# RAFT and Click Chemistry : A Versatile Approach to the Block Copolymer Synthesis

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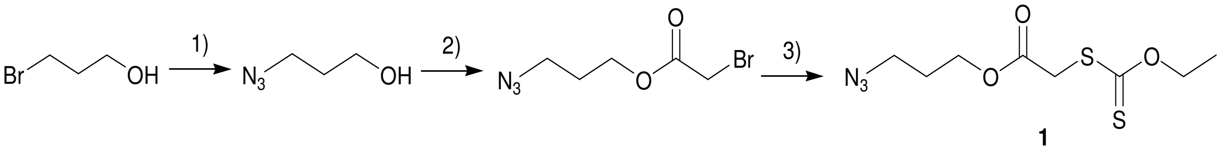
## Supporting information

## General

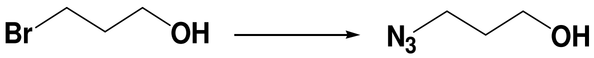
All reagents were purchased with the highest purity and were used as supplied unless otherwise noted. Triethylamine, THF, chloroform were dried over calcium hydride and subsequently distilled. Styrene and Vinyl acetate were purified by passing over a column of basic alumina and subsequently distilled prior to use. (4-cyanopentanoic acid)-4-dithiobenzoate (CPADB) was prepared according to the published method[1]. All polymerization reactions were performed in oven-dried Schlenk flasks fitted with a glass stopper or septum under a positive pressure of nitrogen. Monomer conversions were determined via on-line FT-NIR spectroscopy by following the decrease of the intensity of the vinylic stretching overtone of the monomer at $\nu$ = 6 200 cm$^{-1}$. The FT-NIR measurements were performed using a Bruker IFS66\S Fourier transform spectrometer equipped with a tungsten halogen lamp, a $CaF_2$ beam splitter and a liquid nitrogen cooled InSb detector. Each spectrum in the spectral region of 8 000 to 4 000 cm$^{-1}$ was calculated from the co-added interferograms of twelve scans with a resolution of 4 cm$^{-1}$. For conversion determination, a linear baseline was selected according to the monomer spectrum. The integrated absorbance was subsequently used to calculate the monomer to polymer conversion via Beer-Lambert's law. It should be noted that other integration methods or methods using only the variation of the peak height at 6 200 cm$^{-1}$ have been tested and yield identical results. Gel permeation chromatography (GPC) analyses of the polymers were performed in N,N-dimethylacetamide [DMAc; 0.03% w/v LiBr, 0.05% 2, 6–di-Butyl-4-methylphenol (BHT)] at 50 °C (flow rate = 1 mL/min) with a Shimadzu modular system comprising an SIL-10AD auto-injector, a Polymer Laboratories 5.0-lm bead-size guard column (50 × 7.8 mm) followed by four linear PL (Styragel) columns ($10^5$, $10^4$, $10^3$, and 500Å) and an RID-10A differential refractive-index detector. The GPC calibration was performed with narrow-polydispersity polystyrene standards ranging from 500 to $10^6$ g/mol.

## Synthesis of azido-xanthate agent 1



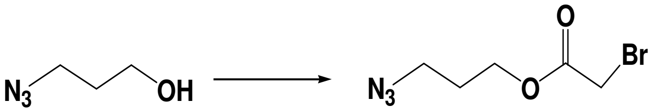
**1**

### 1) *Synthesis of 3-azido-1-propanol*



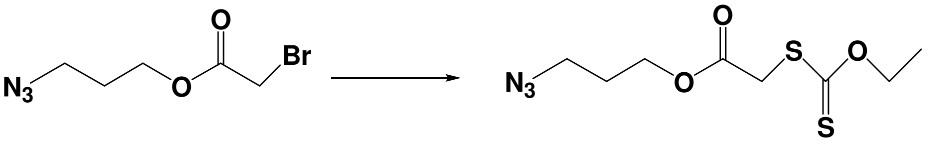
3-bromo-1-propanol (5g, 36 mmol) and sodium azide (3.83 g, 59 mmol) were dissolved in a mixture of acetone (60 mL) and water (10 mL) and the resulting solution was refluxed overnight. Acetone was then removed under reduced pressure, 50 mL of water were added and the mixture was extracted with diethyl ether (3 x 50 mL). The organic layers collected were dried over $MgSO_4$ and, after removal of the solvent under reduced pressure, 3-azido-1-propanol was isolated as colourless oil (2.82 g, 77%).$\delta_H$(300 MHz, $CDCl_3$) 1.68 (1H, s, $CH_2\text{-}O\underline{H}$), 1.76 (2H, quint, *J* 6.3, $CH_2\text{-}C\underline{H_2}\text{-}CH_2$), 3.38 (2H, t, *J* 6.6, $C\underline{H_2}\text{-}N_3$), 3.67 (2H, t, *J* 6.3, $C\underline{H_2}\text{-}OH$). $\delta_C$(300 MHz, $CDCl_3$) 31.32 ($CH_2\text{-}\underline{C}H_2\text{-}CH_2$), 48.27 ($\underline{C}H_2\text{-}N_3$), 59.48 ($\underline{C}H_2\text{-}OH$). $\nu_{max}/cm^{-1}$ 3331, 2945, 2881, 2087, 1455, 1258, 1044, 955, 900.

### 2) *Synthesis of 3-azidopropyl 2-bromoethanoate*



A solution of 2-bromoacetyl bromide (8.82g, 3.8 mL, 43.7 mmol) in THF (25 mL) was added dropwise to a solution of 3-azido-1-propanol (3g, 29.64 mmol) and triethylamine (6.11 mL, 4.44g, 43.7 mmol) in THF (45 mL) at 0°C. After complete addition, the reaction mixture was allowed to stir for 1 hour at 25°C. The excess of acid bromide was quenched by addition of methanol (7 mL). The formed triethylammonium bromide salt was filtered off and the solvent was removed in vacuo. The crude product was dissolved in dichloromethane and washed two times with a saturated ammonium chloride solution and two times with distilled water. The organic layer was dried with magnesium sulfate and the solvent was removed in vacuo, yielding a yellow oil which was purified using flash chromatography ($SiO_2$, hexane/ethyl acetate, 20/1). The product was isolated as a colorless oil which was dried under vacuum (5.3 g, 81%) $\delta_H$(300 MHz, $CDCl_3$) 1.94 (2H, quint, *J* 6.1, $CH_2\text{-}C\underline{H2}\text{-}CH_2$), 3.42 (2H, t, *J* 6.1, $C\underline{H2}\text{-}N_3$), 3.83 (2H, s, $C\underline{H2}\text{-}Br$), 4.26 (2H, t, *J* 6.1, $C\underline{H2}\text{-}O\text{-}$). $\delta_C$(300 MHz, $CDCl_3$) 25.44 ($\underline{C}H_2\text{-}Br$), 27.87 ($\underline{C}H_2\text{-}N_3$), 47.85 ($CH_2\text{-}\underline{C}H_2\text{-}CH_2$), 62.96 ($\underline{C}H_2\text{-}O\text{-}$), 167.02 ($\underline{C}{=}O$). $\nu_{max}/cm^{-1}$ 2979, 2930, 2094, 1735, 1446, 1379, 1334, 1260, 1220, 1155, 1097, 1061, 1029, 763, 675.

## 3) *Synthesis of azido-xanthate RAFT agent (1)*



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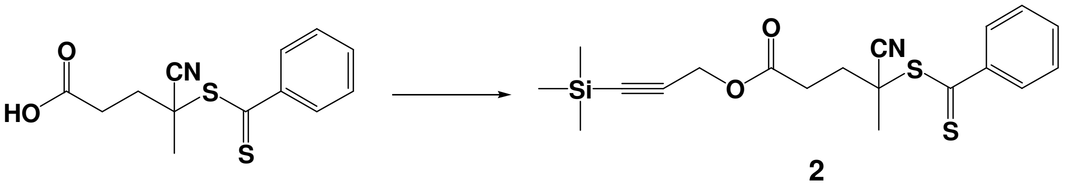
3-azidopropyl 2-bromoethanoate (2.7 g, 12.22 mmol) was dissolved in chloroform (60 mL) and stirred with a 10-fold excess of *O*-ethylxanthic acid potassium salt (19.58 g, 122.14 mmol) for 3 days. The suspended remaining sodium (*O*-ethyl) xanthate was filtered off and washed several times with chloroform. After evaporation of the solvent the product was purified using column chromatography on silica gel (hexane: ethyl acetate 7:3). A yellow oil was obtained and dried under vacuum to constant weight (2.4g, 74%). $\delta_H$(300 MHz, $CDCl_3$) 1.42 (3H, t, *J* 7.0, $CH_2$-CH3), 1.93 (2H, quint, *J* 6.4, $CH_2$-CH2-$CH_2$), 3.41 (2H, t, *J* 5.9, CH2-$N_3$), 3.93 (2H, s, CH2-S), 4.25 (2H, t, *J* 5.9, CH2-O-C(=O)), 4.64 (2H, q, J 7.3 CH2-$CH_3$). $\delta_C$(300 MHz, $CDCl_3$) 13.61 ($CH_3$-$CH_2$-), 27.98 ($N_3$-$CH_2$-), 37.73 ($CH_2$-S-), 47.96 ($CH_2$-$CH_2$-$CH_2$-), 62.58 ($CH_2$-O-C(=O)), 70.66 (O-$CH_2$-$CH_3$), 167.71 (C(=O)), 212.57 (C(=S)). $\nu_{max}/cm^{-1}$ 2979, 2934, 2094, 1731, 1451, 1374, 1293, 1212, 1158, 1111, 1041, 856. m/z (ESI-MS) 299.9 ($M^+$ + Na. $C_9H_{15}N_3O_3S_2$ requires 300.05). This RAFT agent was found to decompose in the mass spectrometer before the ionization. Molecular peak as well as assigned fragments have been detected, but in lower concentration than expected.

## Synthesis of acetylene-dithiobenzoate agent (2)

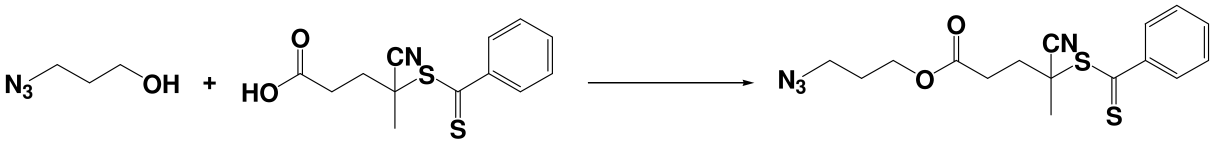


2

A solution of (4-cyanopentanoic acid)-4-dithiobenzoate (CPADB) (1.5g, 5.36 mmol) and 3-(trimethylsilyl)-2-propyn-1-ol (3.44g, 26.8 mmol) in dichloromethane (60 mL) was cooled to 0 ºC and N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (3.08g, 16.08 mmol) and 4-dimethylaminopyridine (0.67g, 5.5 mmol) were subsequently added. The orange solution was stirred at 0 ºC for 2h, then at ambient temperature overnight. The reaction mixture was washed with water (2x50mL) and dried over $MgSO_4$. The volatiles were removed under reduced pressure and the crude product purified by flash chromatography ($SiO_2$, 1) 100% $CH_2Cl_2$ ; 2) Hexane/Ethyl acetate 4/1) (1.84

g, 88%). $\delta_H$(300 MHz, CDCl$_3$) 0.19 (9H, s, Si-(C$\underline{H3}$)$_3$), 1.93 (3H, s, C-C$\underline{H3}$), 2.40-2.75 (4H, m, -C$\underline{H2}$-C$\underline{H2}$-), 4.72 (2H, s, O-C$\underline{H2}$-C), 7.39 (2H, t, *J* 7.5, CH aro.), 7.56 (1H, t, *J* 7.5, CH aro.), 7.89 (2H, d, *J* 8.5, CH aro.). $\delta_C$(300 MHz, CDCl$_3$) -0.42 (Si-($\underline{C}$H$_3$)$_3$), 24.06 (C-$\underline{C}$H$_3$), 29.56 ($\underline{C}$H$_2$-C(=O)), 33.16 (C-$\underline{C}$H$_2$-CH$_2$), 45.61 ($\underline{C}$-CN), 53.19 (O-$\underline{C}$H$_2$-C), 93.02 (Si-$\underline{C}$), 98.34 (O-CH$_2$-$\underline{C}$), 118.32 ($\underline{C}$N), 126.59 (C aro.), 128.49 (C aro.), 132.94 (C aro.), 144.46 (C aro.), 170.65 ($\underline{C}$(=O)), 222.11 ($\underline{C}$(=S)-S). $\nu_{max}$/cm$^{-1}$ 2960, 2125, 1742, 1445, 1384, 1250, 1172, 1107, 1081, 1048, 999, 844, 800, 761, 687. m/z (ESI-MS) 412.1 (M$^+$ + Na. $C_9H_{23}NO_2S_2Si$ requires 412.08).

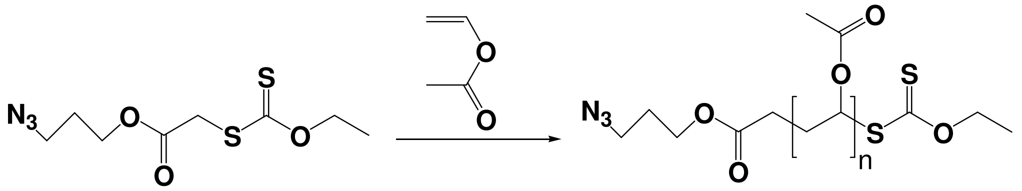
### Synthesis of azido-dithiobenzoate agent (6)



6

A solution of (4-cyanopentanoic acid)-4-dithiobenzoate (0.96g, 3.42 mmol) and 3-azido-1-propanol (1.73g, 17 mmol) in dichloromethane (60 mL) was cooled to 0 ºC and N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (1.96 g, 10 mmol) and 4-dimethylaminopyridine (20.4mg, 0.17 mmol) were subsequently added. The orange solution was stirred at 0 ºC for 2h, then at ambient temperature overnight. The reaction mixture was washed with water (2x50mL) and dried over MgSO$_4$. The volatiles were removed under reduced pressure and the crude product purified by flash chromatography (SiO$_2$, 1) 100% CH$_2$Cl$_2$ ; 2) Hexane/Ethyl acetate 4/1) (0.96 g, 77%). $\delta_H$(300 MHz, CDCl$_3$) 1.85-1.95 (2H, m, CH$_2$-C$\underline{H2}$-CH$_2$), 1.94 (3H, s, C(CN)(C$\underline{H3}$)), 2.38-2.72 (4H, m, (CN)C-C$\underline{H2}$-C$\underline{H2}$-C(=O)), 3.40 (2H, t, *J* 5.7, C$\underline{H2}$-N$_3$), 4.20 (2H, t, *J* 5.7, C$\underline{H2}$-O-C(=O)), 7.39 (2H, t, *J* 7.5, C$\underline{H}$ phenyl), 7.56 (1H, t, *J* 7.5, C$\underline{H}$ phenyl), 7.90 (2H, d, *J* 8.5, C$\underline{H}$ phenyl). $\delta_C$(300 MHz, CDCl$_3$) $\delta$=24.10 (C(CN)($\underline{C}$H$_3$)), 27.97 ($\underline{C}$H$_2$-C(=O)), 29.68 (CH$_2$-$\underline{C}$H$_2$-CH$_2$), 33.30 ($\underline{C}$H$_2$C(CN)), 45.64 ($\underline{C}$(CN)(CH$_3$)), 48.04 ($\underline{C}$H$_2$-N$_3$), 61.91 ($\underline{C}$H$_2$-O-C(=O)), 118.35 ($\underline{C}$N), 126.58 ($\underline{C}$H phenyl), 128.49 ($\underline{C}$H phenyl), 132.96 (C phenyl), 144.45 ($\underline{C}$H phenyl), 171.30 ($\underline{C}$=O(O)), 222.18 ($\underline{C}$=S(S)). $\nu_{max}$/cm$^{-1}$ 2925, 2850, 2091, 1735, 1444, 1293, 1227, 1047, 874, 764, 687. m/z (ESI-MS) 385.0 (M$^+$ + Na. $C_{16}H_{18}N_4O_2S_2$ requires 385.08). This RAFT agent was found to decompose in the mass spectrometer before the ionization. Molecular peak as well as assigned fragments have been detected, but in lower concentration than expected.

## Vinyl acetate polymerization



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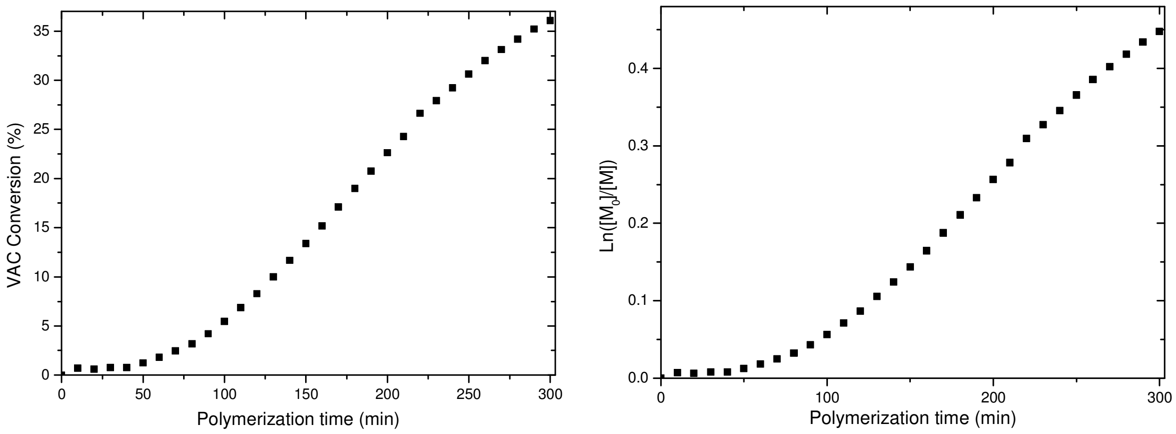
3

Stock solutions of vinyl acetate (4 g, $15.2.10^{-3}$ mol), AIBN (1.54 mg, $9.38.10^{-6}$ mol) and the azido-dithiobenzoate agent **1** ($4.69.10^{-5}$ mol) were transferred into Schlenk tubes, thoroughly deoxygenated by four consecutive freeze-pump-thaw cycles, and subsequently placed in a constant temperature water bath at 60°C. The Schlenk tubes were removed at pre-determined time intervals and the polymerization was stopped by cooling the solutions in liquid nitrogen. The polymer was isolated by evaporating off the residual monomer in the presence of hydroquinone. The conversions were evaluated separately by *in situ* Fourier transform- near infra-red (FT-NIR) spectroscopy, by following the decrease of the intensity of the vinylic stretching overtone of the monomer at $\nu = 6\ 200\ \text{cm}^{-1}$. The molecular weights were confirmed by NMR calculations using the following equation:

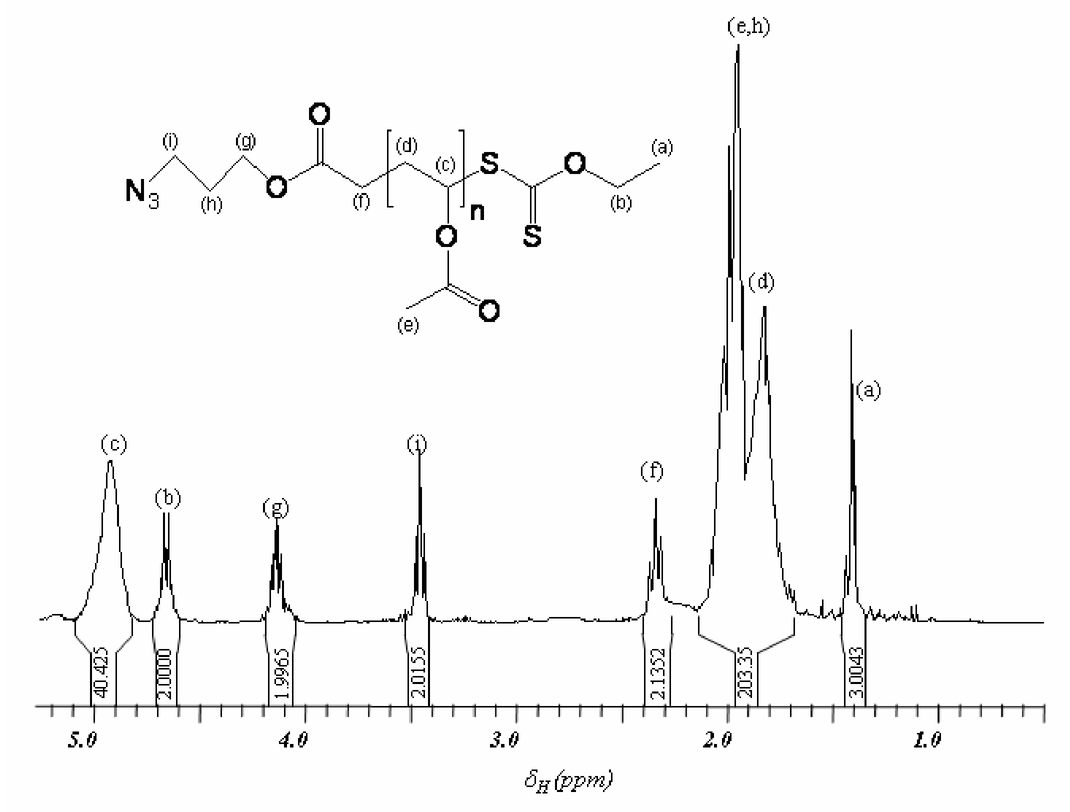
$$\overline{M}_{n,3} = \frac{I_c \times 11 \times M_{VAC}}{(I_a + I_b + I_i + I_f + I_g)} + M_{RAFT1}$$

$I_a$, $I_b$, $I_i$, $I_f$ and $I_g$ are the intensities of signals due to the RAFT end group (see NMR spectrum below) and $I_c$ corresponds to the peak area at 4.8-5.1 ppm due to the vinyl acetate units.

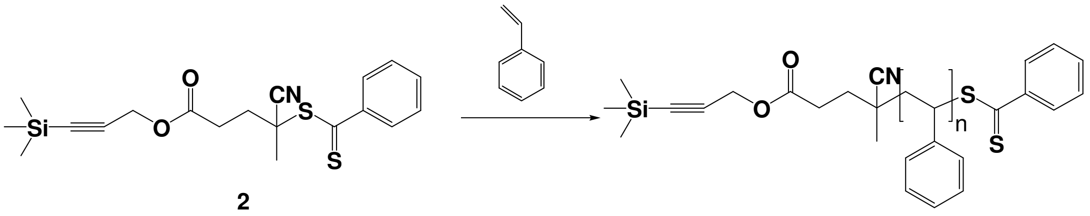
*Kinetic plots of the polymerization of vinyl acetate*



*$^1$H spectrum of poly(vinyl acetate) (PVAC-$N_3$, entry 5, Table 1)*



## Styrene polymerization

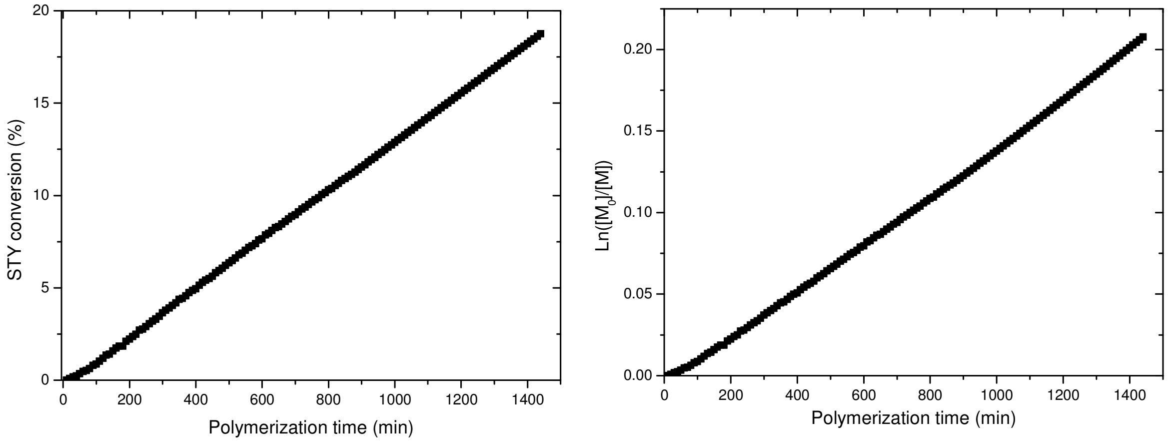


A master batch solution of styrene (4 g, 38.41.10$^{-3}$ mol), acetylene-dithiobenzoate agent (**2**) (31.64 mg, 8.13.10$^{-5}$ mol) (or azido-dithiobenzoate agent (**6**) (29.44 mg, 8.13.10$^{-5}$ mol)) and AIBN (2.67 mg, 1.63.10$^{-5}$ mol) is prepared and aliquots were placed in Schlenk tubes. Tubes were subsequently subjected to four freeze-pump-thaw cycles to remove any residual oxygen. The polymerization reaction was performed at 60°C. The conversions were evaluated separately by *in situ* Fourier transform- near infra-red (FT-NIR) spectroscopy, by following the decrease of the intensity of the vinylic stretching overtone of the monomer at $\nu = 6\ 200\ \text{cm}^{-1}$. The molecular weights were confirmed by NMR calculations using the following equation:

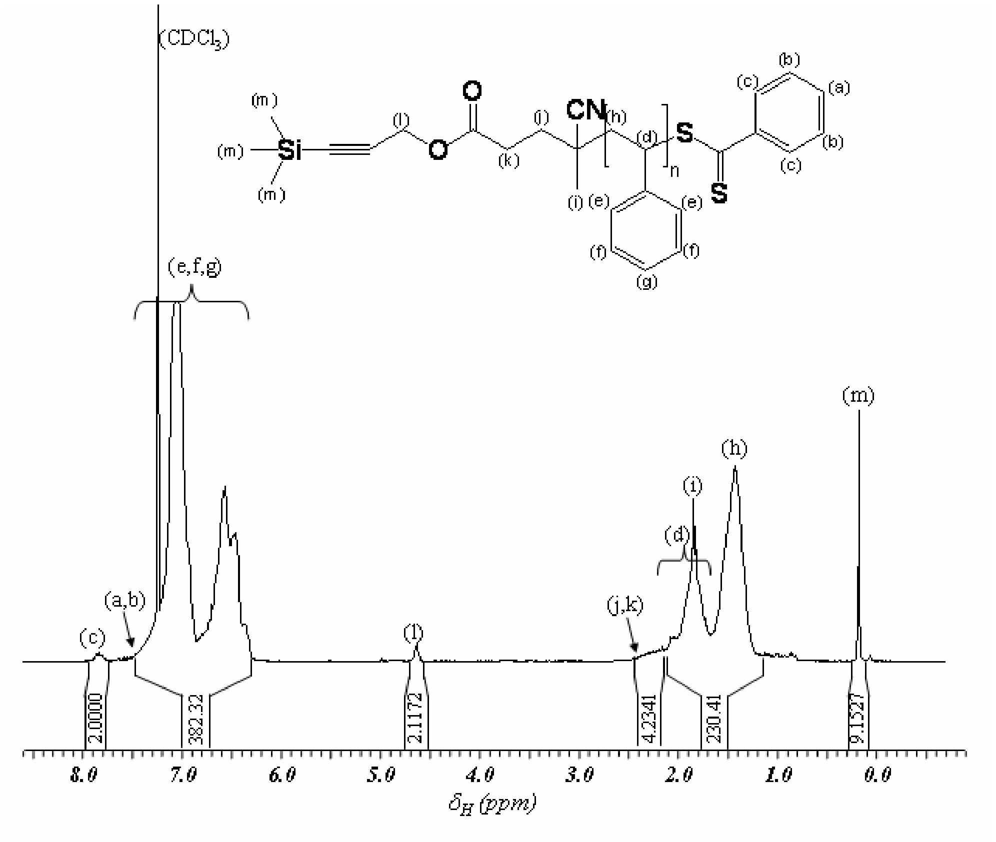
$$\overline{M_{n,PS}} = \frac{9\times(I_{e,f,g})\times M_{STY}}{5\times I_m} + M_{RAFT\,2}$$

$I_{e,f,g}$, is the intensity of signals due to the aromatic protons of styrene units (see NMR spectrum below) and $I_m$ corresponds to the peak area at 0.19 ppm due to the trimethylsilyl group.

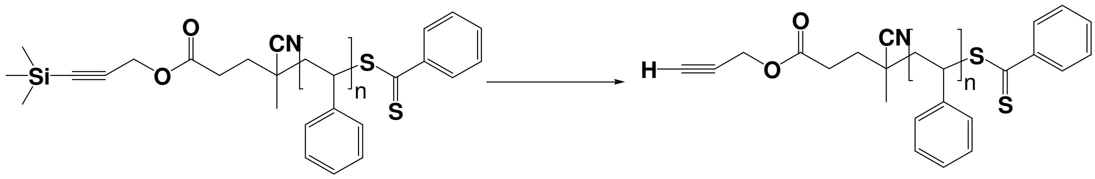
*Kinetic plots of the polymerization of styrene*



*$^1H$ spectrum of "protected" polystyrene (entry 4, Table 1)*



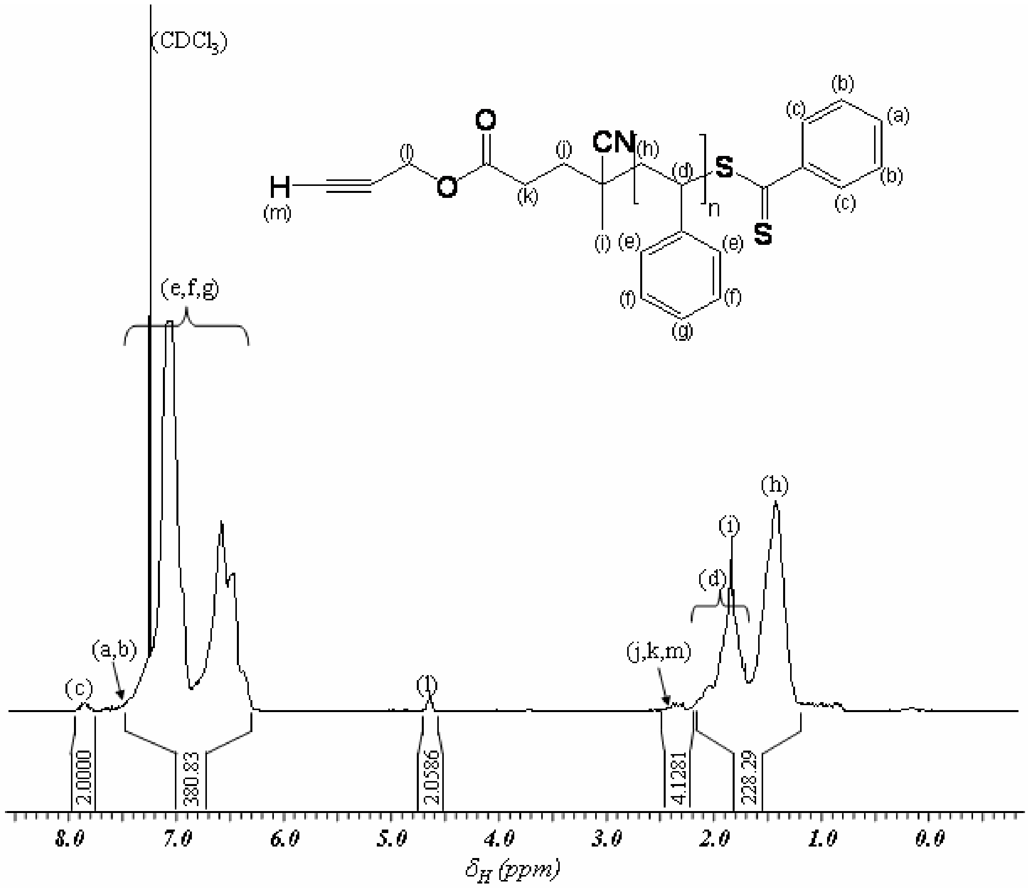
## Polystyrene deprotection



**4**

The trimethyl silyl protected polymer (0.107 g, $1.30.10^{-5}$ mol) is dissolved in tetrahydrofuran (5 mL). Nitrogen was bubbled (ca. 10 min) and the solution was cooled to -20 ºC. A 0.20 M solution of TBAF.3$H_2O$ (10 equiv. mol/mol) was added slowly. The resulting mixture was stirred at this temperature for 30 min and then to ambient temperature for 4 hours. The reaction was passed through a short silica pad in order to remove the excess of TBAF and the pad was subsequently washed with additional THF. The resulting solution was then concentrated under reduced pressure and the polymer was precipitated in cold methanol.

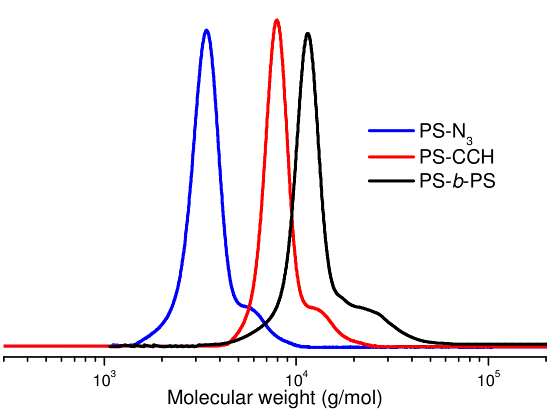
*$^1H$ spectrum of "unprotected" polystyrene (PS-C≡CH, entry 4, Table1)*



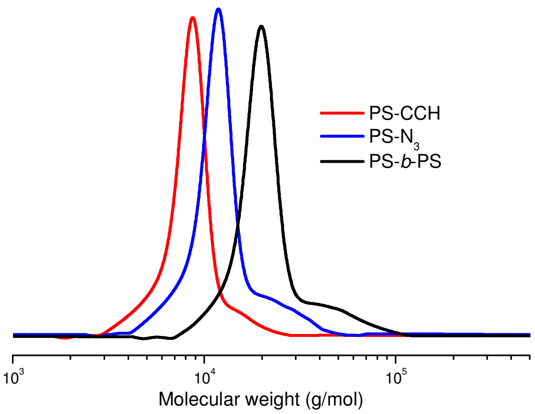
## “Click” coupling between polymers

*Typical experiment (entry 5, Table 1)* : PVAC **3** (0.41 g, 1.1.10$^{-4}$ mol), PS **4** (0.83 g, 1.1.10$^{-4}$ mol) and CuI (4.2 mg, 2.2.10$^{-5}$ mol) were added to an oven-dried Schlenk flask, evacuated for 10 minutes and backfilled with nitrogen. A solution of degassed 1,8-diaza[5.4.0]bicycloundec-7-ene (DBU) (0.335 g, 2.2.10$^{-3}$ mol) in THF (5 mL) was then added. The Schlenk flask was placed in a constant temperature oil bath at 40°C for 2 days. Analytical samples for the GPC were prepared by filtering the solution through a short column of silica gel followed by an evaporation of the solvent under reduced pressure. A powder of the copolymer was then obtained by precipitation in cold distilled water.

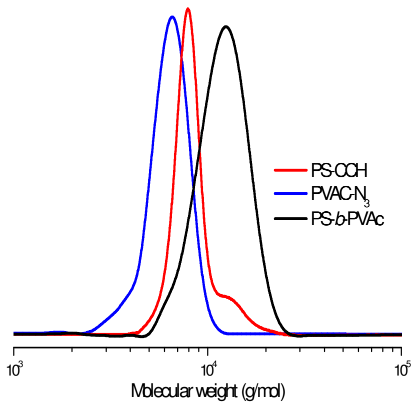
*Size Exclusion Chromatography of the “click” coupling reactions*



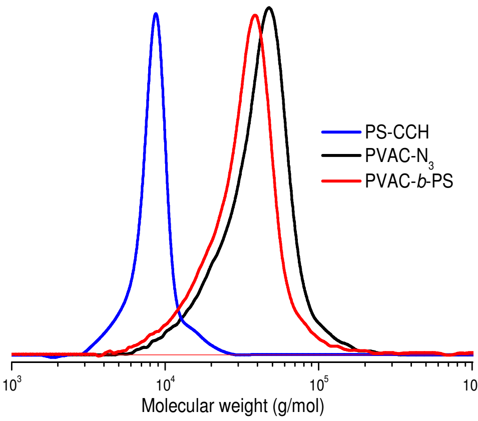
**Entry 1, Table 1**



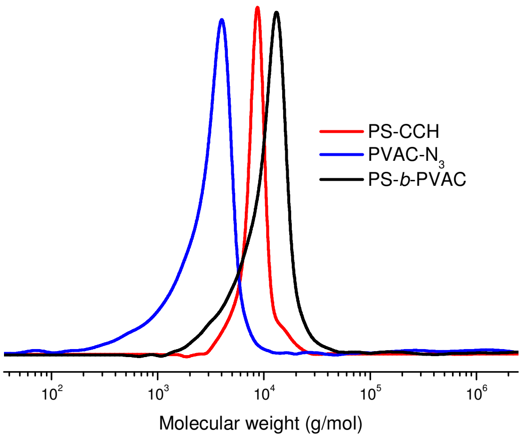
**Entry 2, Table 1**



**Entry 3, Table 1**



**Entry 4, Table 1**



**Entry 5, Table 1**

## References

1. Y. Mitsukami, M.S. Donovan, A. B. Lowe, and C. L. McCormick, *Macromolecules*, 2001, **34**, 2248-2256.