Supporting Information for:

ATRP, azide substitution and 'click' chemistry: three reactions using one catalyst in one pot

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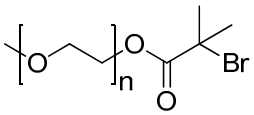
Materials and Methods

Tetrahydrofuran (THF), dichloromethane, n-hexane, diethyl ether and *N*,*N*-dimethylformamide (DMF) were obtained from Biosolve (Valkenswaard, the Netherlands), triethylamine, acetic acid and polyethylene glycol monomethyl ether (mPEG, M_n = 2 kDa) were obtained from Merck (Darmstadt, Germany), toluene, CuBr and $CuBr_2$ from Acros (Geel, Belgium) and CuCl from Alfa-Aesar (Karlsruhe, Germany). $CuCl_2.2H_2O$, 2,2'-bipyridyl (Bpy), tris(2-aminoethyl)amine, *N,N,N',N'',N''*-pentamethyldiethylenetriamine (PMDETA), 2-bromoisobutyrylbromide, (1-bromoethylbenzene), oligo(ethylene glycol) monomethyl ether methacrylate (OEGMA M_n = 300 g mol^{-1}), *N*-Isopropylacrylamide (NIPAm), NaN_3, tetrabutylammonium azide, LiCl, ascorbic

acid, D_2O and CD_3CN were purchased from Sigma-Aldrich (Zwijndrecht, the Netherlands). mPEG was dried by azeotropically distilling off water using toluene. NIPAm was recrystallized twice from a mixture of n-hexane and toluene. CuBr was purified by stirring overnight in glacial acetic acid. Anisole and OEGMA were passed over a short column of basic alumina. All other chemicals were used as received. Tris[2-(dimethylamino)ethyl]amine (Me_6tren) was synthesized by Eschweiler-Clarke methylation of tris(2-aminoethyl)amine[1] and purified by distillation under reduced pressure.

^{1}H Nuclear Magnetic Resonance (NMR) spectrometry was performed on a Gemini 300 MHz spectrometer (Varian Associates Inc., Palo Alto, CA). Chemical shift values are reported in ppm, taking the residual solvent peak as reference ($\delta(CHCl_3) = 7.24$, $\delta(HOD) = 4.79$). Gel Permeation Chromatography (GPC) was performed on a Waters 2695 system equipped with a Refractive Index detector and Fluorescence detector, using 2 PLgel 3 μm Mixed-D columns (Polymer Laboratories). As eluent, 10 mM LiCl in DMF was used at 0.7 ml/min and 40°C. The excitation and emission wavelengths were set to 330 and 560 nm, respectively.

Synthesis of macro-initiator 1



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Anhydrous mPEG (5 g, 2.5 mmol) was dissolved in dry THF (100 mL) under a nitrogen atmosphere and the solution was cooled on ice. Then, triethylamine (0.37 mL, 2.7 mmol, 1.1 eq) was added followed by 2-bromoisobutyrylbromide (0.33 mL, 2.7 mmol, 1.1 eq). After stirring the reaction mixture overnight, the formed triethylammonium bromide was removed by filtration. The filtrate was concentrated at reduced pressure and the residue was redissolved in a

minimal amount of dichloromethane. The product was then isolated by precipitation with ice-cold diethylether. The yield was ~80%. ^{1}H NMR ($CDCl_3$): δ 4.3 (t, 2H, OCH_2), δ 3.85 (t, 2H, OCH_2), δ 3.65 (OCH_2), δ 3.35 (t, 2H, OCH_2), δ 3.30 (s, 3H, OCH_3), δ 1.85 (s, 6H, CCH_3).

Typical procedure for copper-catalyzed azide substitution

A stock solution of catalyst was freshly prepared by placing 8.6 mg (60 μmol) CuBr, 8.9 mg (40 μmol) $CuBr_2$ and 31.2 mg (200 μmol) Bpy in a screw-capped septum vial which was then purged for 15 min with N_2 gas. Subsequently, 300 μL of N_2-purged acetonitrile-d_3 and 700 μl N_2-purged D_2O were added using a gas-tight syringe. Formation of the brown catalytic complex was aided by sonication.

20 mg of **1** (10 μmol) was placed in a screw-capped septum vial containing a magnetic stirrer bar, which was then purged for 15 min with N_2 gas. Subsequently, 300 μL of N_2-purged CD_3CN and 700 μL N_2-purged D_2O were added and the mixture was stirred until all initiator was dissolved. The reaction was started by addition of 100 μL of the catalyst stock solution followed by slow addition of 12 μL of an N_2-purged 1 M solution of NaN_3 in D_2O. At regular time intervals a 20 μL sample was taken and diluted with 700 μL of air-saturated D_2O to quench the reaction. Conversion was determined using ^{1}H NMR by comparing the integrals of the peaks at 1.97 ppm (-C($C\underline{H}_3$)$_2$-Br and 1.55 ppm (-C($C\underline{H}_3$)$_2$-N_3 (Figure S1).

Assuming that the reaction is first-order in both [R-Br] and [N_3^-], the rate constant could be calculated as 0.42 L mol-1 s^{-1}.

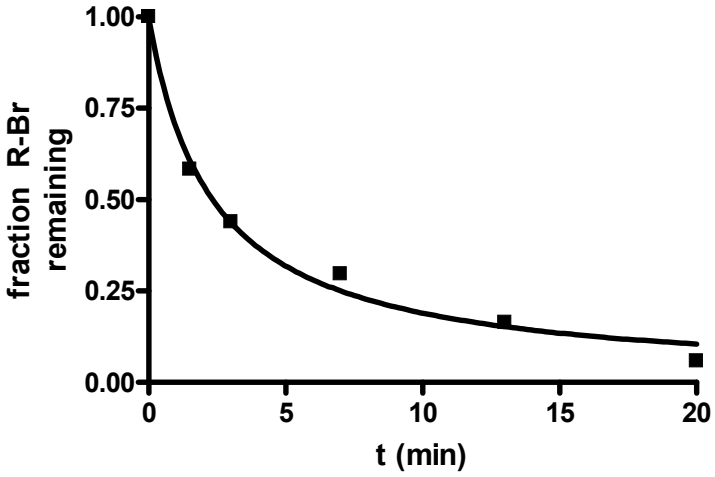

Figure S1.Plot of the bromide to azide conversion in time. **1** was incubated with 1.2 eq. NaN_3 and $CuBr/CuBr_2$/Bpy catalyst

ATRP, azidation and fluorescent labeling of pOEGMA300

20 mg of **1** (10 μmol) was placed in a screw-capped septum vial containing a magnetic stirrer bar, which was then purged for 15 min with N_2 gas. Subsequently, 300 μL of N_2-purged CD_3CN, 700 μL N_2-purged D_2O and 200 μl OEGMA300 were added and the mixture was stirred until all initiator was dissolved. The reaction was started by addition of 100 μL of the same catalyst stock as described above. Conversion was monitored by regularly taking 20 μL samples, which were diluted with 700 μL of air-saturated D_2O and analyzed using ^1H NMR. The integrals of the H_2C=C peaks between 5.5 and 6.5 ppm (2H) were compared with the integrals of the C(=O)OCH_2 peaks (2H) between 4.0 and 4.5 ppm. At 80% conversion (approx. 20 min), 20 μl 1M NaN_3 solution was slowly added. After 5 minutes, the peak at 1.57 ppm of -C(C$\underline{H}_3$)N_3-COOR (2.6 H, 85% conversion) could clearly be observed in ^1H NMR (Figure S2). The monomer conversion was determined again 1h after addition of azide. It was found that the monomer conversion had not increased further indicating that re-activation of the azide-

substituted chain end is negligible. Then, an equimolar amount of dansyl-propargylamide **2** was added and allowed to react overnight at room temperature.

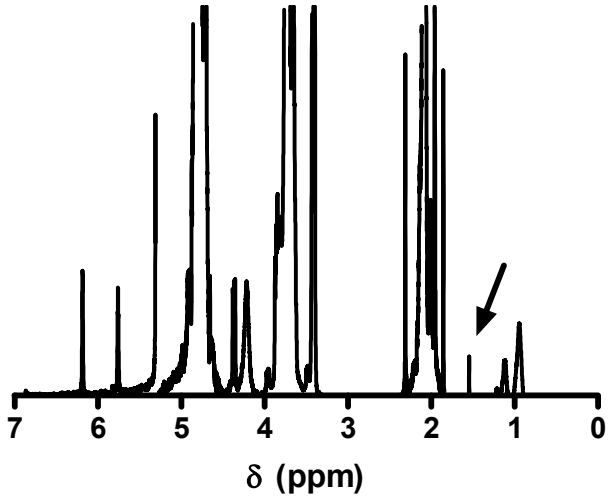

Figure S2. NMR spectrum of PEG-pOEGMA-N_3. Arrow indicates the -C($C\underline{H}_3$)$_2$-N_3 peak

In one control reaction, the same procedure was followed except that the addition of sodium azide was omitted. In another control reaction, 2 molar equivalents of TEMPO were added together with the addition of sodium azide. Termination was evident from fading of the brown color of the copper(I)-bipyridyl complex. An extra 100 μL of catalyst stock was added to compensate for the loss of copper(I) species, which would preclude any CuAAC 'click' reaction, before again an equimolar amount of dansyl-propargylamide was added. The next day, the reaction mixture was analyzed by GPC with fluorescence detection (Figure S3). TEMPO was able to almost completely inhibit the substitution by azide, which lends further support to the proposed radical mechanism of azide substitution.

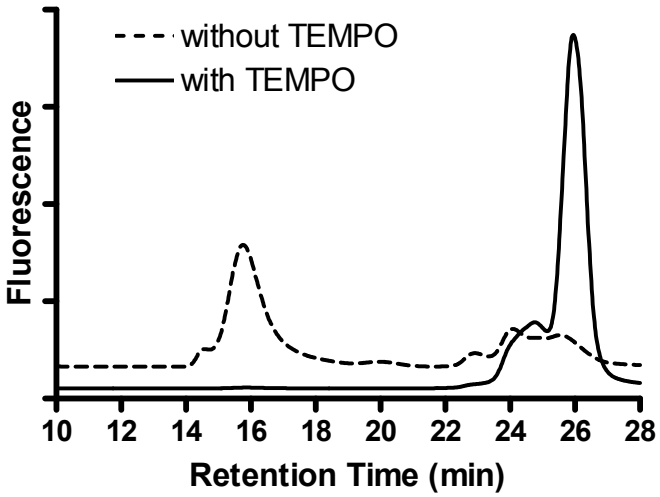

Figure S3. GPC traces of fluorescently labeled pOEGMA (dashed line) and the control reaction to which TEMPO had been added (continuous line).

ATRP, azidation and fluorescent labeling of pNIPAm

The procedure was very similar to the procedure for ATRP of OEGMA300. However, Me_6tren (1:1 molar equivalent to total copper) was used instead of bpy and the polymerization was performed in an ice bath. 160 mg of NIPAm (target M_n=16 kDa) was used and monomer conversion was determined by comparing, in the NMR spectrum, the total vinylic proton peak integral (5.4-6.3 ppm, 3H) to the total isopropyl methyne proton peak integral (3.6-3.85 ppm, 1H). After 15 min, ^{1}H NMR indicated 90% monomer conversion and 2 mol eq. NaN_3 was added. After an additional 20 minutes of stirring, a –C<u>H</u>N_3-CONHR peak could not be observed in ^{1}H NMR due to peak overlap, but the monomer conversion had not increased, which indicated substitution of the bromide by azide which could not re-initiate. Again, dansyl-propargylamide **2** was added and allowed to react overnight at room temperature.

Substitution by azide in aprotic medium

In a preliminary experiment, the copper-catalyzed azide substitution reaction was also applied to (1-bromoethyl)benzene in anisole, as a model for the living chain end of polystyrene. 2.8 mg (0.02 mmol) of CuBr was placed in a screw-capped septum vial which was then purged for 15 min. with N_2. Subsequently, 800 μL of N_2 purged anisole and 2.7 μL (0.02 mmol) of (1-bromoethyl)benzene were added. A sample was taken, diluted in $CDCl_3$ and analyzed by NMR (Figure S4). Then, a solution of 11.4 mg (0.04 mmol) of tetrabutylammonium azide and 4.2 μL (0.02 mmol) of PMDETA in 200 μL N_2 purged anisole were added. The vial was put in an oil bath thermostated at 100 °C and after 15 min another sample was analyzed by NMR (Figure S4).

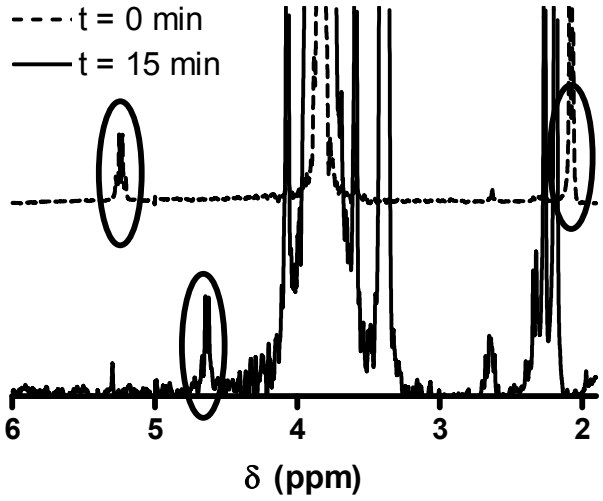

Figure S4. NMR spectra before (top) and after (bottom) azide substitution of (1-bromoethyl)benzene in anisole.

The disappearance of the peaks at 5.2 ppm and 2.0 ppm, characteristic of (1-bromoethyl)benzene, and the appearance of a peak at 4.6 ppm, characteristic of (1-

azidoethyl)benzene,[2] indicate that the procedure might be applicable to hydrophobic monomers in aprotic solvents as well.

References for Supporting Information

1. M. Ciampolini and N. Nardi, *Inorg. Chem.,* 1966, **5**, 41
2. P. L. Golas, N. V. Tsarevsky and K. Matyjaszewski, *Macromol. Rapid Commun.*, 2008, **29**, 1167.