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Notes

Reactive Alkyne and Azide Solid Supports To Increase Purity of Novel Polymeric Stars and Dendrimers via the "Click" Reaction

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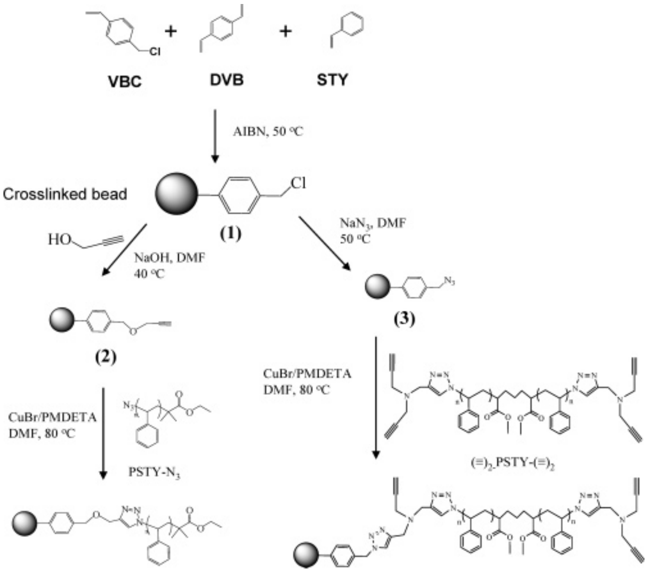
Introduction

"Click" reactions between azide and alkyne functionality on the chain ends or side groups of polymers have arisen as a preferred methodology to make complex polymer architectures.[1−12] Gao and Matyjaszewski[13] have synthesized 3- and 4-arm polystyrene stars in one pot reactions using stoichiometric amounts of azido to alkynyl functional polymers. The starting polystyrene was initially synthesized by "living" radical polymerization, atom transfer radical polymerization (ATRP);[14−16] the bromine end groups were converted to azides[17] and then coupled to a trifunctional alkyne compound in the presence of CuBr and ligand. The yields were increased to greater than 95% when using low molecular weight azido functional polystyrene (PSTY-N_3, $M_n = 1400$) by the addition of an equal amount of Cu(0) to CuBr. However, the yields were lower when higher molecular weight PSTY-N_3 ($M_n = 6400$) was used, ranging between 83 and 89% under the same copper concentrations. Alternatively, Whittaker et al.[12] synthesized mikto 3-arm stars and second-generation polymeric dendrimers in high yields through the slow addition of the small alkyne compound to the azide functional polymer with CuBr/ligand in DMF.

The main problem with attempting to use stoichiometric amounts of polymeric azido end groups to either polymeric or small compound alkynyl groups is that the exact amount of polymer with azido end groups is not known. The polymer used in the "click" reactions consists of not only the azide functional polymer chains but also small amounts of non-azide functional chains formed through either bimolecular radical termination during the ATRP process or loss of end group functionality during the azidation reaction through elimination reactions. The other problem is that there is a small error in determining number-average molecular weight (M_n) by SEC, which is used to calculate the moles and therefore stoichiometry required in subsequent "click" reactions. A simple method to overcome this problem is to use an excess of the azide functional polymer. However, this will result in unreacted azide functional polymer that cannot be removed and which may then become an unwelcome participant in side reactions when synthesizing more complex architectures such as stars and dendrimers. Opsteen and van Hest[18] used azide reactive Merrifield resin to remove the unreacted alkyne functional polymer based on the approach used by Loeber et al.[19] in small molecule "click" reactions. They found that all the unreacted excess alkyne functional poly(methyl methacrylate) (PMMA−≡) was removed, leaving behind a very small amount of dead PMMA formed in the ATRP synthesis of PSTY-Br, the PMMA−≡ precursor. However, Merrifield resins are expensive and are therefore limited to removal of small quantities of polymer.

Scheme 1. Synthesis and Scavenging of Reactive Alkynyl or Azido Functional Cross-Linked Solid Supports with the End Groups of Linear Polystyrene



In this Note, we demonstrate the facile synthesis and use of reactive azide or alkyne functionalized cross-linked solid supports to remove excess polymer with the respective azide or alkyne functionality on the chain end. This strategy was used to increase the yield and purity of novel 3-arm PSTY stars and second-generation PSTY dendrimer with solketals (i.e., protection groups for 1,2-dialcohols) on the peripheral chain ends of the structures. These may be converted easily to hydroxyl groups with acid treatment to yield complex structures with an alcohol functional corona. These hydroxyl groups allow the preparation of many kinds of compounds, including alkyl halides, esters, carboxylic acids, alkenes, ketones, aldehydes, and ethers. Therefore, many types of biological and organic compounds can be coupled to the periphery of the polymeric star or dendrimer.

Results and Discussion

Synthesis of Alkyne and Azide Functional Solid Supports. Cross-linked solid supports with chlorine functionality were first synthesized using monomers, 4-vinylbenzyl chloride (VBC, 4 mL, 0.028 mol), STY (3.2 mL, 0.028 mol), and divinylbenzene (DVB, 0.120 mL, 8.42×10^{-4} mol) which were polymerized

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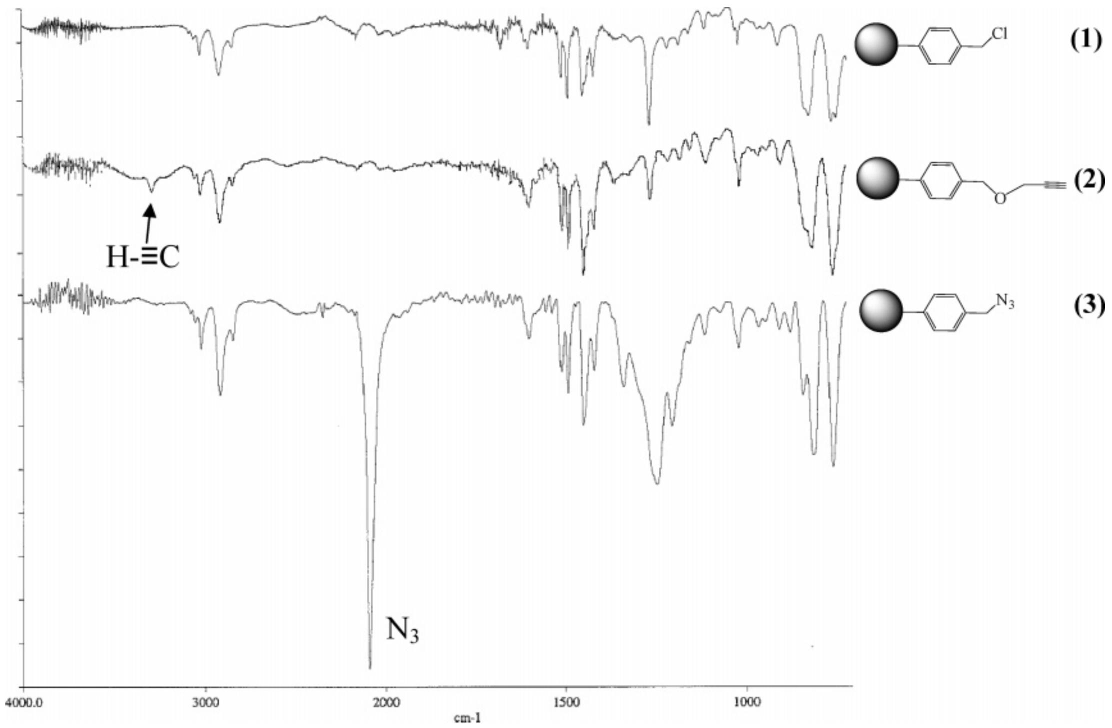


Figure 1. Attenuated total reflectance (ATR) FT-IR spectra of 4-vinylbenzyl chloride cross-linked solid support **(1)**, alkyne-functionalized cross-linked solid support **(2),** and azide-functionalized cross-linked beads **(3)**.

in a deoxygenated reaction vessel in the presence of AIBN (6.9 mg, 4.19×10^{-5} mol) as initiator at 50 °C for 24 h. The resulting gel was ground to a fine white powder using a mortar and pestle, stirred in DMF at 50 °C for 1 h, filtered, washed with DMF and then acetone to remove monomer, initiator, and linear non-cross-linked polymer, and dried under vacuum for 16 h (**1** in Scheme 1). These cross-linked supports contained chlorine groups that were converted to alkynes (**2**) with propagyl alcohol in NaOH and DMF at 40 °C for 24 h. The support was filtered and washed with water and then acetone. The mixture was heated to 90 °C in DMF for 30 min and filtered, and this procedure was carried out two more times. The formation of azide functional support (**3**) was carried out using **1** in the presence of NaN_3 in DMF at 50 °C for 48 h. The support was then cleaned by filtration and washing with DMF and then acetone. It should be noted that the polymerization conditions were chosen for the greatest cross-link density.

Figure 1 shows the attenuated total reflectance (ATR) FT-IR of the support before and after azidation or on conversion to alkynes. The alkyne functional support showed a weak absorption at 3302 cm^{-1}, and the azide functional support showed a strong and sharp absorption at 2107 cm^{-1}. Although ATR only probes the surface of the support, these results do show that we have functionalized our support to the respective alkyne or azide.

Effectiveness of the Reactive Solid Supports. The alkyne-functionalized supports (**2**) were tested for their effectiveness through "click" reactions with PSTY-N_3 ($M_n = 5125$, PDI = 1.09), using an unreactive PSTY standard (110K) as an internal reference. Figure 2A shows that with time the starting PSTY-N_3 decreased with respect to the internal PSTY reference standard, and after 240 min there was only dead (unfunctionalized) polymer most probably formed during the ATRP polymerization of PSTY-Br and a small amount of polymer that was not converted to azido groups. Importantly, the amount of reference PSTY standard was not lost during this process. Figure 2B shows a similar result when azide functional supports (**3**)

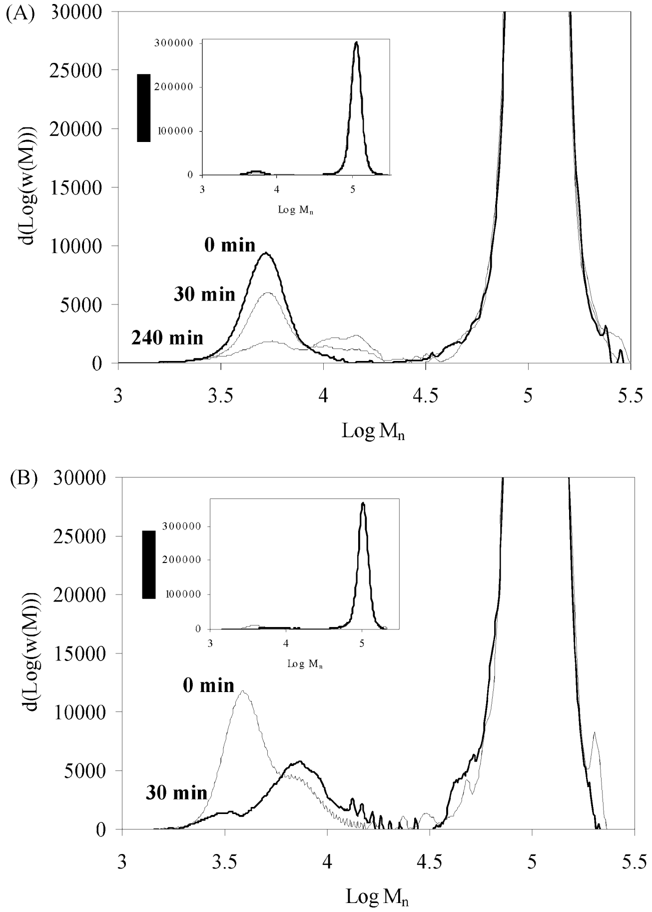
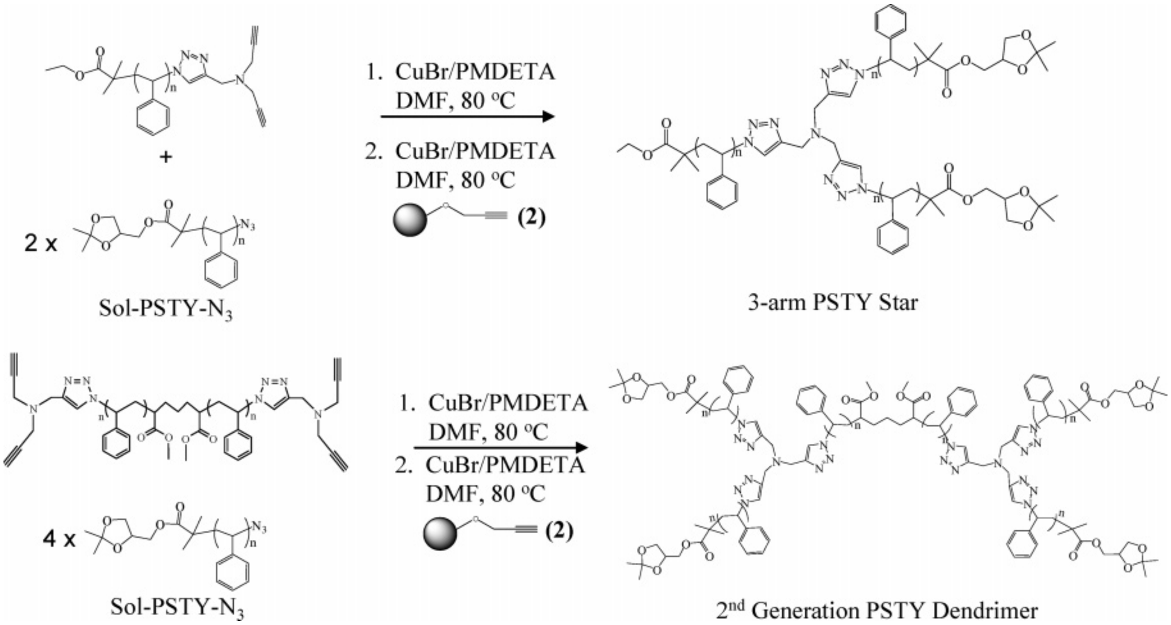


Figure 2. Size exclusion chromatograms (SEC, using RI detection) to monitor the "click" reactions of (A) PSTY-N_3 with alkyne-functionalized cross-linked solid support **(2)** after 0, 30, and 240 min and (B) $(\equiv)_2$−PSTY−$(\equiv)_2$ with azide-functionalized cross-linked support **(3)** after 0 and 30 min in DMF catalyzed using CuBr/PMDETA. The chromatograms are normalized by weight to the polystyrene internal standard (110 000 g/mol). (Inset: complete SEC-RI chromatograms).

Scheme 2. Synthesis Polystyrene Stars and Dendrimers with Sol Ketal End Groups[a]



[a] The yields were increased using reactive alkyne solid support (**2**).

were reacted via a "click" reaction with tetrafunctional alkyne PSTY chains (M_n = 3560, PDI = 1.11). These results show that these supports are very effective scavengers, and there seems to be no side reactions that remove the desired polymer products (same amount of material was collected) or add new undesirable polymer species.

The real test of these supports is in the synthesis of higher order complex polymer architectures (Scheme 2). For example, in a one-pot reaction PSTY-N_3 was added in excess (1.1 equiv to alkynyl groups) to a mixture of difunctional alkyne PSTY (PSTY$-$(≡)$_2$, see Scheme 2 for the synthesis) in DMF and CuBr/ligand at 80 °C for 2 h. The purity of this "click" reaction was 61% measured from the weight fraction of each peak, which after a further "click" reaction with the alkyne functional support (**2**) increased the purity to 85% (Figure 3A). It can be seen that there was little or no 2-arm star formation, suggesting that all the alkyne groups on the PSTY chain ends have been converted to triazol rings. The M_n's of these polymers were close to 5000, which has previously been observed to give poor coupling efficiencies.[13] Therefore, excess PSTY-N_3 allows high yields of complex architectures to be prepared. In another example, PSTY-N_3 was added in excess (1.1 equiv to alkynyl groups) in a one-pot reaction to a mixture of tetrafunctional alkyne polystyrene ((≡)$_2$$-$PSTY$-$(≡)$_2$) in DMF and CuBr at 80 °C for 2 h. The purity was 72%, which increased to 84% after "click" reactions with the alkyne solid support.

It was found for all the above reactions that removal of copper from the polymers prior to the "click" reaction with the reactive solid supports was essential. This was carried out by passing the polymer/copper mixture through an alumina column. If the copper was not removed prior to "click" reactions with the support, the SEC traces after reaction with the support gave inconsistent results and in many cases there was a loss of polymeric 3-arm star or dendrimer. We believe that high levels of copper could induce undesirable side reactions between alkyne end groups.

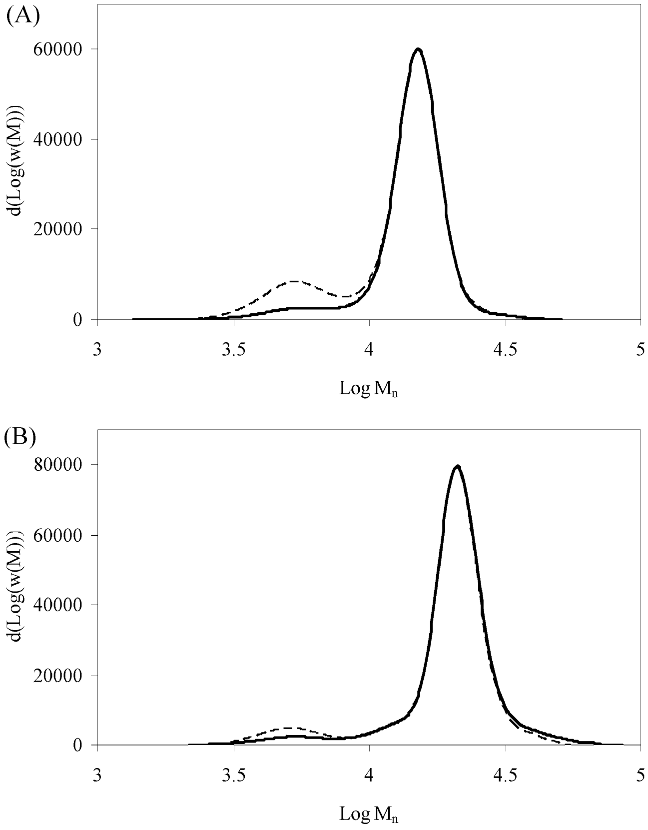


Figure 3. Size exclusion chromatograms (SEC, using RI detection) to monitor the "click" reaction of (A) PSTY-N_3 with PSTY$-$(≡)$_2$ (dotted line) and after purification with **2** (bold line) and (B) PSTY$-$$N_3$ with (≡)$_2$$-$PSTY$-$(≡)$_2$ (dotted line) and after purification with **2** (bold line).

Conclusion

In summary, we have shown the facile synthesis and use of reactive solid supports to remove excess linear polymer to increase the purity of polymeric 3-arm stars and dendrimers. These supports are a cheap alternative to scavenge polymeric species with either azido or alkynyl functionality, after which the solid support can be filtered away from the product. It was found that there was little or no loss of product using this method, and their purity could be substantially increased. Importantly, it was found that copper should be removed from the polymer mixture prior to “click” reactions with the support. We used this strategy to increase the yield and purity of novel 3-arm PSTY stars and second-generation PSTY dendrimer with sol ketals (i.e., protection groups for 1,2-dialcohols) on the peripheral chain ends of the structures. These deprotected hydroxyl groups allow for the preparation of many kinds of compounds, including alkyl halides, esters, carboxylic acids, alkenes, ketones, aldehydes, and ethers. Therefore, many types of biological and organic compounds can be coupled to the periphery of the polymeric star or dendrimer.

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Supporting Information Available: Experimental details for the synthesis and characterization of the solid support, 3-arm stars, and dendrimers. This material is available free of charge via the Internet at http://pubs.acs.org.

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