Metal free thiol-maleimide 'Click' reaction as a mild functionalisation strategy for degradable polymers

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Supplementary Information

Experimental

General Considerations

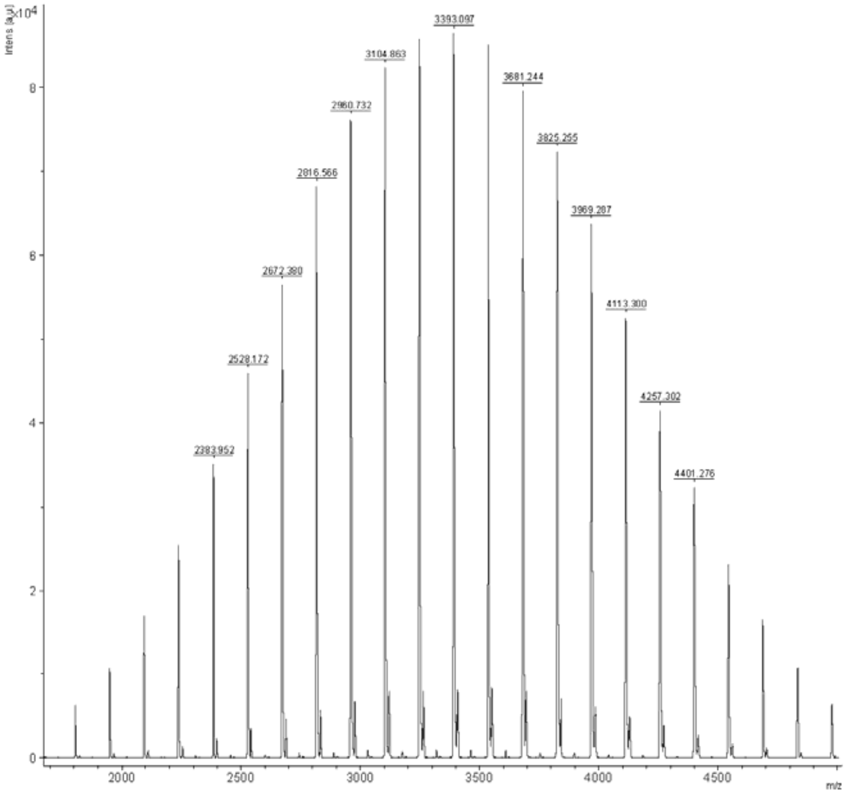
L-Lactide (Aldrich) was purified by recrystallisation from dry dichloromethane and sublimation (2x). Dichloromethane was dried over CaH, distilled and degassed prior to use, THF was dried over K, distilled and degassed prior to use. 4-(2-hydroxyethyl)-10-oxa-4-azatricyclo[5.2.1.0^{2,6}]dec-8-ene-3,5-dione, **1**,[S1] 1,3,5-tri(thiomethyl)benzene[S2] 1-(3,5-bis(trifluoromethyl)phenyl)-3-cyclohexyl-thiourea, **2**, [S3] were prepared as previously reported in the literature. **1** was dried over activated 4Å molecular sieves in a DCM solution, **2** was dissolved in dry THF and stirred at 60 °C for 18 h before being cooled, filtered and dried under vacuum and (-)-Sparteine was dried over CaH and distilled under vacuum. The iodoacetate resin (SulfoLink® Coupling Gel) was purchased from Pierce and used as received. Solvents for conjugation reactions were saturated with $Na_2S_2O_5$, in the presence of 0 – 2 vol% H_2O and were degassed by bubbling with N_2 for 30 minutes. With the exception of 1,4-bis(thiomethyl)benzene (TCI Europe), all other chemicals were obtained from Aldrich and used without further purification.

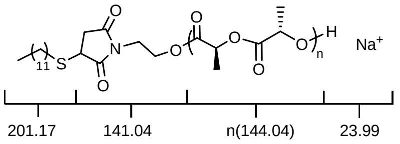
Gel-permeation chromatography (GPC) was used to determine the molecular weights and polydispersities of the synthesized polymers. The system comprised a Polymer Laboratories Midas autosampler and LC1120 HPLC pump equipped with a guard column (Polymer Laboratories PLGel 5 μM, 50×7.5 mm), two mixed D columns (Polymer Laboratories PLGel 5 μM, 300×7.5 mm) and a Polymer Laboratories ERC-7515A differential refractive index (DRI) detector. The mobile phase was chloroform/triethyl amine (95/5) eluent at a flow rate of 1.0 mL.min^{-1} and samples were calibrated against linear poly(styrene) standards (540 to 2.9×10^4 g.mol^{-1}) using Cirrus v3.0; elution time was standardised against that of toluene. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX-300, DPX-400, AC400 or DRX-500 spectrometer at 293 K unless stated. Chemical shifts are reported as δ in parts per million (ppm) and referenced to the chemical shift of the residual solvent resonances ($CDCl_3$ ^{1}H: δ = 7.26 ppm; ^{13}C δ = 77.16 ppm). Mass spectra were acquired by MALDI-ToF (matrix-assisted laser desorption and ionization time-of-flight) mass spectrometry 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 of trans-2-[3-(4-*tert*butylphenyl)-2-methyl-2-propylidene]-malonitrile (DCTB) as matrix (0.3 μL of a 10 gL^{-1} acetone solution), sodium trifluoroacetate as cationization agent (0.3 μL of a 10 gL^{-1} acetone solution) and analyte (0.3 μL of a 1 gL^{-1} DCM solution) were applied sequentially to the target followed by solvent evaporation to prepare a thin matrix/analyte film. The samples were measured in reflectron ion mode and calibrated by comparison to 2×10^3 and 5×10^3 g.mol^{-1} poly(ethylene glycol) standards. Elemental Analyses were performed by Warwick Analytical Services

Synthesis of Maleimide-functional PLA-OH (MI-PLA). 4-(2-hydroxyethyl)-10-oxa-4-azatricyclo[5.2.1.0^{2,6}]dec-8-ene-3,5-dione. **1** (0.36 g, 1.7 mmol), L-LA (5.00 g, 34.7 mmol) and 1-(3,5-bis(trifluoromethyl)phenyl)-3-cyclohexyl-thiourea (0.64 g, 1.7 mmol) were weighed into a vial. DCM (50 mL) was added and the mixture stirred until the solution became clear. The polymerisation reaction was initiated by the addition of (-)-Sparteine (0.19 mL, 0.9 mmol) and stirred for the allotted time. The reaction was quenched by precipitation of the solution into Petroleum Ether 40/60 (500 mL). Residual thiourea catalyst was removed by filtration through a silica plug, initially eluting with DCM/MeOH (100:1) until the catalyst had eluted and then with DCM/MeOH (100:5) until PLA had been completely eluted from the plug. The solvent was reduced under vacuum to *ca.* 10 mL and polymer precipitated into Petroleum Ether 40/60 (250 mL). The polymer was isolated by filtration and dried under vacuum at 100 °C for 12 h, concurrently removing the furan protecting group.

General procedure for 'Click' conjugation reactions. MI-PLA (0.1 g, 0.03 mmol) was placed in a vial and sparged with N_2. Solvent (1 mL) was added with stirring to dissolve the PLA. NEt_3 (2.6 μL, 0.03 mmol) and thiol (1.05 eq) were added to the solution. The solution was stirred for the allotted time before the functionalised polymer was recovered by precipitation into Petroleum Ether 40/60 (20 mL). The polymer was reprecipitated from DCM into Petroleum Ether 40/60 twice before being isolated and dried under vacuum at 60 °C for 12 h.

Figure S1 - MALDI-ToF Spectrum of dodecanethiol functionalised MI-PLA

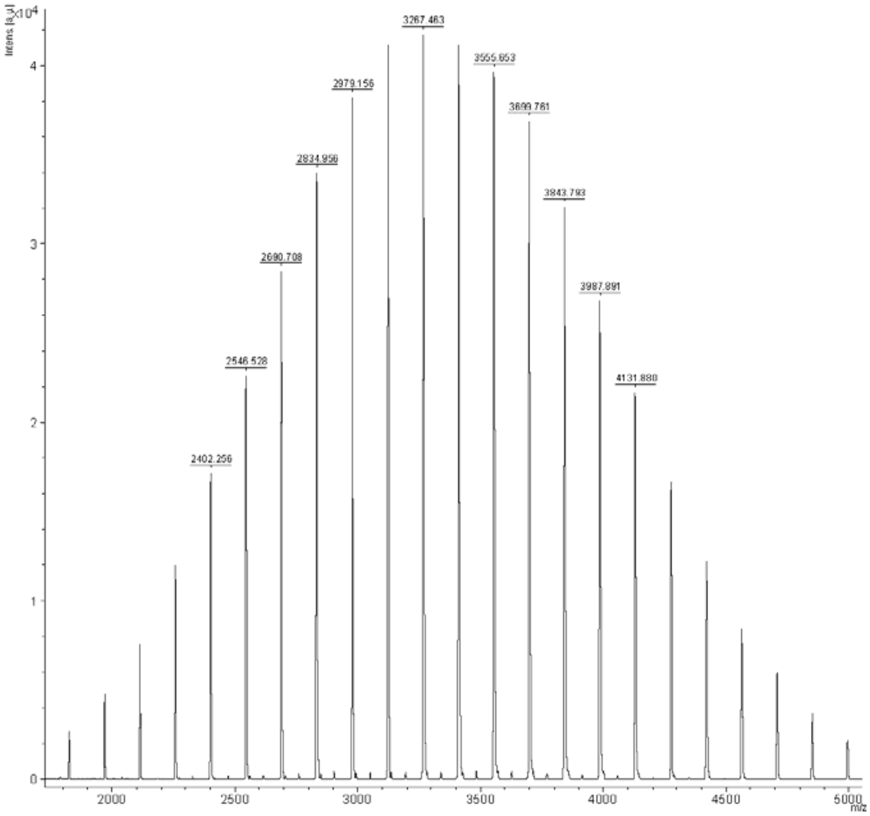


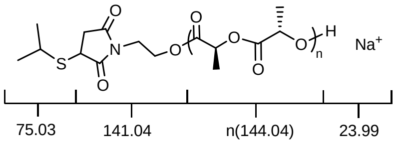


= 366.20 + (n.144.04)

n	m/z
14	2382.76
15	2526.8
16	2670.84
17	2814.88
18	2958.92
19	3102.96
20	3247
21	3391.04
22	3535.08
23	3679.12
24	3823.16
25	3967.2
26	4111.24
27	4255.28
28	4399.32

Figure S2 - MALDI-ToF Spectrum of 2-propanethiol functionalised MI-PLA

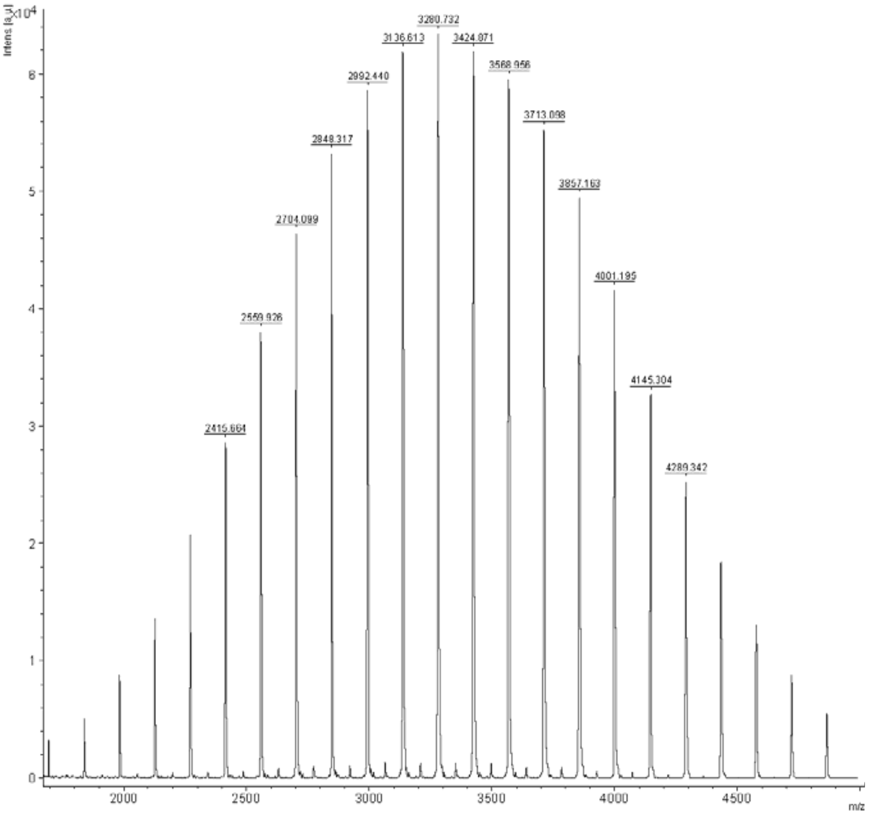


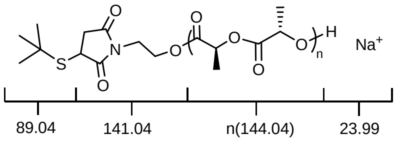


= 240.06 + (n.144.04)

n	m/z
14	2256.62
15	2400.66
16	2544.7
17	2688.74
18	2832.78
19	2976.82
20	3120.86
21	3264.9
22	3408.94
23	3552.98
24	3697.02
25	3841.06
26	3985.1
27	4129.14
28	4273.18

Figure S3 - MALDI-ToF Spectrum of 2-methyl-2-propanethiol functionalised MI-PLA

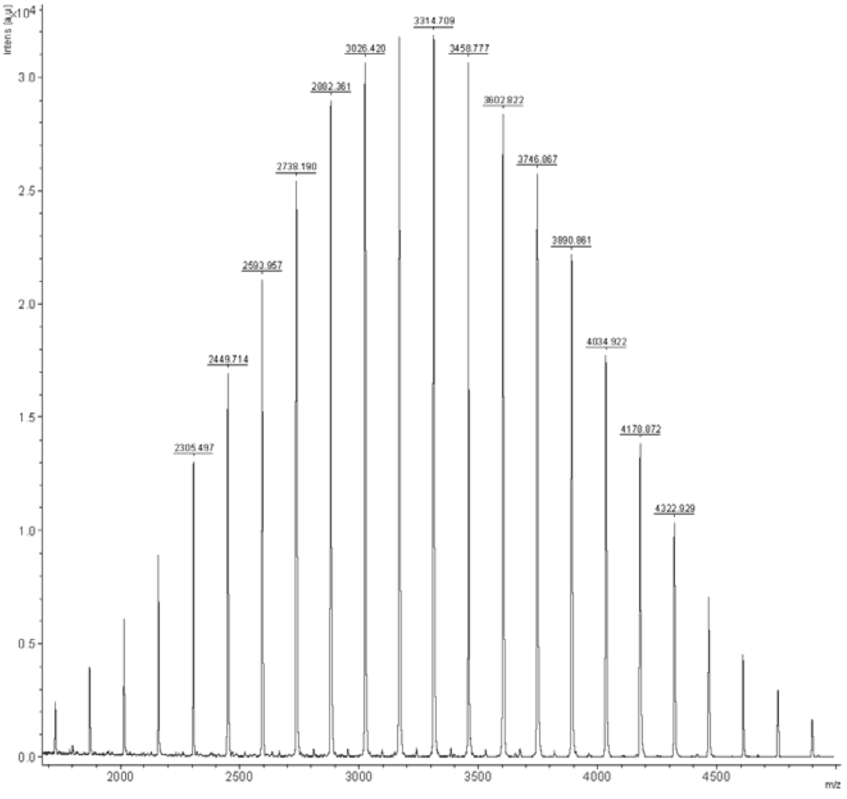


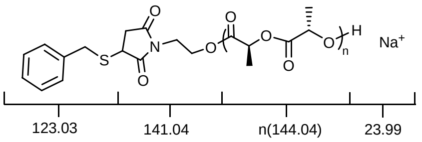


= 254.07 + (n.144.04)

n	m/z
14	2270.63
15	2414.67
16	2558.71
17	2702.75
18	2846.79
19	2990.83
20	3134.87
21	3278.91
22	3422.95
23	3566.99
24	3711.03
25	3855.07
26	3999.11
27	4143.15
28	4287.19

Figure S4 - MALDI-ToF Spectrum of benzylmercaptan functionalised MI-PLA

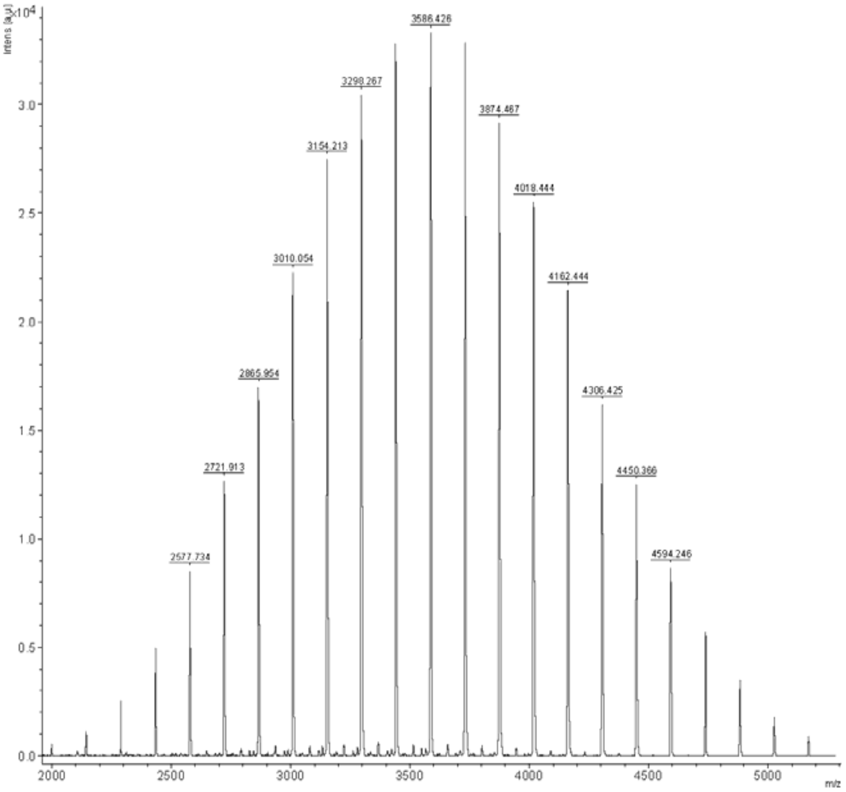


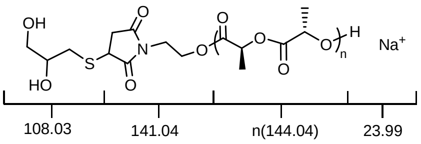


= 288.06 + (n.144.04)

n	m/z
14	2304.62
15	2448.66
16	2592.7
17	2736.74
18	2880.78
19	3024.82
20	3168.86
21	3312.9
22	3456.94
23	3600.98
24	3745.02
25	3889.06
26	4033.1
27	4177.14
28	4321.18

Figure S5 - MALDI-ToF Spectrum of thioglycerol functionalised MI-PLA

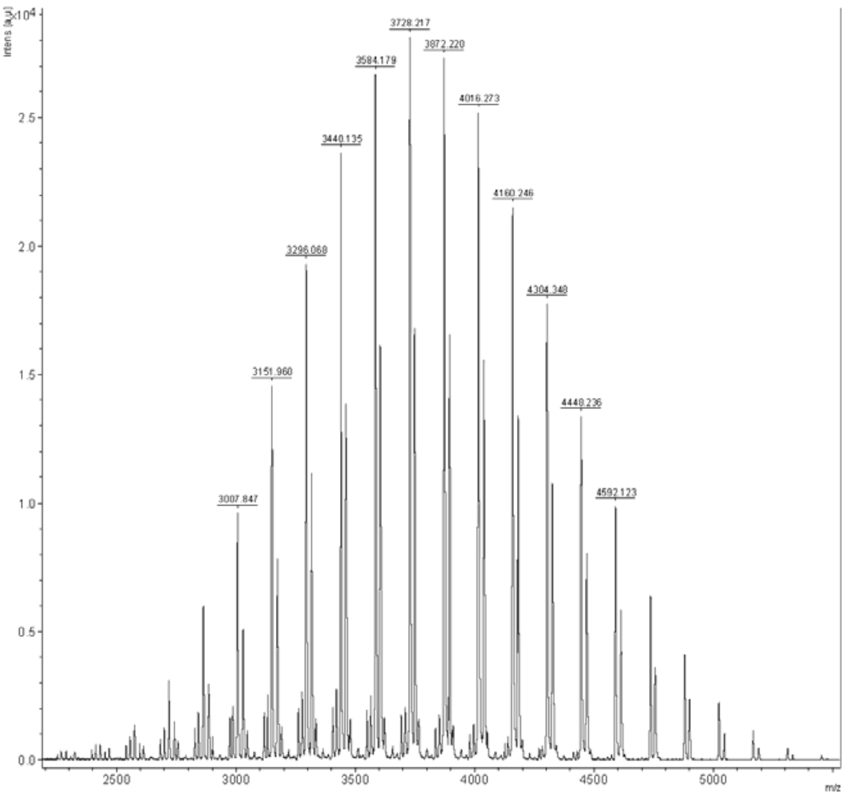


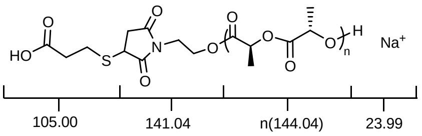


= 273.06 + (n.144.04)

n	m/z
14	2289.62
15	2433.66
16	2577.7
17	2721.74
18	2865.78
19	3009.82
20	3153.86
21	3297.9
22	3441.94
23	3585.98
24	3730.02
25	3874.06
26	4018.1
27	4162.14
28	4306.18

Figure S6 - MALDI-ToF Spectrum of 3-mercaptopropionic acid functionalised MI-PLA

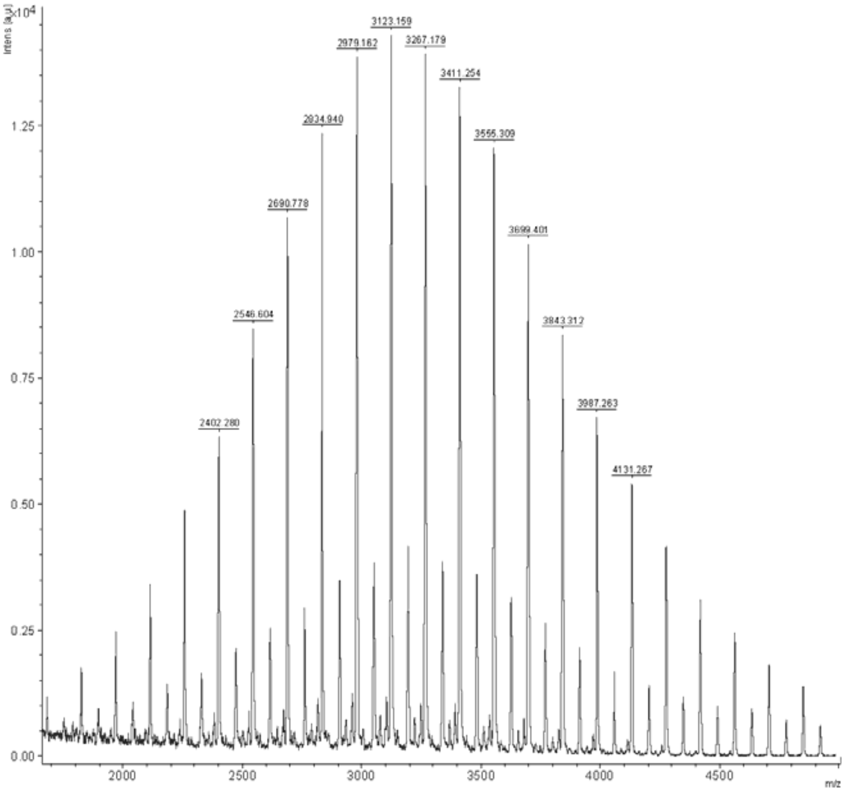


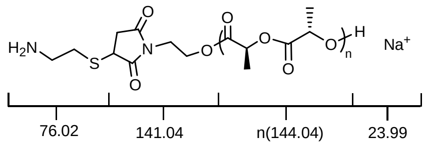


= 270.03 + (n.144.04)

n	m/z
14	2286.59
15	2430.63
16	2574.67
17	2718.71
18	2862.75
19	3006.79
20	3150.83
21	3294.87
22	3438.91
23	3582.95
24	3726.99
25	3871.03
26	4015.07
27	4159.11
28	4303.15

Figure S7 - MALDI-ToF Spectrum of cysteamine functionalised MI-PLA

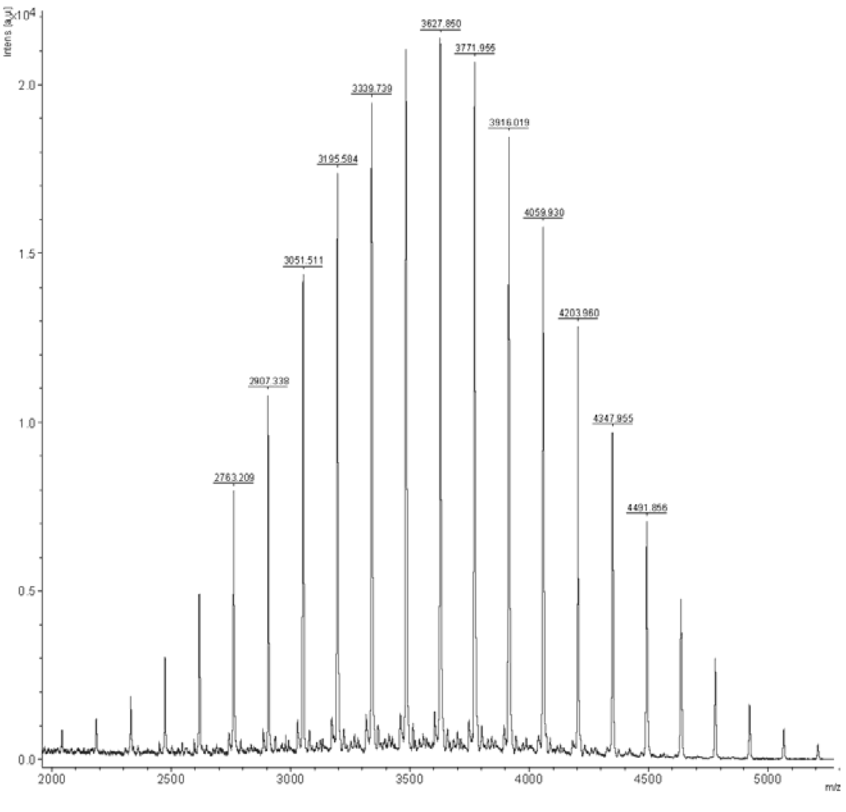


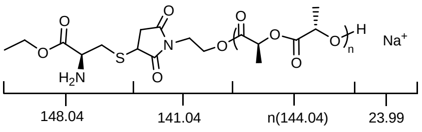


= 241.05 + (n.144.04)

n	m/z
14	2257.61
15	2401.65
16	2545.69
17	2689.73
18	2833.77
19	2977.81
20	3121.85
21	3265.89
22	3409.93
23	3553.97
24	3698.01
25	3842.05
26	3986.09
27	4130.13
28	4274.17

Figure S8 - MALDI-ToF Spectrum of cysteine ethyl ester functionalised MI-PLA





= 313.07 + (n.144.04)

n	m/z
14	2329.63
15	2473.67
16	2617.71
17	2761.75
18	2905.79
19	3049.83
20	3193.87
21	3337.91
22	3481.95
23	3625.99
24	3770.03
25	3914.07
26	4058.11
27	4202.15
28	4346.19

Table S1 Effect of solvent in 'Click' conjugation of thiols to maleimide-functional PLAs

Entry	Solvent	% Conversion[a]
1	DCM	100
2	THF	97
3	1,4-Dioxane	38
4	DMF	85
5	DMSO	76
6	Acetone	86

Reactions carried out in 7 mM solution of DP20 MI-PLA, 5 eq dodecanethiol and 2 eq NEt_3 for 6 h [a] determined by ^1H NMR.

Table S2 Synthesis of telechelic and star-shaped polymers by conjugation of thiols to MI-PLAs

Entry	DP[a]	R-$(SH)_n$	Solvent	Mn[b]	PDI[b]
1	20	-	-	5240	1.09
2	20	biphenyl-4,4'-dithiol	1,4-Dioxane	11030	1.06
3	20	1,3,5-tri(thiomethyl)benzene	DCM	13900	1.10
4	50	-	-	13400	1.09
5	50	biphenyl-4,4'-dithiol	1,4-Dioxane	28630	1.05
6	50	1,3,5-tri(thiomethyl)benzene	DCM	43060	1.10

Reactions carried out in 7 mM solution of MI-PLA, 1.1 eq 'SH' and 1 eq NEt_3 for 2 h, Iodoacetate resin reaction for a further 24 h [a] Degree of polymerisation of maleimide functional PLA, measured by ^1H NMR. [b] determined by GPC.

References

(S1) G. Mantovani, F. Lecolley, L. Tao, D. M. Haddleton, J. Clerx, J. Cornelissen and K. Velonia, *J. Am. Chem. Soc.*, **2005**, *127*, 2966-2973.
(S2) J. Houk and G. M. Whitesides, *J. Am. Chem. Soc.*, **1987**, *109*, 6825-6836.
(S3) R. C. Pratt, B. G. G. Lohmeijer, D. A. Long, P. N. P. Lundberg, A. P. Dove, H. B. Li, C. G. Wade, R. M. Waymouth and J. L. Hedrick, *Macromolecules*, **2006**, *39*, 7863-7871.