Supplementary Information for

In Situ Deprotection and Dynamic Covalent Assembly Using a Dual Role Catalyst

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General Experimental Procedures

All chemicals and reagents, unless specified, were purchased from commercial sources and used as received without any further purification. ^{1}H and ^{13}C NMR spectra were collected using Varian MR400, MR500 and Varian VNMRS 500 spectrometers. Chemical shifts were measured in δ (ppm) relative to residual solvent signals as internal standards (CD_3OD: 4.87 for ^{1}H, 49.15 for ^{13}C; CD_3CN: 1.94 for ^{1}H; DMSO: 2.50 for ^{1}H). Matrix-assisted laser desorption/ionization (MALDI) mass spectra were recorded using a Bruker Autoflex mass spectrometer, whereas electrospray ionization (ESI) mass spectra were recorded using an Agilent Q-TOF 1200 series spectrometer. All MALDI analyses were performed in reflectron positive ion mode using 2-(4-hydroxyphenylazo)benzoic acid (HABA) as the matrix, where 2 μL of a solution of the sample (1 mM) was mixed with 6 μL of a mixture of 6 mg matrix in 300 μL acetonitrile, spotted on a MALDI sample plate (Bruker), and allowed to air dry. Reverse phase high performance liquid chromatography (RP-HPLC) was performed using a Shimadzu LC-6AD HPLC pump, equipped with a Shimadzu FRC 70A fraction collector, using analytical and preparative reversed phase Phenomenex Luna C18(2) columns with a linear gradient of water and acetonitrile as the eluent at 30°C, and monitored with a Shimadzu Prominence UV/vis detector at 214 nm.

Abbreviations

Et_2O: diethyl ether

EtOAc: ethyl acetate

HEX: hexanes

DCM: dichloromethane

DIC: *N*,*N*′-diisopropylcarbodiimide

DMAC: dimethylacetamide

DMF: *N*,*N*-dimethylformamide

Et_3N: triethylamine

MeCN: acetonitrile

NMP: *N*-methyl-2-pyrrolidone

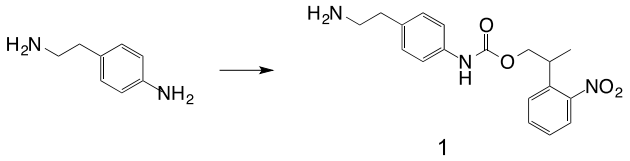
TFA: trifluoroacetic acid

THF: tetrahydrofuran

TPP: triphenylphosphine

MEA: 2-methoxyethylamine

Synthesis of 4-(2-aminoethyl)-N-(2-(2-nitrophenyl)propylcarbonyloxy)phenylamine



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Scheme **S1**. Synthesis of 4-(2-aminoethyl)-N-(2-(2-nitrophenyl)propylcarbonyloxy)phenylamine (**1**). Reagents and conditions: 2-(2-nitrophenyl)propyl chloroformate (NPPOC chloride), 10% aq. acetic acid, 1,4-dioxane, r.t. overnight.

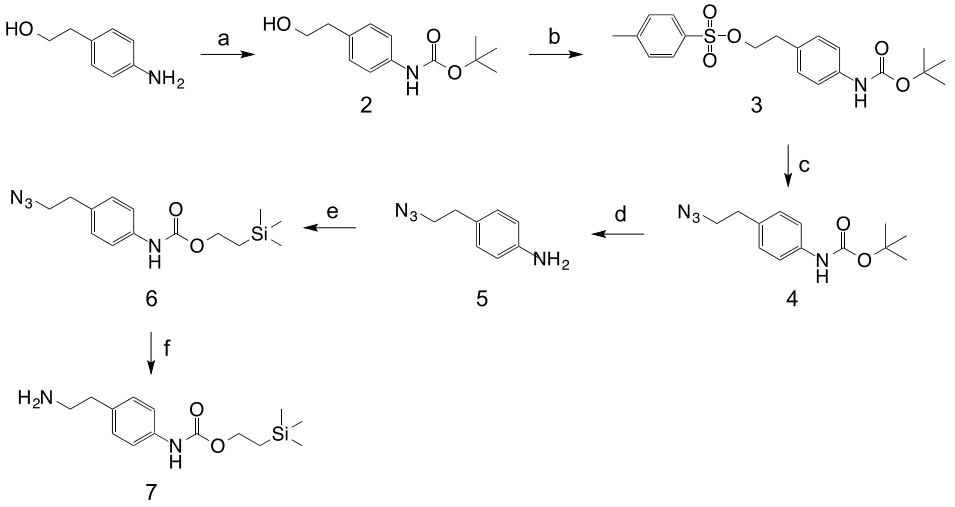
NPPOC chloride (0.58 g, 2.4 mmol) in 20 mL 1, 4-dioxane was added dropwise to a stirred solution of 4-(2-aminoethyl)aniline (0.3 g, 2 mmol) in 20 mL 10% aq. acetic acid at 0°C. The reaction mixture was stirred at room temperature overnight. The reaction mixture was diluted with a large amount of deionized (DI) water and washed with Et_2O three times. The aqueous phase was adjusted to pH 14 by 2 M NaOH (aq) and was extracted with Et_2O three times. The combined organic layer was washed with DI water three times, dried over Na_2SO_4, filtered, and evaporated to dryness to yield **1** as a yellow oil (0.48 g, 70%).

^{1}H NMR (400 MHz, CD_3OD) δ: 7.78 (d, 1H), 7.64-7.70 (m, 2H), 7.43-7.48 (m, 1H), 7.32 (d, 2H), 7.12 (2H), 4.30-4.40 (m, 2H), 3.63-3.70 (m, 1H), 2.85 (t, 2H), 2.71 (t, 2H), 1.41 (d, 3H).

^{13}C NMR (100 MHz, CD_3OD) δ: 155.72, 152.03, 138.42, 135.67, 133.77, 130.08, 129.57, 128.67, 124.97, 120.29, 69.46, 44.21, 39.45, 35.01, 18.36.

MS (ESI+): calcd for $C_{18}H_{21}N_3O_4$: $[M+H]^+$ = 344.1605 $[M+Na]^+$ = 366.1424, found: m/z = 344.1624, $[M+H]^+$, m/z = 366.1422 $[M+Na]^+$.

Synthesis of 4-(2-aminoethyl)-N-(2-(trimethylsilyl)ethoxycarbonyloxy)phenylamine



Scheme **S2**. Synthesis of 4-(2-aminoethyl)-N-(2-(trimethyl)ethoxycarbonyloxy)phenylamine (**7**). Reagents and conditions: (a) di-tert-butyl dicarbonate, THF, r.t., overnight; (b) tosyl chloride, THF, 6 M NaOH, 0°C; (c) NaN_3, DMF, 60°C; (d) TFA, DCM, r.t., 30 min; (e) N-[2-(trimethylsilyl) ethoxycarbonyloxy] succinimide, DMF, 60°C, overnight; (f) TPP, THF, DI water.

***tert*-butyl (4-(2-hydroxyethyl)phenyl)carbamate (2).** Di-*tert*-butyl dicarbonate (g, mmol) was added into a solution of 2-(4-aminophenyl)ethanol (2g, 14.6 mmol) in 50 mL THF. The reaction mixture was stirred at room temperature overnight, concentrated by reduced vacuum, and then precipitated in hexanes. The precipitate was filtered and dried under high vacuum to yield white powder (3.24 g, 94%).

^{1}H NMR (500 MHz, CD_3OD) *δ*: 7.29 (d, 2H, Ar), 7.13 (d, 2H, Ar), 3.71 (t, 2H, -CH_2-OH), 2.75 (t, 2H, -CH_2-Ar), 1.51 (s, 9H, (-CH_3)$_3$).

4-((*tert*-butoxycarbonyl)amino)phenethyl 4-methylbenzenesulfonate (3). Compound **2** (1.68 g, 7.07 mmol) and 10 mL of THF were charged to a 100 mL round bottom flask with a magnetic stirrer. This mixture was cooled to 0°C and 10 mL of 6 M NaOH aq. was added, followed by dropwise addition of tosyl chloride (2.7g, 14.14 mmol) in 20 mL THF under N_2. After stirring for 1 h at 0°C, the reaction mixture was allowed to reach room temperature and stirred overnight. The resulting mixture was extracted with EtOAc and the organic layer was washed with 1 M NaOH and DI water. The solution was evaporated under vacuum and the resultant solids were recrystallized in hexanes with a trace of THF to yield **3** as a white crystalline solid (2.71 g, 98 %).

^{1}H NMR (500 MHz, DMSO) *δ*: 9.26 (s, 1H, -N*H*-COO-), 7.64 (d, 2H, -S-C=C*H*-CH), 7.30 (d, 2H, -S-C=CH-C*H*), 7.30 (d, 2H, -CH_2-C=CH-C*H*), 7.01 (d, 2H, -CH_2-C=C*H*-CH), 4.17 (t, 2H, -SO_2-O-CH_2-), 2.79 (t, 2H, -CH_2-CH_2-Ar), 2.40 (s, 3H, -Ar-CH_3), 1.47 (s, 9H, (-CH_3)$_3$).

***tert*-butyl (4-(2-azidoethyl)phenyl)carbamate (4).** NaN_3 (0.6 g, 8.2 mmol) was added into a solution of compound **3** (1.5 g, 3.83 mmol**)** in 20 mL of DMF. The reaction mixture was purged with N_2, stirred at 60°C for 36 h, and then cooled to room temperature. The reaction mixture with diluted with a large amount of water and extracted with extracted with EtOAc. The organic layer was washed with water, dried over $NaSO_4$, and evaporated under vacuum to afford **4** as an off-white solid (0.90 g, 90%).
^{1}H NMR (500 MHz, CD_3OD) δ: 7.33 (d, 2H, -CH_2-C=CH-C*H*), 7.16 (d, 2H, -CH_2-C=C*H*-CH), 3.47 (t, 2H, -CH_2-C*H*$_2$-Ar), 2.82 (t, 2H, N_3-C*H*$_2$-CH_2-Ar), 1.52 (s, 9H, (-CH_3)$_3$).

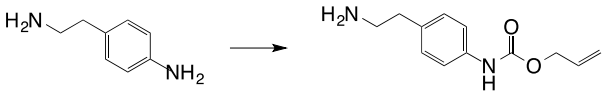
4-(2-azidoethyl)aniline (5). Compound **4** (0.9 g, 3.50 mmol) was subjected to 20% of TFA in DCM (v/v, 20 mL) at room temperature for 30 min. After concentrated under reduced vacuum, the mixture was dissolved in water, treated with saturated $NaHCO_3$ to adjust pH to 8, subsequently extracted with EtOAc three times. The organic layers were combined, washed with DI water three times, dried over Na_2SO_4, filtered, and evaporated to dryness to yield **5** as a yellow oil (0.45 g, 79%).
^{1}H NMR (500 MHz, CD_3CN) δ: 6.99 (d, 2H, -CH_2-C=C*H*-CH), 6.70 (d, 2H, -CH_2-C=CH-C*H*), 3.47 (t, 2H, -CH_2-C*H*$_2$-Ar), 2.82 (t, 2H, N_3-C*H*$_2$-CH_2-Ar).

2-(trimethylsilyl)ethyl (4-(2-azidoethyl)phenyl)carbamate (6). *N*-[2-(trimethylsilyl) ethoxycarbonyloxy] succinimide (0.84 g, 3.24 mmol) was added into a solution of compound **5** (0.50 g, 3.08 mmol) in 30 mL DMF. The reaction mixture was stirred at 60°C overnight, then cooled to room temperature and concentrated by reduced vacuum. The crude product was purified by silica gel column chromatography using 3:1 HEX/EtOAc (v/v) to yield **6** as a white crystalline solid (0.95 g, 96%).
^{1}H NMR (500 MHz, CD_3CN) δ: 7.61 (s, 1H, -N*H*-COO-), 7.37 (d, 2H, -CH_2-C=CH-C*H*), 7.17 (d, 2H, -CH_2-C=C*H*-CH), 4.21 (t, 2H, -O-C*H*$_2$-CH_2-Si-), 3.48 (t, 2H, -CH_2-C*H*$_2$-Ar), 2.82 (t, 2H, N_3-C*H*$_2$-CH_2-Ar), 1.03 (t, 2H, -O-CH_2-C*H*$_2$-Si-), 0.05 (s, 9H, -Si-(C*H*$_3$)$_3$).

4-(2-aminoethyl)-N-(2-(trimethylsilyl)ethoxycarbonyloxy)phenylamine (7). Triphenylphosphine (0.89 g, 3.42 mmol) was added into a solution of compound **6** (0.95 g, 3.11 mmol) in 20 mL THF. The reaction mixture was stirred at room temperature overnight under N_2.The reaction mixture was quenched with 28 mL water, allowed to stir for another day, and concentrated to yield viscous oil. The oil was further purified on a silica gel column, initially flushed with EtOAc and subsequently eluted with a 9/1 to 8/2 chloroform/methanol (v/v) gradient. The fractions were combined and evaporated to yield **7** as an off-white solid (0.62, 71%).

^{1}H NMR (500 MHz, CD_3CN) δ: 7.94 (s, 1H, -N*H*-COO-), 7.33 (d, 2H, -CH_2-C=CH-C*H*), 7.09 (d, 2H, -CH_2-C=C*H*-CH), 4.17 (t, 2H, -O-CH_2-CH_2-Si-), 2.78 (t, 2H, NH_2-CH_2-CH_2-Ar), 2.61 (t, 2H, NH_2-CH_2-CH_2-Ar), 1.00 (t, 2H, -O-CH_2-CH_2-Si-), 0.01 (s, 9H, -Si-(CH_3)$_3$).
MS (ESI+): calcd for $C_{14}H_{24}N_2O_2Si$: $[M+H]^+$ = 281.1680 $[M+Na]^+$ = 303.1499, found: *m*/*z* = 281.1728, $[M+H]^+$, *m*/*z* = 303.1510 $[M+Na]^+$.

Synthesis of 4-(2-aminoethyl)-N-(allylcarbonyloxy)phenylamine



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Scheme **S3**. Synthesis of 4-(2-aminoethyl)-N-(allylcarbonyloxy)phenylamine. Conditions: allyl chloroformate, 10% aq. acetic acid, 1,4-dioxane, r.t. overnight.

Allyl chloroformate (4.9 g, 40.4 mmol) in 150 mL 1,4-dioxane was added into to a solution of 4-(2-aminoethyl)aniline (5 g, 36.7 mmol) in 150 mL 10% aq. acetic acid. The reaction mixture was stirred at room temperature overnight and then diluted with 500 mL deionized (DI) water and washed with Et_2O (300 mL) three times. The aqueous phase was adjusted to pH 14 by addition of 2 M NaOH (aq) and was extracted with Et_2O (150 mL) three times. The combined organic layer was washed with DI water three times, dried over Na_2SO_4, filtered, and evaporated to dryness to yield **1** as a light yellow solid (5.6 g, 69%).

^{1}H NMR (500 MHz, CD_3OD) δ: 7.36 (d, 2H, Ar), 7.15 (d, 2H, Ar), 5.95-6.04 (m, 1H, -C*H*=CH_2), 5.39 (d, 1H, -CH=C*H*H), 5.34 (d, 1H, -CH=CH*H*), 4.63 (d, 2H, -CH_2-CH=CH_2), 2.82-2.86 (m, 2H, -CH_2-NH_2), 2.70 (t, 2H, -CH_2-Ar).

^{13}C NMR (125 MHz, CD_3OD) δ: 154.85, 137.00, 134.98, 133.51, 129.36, 119.41, 116.92, 65.62, 59.89, 43.47, 38.72.

MS (ESI+): calcd for $C_{12}H_{16}N_2O_2$: $[M+H]^+$ = 221.1285 $[M+Na]^+$ = 243.1104, found: *m*/*z* = 221.1286, $[M+H]^+$, *m*/*z* = 243.1101 $[M+Na]^+$.

Solid-phase synthesis of oligo(peptoid)s

The synthesis of oligo(peptoid) NPPOC-Am_**3** was performed on 222 mg of Rink amide resin (0.1 mmol scale, 100-200 mesh, 1% DVB, ChemPrep Inc.), whereas oligo(peptoid)s Teoc-Am_**4**, ActAl_**4**, ActAl_**2**-Am_**2** and ActAl_**4**-Am_**4** were synthesized on Fmoc-Photolabile SS (0.1 mmol scale, 100-200 mesh, 1% DVB, Advanced ChemTech). All solid-phase peptoid syntheses were performed using an automated microwave peptide synthesizer (Liberty Blue, CEM Corporation). Three primary amine

monomers, 4-(1,3-dioxacyclopent-2-yl)benzylamine, 2-(2-ethoxyethoxy)ethylamine (E^3A), and 2-(2-(2-methoxyethoxy)ethoxy)ethyl amine (ME^3A) were synthesized according to a published approach.[1] 4-(2-aminoethyl)-N-(2-(2-nitrophenyl)propylcarbonyloxy)phenylamine (**1**), 4-(2-aminoethyl)-N-(2-(trimethylsilyl)ethoxycarbonyloxy) phenylamine (**7**), and 4-(2-aminoethyl)-N-(allylcarbonyloxy)phenylamine (**8**) were synthesized as described above. All other monomers, reagents, and solvents were purchased from commercial sources and directly used without further purification. Oligo(peptoid)s were synthesized according to a published submonomer approach to solid-phase peptoid synthesis.[1] The resin was swelled for 5 min at room temperature and subsequently deprotected with 20% 4-methylpiperidine in DMF (v/v) for 30 s at 75°C and 90 s at 90°C, followed by bromoacetylation for 5 min at 75°C with simultaneous addition of 1.5 mL of 1.0 M bromoacetic acid in DMF and 1.5 mL of 1.0 M DIC in DMF. Halide displacement was then carried out by adding 2.5 mL of 0.5 M primary amine monomer in NMP followed by an incubation of 5 min at 75°C. These bromoacetylation and displacement reactions were alternated until the desired peptoid sequence was achieved. All synthesized oligo(peptoid)s were acetylated by treatment with acetic anhydride to cap the secondary amine end groups.

TFA cleavage from the resin

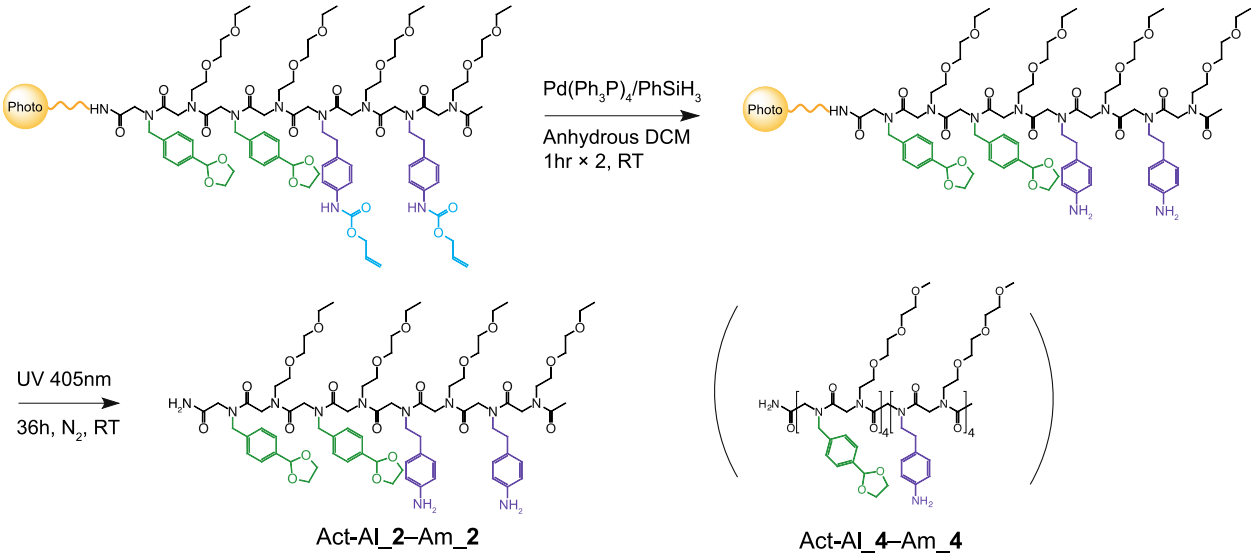
The TFA cleavage procedure was followed by a published approach.[2] Resin I was transferred to a 25 mL solid-phase peptide synthesis vessel (CG-1866, Chemglass), rinsed with DCM three times, and further treated with 4 mL of TFA cleavage cocktail (95% TFA in DCM) for 10 min while bubbling with nitrogen at room temperature. The TFA cleavage solution was collected by filtering through the fritted glass into a 25 mL round bottom flask. The remaining resin was further rinsed twice with 2 mL of fresh TFA cleavage cocktail to collect any residual oligo(peptoid). The cleavage solution was combined and evaporated by blowing a gentle stream of nitrogen to yield crude oligo(peptoid) NPPOC-Am_**3**, the structure of which is shown in Figure S1(b). The crude product was reconstituted in HPLC grade 50% MeCN/water (v/v) and further purified by preparative HPLC.

Photo-cleavage from the resin

The resultant resins were suspended in 10 mL DMF in 20 mL glass vial respectively and, after purging with nitrogen for 1 min, the vial capped and the suspension stirred while under irradiation at approximately 25 $mW.cm^{-2}$ with 405 nm for 36 h. The DMF cleavage solution was collected by filtering the suspension through a glass frit and were pooled and evaporated to dryness under vacuum to yield

crude oligo(peptoid)s ActAl_**2**–Boc-Am_**2**, Teoc-Am_**4**, and ActAl_**4** as light yellow oils. Each crude product was reconstituted in 50% HPLC grade MeCN/H_2O and further purified by preparative RP-HPLC.

Alloc deprotection and photo-cleavage



Scheme **S4.** Synthetic procedure for oligo(peptoid)s Act-Al_**2**–Am_**2** and Act-Al_**4**–Am_**4**.

The method to remove Alloc protecting groups was adapted from a published approach.[3] Resin (0.1 mmol, 0.75 mmol/g) was suspended in dry DCM (0.4 mL) and subjected to Alloc deprotection by treatment with phenylsilane ($PhSiH_3$, 0.62mL, 5 mmol, 25 eq. per Alloc group) and tetrakis(triphenylphosphine) palladium(0) [$Pd(PPH_3)_4$, 23.1 mg, 0.02 mmol, 0.1 eq. per Alloc group] at room temperature for 1 h. Reagents and solvent were removed by filtration under reduced pressure, the resin was washed with dry DCM, and the deprotection procedure was repeated twice. The resin was finally washed with DCM and MeOH, dried and further subjected to photo-cleavage *via* the aforementioned approach to yield oligo(peptoid) Act-Al_**2**–Am_**2**. Oligo(peptoid) Act-Al_**4**–Am_**4** was prepared using the same approach. The crude product was reconstituted in 20% ~ 30% HPLC grade MeCN/H_2O and further purified by preparative RP-HPLC.

Purification of Oligo(peptoid)s by Preparative RP-HPLC

All oligo(peptoid)s were purified by preparative RP-HPLC using a linear gradient of H_2O (A) and MeCN (B) at a flow rate of 10 mL/min. The purified fractions were combined, concentrated, reconstituted in

50% MeCN/H_2O (v/v), frozen with liquid nitrogen, and lyophilized to afford fluffy white powder. The purity of the collected oligo(peptoid)s was examined by analytical RP-HPLC.

Preparative HPLC method:

1) Act-Al_**2**–Boc-Am_**2**: (a) 30%, 0.1 – 4.1 min; (b) 30% – 85%, 4.1 min – 22.5 min; (c) 85% – 30%, 22.5 min – 24.5 min.
2) NPPOC-Am_**3**: (a) 50%, 0.1 – 4.1 min; (b) 50% – 90%, 4.1 – 30.1 min; (c) 90% – 50%, 30.1 – 32.1 min.
3) Teoc-Am_**4**: (a) 75%, 0.1 – 2.1 min; (b) 75% – 95%, 2.1 min – 18.1 min: (c) 95%, 18.1 min – 26.1 min; (d) 95% – 75%, 26.1 min – 28.1 min.
4) Act-Al_**4**: (a) 30% B, 0.1 – 4.1 min; (b) 30% – 75% B, 4.1 – 26.1 min; (c) 75% – 30% B, 26.1 – 28.1 min.
5) ActAl_**2**–Am_**2**: (a) 30% B, 0.1 – 4.1 min; (b) 30% – 70% B, 4.1 – 24.1 min; (c) 70% – 30% B, 24.1 – 26.1 min.
6) ActAl_**4**–Am_**4**: (a) 30%, 0.1 – 4.1 min; (b) 30% – 80%, 4.1 min – 33.1 min; (c) 80% – 30%, 33.1 min – 35.1 min.

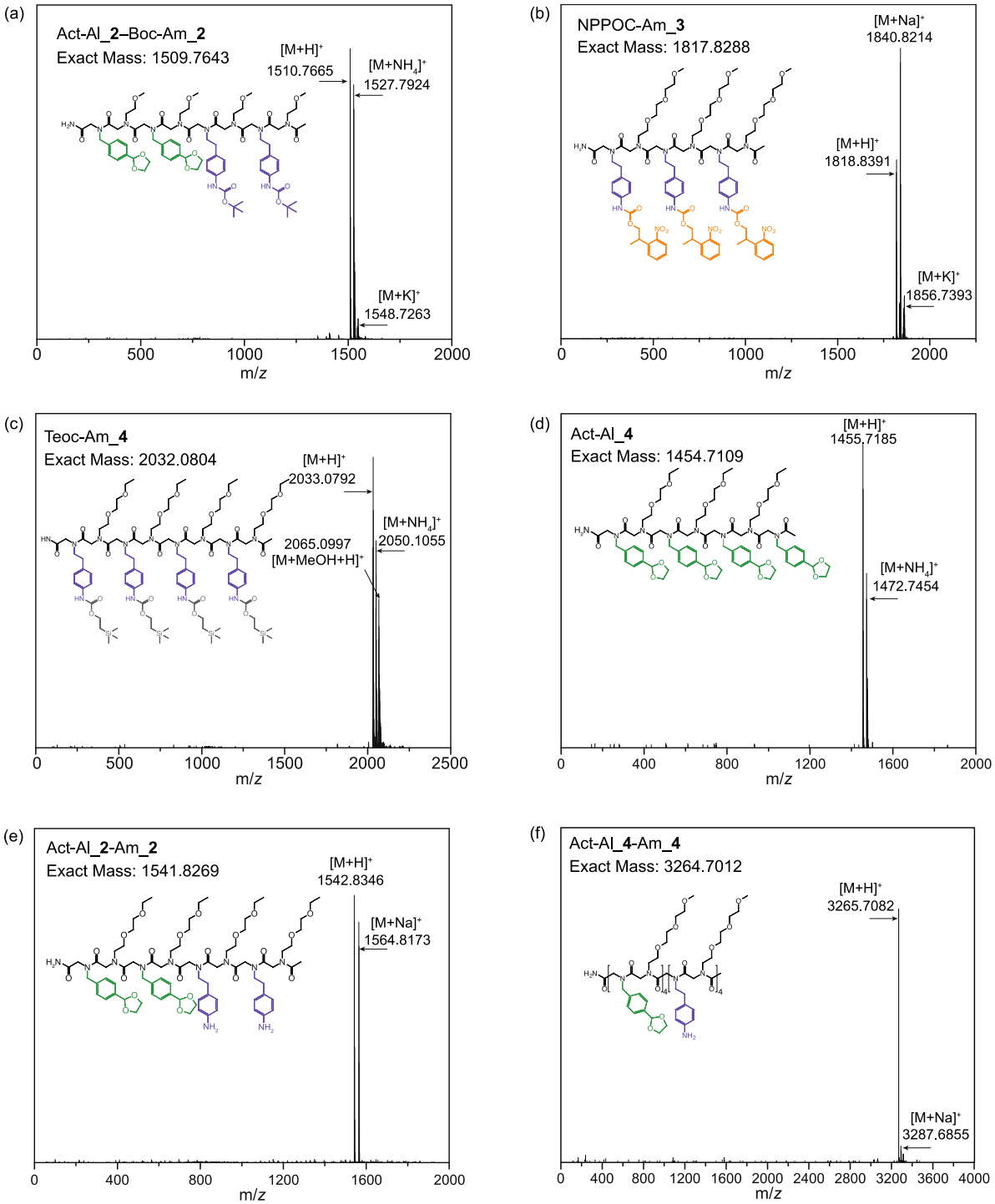


Fig. **S1.** ESI spectra of oligo(peptoid)s purified by preparative HPLC. (a) Act-Al_**2**–Boc-Am_**2**: expected $[M+H]^+$ = 1510.7716, $[M+NH_4]^+$ = 1527.7981, $[M+K]^+$ = 1548.7274, purity: 99.2%; (b) NPPOC-Am_**3**: expected $[M+H]^+$ = 1818.8361, $[M+Na]^+$ = 1840.8180, $[M+K]^+$ = 1856.7920, purity: 99.0%; (c) Teoc-Am_**4**: expected $[M+H]^+$ = 2033.0877, $[M+NH_4]^+$ = 2050.1142, $[M+MeOH+H]^+$ = 2065.1139, purity: 99.3%; (d) Act-Al_**4**: expected $[M+H]^+$ = 1455.7182, $[M+NH_4]^+$ = 1472.7447, purity: 98.5%; (e) Act-Al_**2**–Am_**2**: expected $[M+H]^+$ = 1542.8342, $[M+Na]^+$ = 1564.8161, purity: 99.0%; (f) Act-Al_**4**–Am_**4**: expected $[M+H]^+$ = 3265.7085, $[M+Na]^+$ = 3287.6904, purity: 98.9%.

Deprotection of amine protecting groups

(a) NPPOC protecting group

1 µmol of the oligo(peptoid) NPPOC-Am_**3** (10 mM stock solution in MeCN) was mixed in a solution of 10 mM pyrene (a photosensitizer) in DMAC/EtOH/dioxane (v/v/v: 1:1:1) and purged with nitrogen. This reaction mixture was stirred under 365 nm UV irradiation at 10.8 mW.cm^{-2} for 5 hours. Aliquots were taken and subjected to LCMS analysis. As indicated by ESI spectra, deprotection of the NPPOC-Am_**3** oligomer by UV irradiation did not proceed to completion, even after extended periods and in the presence of photosensitizers, as partially- and fully-protected oligomers were still observed in mass spectra of the reaction mixtures.

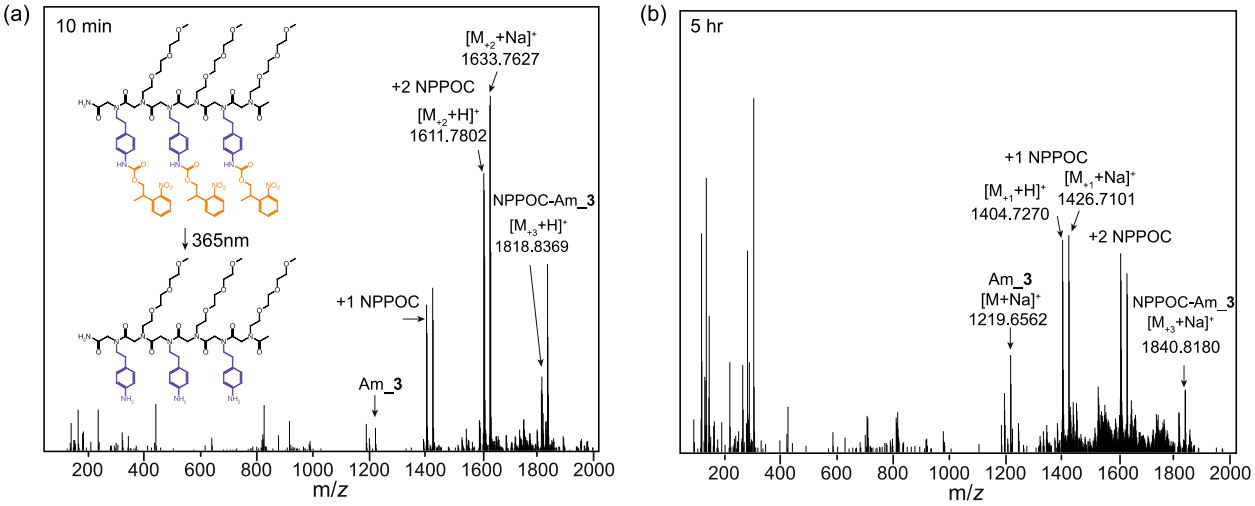


Fig. **S2**. Photodeprotection of NPPOC. ESI spectra of NPPOC-Am_**3** irradiated at 365 nm in the presence of pyrene for (a) 10 min and (b) 5 hour. Am_**3** denotes the fully-deprotected oligo(peptoid), whereas +1 and +2 NPPOC indicate partially-deprotected oligo(peptoid)s with one or two NPPOC protecting groups remaining. Expected exact mass: Am_3 $[M_{Am\_3}+Na]^+$ = 1219.6585; +1 NPPOC: $[M_{+1}+H]^+$ = 1404.7297, $[M_{+1}+Na]^+$ = 1426.7116; +2 NPPOC: $[M_{+2}+H]^+$ = 1611.7829, $[M_{+2}+Na]^+$ = 1633.7648.

(b) Teoc protecting group

(1) Er(III)-mediated deprotection

0.2 µmol of oligo(peptoid) Teoc-Am_**4** (10 mM stock solution in MeCN) was treated with 5 equivalents of erbium (III) triflate in chloroform saturated with water at room temperature overnight and the reaction mixture was directly subjected to ESI analysis. As suggested by ESI, deprotection of Teoc-Am_**4** by Er(III) did not approach completion as partially-deprotected oligomers were detected in mass spectra of the reaction mixtures.

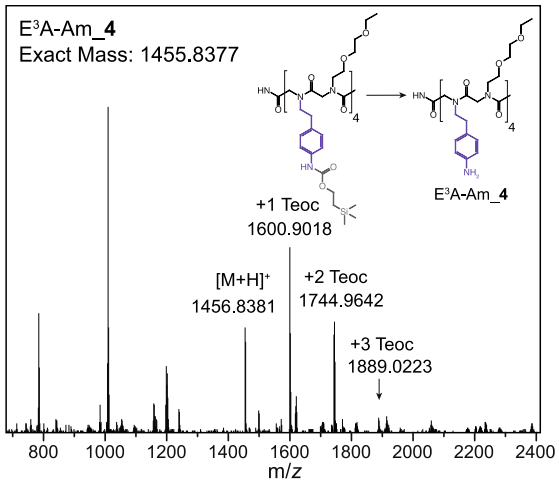


Fig. **S3**. Erbium(III)-mediated deprotection of Teoc. E^3A-Am_**4** denotes the fully-deprotected oligo(peptoid), whereas +1, +2 and +3 Teoc indicate partially-deprotected oligo(peptoid)s with one, two and three Teoc protecting groups remaining. Expected exact mass: E^3A-Am_**4** $[M_{E3A\text{-}Am\_4}+H]^+$ = 1455.8387; +1 Teoc $[M_{+1}+H]^+$ = 1600.9057; +2 Teoc $[M_{+2}+H]^+$ = 1744.9664; +3 Teoc $[M_{+3}+Na]^+$ = 1889.0270.

(2) TBAF deprotection

0.5 μmol of the oligo(peptoid) Teoc-Am_**4** (10 mM stock solution in MeCN) was treated with 7 eq. of 1M TBAF in THF overnight and the reaction mixture was further subjected to both ESI and analytical HPLC analysis.

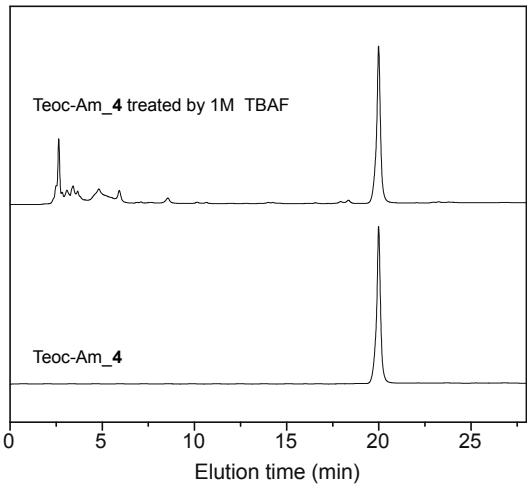


Fig. **S4**. Analytical HPLC traces of oligo(peptoid) Teoc-Am_4 before and after treatment with 1 M TBAF. The elution time of both traces is 19.846 min, suggesting that F^--mediated Teoc deprotection did not proceed under the applied reaction conditions.

(c) Alloc protecting group: The deprotection of Alloc groups was carried out by the aforementioned procedure using oligo(peptoid) Alloc-Am_**4**.

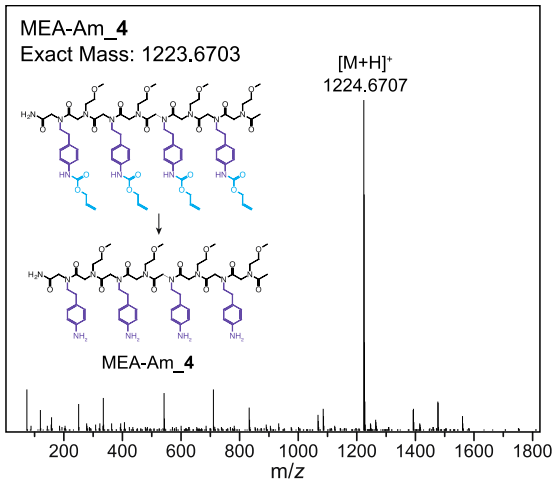


Fig. **S5**. Deprotection of Alloc by Pd(0) in the presence of phenylsilane. MEA-Am_**4** denotes the fully-deprotected oligo(peptoid). Expected exact mass: MEA-Am_**4** $[M_{Am\_4}+H]^+$ = 1455.8387; +1 Teoc $[M_{+1}+H]^+$ = 1600.9057; +2 Teoc $[M_{+2}+H]^+$ = 1744.9664; +3 Teoc $[M_{+3}+Na]^+$ = 1889.0270.

Deprotection of acetal group by Lewis acids

0.2 μmol of oligo(peptoid) Act-Al_**4** (10 mM in MeCN) was treated with 5 equivalents of either $Er(OTf)_3$ or $Sc(OTf)_3$ in chloroform saturated with water at room temperature overnight and the reaction mixture was directly subjected to MALDI analysis.

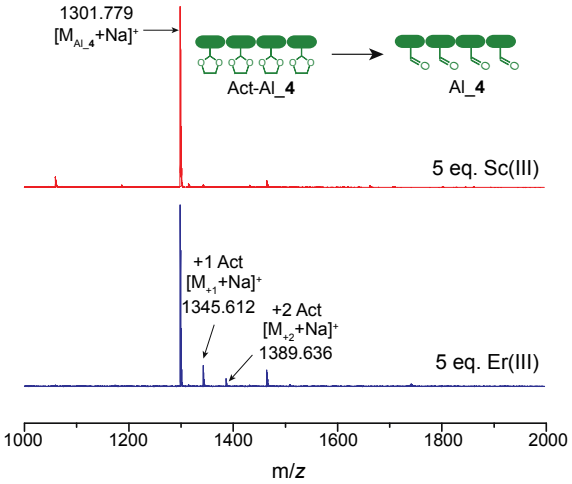


Fig. **S6**. Deprotection of acetal group by Lewis acids. Oligo(peptoid) Act-Al_**4** bearing ethylene acetal-protected aldehydes was treated with 5 eq. $Er(OTf)_3$ or 5 eq. $Sc(OTf)_3$ to yield Al_**4**. +1 and +2 Act denote partially-deprotected oligo(peptoid)s with one or two acetal groups remaining. Expected exact mass: Al_**4** $[M_{Act\text{-}Al\_4}+Na]^+$ = 1301.441 g/mol; +1 Act $[M_{+1}+Na]^+$ = 1345.621 g/mol; +2 Act $[M_{+2}+Na]^+$ = 1389.648 g/mol.

Optimization of acetal deprotection by Sc(III)

(a) Influence of solvent on conversion

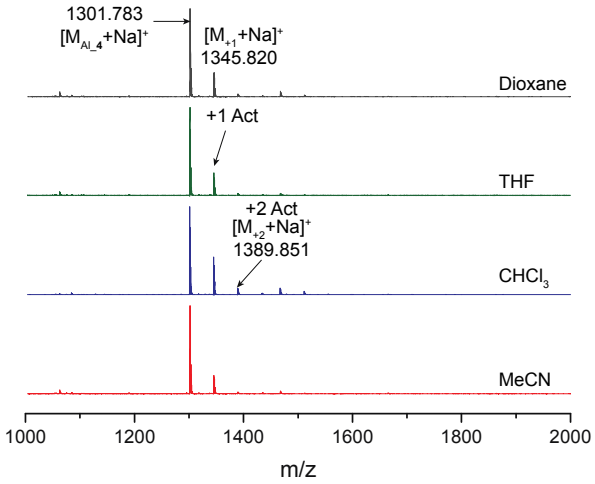


Fig. **S7**. Influence of solvent on acetal deprotection by Sc(III). Oligo(peptoid) Act-Al_**4** bearing ethylene acetal-protected aldehydes was treated with 0.2 eq. Sc(III) at 50°C in different solvents overnight and the reaction mixture was directly subjected to MALDI analysis.

Table **S1**. Yields of acetal deprotection by 0.2 eq. Sc(III) at 50°C in different solvents.

Solvent	MeCN	$CHCl_3$	THF	Dioxane
Yield of fully-deprotected oligomer (%)	81.4	64.6	75.1	75.6

(b) Influence of water content on conversion

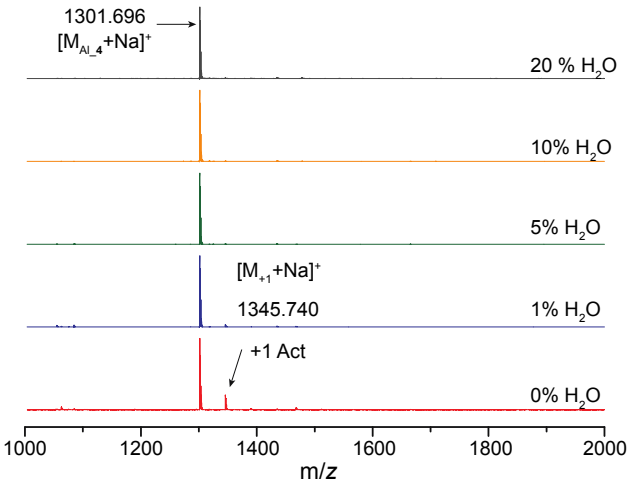


Fig. **S8**. Influence of water content on acetal deprotection at 50°C. Oligo(peptoid) Act-Al_**4** bearing ethylene acetal-protected aldehydes was treated with 0.2 eq. Sc(III) at 50°C overnight in a mixture of water/MeCN. The volume percentage of water in MeCN was varied from 0% to 20%. The reaction mixture was directly subjected to MALDI analysis.

Table **S2**. Yields of acetal deprotection by 0.2 eq. Sc(III) at 50°C with different water contents.

Amount of H_2O in MeCN (v/v%)	0	1	5	10	20
Yield of fully-deprotected oligomer (%)	81.4	97.3	99.2	99.5	99.3

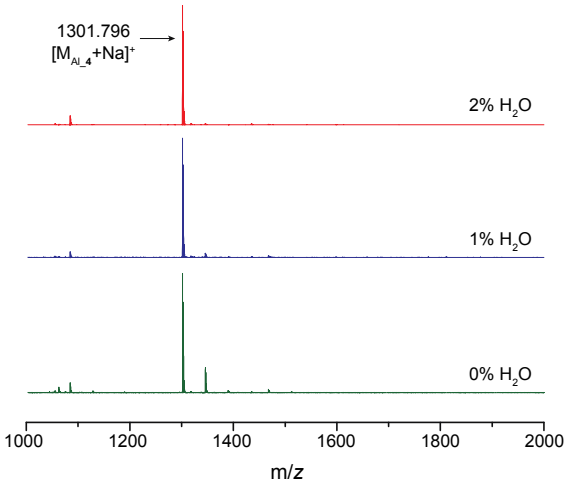


Fig. **S9**. Influence of water content on acetal deprotection at 70°C. Oligo(peptoid) Act-Al_**4** bearing ethylene acetal-protected aldehydes was treated with 0.2 eq. Sc(III) at 70°C overnight in a mixture of water/MeCN. The volume percentage of water in MeCN was varied from 0% to 20%. The reaction mixture was directly subjected to MALDI analysis.

Table **S3**. Yields of acetal deprotection by 0.2 eq. Sc(III) at 70°C with different water contents.

Amount of H_2O (v/v%)	0	1	2
Yield of fully-deprotected oligomer (%)	81.0	97.4	99.0

(c) Effect of Sc(III) concentration on conversion

Table **S4**. Yields of acetal deprotection in 2 v/v% water/MeCN at 50°C with different equivalents of Sc(III).

Sc(III) equivalents	0.05	0.10	0.15	0.20
Yield of fully-deprotected oligomer (%)	–	8.1	98.0	99.2

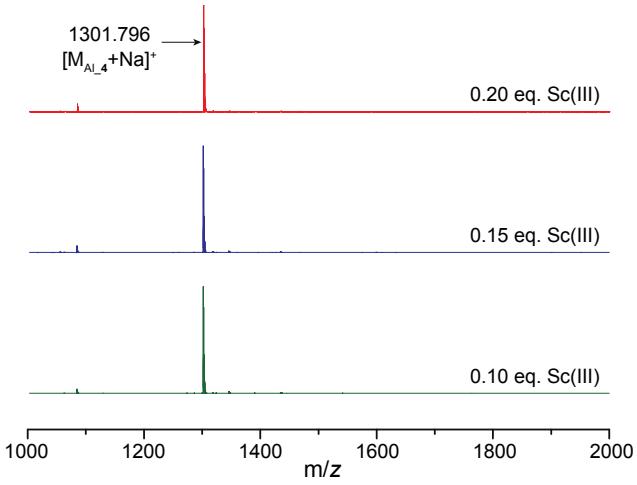


Fig. **S10**. Effect of Sc(III) on acetal deprotection at 70°C. Oligo(peptoid) Act-Al_**4** bearing acetal-protected aldehydes was treated with 0.10 – 0.20 equivalents Sc(III) in 2 v/v% water/MeCN at 70°C overnight. The reaction mixture was directly subjected to MALDI analysis.

Table **S5**. Yields of acetal deprotection in 2 v/v% water/MeCN at 70°C with different equivalents of Sc(III).

Sc(III) equivalents	0.10	0.15	0.20
Yield of fully-deprotected oligomer (%)	98.1	98.4	99.0

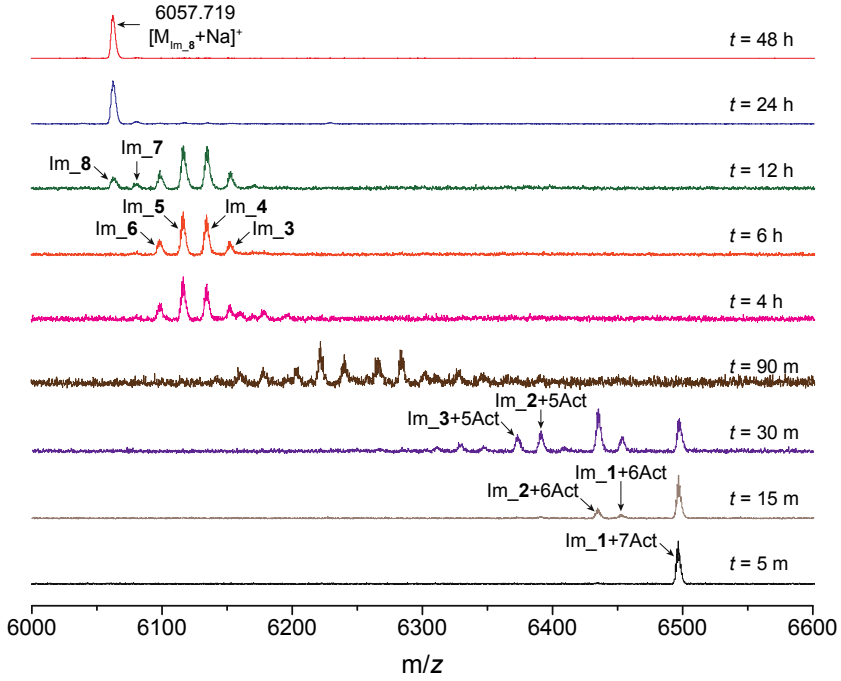


Fig. **S11**. Kinetics of *in situ* deprotection and molecular ladder formation for Act-Al_**4**–Am-**4**, treated with 0.20 equivalents Sc(III) in 2 v/v% water/MeCN at 70°C. MALDI mass spectra of the crude reaction mixture are shown at increasing time intervals. Im_**8** (expected exact mass: $[M_{Im\_8}+Na]^+$ = 6056.097 g/mol) is the desired in-registry molecular ladder. Im_**7**, Im_**6**, Im_**5**, Im_**4**, and Im_**3** are out-of-registry, fully deprotected ladders bearing seven, six, five, four, and three imine groups, respectively. Im_**3**+5Act, Im_**2**+5Act, Im_**2**+6Act, Im_**1**+6Act, and Im_**1**+7Act are out-of-registry, partially deprotected ladders bearing three imine/five acetal, two imine/five acetal, two imine/six acetal, one imine/six acetal, and one imine/seven ethylene acetal groups, respectively.

References

1. T. Wei, J. H. Jung and T. F. Scott, *J. Am. Chem. Soc.*, 2015, **137**, 16196-16202.
2. T. Wei, J. C. Furgal, J. H. Jung and T. F. Scott, *Polym. Chem.*, 2017, **8**, 520-527.
3. D. Verzele, S. Figaroli and A. Madder, *Molecules*, 2011, **16**, 10168-10186.