4. Experimental

4.1. General

All reagents were obtained from the Aldrich, Lancaster or Acros chemical companies and were used without further purification. All moisture sensitive reactions were carried out in dried glassware under a N_2 atmosphere. Tetrahydrofuran was distilled under a N_2 atmosphere over sodium and benzophenone. Dichloromethane was distilled under a N_2 atmosphere over calcium hydride Merck silica gel 60 (230-400 mesh) was used for chromatography. Thin layer chromatography analysis was performed using glass plates coated with silica gel 60 F_{254}. The NMR spectra were recorded using a Bruker DRX 300 spectrometer. Chemical shift data is expressed in ppm with reference to TMS. EI-MS data was recorded on a Finnigan MAT 96 mass spectrometer.

4.2.1. (4-Ethenylphenyl)diphenyl methanol (1a).

Procedure A. Benzophenone (12.4 g, 68 mmol) was added dropwise at 0 °C to a solution of the Grignard reagent prepared from 4-bromostyrene (14.0 g, 76 mmol) and Mg (2.2 g, 92 mmol) in dry THF (250 mL). After TLC analysis indicated electrophile consumption was complete, the reaction mixture was diluted with diethyl ether (1 L), and then washed sequentially with water (500 mL), 10% aqueous HCl (500 mL), saturated aqueous $NaHCO_3$ (500 mL) and brine (500 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (5% EtOAc/hexanes) to afford **1a** as a white solid (12.6 g, 44 mmol, 65%). Mp 72-73 °C. ^{1}H NMR (300 MHz, CDCl$_3$) δ 2.77 (s, 1H, exchangeable with D$_2$O), 5.24 (dd, 1H, J = 10.9, 0.9 Hz), 5.74 (dd, 1H, J = 17.6, 0.9 Hz), 6.68 (dd, 1H, J = 17.6, 10.9 Hz), 7.17-7.36 (m, 14H). ^{13}C NMR (75 MHz, CDCl$_3$) δ 81.9, 114.1, 125.8, 127.3 (2C), 127.9 (4C), 128.0 (4C), 128.2 (2C), 128.7 (2C), 136.4, 144.3, 146.8 (2C). HR EI-MS: calcd for C$_{21}$H$_{18}$O, 286.1358; found 286.1356.

4.2.2. (4-Ethenylphenyl)-(4-methylphenyl)phenyl methanol (1b).

This was prepared by procedure A using 4-methylbenzophenone (1.4 g, 6.9 mmol) to afford **1b** as a pale yellow solid (1.3 g, 4.5 mmol, 65%). Mp 74-76 °C. ^{1}H NMR (300MHz, CDCl$_3$) δ 2.34 (s, 3H), 2.73 (s, 1H, exchangeable with D$_2$O), 5.40 (dd, 1H, J = 10.9, 0.9 Hz), 5.73 (dd, 1H, J = 17.6, 0.9 Hz), 6.68 (dd, 1H, J = 17.6, 10.9 Hz), 7.10-7.36 (m, 13H). ^{13}C NMR (75 MHz, CDCl$_3$) δ 21.0, 81.8, 114.0, 125.7 (2C), 127.2, 127.8 (2C), 127.90 (2C), 127.92 (2C), 128.1 (2C), 128.7 (2C), 136.38, 136.44, 137.0, 143.9, 146.6, 146.9. HR EI-MS: calcd for C$_{22}$H$_{20}$O, 300.1514; found 300.1512.

4.2.3. (4-Ethenylphenyl)-(4-methoxyphenyl)phenyl methanol (1c).

This was prepared by procedure A using 4-methoxybenzophenone (6.5 g, 31 mmol) to afford **1c** as a pale yellow liquid (6.5 g, 21 mmol, 67%). ^{1}H NMR (300 MHz, CDCl$_3$) δ 2.76 (s, 1H, exchangeable with D$_2$O), 3.78 (s, 3H), 5.23 (dd, 1H, J = 10.9, 0.9 Hz), 5.73 (dd, 1H, J = 17.6, 0.9 Hz), 6.68 (dd, 1H, J = 17.6, 10.9 Hz), 6.81-7.35 (m, 13H). ^{13}C NMR (75 MHz, CDCl$_3$) δ 55.3, 81.6, 113.3 (2C), 114.0, 125.8 (2C), 127.2, 127.8 (2C), 127.9 (2C), 128.0 (2C), 129.2 (2C), 136.4, 136.5, 139.1, 146.7, 147.0, 158.8. HR EI-MS: calcd for C$_{22}$H$_{20}$O$_2$, 316.1463; found 316.1459.

4.2.4. Bis(4-methoxyphenyl)phenyl methanol (1d).

This was prepared by procedure A using 4,4'-dimethoxybenzophenone (1.5 g, 6.1 mmol) to afford **1d** as a pale yellow liquid (1.6 g, 4.6 mmol, 75%). ^{1}H NMR (300MHz, CDCl$_3$) δ 2.71 (s, 1H, exchangeable with D$_2$O), 3.79 (s, 6H), 5.23 (dd, 1H, J = 10.9, 0.9 Hz), 5.73 (dd, 1H, J = 17.6, 0.9 Hz), 6.67 (dd, 1H, J = 17.6, 10.9 Hz), 6.81-7.36 (m, 12H). ^{13}C NMR (75 MHz, CDCl$_3$) δ 55.4 (2C), 81.4, 113.3 (4C), 114.1, 125.8 (2C), 128.1 (2C), 129.2 (4C), 136.47, 136.51, 139.5 (2C), 147.0, 158.8 (2C). HR EI-MS: calcd for C$_{23}$H$_{22}$O$_3$, 346.1569; found 346.1545.

4.2.5. (2-Chlorophenyl)-(4-ethenylphenyl)phenyl methanol (1e).

This was prepared by procedure A using 2-chlorobenzophenone (7.5 g, 35 mmol) to afford **1e** as a colourless liquid. (8.5 g, 27 mmol, 77%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 4.39 (s, 1H, exchangeable with D$_2$O), 5.20 (dd, 1H, J = 10.9, 0.8 Hz), 5.71 (dd, 1H, J = 17.6, 0.8 Hz), 6.69 (dd, 1H, J = 17.6, 10.9 Hz), 6.74-7.34 (m, 13H). ^{13}C NMR (100 MHz, CDCl$_3$) δ 82.4, 114.1, 125.9 (2C), 126.4, 127.4, 127.7 (2C), 127.96 (2C), 128.0 (2C), 129.1, 131.3, 131.4, 133.2, 136.4, 136.6, 143.6, 145.2, 145.5. HR EI-MS: calcd for C$_{21}$H$_{17}$ClO, 320.0968; found 320.0971.

4.2.6. (4-Chlorophenyl)-(4-ethenylphenyl)phenyl methanol (1f).

This was prepared by procedure A using 4-chlorobenzophenone (7.5 g, 35 mmol) to afford **1f** as a pale yello liquid. (8.0 g, 25 mmol, 72%). ^{1}H NMR (300 MHz, CDCl$_3$) δ 2.75 (s, 1H, exchangeable with D$_2$O), 5.25 (dd, 1H, J = 10.9, 0.7 Hz), 5.76 (dd, 1H, J = 17.6, 0.7 Hz), 6.69 (dd, 1H, J = 17.6, 10.9 Hz), 7.13-7.41 (m, 13H). ^{13}C NMR (75 MHz, CDCl$_3$) δ 81.6, 114.4, 126.0 (2C), 127.6 (2C), 127.9 (2C), 128.1 (2C), 128.2 (2C), 129.4 (2C), 130.2, 133.3,

136.3, 136.8, 145.4, 146.1, 146.4. HR EI-MS: calcd for $C_{21}H_{17}ClO$, 320.0968; found 320.0960.

4.2.7. Bis(4-chlorophenyl)phenyl methanol (1g). This was prepared by procedure A using 4,4'-dichlorobenzophenone (1.7 g, 6.8 mmol) to afford **1g** as a pale yellow liquid (2.0 g, 5.6 mmol, 82%). ^{1}H NMR (300 MHz, CDCl$_3$) δ 2.72 (s, 1H, exchangeable with D$_2$O), 5.27 (dd, 1H, J = 10.9, 0.7 Hz), 5.75 (dd, 1H, J = 17.6, 0.7 Hz), 6.69 (dd, 1H, J = 17.6, 10.9 Hz), 7.14-7.35 (m, 12H). ^{13}C NMR (75 MHz, CDCl$_3$) δ 81.2, 114.6, 126.0 (2C), 127.9 (2C), 128.2 (4C), 129.2 (4C), 133.5 (2C), 136.1, 137.0, 144.8 (2C), 145.5. HR EI-MS: calcd for $C_{21}H_{16}Cl_2O$, 354.0578; found 354.0576.

4.3.1. Poly(styrene-co-[4-ethenylphenyl]diphenyl-methanol) (2a). *Procedure B.* To a solution of styrene (18.2 g, 175 mmol) and **1a** (5.0 g, 17 mmol) in toluene (100 mL) was added AIBN (0.3 g, 1.7 mmol). The mixture was purged with N$_2$ for 30 min and the solution was stirred at 90 °C for 24 h. The solution was concentrated *in vacuo* and then the residue was taken up in 10 mL of THF. This solution was added dropwise to vigorously stirred cold methanol (200 mL). The white precipitate was filtered and dried to afford **2a** as a white powder (11.6 g, 50%). ^{1}H NMR (300 MHz, CDCl$_3$) δ 1.25-2.16 (bm, 33H), 6.47–7.48 (bm, 58H). Polymers **2** are soluble in THF, EtOAc, CH$_2$Cl$_2$, DMF. They are not soluble in methanol, ethanol, ether, water.

4.3.2. Poly(styrene-co-[4-ethenylphenyl]-[4-methoxyphenyl]phenyl-methanol) (2b). This was prepared by procedure B using styrene (16.5 g, 158 mmol), **1c** (5.0 g, 16 mmol) and AIBN (0.3 g, 1.6 mmol) in toluene (100 mL) to afford **2b** as a white powder (8.8 g, 45%). ^{1}H NMR (300 MHz, CDCl$_3$) δ 1.25-2.16 (bm, 33H), 3.74 (bs, 3H), 6.47–7.48 (bm, 57H). The ratio of monomer incorporation into **2b** was determined by ^{1}H NMR to be 8.8:1 (styrene:**1c**). This corresponds to a loading level of 0.8 mmol/g of polymer.

4.4.1. Poly(styrene-co-[4-ethenylphenyl]diphenyl methanol-co-1,4-bis[4-vinylphenoxy]butane) (*JandaJel-Tr-OH, 3a*). *Procedure C.* A solution of acacia gum (6.0 g) and NaCl (2.75 g) in warm deionion water (45 °C, 150 mL) was placed in a 150 mL flanged reaction vessel equipped with a mechanical stirrer and deoxygenated by purging with N$_2$ for 2 h.[31] A solution of **1a** (4.3 g, 15.0 mmol), styrene (6.3 mL, 57 mmol), cross-linker (0.4 g, 1.5 mmol), AIBN (0.2 g) in chlorobenzene (10 mL) was injected into the rapidly stirred aqueous solution. This mixture was heated at 85 °C for 20 h. The crude polymer was collected and washed with hot water (3 x 100 mL) and then placed in a Soxhlet extractor and washed with THF for one day. The beads were recovered, washed with methanol, diethyl ether and hexanes. The shrunken beads **3a** (8.0 g, 80%) were dried *in vacuo*. Polymers **3** were isolated as beads that mostly ranged in size between 100 and 200 mesh. They exhibit good swelling in solvents such as THF, benzene and

CH$_2$Cl$_2$. They exhibit poor or no swelling in solvents such as acetonitrile, dimethyl formamide, ethanol and water.

4.4.2. Poly(styrene-co-[2-chlorophenyl]-[4-ethenylphenyl]phenyl methanol-co-1,4-bis[4-vinylphenoxy]butane) (*JandaJel-2-Cl-Tr-OH, 3b*). This was prepared by procedure C using of **1e** (4.8 g, 15.0 mmol), styrene (5.7 mL, 50 mmol), cross-linker (0.4 g, 1.5 mmol), and AIBN (0.2 g) in chlorobenzene (10 mL) to afford **3b** (7.3 g, 73%). Elemental analysis was used to determine the chlorine content (4.6%) and thus the loading level of 1.3 mmol Cl/g of **3b**.

4.4.3. Poly(styrene-co-[4-chlorophenyl]-[4-ethenylphenyl]phenyl methanol-co-1,4-bis[4-vinylphenoxy]butane) (*JandaJel-4-Cl-Tr-OH, 3c*). This was prepared by procedure C using of **1f** (4.8 g, 15.0 mmol), styrene (5.7 mL, 50 mmol), cross-linker (0.4 g, 1.5 mmol), and AIBN (0.2 g) in chlorobenzene (10 mL) to afford **3c** (7.2 g, 72%). Elemental analysis was used to determine the chlorine content (3.7%) and thus the loading level of 1.1 mmol Cl/g of **3c**.

4.5. Poly(styrene-co-[4-ethenylphenyl]diphenyl chloride-co-1,4-bis[4-vinylphenoxy]butane) (*JandaJel-Tr-Cl, 4*). To a magnetically stirred suspension of **3a** (2.0 g) in anhydrous CH$_2$Cl$_2$ (20 mL) at rt and under a N$_2$ atmosphere was added *tert*-butyldimethylsilyl chloride (2.3 g, 15.0 mmol) and dimethyl sulfoxide (0.5 g, 6.0 mmol). Stirring was continued for 3 h at rt, at which time the resin was filtered off, and washed sequentially with dichloromethane, diethyl ether, and hexanes. The shrunken beads **4** (2.2 g) were dried *in vacuo*. Elemental analysis was used to determine the chlorine content (5.4%) and thus the loading level of 1.5 mmol Cl/g of **4**.

4.6. Poly(styrene-co-[4-ethenylphenyl]diphenyl benzylamine -co-1,4-bis[4-vinylphenoxy]butane) (*JandaJel-Tr-NHCH$_2$Ph, 5*). To a magnetically stirred suspension of **4** (0.2 g, 0.3 mmol) in THF (5 mL) at rt was added benzylamine (0.2 g, 1.5 mmol). Stirring was continued for 24 h at rt, at which time the resin was filtered off, and washed sequentially with dichloromethane, methanol, diethyl ether, and hexanes. The shrunken beads **5** (0.2 g) were dried *in vacuo*. Elemental analysis was used to determine the nitrogen content (2.1%) and thus the loading level of 1.5 mmol N/g of **5**.

Chemical Company for supplying many of the reagents used in this study.

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