

SUPPORTING INFORMATION to

Reactive Alkyne and Azide Solid Supports to Increase Yields and Purity of Polymeric Stars and Dendrimers via the ‘Click’ Reaction.

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EXPERIMENTAL

Materials

The following monomers were deinhibited before use by passing through a basic alumina column; 4-vinylbenzyl chloride (VBC: Aldrich, 97 %), divinylbenzene (DVB: Aldrich, 80 %, mixture of isomers, tech grade) and styrene (STY: Aldrich, >99 %).

The following chemicals were used as received: alumina, activated basic alumina (Aldrich: Brockmann I, standard grade, ~ 150 mesh, 58 Å), anhydrous magnesium sulfate (MgSO₄: Scharlau, extra pure), sodium chloride (NaCl: Univar, 99.9 %), sodium hydroxide (NaOH: Univar, AR grade), triethylamine (TEA: Fluka, 98 %), 2-bromoisobutyryl bromide (BIB: Aldrich, 98 %), DL-1,2-isopropylideneglycerol

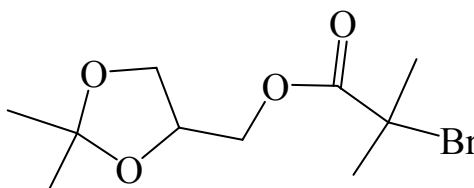
(Solketal: Aldrich, 98 %), acetone (ChemSupply, AR), diethyl ether (Univar, AR grade), hydrochloric acid (HCl, Univar, 32 %), methanol, anhydrous (MeOH: Mallinckrodt, 99.9 %, HPLC grade), Milli-Q water (Biolab, 18.2 MΩm), N,N-dimethylformamide (DMF: Labscan, AR grade), tetrahydrofuran (THF: Labscan, HPLC grade), bromoacetyl bromide (BAB: Fluka, 98 %), propargyl alcohol (Aldrich, 99 %), sodium azide (NaN₃: Aldrich, ≥ 99.5 %), tripropargylamine (TPA: Aldrich, 98 %).

The following initiators, ligands and metals for the various polymerizations are given below and used as received unless otherwise stated. N,N,N',N',N''-pentamethyldiethylenetriamine (PMDETA: Aldrich, 99 %), copper (I) bromide (CuBr: Aldrich, 99.999 %), copper (II) bromide (CuBr₂: Aldrich, 99 %), ethyl-2-bromoisobutyrate (EBiB: Aldrich, 98 %), and dimethyl 2,6-dibromoheptanedioate (DMDBHD: Aldrich, 97 %). 2,2-azobis(isobutyronitrile) (AIBN: Riedel-de Haën, 98 %) was recrystallized from methanol before use.

Synthesis of Functional ATRP Initiator

Synthesis of (2,2-dimethyl-1,3-dioxolan-4-yl)methyl 2-bromo-2-methylpropanoate:

This compound was prepared according to the literature procedure.¹



DL-1,2-Isopropylideneglycerol (10.63 g, 0.080 mol), TEA (9.77 g, 0.097 mol) and THF (50 mL) were added to a round bottom flask and stirred at 0 °C under N₂. A solution of 2-bromoisobutyryl bromide (23.064 g, 0.10 mol) in THF (100 mL) was

added drop wise to the stirred solution over a 1 h period. The reaction mixture was then stirred at room temperature for a further 3 h. The solvent was removed by rotary evaporation and the residue taken up into diethyl ether (50 mL) and filtered. The organic layer was washed with a 10 % HCl solution, brine and Milli-Q water. The organic layer was dried over MgSO_4 and the solvent removed by rotary evaporation and dried *in vacuo*. The product was used without further purification. ^1H NMR (CDCl_3) δ = 0.196 ($\text{Si}(\text{CH}_3)_3$), 1.350 (3H s, $\text{CHCH}_2\text{OCCH}_2$), 1.425 (3H s, $\text{CH}_2\text{CHOCCCH}_2$), 1.930 (6H s, $\text{OC}(=\text{O})\text{C}(\text{CH}_3)_2$), 3.8 – 4.3 (5H m)

Synthesis of polymers using ATRP

Synthesis of PSTY-Br: Styrene (15.06 g, 0.145 mol), PMDETA (0.190 mL, 9.09×10^{-4} mol), EBiB (0.145 g, 7.44×10^{-4} mol) and CuBr_2 (0.0346 g, 1.55×10^{-4} mol) were added to a 50 mL Schlenk flask then purged with N_2 for 20 min. After 1 h stirring, CuBr (0.109 g, 7.60×10^{-4} mol) was added under positive N_2 flow, the flask sealed and purged with N_2 for a further 5 min. The polymerisation was carried out at 80 °C in a temperature controlled oil bath for 205 min. The polymerisation was terminated by quenching in liquid nitrogen and then exposure to air. The polymerization mixture was diluted with THF then the copper salts were removed by passage through an activated basic alumina column. The solution was concentrated by airflow and the polymer recovered by precipitation into methanol, filtration and drying for 48 h under high vacuum at 25 °C. The polymer was characterized by SEC (M_n = 5125, PDI = 1.09).

Synthesis of Br-PSTY-Br: Styrene (16.236 g, 0.156 mol), PMDETA (0.332 mL, 1.59×10^{-3} mol) and DMDBHD (0.279 g, 8.1×10^{-4} mol) were added to a 50 mL Schlenk flask equipped with a magnetic stirrer. The solution was degassed by 4 freeze-pump-

thaw cycles under high vacuum. The Schlenk flask was then flushed with high purity argon and CuBr (0.114 g, 7.9×10^{-4} mol) was carefully added under positive argon flow. The polymerisation was carried out in a temperature controlled oil bath at 100 °C for 20 min. The polymerisation was terminated by quenching in liquid nitrogen and exposure to air. The polymerization mixture was diluted with THF, and the copper salts were removed by passage through an activated basic alumina column. The solution was concentrated by airflow, and the polymer recovered by precipitation into methanol. The recovered polymer was dried for 48 h under high vacuum at 25 °C. The polymer was characterized by SEC ($M_n = 3560$, PDI = 1.11).

Synthesis of Sol-PSTY-Br: Styrene (30.0 g, 0.288 mol), PMDETA (0.262 g, 1.5×10^{-3} mol), (2,2-dimethyl-1,3-dioxolan-4-yl)methyl 2-bromo-2-methylpropanoate (0.427 g, 1.5×10^{-3} mol) and pre-formed CuBr₂/PMDETA complex (0.061 g, 1.5×10^{-4} mol) were added to a 50 mL Schlenk flask equipped with a magnetic stirrer, and purged with N₂ for 20 min. CuBr (0.216 g, 1.5×10^{-3} mol) was then added under a positive N₂ flow, and the flask sealed and purged with N₂ for a further 5 min. The flask was placed in an oil bath at 80 °C for 2 h after which the polymerization was terminated by quenching in liquid N₂ and exposure to air. The polymerization mixture was diluted with THF, and the copper salts were removed by passage through an activated basic alumina column. The solution was concentrated by airflow, and the polymer recovered by precipitation into methanol. The recovered polymer was dried for 48 h under high vacuum at 25 °C. The polymer was analysed by SEC ($M_n = 4661$, PDI = 1.09).

Synthesis of polymers with azide functionality

Synthesis of PSTY-N₃: A typical azidation procedure was as follows: PSTY-Br (2.0 g, 0.39 mmol) was dissolved in 20 mL of DMF in a 50 mL reaction vessel. NaN₃ (0.278

g, 4.3 mmol) was added and the mixture stirred for 24 h at 50 °C. The polymer was precipitated into MeOH, recovered by vacuum filtration and washed exhaustively with water and MeOH. The polymer was dried under vacuum for 48 h at 25 °C.

Similarly, N₃-PSTY-N₃ and Sol-PSTY-N₃ were prepared from Br-PSTY-Br and Sol-PSTY-Br respectively.

Synthesis of functionalized crosslinked solid supports

Synthesis of 4-vinylbenzyl chloride crosslinked Solid supports (1): 4-vinylbenzyl chloride (4 mL, 0.028 mol), styrene (3.2 mL, 0.028 mol), divinylbenzene (0.120 mL, 8.42×10^{-4} mol) and AIBN (6.9 mg, 4.19×10^{-5} mol) were added to a 20 mL glass vial equipped with a magnetic stirrer and sealed with rubber septa. The mixture was purged with N₂ for 10 min then heated in a temperature controlled oil bath set at 50 °C for 24 h. The crosslinked polymer was ground to a fine powder with mortar and pestle then stirred in 50 mL of DMF at 50 °C for 1 h. The mixture was filtered hot, and the washing procedure repeated twice. The polymer was then filtered and washed with DMF and then acetone. The functional crosslinked polymer was then dried under high vacuum for 16 h.

Synthesis of alkyne functionalized crosslinked Solid supports (2): Propargyl alcohol (4.9 mL, 0.087 mol), NaOH (0.07 g, 0.017 mol) and DMF (40 mL) were added to a 50 mL round bottom flask. The mixture was heated under nitrogen in a temperature controlled oil bath at 40 °C. After 20 min, **1** (4 g) was added and the mixture was stirred for a further 24 h. The reaction mixture was filtered hot and washed with water and then acetone. The functionalised crosslinked polymer was then stirred in 50 ml of DMF at 90 °C for 30 min after which the mixture was filtered hot and this washing

procedure repeated twice. Finally, the polymer was filtered and washed with DMF and then acetone. The polymer was then dried under high vacuum.

Synthesis of azide functionalized crosslinked Solid supports (3): **1** (4 g), NaN₃ (5.68 g, 0.087 mol) and DMF (40 mL) were added to a 50 mL round bottom flask equipped with a magnetic stirrer. The mixture was heated in a temperature controlled oil bath at 50 °C for 48 h. The mixture was filtered hot and washed with water and acetone. The functionalised crosslinked polymer was then stirred in 50 ml of DMF at 90 °C for 30 min after which the mixture was filtered hot and this washing procedure repeated twice. Finally, the polymer was filtered and washed with DMF and then acetone. The polymer was then dried under high vacuum.

Evaluation of effectiveness of functionalized crosslinked solid supports

Testing of alkyne functionalized crosslinked solid supports: PSTY-N₃ (10.0 mg, 1.95×10^{-6} mol), PSTY Standard (Internal Standard 110000 g/mol, 10.1 mg) and DMF (1 mL) were added to a 10 mL Schlenk flask. An aliquot from the mixture was removed for SEC analyses. Alkyne functionalised crosslinked solid supports, **2**, and PMDETA (4.1 µL, 1.96×10^{-5} mol) were then added to the mixture and purged with nitrogen for 10 min. CuBr (2.7 mg, 1.88×10^{-5} mol) was carefully added under a positive flow of N₂ and the solution purged with N₂ for a further 5 min. The flask was placed in a temperature controlled oil bath at 80 °C for 4 h. Samples were taken during the reaction for SEC analyses.

Similarly, the azide functionalized crosslinked solid supports, **3**, were tested using (≡)₂-PSTY-(≡)₂.

3-arm PSTY Star

Synthesis of 3-arm core PSTY-(\equiv)₂: PSTY-N₃ (0.179 g, 3.49×10^{-5} mol), PMDETA (0.075 mL, 3.59×10^{-4} mol), TPA (0.100 mL, 7.07×10^{-4} mol) and DMF (1.8 mL) were added to a 10 mL Schlenk flask and the solution purged with N₂ for 10 min. CuBr (0.0521 g, 3.63×10^{-4} mol) was carefully added under a positive flow of N₂ and the solution purged with N₂ for a further 5 min. The flask was placed in a temperature controlled oil bath at 80 °C for 2 h. The reaction was diluted with 5 mL THF, and passed through activated basic alumina to remove the copper salts. The polymer was precipitated in MeOH, then filtered and dried for 24 h under vacuum.

Synthesis of 3-arm PSTY Star: PSTY-(\equiv)₂ (0.110 g, 2.15×10^{-5} mol), Sol-PSTY-N₃ (0.226 g, 4.76×10^{-5} mol), PMDETA (0.014 mL, 6.70×10^{-5} mol) and DMF (3.5 mL) were added to a 10 mL Schlenk flask, and the solution purged with N₂ for 10 min. CuBr (0.0104 g, 7.3×10^{-5} mol) was carefully added under a positive flow of N₂, the flask sealed and purged with N₂ for a further 5 min. The flask was placed in a temperature controlled oil bath at 80 °C for 2 h. The reaction was diluted with 5 mL of THF then passed through activated basic alumina to remove the copper salts.

THF was removed by evaporation and the polymer in residual DMF was added to a 10 mL Schlenk flask equipped with magnetic stirrer. PMDETA (0.023 mL, 1.1×10^{-4} mol) and **2** (0.1 g) were added, and the mixture purged with N₂ for 10 min. CuBr (1.6 mg, 1.11×10^{-5} mol) was carefully added under a positive flow of N₂, the flask was sealed and purged with N₂ for a further 5 min. The flask was placed in a temperature controlled oil bath at 80 °C for 4 h. The reaction was filtered hot through a fine glass frit and the solid supports washed with THF (10 mL). The filtrate was passed through

activated basic alumina to remove the copper salts, and the polymer was precipitated in MeOH, filtered and dried for 24 h under vacuum.

2nd Generation PSTY Dendrimer

Synthesis of 1st Generation PSTY Dendrimer (\equiv)₂-PSTY-(\equiv)₂: N₃-PSTY-N₃ (0.5 g, 1.40×10^{-4} mol), PMDETA (0.587 mL, 2.81×10^{-3} mol), TPA (0.791 mL, 5.60×10^{-3} mol) and DMF (5 mL) were added to a 10 mL Schlenk flask equipped with magnetic stirrer. The solution was purged with N₂ for 10 min and then CuBr (0.403 g, 2.81×10^{-3} mol) was carefully added under a positive flow of N₂. The reaction mixture was purged with N₂ for a further 5 min. The flask was placed in a temperature controlled oil bath at 80 °C for 2 h. The reaction was diluted with 5 mL THF, and passed through activated basic alumina to remove the copper salts. The polymer was precipitated in MeOH, filtered and dried for 24 h under vacuum.

Synthesis of 2nd Generation PSTY Dendrimer: (\equiv -)₂-PSTY-(\equiv)₂ (0.1 g, 2.5×10^{-5} mol), Sol-PSTY-N₃ (0.512 g, 1.1×10^{-4} mol), PMDETA (0.209 mL, 1.0×10^{-3} mol) and 5 mL of DMF were added to a 10 mL Schlenk flask. The solution was purged with N₂ for 10 min after which CuBr (0.148 mg, 1.03×10^{-3} mol) was carefully added under a positive flow of N₂. The reaction mixture was purged with N₂ for a further 5 min. The flask was placed in a temperature controlled oil bath at 80 °C for 2 h. The reaction was diluted with 5 mL of THF, and passed through activated basic alumina to remove the copper salts to give dendrimer.

THF was removed by evaporation and the polymer in residual DMF was added to a 10 mL Schlenk flask, equipped with magnetic stirrer. PMDETA (0.057 mL, 0.27×10^{-4} mol) and **2** (0.18 g) were added to the flask and the mixture purged with N₂ for 10 min. CuBr (0.036 g, 2.5×10^{-4} mol) was then carefully added under a positive flow of N₂ and

the solution purged with N₂ for a further 5 min. The flask was placed in a temperature controlled oil bath set at 80 °C for 4 h. The reaction was filtered hot through a fine glass frit and the solid supports washed with 10 mL of THF. The filtrate was passed through activated basic alumina to remove the copper salts and the polymer was precipitated in MeOH, then filtered and dried for 24 h under vacuum.

Analytical Methodologies

Attenuated Total Reflectance Fourier Transform Spectroscopy (ATR-FTIR): ATR-FTIR spectra were recorded between 4000 and 550 cm⁻¹ in a Perkin Elmer FT-2000 FTIR spectrometer equipped with a single reflection diamond window. Each spectrum had a 32 scan accumulation using a spectral resolution of 8 cm⁻¹.

Size Exclusion Chromatography (SEC): The molecular weight distributions of nanoparticles were measured by SEC. All polymer samples were dried prior to analysis in a vacuum oven for two days at 40 °C. The dried polymer was dissolved in tetrahydrofuran (THF) (Labscan, 99%) to a concentration of 1 mg/mL. This solution was then filtered through a 0.45 µm PTFE syringe filter. Analysis of the molecular weight distributions of the polymer nanoparticles was accomplished by using a Waters 2695 Separations Module, fitted with two Ultrastyrigel linear columns (7.8 x 300 mm) kept in series. These columns were held at a constant temperature of 35°C for all analyses. The columns used separate polymers in the molecular weight range of 500 – 2 million g/mol with high resolution. THF was the eluent used at a flow rate of 1.0 mL/min. Calibration was carried out using narrow molecular weight PSTY standards (PDI ≤ 1.1) ranging from 500 – 2 million g/mol. Data acquisition was performed using

Waters Millenium software (ver. 3.05.01) and molecular weights were calculated by using a 5th order polynomial calibration curve.

REFERENCE

1. Perrier, S.; Armes, S. P.; Wang, X. S.; Malet, F.; Haddleton, D. M. *Journal of Polymer Science, Part A: Polymer Chemistry* **2001**, 39, (10), 1696-1707.