Electronic Supplementary Material (ESI) for Green Chemistry.

# Supporting Information

## Dihydrolevoglucosenone (Cyrene™) as a bio-renewable solvent for Cu(0)-mediated reversible deactivation radical polymerization (RDRP) without external deoxygenation

Arkadios Marathianos,‡[a] Evelina Liarou,‡[a] Ellis Hancox,[a] James L. Grace,[b,c] Daniel W. Lester[a] and David M. Haddleton*[a]

[a] *Department of Chemistry, University of Warwick, Library Road, Coventry, CV4 7AL, UK*

[b] *ARC Centre of Excellence in Convergent Bio-Nano Science and Technology, Monash Institute of Pharmaceutical Sciences, Monash University, Parkville, VIC 3052, Australia*

[c] *Drug Delivery, Disposition and Dynamics Theme, Monash Institute of Pharmaceutical Sciences, Monash University, Parkville, VIC 3052, Australia*

E-mail: d.m.haddleton@warwick.ac.uk

‡*These authors contributed equally to this work.*

## Experimental section

## Materials

All materials were purchased from Sigma-Aldrich and Cornelius (benzyl acrylate) and used as received unless otherwise stated. Cu(0) wire (gauge 0.25 mm) was purchased from Comax Engineered wires and purified by immersion in concentrated 37% HCl for 12 minutes, subsequently washed with deionized water and acetone and dried with compressed air prior to use. Tris-(2-(dimethylamino)ethyl)amine ($Me_6Tren$) was prepared according to the literature and stored in fridge.[1]

### Instrumentation

*Nuclear Magnetic Resonance (NMR).* $^1H$ NMR spectra were recorded on Bruker DPX-300 spectrometers in deuterated chloroform ($CDCl_3$) obtained from Sigma-Aldrich. Chemical shifts are given in ppm downfield from the internal standard tetramethylsilane. Monomer conversions were determined *via* $^1H$ NMR spectroscopy by comparing the integrals of monomeric vinyl protons to polymer signals.

***Size Exclusion Chromatography (SEC).*** SEC was carried out using an Agilent Infinity II 1260 MDS instrument equipped with differential refractive index (DRI), viscometry (VS), dual angle light scatter (LS) and multiple wavelength UV detectors. The system was equipped with 2 x PLgel Mixed C columns (300 x 7.5 mm) and a PLgel 5 µm guard column. The eluent was $CHCl_3$ run at 1 ml/min at 30 $^{o}$C. Poly(methyl methacrylate) standards (Agilent EasiVials) were used to create a 3rd order calibration between 1,020,000 – 1,840 g mol$^{-1}$. Analyte samples were filtered through 0.22 µm pore size GVHP filters before injection. Respectively, experimental molar mass ($M_{n,SEC}$) and dispersity ($Đ$) values of synthesized polymers were determined by conventional calibration using Agilent GPC/SEC software.

***Matrix-assisted laser desorption/ionization time-of-flight (MALDI-ToF-MS).*** The measurements were conducted using a Bruker Daltonics Ultraflex II MALDI-ToF mass spectrometer, equipped with a nitrogen laser delivering 2 ns laser pulses at 337 nm with positive ion ToF detection performed using an accelerating voltage of 25 kV. Solutions in tetrahydrofuran (THF) (50 µL) of trans-2-[3-(4-tert-butylphenyl)-2-methyl-2-propyldene] malononitrile (DCTB) as a matrix (saturated solution), sodium iodide as the cationization agent (1.0 mg mL$^{-1}$) and sample (1.0 mg mL$^{-1}$) were mixed, and 0.7 µL of the mixture was applied to the target plate. Spectra were recorded in reflectron mode calibrated with poly(ethylene glycol) monomethyl ether (PEGMe) 1900 Da.

***Oxygen Probe; Pocket Oxygen Meter - FireStingGO2 (from Pyro Science):*** For the determination of dissolved oxygen concentration and the *in-situ* monitoring of $O_2$-consumption, the solvent resistant oxygen probe OXSOLV was immersed in septum-sealed polymerization reactions. The starting point of the measurements (t=0) was determined as the time that the initiator was added. Upon completion of the measurement, the oxygen probe was cleaned with acetone-methanol-$H_2O$-acetone and was left to dry (excess of acetone was removed by careful wiping with soft tissue). The analysis of the data was conducted with the FireStingGO2 Manager software.

## Experimental Procedures

### Typical procedure for Cu(0) wire mediated RDRP of MA or MMA under inert conditions

A glass vial with total volume capacity of 20 mL was charged with Cu(II)$Br_2$ (0.05 eq.) and cyrene (4 mL). $Me_6$Tren (0.18 eq.) was added through a microliter syringe and the solution was sonicated until total dissolution of Cu(II)$Br_2$ (~10-15 mins). Subsequently, monomer (MA or MMA) (4 mL, 50 eq.), initiator (EBiB or DBiB or MBPA) (1 eq.) and pre-activated Cu(0) wire (5 cm) wrapped around a stirring bar were added to the vial and the vial sealed with a septum and wrapped with foil. Then, the mixture was deoxygenated under $N_2$ bubbling for 15 minutes. The polymerization was left to commence at ambient temperature.

### Typical procedure for Cu(0) wire mediated RDRP of (meth)acrylates and styrene with targeted $DP_n$ = 50, without external deoxygenation

Cu(II)$Br_2$ (0.05 eq.) cyrene (1 mL) and $Me_6$Tren (0.18 eq.) were added to a 2 mL glass vial and the solution was sonicated until total dissolution of Cu(II)$Br_2$ (~10-15 mins). Subsequently, monomer (1 mL, 50 eq.), EBiB (1 eq.) and pre-activated Cu(0)wire (5 cm) wrapped around a stirring bar were added to the vial and the vial sealed with a septum. The polymerization was left to commence at ambient temperature. Following the polymerization reaction, samples were taken and passed through a short column of neutral alumina to remove dissolved copper salts prior to analysis by $^1H$ NMR in $CDCl_3$ and SEC in $CHCl_3$.

Purification: Cyrene, residual monomer and copper salts were removed by precipitation (x 3) in cold MeOH-$H_2O$ mixtures (excess water ~ 100 mL). The polymer was dried in vacuum oven at 40 $^oC$ for 24 hrs before $^1H$ NMR analysis.

Monomers used: methyl acrylate (MA), methyl methacrylate (MMA), *tert*-butyl acrylate (*t*-BA), styrene, benzyl acrylate (BzA) and trifluoroethyl acrylate (TFEA).

### Typical procedure for *in situ* chain extensions

Initially, pMA with targeted $DP_n$ =10 was synthesized following the typical procedure for the homopolymerization of MA described above. After 3 hrs, an aliquot (~ 100 μL) was taken for $^1$H NMR and SEC analysis. Upon reaching 95% conversion, 900 μL of the polymerization solution was withdrawn with a 1 mL plastic syringe, without opening the vial, and the solution of cyrene and EA (targeted $DP_n$ for the pEA block = 10, with 50 % v/v cyrene) were added in the pMA-Br macroinitiator solution. The polymerization was left to commence and upon reaching 95 % conversion, 900 μL of the pMA-pEA solution was withdrawn. For the formation of the third block, a solution of cyrene and MA (targeted $DP_n$ for the pMA block = 10, with 50 % v/v cyrene) was added in the pMA-pEA solution.

## Supporting Figures and Tables

### Cu(0) wire mediated RDRP of MA in cyrene. Targeted DP$_n$ = 50

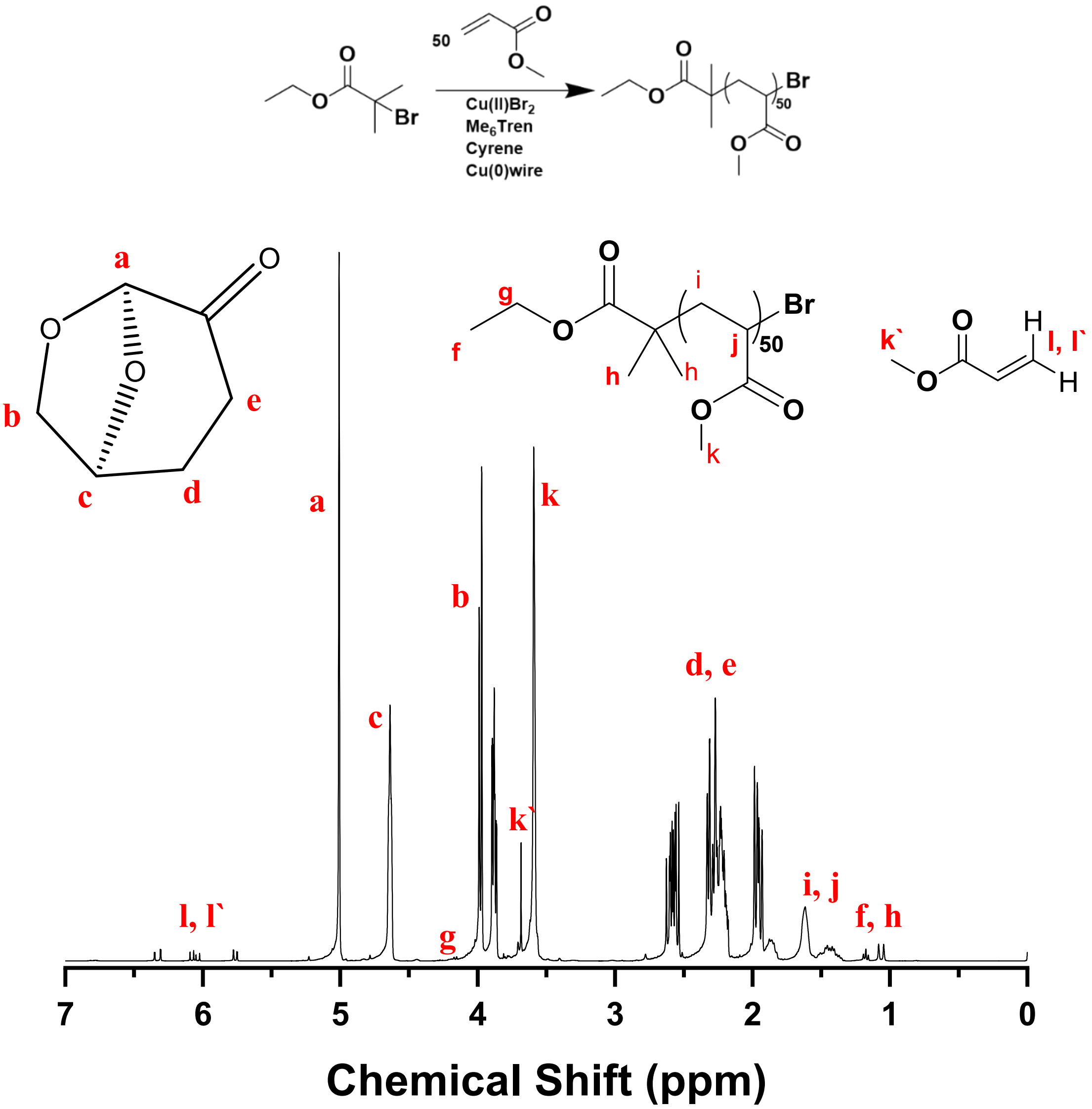


**Figure S 1.** Reaction scheme and $^1$H NMR for Cu(0) wire-mediated RDRP of MA using EBiB as initiator and cyrene as solvent under $N_2$. Conditions: [M]: [I]: [Cu(II)Br$_2$]: [Me$_6$Tren] = 50: 1: 0.05: 0.18, $V_{cyrene}$ = 50 % v/v with respect to monomer. Conversion was determined by comparing the integrals of monomeric vinyl protons (l, l`) to polymer signals (k).

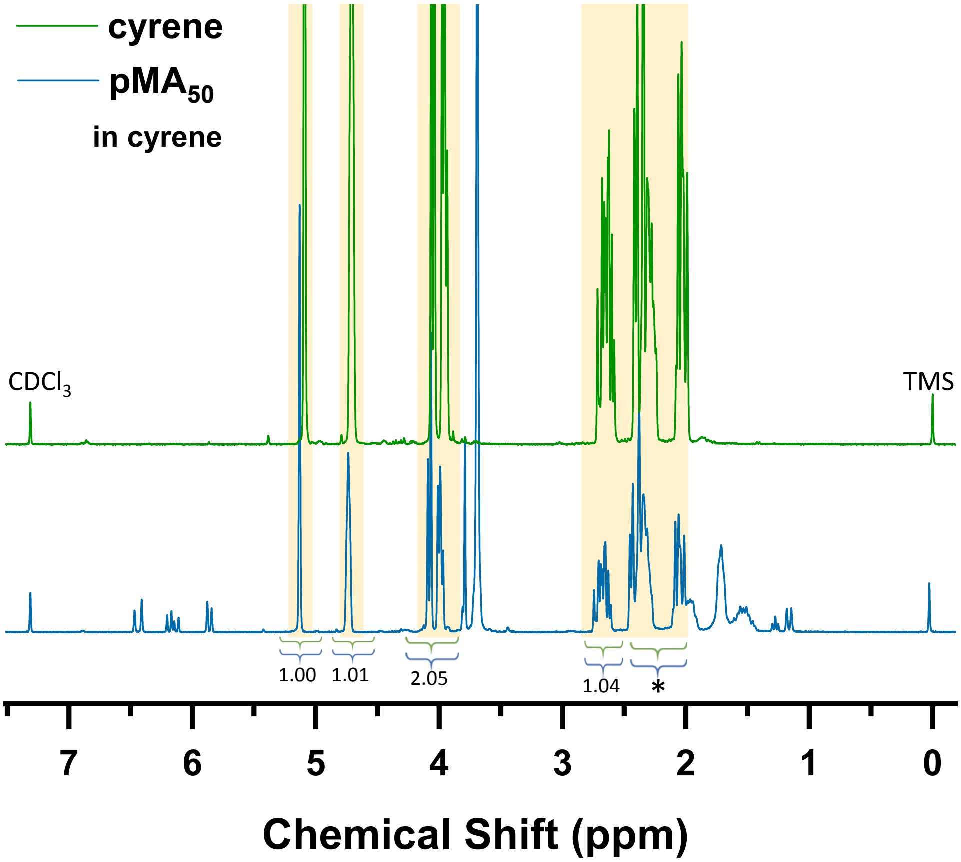
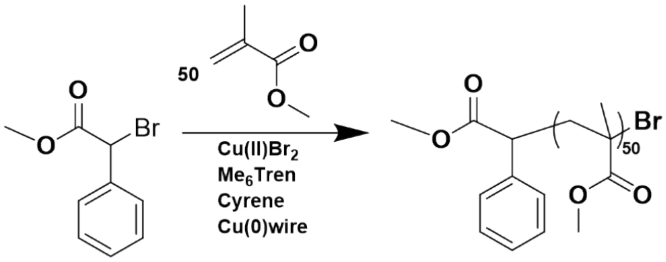


**Figure S 2.** $^1$H NMR spectra of cyrene and pMA$_{50}$ (in cyrene) showing no evidence of side reactions or degradation of the solvent.[2] Integration values at: 5.10 ppm (1.00), 4.71 ppm (1.01), ~3.96 – 4.06 ppm (2.05), ~2.63 ppm (1.04), ~2.35 ppm and ~2.03 ppm (* overlaid with polymer peaks).

### Cu(0) wire mediated RDRP of MMA in cyrene. Targeted DP$_n$ = 50



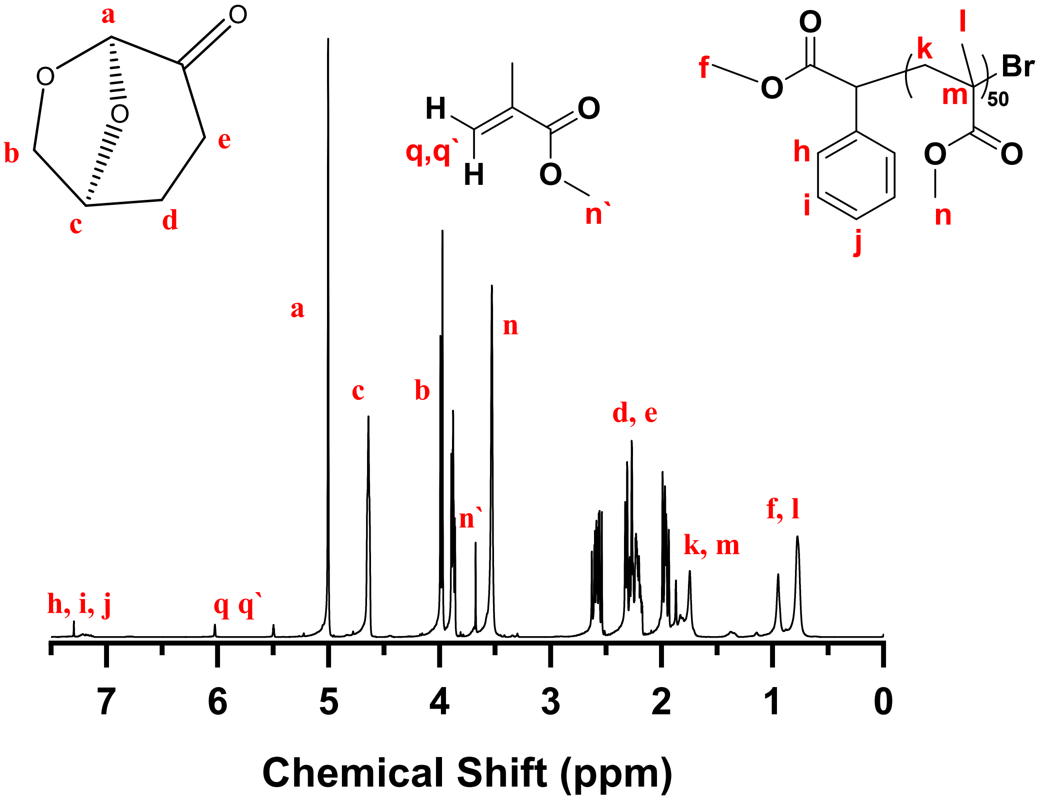


**Figure S 3.** Reaction scheme and $^1$H NMR for Cu(0) wire mediated RDRP of MMA using MBPA as initiator and cyrene as solvent under $N_2$. Conditions: [M]: [I]: [Cu(II)Br$_2$]: [Me$_6$Tren] = 50: 1: 0.05: 0.18, $V_{cyrene}$ = 50 % v/v with respect to monomer. Conversion was determined by comparing the integrals of monomeric vinyl protons (q, q`) to polymer signals (n).

**Table S1.** $^1$H NMR and SEC analysis for the Cu(0) wire mediated RDRP of MA and MMA using cyrene as solvent. Inert conditions were applied.

| **Entry**[a] | **Monomer /Initiator** | **Time (h)** | **Monomer Conv.** [b] **(%)** | $M_{n,\,theor.}$ **(g mol$^{-1}$)** | $M_{n,\,SEC}$[c] | $Đ$ |
|---|---|---|---|---|---|---|
| **1** | MA/EBiB | 18 | 90 | 4400 | 4800 | 1.08 |
| **2** | MA/dodecyl-BiB | 24 | 75 | 4000 | 5600 | 1.23 |
| **3** | MMA/MBPA | 18 | 97 | 6400 | 7200 | 1.11 |

[a] In all polymerizations, the volume ratio of monomer to solvent was maintained at 1: 1. [b] Conversion was calculated *via* $^1$NMR in $CDCl_3$. [c] Determined by $CHCl_3$ SEC analysis and expressed as molecular weight relative to pMMA narrow molecular weight standards.

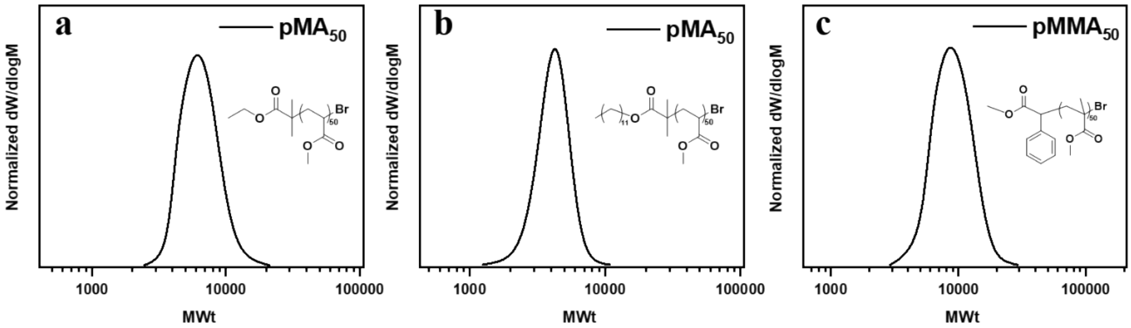


**Figure S 4.** $CHCl_3$-SEC derived molecular weight distributions showing the evolution of MWts for (a) $pMA_{50}$ using EBiB as initiator, (b) $pMA_{50}$ using dodecyl-BiB as initiator and (c) $pMMA_{50}$ using MBPA as initiator. Conditions: [M]: [I]: [$Cu(II)Br_2$]: [$Me_6Tren$] = 50: 1: 0.05: 0.18, $V_{cyrene}$ = 50 % v/v with respect to monomer. Reagents were deoxygenated.

**Table S2.** $^1$H NMR and SEC analysis for the Cu(0) wire mediated RDRP without deoxygenation of various hydrophobic monomers using cyrene as solvent.

| **Entry**$^a$ | **Time (h)** | **Monomer Conv.**$^b$ **(%)** | $M_{n, theor.}$ **(g mol$^{-1}$)** | $M_{n, SEC}$$^c$ | **Đ** |
|---|---|---|---|---|---|
| **p(MA)$_{50}$** | 3 | 90 | 4400 | 4800 | 1.08 |
| **p(MMA)$_{50}$** | 20 | 75 | 4000 | 5600 | 1.23 |
| **p(*t*BA)$_{50}$** | 20 | 97 | 6400 | 7200 | 1.11 |
| **p(St)$_{50}$** | 36 | 98 | 7300 | 7000 | 1.37 |
| **p(BzA)$_{50}$** | 24 | 88 | 7300 | 6000 | 1.18 |
| **p(TFEA)** | 45 | 94 | 7400 | 4500 | 1.11 |

[a] In all polymerizations, the volume ratio of monomer to solvent was maintained 1: 1. [b] Conversion was calculated *via* $^1$NMR in $CDCl_3$. [c] Determined by $CHCl_3$ SEC analysis and expressed as molecular weight relative to pMMA narrow molecular weight standards.

**Cu(0) wire mediated RDRP of MA in cyrene without any type of deoxygenation. Targeted $DP_n = 50$**

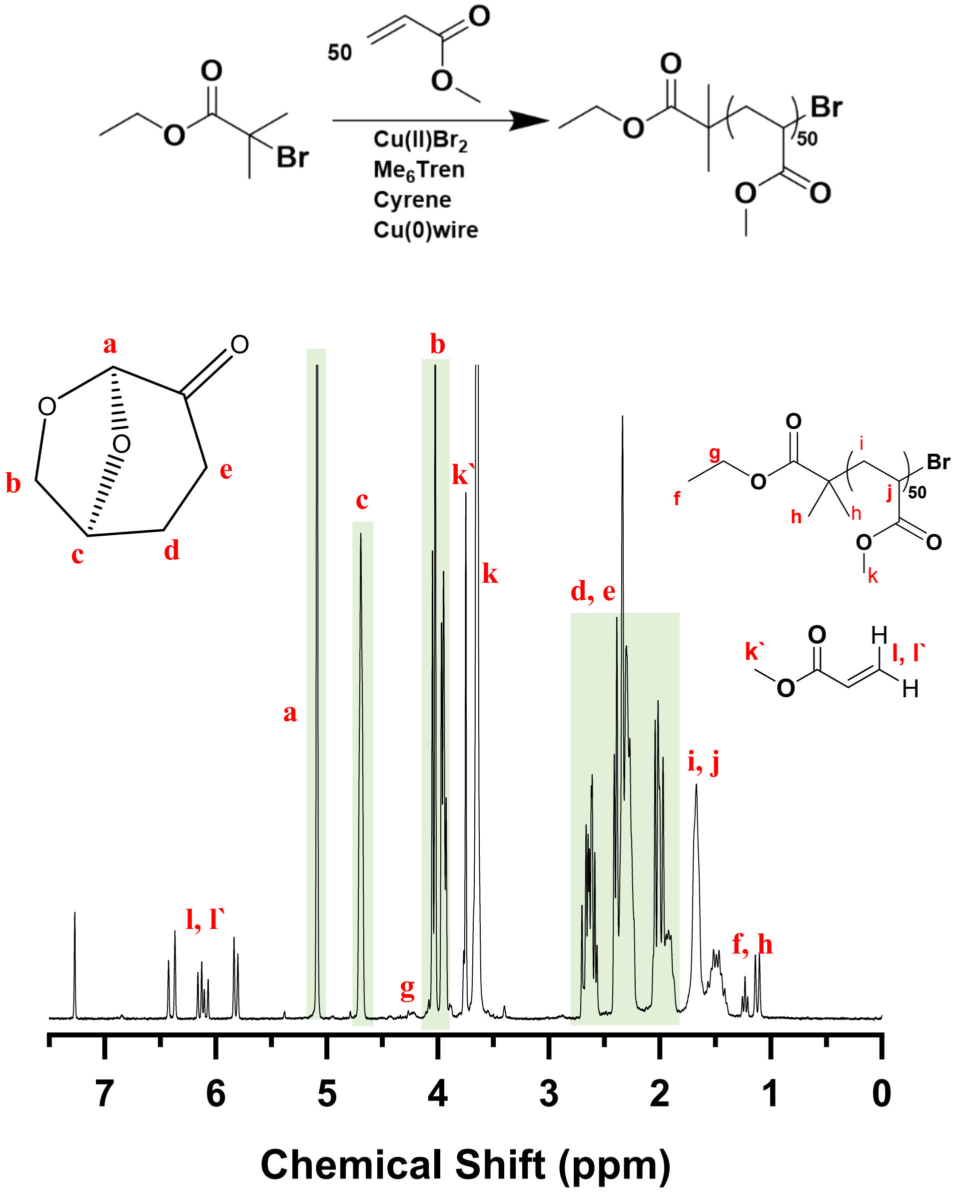


**Figure S 5.** Reaction scheme and $^1$H NMR for Cu(0) wire mediated RDRP of MA using EBiB as initiator and cyrene as solvent. Conditions: [M]: [I]: [Cu(II)Br$_2$]: [Me$_6$Tren] = 50: 1: 0.05: 0.18, $V_{cyrene}$ = 50 % v/v with respect to monomer, no deoxygenation of reagents. Conversion was determined by comparing the integrals of monomeric vinyl protons (l, l`) to polymer signals (k).

**Cu(0) wire mediated RDRP of MMA in cyrene without any type of deoxygenation. Targeted DP$_n$ = 50**

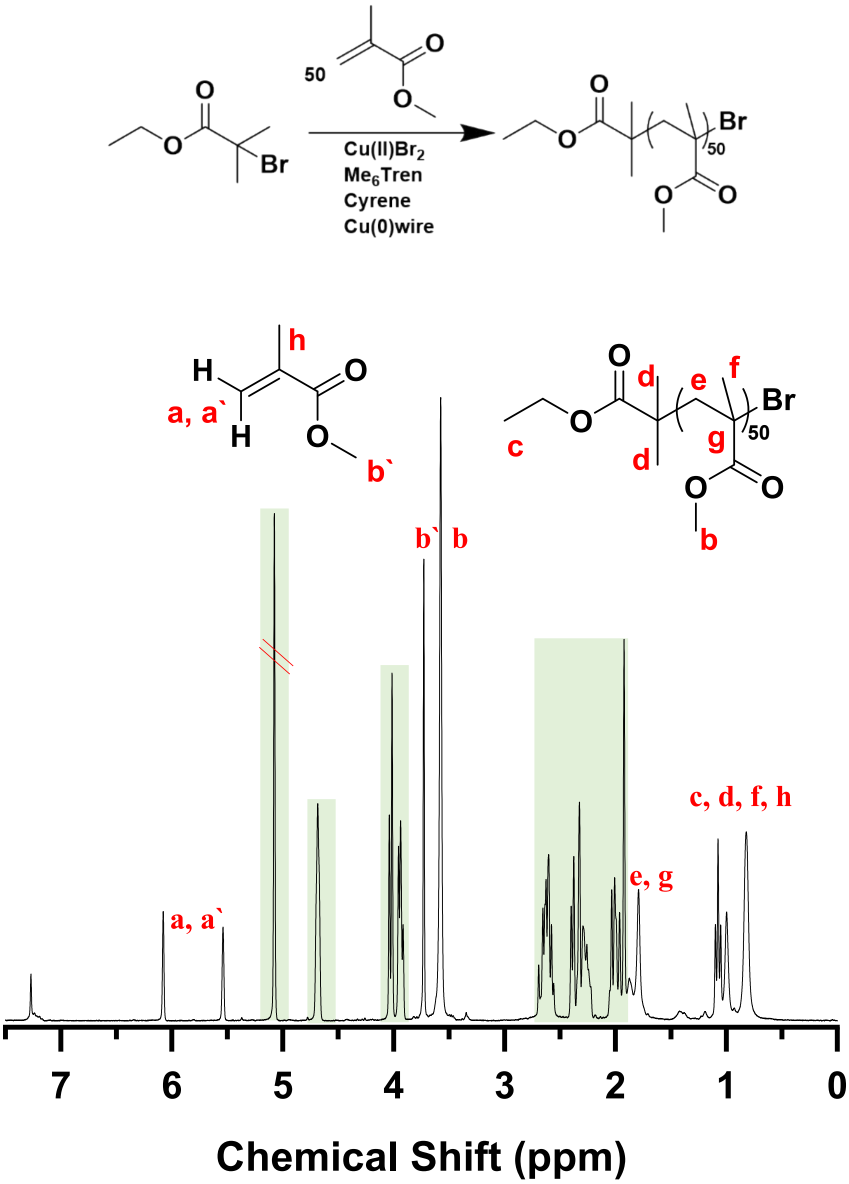


**Figure S 6.** Reaction scheme and $^1$H NMR for Cu(0) wire mediated RDRP of MMA using EBiB as initiator and cyrene as solvent. Conditions: [M]: [I]: [Cu(II)Br$_2$]: [Me$_6$Tren] = 50: 1: 0.05: 0.18, $V_{cyrene}$ = 50 % v/v with respect to monomer, no deoxygenation of reagents. Conversion was determined by comparing the integrals of monomeric vinyl protons (a, a`) to polymer signals (b).

### Cu(0) wire mediated RDRP of *tert*-BA in cyrene without any type of deoxygenation. Targeted DP$_n$ = 50

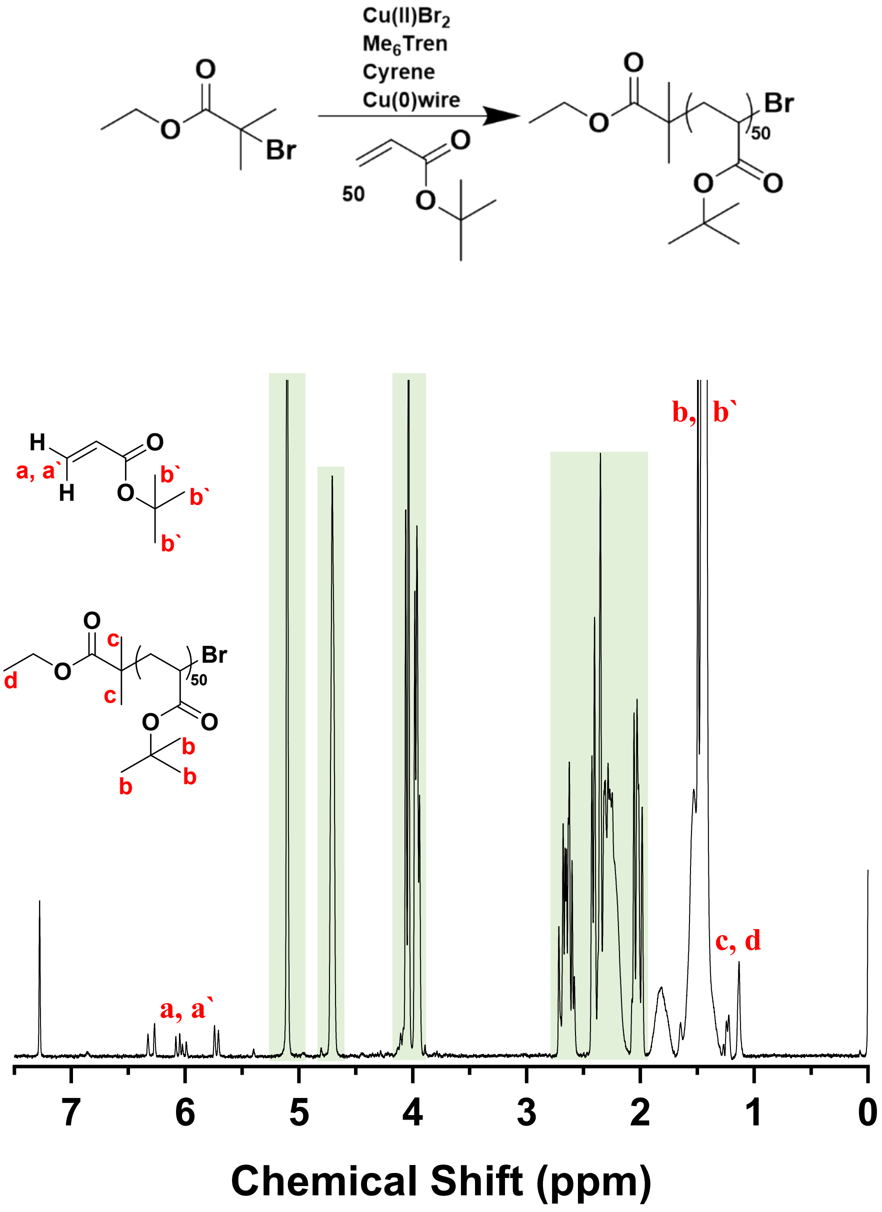


**Figure S 7.** Reaction scheme and $^1$H NMR for Cu(0) wire mediated RDRP of *t*BA using EBiB as initiator and cyrene as solvent. Conditions: [M]: [I]: [Cu(II)Br$_2$]: [Me$_6$Tren] = 50: 1: 0.05: 0.18, V$_{\mathrm{cyrene}}$ = 50 % v/v with respect to monomer, no deoxygenation of reagents. Conversion was determined by comparing the integrals of monomeric vinyl protons (a, a`) to polymer signals (b).

### Cu(0) wire mediated RDRP of styrene in cyrene without any type of deoxygenation. Targeted DP$_n$ = 50

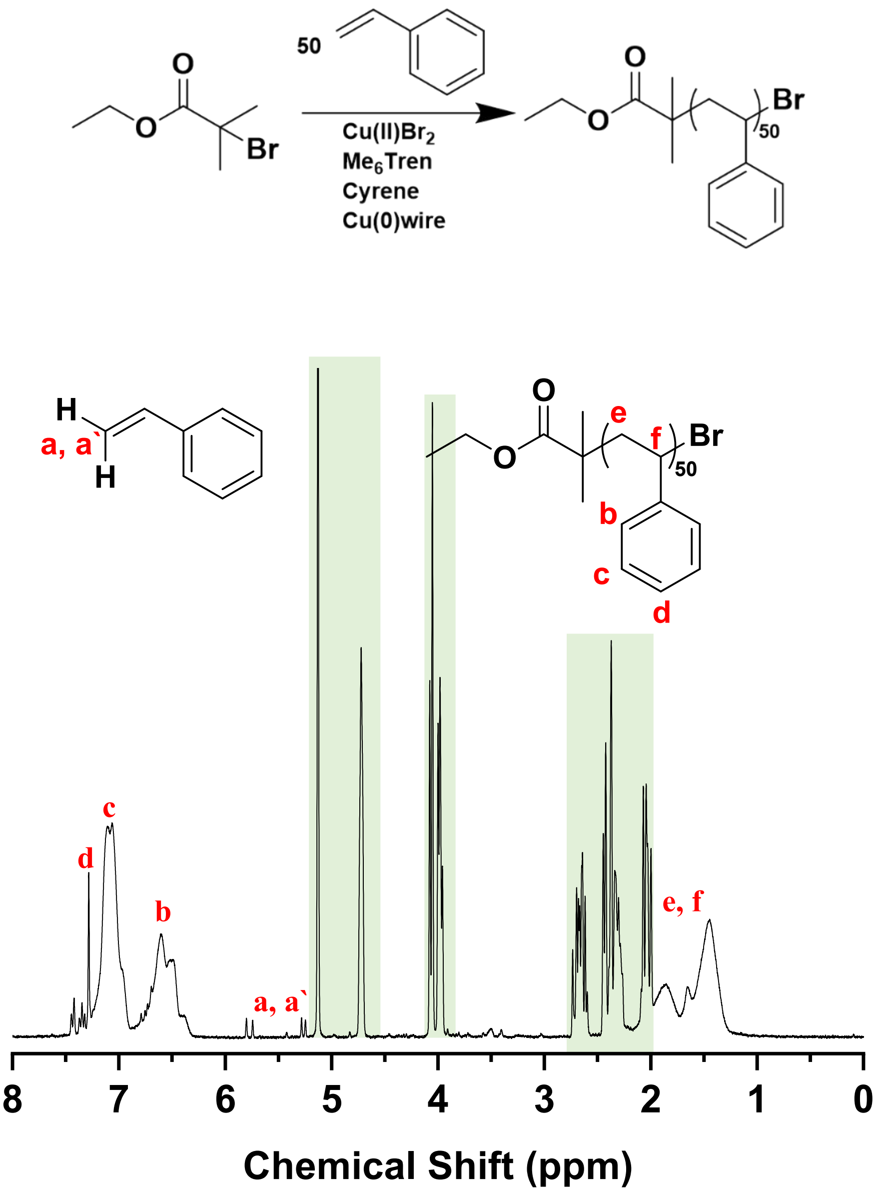
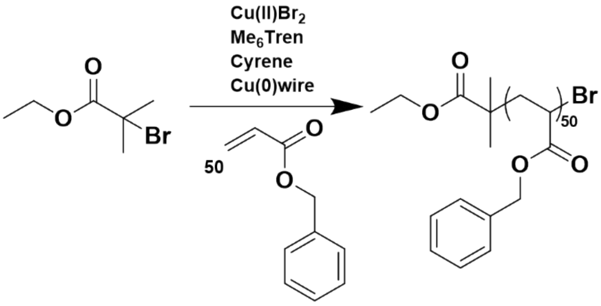


**Figure S 8.** Reaction scheme and $^1$H NMR for Cu(0) wire mediated RDRP of styrene using EBiB as initiator and cyrene as solvent. Conditions: [M]: [I]: [Cu(II)Br$_2$]: [Me$_6$Tren] = 50: 1: 0.05: 0.18, $V_{cyrene}$ = 50 % v/v with respect to monomer, no deoxygenation of reagents. Conversion was determined by comparing the integrals of monomeric vinyl protons (a, a`) to polymer signals (b).

**Cu(0) wire mediated RDRP of BzA in cyrene without any type of deoxygenation. Targeted DP$_n$ = 50**



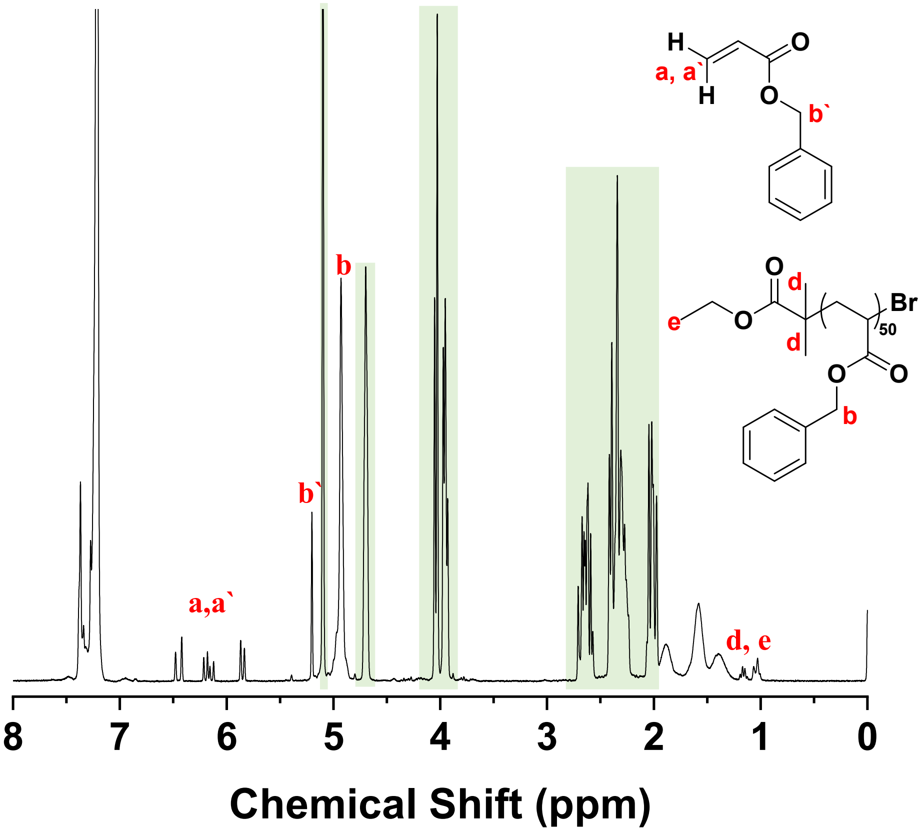


**Figure S 9.** Reaction scheme and $^1$H NMR for Cu(0) wire mediated RDRP of BzA using EBiB as initiator and cyrene as solvent. Conditions: [M]: [I]: [Cu(II)Br$_2$]: [Me$_6$Tren] = 50: 1: 0.05: 0.18, V$_{cyrene}$ = 50 % v/v with respect to monomer, no deoxygenation of reagents. Conversion was determined by comparing the integrals of monomeric vinyl protons (a, a`) to polymer signals (b).

### Cu(0) wire mediated RDRP of TFEA in cyrene without any type of deoxygenation. Targeted DP$_n$ = 50

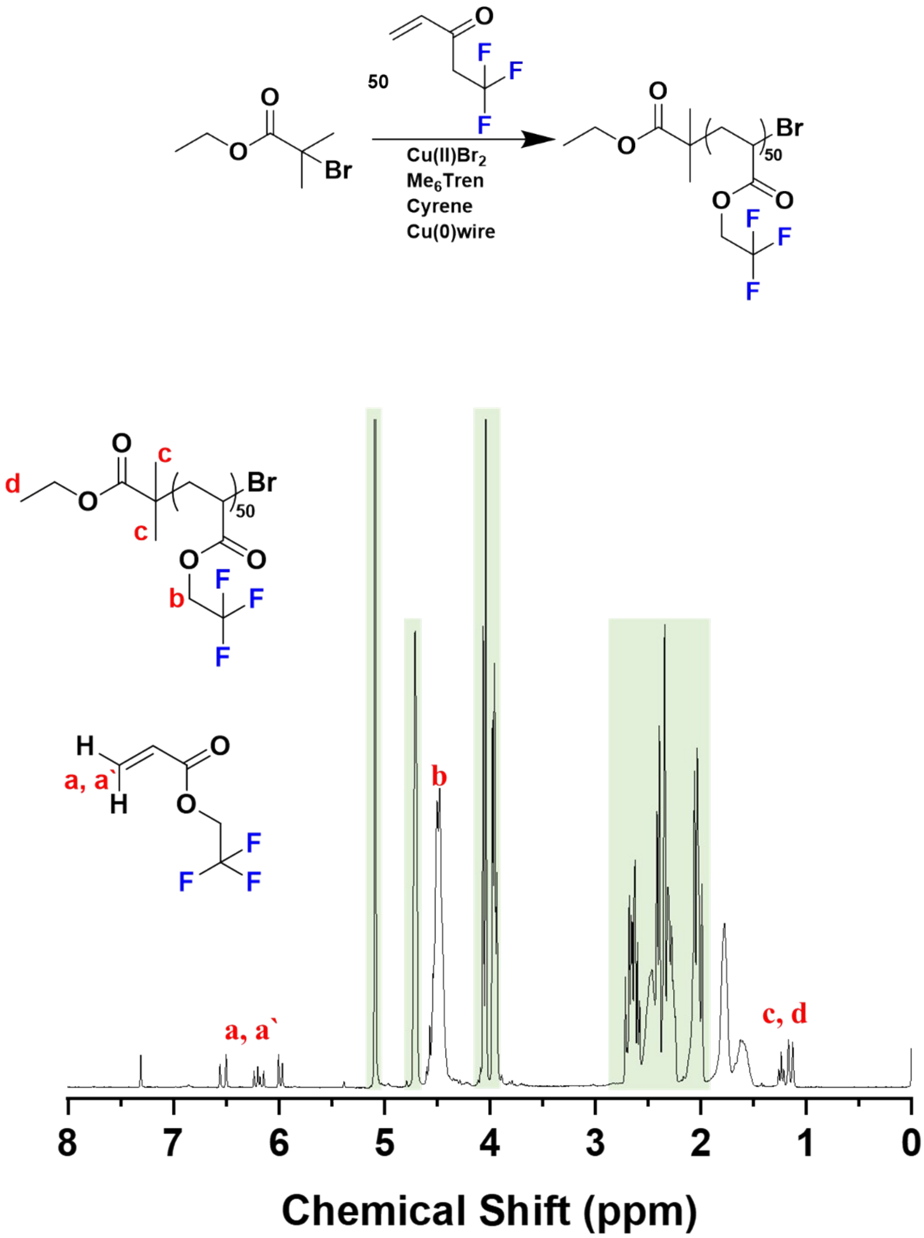


**Figure S 10.** Reaction scheme and $^1$H NMR for Cu(0) wire mediated RDRP of TFEA using EBiB as initiator and cyrene as solvent. Conditions: [M]: [I]: [Cu(II)Br$_2$]: [Me$_6$Tren] = 50: 1: 0.05: 0.18, V$_{cyrene}$ = 50 % v/v with respect to monomer, no deoxygenation of reagents. Conversion was determined by comparing the integrals of monomeric vinyl protons (a, a`) to polymer signals (b).

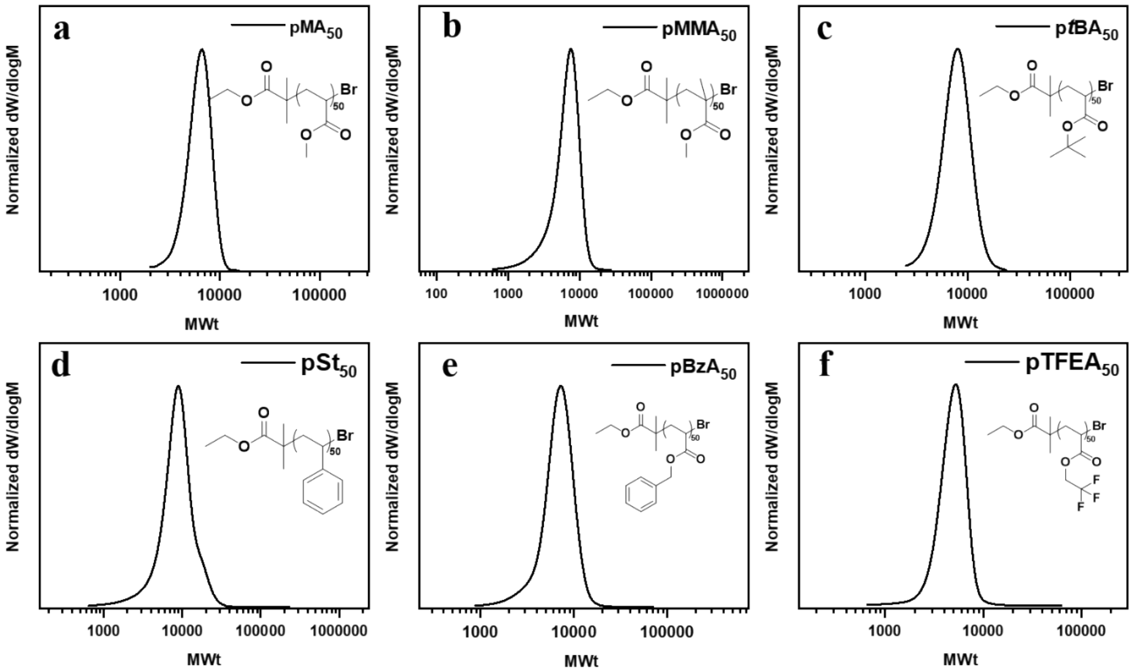


**Figure S 11.** $CHCl_3$-SEC derived molecular weight distributions showing the evolution of MWts for (a) $pMA_{50}$, (b) $pMMA_{50}$, (c) p*t*BA, (d) $pSt_{50}$, (e) pBzA and (f) pTFEA synthesized by Cu(0) wire mediated RDRP in cyrene. Conditions: [M]: [EBiB]: $[Cu(II)Br_2]$: $[Me_6Tren]$ = 50: 1: 0.05: 0.18, $V_{cyrene}$ = 50 % v/v with respect to monomer. No deoxygenation of reagents.

**Table S3.** $^1$H NMR and SEC analysis for the *in-situ* chain extensions through Cu(0) wire mediated RDRP without any type of deoxygenation.

| **Polymer**[a] | **Time (h)** | **Mon. Conv.**[b] **(%)** | **$M_{n,\ theor.}$ (g mol$^{-1}$)** | **$M_{n,\ SEC}$**[c] | **$Đ$** |
|---|---|---|---|---|---|
| **$pMA_{10}$** | 3 | 95 | 1000 | 1200 | 1.11 |
| **$pMA_{10}$-*b*-$pEA_{10}$** | 15 | 95 | 2000 | 2300 | 1.12 |
| **$pMA_{10}$-*b*-$pEA_{10}$-*b*-$pMA_{10}$** | overnight | 75 | 2600 | 3500 | 1.21 |

[a] In all polymerizations, the volume ratio of monomer to solvent was maintained 1: 1. [b] Conversion was calculated *via* $^1$NMR in $CDCl_3$. [c] Determined by $CHCl_3$ SEC analysis and expressed as molecular weight relative to pMMA narrow molecular weight standards.

**Cu(0) wire mediated RDRP of MA in cyrene. Targeted DP*ₙ* = 5**

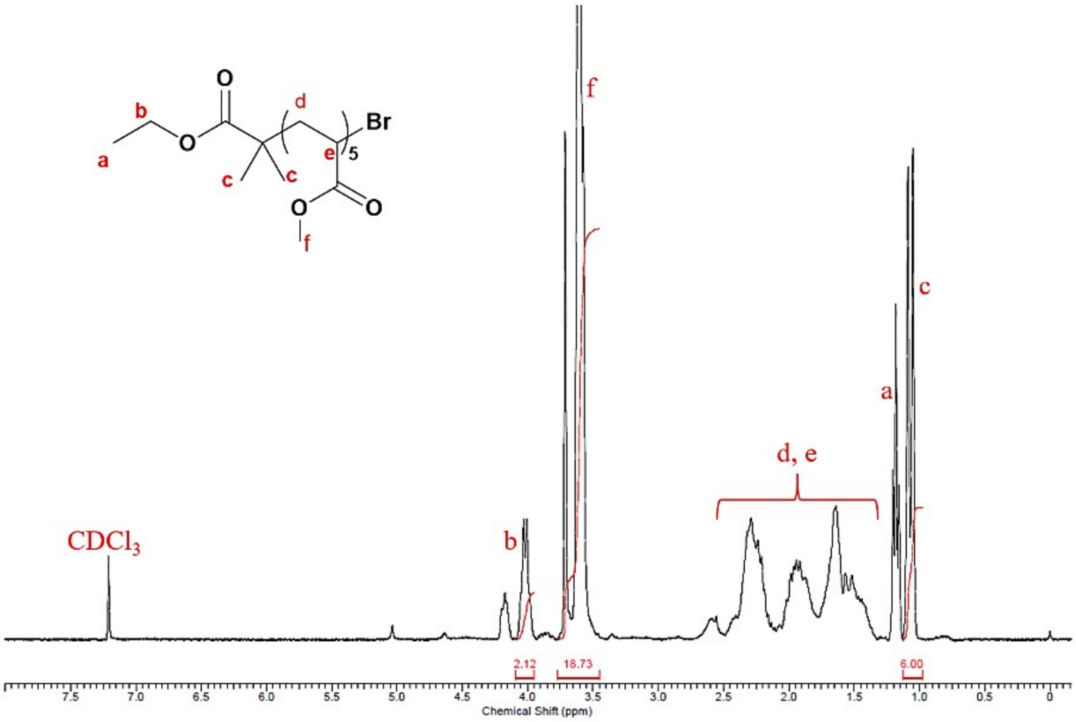


**Figure S 12.** $^1$H NMR for Cu(0) wire-mediated RDRP of MA using EBiB as initiator and cyrene as solvent under $N_2$. Conditions: [M]: [I]: [Cu(II)$Br_2$]: [$Me_6$Tren] = 5: 1: 0.05: 0.18, $V_{cyrene}$ = 50 % v/v with respect to monomer. Spectrum was collected after the purification of the polymer for the determination of $I_{eff}$ and the $M_{n,\ NMR}$.

### Cu(0) wire mediated RDRP of MA in cyrene. Targeted DP$_n$ = 10

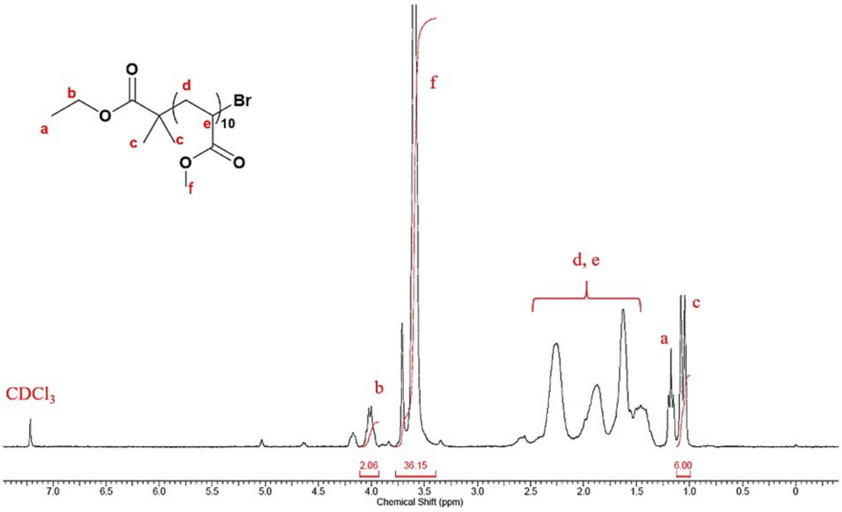


**Figure S 13.** $^1$H NMR for Cu(0) wire-mediated RDRP of MA using EBiB as initiator and cyrene as solvent under $N_2$. Conditions: [M]: [I]: [Cu(II)Br$_2$]: [Me$_6$Tren] = 10: 1: 0.05: 0.18, $V_{cyrene}$ = 50 % v/v with respect to monomer. Spectrum was collected after the purification of the polymer for the determination of $I_{eff}$ and the $M_{n,\ NMR}$.

### Cu(0) wire mediated RDRP of MA in cyrene. Targeted DP$_n$ = 20

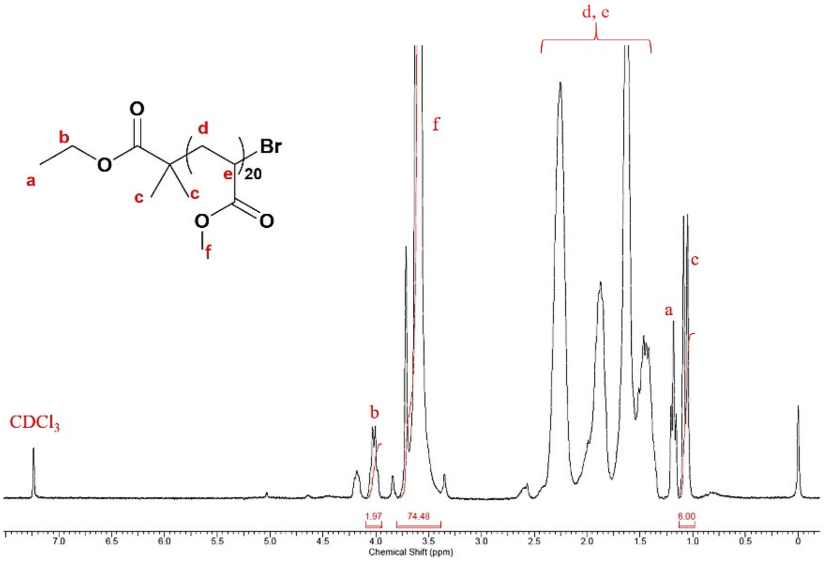


**Figure S 14.** $^1$H NMR for Cu(0) wire-mediated RDRP of MA using EBiB as initiator and cyrene as solvent under $N_2$. Conditions: [M]: [I]: [Cu(II)Br$_2$]: [Me$_6$Tren] = 20: 1: 0.05: 0.18, $V_{cyrene}$ = 50 % v/v with respect to monomer. Spectrum was collected after the purification of the polymer for the determination of $I_{eff}$ and the $M_{n,\ NMR}$.

### Cu(0) wire mediated RDRP of MA in cyrene. Targeted DP$_n$ = 50

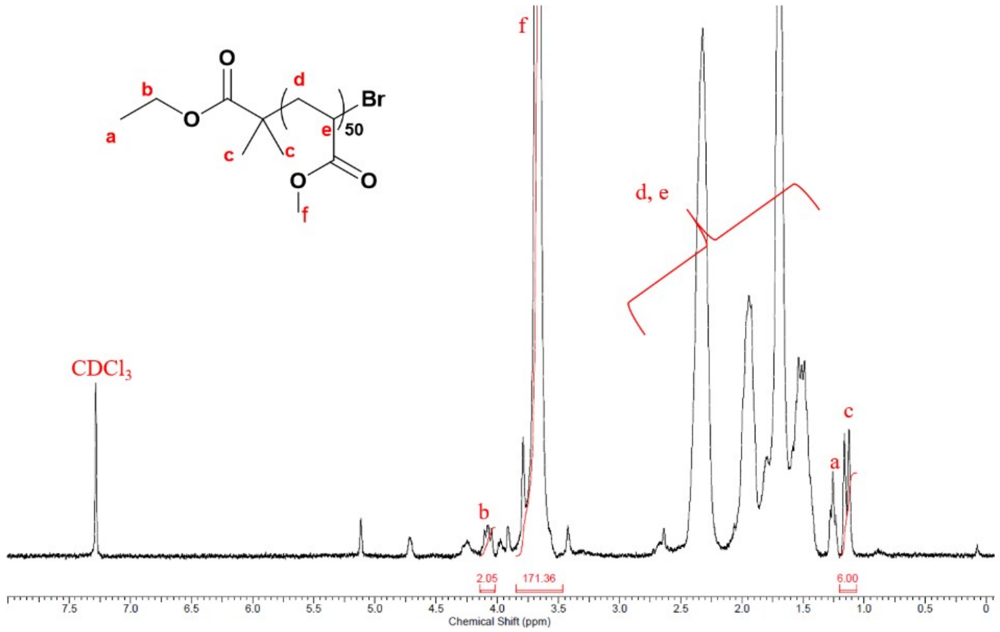


**Figure S 15.** $^1$H NMR for Cu(0) wire-mediated RDRP of MA using EBiB as initiator and cyrene as solvent under $N_2$. Conditions: [M]: [I]: [Cu(II)Br$_2$]: [Me$_6$Tren] = 50: 1: 0.05: 0.18, $V_{cyrene}$ = 50 % v/v with respect to monomer. Spectrum was collected after the purification of the polymer for the determination of I$_{eff}$ and the $M_{n, NMR}$.

### Cu(0) wire mediated RDRP of MA in cyrene. Targeted DP$_n$ = 100

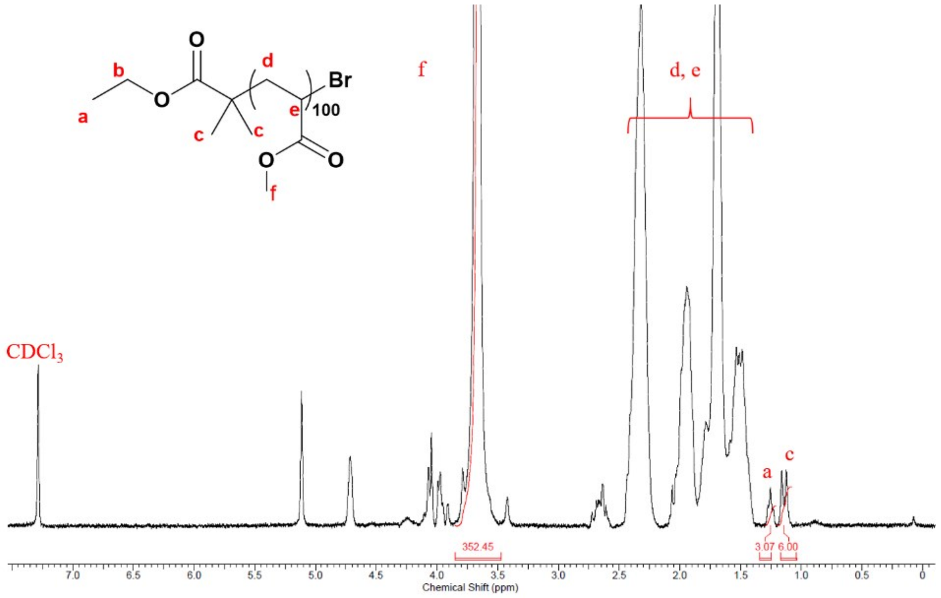


**Figure S 16.** $^1$H NMR for Cu(0) wire-mediated RDRP of MA using EBiB as initiator and cyrene as solvent under $N_2$. Conditions: [M]: [I]: [Cu(II)Br$_2$]: [Me$_6$Tren] = 100: 1: 0.05: 0.18,

$V_{cyrene}$ = 50 % v/v with respect to monomer. Spectrum was collected after the purification of the polymer for the determination of $I_{eff}$ and the $M_{n, NMR}$.

### Cu(0) wire mediated RDRP of MA in cyrene. Targeted DP$_n$ = 200

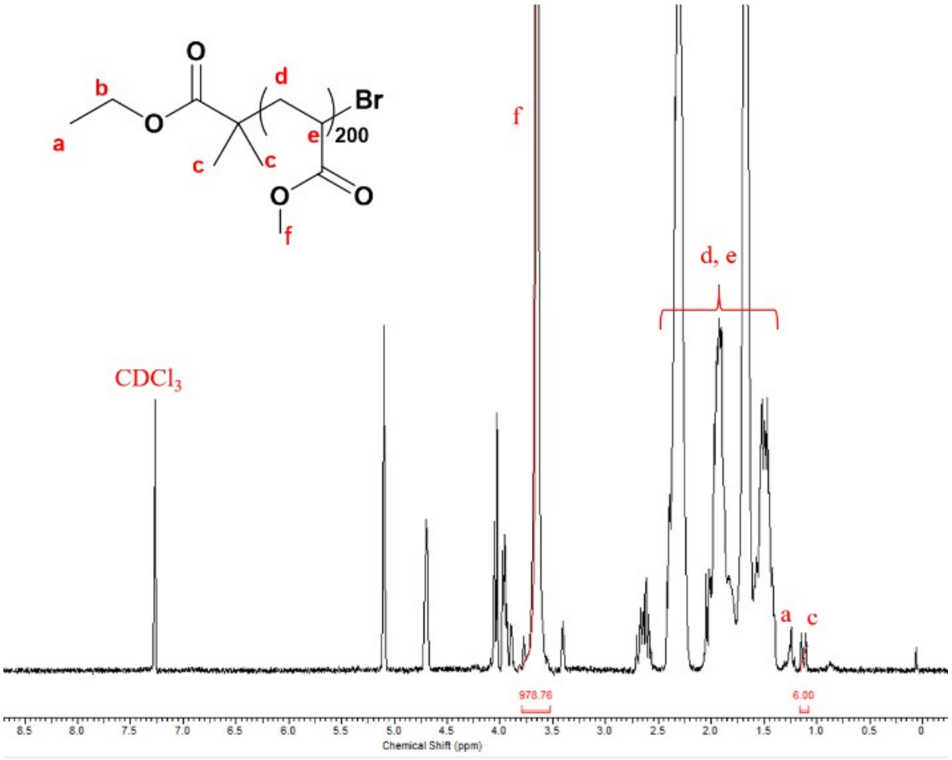


**Figure S 17.** $^1$H NMR for Cu(0) wire-mediated RDRP of MA using EBiB as initiator and cyrene as solvent under $N_2$. Conditions: [M]: [I]: [Cu(II)Br$_2$]: [Me$_6$Tren] = 200: 1: 0.05: 0.18, $V_{cyrene}$ = 50 % v/v with respect to monomer.

**Cu(0) wire mediated RDRP of MA in cyrene. Targeted DP$_n$ = 800**

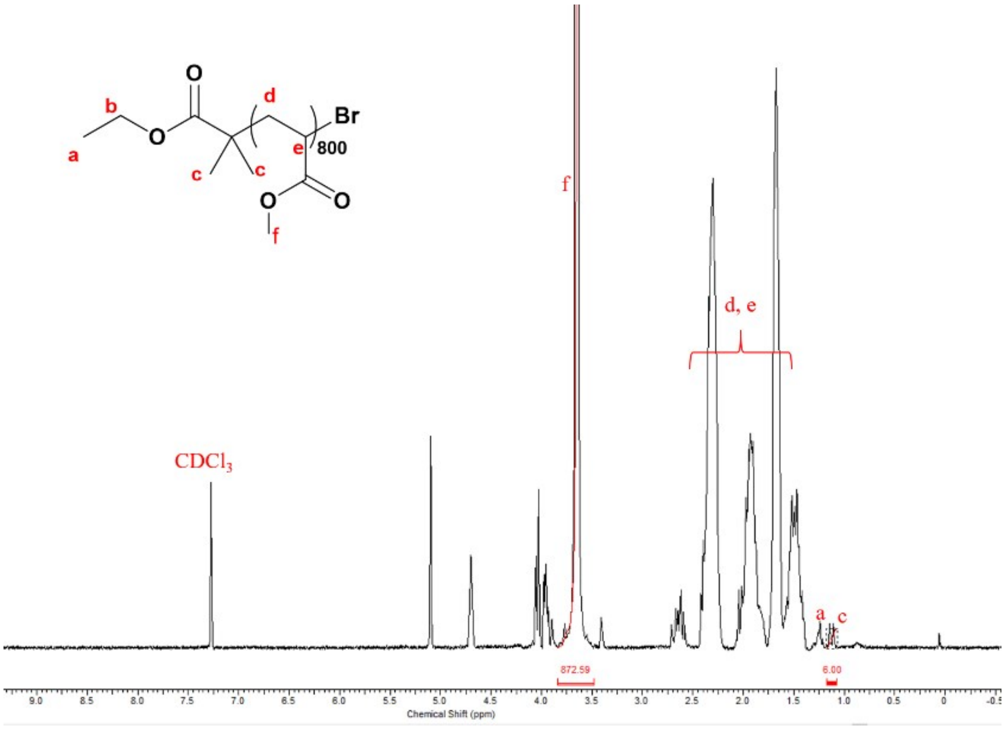


**Figure S 18.** $^1$H NMR for Cu(0) wire-mediated RDRP of MA using EBiB as initiator and cyrene as solvent under $N_2$. Conditions: [M]: [I]: [Cu(II)$Br_2$]: [$Me_6$Tren] = 800: 1: 0.05: 0.18, $V_{cyrene}$ = 50 % v/v with respect to monomer.

**Table S4.** $^1$H NMR analysis of the purified polymers obtained from Cu(0)wire-mediated RDRP of MA without deoxygenation.

| **Targeted Polymer** | ***Conversion (%)*** | **$M_{\text{n, th.}}$ (g mol$^{-1}$)** | **$M_{\text{n, NMR.}}$ (g mol$^{-1}$)** | **$I_{eff}$ (%)** |
|---|---|---|---|---|
| $pMA_5$ | 99 | 630 | 710 | 89 |
| $pMA_{10}$ | >99 | 1100 | 1200 | 92 |
| $pMA_{20}$ | >99 | 1900 | 2300 | 83 |
| $pMA_{50}$ | 90 | 4100 | 5100 | 80 |
| $pMA_{100}$ | 86 | 7600 | 10300 | 74 |
| $pMA_{200}{}^a$ | 88 | 15000 | - | - |
| $pMA_{800}{}^a$ | 43 | 29800 | - | - |

[a] The initiator efficiency for the polymerizations of MA with targeted DP$_n$=200 and 800 are not reported due to the low intensity of the peaks that correspond to initiator.

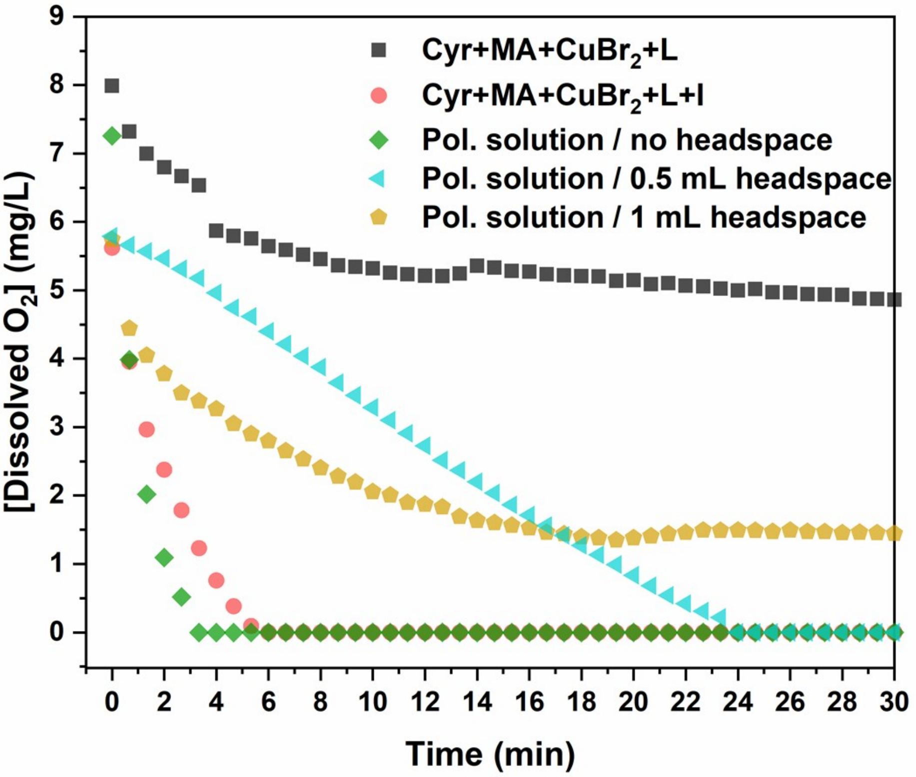


**Figure S 19.** Graphical illustration of the dissolved oxygen consumption during Cu(0) wire mediated RDRP of MA, effect of headspace and role of the polymerization components.

## References

1. M. Ciampolini and N. Nardi, *Inorg. Chem.*, 1966, **5**, 41-44.
2. K. L. Wilson, A. R. Kennedy, J. Murray, B. Greatrex, C. Jamieson and A. J. B. Watson, *Beilstein J. Org. Chem.*, 2016, **12**, 2005-2011.