Supporting Information: Nichol, Clark, Dolinski, Read de Alaniz

Multi-stimuli Responsive Trigger for Temporally Controlled Depolymerization of Self-immolative Polymers

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Materials and Methods

Unless stated otherwise, reactions were conducted in oven dried glassware under an atmosphere of N₂ using reagent grade solvents. All commercially obtained reagents were used as received. Reaction temperatures were controlled using a Heidolph temperature modulator, and unless otherwise, reactions were performed at room temperature (rt, approximately 23 °C). Thin-layer chromatography (TLC) was conducted with E. Merck silica gel 60 F254 pre-coated plates (0.25 mm) and visualized by exposure to UV light (254 nm) or stained with potassium permanganate or panisaldehyde. Flash chromatography was preformed using normal phase silica gel (60 Å, 230-240 mesh, Geduran®) ¹H NMR spectra were recorded on Varian Spectrometers (at 400, 500, and 600 MHz) and are reported relative to deuterated solvent signals. Data for ¹H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz) and integration. ¹³C NMR spectra were recorded on Varian Spectrometers (at 100, 125, and 150 MHz). Data for ¹³C NMR spectra are reported in terms of chemical shift. IR spectra were recorded on a Perkin Elmer Spectrum 100 FT/IR and a Bruker Alpha FT/IR and are reported in terms of frequency of absorption (cm⁻¹). High resolution mass spectra were obtained from the UC Santa Barbara Mass Spectrometry Facility.

Experimental Procedures and Data:

Synthesis Procedures:



Furan-2-ylmethyl (4-nitrophenyl) carbonate (3): To a 100 mL oven dried round bottom flask is added 4-nitrophenyl chloroformate **2** (2.8 g, 13.8 mmol, 1.2 eq) in DCM (anhydrous, 30 mL). While under an atmosphere of nitrogen furfuryl alcohol **1** (1 mL, 11.5 mmol, 1.0 eq) is added via syringe to the flask. Triethylamine (3.2 mL, 23 mmol, 2.0 eq) is added dropwise to the reaction via syringe. The reaction is allowed to stir for one hour before being quenched with 1 M HCl (1 x 30 mL) and saturated potassium carbonate (3 x 30 mL). The organic layer was dried over magnesium sulfate prior to being concentrated *in vacuo* to afford a pale yellow solid (2.42 g, 80%). ¹H NMR (500 MHz, Chloroform-*d*) δ 8.30 – 8.24 (m, 2H), 7.48 (dd, *J* = 1.9, 0.8 Hz, 1H), 7.41 – 7.35 (m, 2H), 6.54 (dd, *J* = 3.2, 0.8 Hz, 1H), 6.41 (dd, *J* = 3.3, 1.9 Hz, 1H), 5.26 (s, 2H); ¹³C NMR (125 MHz, Chloroform-*d*) δ 155.6, 152.4 147.9, 145.6, 144.2, 125.4, 121.9, 112.3, 110.9, 62.6; IR 3120, 3086, 2973, 1748, 1594, 1523, 1492, 1345, 1263, 1214, 923, 744, 499 cm⁻¹.



Furan-2-ylmethyl (4-(hydroxymethyl)phenyl)carbamate (7): To a 100 mL oven dried round bottom flask is added 3 (2.4 g, 9.1 mmol, 1.0 eg), 4-aminobenzyl alcohol 6 (1.24 g, 10.0 mmol, 1.1 eq), and hydroxybenzotriazole (0.42 g, 2.7 mmol, 0.3 eq) in DMF (anhydrous, 10 mL). Through a septa cap, N,N-diisopropylethylamine (1.6 mL, 9.1 mmol, 1.0 eq) is added and the reaction is allowed to stir at room temperature for 48 hours. The solution is diluted with a solution of 9:1 ethyl acetate: isopropyl alcohol (20 mL) and set to stir for one additional hour. The solution is then guenched with saturated sodium bicarbonate (1 x 30 mL), saturated sodium bisulfite (1 x 30 mL), and brine (3 x 30 mL). The organic layer is dried over magnesium sulfate and concentrated *in vacuo*. The crude product was dry loaded onto Celite and purified via flash chromatography with an increasing gradient of ethyl acetate in hexanes (40 \rightarrow 70%) to afford **7** as a light tan solid (1.2 g, 52%). ¹H NMR (500 MHz, Chloroform-d) δ 7.43 (dd, J = 1.8, 0.9 Hz, 1H), 7.35 (d, J = 8.3 Hz, 2H), 7.30 – 7.26 (m, 2H), 6.75 (s, 1H), 6.45 (dd, J = 3.2, 0.7 Hz, 1H), 6.37 (dd, J = 3.3, 1.8 Hz, 1H), 5.15 (s, 2H), 4.62 (s, 2H), 1.80 (s, 1H); ¹³C NMR (125 MHz, Chloroform-d) δ 153.1, 149.7, 143.5, 137.3, 136.2, 128.1, 119.0, 110.9, 110.8, 65.0, 58.9; IR 3317, 3119, 2944, 1697, 1610, 1540, 1413, 1220, 1042, 1004, 918, 750, 599 cm⁻¹; HRMS (ESI), calculated for C₁₃H₁₃NO₄: (M+Na⁺) 270.0742; observed 270.0735.



Furan-2-ylmethyl (4-((((4-nitrophenoxy)carbonyl)oxy)methyl)phenyl)carbamate (9): To a 100 mL oven dried round bottom flask is added **7** (1.8 g, 7.28 mmol, 1.0 eq) and **2** (1.76 g, 8.74 6 mmol, 1.2 eq) in DCM (anhydrous, 30 mL). While under an atmosphere of nitrogen, triethylamine (2.03 mL, 14.56 mmol, 2.0 eq) is added dropwise to the reaction via syringe. The reaction is allowed to stir at room temperature for 1.5 hours before being quenched with 1 M HCl (1 x 30 mL) and saturated potassium carbonate (3 x 30 mL). The organic layer is dried over magnesium sulfate and concentrated *in vacuo* to afford a white solid (2.52 g, 84%). ¹H NMR (500 MHz, Chloroform-*d*) δ 8.29 – 8.24 (m, 2H), 7.47 – 7.33 (m, 7H), 6.76 (s, 1H), 6.46 (dd, *J* = 3.2, 0.7 Hz, 1H), 6.38 (dd, *J* = 3.2, 1.8 Hz, 1H), 5.24 (s, 2H), 5.16 (s, 2H); ¹³C NMR (125 MHz, Chloroform-*d*) δ 155.7, 153.0, 152.6, 149.5, 145.5, 143.6, 138.7, 130.1, 129.6, 129.3, 125.4, 121.9, 111.0, 110.8, 70.8, 59.0; IR 3347, 3117, 2924, 1754, 1711, 1523, 1270, 1211, 1054, 863, 759, 663 cm⁻¹; HRMS (ESI), calculated for C₂₀H₁₆N₂O₈: (M+Na⁺) 435.0804; observed 435.0806.



Furan-2-ylmethyl (4-(((p-tolylcarbamoyl)oxy)methyl)phenyl)carbamate (12): To a 15 mL oven dried round bottom flask is added 9 (200 mg, 0.49 mmol, 1.0 eg), 4methylaniline 11 (57 mg, 0.53 mmol, 1.1 eg), and hydroxybenzotriazole (22 mg, 0.15 mmol, 0.3 eq) in DMF (anhydrous, 2 mL). Through a septa cap, N.Ndiisopropylethylamine (84 µL, 0.49 mmol, 1.0 eq) is added and the reaction is allowed to stir at room temperature for 48 hours. The solution is diluted with a solution of 9:1 ethyl acetate: isopropyl alcohol (10 mL) and set to stir for one additional hour. The solution is then washed with saturated sodium bicarbonate (1 x 10 mL), saturated sodium bisulfite (1 x 10 mL), and brine (3 x 10 mL). The organic layer is dried over magnesium sulfate and concentrated in vacuo. The crude product was dry loaded onto Celite and purified via flash chromatography with an increasing gradient of ethyl acetate in hexanes (5 \rightarrow 40%) to afford **12** as a light tan solid (141 mg, 76%). ¹H NMR (400 MHz, Chloroform-*d*) δ 7.46 – 7.42 (m, 1H), 7.36 (q, J = 8.5 Hz, 5H), 7.24 (s, 2H), 7.10 (d, J = 8.1 Hz, 2H), 6.70 (s, 1H), 6.59 (s, 1H), 6.46 (d, J = 3.2 Hz, 1H), 6.38 (dd, J = 3.3, 1.9 Hz, 1H), 5.16 (s, 2H), 5.13 (s, 2H), 2.30 (s, 3H); ¹³C NMR (125 MHz, Chloroform-d) δ 162.0, 153.2, 149.5, 143.5, 137.8, 133.5, 131.4, 129.7, 129.5, 126.3, 115.8, 111.0, 110.8, 66.8, 59.0, 20.9; IR 3329, 2963, 1704, 1599, 1536, 1314, 1226, 1045, 817, 509 cm⁻¹; HRMS (ESI), calculated for C₂₁H₂₀N₂O₅: (M+Na⁺) 403.1270; observed 403.1282.



((3aS,4R,7R,7aR)-2-ethyl-1,3-dioxo-1,2,3,3a,7,7a-hexahydro-4H-4,7-epoxyisoindol-4-yl)methyl (4-nitrophenyl) carbonate (5): To a 15 mL oven dried round bottom flask is added **3** (1 g, 3.8 mmol, 1.0 eq) and *N*-ethylmaleimide **4** (1.43 g, 11.4 mmol, 3.0 eq) in DCM (anhydrous, 5 mL). The solution is allowed to stir at room temperature for five days. The solution is then concentrated *in vacuo* and dry loaded onto Celite and purified via flash chromatography with an increasing gradient of ethyl acetate in hexanes (10 → 50%) to afford **5** as a white solid (674 mg, 46%). ¹H NMR (500 MHz, Chloroform-*d*) δ 8.31 – 8.26 (m, 2H), 7.45 – 7.40 (m, 2H), 6.51 (dd, *J* = 5.8, 1.7 Hz, 1H), 6.38 (d, *J* = 5.8 Hz, 1H), 5.35 (dd, *J* = 5.5, 1.7 Hz, 1H), 4.92 (dd, *J* = 101.5, 12.3 Hz, 2H), 3.68 (dd, *J* = 7.7, 5.5 Hz, 1H), 3.46 (d, *J* = 7.7 Hz, 1H), 3.40 (q, *J* = 7.2 Hz, 2H), 1.05 (t, *J* = 7.2 Hz, 3H); ¹³C NMR (125 MHz, Chloroform-*d*) δ 174.3, 155.5, 152.4, 145.7, 136.2, 133.9, 125.5, 121.9, 89.1, 79.9, 66.5, 47.8, 46.9, 33.8, 12.8; IR 3086, 1761, 1691, 1533, 1347, 1260, 1210, 1131, 863, 722, 636, 434 cm⁻¹; HRMS (ESI), calculated for C₁₈H₁₆N₂O₈: (M+Na⁺) 411.0804; observed 411.0795.



((3aS,4R,7R,7aR)-2-ethyl-1,3-dioxo-1,2,3,3a,7,7a-hexahydro-4H-4,7-epoxyisoindol-4-yl)methyl (4-(hydroxymethyl)phenyl)carbamate (8): To a 15 mL oven dried round bottom flask is added 5 (300 mg, 0.77 mmol, 1.0 eq), 6 (105 mg, 0.85 mmol, 1.1 eq), and hydroxybenzotriazole (35 mg, 0.23 mmol, 0.3 eq) in DMF (anhydrous, 3 mL). Through a septa cap N,N-diisopropylethylamine (0.14 mL, 0.77 mmol, 1.0 eq) is added and the reaction is allowed to stir for 48 hours. The solution is diluted with a solution of 9:1 ethyl acetate: isopropyl alcohol (10 mL) and set to stir for one additional hour. The solution is then washed with saturated sodium bicarbonate (1 x 10 mL), saturated sodium bisulfite (1 x 10 mL), and brine (3 x 10 mL). The organic layer is dried over magnesium sulfate and concentrated in vacuo. The crude product was dry loaded onto Celite and purified via flash chromatography with an increasing gradient of ethyl acetate in hexanes (30 \rightarrow 70%) to afford **8** as a light tan solid (203 mg, 71%). ¹H NMR (500 MHz, Chloroform-*d*) δ 7.41 – 7.27 (m, 4H), 6.90 (s, 1H), 6.45 (dd, *J* = 5.8, 1.6 Hz, 1H), 6.35 (d, J = 5.7 Hz, 1H), 5.34 – 5.28 (m, 1H), 4.96 (d, J = 12.5 Hz, 1H), 4.68 (d, J = 12.6 Hz, 1H), 4.63 (s, 2H), 3.63 (dd, J = 7.7, 5.5 Hz, 1H), 3.42 – 3.33 (m, 3H), 1.04 (t, J = 7.2 Hz, 3H); ¹³C NMR (125 MHz, Chloroform-d) δ 174.5, 174.3, 137.1, 136.4, 135.8, 134.5, 129.8, 128.1, 90.0, 79.8, 65.0, 62.9, 47.8, 46.9, 33.7, 12.8; IR 3353, 2952, 2871, 1736, 1692, 1525, 1399, 1245, 1135, 1057, 630 cm⁻¹; HRMS (ESI), calculated for C₁₉H₂₀N₂O₆: (M+Na⁺) 395.1219; observed 395.1232.



((3aS,4R,7R,7aR)-2-ethyl-1,3-dioxo-1,2,3,3a,7,7a-hexahydro-4H-4,7-epoxyisoindol-4-yl)methyl (4-((((4-nitrophenoxy)carbonyl)oxy)methyl)phenyl)carbamate (10): To a 15 mL oven dried round bottom flask was added 8 (175 mg, 0.47 mmol, 1.0 eg) and 2 (114 mg, 0.56 mmol, 1.2 eq) in DCM (anhydrous, 5 mL). While under an atmosphere of nitrogen, triethylamine (0.13 mL, 0.94 mmol, 2.0 eq) was added dropwise to the reaction via syringe. The reaction is allowed to stir at room temperature for 1.5 hours before being guenched with 1 M HCl (1 x 10 mL) and saturated potassium carbonate (3 x 10 mL). The organic layer is dried over magnesium sulfate and concentrated in vacuo to afford a white solid (126 mg, 72%). ¹H NMR (500 MHz, Chloroform-d) δ 8.31 – 8.23 (m, 2H), 7.48 – 7.34 (m, 6H), 6.88 (s, 1H), 6.47 (dd, J = 5.7, 1.7 Hz, 1H), 6.36 (d, J = 5.8Hz, 1H), 5.33 (dd, J = 5.5, 1.7 Hz, 1H), 5.24 (s, 2H), 4.84 (dd, J = 139.6, 12.5 Hz, 2H), 3.65 (dd, J = 7.7, 5.5 Hz, 1H), 3.43 – 3.34 (m, 3H), 1.05 (t, J = 7.2 Hz, 3H); ¹³C NMR (125 MHz, Chloroform-d) δ 174.42, 174.26, 155.65, 152.65, 152.57, 145.54, 138.47, 135.85, 134.45, 130.09, 129.53, 125.43, 121.91, 118.89, 89.94, 79.79, 77.41, 77.16, 76.91, 70.76, 63.06, 47.84, 46.94, 33.71, 12.79; IR 3327, 3083, 2953, 1764, 1735, 1691, 1523, 1345, 1201, 1057, 862, 724 cm⁻¹; HRMS (ESI), calculated for C₂₆H₂₃N₃O₁₀: (M+Na⁺) 560.1281; observed 560.1283.



((3aS,4R,7R,7aR)-2-ethyl-1,3-dioxo-1,2,3,3a,7,7a-hexahydro-4H-4,7-epoxyisoindol-4-yl)methyl (4-(((p-tolylcarbamoyl)oxy)methyl)phenyl)carbamate (13): To a 15 mL oven dried round bottom flask was added 10 (210 mg, 0.39 mmol, 1.0 eq), 11 (46 mg, 0.43 mmol, 1.1 eq), and hydroxybenzotriazole (18 mg, 0.12 mmol, 0.3 eq) in DMF (anhydrous, 2 mL). Through a septa cap *N*,*N*-diisopropylethylamine (68 µL, 0.39 mmol, 1.0 eq) is added and the solution is allowed to stir for 48 hours. The solution is diluted with a solution of 9:1 ethyl acetate: isopropyl alcohol (10 mL) and set to stir for one additional hour. The solution is then washed with saturated sodium bicarbonate (1 x 10 mL), saturated sodium bisulfite (1 x 10 mL), and brine (3 x 10 mL). The organic layer is dried over magnesium sulfate and concentrated *in vacuo*. The crude product was dry loaded onto Celite and purified via flash chromatography with an increasing gradient of ethyl acetate in hexanes (30 \rightarrow 70%) to afford 13 as a light tan solid (155 mg, 81%). ¹H NMR (500 MHz, Chloroform-*d*) δ 7.43 – 7.30 (m, 4H), 7.25 (s, 1H), 7.09 (d, *J* = 8.1 Hz, 2H), 6.91 (s, 1H), 6.72 – 6.63 (m, 1H), 6.45 (dd, *J* = 5.7, 1.7 Hz, 1H), 6.35 (d, *J* = 5.8 Hz, 1H), 5.31 (dd, J = 5.5, 1.7 Hz, 1H), 5.12 (s, 2H), 4.82 (dd, J = 142.7, 12.5 Hz, 2H), 3.63 (dd, J = 7.7, 5.5 Hz, 1H), 3.42 – 3.31 (m, 3H), 2.29 (s, 3H), 1.04 (t, J = 7.2 Hz, 3H); ¹³C NMR (125 MHz, Chloroform-*d*) δ 174.48, 174.28, 152.73, 137.75, 135.78, 135.29, 134.47, 131.56, 129.67, 129.55, 118.82, 89.97, 79.75, 77.41, 77.16, 76.91, 66.64, 62.94, 47.82, 46.88, 33.68, 20.87, 12.77; IR 3335, 3083, 2974, 1764, 1734, 1691, 1523, 1345, 1201, 1058, 862, 725 cm⁻¹; HRMS (ESI), calculated for C27H27N3O7: (M+Na⁺) 528.1747; observed 528.1755.



Phenyl (4-(hydroxymethyl)phenyl)carbamate (15): 6 (3 g, 24.4 mmol, 1.0 eq) was suspended in a mixture of THF: sat. NaHCO₃: water (45 mL, ratio 2:2:1). Phenyl chloroformate **14** (3.12 mL, 24.85 mmol, 1.02 eq) was added dropwise over five minutes. Once the reaction reached completion, ethyl acetate was added and the organic phase was washed twice with saturated NH₄Cl solution. The solution was concentrate *in vacuo*. The crude product was dry loaded onto Celite and purified via flash chromatography to afford **15** as a white solid (4.61 g, 78%). Spectral data matches literature values.¹



Furan endcapped polyurethane (16): To a 25 mL flame dried round bottom flask was added **15** (1.5 g, 6.2 mmol, 1.0 eq) and DBTL (0.183 mL, 0.31 mmol, 0.05 eq) in DMSO (anhydrous, 2.0 mL). The flask was heated to 85 °C for 2.5 hours. **1** (0.134 mL, 1.54 mmol, 0.25 eq) was added to the reaction and stirred overnight. After cooling to room temperature, the polymer was precipitated into cold methanol (30 mL), filtered and dried. In order to obtain completely encapped polymer, the crude polymer is then subjected to 9:1 DMSO:H₂O with 10% piperidine for 2 days at 60 °C prior to being precipitated a second time into cold methanol. Polymer **16** was obtained as a light tan solid (870 mg). ¹H NMR (600 MHz, DMSO-*d*₆) δ 9.80 (s, 1H), 9.74 (s, 15H), 9.61 (s, 1H), 7.66 (s, 1H), 7.43 (d, *J* = 8.1 Hz, 30H), 7.36 (d, *J* = 8.1 Hz, 2H), 7.30 (d, *J* = 8.2 Hz, 30H), 7.16 (d, *J* = 7.8 Hz, 2H), 6.52 (s, 1H), 6.43 (s, 1H), 5.07 (s, 2H), 5.01 (s, 30H), 4.36 (d, *J* = 5.7 Hz, 2H). GPC: M_n = 4.6 kg/mol, M_w = 8.8 kg/mol, *Đ* = 1.9.



Diels–Alder endcapped polyurethane (17): To a 15 mL oven dried round bottom flask is added **16** (250 mg, 0.104 mmol, 1.0 eq) and **4** (130 mg, 1.04 mmol, 10.0 eq) in DMSO (anhydrous, 2 mL). The solution is allowed to stir for one week at room temperature. The polymer is then precipitated into cold methanol, filtered, and dried to afford polymer **17** as a tan solid (125 mg; 25 % no conversion, 25 % *exo* adduct, and 50 % *endo* adduct). GPC: $M_n = 5.1$ kg/mol, $M_w = 7.8$ kg/mol, D = 1.9.



Tert-butyl (4-(hydroxymethyl)phenyl)carbamate (18): 4-aminobenzyl alcohol (0.5 g, 4.06 mmol, 1 eq) was dissolved in a 1:2:3 mixture of Dioxane:H₂O:1N NaOH (15 mL total). Boc₂O (1.33 g, 6.09 mmol, 1.5 eq) was dissolved in 2.5 mL dioxane and added dropwise. The mixture was stirred at room temperature overnight. After confirmation of reaction completion by TLC, the dioxane was removed *in vacuo* and the remaining solution was extracted with ethyl acetate (3 x 10 mL). After removing the ethyl acetate *in vacuo*, the product was purified via column chromatography (1:1 hexanes:ethyl acetate) to yield **18** (0.706 g) as a white powder. Spectral data matches literature values.²



Boc endcapped polyurethane (19): To a 25 mL flame dried round bottom flask was added **15** (1.5 g, 6.17 mmol, 1.0 eq) and DBTL (0.183 mL, 0.31 mmol, 0.05 eq) in DMSO (anhydrous, 2 mL). The flask was heated to 85 °C for 2.5 hours. **18** (0.346 g, 1.55 mmol, 0.25 eq) was added to the reaction and stirred overnight. After cooling to room temperature, the polymer was precipitated into cold methanol (20 mL), filtered and dried. In order to obtain completely encapped polymer, the crude polymer is then subjected to 9:1 DMSO:H₂O with 10% piperidine for 2 days at 60 °C prior to being precipitated a second time into cold methanol. Polymer **19** was obtained as a light tan solid (740 mg). Spectral data matches literature values.²

Small Molecule Studies

Thermal Stability of furan small molecule model

Compound **12** (10 mg) was dissolved in MeCN-d₃ (0.7 mL). The sample was placed in a preheated heating block at 80 °C. The sample was allowed to stir between NMR spectra taken to monitor the sample. NMR spectra were obtained at t=0 (prior to heating) and t=6 (hours). As demonstrated by having no observable change via NMR at elevated temperature, this indicates that heat alone is not a suitable trigger.



Figure S1. Full NMR spectra for compound **12** before and after being heated at 80 °C. There is no structural change from its initial state (navy) after 6 hours of heating at 80 °C (red), supporting our need for a dual-stimuli system.

Quantitative retro-Diels–Alder on small molecule model

Compound **13** (10 mg) was dissolved in MeCN-d₃ (0.7 mL). The sample was placed in a preheated heating block at 80 °C. The sample was allowed to stir and NMR spectra were obtained prior to heating and every 2 hours after for a total of 6 hours of heating.



Figure S2. NMR spectra for compound **13** at its initial state (red), after 2 hours (green), 4 hours (teal), and 6 hours (purple). Protons for the maleimide appear at 6.77 ppm and a shift in furan peaks is seen between 6.54-6.38 ppm. As demonstrated by the NMR spectrum, near quantitative retro Diels-Alder can be observed over this time period supporting the successful "unlocking" of the trigger system.

Acid Stability of Diels–Alder model

Compound **13** (10 mg) was dissolved in MeCN-d₃ (0.7 mL) with Sc(OTf)₃ (1 mg). An initial t0 ¹H NMR spectrum was obtained and the sample was left to stir at room temperature over 48 hours. A t48 ¹H NMR spectrum was obtained and shows there was no structural changes to **13** over the 48 hour period while in an acidic environment. This was also done with **13** in DMSO-d₆ (0.7 mL) with TFA-d (0.1 mL) as shown in Figure 2c. This stability supports the advantage of using the Diels–Alder lock to ensure long term stability as well as prohibit any premature depolymerization from occurring.



Figure S3. ¹H NMR spectra of **13** at t0 and t48 hours of being exposed to the acid catalyst Sc(OTf)₃. No structural changes were observed indicating that the Diels–Alder lock on the furan adduct acts as a protecting group to eliminate premature activation of the furan cleavage.

Controlled retro-Diels–Alder and release

Compound **13** (10 mg) in DMSO-d₆ (0.7 mL) with TFA-d (0.1 mL) was placed in a preheated heating block at 80 °C. After one hour of heating, the sample is cooled in an ice bath (0 °C) for one minute before being left to reach room temperature. After sitting at room temperature for one hour the sample is placed back into the heating block. These cycles continue until the sample has reached quantitative release (some time periods are longer than one hour and shown below). NMR spectra are obtained after each heating and each room temperature time period to monitor the progress of the release.



Figure S4. Controlled release of the reporter molecule **11** using TFA. The red bars representing heating at 80 °C and the white bars represent holding at room temperature. For this ON/OFF study, 98% conversion was observed after 10 cycles of heating.

Kinetics Studies

Diels–Alder adducts

A NMR sample of **5** (10 mg) with 10 mol% $Sc(OTf)_3$ (1 mg) in MeCN-d₃ (0.7 mL) is monitored overnight (14 h 31 min 10 s) with NMR spectra saved every 2.9 minutes. This was repeated for samples to be run at 50 °C, 60 °C, 65 °C, and 70 °C.



Figure S5. NMR spectra of three different states of progress through the kinetics studies at 60 °C showing the peaks used for conversion calculations. The percent shown indicates the amount of our starting Diels–Alder (DA) adduct is still present.

NMR processing: Samples as described above were prepared and then placed in an NMR spectrometer and equilibrated at the given temperature for about 5 minutes before collecting the data. The disappearance of the starting DA adduct was tracked over time. The data was collected as an array collecting 300 scans on the Varian Unity Inova AS600 600 MHz spectrometer. This data was then processed in MestReNova software. A spectrum that was roughly in the middle of the overall transformation was chosen to phase and baseline the entire data set. In MeCN-d₃, the peaks with δ = 4.78 and 4.97 ppm were integrated as the starting material and the peaks with δ = 6.72 and 7.57 ppm were integrated as the released material. These integrations were then exported as a Script: 1D Integral series. The ratio of the remaining DA adduct was determined by the following equation:

Equation 1:

$$\frac{[DA \ adduct]}{[DA \ adduct]_{o}} = \frac{\int peak \ c}{\int peak \ c + \frac{2}{3} \int (peaks \ a + b)}$$



Figure S6. Conversion vs time data for adduct 5 at various temperatures as described above in the *Kinetics Studies* section.



Figure S7. Linearized kinetics data for adduct **5** at various temperatures to extrapolate the rate values for further calculations.

The data was then fit onto a logarithmic scale and the reaction rate constants were determined from the slopes of the reaction progression. A t_{lag} value was added to the model to extrapolate all the starting data points to 0% of the reporter molecule for each sample. By plotting the rate constants relative to 1/T, we could use the Arrhenius expression to extract the activation energy.

T (°C)	k
50	0.0087
60	0.0317
65	0.0581
70	0.0983
80*	0.3090

Table S1. A_o and k values for the rate order equations found in Figure S7. All rate order equations are all in the form of A = A_o e^{-k*t}, where A_o = 1.0 for all temperatures. *The 80 °C k value was determined from Figure S6.



Figure S8. Arrhenius plot for the kinetics studies done on **5** to calculate the activation energy of the overall rDA and release of the trigger system, as well as the calculated data point for 80 °C.



Figure S9. Experimental and calculated data for the controlled rDA and release of **13** at 60 °C and 80 °C as described in the *Controlled retro-Diels–Alder and release* section. The calculated data was determined from models described above in the *Kinetics Studies* section (Table S1).

Furan adducts

A NMR sample of **7** (10 mg) in DMSO-d₆ (0.7 mL) with TFA-d (0.1 mL) is monitored overnight (14 h) with NMR spectra saved every 2.8 minutes. This was repeated for samples which were ran at 50 °C, 60 °C, 65 °C, and 70 °C.



Figure S10. NMR spectra of three different states of progress through the kinetics studies at 60 °C showing the peaks used for conversion calculations. The percent shown indicates the amount of our starting furan adduct is still present.

NMR processing: Samples as described above were prepared and then placed in an NMR spectrometer and equilibrated at the given temperature for about 5 minutes before collecting the data. The disappearance of the starting furan adduct was tracked over time. The data was collected as an array collecting 300 scans on the Varian Unity Inova AS600 600 MHz spectrometer. This data was then processed in MestReNova software. A spectrum that was roughly in the middle of the overall transformation was chosen to phase and baseline the entire data set. In DMSO-d₆, the peaks with δ = 4.39, 7.17, and 7.37 ppm were integrated as the starting material and the peaks with δ = 5.29, 7.29, and 7.48 ppm were integrated as the released material. These integrations were then exported as a Script: 1D Integral series. The ratio of the remaining DA adduct was determined by the following equation:

Equation 2:

$$\frac{[furan \ adduct]}{[furan \ adduct]_{o}} = \frac{\int (peak \ a + peak \ b + peak \ c + peak \ c + peak \ d + peak \ e + peak \ f)}{\int (peak \ a + peak \ b + peak \ c + peak \ d + peak \ e + peak \ f)}$$



Figure S11. Conversion vs time for **7** at various temperatures as described above in the *Kinetics Studies* section. This acid catalyzed release mimics that of the *aza*-Piancatelli rearrangement. From previous studies in our group on the *aza*-Piancatelli mechanism, the rate changes observed are due to the release of the aniline reporter **6**. As previous studies show, the concentration of aniline present can alter the rate at which the reaction takes place due to off-cycle binding between the aniline and acid catalyst.³ With an increased concentration of aniline vs furan adduct, the rate of reaction decreases, similar to the kinetics data shown above.

Polymer Studies

Heat and Acid Release

Diels-Alder trigger

A sample of polymer **17** (10 mg) with TFA-d (0.1 mL) in DMSO-d₆ (0.7 mL) was placed in a preheated heating block at 80 °C. After one hour of heating, the sample is cooled in an ice bath for one minute before being left to reach room temperature. After sitting at room temperature for one hour the sample is placed back into the heating block. These cycles continue until the sample has reached quantitative release (some time periods are longer than one hour and shown below). NMR spectra are obtained after each heating and each room temperature time period to monitor the progress of the release.



Figure S12. Controlled degradation of the DA locked polymer **17** during cycles of heating at 80 °C (red) and room temperature in the presence of acid.



Figure S13. Stacked NMR spectra of polymer **17** at various times throughout the experiment shown in Figure S9. This shows that the DA adducts are still present throughout the experiment until cleavage takes place allowing for the pausing effect. The methyl group from the maleimide substrates are seen within this spectral range—the *endo* DA adduct of polymer **17** is seen at 0.86 ppm, the *exo* DA adduct of polymer **17** is seen at 0.96 ppm, and the maleimide small molecule being thermally cleaved begins to appear at 0.99 ppm.

Furan trigger

A sample of polymer **16** (10 mg) with TFA-d (0.1 mL) in DMSO-d₆ (0.7 mL) was placed in a preheated heating block at 80 °C. After one hour of heating, the sample is cooled in an ice bath for one minute before being left to reach room temperature. After sitting at room temperature for one hour the sample is placed back into the heating block. These cycles continue until the sample has reached quantitative release (some time periods are longer than one hour and shown below). NMR spectra are obtained after each heating and each room temperature time period to monitor the progress of the release.



Figure S14. Controlled degradation of the furan capped polymer **16** during cycles of heating at 80 °C (red) and room temperature in the presence of acid.

Temperature Studies

A sample of polymer **16** and **17** (10 mg) in DMSO-d₆ (0.7 mL) with TFA-d (0.1 mL) was placed in a preheated heating block. Conversion of the sample is monitored via ¹H NMR spectroscopy every hour. This was done with **16** and **17** at 50 °C and 80 °C.



Figure S15. Conversion of 16 and 17 at 50 °C and 80 °C in the presence of acid over a 9 hour period.

Kinetics Studies

A NMR sample of **16** (10 mg) in DMSO-d₆ (0.7 mL) with TFA-d (0.1 mL) is monitored overnight (14 h) with NMR spectra saved every 2.8 minutes. This was repeated for samples which were ran at 50 °C, 60 °C, 65 °C, and 70 °C.



Figure S16. Conversion vs time of polymer 16 at various temperatures as described above in the *Kinetics Studies* section.

Acid-Triggered Release

A sample of polymer **16** (10 mg) with TFA (0.1 mL) in DMSO-d₆ (0.7 mL) was placed in a preheated heating block at 50 °C. The reaction was monitored via NMR at various time intervals spanning a 10 day period. This indicates that the polymer behaves as a SIP by going through full end-to-end depolymerization.



Figure S17. Degradation of the non-Diels–Alder furan polymer **16** monitored over time when exposed to an acid stimulus at 50 °C, showing that when exposed to the triggering stimulus (acid + heat), the SIP can undergo complete depolymerization.

Trigger Stability to Acidic Environment

A NMR sample of polymer **16** (10 mg) in DMSO-d₆ (0.7 mL) with TFA-d (0.1 mL) was prepared and kept at room temperature. A sample of polymer **17** was prepared as well. Both polymer samples were monitored via ¹H NMR spectroscopy over a 4 day period to show stability to an acidic environment.



Figure S18. Conversion of **16** (**■**) and **17** (**■**) over a 4 day period when left at ambient temperatures in an acidic environment.

Acid Sensitive Boc-SIP Control Study

A sample of polymer **19** (10 mg) was dissolved in DMSO-d₆ (0.7 mL). An initial ¹H NMR spectrum was obtained. TFA-d (0.1 mL) was added to the polymer sample at room temperature and a ¹H NMR spectrum was obtained after 5 min to observe the deprotection and depolymerization.



Figure S19. NMR spectra of polymer **19** before and after addition of the TFA-d catalyst at room temperature. Depolymerization is expressed by the loss of the backbone benzylic protons (\blacktriangle).

References

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