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Supporting Information

High-Throughput Polymer Screening in Microreactors: Boosting the Passerini-Three Component Reaction

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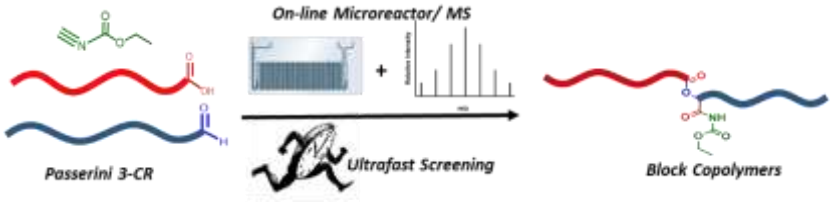

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Table of contents:

1. Materials

The monomers *n*-butyl acrylate (*n*BA, Acros, 99%), ethylene glycol methyl ether acrylate ( ) and methyl acrylate (MA, Acros, 99%) were deinhibited over a column of activated basic alumina prior to use. 1,1'-azobis(isobutyronitrile) (AIBN, Sigma-Aldrich, 98%) was recrystallized twice from ethanol prior to use. Ethylisocyano acetate (Sigma-Aldrich, 98%) was used as received. All solvents used are obtained from commercial sources (Acros and Sigma-Aldrich) and used without further purification.

2. Characterization

NMR spectra were recorded in deuterated chloroform with a Varian Inova 300 spectrometer at 300 MHz for ^{1}H NMR and at 75 MHz for ^{13}C NMR using a Varian probe (5 mm-4-nucleus AutoSWPFG) and a pulse delay of 12 s. NMR spectra were analyzed in MestReNova software.

Analysis of the MWDs of the polymer samples were performed on a Tosoh **EcoSEC** operated by PSS WinGPC software, equipped with a PLgel 5.0 µm guard column (50 × 8 mm), followed by three PLgel 5 µm Mixed-C columns (300 × 8 mm) and a differential refractive index detector using THF as the eluent at 40 °C with a flow rate of 1 mL·min^{-1}. The SEC system was calibrated using linear narrow polystyrene standards ranging from 474 to 7.5 x 10^{6} g·mol^{-1} PS (K = 14.1 × 10^{-5} dL·g^{-1} and α = 0.70), and toluene as a flow marker.

ESI-MS was performed using an LTQ orbitrap velos pro mass spectrometer (ThermoFischer Scientific) equipped with an atmospheric pressure ionization source operating in the nebulizer assisted electro spray mode. The instrument was calibrated in the m/z range 220-2000 using a standard solution containing caffeine, MRFA and Ultramark 1621. A constant spray voltage of 5 kV was used and nitrogen at a dimensionless sheath gas flow-rate of 7 was applied. capillary temperature was set to 275°C. A mixture of THF and methanol (THF:MeOH = 3:2), all HPLC grade, were used as solvent. Spectra were analyzed in Thermo Xcalibur Qual Browser software.

3. On-line ESI-MS/Microreactor Coupling

Full details of the ESI-MS /Microreactor setup were described previously.[1]

In short, reactions take place in a conventional microreactor chip (**D**). When the microreactor is operated under true synthesis conditions, a reactor mixture is obtained at the reactor outlet that is unsuitable for MS analysis due to a mismatch in sample concentration, solvent, absence of doping agents and flow rate. These issues can, however, be conveniently overcome by a strong dilution of the reactor flow mixture (**F**) with suitable doped ESI solvent mixtures (**G,J**) followed by a flow T-splitter (**I**) to meet the requirements of the ESI-MS nozzle (**K**). Dilution also serves thereby as an effective solvent change next to the decrease in sample concentration down to the micromolar range. One of the many advantages of such a setup is the high flexibility in terms of concentrations and reaction conditions that can be investigated. A wide concentration window in the microreactor can be accessed; higher flow rates of increased sample concentration can be dynamically compensated by adjusting the dilution factor.

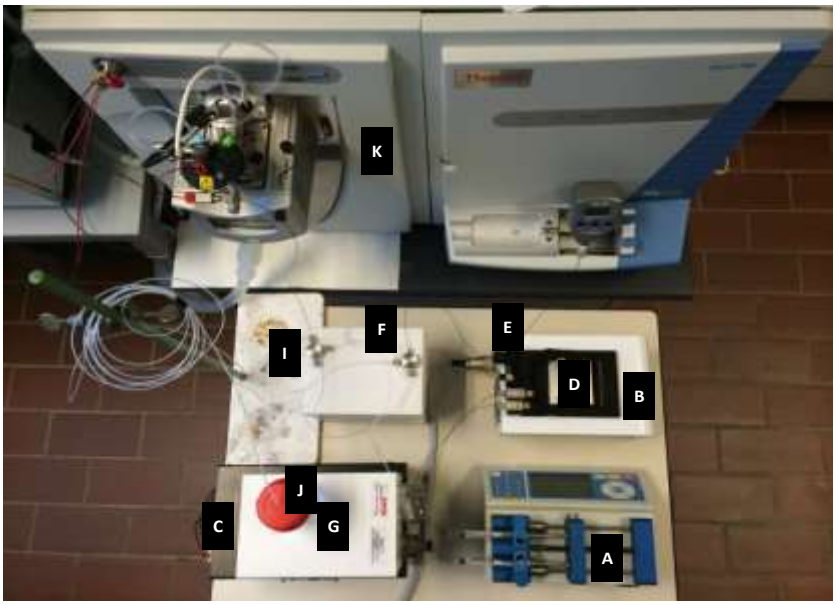
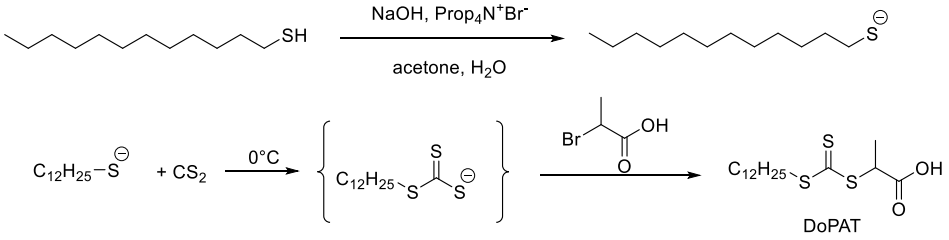


Figure S3.1 Photo of the on-line setup.

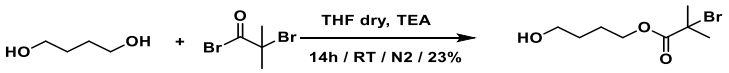
4. Experimental procedures

a. Synthesis of 2-(Dodecylthiocarbonothioylthio)propionic acid (DoPAT)



NaOH (10.0 g, 250 mmol) was dissolved with stirring and gentle heating in a mixture of dodecanethiol (60 mL, 50 g, 250 mmol), acetone (800 mL), water (100 mL), and tetrapropylammonium bromide (5.4 g, 2 mmol). The resulting solution was cooled in an ice bath and treated with carbon disulfide (15 mL, 19 g, 250 mmol). After 20 min, 2-bromopropanoic acid (22.6 mL, 38.2 g, 250 mmol) was added and the mixture was stirred at ambient temperature for 16 h. The solution was evaporated to a quarter of the original volume and slowly acidified with 2 M hydrochloric acid (1 L) then further diluted with water (1.5 L). The precipitate was collected and recrystallized twice from Hexane to give the desired trithiocarbonate as fine yellow platelets (56.4 g, 65%).^{1}H NMR ($CDCl_3$): δ (ppm) = 10.2 (br, 1H, CO_2H), 4.88 (q, 1H, CH), 3.36 (t, 2H, CH_2), 1.70 (quint, 2H, CH_2), 1.63 (d, 3H, CH_3), 1.40 (quint, 2H, CH_2), 1.22−1.35 (m, 16H, CH_2), 0.88 (t, 3H, CH_3). ^{13}C NMR ($CDCl_3$): δ (ppm) = 221.8, 177.2, 47.5, 37.5, 32.0, 29.7, 29.6, 29.5, 29.4, 29.1, 28.9, 27.9, 22.7, 16.7, 14.1. ESI-MS: $[373.130]^{Na+}$

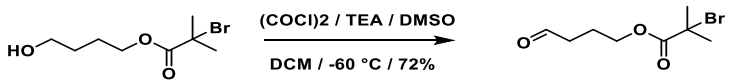
b. Synthesis of 3-hydroxybutyl-2-bromo-2-methylpropionate (3-HBBMP)



Anhydrous THF (60 ml) , 1,4-Butanediol (39.7 g, 0.44 mol) and triethylamine (22.2 g, 0.22 mol) were added to a 250 mL round bottom flask under an argon blanket and cooled to 0 ^{o}C To this stirred solution, 2-Bromoisobutyryl bromide (46.0 g, 0.20 mol) in anhydrous THF (40 ml) was added drop-wise and the reaction mixture was stirred for 15 h at room temperature. The solvent was removed via rotary evaporation and the residue taken up in diethyl ether (100 mL). The white precipitate was filtered off and the organics were extracted with 1 N HCl aqueous solution, brine and water. The organic layer was dried ($MgSO_4$), filtered and the volatiles were evaporated to give a colorless oil. The final product was isolated by column chromatography 40/60 diethyl ether/hexane to yield a clear oil (12.7 g, 27%). ^{1}H NMR ($CDCl_3$): δ (ppm) = 4.16 (t, 2H, CH_2), 3.62 (t, 2H, CH_2); 3.20 (s, 1H, OH), 1.87 (s,

6H, CH_3), 1.78-1.68 (m, 2H, CH_2), 1.67-1.55 (m, 2H, CH_2). ^{13}C NMR ($CDCl_3$): δ (ppm) = 171.8, 65.9, 62.0, 56.0, 30.7, 28.9, 24.9.

c. Synthesis of 3-butanal-2-bromo-2-methylpropionate (3-BBMP)

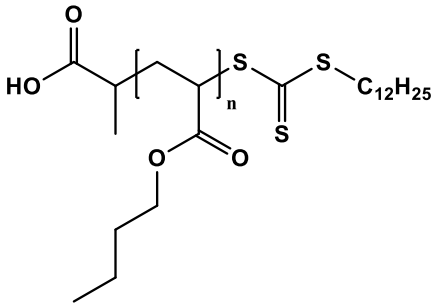


Procedure for the Swern type oxidation of 3-HBBMP. All glassware was dried from volatiles before use. Oxalylchloride (2.20 mL, 25.63 mmol) and CH_2Cl_2 (70 mL) were placed in a 3-necked round bottom flask under inert nitrogen atmosphere equipped with a stirrer. The mixture was cooled to -60 °C ($(CH_3)_2CO/N_2$ bath). Dry DMSO (3.96 mL, 55.77 mmol) was added dropwise while stirring was continued at -60 °C. After *ca* 10 minutes a solution of 3-HBBMP (5.50 g, 23.43mmol) in CH_2Cl_2 (25 mL) was added dropwise to the reaction mixture. The mixture was stirred for 15 minutes when Et_3N (16 mL, 115.40 mmol) was added slowly at -60 °C. The cooling batch was removed and water (70 mL) was added, the stirring continued to room temperature. The organic layer was separated and the aqueous phase twice re-extracted with CH_2Cl_2 (50 mL). The organic layers were combined and the volume reduced to 50 mL by vacuum distillation. The solution was successively washed by HCl (1N), water, Na_2CO_3 (diluted) and water and evaporated to dryness. The final product was isolated by column chromatography (silica, gradient Et_2O/hexane 20 → 40% Et_2O) to yield a yellowish oil (3.90 g, 72%). ^{1}H NMR ($CDCl_3$): δ (ppm) = 9.64 (s, 1H, -COH), 4.04 (t, 2H, CH_2), 2.45 (t, 2H, CH_2), 1.92-1.82 (m, 2H, CH_2), 1.76 (s, 6H, CH_3). ^{13}C NMR ($CDCl_3$): δ (ppm) = 200.9, 171.1, 64.7, 55.8, 40.0, 30.4, 20.8.

d. Synthesis of tris[2-(dimethylamino)ethyl]amine (Me_6TREN)

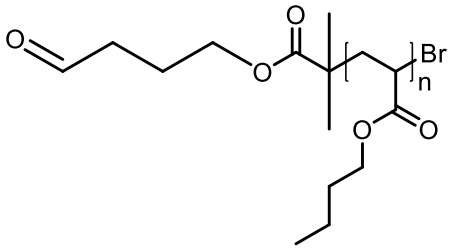
In a 250 mL three-necked flask equipped with a condenser, addition funnel, and stirrer tris(2-aminoethyl)amine (4.0 mL, 0.027 mol) was added in 50 mL of methanol. To this mixture HCl (60 mL, 3N) in methanol was added dropwise and stirred at room temperature. After 1 h the precipitate was filtered washed trice with MeOH (50 mL) to yield the product (salt) as a white solid. To this water (10 mL), formic acid (50 mL) and formaldehyde (aq., 46 mL) was added in a 250 mL round bottom flask. The reaction mixture was stirred under reflux for 6 h. Volatiles were removed by vacuum distillation. The crude product was redissolved in NaOH (aq., 10 wt%) and extracted with diethyl ether (4 x 100 mL). The organic layer was dried by NaOH pellets and the solvent was removed by vacuum distillation to give a yellowish liquid (6.0g, 89%). ^{1}HNMR ($CDCl_3$): δ (ppm) = 2.560-2.597 (m, 6H, CH_2), 2.332-2.369 (m, 6H, CH_2), 2.198 (s, 18H, CH_3).

f. Synthesis of Poly(n-butyl acrylate) (PnBA) via RAFT polymerization



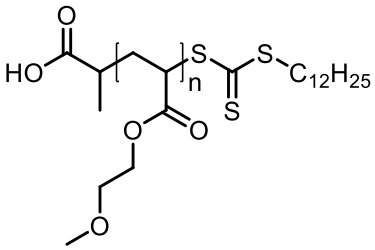
Poly(n-butyl acrylate). In a typical procedure 1.1'-azobis(isobutyronitrile) (AIBN) (0.11 g, 0.0007 mol), (dodecylthiocarbonothioylthio)propionic acid (DoPAT) RAFT agent (5.0 g, 0.014 mol), monomer *n*BA (17.90 g, 0.14 mol) and butyl acetate (20.1 ml) were added a 100 mL round bottom flask and stirred until dissolved. The flask was sealed by a rubber septum, the solution was degassed for 30 min by N_2 purging and placed in a thermolysed preheated oil batch of 100 °C. After a reaction time of 5 min, the reaction mixture was cooled down in liquid nitrogen and quenched by a hydroquinone solution in MeOH. The polymer mixture was transferred into an aluminum pan to evaporate all volatiles yielding 30.0 g of P*n*BA. ^{1}HNMR ($CDCl_3$) yielded 92% conversion of *n*BA monomer. SEC (THF): M_n = 1300 g mol^{-1} and PDI = 1.11.

f. Synthesis of Poly(n-butyl acrylate) (PnBA) via SET-LRP



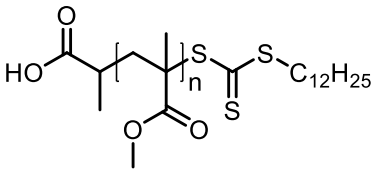
Poly(n-butyl acrylate). In a typical procedure initiator 3-*butanal-2-bromo-2-methylpropionate (3-BBMP) (*1 equiv.*),* monomer *n*BA (10 equiv.), ligand tris[2-(dimethylamino)ethyl]amine (Me_6TREN) (0.16 equiv.) and dimethylformamide (2 ml) were added to a 10 mL glass vial. The glass vial was sealed by a rubber septum, the solution was degassed for 10 min by N_2 purging and subsequently inserted into the glovebox. Copper powder (Cu(0), 0.16 equiv.) and a stirrer were added to the glass vial. The glass vial was resealed and the reaction was stirred at room temperature. After 20 minutes a sample of the reaction was withdrawn for ^{1}HNMR analysis to determine monomer conversion (76%). The reaction mixture was diluted with THF and passed over silica gel to remove metal complexes. Volatiles were removed by vacuum distillation and the polymer was dried under vacuum overnight. ^{1}HNMR ($CDCl_3$): 76% conversion of *n*BA monomer. SEC (THF) M_n = 1050 g mol^{-1}, Mp = 1150 g mol^{-1} and PDI = 1.14.

g. Synthesis of Poly(ethylene glycol methyl ether) (PEGMEA) via RAFT polymerization



Poly(*ethylene glycol methyl ether*). In a typical procedure 1.1'-azobis(isobutyronitrile) (AIBN) (8.21 mg, 0.05 mmol), (dodecylthiocarbonothioylthio)propionic acid (DoPAT) RAFT agent (350.60 mg, 1.00 mmol), monomer *ethylene glycol methyl ether acrylate* (1.48 mL, 8.00 mmol) and butyl acetate (3 ml) were added to a 10 mL glass vial together with a magnetic spin bar. The glass vial was sealed by a rubber septum, the solution was degassed for 10 min by N_2 purging and subsequently inserted into the glovebox. The glass vial was placed in a preheated copper block at 100 °C. After a reaction time of 5 min the glass vial was subsequently quenched by cooling the vial in liquid nitrogen and subjecting to ambient atmosphere. Subsequently the mixture was transferred into an aluminium pan to evaporate excess of solvent and monomer, yielding 1.750 g of crude product mixture. ^{1}H NMR ($CDCl_3$): 92% conversion of *n*BA monomer, SEC M_n = 1650 g mol^{-1}, Mp = 1900 g mol^{-1} and PDI = 1.13.

h. Synthesis of Poly(methyl methacrylate) (PMMA) via RAFT polymerization



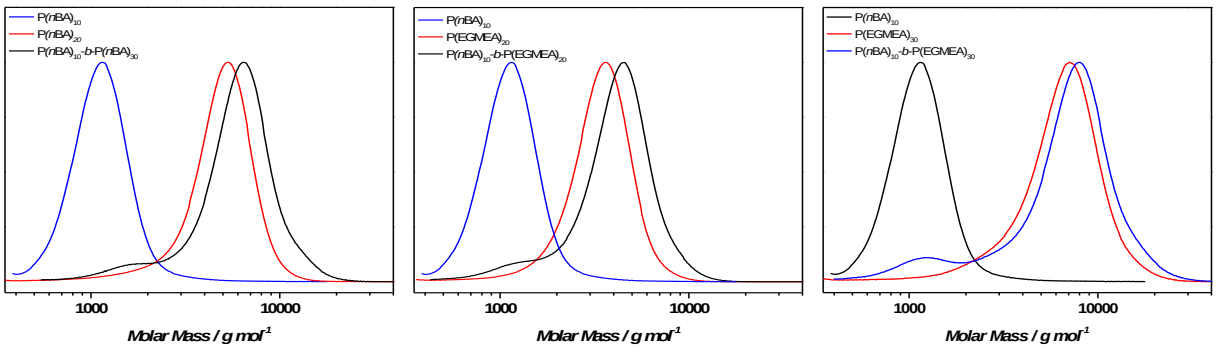
***Poly(methyl methacrylate*).** In a typical procedure 1.1'-azobis(isobutyronitrile) (AIBN) (0.05 equiv.), (dodecylthiocarbonothioylthio)propionic acid (DoPAT) RAFT agent (1 equiv.), monomer *methyl methacrylate* (25 equiv.) and butyl acetate (3 ml) were added to a 10 mL glass vial together with a magnetic spin bar. The glass vial was sealed by a rubber septum, the solution was degassed for 10 min by N_2 purging and subsequently inserted into the glovebox. The glass vial was placed in a preheated copper block at 100 °C. After a reaction time of 5 min the glass vial was subsequently quenched by cooling the vial in liquid nitrogen and subjecting to ambient atmosphere. Subsequently the mixture was transferred into an aluminium pan to evaporate excess of solvent and monomer. ^{1}H NMR ($CDCl_3$): 80% conversion of *n*BA monomer, SEC M_n = 1700 g mol^{-1}, Mp = 2200 g mol^{-1} and PDI = 1.25.

I. Synthesis of diblock copolymers

All diblock copolymers were synthesized according to the conditions identified in this manuscript. In a typical procedure an equimolar amount of the two corresponding homopolymers (1 equiv.), ethyl isocyanoacetate (2 equiv.) and dichloromethane as the reaction solvent were weighted in a glass vial. A magnetic stirrer was added and the reaction mixture was reacted for 1 hour at 100 °C in a pre-heated copper heating block on a heating plate. The diblock copolymers were analysed by SEC and ESI-MS without further purification.

Figure S4.1 shows the low molecular weight shoulders, increased reaction times are required to reach full conversion of the starting polymers.

	M_p (F) (g mol^{-1})	M_n (F) (g mol^{-1})	PDI (F)	M_p (H) (g mol^{-1})	M_n (H) (g mol^{-1})	PDI (H)	M_p (I) (g mol^{-1})	M_t (I) (g mol^{-1})	PDI (I)
P(nBA)$_{10}$-b-P(nBA)$_{30}$ (Batch)	1150	1050	1.14	5350	4200	1.23	6400	5000	1.28
P(nBA)$_{10}$-b-P(EGMEA)$_{20}$ (Batch)	1150	1050	1.14	3600	3200	1.14	4500	3450	1.29
P(nBA)$_{10}$-b-P(EGMEA)$_{30}$ (Batch)	1150	1050	1.14	7050	5750	1.23	8000	4750	1.61



Figuur S4.1 Synthesis of diblock copolymers with starting polymers with DP 10 or higher. It can be observed in SEC analysis that 1 hour reaction time is not sufficient to reach full conversion of the starting materials.

5. References

[1] J.J. Haven, J. Vandenbergh and T. Junkers, *Chem. Commun.*, 2015, **51**, 4611.