Supporting Information

On-DNA Hydroalkylation to Introduce Diverse Bicyclo[1.1.1]pentanes and Abundant Alkyls via Halogen Atom Transfer

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1. General Considerations

1.1 General: All chemical transformations requiring inert atmospheric conditions were carried out using Schlenk line techniques with a 4- or 5-port dual-bank manifold. For blue light irradiation, one Kessil H150-Blue lamp (19 V DC 40 W Max) was placed 1.5 inches away from PCR tubes. NMR spectra (^{1}H, ^{13}C, ^{19}F) were obtained at 298 K using 400, 500 or 600 MHz spectrometers. ^{1}H NMR spectra were referenced to residual $CHCl_3$ (δ 7.26 ppm) in $CDCl_3$. ^{13}C NMR spectra were referenced to $CDCl_3$ (δ 77.16 ppm). Reactions were monitored by LC/MS, GC/MS, ^{1}H NMR, and/or TLC on silica gel plates (60 Å porosity, 250 µm thickness). TLC analysis was performed using hexanes/EtOAc as the eluent and visualized with UV light. Flash chromatography was accomplished using an automated system (CombiFlash®, UV detector, λ = 254 nm and 280 nm) with RediSep® R_f silica gel disposable flash columns (60 Å porosity, 40–60 µm) or RediSep R_f Gold® silica gel disposable flash columns (60 Å porosity, 20–40 µm). Accurate mass measurement analyses were conducted using electron ionization (EI) or electrospray ionization (ESI). The signals were mass measured against an internal lock mass reference of perfluorotributylamine (PFTBA) for EI-GCMS, and leucine enkephalin for ESI-LC/MS. The utilized software calibrates the instruments and reports measurements by use of neutral atomic masses. The mass of the electron is not included. IR spectra were recorded on an FT-IR using either neat oil or solid products. Solvents were purified with drying cartridges through a solvent delivery system. Melting points (°C) are uncorrected. 10 W blue LED irradiation for preparation of BCP-I was accomplished *via* the LED reactor described in a previous report.[1] The set up for on-DNA reaction was described in a previous report.[2]

1.2 Chemicals: Deuterated NMR solvents were purchased and stored over 4Å molecular sieves. CH_2Cl_2, DMA, EtOAc, hexanes, MeCN, DMSO, DIPEA, Et_3N and HATU (*N*-[(dimethylamino)-1*H*-1,2,3-triazolo-[4,5-*b*]pyridin-1-ylmethylene]-*N*-methylmethanaminium hexafluorophosphate *N*-oxide) were purchased from commercial suppliers and used without further purification. The synthesis of all new alkyl halides and iodobicyclo[1.1.1]pentane (BCP) derivatives and new on-DNA substrates is outlined here. Additional alkyl halides, carboxylic acids, or alcohols were purchased from commercial suppliers. 4CzIPN, $Ru(bpy)_3(PF_6)_2$ and $Ir(ppy)_3$ catalysts were prepared according to reported literature.[3] All other reagents were purchased commercially and used as received. Photoredox-catalyzed reactions were performed using PCR 8-strip tubes (Ref. Fisher 781320) with PCR strips of 8 caps (Ref. Fisher 781340). HyPure™ Molecular Biology Grade Water was purchased and used as received without further manipulation.

1.3 Analysis of on-DNA reactions: Analysis of on-DNA reactions was performed by LC/MS: After reaction completion, an aliquot of the reaction mixture was diluted with H_2O to approximately 0.05–0.13 mM. At this point, 6 - 8 µL aliquots of the LC/MS sample was injected onto a reverse-phase chromatography column (Clarity 2.6 µm Oligo-MS 100 Å 2.1x50 mm) and eluted (10-90% B over 4 min at 0.5 mL/min flow rate; Solvent A: 0.75% v/v/ HFIP / 0.038% Et_3N in H_2O; Solvent B: 0.75% HFIP, 0.038% Et_3N in 90/10 MeOH/deionized H_2O) with no UV monitoring. Effluent was analyzed on a Waters SQ Detector 2 ACQUITY UPLC System in Thermo Exactive Plus LC-esiMS with a Vanquish UHPLC. For the functionalized headpiece samples, % conversion was determined based on reported peak intensities following deconvolution (between 3,000-8,000 Da) of the DNA charge states using Intact Mass™ by Protein Metrics Inc. (version 3.7-32x64). For the photoredox scope reactions, %

[1] Molander, G. A. *et al. Org. Lett.* **2016**, *18*, 764 − 767
[2] Molander, G. A. *et al. J. Am. Chem. Soc.,* **2019**, *141*, 3723 − 3732
[3] Kelly C. B. *et al. Org. Synth.* **2019**, *96*, 455 − 473 ; Weaver J. D *et al. Org. Synth.* **2018**, *95*, 29 − 45

conversion was determined using Intact Mass™ by Protein Metrics Inc. (version 3.7-32x64). Data was scanned between 1.0 - 2.4 min and deconvoluted between 3,000-8,000 Da, with a mass tolerance window of 3 - 4 Da, with 10% of base peak threshold set for reporting. Na, K, NH_4, Cu, Ni and HFIP adducts were included in the product percentage. Detailed parameters can be found later in the Supporting Information.

1.4 Materials for on-DNA synthesis: DNA headpiece HP (5'-/Phos/GAGTCA/iSp9-PEG/iAm C7_CO-PEG4-NH2/iSp9-PEG/TGACTCCC-3') was obtained from WuXi AppTec, Shanghai, China.

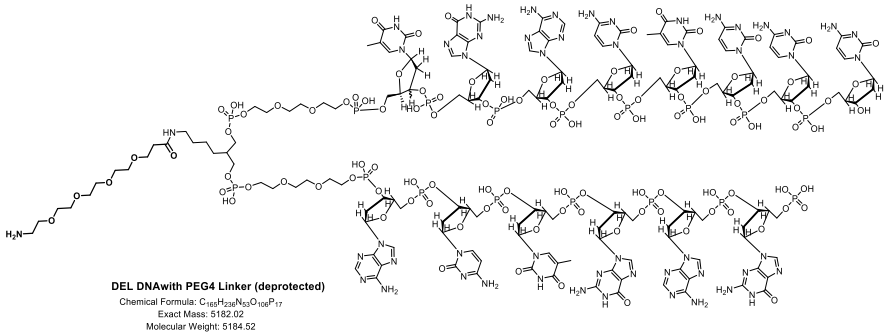
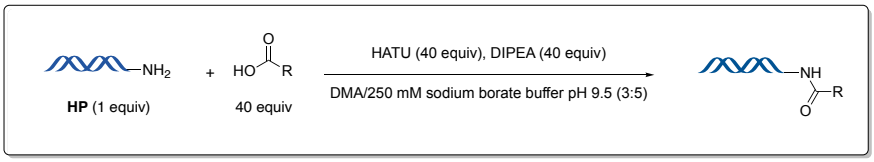


Figure S1. Sequence and structure of the DNA-headpiece (molecular weight = 5184.5220).

2. Preparation of on-DNA Substrates

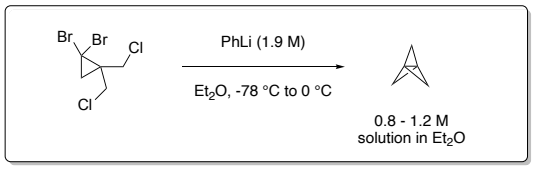


2.1 HATU premix protocol for acylation of DNA headpieces: The HATU (200 mM in DMA, 40.0 equiv), DIPEA (200 mM in DMA, 40.0 equiv), and the corresponding carboxylic acid (200 mM in DMA, 40.0 equiv) solutions were individually cooled at 4 °C for 5 min. Once chilled, the acid, DIPEA, and HATU solutions were added sequentially to a centrifuge tube, vortexed briefly, and allowed to react at 4 °C for 20 min. The oligomer solution (1 mM in 250 mM pH 9.4 sodium borate buffer) was then added, and the mixture was vortexed. The reaction was allowed to proceed at rt and monitored by LC/MS. Upon completion, the reaction was worked up following the EtOH precipitation protocol below.

2.2 EtOH precipitation protocol: The reaction mixture was transferred to a centrifuge tube where it filled at most 1/4 of the total volume. A volume of 5 M aq NaCl equal to 1/10 of the reaction volume was then added, followed by cold (–20 °C) EtOH equal to 2.5 reaction volumes. The resulting mixture was then left to stand in a –20 °C freezer for at least 1 h or overnight. The chilled mixture was then centrifuged for 30 min at 4 °C at 4,000 rpm. The supernatant was then decanted and allowed to dry under reduced pressure. The resulting pellet was re-dissolved in H_2O to give a theoretical concentration of 2 mM. Purity was assessed by LC/MS. For long term storage, solutions were frozen in liquid nitrogen and lyophilized to dryness to give a white solid.

3. Synthesis of Alkyl Halides and BCP-Halides

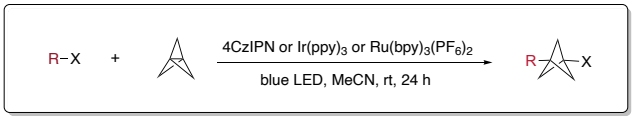
Procedure for preparation of tricyclo[1.1.1]pentane



The procedure was adapted from the report of the Baran group.[4] To an appropriately-sized round bottom flask was added 1,1-dibromo-2,2-bis(chloromethyl)cyclopropane (5.0 g, 16.8 mmol) and Et_2O (10 - 12 mL) under inert atmosphere. Once dissolved, the reaction was cooled to –78 °C in a Dry Ice-acetone bath. The reaction turned into a slurry at –78 °C. To the light brown slurry was added PhLi (20 mL, 38.0 mmol, 2.3 equiv, 1.9 M soln in *n*-Bu_2O) dropwise over 10 to 15 min. The reaction was then stirred at –78 °C for another 30 min and then was allowed to warm to 0 °C using an ice-water bath. After 2 h, the reaction turned into a dark-brown slurry, which indicates the reaction is finished. The product propellane is co-distilled with Et_2O by house vacuum (ca. 4 Torr) as a clear, colorless solution. The receiving flask was submerged in a –78 °C bath or liquid nitrogen bath.

Note: *Concentration was determined by ^1H NMR using 1,3,5-trimethoxybenzene as internal standard. The tricyclo[1.1.1]pentane solution was kept in the freezer.*

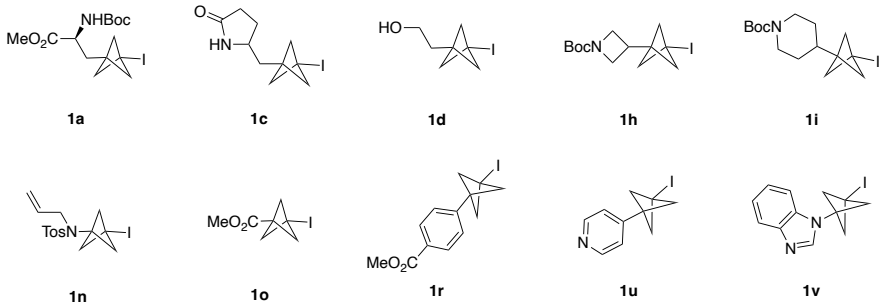
General procedure for preparation of BCP halides



Preparation of BCP halides were adapted from reported literature[5]: To a screw-capped vial equipped with a stirrer bar was added *fac*-$Ir(ppy)_3$/4CzIPN/$Ru(bpy)_3(PF_6)_2$ (0.01 – 0.025 equiv), the specified halide (1.0 equiv), if solid. The reaction vial was evacuated and back-filled with nitrogen three times. MeCN (0.1 M) and tricyclo[1.1.1]pentane (2.0 equiv, 0.8 – 1.2 M solution in Et_2O) were added. The vial was sealed. The stirred mixture was irradiated with blue LEDs for 24 h. The reaction mixture was concentrated, and the residue was purified by column chromatography.

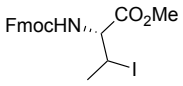
[4] Gianatassio R. *et al. Science* **2016**, *351*, 241 − 246
[5] Anderson E. A. *et al. ACS Catal.* **2019**, *9*, 9568 − 9574

Compounds **1a**,[2] **1c**,[2] **1d**,[6] **1h**,[2] **1i**,[7] **1n**,[8] **1o**,[9]**1r**,[2] **1u**[2] and **1v**[10] were prepared according to the indicated reports.



Characterization of new compounds

Methyl (2R)-2-((((9H-Fluoren-9-yl)methoxy)carbonyl)amino)-3-iodobutanoate (S3)

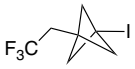


Following the reported procedure:[11] To a flame-dried flask containing a mixture of DDQ (545 mg, 2.40 mmol) and PPh_3 (629 mg, 2.40 mmol) in dry CH_2Cl_2 (30 mL), (n-Bu)$_4$NI (877 mg, 2.40 mmol) was added at rt. Methyl (((9H-fluoren-9-yl)methoxy)carbonyl)-D-threoninate (711 mg, 2.0 mmol) was then added to the solution. After 1 h, the solvent was evaporated. **S3** was obtained (271 mg, 0.583 mmol, 29% yield) as a white powder by flash chromatography (15% EtOAc/hexanes). The product was obtained as a mixture of diastereoisomers.

^{1}H NMR (600 MHz, $CDCl_3$), δ (ppm) 7.77 (dd, J = 7.6, 1.1 Hz, 2H), 7.65 – 7.57 (m, 2H), 7.47 – 7.38 (m, 2H), 7.33 (tdd, J = 7.4, 4.6, 1.2 Hz, 2H), 5.63 (d, J = 8.5 Hz, 1H), 4.52 – 4.30 (m, 4H), 4.25 (t, J = 7.2 Hz, 1H), 3.89 – 3.76 (m, 3H), 2.12 – 1.92 (m, 3H).
^{13}C NMR (151 MHz, $CDCl_3$), δ (ppm) 169.4, 164.9, 155.6, 143.9, 143.9, 143.8, 141.5, 127.9, 127.9, 127.3, 127.2, 125.3, 125.2, 125.2, 120.2, 120.2, 77.2, 67.5, 67.2, 60.8, 53.0, 52.4, 47.3, 47.2, 26.5, 25.2, 14.4.
FT-IR (cm^{-1}, neat, ATR) 1739, 1719, 1687, 1524, 1444, 1357, 1337, 1277, 1250, 1234, 1209, 1181, 1147, 1077, 1049, 1024, 990, 757, 739.
HRMS (ESI) calc. for $C_{20}H_{21}INO_4$ $[M+H]^+$: 466.0515, found: 466.0527.
Melting point (°C) 104.7 - 105.9.

[6] Anderson E. A. *et al. Chem. Sci.* **2018**, *9*, 5295 − 5300
[7] Anderson E. A. *et al. Angew. Chem. Int. Ed.* **2020**, *59*, 11866 – 11870
[8] Anderson E. A. *et al. J. Am. Chem. Soc.* **2021**, *143,* 9729 – 9736
[9] Shang R. *et al. Org. Lett.* **2020,** *22*, 8572 − 8577
[10] Aïssa C. *et al. Angew.Chem.Int.Ed.* **2022**, *61*, e202111291
[11] Gothelf K. V. *et al. Eur. J. Org. Chem.* **2007**, 5826 − 5833

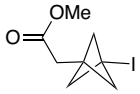
1-Iodo-3-(2,2,2-trifluoroethyl)bicyclo[1.1.1]pentane (1b)



Following the general procedure for the preparation of BCP halides: starting from the corresponding alkyl iodide (126 mg, 59.1 μL, 0.60 mmol), using $Ru(bpy)_3(PF_6)_2$ (5.6 mg, 0.006 mmol) as photocatalyst, the compound **1b** (53 mg, 0.19 mmol, 32% yield) was obtained as an clear oil by flash chromatography (100% hexanes).

^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm) δ 2.47 – 2.27 (m, 8H).
^{13}C NMR (151 MHz, $CDCl_3$), δ (ppm) 125.7 (q, J = 277.8 Hz), 61.1, 41.5 (d, J = 3.0 Hz), 41.5, 36.3 (q, J = 28.7 Hz), 4.9.
^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) -64.88.
FT-IR (cm^{-1}, neat, ATR) 2921, 1738, 1366, 1179, 840.
HRMS (ESI) calc. for $C_7H_8F_3$ $[M\text{-}I]^+$: 149.5078, found: 149.5078.

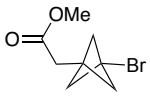
Methyl 2-(3-Iodobicyclo[1.1.1]pentan-1-yl)acetate (1ea)



Following the general procedure for the preparation of BCP halides: starting from the corresponding alkyl iodide (120 mg, 0.6 mmol), using $Ir(ppy)_3$ (4.0 mg, 0.006 mmol) as photocatalyst, compound **1ea** (131 mg, 0.49 mmol, 82% yield) was obtained as a clear oil by flash chromatography (5% EtOAc/hexanes).

^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm) 3.67 (s, 3H), 2.55 (s, 2H), 2.32 (s, 6H).
^{13}C NMR (101 MHz, $CDCl_3$), δ (ppm) 170.9, 61.0, 51.8, 43.7, 37.2, 6.1.
FT-IR (cm^{-1}, neat, ATR) 2994, 2950, 2914, 1735, 1435, 1353, 1311, 1281, 1255, 1198, 1173, 1135, 1117, 1092, 1045, 1004, 977, 843, 787.
HRMS (EI) calc. for $C_7H_8IO_2$ $[M\text{-}OMe]^+$: 234.9620, found: 234.9639.

Methyl 2-(3-Bromobicyclo[1.1.1]pentan-1-yl)acetate (1eb)

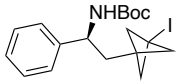


Following the general procedure for the preparation of BCP halides: starting from the corresponding alkyl bromide (92 mg, 67 μL, 0.60 mmol), using $Ir(ppy)_3$ (4.0 mg, 0.006 mmol) as photocatalyst, compound **1eb** (65.1 mg, 0.29 mmol, 49% yield) was obtained as a clear oil by flash chromatography (100% hexanes).

^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm) 3.67 (s, 3H), 2.59 (s, 2H), 2.23 (s, 6H).
^{13}C NMR (101 MHz, $CDCl_3$), δ (ppm) 171.0, 59.2, 51.8, 37.2, 36.2, 36.1.

FT-IR (cm^{-1}, neat, ATR) 2975, 2916, 2878, 1737, 1435, 1410, 1357, 1316, 1287, 1257, 1200, 1178, 1117, 1094, 1050, 1007, 985, 887, 858.
HRMS (EI) calc. for C_7H_8BrO $[M\text{-}OMe]^+$: 186.9759, found:186.9758.

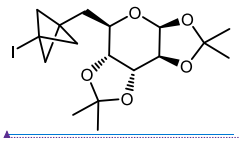
tert-Butyl (*S*)-(2-(3-Iodobicyclo[1.1.1]pentan-1-yl)-1-phenylethyl)carbamate (1f)



Following the general procedure for the preparation of BCP halides: starting from the corresponding alkyl iodide (139.0 mg, 0.40 mmol), using $Ru(bpy)_3(PF_6)_2$ (7 mg, 0.02 mmol) as photocatalyst, compound **1f** (45 mg, 0.11 mmol, 27% yield) was obtained as a white powder by flash chromatography (5% EtOAc/hexanes).

^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm) 7.37 – 7.26 (m, 3H), 7.26 – 7.21 (m, 2H), 4.68 – 4.60 (m, 1H), 2.12 (dd, J = 9.4, 1.7 Hz, 6H), 2.02 (td, J = 14.3, 7.0 Hz, 2H), 1.41 (s, 9H).
^{13}C NMR (151 MHz, $CDCl_3$), δ (ppm) 155.0, 142.2, 128.9, 127.8, 126.6, 79.8, 61.0, 53.5, 46.2, 38.5, 28.6, 7.3.
FT-IR (cm^{-1}, neat, ATR) 3379, 2981, 2912, 1680, 1516, 1455, 1430, 1390, 1364, 1269, 1251, 1178, 1045, 1017, 868, 841, 758.
HRMS (ESI) calc. for $C_{20}H_{27}IN_2NaO_2$ $[M+Na+MeCN]^+$: 477.1015, found: 477.1018.
Melting point (°C) 133.3 – 134.5

(3aS,5R,5aR,8aR,8bS)-5-((3-iodobicyclo[1.1.1]pentan-1-yl)methyl)-2,2,7,7-tetramethyltetrahydro-5H-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran (1g)

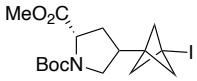


Field Code Changed

Following the general procedure for the preparation of BCP halides: starting from the corresponding alkyl iodide (72.0 mg, 0.20 mmol), using $Ir(ppy)_3$ (2.0 mg, 0.003 mmol) as photocatalyst, compound **1g** (87.0 mg, 0.20 mmol, 99% yield) was obtained as a white solid by flash chromatography (5% EtOAc/hexanes).

^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm) 5.50 (d, J = 5.1 Hz, 1H), 4.56 (dd, J = 7.9, 2.3 Hz, 1H), 4.28 (dd, J = 5.2, 2.3 Hz, 1H), 4.03 (dd, J = 8.0, 1.8 Hz, 1H), 3.70 (dt, J = 9.9, 2.3 Hz, 1H), 2.28 (s, 6H), 1.93 (dd, J = 14.8, 10.0 Hz, 1H), 1.74 – 1.63 (m, 1H), 1.54 (s, 3H), 1.43 (s, 3H), 1.33 (s, 3H), 1.32 (s, 3H).
^{13}C NMR (101 MHz, $CDCl_3$), δ (ppm) 109.3, 108.5, 96.8, 73.2, 71.1, 70.4, 66.1, 61.4, 51.3, 46.4, 32.6, 26.14, 26.10, 25.0, 24.5, 7.8.
FT-IR (cm^{-1}, neat, ATR) 2989, 2912, 1381, 1255, 1210, 1174, 1106, 1069, 1014, 995, 918, 907, 837.
HRMS (EI) calc. for $C_{17}H_{25}O_5$ $[M\text{-}I]^+$: 309.1702, found: 309.1707.
Melting point (°C) 76.6 – 77.4

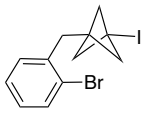
1-(*tert*-Butyl) 2-Methyl (2*S*)-4-(3-Iodobicyclo[1.1.1]pentan-1-yl)pyrrolidine-1,2-dicarboxylate (1j)



Following the general procedure for the preparation of BCP halides: starting from the corresponding alkyl iodide (107 mg, 0.30 mmol), using $Ir(ppy)_3$ (4.0 mg, 0.006 mmol) as photocatalyst, compound **1j** (61 mg, 0.14 mmol, 48% yield) was obtained as a colorless oil by flash chromatography (15% EtOAc/hexanes). The product was obtained as a mixture of diastereoisomers.

^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm) 4.36 – 4.15 (m, 1H), 3.71 (d, J = 5.1 Hz, 3H), 3.69 – 3.48 (m, 1H), 3.17 – 3.00 (m, 1H), 2.55 – 2.22 (m, 1.5H), 2.19 (s, 6H), 1.98 – 1.85 (m, 1H), 1.65 – 1.58 (m, 0.5H), 1.50 – 1.33 (m, 9H).
^{13}C NMR (101 MHz, $CDCl_3$), δ (ppm) 173.4, 173.4, 173.3, 154.3, 153.7, 153.6, 80.4, 80.3, 59.5, 59.1, 59.0, 59.0, 58.7, 52.4, 52.2, 52.2, 49.3, 49.1, 49.0, 48.8, 48.5, 48.5, 47.9, 40.1, 39.3, 39.0, 38.2, 34.3, 33.8, 33.4, 33.0, 28.5, 28.5, 28.4, 28.3, 6.4(1), 6.3(9).
FT-IR (cm^{-1}, neat, ATR) 2975, 2978, 1749, 1701, 1478, 1450, 1435, 1397, 1365, 1256, 1200, 1177, 1119, 1029, 991, 899, 839, 772.
HRMS (ESI) calc. for $C_{16}H_{25}INO_4$ $[M+H]^+$: 422.0822, found: 422.0828.

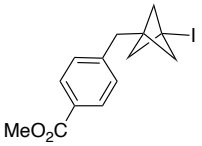
1-(2-Bromobenzyl)-3-iodobicyclo[1.1.1]pentane (1k)



Following the general procedure for the preparation of BCP halides: starting from the corresponding alkyl iodide (119 mg, 0.40 mmol), using $Ru(bpy)_3(PF_6)_2$ (7.5 mg, 0.008 mmol) as photocatalyst, compound **1k** (109 mg, 0.30 mmol, 75% yield) was obtained as a white solid by flash chromatography (100% hexanes)

^{1}H NMR (600 MHz, $CDCl_3$), δ (ppm) 7.56 – 7.49 (m, 1H), 7.23 (td, J = 7.4, 1.3 Hz, 1H), 7.11 – 7.03 (m, 2H), 3.02 (s, 2H), 2.19 (s, 6H).
^{13}C NMR (151 MHz, $CDCl_3$), δ (ppm) 138.0, 133.1, 131.0, 128.2, 127.6, 124.5, 60.7, 47.6, 38.8, 7.9.
FT-IR (cm^{-1}, neat, ATR) 2988, 2965, 2909, 2872, 1465, 1432, 1213, 1167, 1138, 1034, 1020, 979, 938, 831, 777, 747, 721, 657.
HRMS (EI) calc. for $C_{12}H_{12}BrI$ $[M]^+$: 361.9167, found: 361.9176.
Melting point (°C) 51.4 – 51.6.

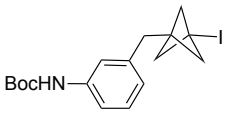
Methyl 4-((3-Iodobicyclo[1.1.1]pentan-1-yl)methyl)benzoate (1l)



Following the general procedure for the preparation of BCP halides: starting from the corresponding alkyl iodide (110 mg, 0.4 mmol), using $Ru(bpy)_3(PF_6)_2$ (7.5 mg, 0.008 mmol) as photocatalyst, compound **1l** (110.4 mg, 0.32 mmol, 80% yield) was obtained as a white solid by flash chromatography (7% EtOAc/hexanes).

^{1}H NMR (600 MHz, $CDCl_3$), δ (ppm) 7.96 (d, J = 8.3 Hz, 2H), 7.12 (d, J = 8.2 Hz, 2H), 3.91 (s, 3H), 2.86 (s, 2H), 2.15 (s, 6H).
^{13}C NMR (151 MHz, $CDCl_3$), δ (ppm) 167.0, 143.5, 129.8, 128.8, 128.4, 60.2, 52.1, 47.7, 39.2, 7.6.
FT-IR (cm^{-1}, neat, ATR) 2983, 1710, 1610, 1433, 1416, 1305, 1277, 1197, 1173, 1103, 1019, 977, 863, 843, 805, 776, 753, 705.
HRMS (EI) calc. for $C_{14}H_{15}O_2$ $[M\text{-}I]^+$: 215.1072, found: 215.1074.
Melting point (°C) 81.2 – 81.4.

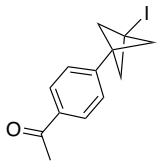
tert-Butyl (3-((3-Iodobicyclo[1.1.1]pentan-1-yl)methyl)phenyl)carbamate (1m)



Following the general procedure for the preparation of BCP halides: starting from the corresponding alkyl iodide (100 mg, 0.3 mmol), using $Ir(ppy)_3$ (4.0 mg, 0.006 mmol) as photocatalyst, compound **1m** (41 mg, 0.13 mmol, 43% yield) was obtained as a white solid by flash chromatography (3% EtOAc/hexanes).

^{1}H NMR (600 MHz, $CDCl_3$), δ (ppm) 7.19 (td, J = 7.5, 0.8 Hz, 1H), 7.13 (d, J = 8.7 Hz, 2H), 6.72 (dt, J = 7.4, 1.4 Hz, 1H), 6.42 (s, 1H), 2.77 (s, 2H), 2.16 (s, 6H), 1.52 (s, 9H).
^{13}C NMR (151 MHz, $CDCl_3$), δ (ppm) 152.8, 139.4, 138.6, 129.1, 123.6, 118.8, 116.5, 60.5, 48.2, 39.3, 28.5, 28.5, 8.4.
FT-IR (cm^{-1}, neat, ATR) 3331, 2978, 2912, 1695, 1610, 1592, 1535, 1491, 1440, 1392, 1367, 1302, 1239, 1159, 1055, 868, 838, 771.
HRMS (ESI) calc. for $C_{17}H_{23}INO_2$ $[M+H]^+$: 400.0774, found: 400.0776.
Melting point (°C) 138.6 – 139.4.

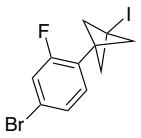
1-(4-(3-Iodobicyclo[1.1.1]pentan-1-yl)phenyl)ethan-1-one (1p)



Following the general procedure for the preparation of BCP halides: starting from the corresponding aryl iodide (98.4 mg, 0.4 mmol), using $Ir(ppy)_3$ (5.0 mg, 0.008 mmol) as photocatalyst, compound **1p** (35.9 mg, 0.15 mmol, 29% yield) was obtained as a white solid by flash chromatography (5% EtOAc/hexanes).

^{1}H NMR (600 MHz, $CDCl_3$), δ (ppm) 7.90 (d, J = 8.4 Hz, 2H), 7.21 (d, J = 8.3 Hz, 2H), 2.63 (s, 6H), 2.58 (s, 3H).
^{13}C NMR (151 MHz, $CDCl_3$), δ (ppm) 197.7, 143.5, 136.0, 128.7, 126.4, 61.9, 50.3, 26.8, 6.3.
FT-IR (cm^{-1}, neat, ATR) 1681, 1605, 1423, 1402, 1350, 1294, 1266, 1241, 1195, 1138, 1078, 1057, 1015, 956, 843, 827, 747, 607.
HRMS (ESI) calc. for $C_{13}H_{14}IO$ $[M+H]^+$: 313.0089, found: 313.0090.
Melting point (°C) decomposition (90 °C).

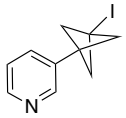
1-(4-Bromo-2-fluorophenyl)-3-iodobicyclo[1.1.1]pentane (1q)



Following the general procedure for the preparation of BCP halides: starting from the corresponding aryl iodide (90.3 mg, 0.3 mmol), using $Ir(ppy)_3$ (4.0 mg, 0.006 mmol) as photocatalyst, compound **1q** (18.1 mg, 0.05 mmol, 14% yield) was obtained as a white solid by flash chromatography (100% hexanes).

^{1}H NMR (600 MHz, $CDCl_3$), δ (ppm) 7.21 (ddd, J = 8.1, 1.9, 0.7 Hz, 1H), 7.17 (dd, J = 9.6, 1.9 Hz, 1H), 6.90 (t, J = 8.1 Hz, 1H), 2.64 (d, J = 0.8 Hz, 6H).
^{13}C NMR (151 MHz, $CDCl_3$) δ (ppm) 161.2 (d, J = 252.3 Hz), 129.8 (d, J = 5.2 Hz), 127.3 (d, J = 3.8 Hz), 124.6 (d, J = 15.4 Hz), 121.3 (d, J = 9.3 Hz), 119.4 (d, J = 24.5 Hz), 61.9, 46.5, 6.6.
^{19}F NMR (376 MHz, $CDCl_3$) δ -113.65.
FT-IR (cm^{-1}, neat, ATR) 2915, 1879, 1605, 1569, 1509, 1483, 1399, 1211, 1187, 1144, 1056, 926, 857, 837, 813, 758, 579.
HRMS (EI) calc. for $C_{11}H_8BrF$ $[M-HI]^+$: 237.9793, found:237.9789.
Melting point (°C) 69.8 – 71.1.

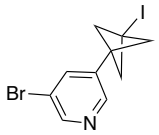
3-(3-Iodobicyclo[1.1.1]pentan-1-yl)pyridine (1s)



Following the general procedure for the preparation of BCP halides: starting from the corresponding aryl iodide (123 mg, 0.6 mmol), using 4-CzIPN (4.7 mg, 0.006 mmol) as photocatalyst, compound **1s** (54 mg, 0.2 mmol, 33% yield) was obtained as a pale-yellow solid by flash chromatography (10% EtOAc/hexanes).

^{1}H NMR (600 MHz, $CDCl_3$), δ (ppm) 8.50 (dd, J = 4.8, 1.6 Hz, 1H), 8.41 (d, J = 2.0 Hz, 1H), 7.47 (dt, J = 7.8, 2.0 Hz, 1H), 7.29 – 7.20 (m, 1H), 2.64 (s, 6H).
^{13}C NMR (151 MHz, $CDCl_3$), δ (ppm) 148.0, 147.2, 134.0, 123.4, 61.7, 48.2, 5.6.
FT-IR (cm^{-1}, neat, ATR) 2966, 2909, 2871, 1739, 1569, 1475, 1444, 1412, 1198, 1183, 1133, 1080, 1028, 831, 813, 751, 710, 621.
HRMS (ESI) calc. for $C_{10}H_{11}IN$ $[M+H]^+$: 271.9936, found: 271.9938.
Melting point (°C) 44 – 46

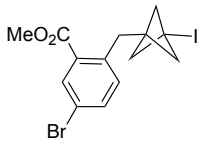
3-Bromo-5-(3-iodobicyclo[1.1.1]pentan-1-yl)pyridine (1t)



Following the general procedure for the preparation of BCP halides: starting from the corresponding aryl iodide (114 mg, 0.4 mmol), using 4-CzIPN (6.3 mg, 0.008 mmol) as photocatalyst, compound **1t** (19.0 mg, 0.0543mmol, 14% yield) was obtained as a white solid by flash chromatography (5% EtOAc/hexanes).

^{1}H NMR (600 MHz, $CDCl_3$), δ (ppm) 8.56 (d, J = 2.2 Hz, 1H), 8.30 (d, J = 1.9 Hz, 1H), 7.56 (t, J = 2.0 Hz, 1H), 2.63 (s, 6H).
^{13}C NMR (151 MHz, $CDCl_3$), δ (ppm) 149.6, 145.9, 136.4, 135.5, 120.8, 61.7, 47.7, 5.1.
FT-IR (cm^{-1}, neat, ATR) 2995, 2971, 2914, 2876, 1576, 1549, 1433, 1413, 1198, 1171, 1131, 1092, 1071, 1020, 939, 880, 849, 748, 701.
HRMS (ESI) calc. for $C_{10}H_{10}BrIN$ $[M+H]^+$: 349.9041, found: 349.9056.
Melting point (°C) 97.9 – 98.1.

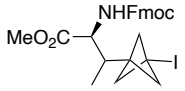
Methyl 5-Bromo-2-((3-iodobicyclo[1.1.1]pentan-1-yl)methyl)benzoate (1w)



Following the general procedure for the preparation of BCP halides: starting from the corresponding alkyl iodide (142 mg, 0.4 mmol), using $Ir(ppy)_3$ (5.3 mg, 0.008 mmol) as photocatalyst, compound **1v** (80.4 mg, 0.191 mmol, 48% yield) was obtained as a white solid by flash chromatography (100% hexanes).

^{1}H NMR (600 MHz, $CDCl_3$), δ (ppm) 7.76 (d, J = 8.4 Hz, 1H), 7.42 (dd, J = 8.4, 2.0 Hz, 1H), 7.26 (s, 1H), 3.87 (s, 3H), 3.26 (s, 2H), 2.13 (s, 6H).
^{13}C NMR (151 MHz, $CDCl_3$), δ (ppm) 167.2, 142.2, 134.5, 132.6, 129.9, 128.4, 126.9, 60.6, 52.2, 48.0, 36.5, 7.6.
FT-IR (cm^{-1}, neat, ATR) 2995, 1720, 1587, 1560, 1477, 1432, 1281, 1258, 1217, 1174, 1140, 1090, 1074, 978, 878, 863, 840, 809, 768, 713.
HRMS (EI) calc. for $C_{14}H_{14}BrO_2$ $[M-I]^+$: 292.0099, found: 292.0103.
Melting point (°C) 79.6 – 80.3.

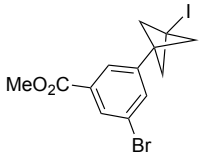
Methyl (2*S*)-2-((((9*H*-Fluoren-9-yl)methoxy)carbonyl)amino)-3-(3-iodobicyclo[1.1.1] pentan-1-yl)butanoate (1x)



Following the general procedure for the preparation of BCP halides: starting from the corresponding alkyl iodide (140 mg, 0.30 mmol), using $Ir(ppy)_3$ (3.9 mg, 0.006 mmol) as photocatalyst, compound **1w** (50.8 mg, 0.096 mmol, 32% yield) was obtained as a white solid by flash chromatography (10% EtOAc/hexanes). The product was obtained as a mixture of diastereoisomers.

^{1}H NMR (600 MHz, $CDCl_3$), δ (ppm) 7.81 – 7.73 (m, 2H), 7.63 – 7.53 (m, 2H), 7.45 – 7.38 (m, 2H), 7.38 – 7.29 (m, 2H), 5.17 – 5.03 (m, 1H), 4.61 – 4.37 (m, 3H), 4.32 – 4.17 (m, 2H), 3.80 – 3.67 (m, 3H), 2.27 – 2.06 (m, 6H), 0.95 – 0.76 (m, 3H).
^{13}C NMR (151 MHz, $CDCl_3$), δ (ppm) 172.2, 156.0, 144.0, 143.7, 143.7, 141.6, 141.5, 128.0, 128.0, 127.9, 127.3, 127.3, 127.2, 125.1, 125.1, 120.2, 120.2, 67.1, 66.9, 59.6, 59.2, 57.0, 55.9, 52.7, 52.5, 50.1, 49.9, 47.4(4), 47.3(7), 38.1, 37.2, 14.3, 12.0, 6.9, 6.5.
FT-IR (cm^{-1}, neat, ATR) 3336, 2969, 1720, 1511, 1448, 1334, 1216, 1179, 1083, 1055, 1015, 834, 758, 738, 539.
HRMS (ESI) calc. for $C_{25}H_{27}INO_4$ $[M+H]^+$: 532.0985, found: 532.0987.
Melting point (°C) 54.0 – 56.2.

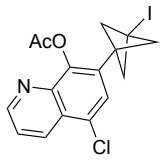
Methyl 3-Bromo-5-(3-iodobicyclo[1.1.1]pentan-1-yl)benzoate (1y)



Following the general procedure for the preparation of BCP halides: starting from the corresponding aryl iodide (170 mg, 0.50 mmol), using $Ir(ppy)_3$ (4.9 mg, 0.007 mmol) as photocatalyst, compound **1x** (33.2 mg, 0.08 mmol, 16% yield) was obtained as a pale-yellow solid by flash chromatography (100% hexanes).

^{1}H NMR (600 MHz, $CDCl_3$), δ (ppm) 8.04 (t, J = 1.7 Hz, 1H), 7.70 (t, J = 1.5 Hz, 1H), 7.43 (t, J = 1.7 Hz, 1H), 3.92 (s, 3H), 2.61 (s, 6H).
^{13}C NMR (151 MHz, $CDCl_3$), δ (ppm) 165.7, 140.9, 133.6, 132.2, 131.3, 126.1, 122.6, 61.9, 52.7, 49.6, 5.6.
FT-IR (cm^{-1}, neat, ATR) 1717, 1568, 1439, 1422, 1322, 1263, 1248, 1187, 1122, 1098, 992, 943, 886, 852, 833, 770, 756, 733, 718, 680.
HRMS (EI) calc. for $C_{13}H_{11}BrO_2$ $[M-HI]^+$: 277.9942, found: 277.9956.
Melting point (°C) 124.2 – 126.8.

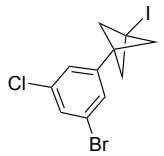
5-Chloro-7-(3-iodobicyclo[1.1.1]pentan-1-yl)quinolin-8-yl acetate (1z)



Following the general procedure for the preparation of BCP halides: starting from the corresponding aryl iodide (174 mg, 0.50 mmol), using $Ir(ppy)_3$ (4.9 mg, 0.007 mmol) as photocatalyst, compound **1y** (32.4 mg, 0.078 mmol, 16% yield) was obtained as a white solid by flash chromatography (10% EtOAc/hexanes).

^{1}H NMR (600 MHz, $CDCl_3$), δ (ppm) 8.92 (dd, J = 4.2, 1.6 Hz, 1H), 8.50 (dd, J = 8.5, 1.6 Hz, 1H), 7.50 (dd, J = 8.5, 4.2 Hz, 1H), 7.36 (s, 1H), 2.73 (s, 6H), 2.53 (s, 3H).
^{13}C NMR (151 MHz, $CDCl_3$), δ (ppm) 169.5, 151.4, 144.5, 141.9, 133.1, 130.1, 128.7, 126.6, 125.9, 122.4, 62.2, 47.6, 21.1, 6.0.
FT-IR (cm^{-1}, neat, ATR) 1766, 1592, 1456, 1370, 1352, 1173, 1130, 1075, 1040, 1003, 944, 892, 856, 831, 811, 796, 766, 749, 630.
HRMS (ESI) calc. for $C_{16}H_{14}ClINO_2$ $[M+H]^+$: 413.9758, found:413.9759.
Melting point (°C) 123.3 – 125.3.

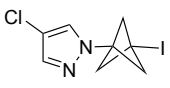
1-(3-Bromo-5-chlorophenyl)-3-iodobicyclo[1.1.1]pentane (1aa)



Following the general procedure for the preparation of BCP halides: starting from the corresponding aryl iodide (127 mg, 0.4 mmol), using $Ru(bpy)_3(PF_6)_2$ (4.0 mg, 0.006 mmol) as photocatalyst, compound **1z** (55 mg, 0.14 mmol, 36% yield) was obtained as a white solid by flash chromatography (100% hexanes).

^{1}H NMR (500 MHz, $CDCl_3$), δ (ppm) 7.39 (t, J = 1.8 Hz, 1H), 7.13 (t, J = 1.6 Hz, 1H), 7.02 (t, J = 1.7 Hz, 1H), 2.57 (s, 6H).
^{13}C NMR (151 MHz, $CDCl_3$), δ (ppm) 141.9, 135.3, 130.2, 127.8, 125.3, 122.9, 61.8, 49.3, 5.3.
FT-IR (cm^{-1}, neat, ATR) 2994, 2910, 2874, 1589, 1557, 1429, 1408, 1376, 1311, 1192, 1114, 1090, 1073, 876, 860, 837, 789, 764, 729, 678.
HRMS (ESI, EI): Not found.
Melting point (°C) 111.8 – 113.1.

4-Chloro-1-(3-iodobicyclo[1.1.1]pentan-1-yl)-1*H*-pyrazole (1ab)



Following a reported procedure:[12] A round-bottomed vial with a stir-bar was charged with iodine (168 mg, 0.66 mmol), 4-chloro-1H-pyrazole (61.5 mg, 0.6 mmol), Cs_2CO_3 (621 mg, 1.2 mmol), and MeCN (6 mL), then sealed with a Teflon septum cap and stirred at rt for 30 min. The vial was then charged with a solution of [1.1.1]propellane (3.31 mL, 0.8 M in Et_2O, 0.72 mmol), and the reaction was stirred at rt for 14 h. The reaction mixture was then diluted with MeCN (10 mL) and filtered through a pad of Celite©. The resulting solution was concentrated under vacuum. Purification of the resulting crude by silica gel chromatography with 0 - 40% EtOAc in hexanes as eluent afforded **1aa** (36.9 mg, 0.12 mmol, 21% yield) as a white solid.

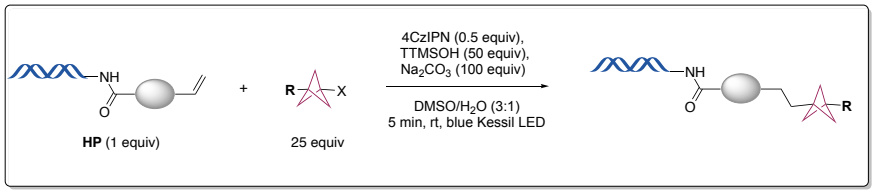
^{1}H NMR (600 MHz, $CDCl_3$), δ (ppm) 7.44 (s, 1H), 7.35 (s, 1H), 2.72 (s, 6H).
^{13}C NMR (151 MHz, $CDCl_3$), δ (ppm) 138.8, 125.6, 110.8, 61.6, 56.6, -2.2.
FT-IR (cm^{-1}, neat, ATR) 3091, 1738, 1426, 1383, 1337, 1294, 1213, 1194, 1168, 1075, 989, 965, 869, 837, 615.
HRMS (ESI) calc. for $C_8H_9ClIN_2$ $[M+H]^+$: 294.9499, found: 294.9485.
Melting point (°C) 73.3 – 74.0.

[12] Zarate, C. *et al*. *Org. Process Res. Dev*. **2021**, *25*, 642 – 647

4. General Procedures for Photoinduced Transformations on-DNA

General Procedure I

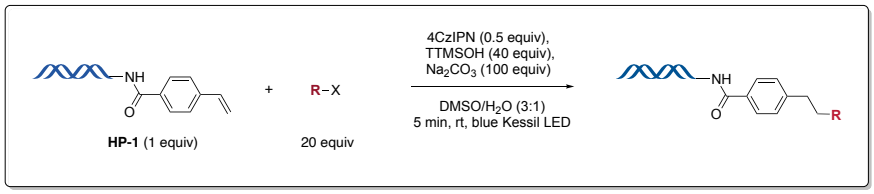
Photoinduced on-DNA alkylation reaction for BCP iodide



To a PCR Eppendorf tube was added 4CzIPN (5 μL of a 1 nmol/μL soln in DMSO, 5 nmol, 0.5 equiv), BCP-iodide (10 μL of a 25 nmol/μL soln in DMSO, 250 nmol, 25 equiv), TTMSOH (10 μL of a 50 nmol/μL soln in DMSO, 500 nmol, 50 equiv), Na_2CO_3 (2.5 μL of a 400 nmol/μL soln in H_2O, 1000 nmol, 100 equiv), and DNA-tethered alkene (5 μL of a 2 nmol/μL soln in H_2O, 10 nmol, 1.0 equiv). The mixture was mixed by pipetting back and forth. The PCR tube was then capped and irradiated for 5 min with Kessil H150-blue lamps at a distance of 1.5 inches. The reaction was then diluted with H_2O (100 μL), filtered, and analyzed by LC/MS.

General Procedure II

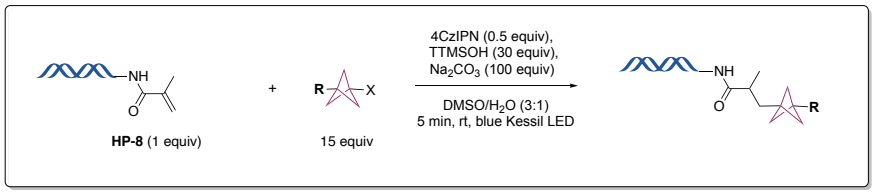
Photoinduced on-DNA alkylation reaction for alkyl halides



To a PCR Eppendorf tube was added 4CzIPN (5 μL of a 1 nmol/μL soln in DMSO, 5 nmol, 0.5 equiv), BCP-iodide (10 μL of a 20 nmol/μL soln in DMSO, 200 nmol, 20 equiv), TTMSOH (10 μL of a 40 nmol/μL soln in DMSO, 400 nmol, 40 equiv), Na_2CO_3 (2.5 μL of a 400 nmol/μL soln in H_2O, 1000 nmol, 100 equiv), and DNA-tethered alkene (5 μL of a 2 nmol/μL soln in H_2O, 10 nmol, 1.0 equiv). The mixture was mixed by pipetting back and forth. The PCR tube was then capped and irradiated for 5 min with Kessil H150-blue lamps at a distance of 1.5 inches. The reaction was then diluted with H_2O (100 μL), filtered, and analyzed by LC/MS.

General Procedure III

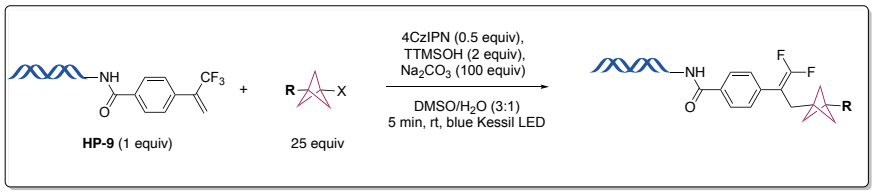
Photoinduced on-DNA alkylation reaction for BCP iodide with **HP-8**



To a PCR Eppendorf tube was added 4CzIPN (5 µL of a 1 nmol/µL soln in DMSO, 5 nmol, 0.5 equiv), BCP-iodide (5 µL of a 30 nmol/µL soln in DMSO, 150 nmol, 15 equiv), TTMSOH (5 µL of a 60 nmol/µL soln in DMSO, 300 nmol, 30 equiv), Na_2CO_3 (2.5 µL of a 400 nmol/µL soln in H_2O, 1000 nmol, 100 equiv), 5 µL of DMSO and DNA-tethered alkene **HP-8** (5 µL of a 2 nmol/µL soln in H_2O, 10 nmol, 1.0 equiv). The mixture was mixed by pipetting back and forth. The PCR tube was then capped, and irradiated for 5 min with Kessil H150-blue lamps at a distance of 1.5 inches. The reaction was then diluted with H_2O (100 µL), filtered, and analyzed by LC/MS.

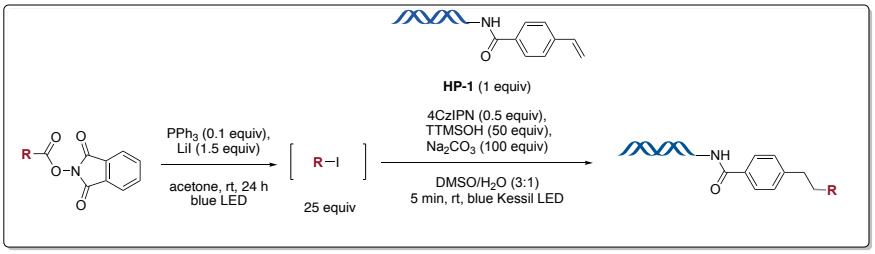
General Procedure IV

Photoinduced on-DNA alkylation reaction for BCP iodide with **HP-9**

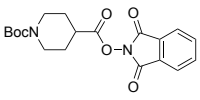


To a PCR Eppendorf tube was added 4CzIPN (5 µL of a 1 nmol/µL soln in DMSO, 5 nmol, 0.5 equiv), BCP-iodide (10 µL of a 25 nmol/µL soln in DMSO, 250 nmol, 25 equiv), TTMSOH (10 µL of a 2 nmol/µL soln in DMSO, 20 nmol, 2 equiv), Na_2CO_3 (2.5 µL of a 400 nmol/µL soln in H_2O, 1000 nmol, 100 equiv), and DNA-tethered alkene **HP-9** (5 µL of a 2 nmol/µL soln in H_2O, 10 nmol, 1.0 equiv). The mixture was mixed by pipetting back and forth. The PCR tube was then capped and irradiated for 5 min with Kessil H150-blue lamps at a distance of 1.5 inches. The reaction was then diluted with H_2O (100 µL), filtered, and analyzed by LC/MS.

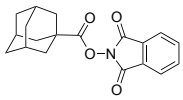
General Procedure for telescoped reaction from redox active ester



Redox active ester **S4**, **S5** were prepared according to the indicated literature procedures. [13]



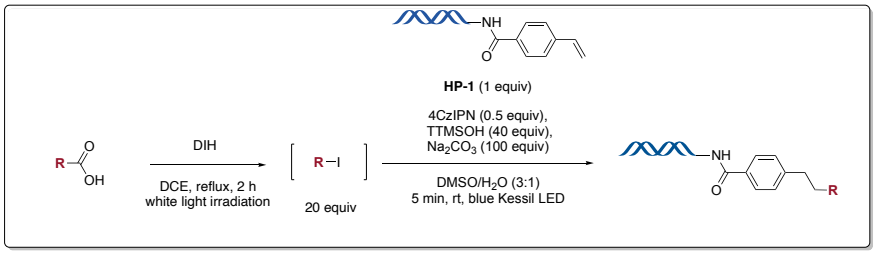
S4



S5

From a modified procedure[14]
Redox-active esters (1.0 equiv, 0.1 mmol), LiI (1.5 equiv, 0.3 mmol), and PPh_3 (10 mol %) were added to a 3 mL reaction vial. The vial was evacuated and back-filled with nitrogen (three cycles). Acetone (1.0 mL) was added under a N_2-atmosphere. The reaction mixture was stirred under irradiation with blue LEDs (Kessil, PR160-456 nm), maintained at rt. After 24 h, the mixture was concentrated on a rotary evaporator. 1 mL of acetone was added to dilute the reaction mixture (to prevent any solvent loss during reaction time). 100 µL of reaction crude was taken and the solvent was removed to give 10 µmol of iodide (assuming full completion was reached). The crude was then diluted in 400 µL of DMSO (25 mmol/L).
10 µL of the iodide solution (25 mmol/L, 25 equiv) was then added to a PCR Eppendorf tube containing 4CzIPN (5 µL of a 1 nmol/µL soln in DMSO, 5 nmol, 0.5 equiv). TTMSOH (10 µL of a 50 nmol/µL soln in DMSO, 500 nmol, 50 equiv), Na_2CO_3 (2.5 µL of a 400 nmol/µL soln in H_2O, 1000 nmol, 100 equiv), and DNA-tethered alkene (5 µL of a 2 nmol/µL soln in H_2O, 10 nmol, 1.0 equiv) were then added, and the mixture was mixed by pipetting back and forth. The PCR tube was then capped and irradiated for 5 min with Kessil H150-blue lamps at a distance of 1.5 inches. The reaction was then diluted with H_2O (100 µL), filtered, and analyzed by LC/MS.

General Procedure for telescoped reaction from carboxylic acid



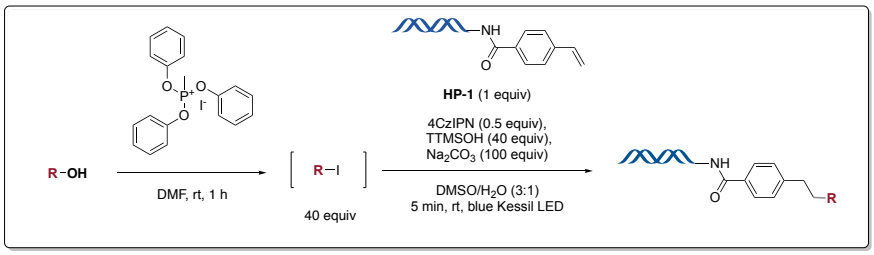
From a modified procedure:[15] In a sealed tube, a mixture of the alkyl carboxylic acid (0.2 mmol, 1 equiv), 1,3-diiodo-5,5-dimethylhydantoin (DIH, 0.24 mmol, 91.2 mg, 1.2 equiv), and DCE (1.2 mL, 0.17 M) was irradiated (CFL) for 2 h under reflux conditions. After cooling, the reaction mixture was washed with aq 1 M $NaHSO_3$. The aqueous phase was extracted with CH_2Cl_2, and the combined organic fractions were dried (Na_2SO_4), filtered through short silica pad, and concentrated under vacuum to give substantially pure iodide derivative. 10 µL of the iodide solution (20 mmol/L in DMSO, 20 equiv) are

[13] Baran P. *et al. J. Am. Chem. Soc.* **2016**, *138*, 2174 − 2177
[14] Shang, R. *et al. Org. Lett.* **2020**, *22,* 8572 − 8577.

[15] Gandelman M. *et al. Adv. Synth. Catal.* **2011**, *353*, 1438 − 1442

then added to a PCR Eppendorf containing 4CzIPN (5 µL of a 1 nmol/µL soln in DMSO, 5 nmol, 0.5 equiv). TTMSOH (10 µL of a 40 nmol/µL soln in DMSO, 400 nmol, 40 equiv), Na_2CO_3 (2.5 µL of a 400 nmol/µL soln in H_2O, 1000 nmol, 100 equiv), and DNA-tethered alkene (5 µL of a 2 nmol/µL soln in H_2O, 10 nmol, 1.0 equiv) were then added, and the mixture was mixed by pipetting back and forth. The PCR tube was then capped and irradiated for 5 min with Kessil H150-blue lamps at a distance of 1.5 inches. The reaction was then diluted with H_2O (100 µL), filtered, and analyzed by LC/MS.

General Procedure for telescoped reactions from alcohol



From a modified procedure[16]:
To a stirred solution of alcohol (0.1 mmol) in dry DMF (0.2 mL) was added a solution of methyltriphenoxyphosphonium iodide (0.1 mmol, 1 equiv) in dry DMF (0.2 mL). The reaction was stirred at rt under a N_2-atmosphere, and the flask was covered with aluminum foil. After 1 h, 16 µL of reaction mixture was diluted with 84 µL of DMSO. Assuming full conversion of the alcohol to the corresponding iodide is reached, the concentration of this solution is 40 mM in a mixture of DMF/DMSO (1:5.2).
10 µL of the iodide solution (40 mmol/L, 40 equiv) is then added to a PCR Eppendorf containing 4CzIPN (5 µL of a 1 nmol/µL soln in DMSO, 5 nmol, 0.5 equiv). TTMSOH (10 µL of a 40 nmol/µL soln in DMSO, 400 nmol, 40 equiv), Na_2CO_3 (2.5 µL of a 400 nmol/µL soln in H_2O, 1000 nmol, 100 equiv), and DNA-tethered alkene (5 µL of a 2 nmol/µL soln in H_2O, 10 nmol, 1.0 equiv) were then added, and the mixture was mixed by pipetting back and forth. The PCR tube was then capped and irradiated for 5 min with Kessil H150-blue lamps at a distance of 1.5 inches. The reaction was then diluted with H_2O (100 µL), filtered, and analyzed by LC/MS.

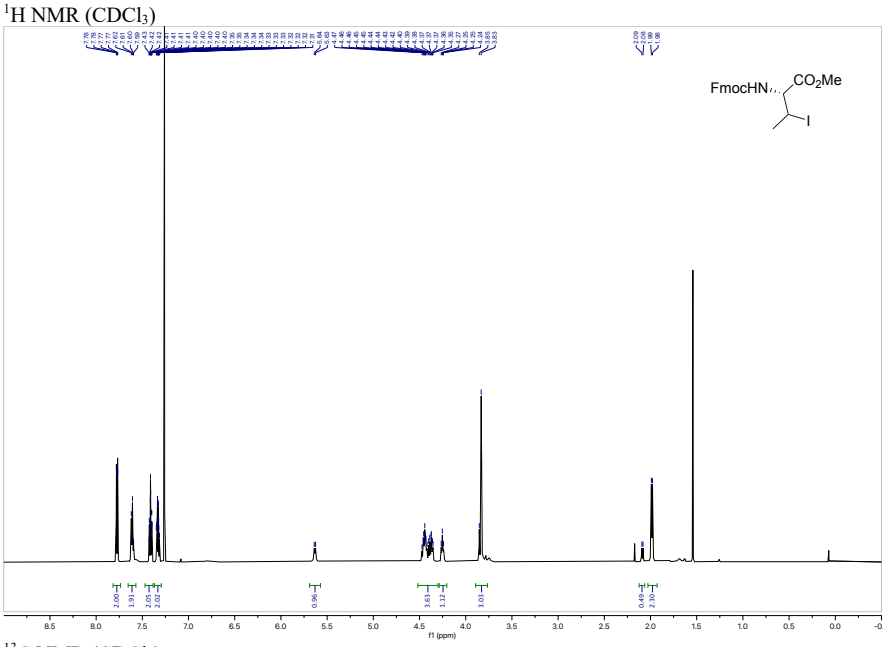
***Note**: TTMSOH was kept in the freezer under argon. The TTMSOH stock solution has to be prepared freshly and used directly.*

[16] Bunch L. *et al. ACS Chem. Neurosci.* **2020**, *11*, 702 − 714

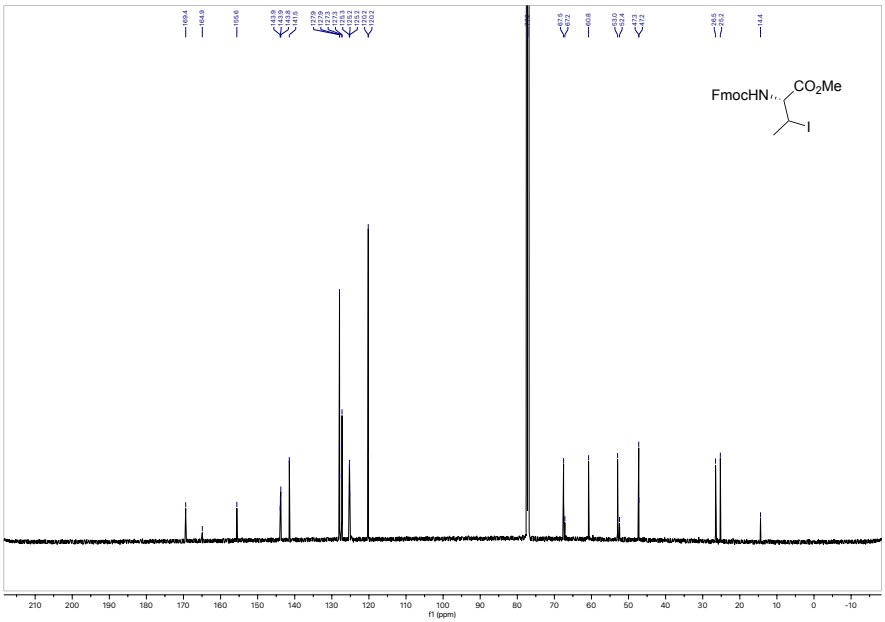
5. NMR Spectra

Methyl (2R)-2-((((9H-Fluoren-9-yl)methoxy)carbonyl)amino)-3-iodobutanoate (S3)

^{1}H NMR ($CDCl_3$)

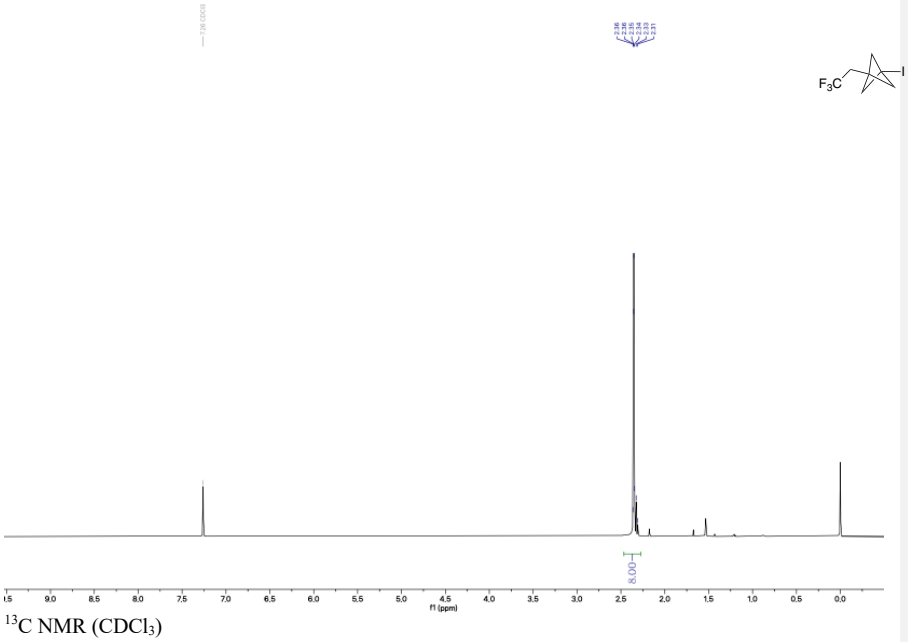


^{13}C NMR ($CDCl_3$)

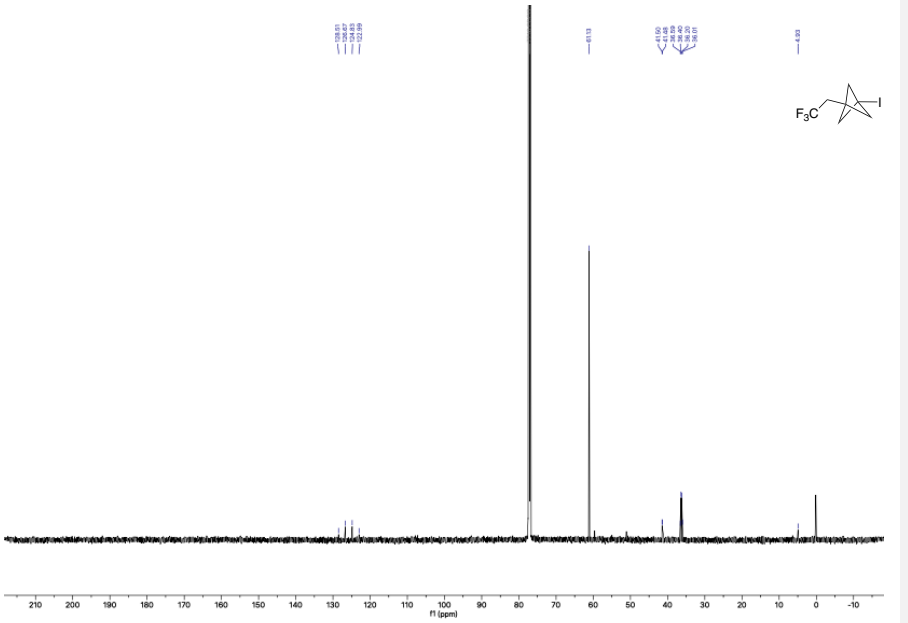


1-Iodo-3-(2,2,2-trifluoroethyl)bicyclo[1.1.1]pentane (1b)

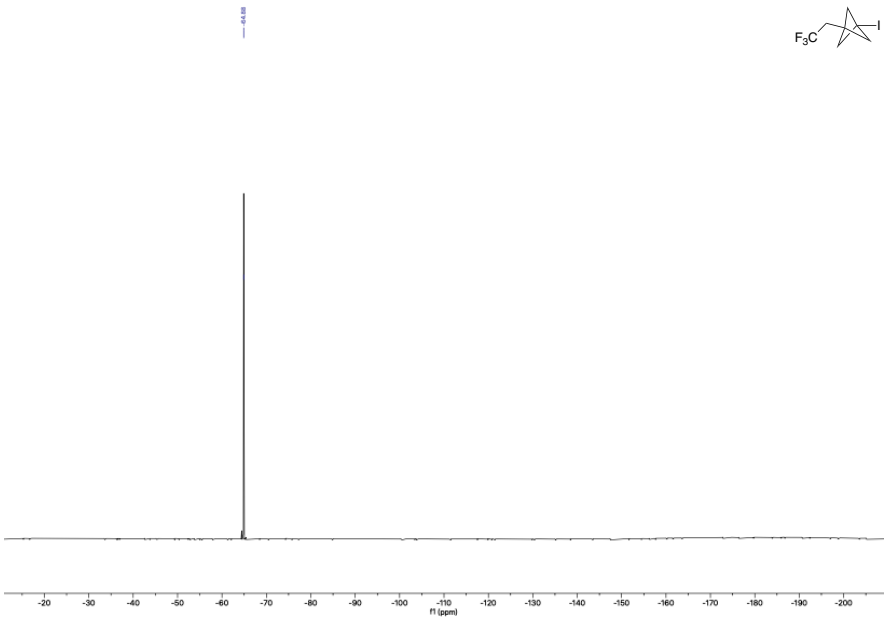
^{1}H NMR ($CDCl_3$)



^{13}C NMR ($CDCl_3$)

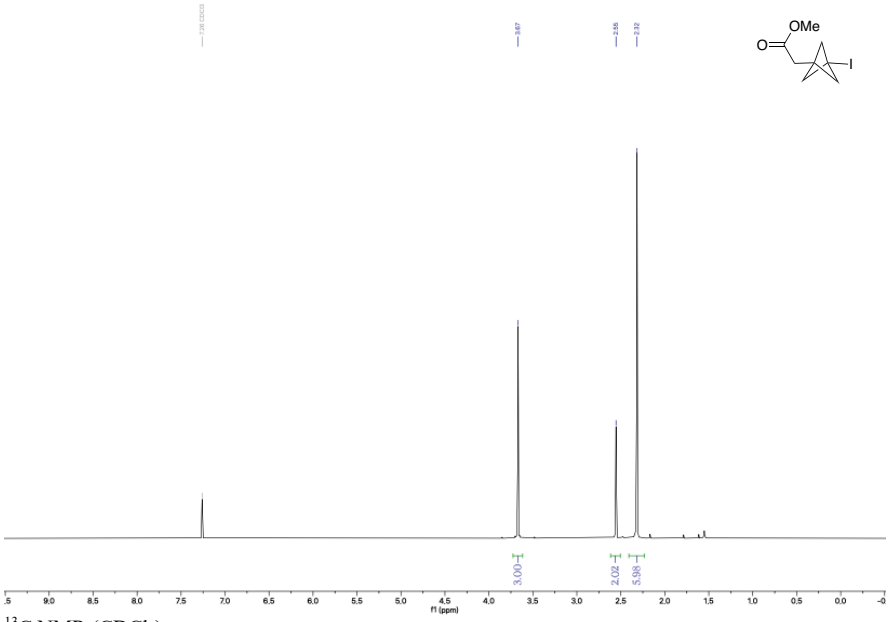


^{19}F NMR ($CDCl_3$)

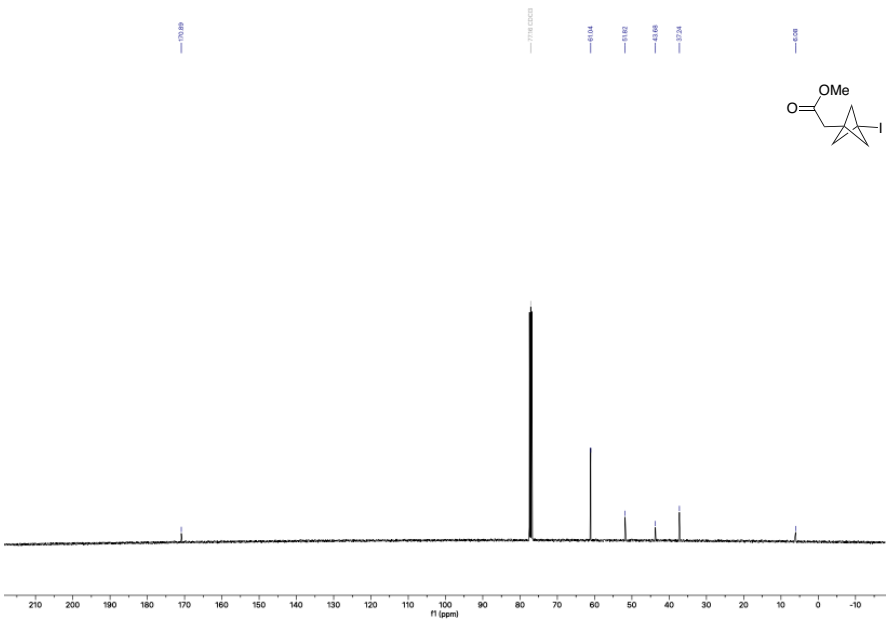


Methyl 2-(3-Iodobicyclo[1.1.1]pentan-1-yl)acetate (1ea)

^{1}H NMR ($CDCl_3$)

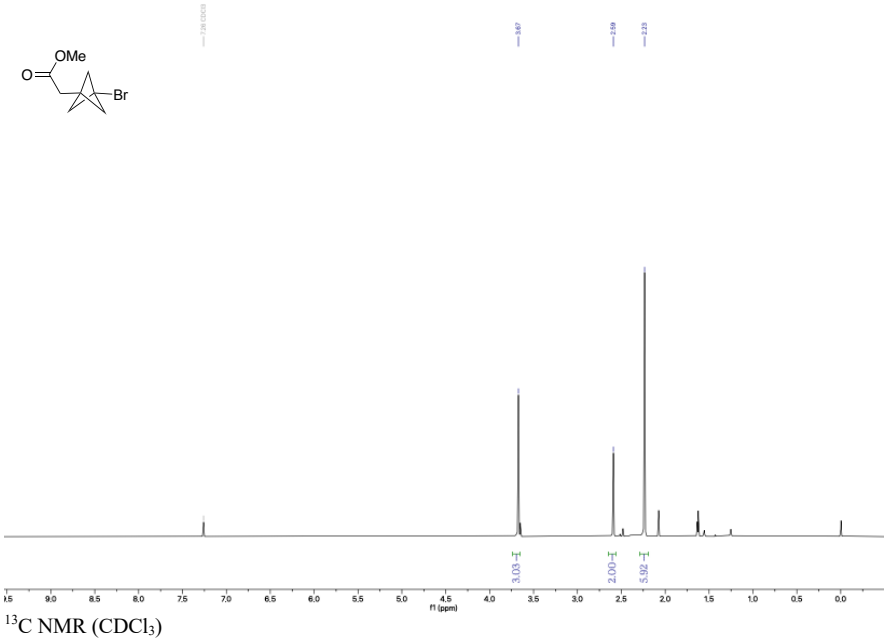


^{13}C NMR ($CDCl_3$)

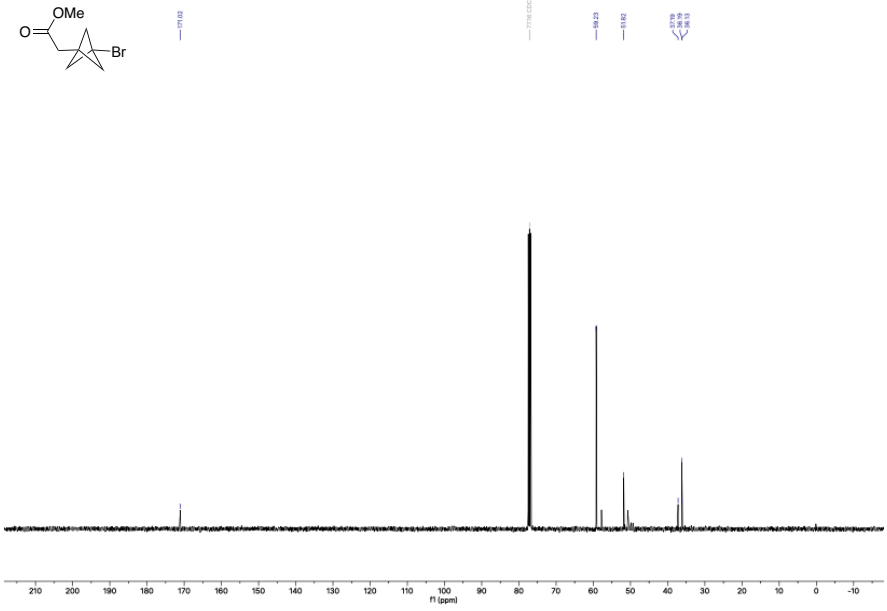


Methyl 2-(3-Bromobicyclo[1.1.1]pentan-1-yl)acetate (1eb)

^{1}H NMR ($CDCl_3$)

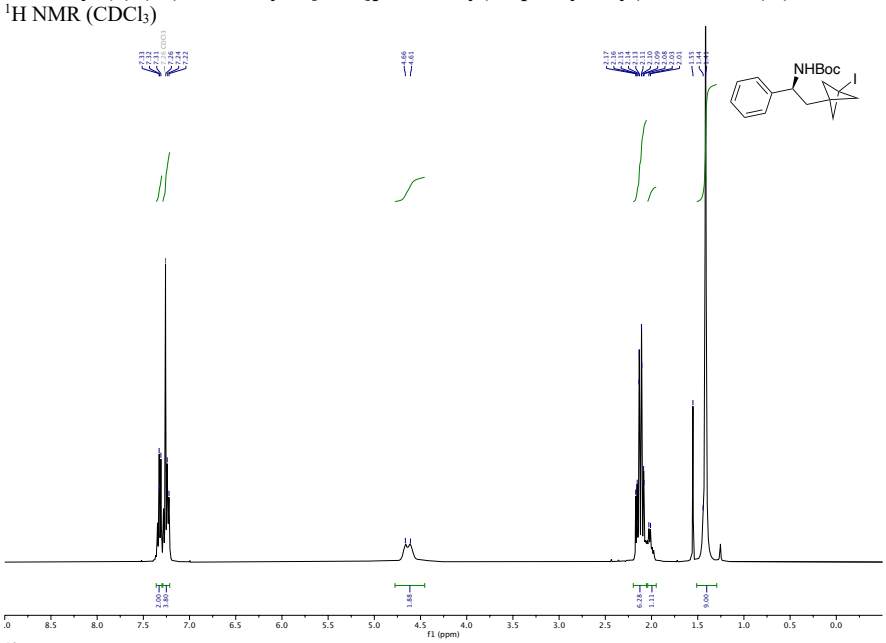


^{13}C NMR ($CDCl_3$)

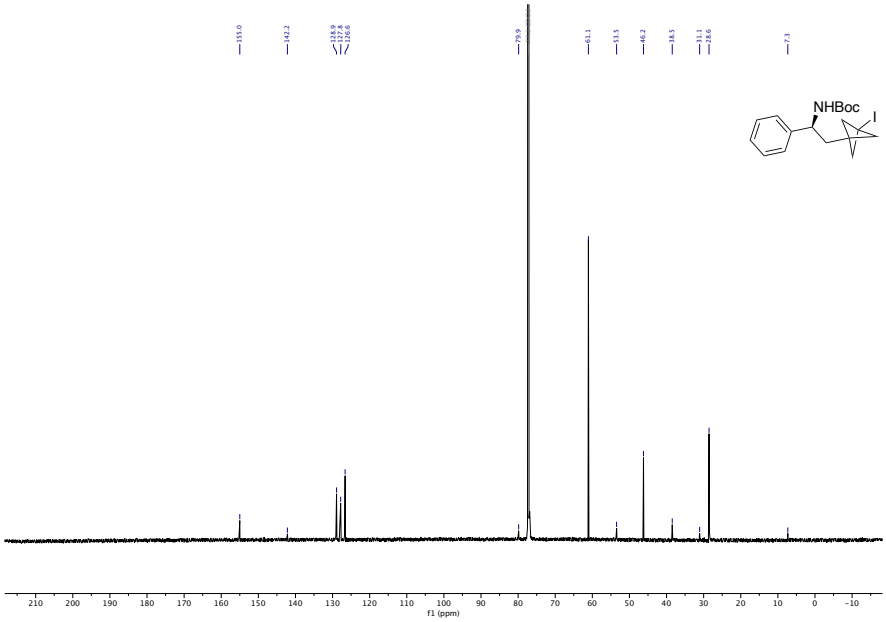


***tert*-Butyl (*S*)-(2-(3-Iodobicyclo[1.1.1]pentan-1-yl)-1-phenylethyl)carbamate (1f)**

^{1}H NMR ($CDCl_3$)

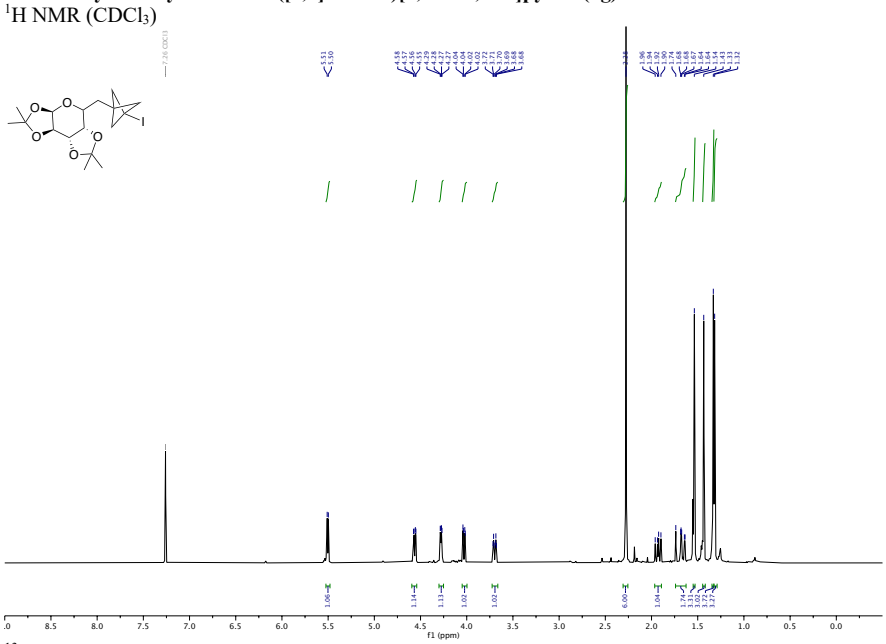


^{13}C NMR ($CDCl_3$)

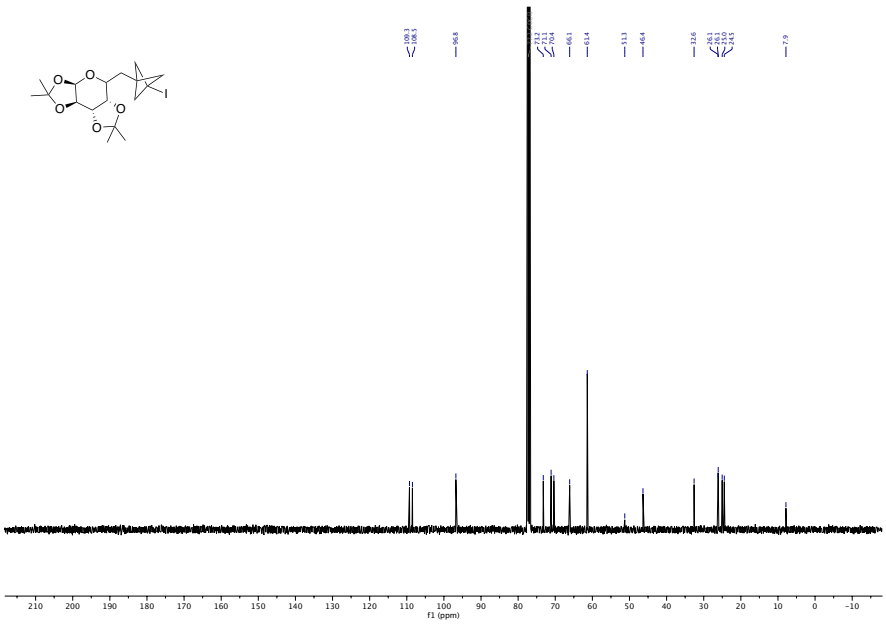


(3aS,5R,5aR,8aR,8bS)-5-((3-iodobicyclo[1.1.1]pentan-1-yl)methyl)-2,2,7,7-tetramethyltetrahydro-5H-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran (1g)

^{1}H NMR ($CDCl_3$)

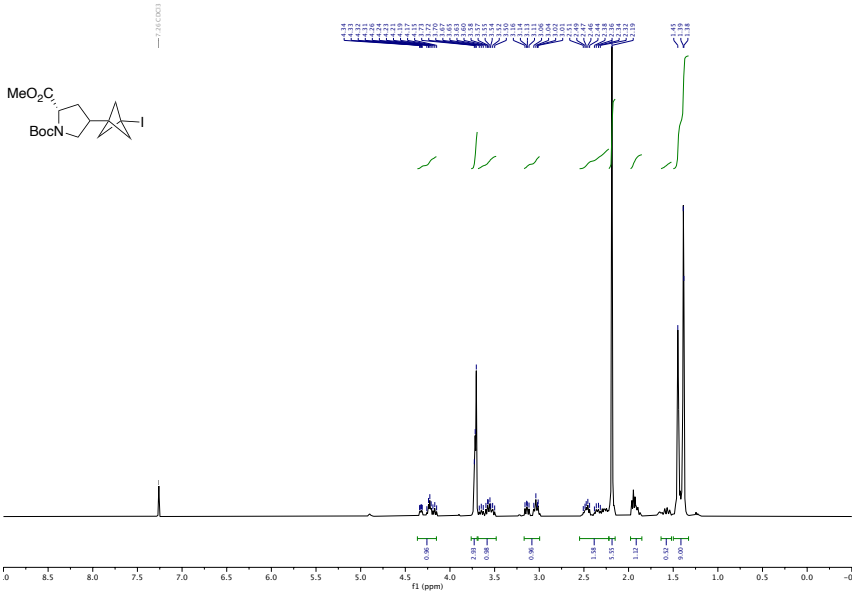


^{13}C NMR ($CDCl_3$)

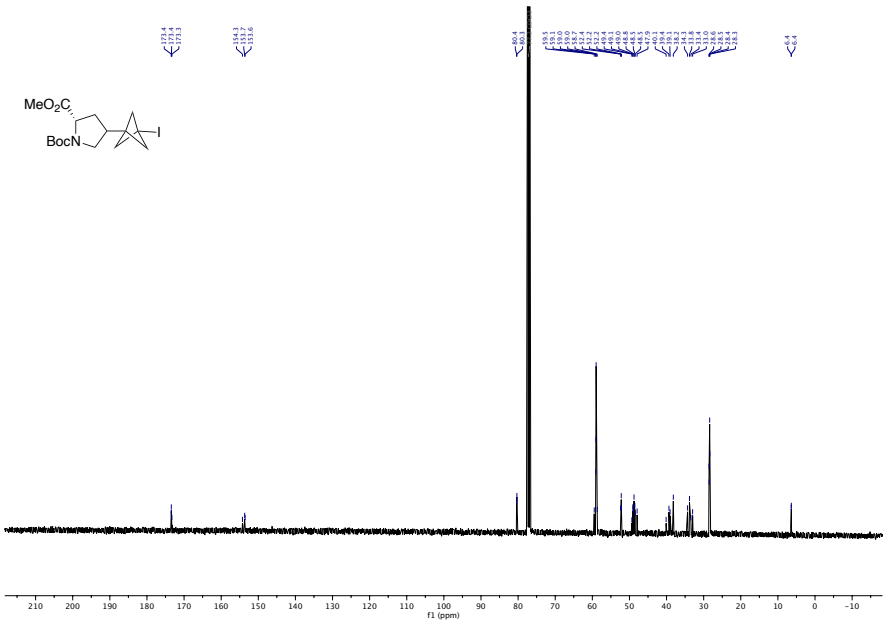


1-(*tert*-Butyl) 2-Methyl (2*S*)-4-(3-iodobicyclo[1.1.1]pentan-1-yl)pyrrolidine-1,2-dicarboxylate (1j)

^{1}H NMR ($CDCl_3$)

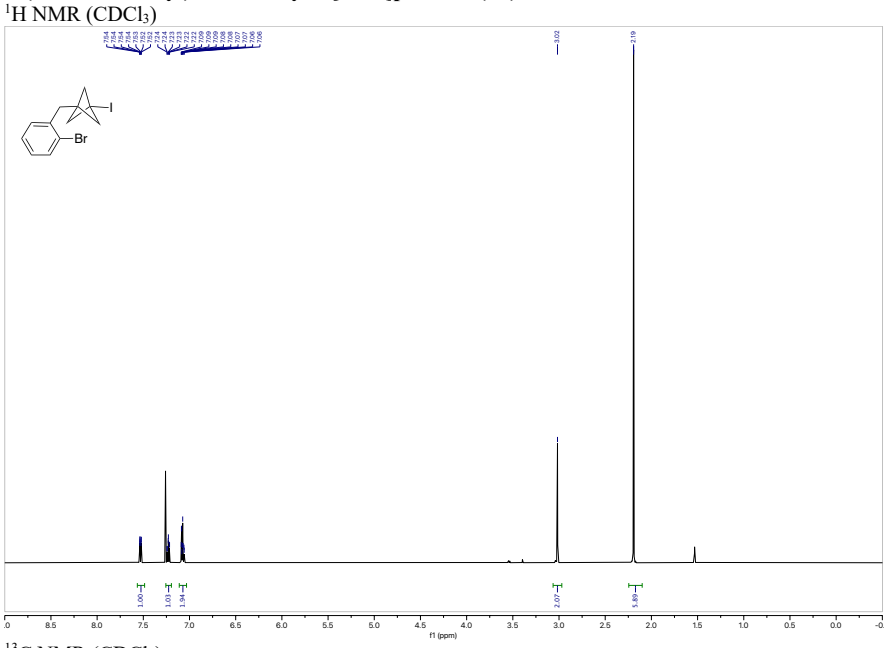


^{13}C NMR ($CDCl_3$)

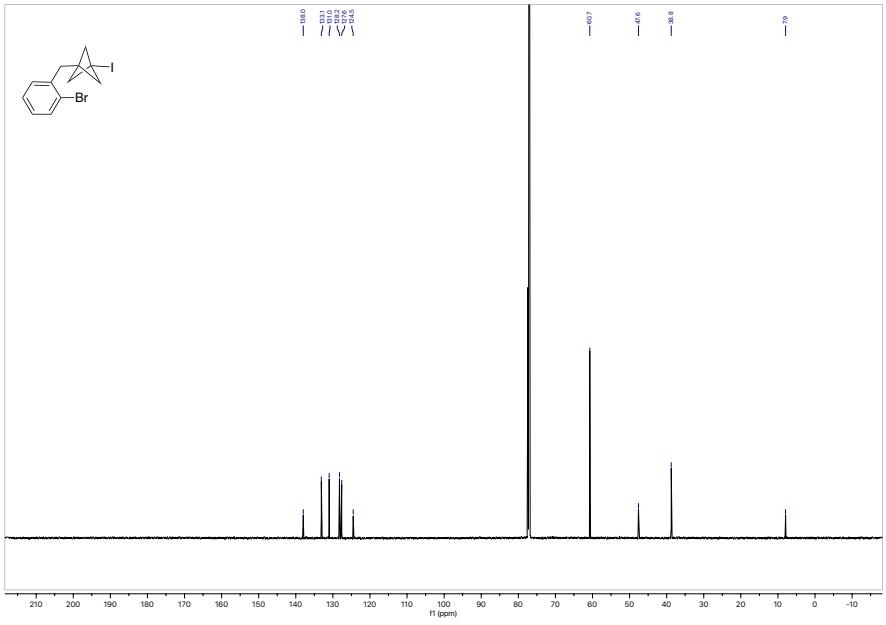


1-(2-Bromobenzyl)-3-iodobicyclo[1.1.1]pentane (1k)

^{1}H NMR ($CDCl_3$)

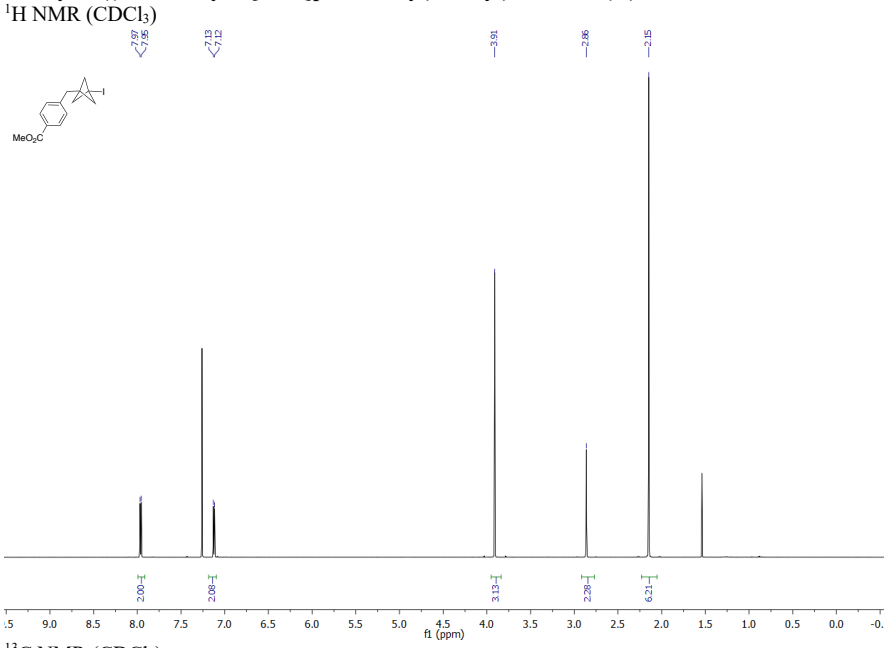


^{13}C NMR ($CDCl_3$)

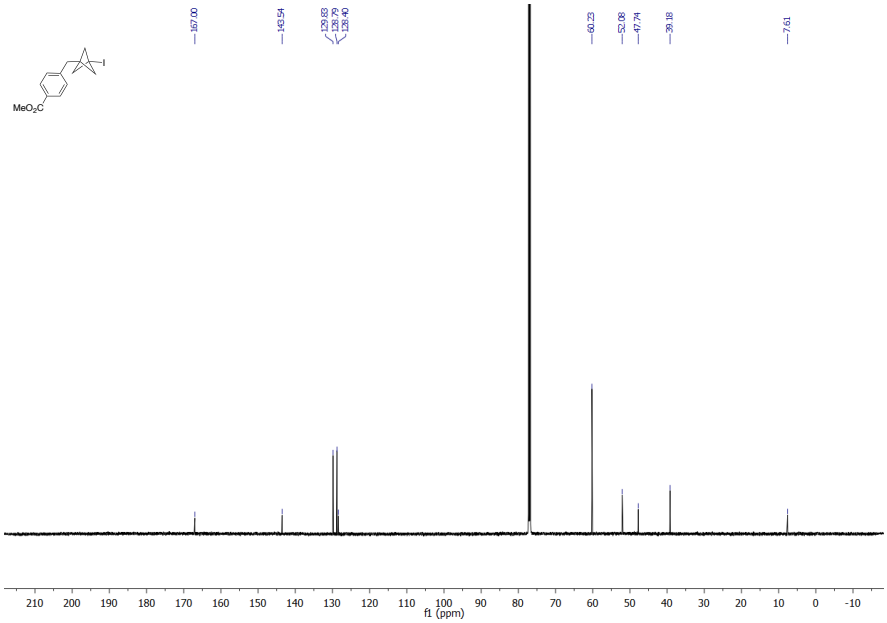


Methyl 4-((3-Iodobicyclo[1.1.1]pentan-1-yl)methyl)benzoate (1l)

^{1}H NMR ($CDCl_3$)

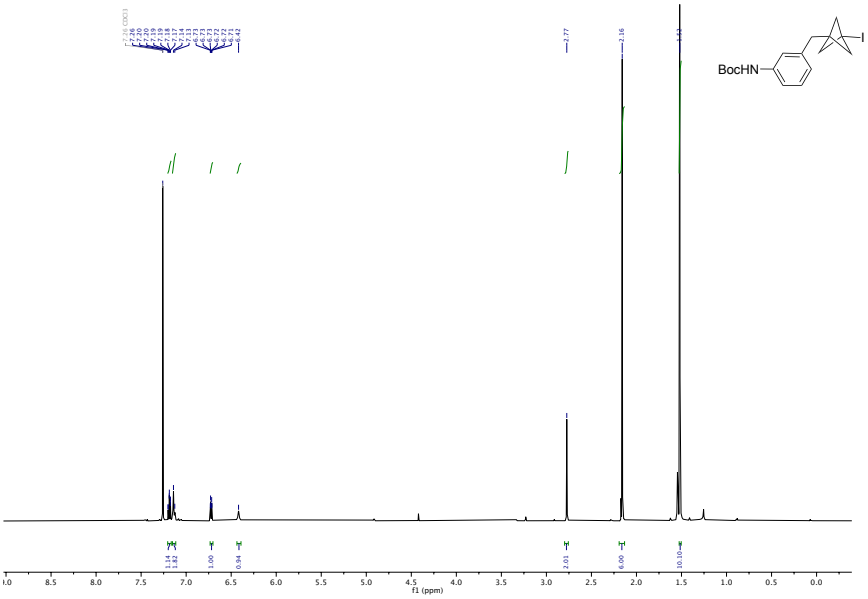


^{13}C NMR ($CDCl_3$)

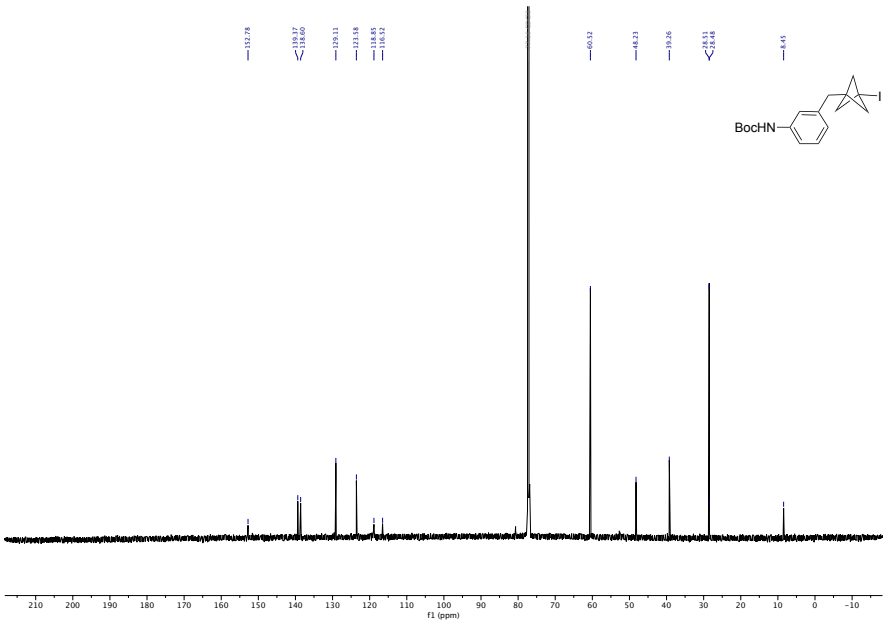


***tert*-Butyl (3-((3-iodobicyclo[1.1.1]pentan-1-yl)methyl)phenyl)carbamate (1m)**

^{1}H NMR ($CDCl_3$)

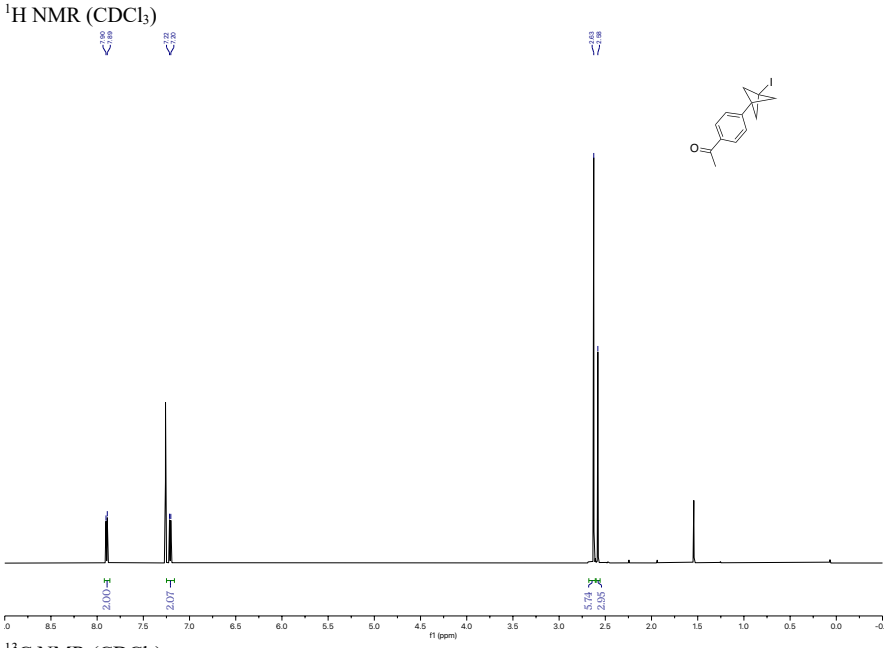


^{13}C NMR ($CDCl_3$)

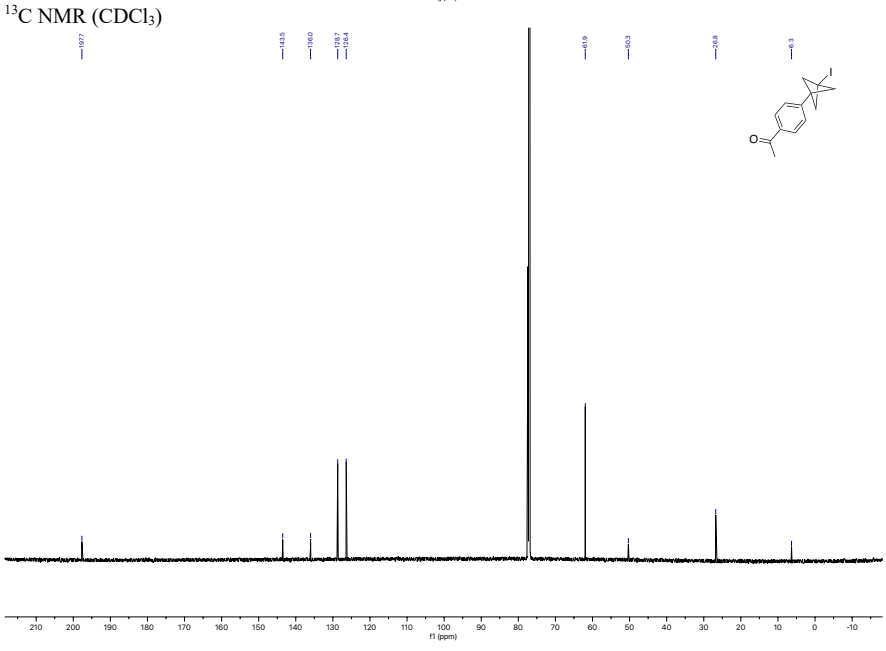


1-(4-(3-Iodobicyclo[1.1.1]pentan-1-yl)phenyl)ethan-1-one (1p)

^{1}H NMR ($CDCl_3$)

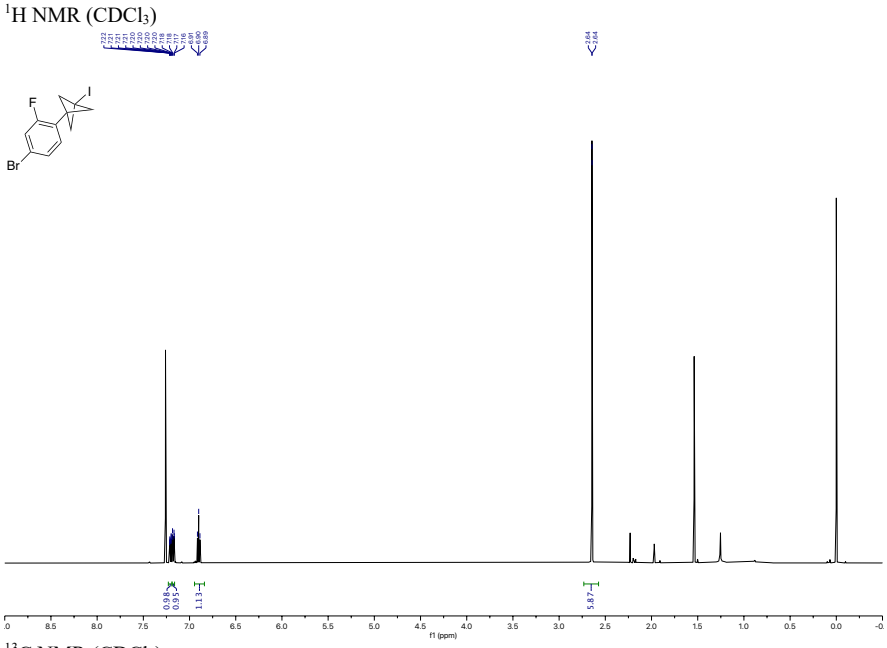


^{13}C NMR ($CDCl_3$)

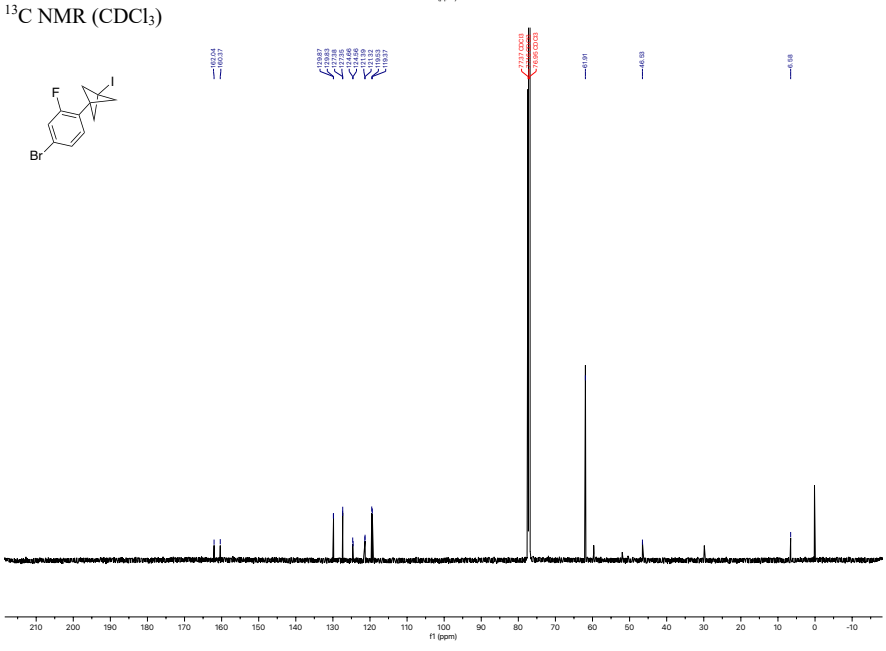


1-(4-Bromo-2-fluorophenyl)-3-iodobicyclo[1.1.1]pentane (1q)

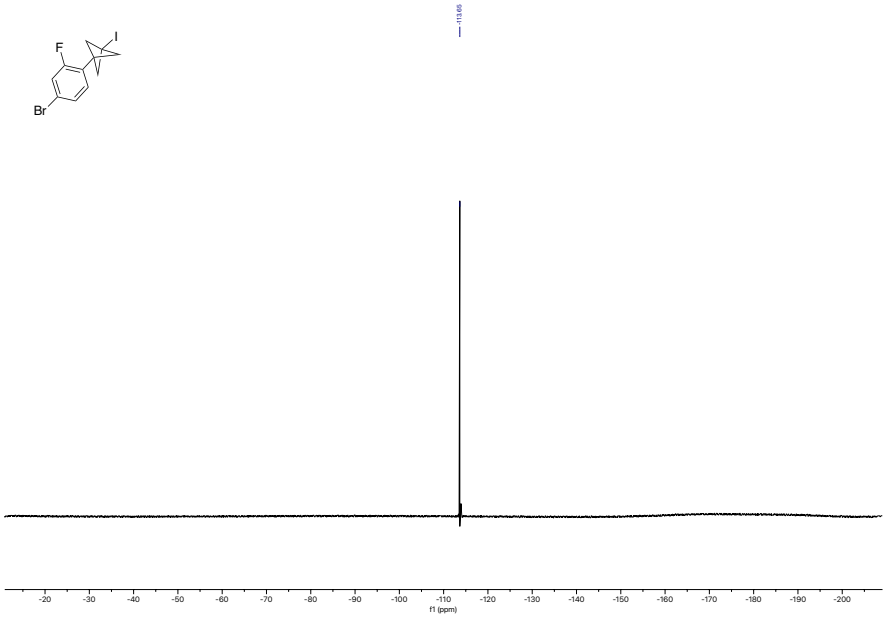
^{1}H NMR ($CDCl_3$)



^{13}C NMR ($CDCl_3$)

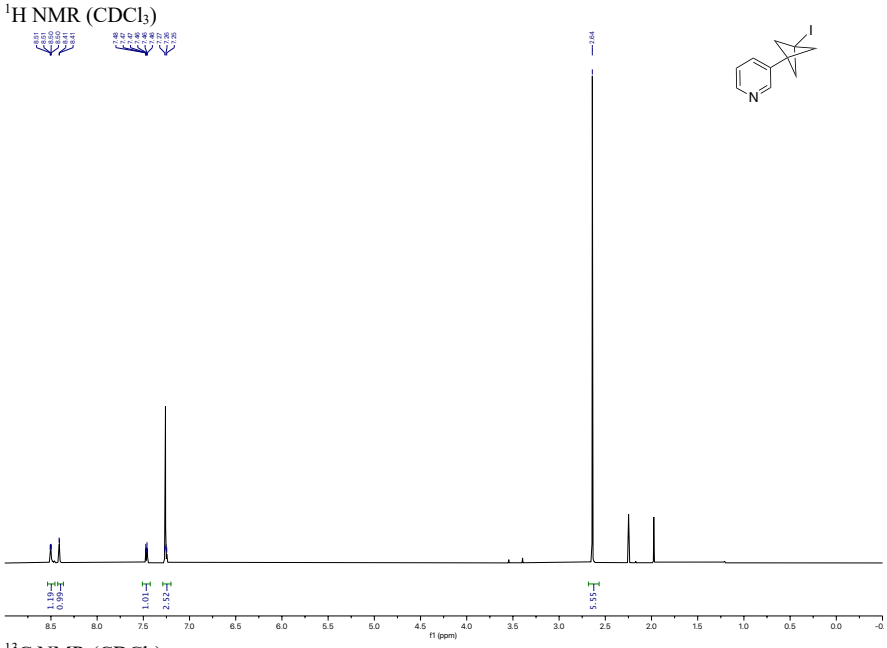


^{19}F NMR ($CDCl_3$)

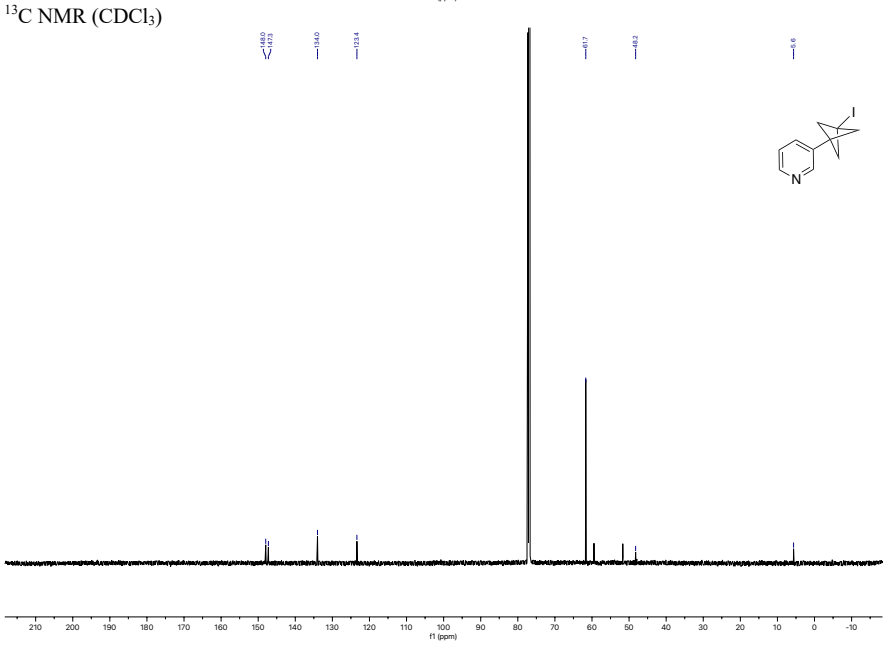


3-(3-Iodobicyclo[1.1.1]pentan-1-yl)pyridine (1s)

^{1}H NMR ($CDCl_3$)

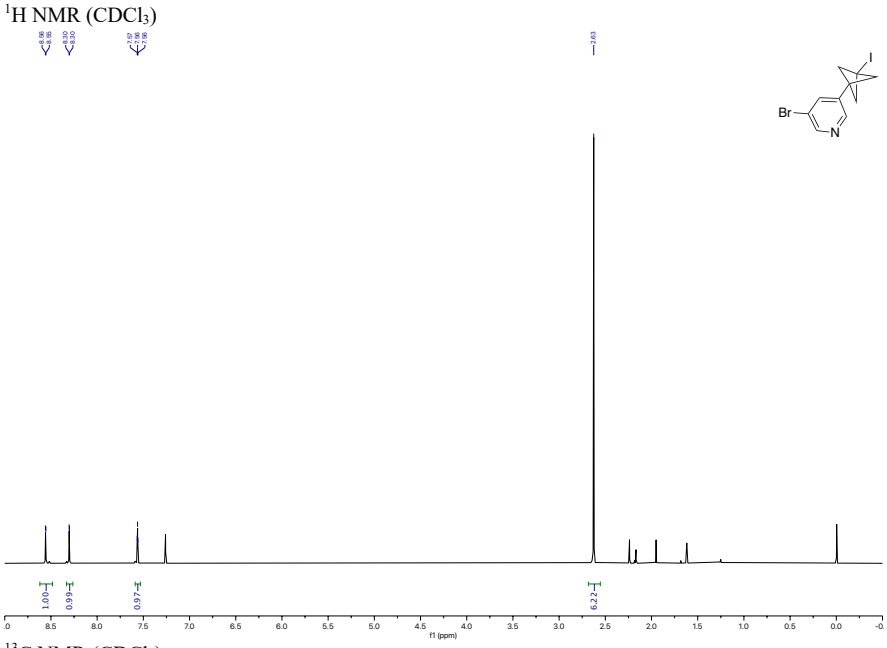


^{13}C NMR ($CDCl_3$)

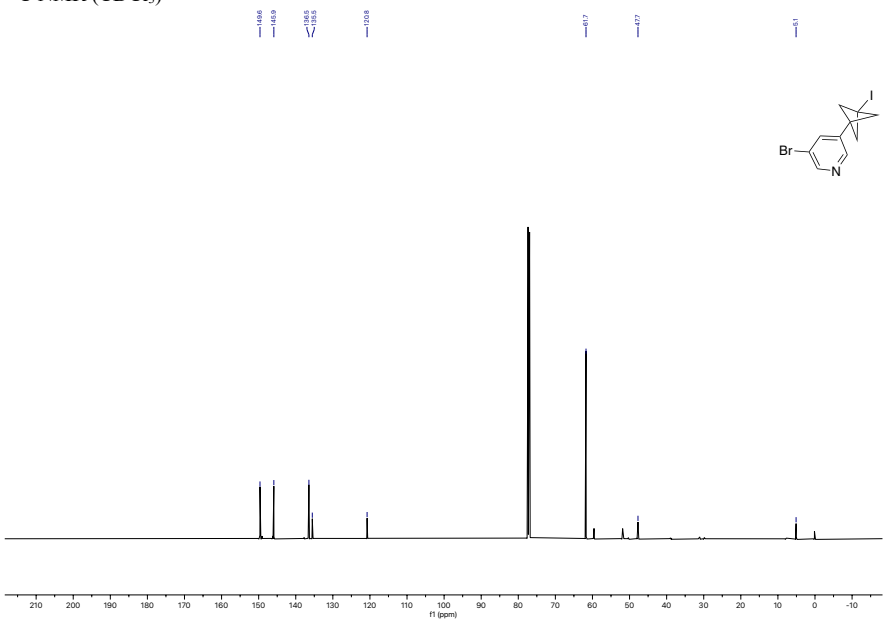


3-Bromo-5-(3-iodobicyclo[1.1.1]pentan-1-yl)pyridine (1t)

^{1}H NMR ($CDCl_3$)

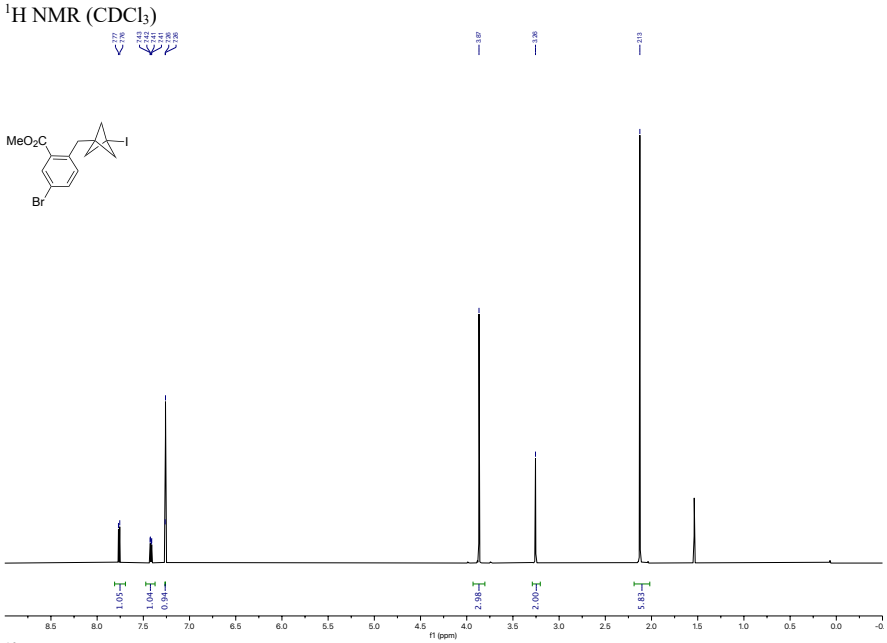


^{13}C NMR ($CDCl_3$)

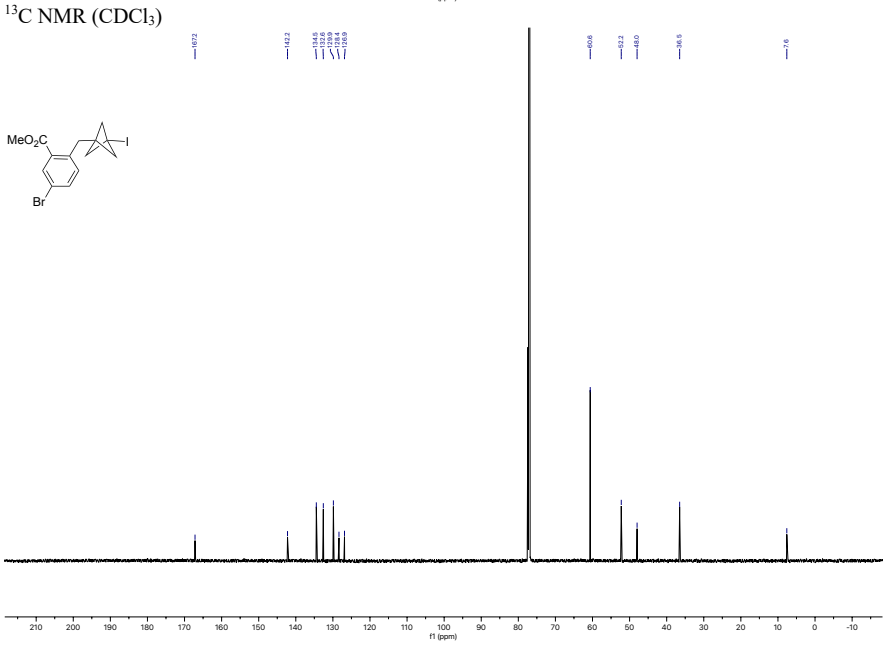


Methyl 5-bromo-2-((3-iodobicyclo[1.1.1]pentan-1-yl)methyl)benzoate (1w)

^{1}H NMR ($CDCl_3$)

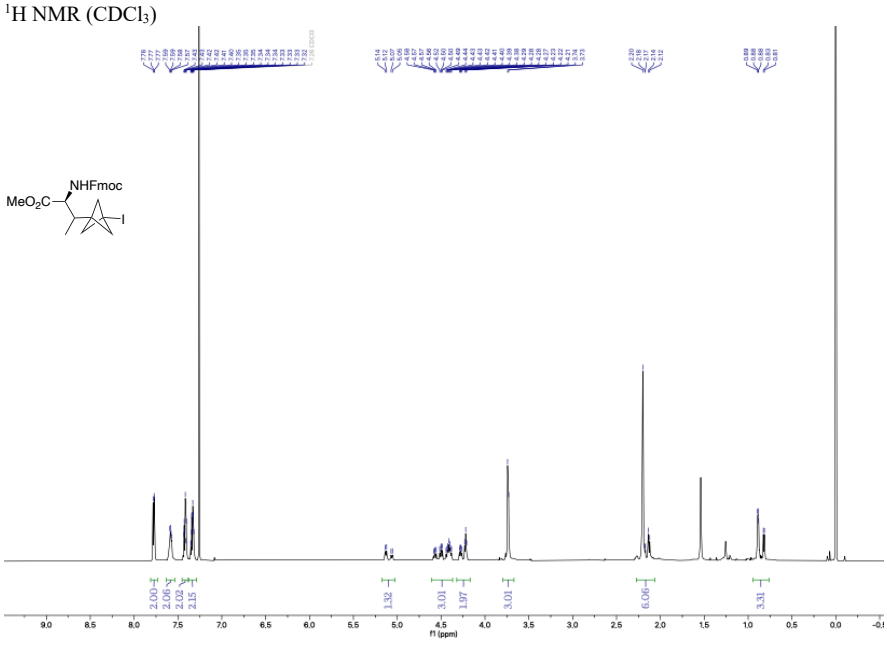


^{13}C NMR ($CDCl_3$)

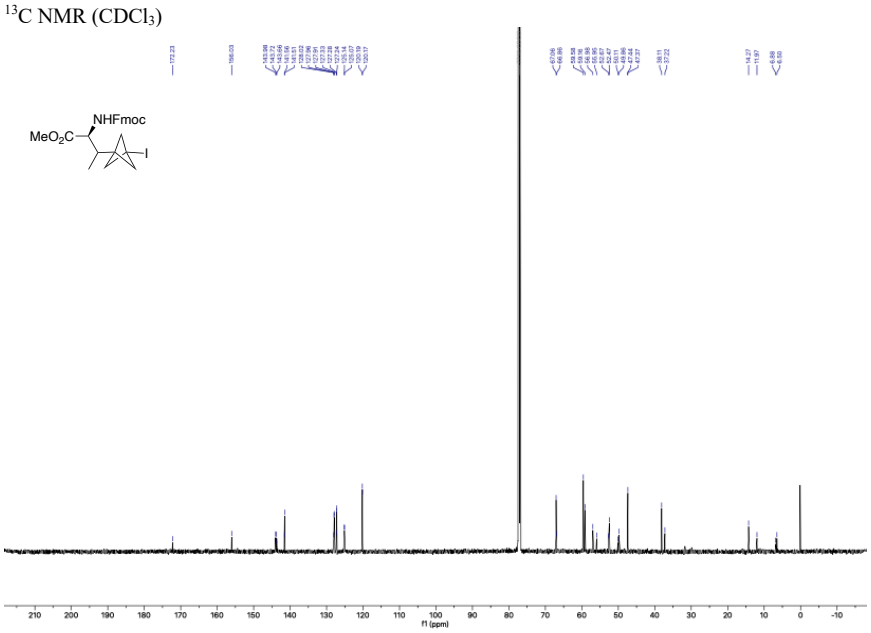


Methyl (2*S*)-2-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-3-(3-iodobicyclo[1.1.1]pentan-1-yl)butanoate (1x)

^{1}H NMR ($CDCl_3$)

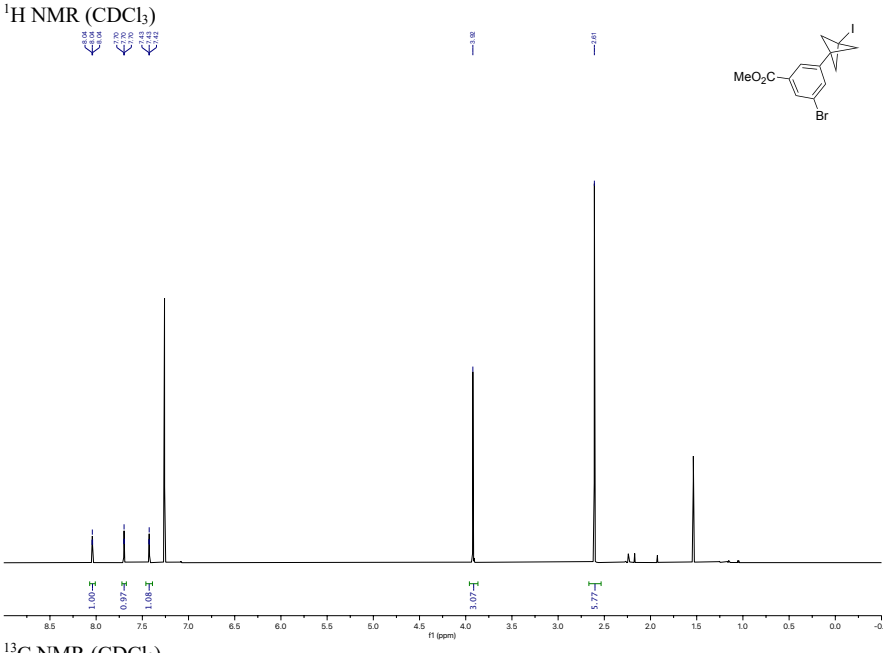


^{13}C NMR ($CDCl_3$)

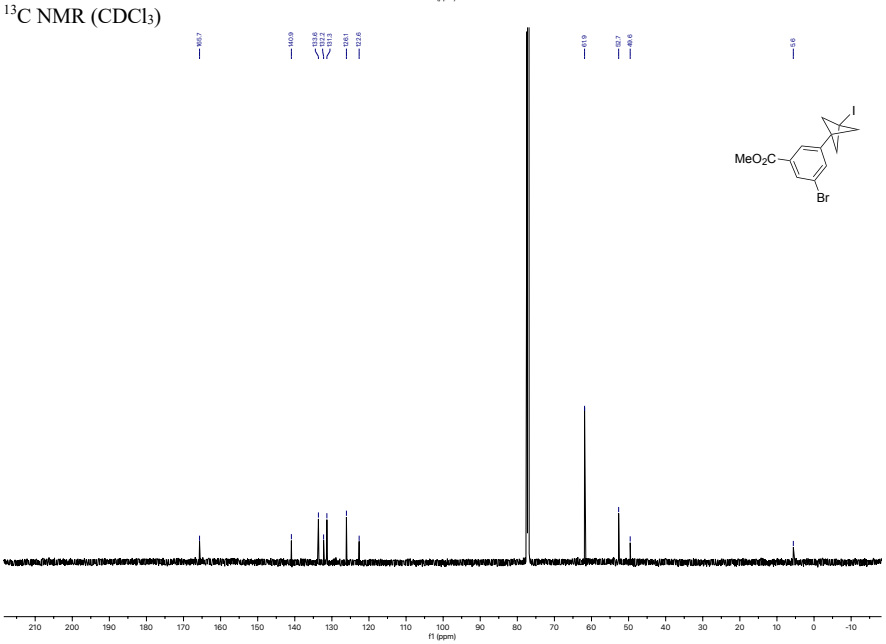


Methyl 3-bromo-5-(3-iodobicyclo[1.1.1]pentan-1-yl)benzoate (1y)

^{1}H NMR ($CDCl_3$)

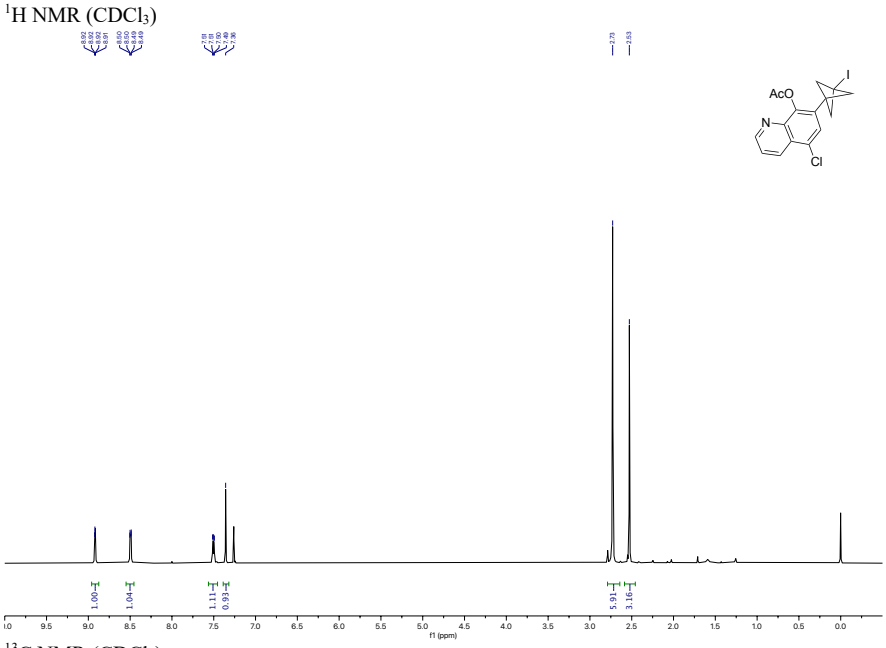


^{13}C NMR ($CDCl_3$)

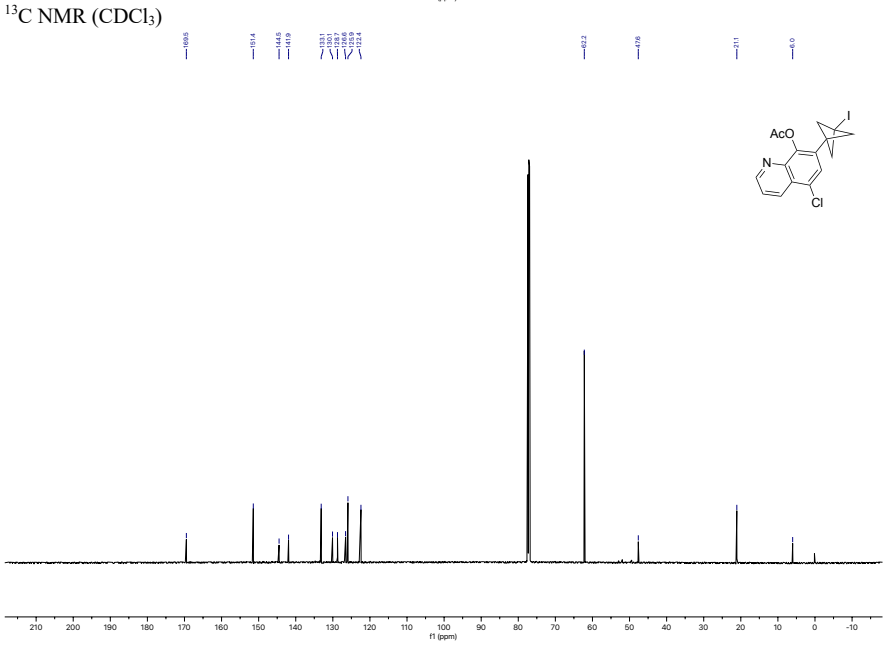


5-Chloro-7-(3-iodobicyclo[1.1.1]pentan-1-yl)quinolin-8-yl acetate (1z)

^{1}H NMR ($CDCl_3$)

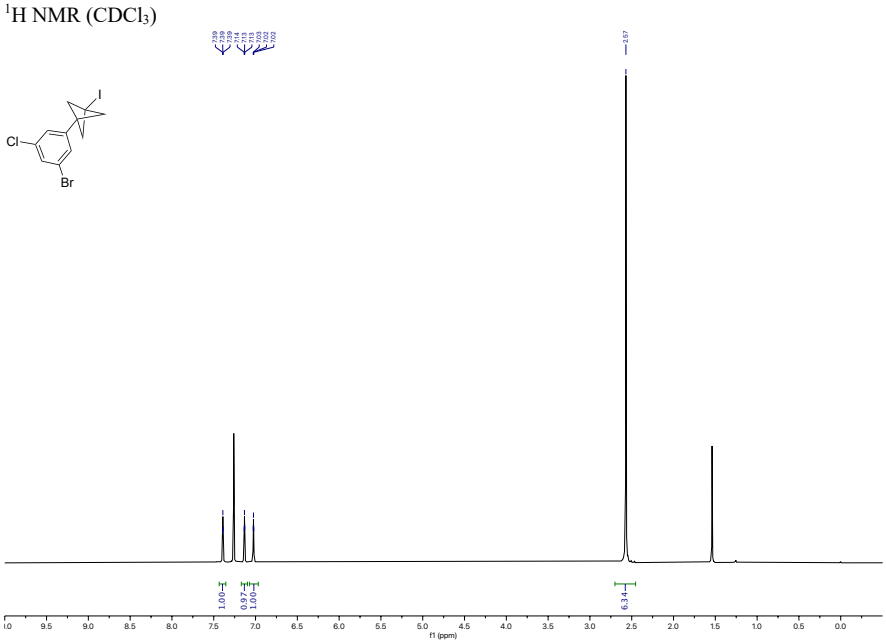


^{13}C NMR ($CDCl_3$)

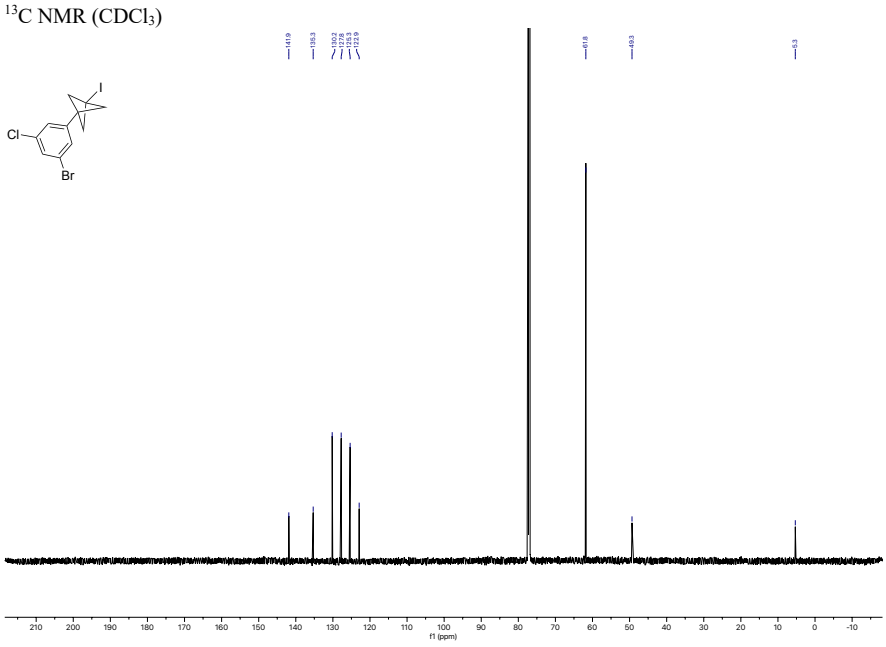


1-(3-Bromo-5-chlorophenyl)-3-iodobicyclo[1.1.1]pentane (1aa)

^{1}H NMR ($CDCl_3$)

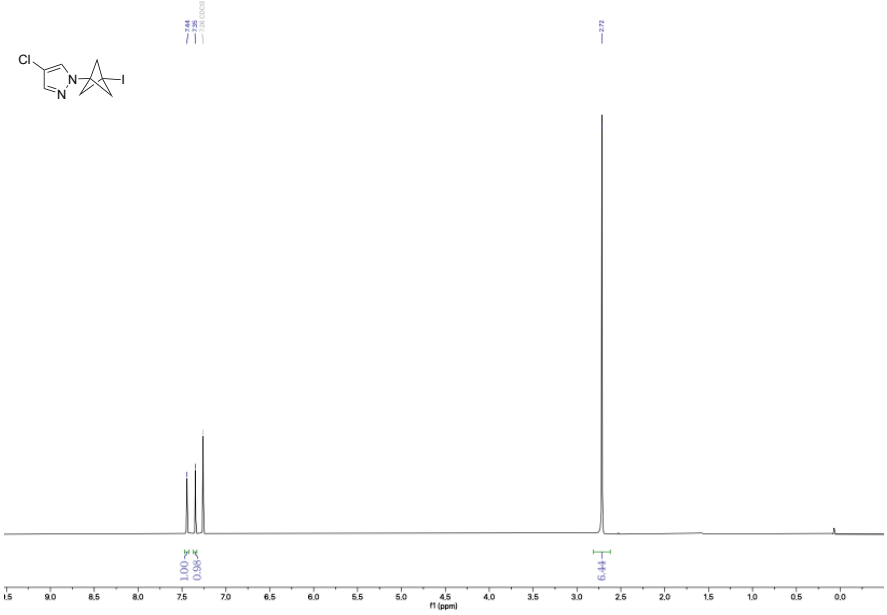


^{13}C NMR ($CDCl_3$)

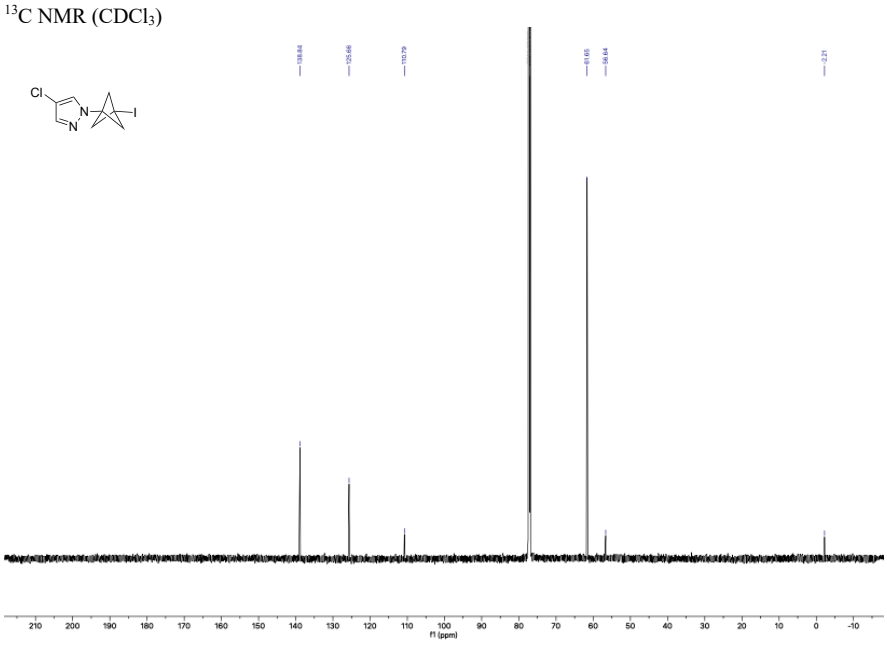


4-Chloro-1-(3-iodobicyclo[1.1.1]pentan-1-yl)-1*H*-pyrazole (1ab)

^{1}H NMR ($CDCl_3$)



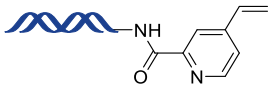
^{13}C NMR ($CDCl_3$)



6. UPLC/MS Spectra of DNA headpieces

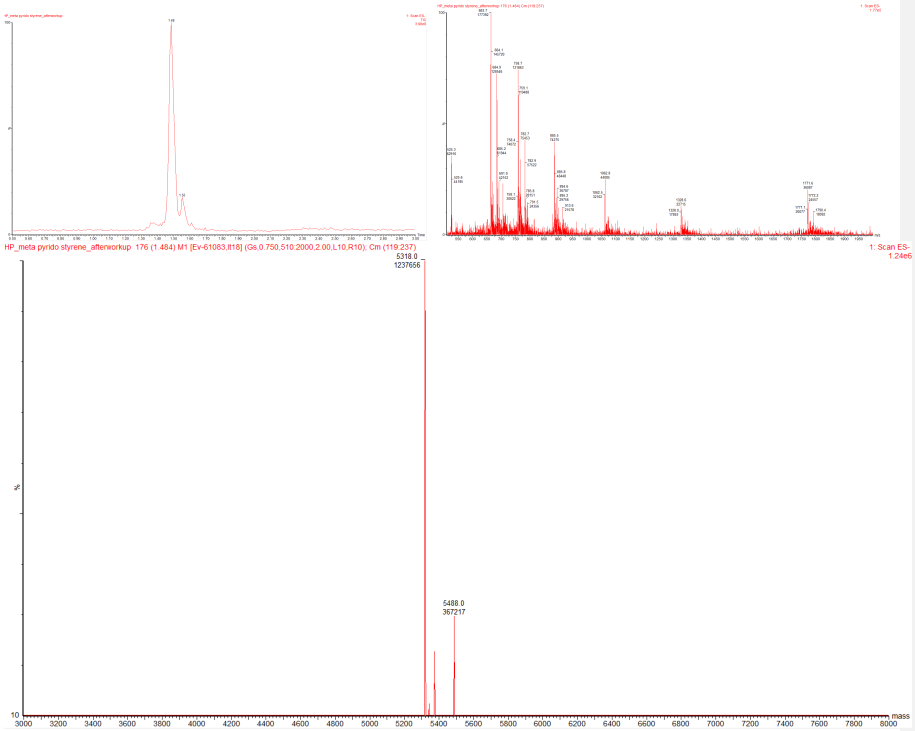
The synthesis of DNA- headpieces **HP-1**, **HP-2**, **HP-3**, **HP-4, HP-8** and **HP-9** was previously reported.[17, 2] **HP-5**, **HP-6** and **HP-7** were prepared according to a described procedure starting from the corresponding carboxylic acid.[2]

Mass spectra of HP-5



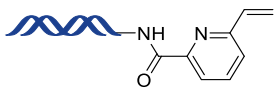
HP-5

5315.48 g/mol



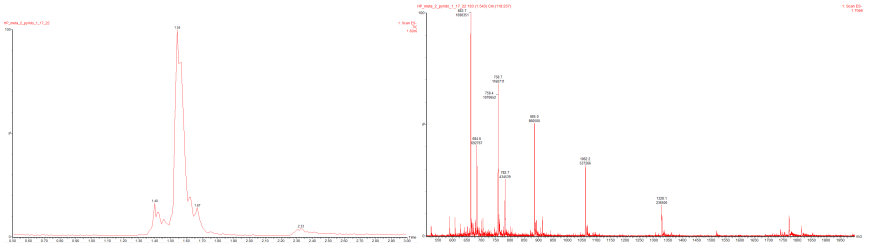
[17] Flanagan M. E. *et al. ChemMedChem* **2018**, *13*, 2159 – 2165

Mass spectra of HP-6

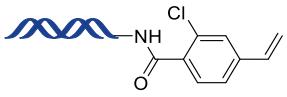


HP-6

5315.48 g/mol

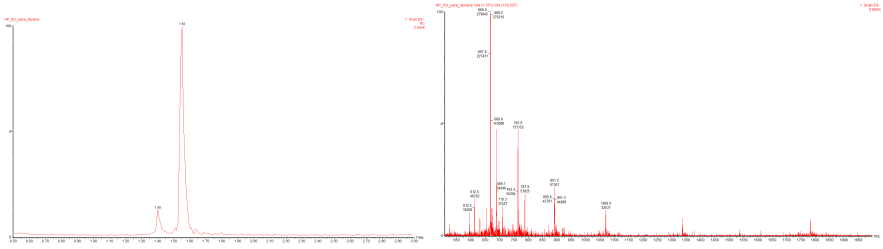


Mass spectra of HP-7



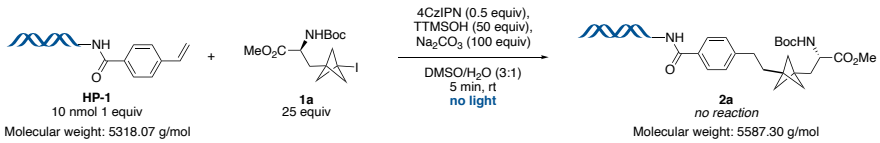
HP-7

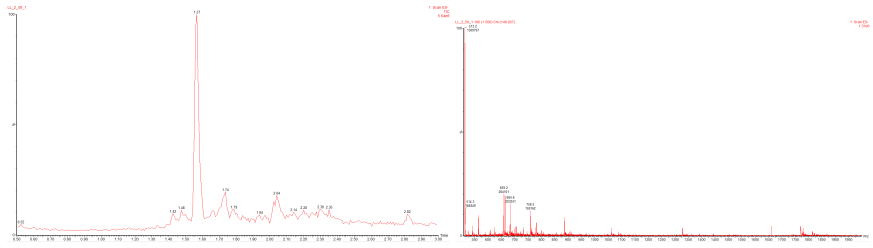
5349.04 g/mol

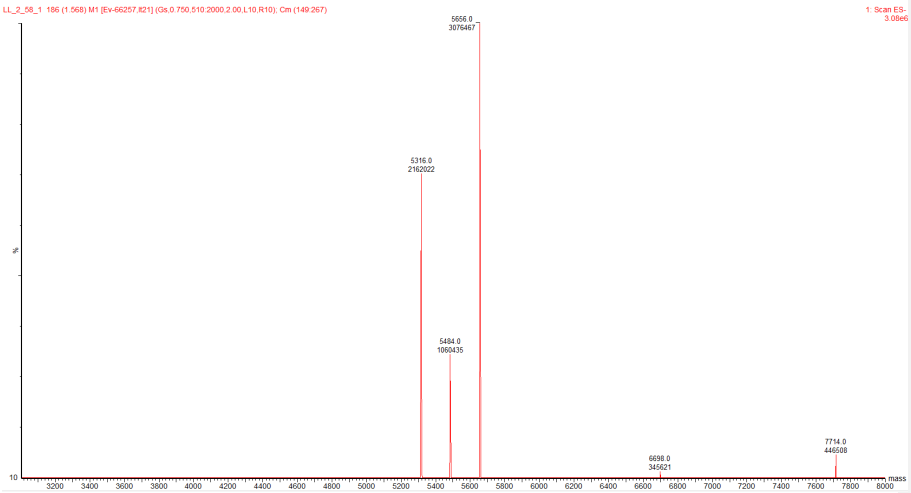


7. Control experiments for On-DNA reactions

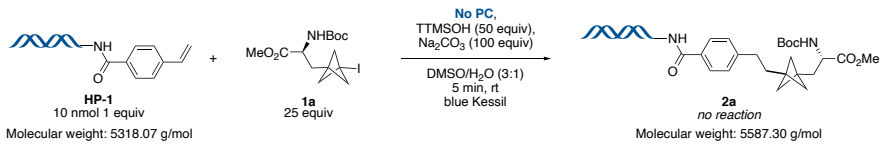
no light: *no reaction*

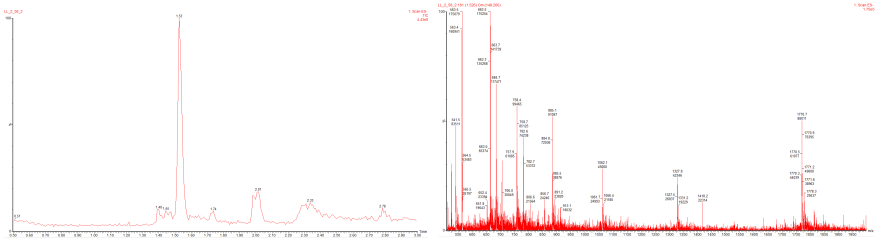


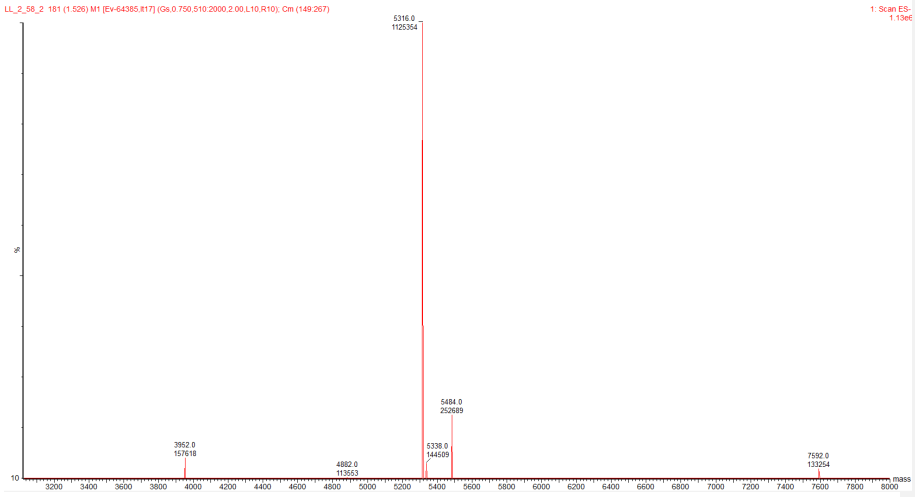




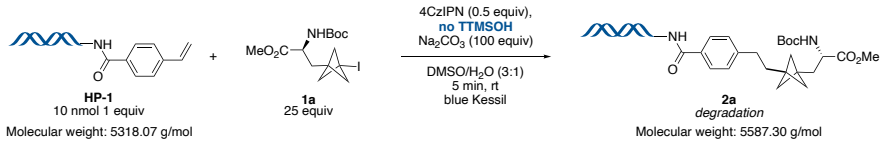
no photocatalyst: *no reaction*

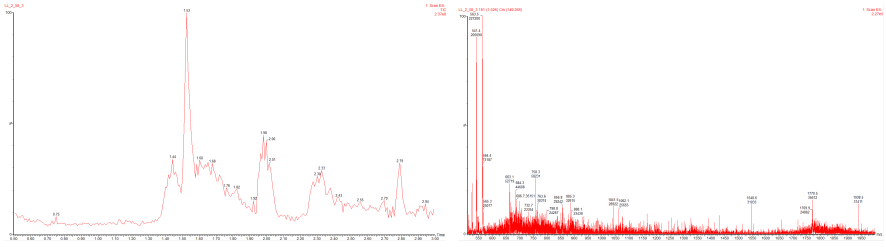


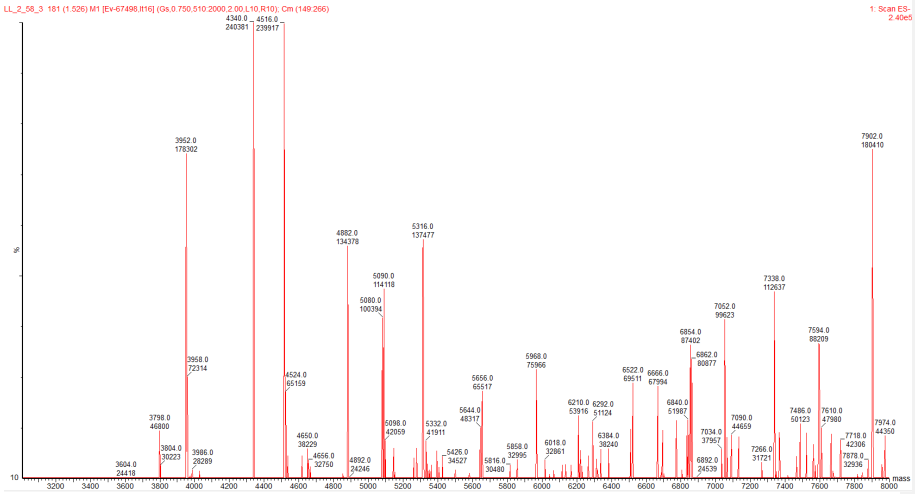




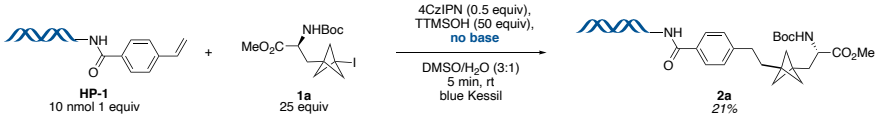
No TTMSOH: *degradation*

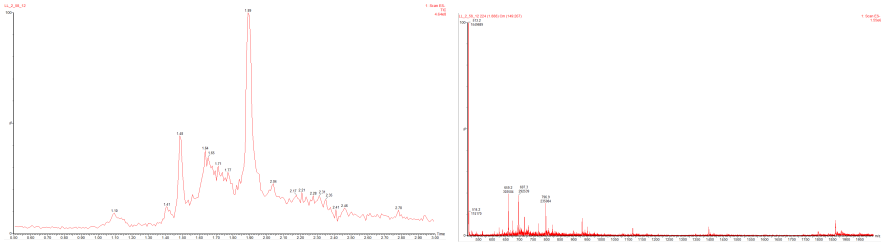


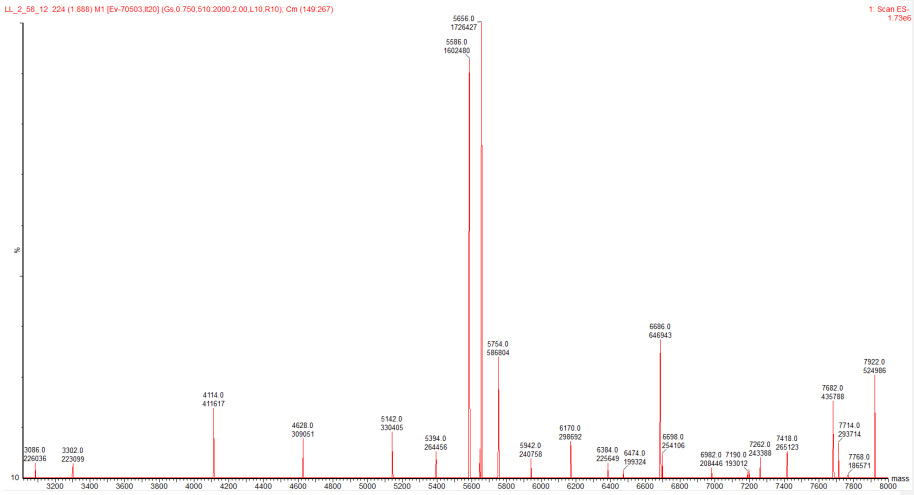




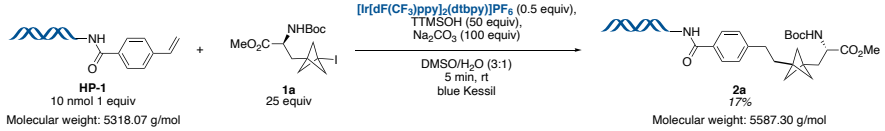
no base: *21% yield*

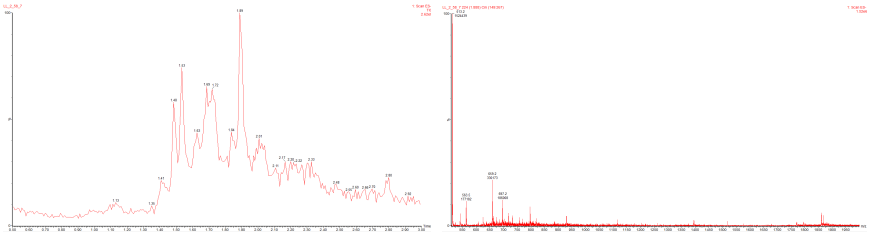


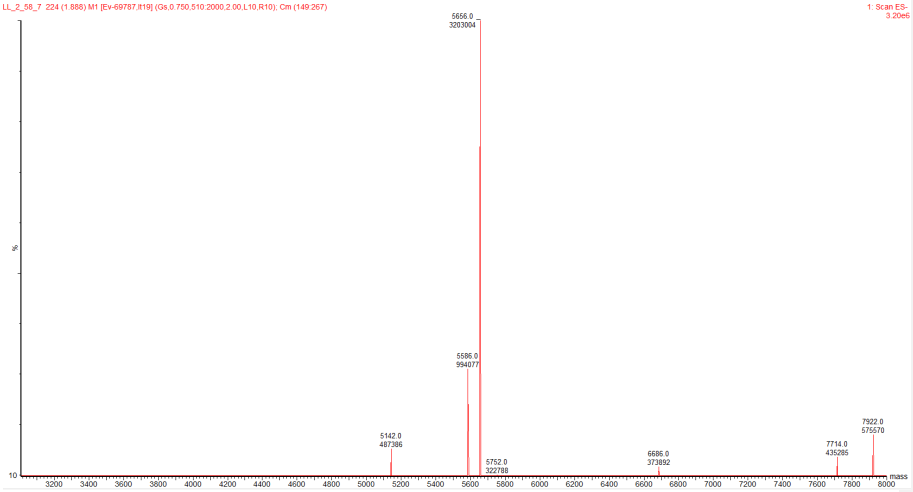




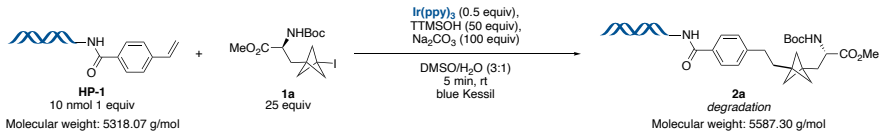
[Ir[dF(CF$_3$)ppy]$_2$(dtbbpy)]PF$_6$ instead of 4CzIPN: *17% yield*

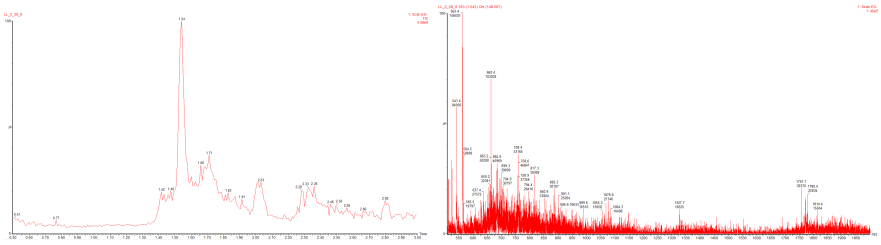


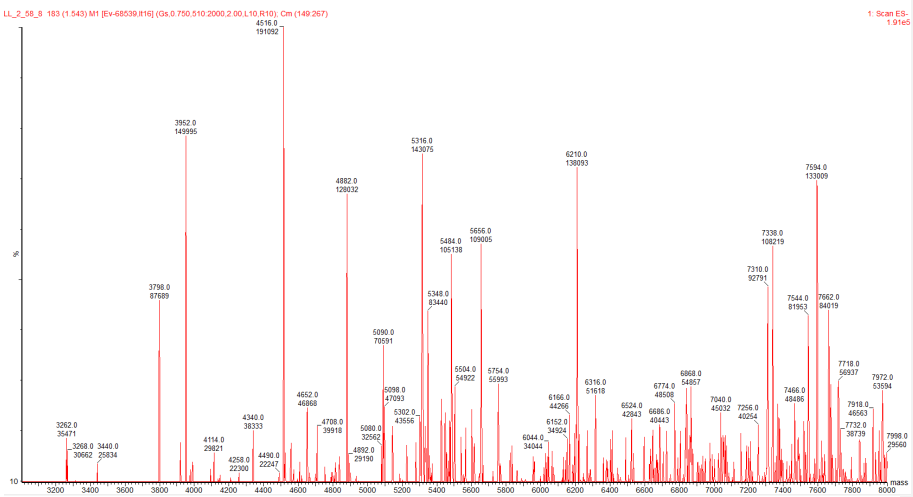




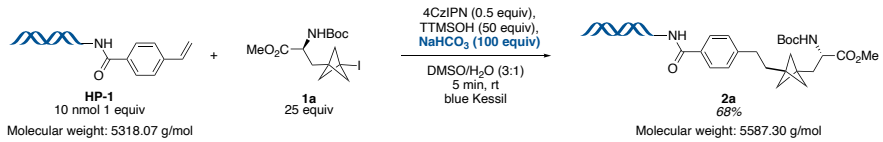
$Ir(ppy)_3$ instead of 4-CzIPN: *degradation*

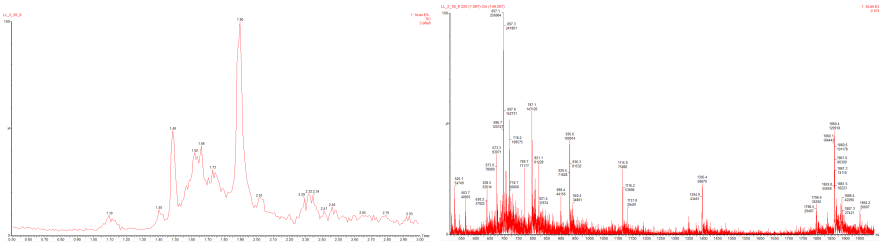


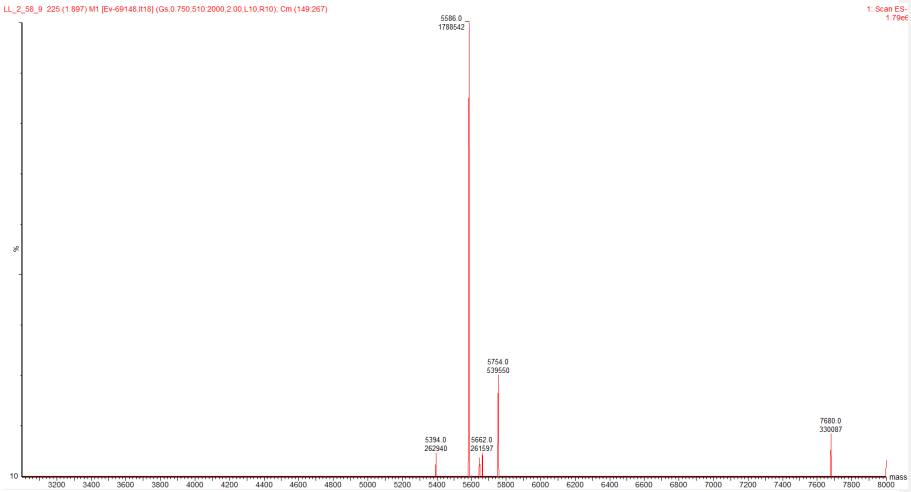




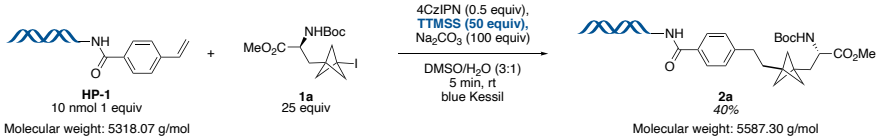
$NaHCO_3$ instead of Na_2CO_3: *68% yield*





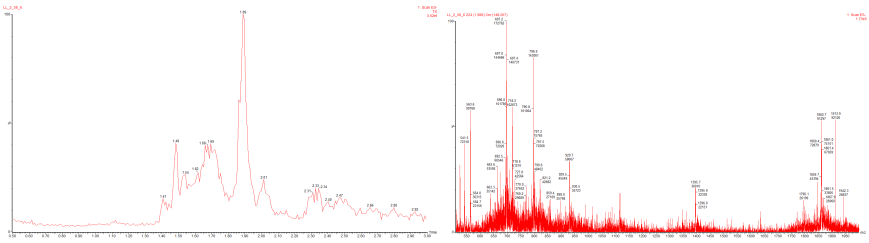


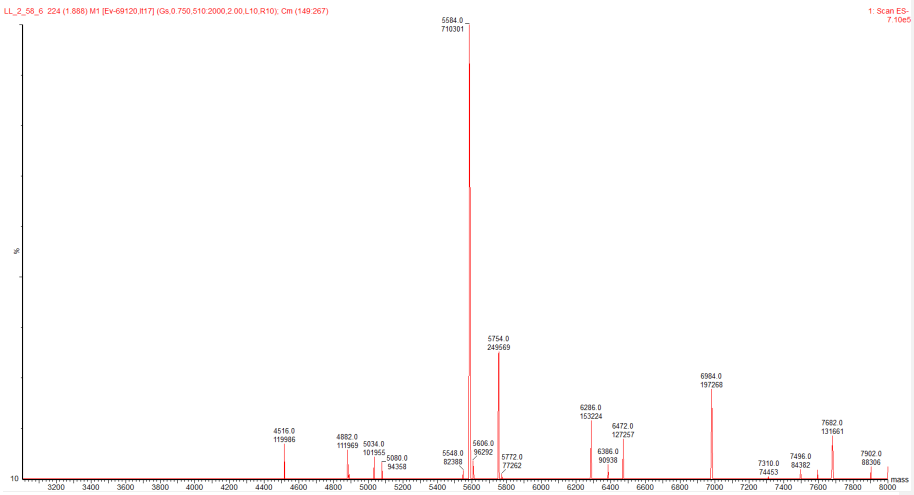
TTMSS instead of TTMSOH: *40% yield*



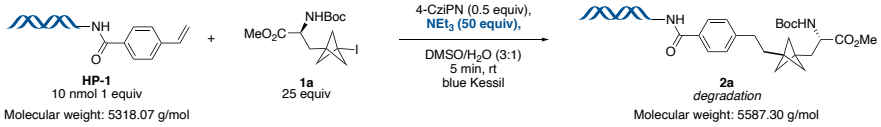
Molecular weight: 5318.07 g/mol

Molecular weight: 5587.30 g/mol





NEt_3 instead of TTMSOH: *degradation*



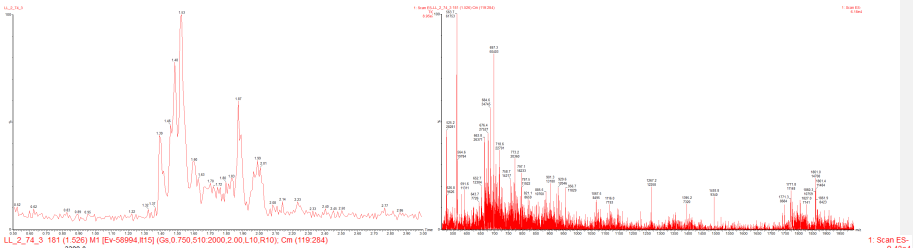
HP-1
10 nmol 1 equiv

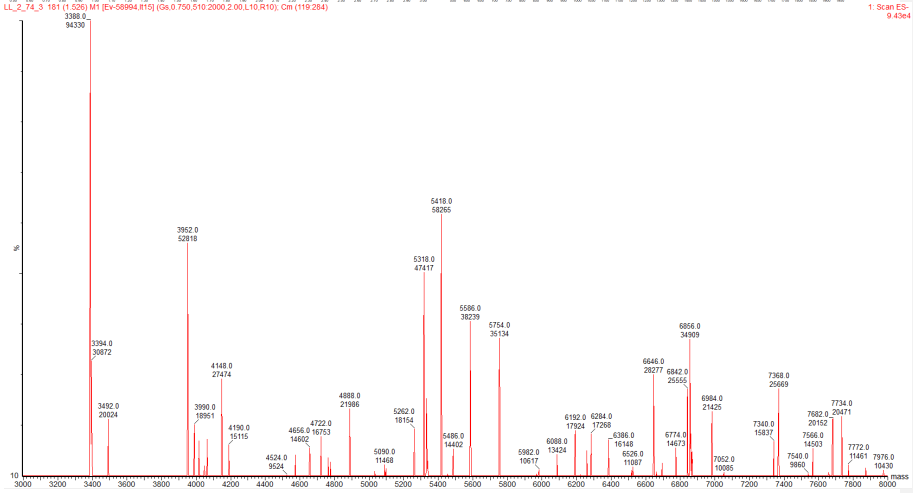
1a
25 equiv

2a
degradation

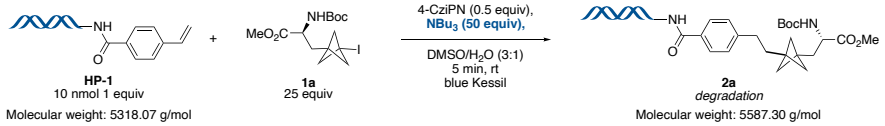
Molecular weight: 5318.07 g/mol

Molecular weight: 5587.30 g/mol





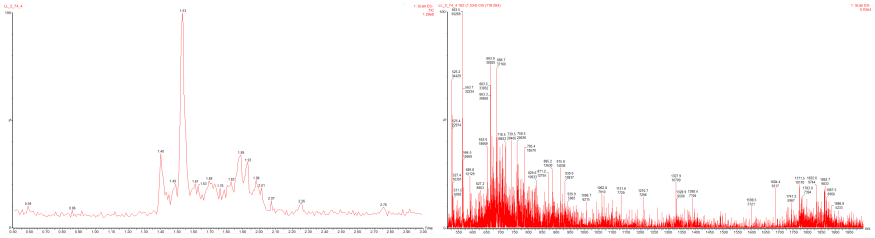
NBu_3 instead of TTMSOH: *degradation*

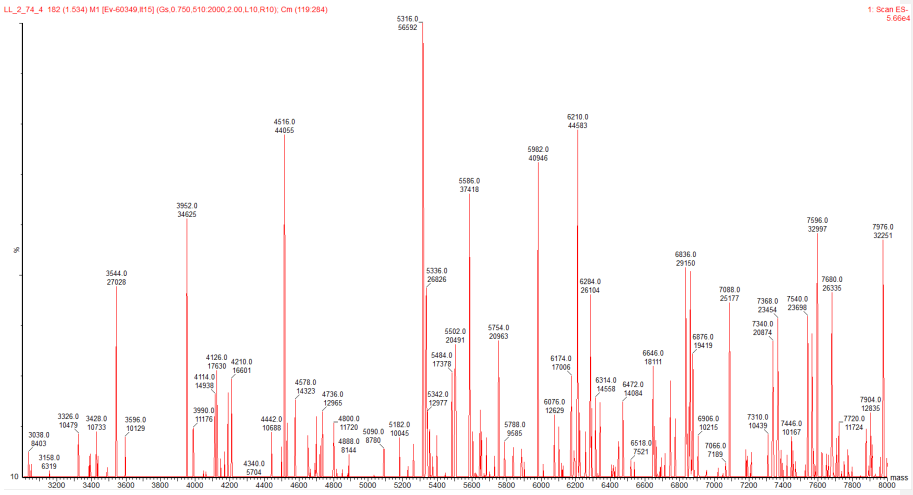


HP-1
10 nmol 1 equiv
Molecular weight: 5318.07 g/mol

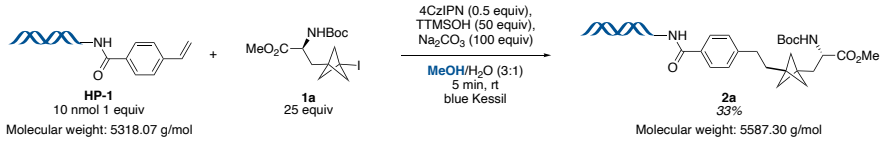
1a
25 equiv

2a
degradation
Molecular weight: 5587.30 g/mol





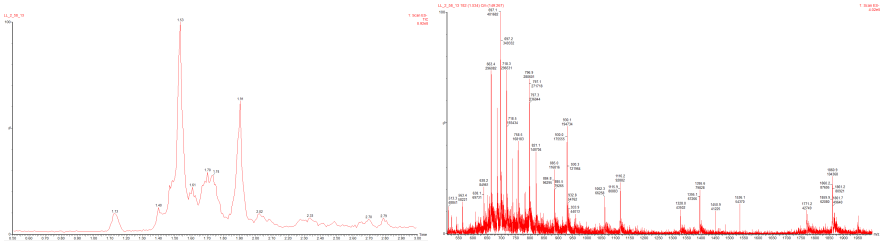
MeOH instead of DMSO: *33% yield*

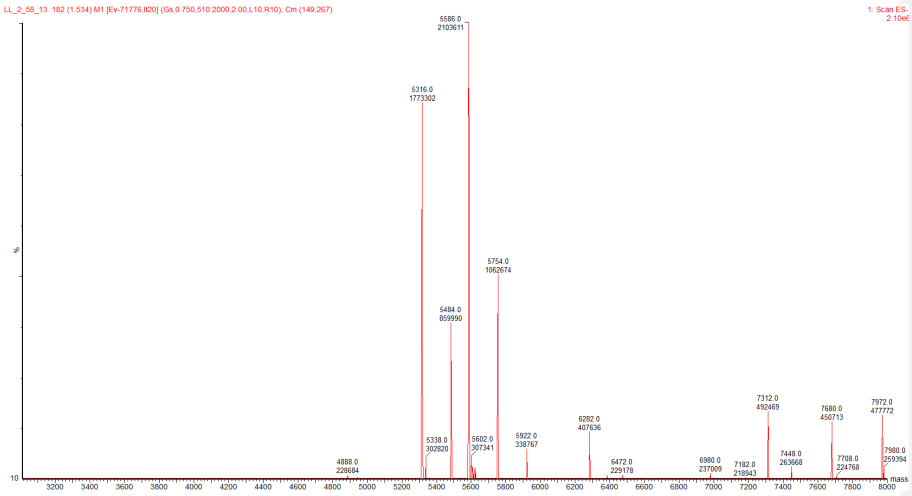


HP-1
10 nmol 1 equiv
Molecular weight: 5318.07 g/mol

1a
25 equiv

2a
33%
Molecular weight: 5587.30 g/mol



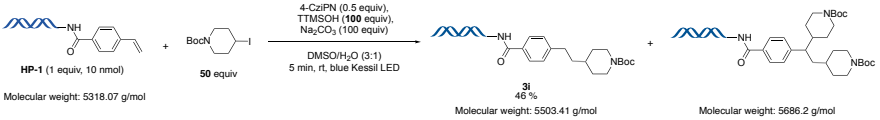


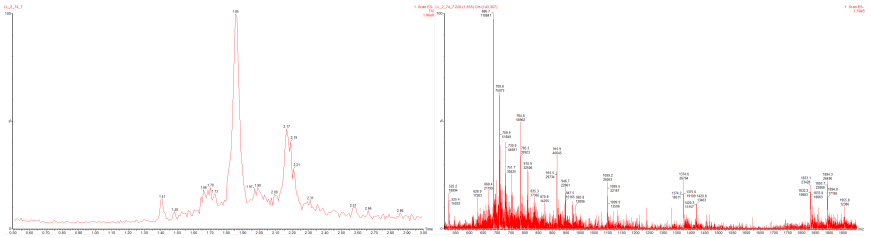
8. Investigation for double alkylation on-DNA

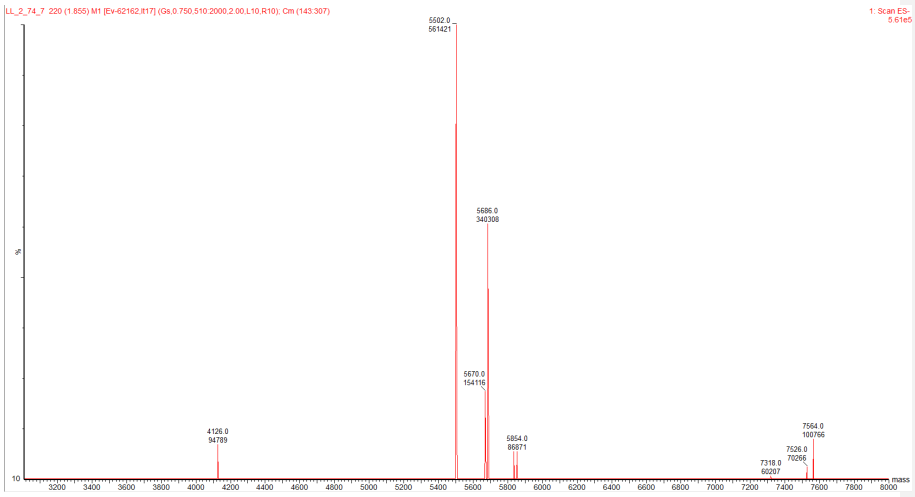
To perform this study, the number of equivalents of both piperidine iodide and mediator were decreased. The global volume was identical to the one described in procedure II and analyzed the mixture by LCMS after 5 min of irradiation with blue LED.

For 20 equiv of 1-Boc-4-iodo-piperidine and 40 equiv of TTMSOH (See page S93)

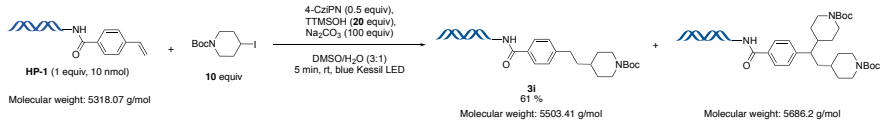
With 50 equiv of 1-Boc-4-iodo-piperidine and 100 equiv of TTMSOH

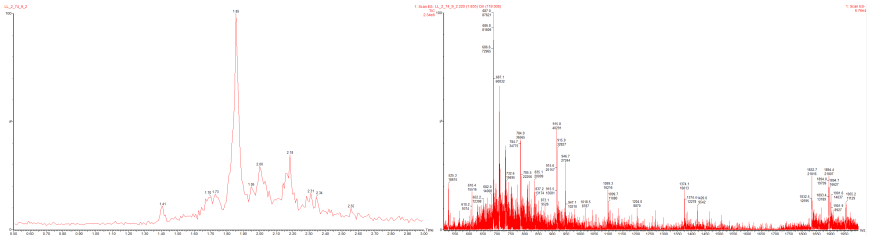




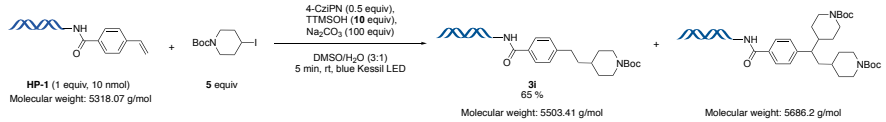


With 10 equiv of 1-Boc-4-iodo-piperidine and 20 equiv of TTMSOH





With 5 equiv of 1-Boc-4-iodo-piperidine and 10 equiv of TTMSOH

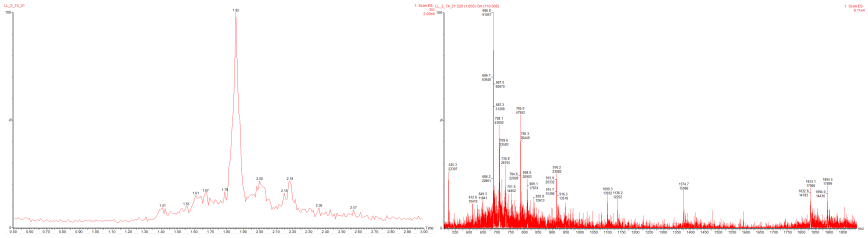


HP-1 (1 equiv, 10 nmol)
Molecular weight: 5318.07 g/mol

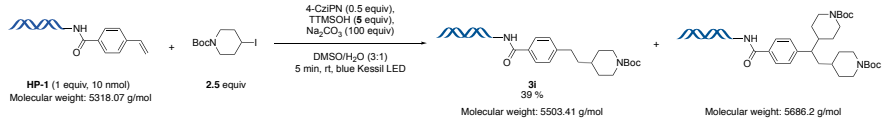
5 equiv

3i
65 %
Molecular weight: 5503.41 g/mol

Molecular weight: 5686.2 g/mol



With 2.5 equiv of 1-Boc-4-iodo-piperidine and 5 equiv of TTMSOH

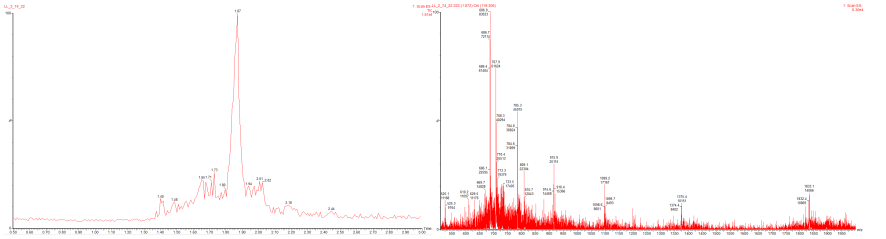


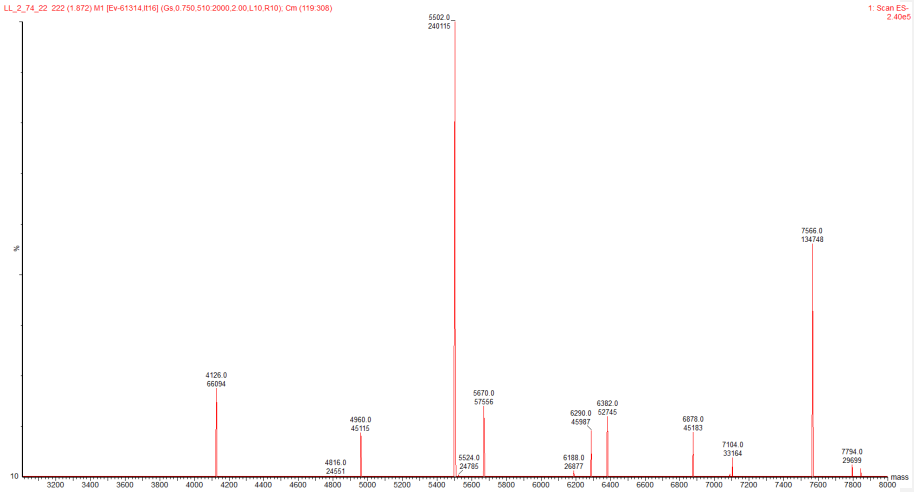
HP-1 (1 equiv, 10 nmol)
Molecular weight: 5318.07 g/mol

2.5 equiv

3i
39 %
Molecular weight: 5503.41 g/mol

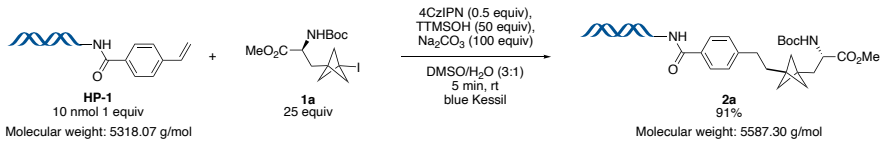
Molecular weight: 5686.2 g/mol

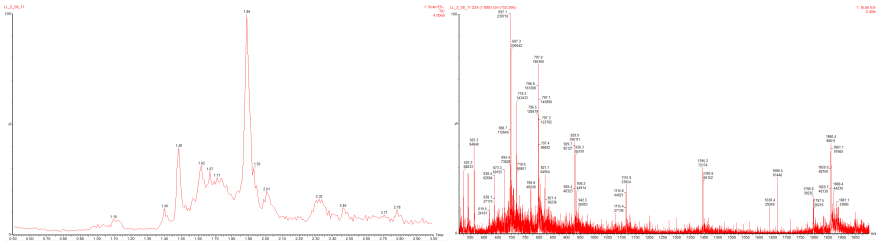


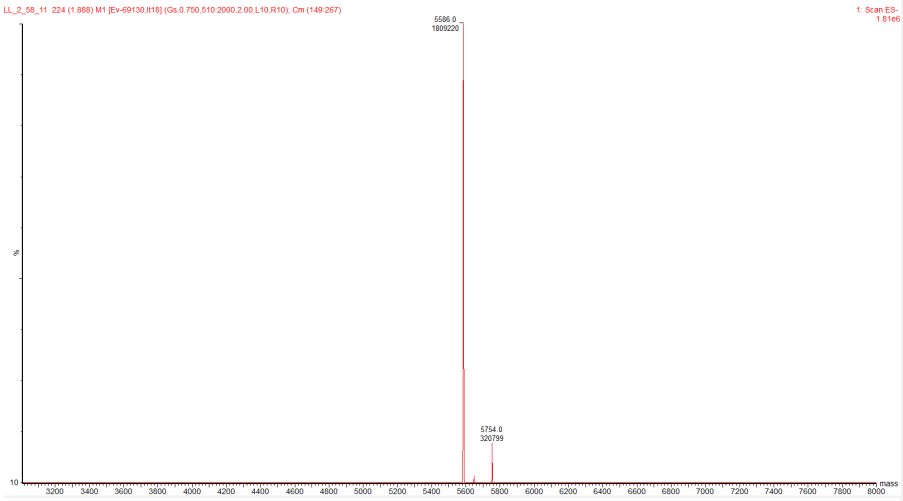


9. Determination of yields for On-DNA reactions

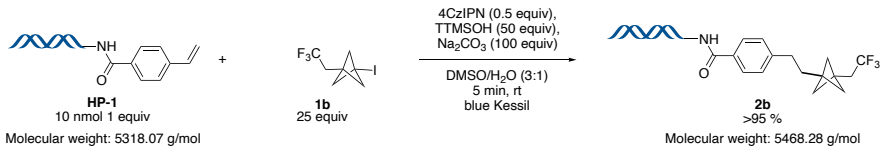
General procedure I : Compound **2a**, *91% yield*







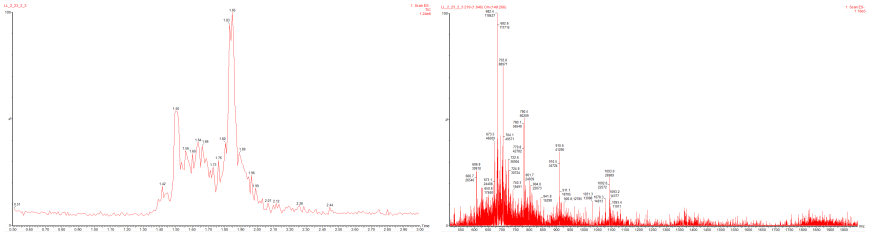
General procedure I : Compound **2b**, *>95% yield*



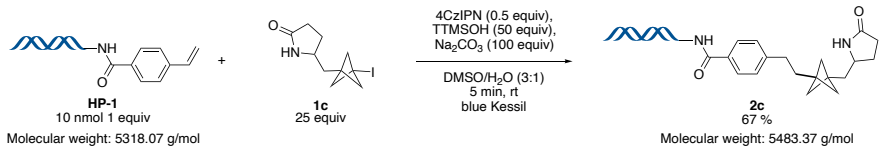
HP-1
10 nmol 1 equiv
Molecular weight: 5318.07 g/mol

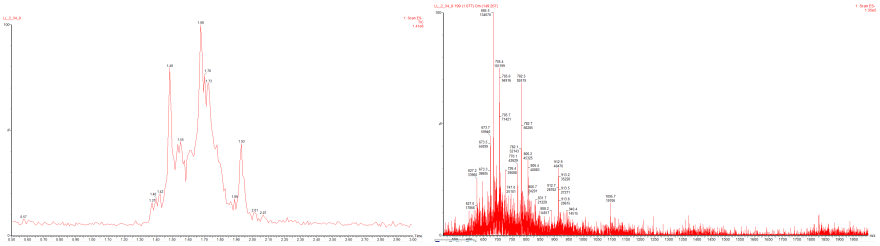
1b
25 equiv

2b
>95 %
Molecular weight: 5468.28 g/mol

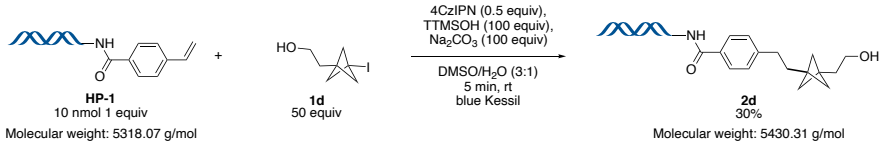


General procedure I : Compound **2c**, *67% yield*





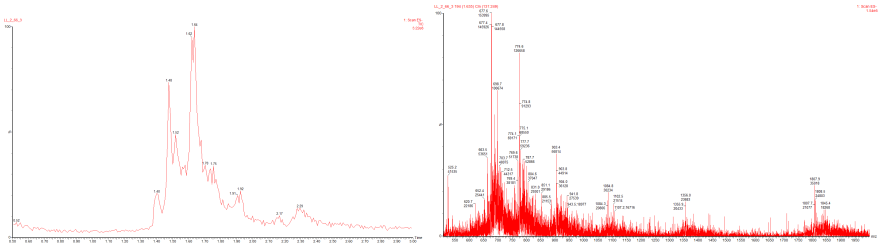
General procedure I : Compound **2d**, *30% yield*
With the following modification: using 50 equiv of **1d** (50 mM) and 100 equiv of TTMSOH (100 mM)

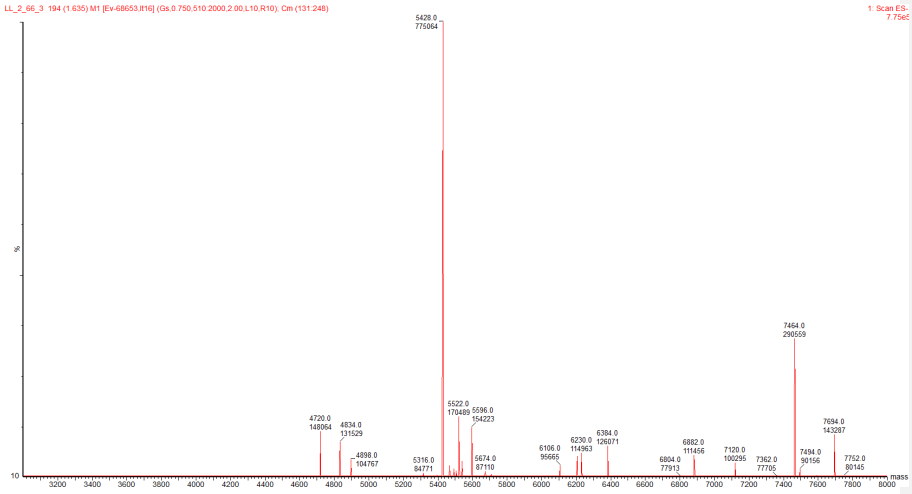


HP-1
10 nmol 1 equiv
Molecular weight: 5318.07 g/mol

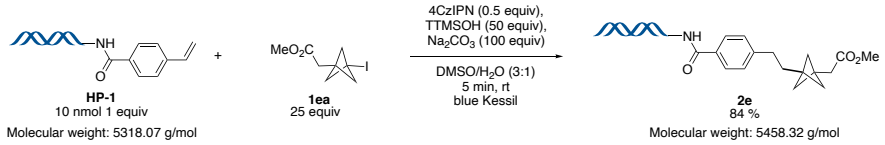
1d
50 equiv

2d
30%
Molecular weight: 5430.31 g/mol





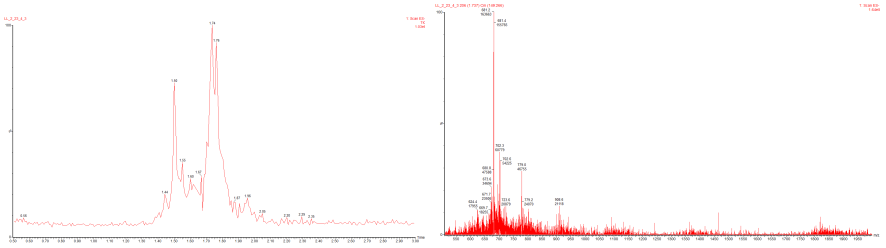
General procedure I : Compound **2e** (from BCP-I **1ea**), *84% yield*



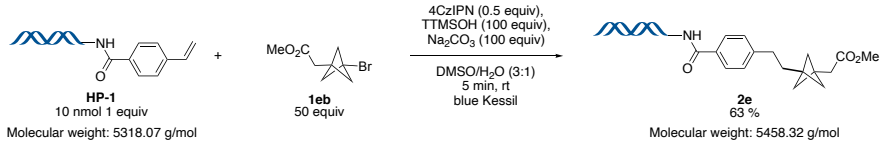
HP-1
10 nmol 1 equiv
Molecular weight: 5318.07 g/mol

1ea
25 equiv

2e
84 %
Molecular weight: 5458.32 g/mol



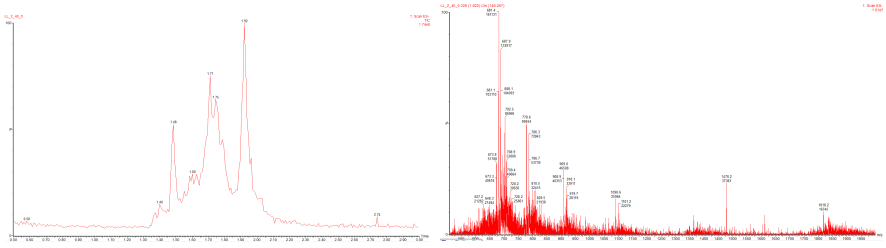
General procedure I : Compound **2e** (from BCP-Br **1eb**), *63% yield*
with the following modification: using 50 equiv of **1eb** (50 mM) and 100 equiv of TTMSOH(100 mM)



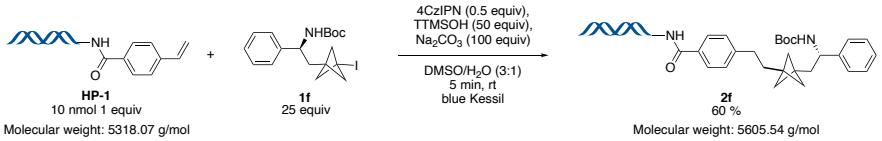
HP-1
10 nmol 1 equiv
Molecular weight: 5318.07 g/mol

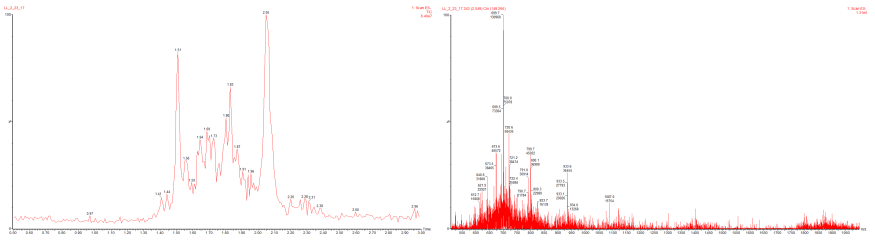
1eb
50 equiv

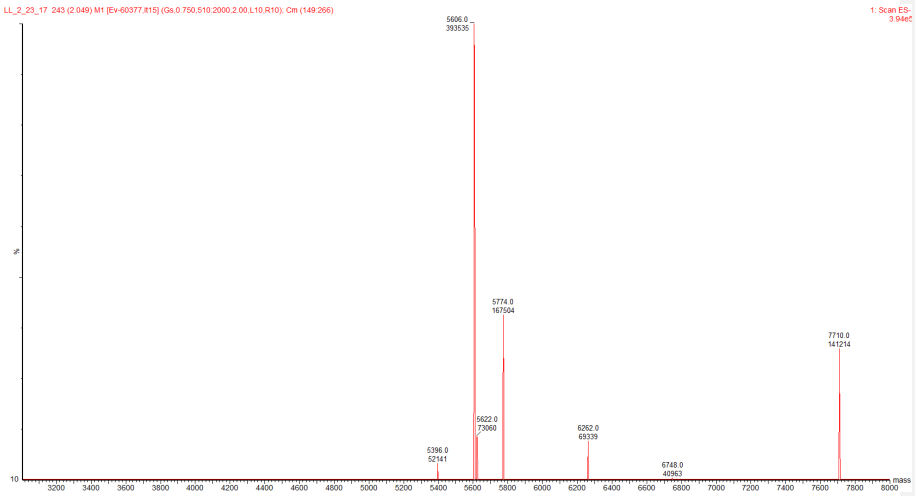
2e
63 %
Molecular weight: 5458.32 g/mol



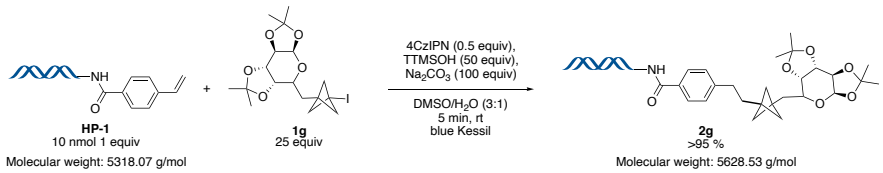
General procedure I : Compound **2f** , *60% yield*

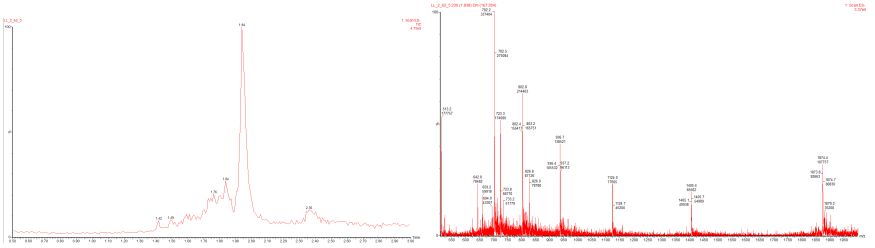




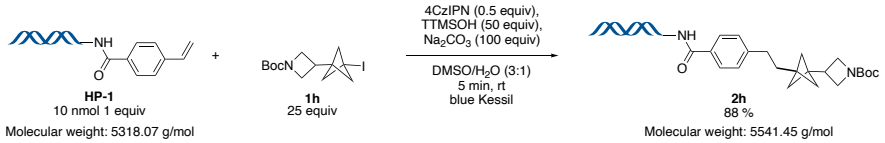


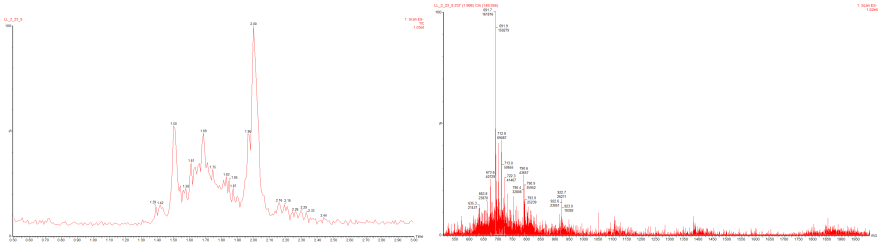
General procedure I : Compound **2g** , *>95% yield*

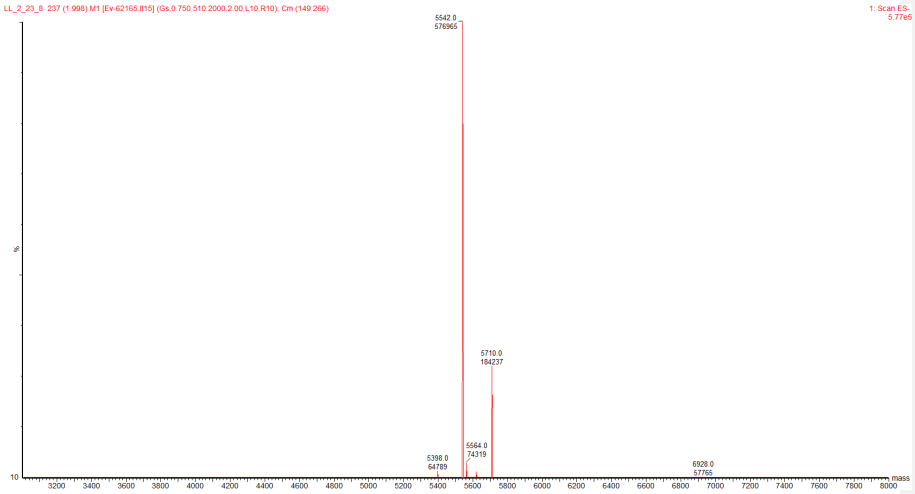




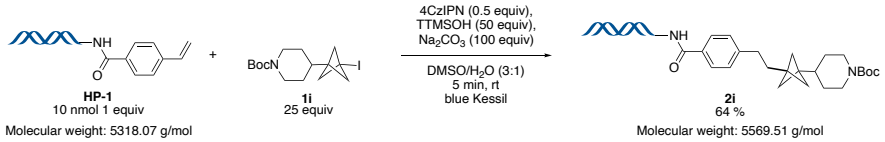
General procedure I : Compound **2h** , *88% yield*







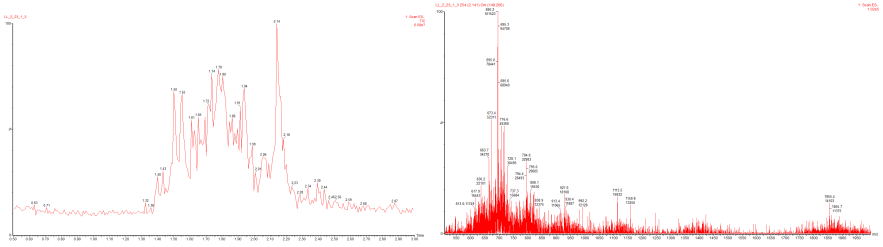
General procedure I : Compound **2i** , *64% yield*

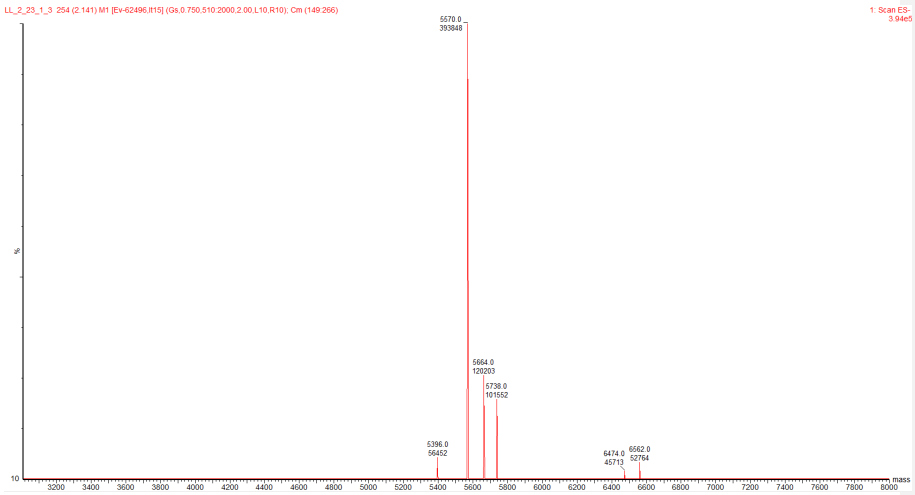


HP-1
10 nmol 1 equiv
Molecular weight: 5318.07 g/mol

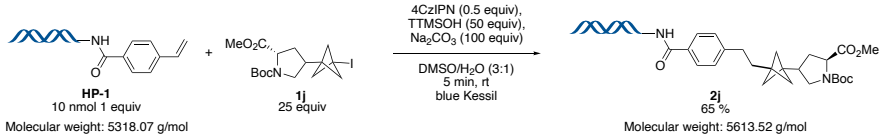
1i
25 equiv

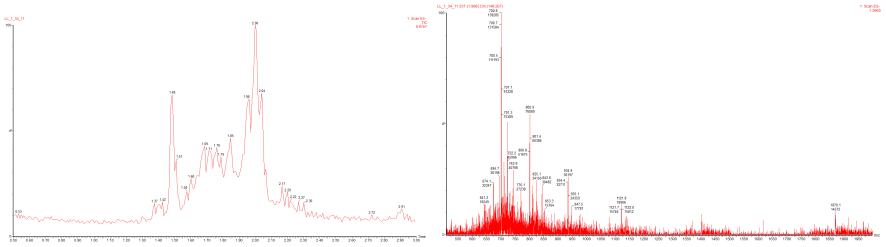
2i
64 %
Molecular weight: 5569.51 g/mol



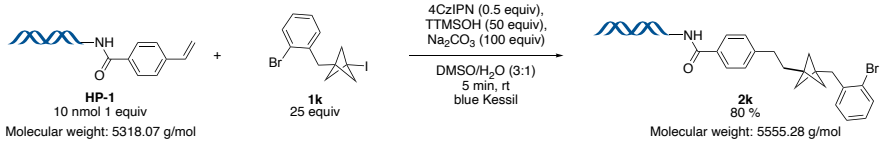


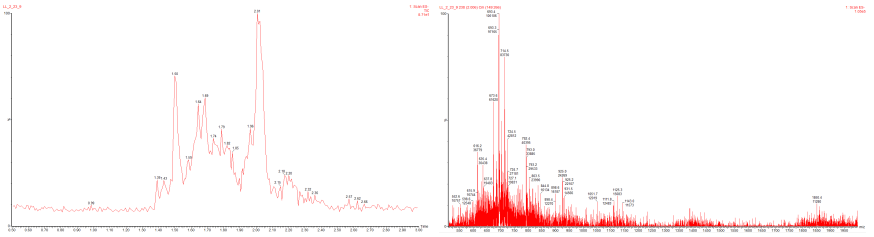
General procedure I : Compound **2j** , *65% yield*

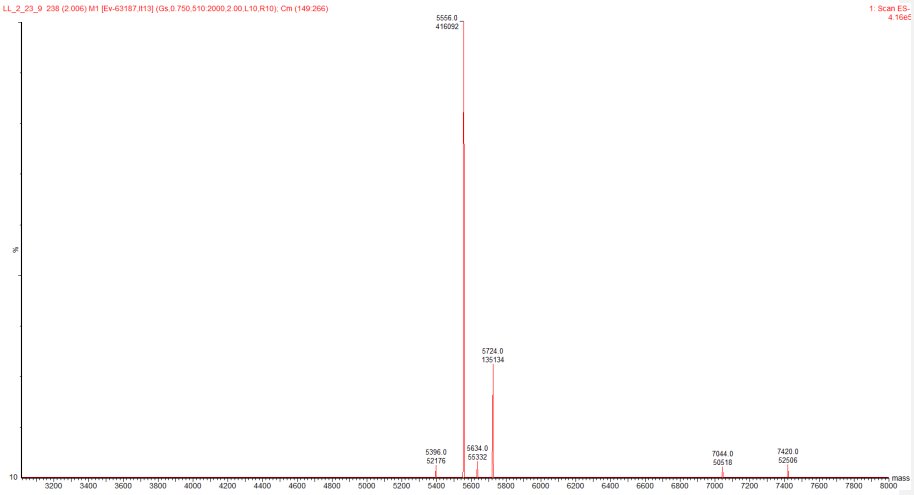




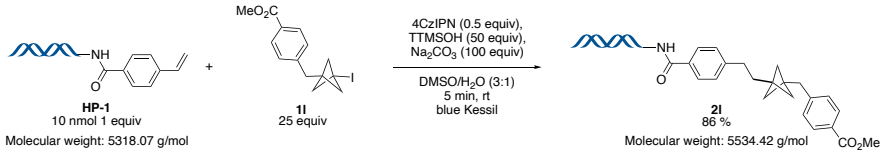
General procedure I : Compound **2k**, *80% yield*







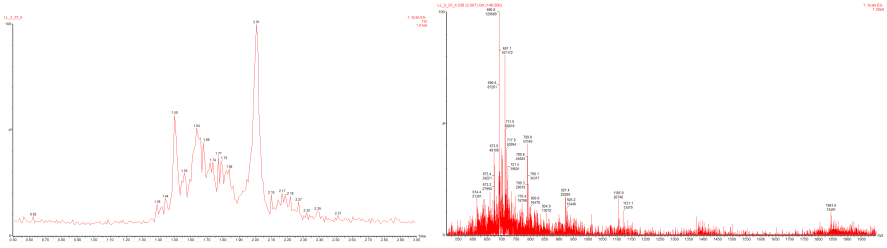
General procedure I : Compound **2l**, *86% yield*

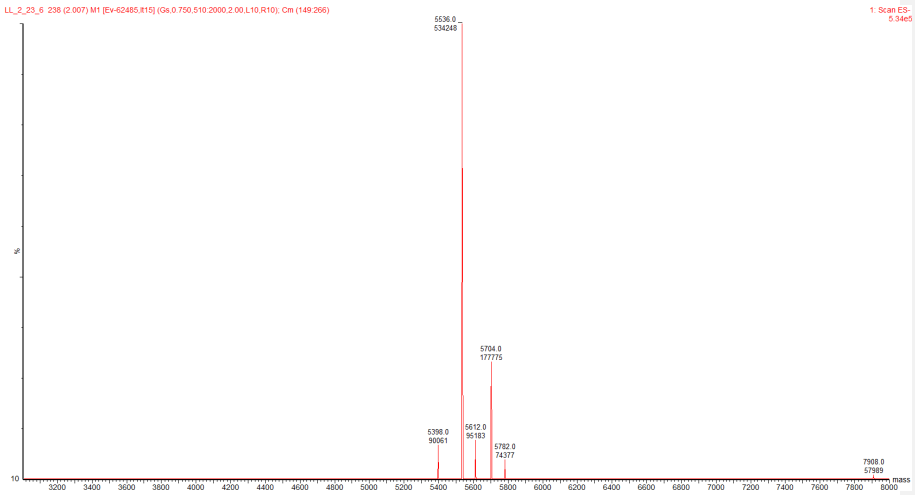


HP-1
10 nmol 1 equiv
Molecular weight: 5318.07 g/mol

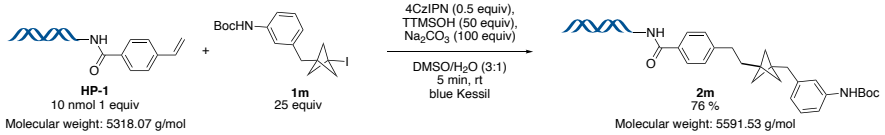
1l
25 equiv

2l
86 %
Molecular weight: 5534.42 g/mol





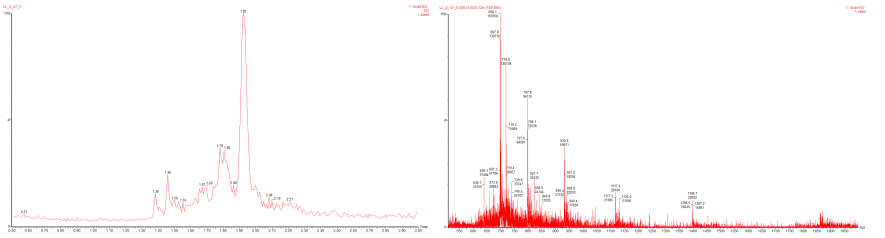
General procedure I : Compound **2m**, *76% yield*



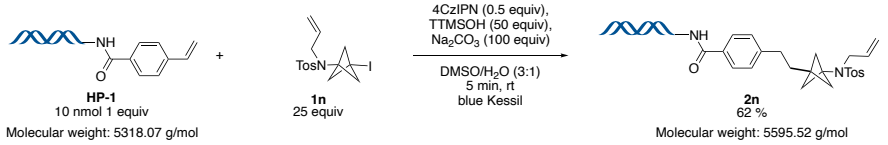
HP-1
10 nmol 1 equiv
Molecular weight: 5318.07 g/mol

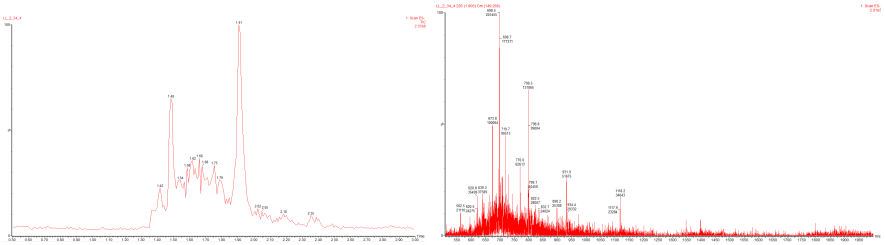
1m
25 equiv

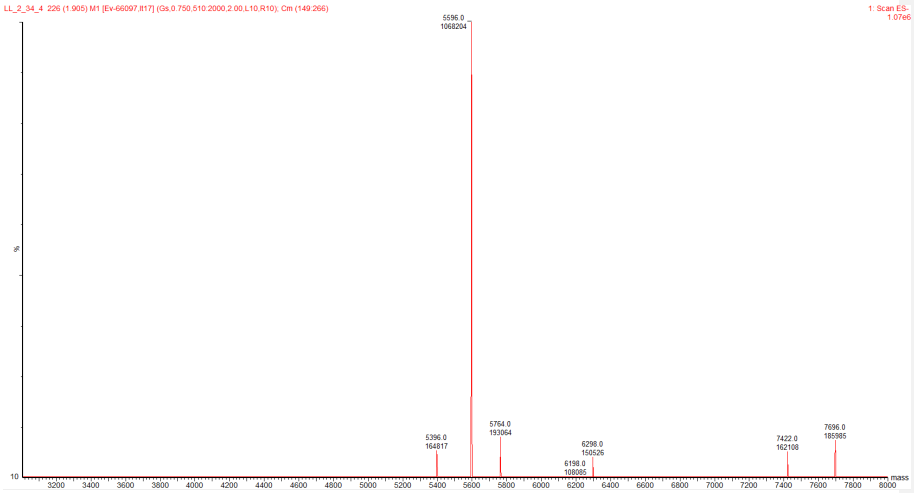
2m
76 %
Molecular weight: 5591.53 g/mol



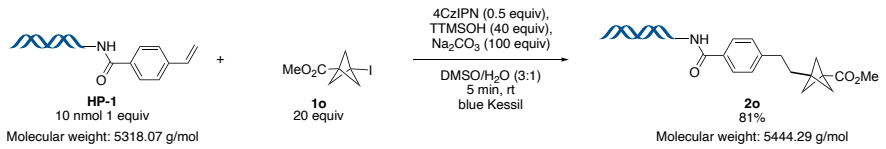
General procedure I : Compound **2n**, *62% yield*

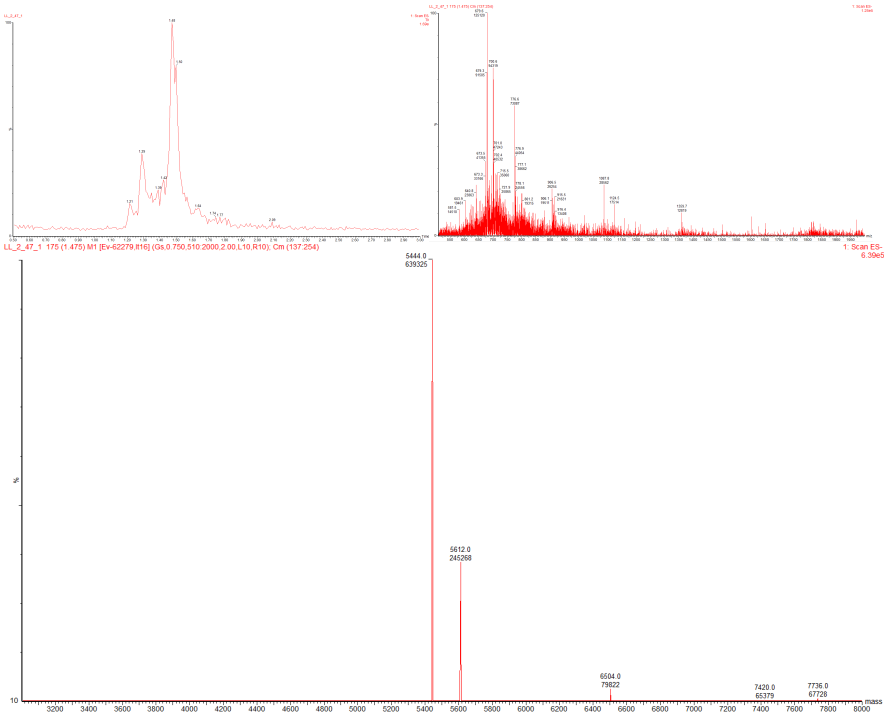




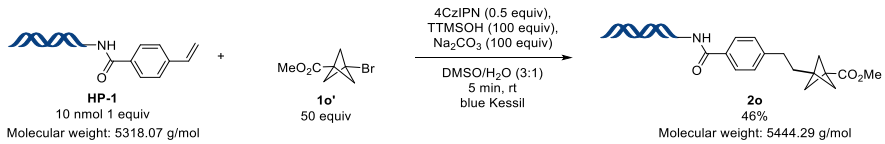


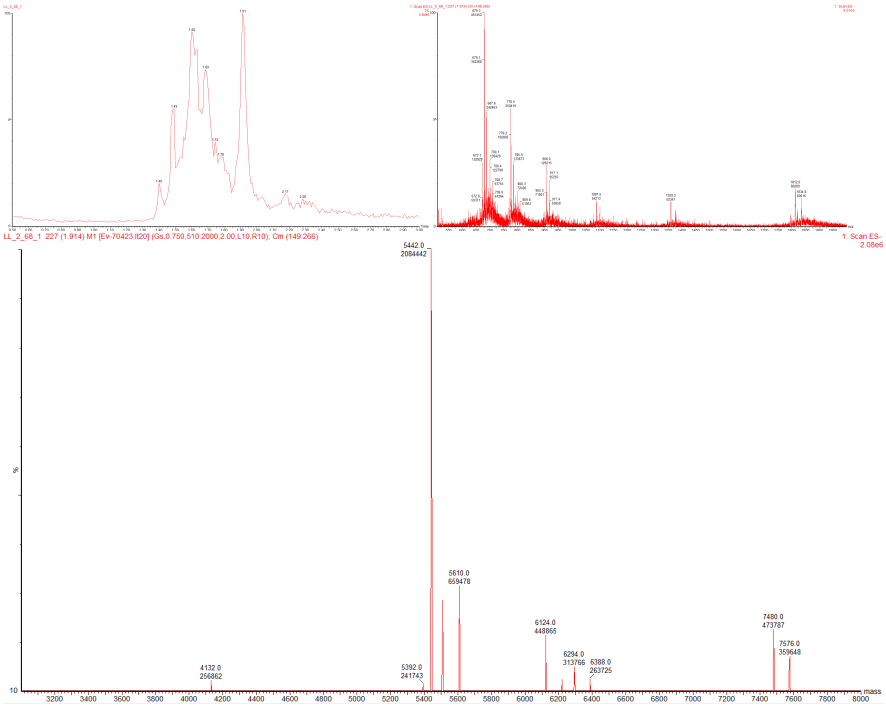
General Procedure II : Compound **2o**, *81% yield*



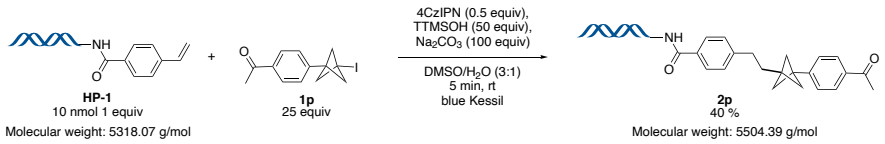


General Procedure II : Compound **2o**, *46% yield*
with the following modification: using 50 equiv of **1o'** (50 mM) and 100 equiv of TTMSOH(100 mM)





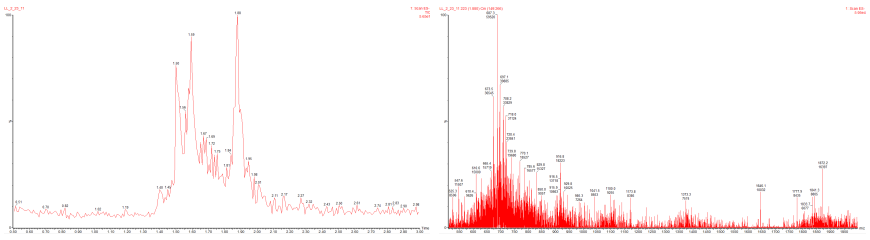
General procedure I : Compound **2p**, *40% yield*

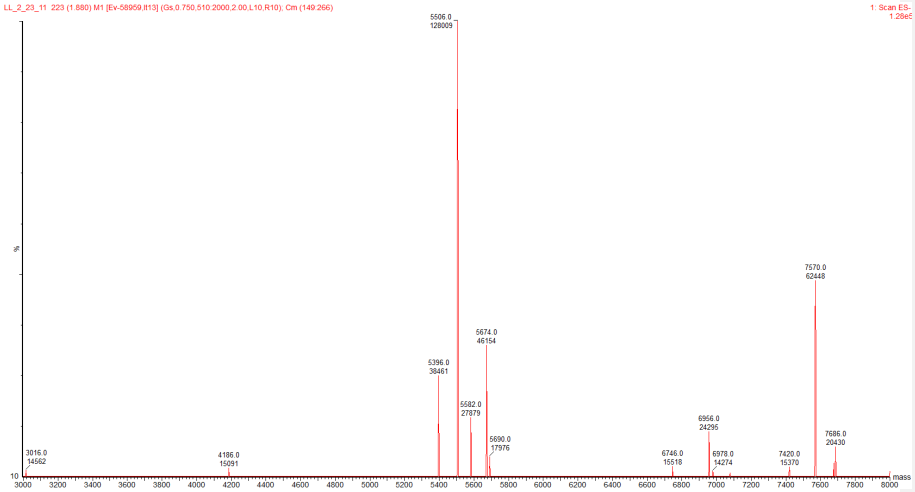


HP-1
10 nmol 1 equiv
Molecular weight: 5318.07 g/mol

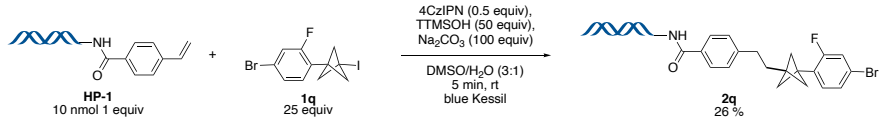
1p
25 equiv

2p
40 %
Molecular weight: 5504.39 g/mol





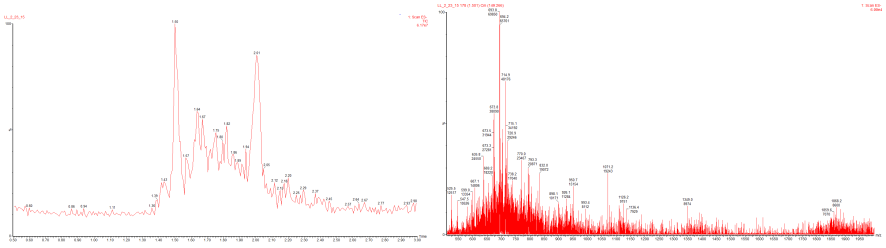
General procedure I : Compound **2q**, *26% yield*

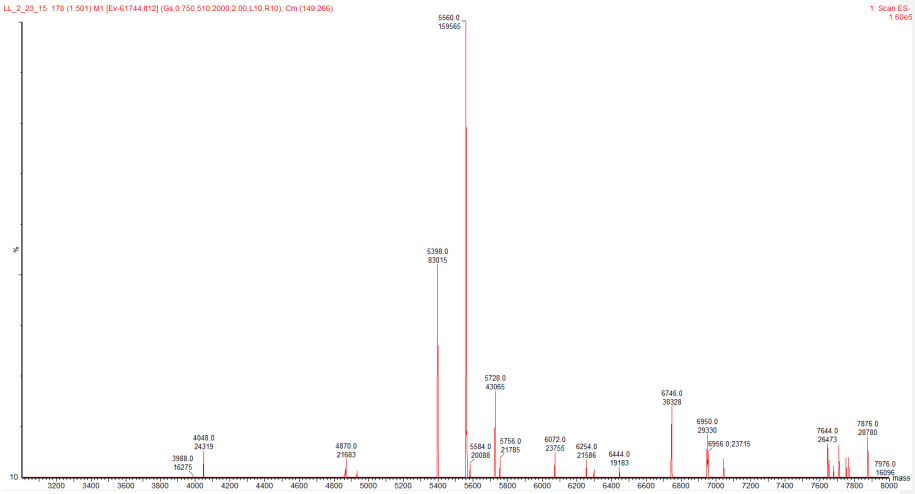


HP-1
10 nmol 1 equiv
Molecular weight: 5318.07 g/mol

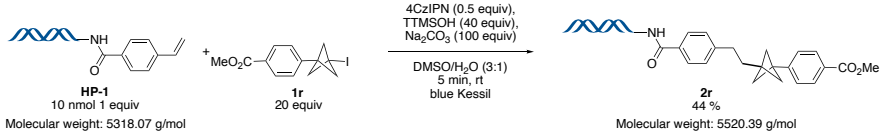
1q
25 equiv

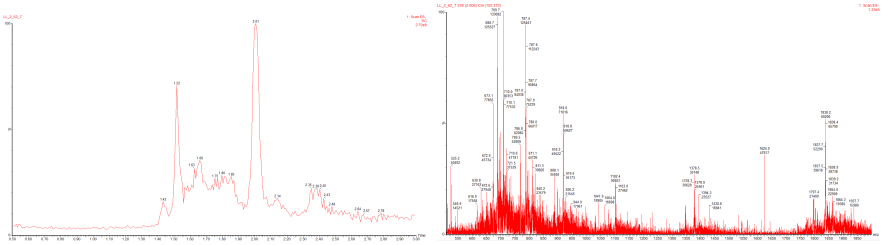
2q
26 %
Molecular weight: 5559.24 g/mol



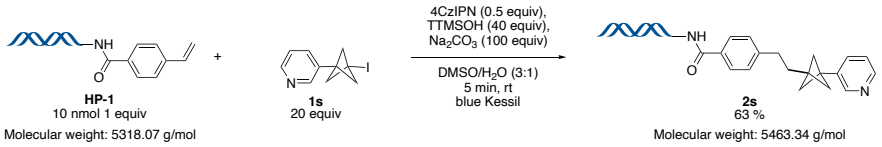


General procedure II : Compound **2r**, *44% yield*





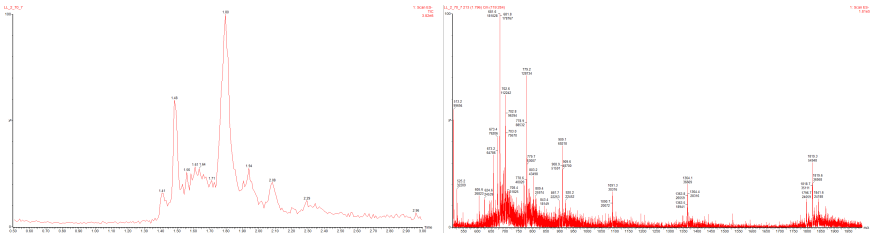
General procedure II : Compound **2s**, *63% yield*



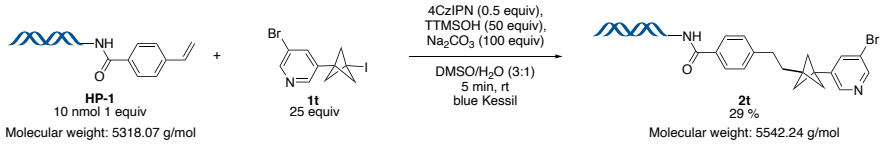
HP-1
10 nmol 1 equiv
Molecular weight: 5318.07 g/mol

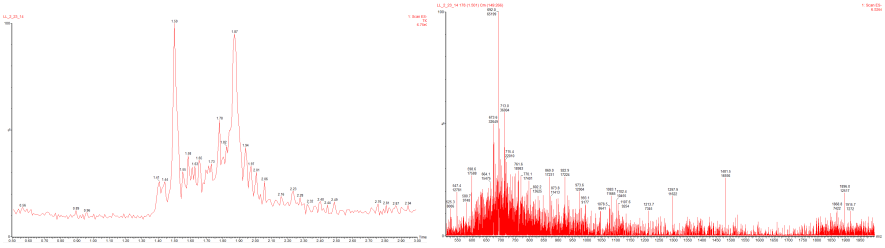
1s
20 equiv

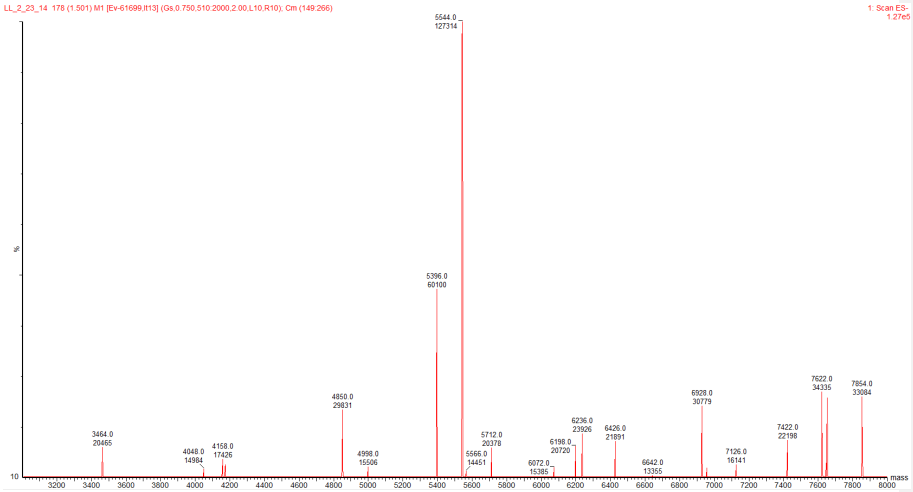
2s
63 %
Molecular weight: 5463.34 g/mol



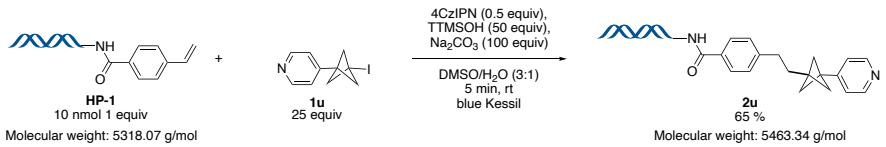
General procedure I : Compound **2t**, *29% yield*

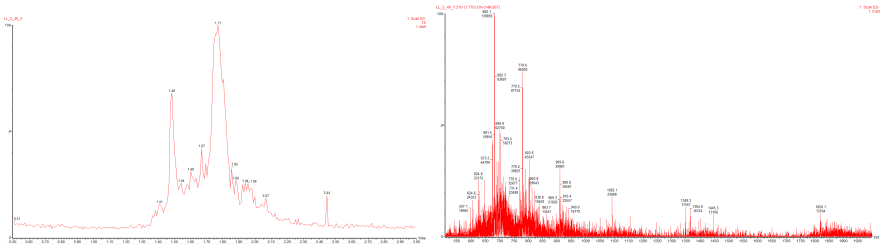


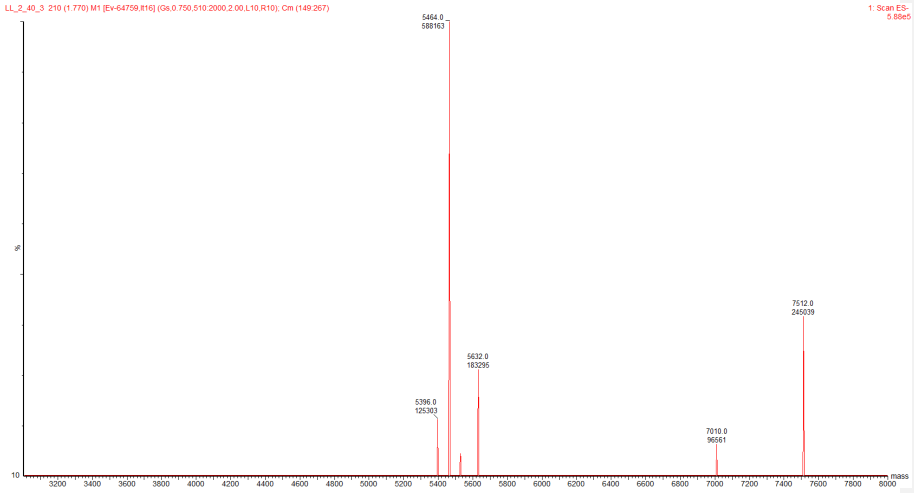




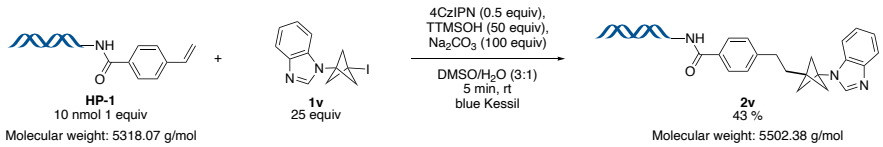
General procedure I : Compound **2u**, 65*% yield*

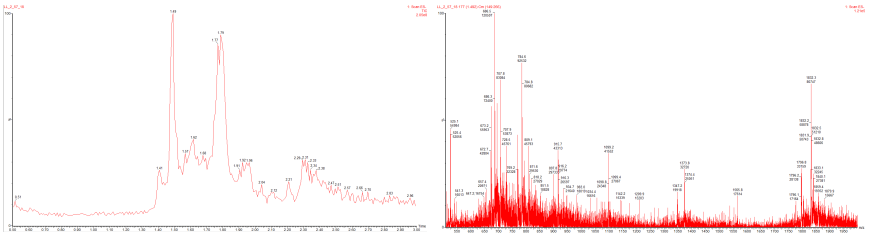


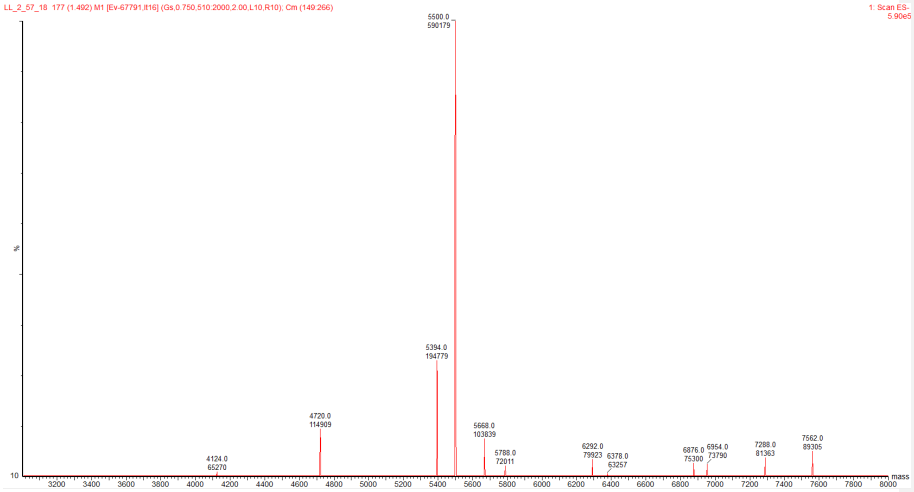




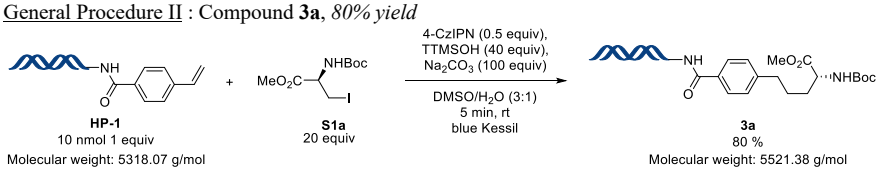
General procedure I : Compound **2v**, 43*% yield*

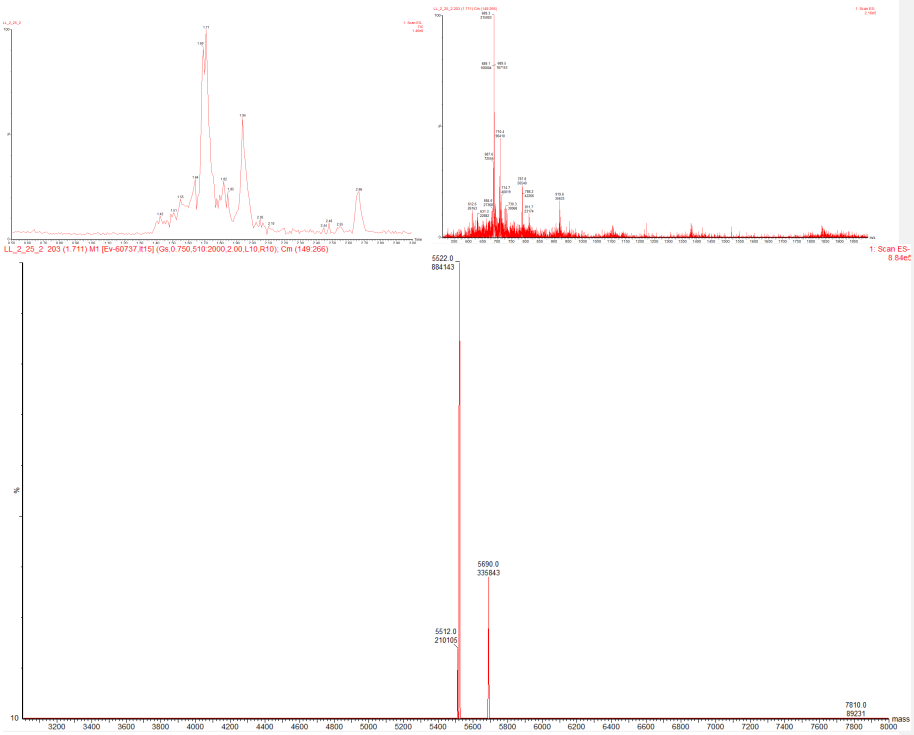




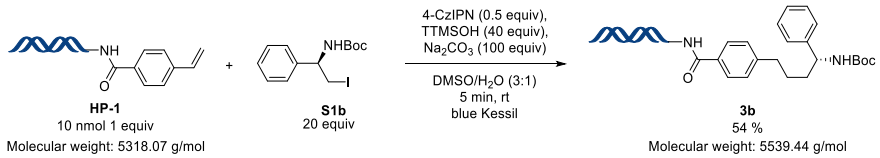


General Procedure II : Compound **3a**, *80% yield*





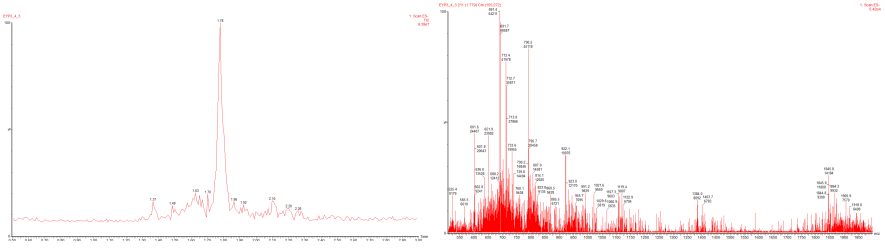
General Procedure II : Compound **3b**, *54% yield*

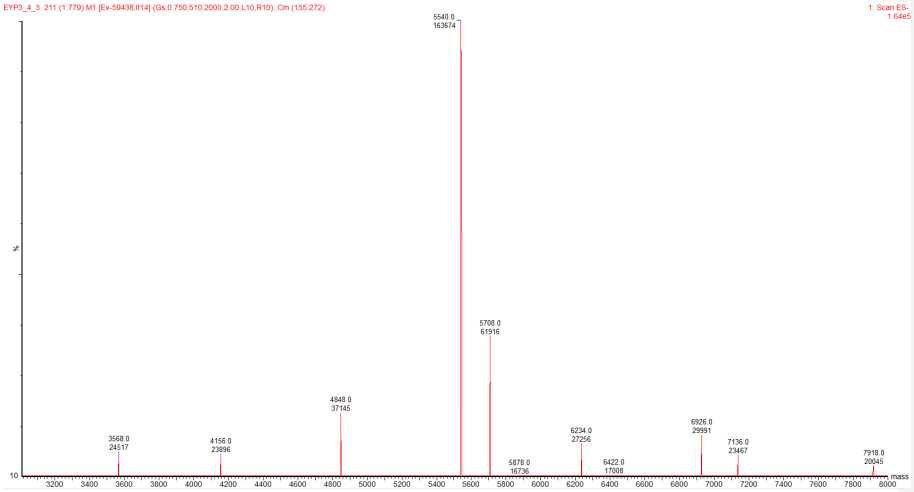


HP-1
10 nmol 1 equiv
Molecular weight: 5318.07 g/mol

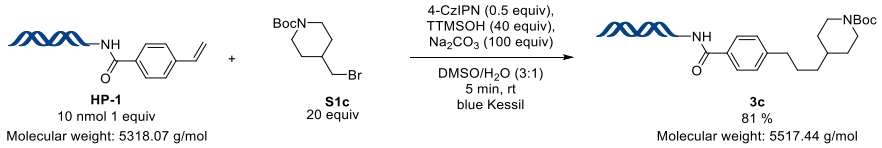
S1b
20 equiv

3b
54 %
Molecular weight: 5539.44 g/mol





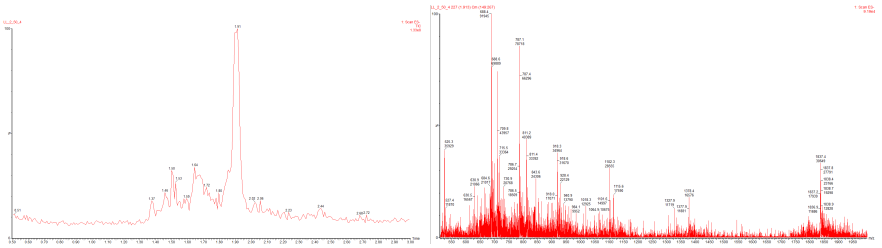
General Procedure II : Compound **3c**, *81% yield*



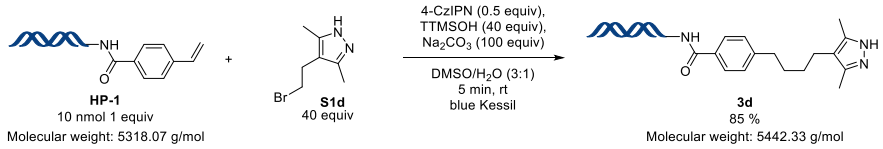
HP-1
10 nmol 1 equiv
Molecular weight: 5318.07 g/mol

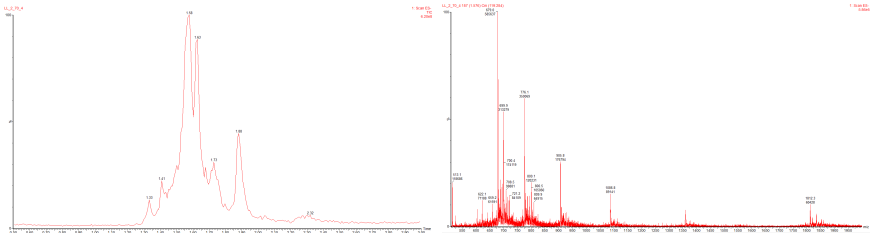
S1c
20 equiv

3c
81 %
Molecular weight: 5517.44 g/mol

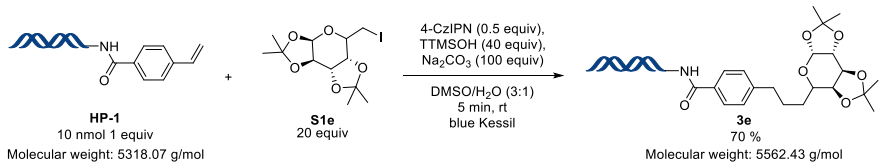


General Procedure II : Compound **3d**, *85% yield*
With the following modification TTMSOH 40 equiv, 40 mM in DMSO





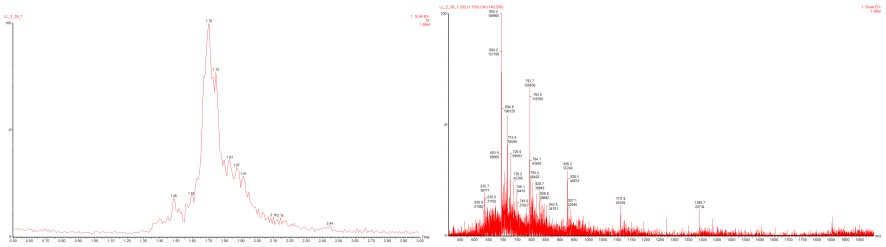
General Procedure II : Compound **3e**, *70% yield*

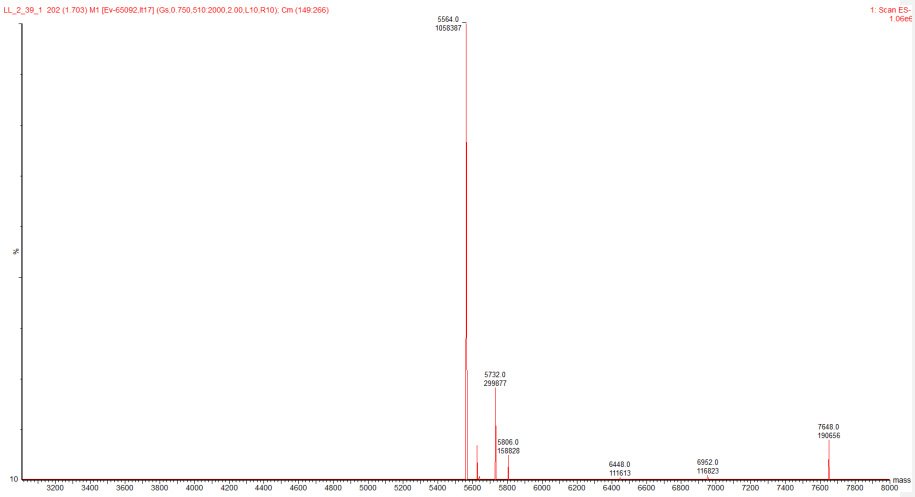


HP-1
10 nmol 1 equiv
Molecular weight: 5318.07 g/mol

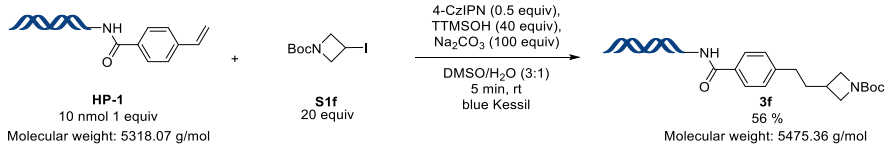
S1e
20 equiv

3e
70 %
Molecular weight: 5562.43 g/mol





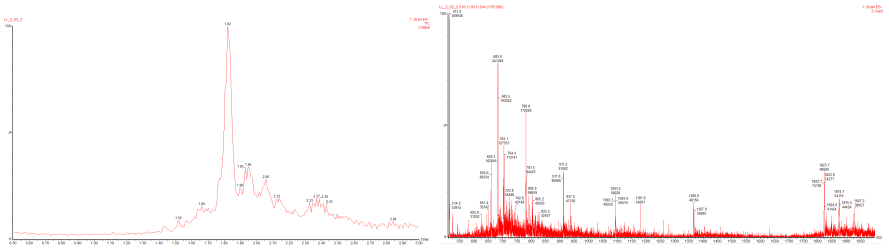
General Procedure II : Compound **3f**, *56% yield*

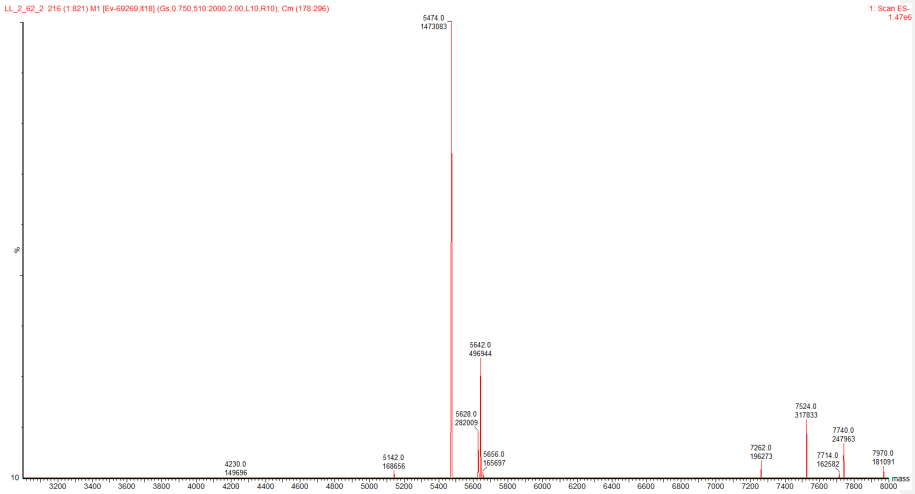


HP-1
10 nmol 1 equiv
Molecular weight: 5318.07 g/mol

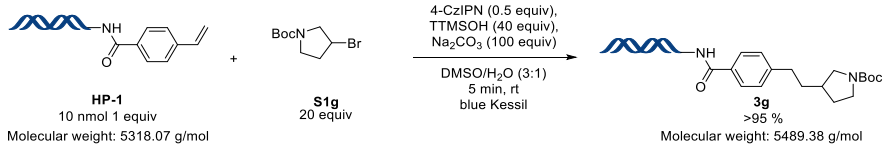
S1f
20 equiv

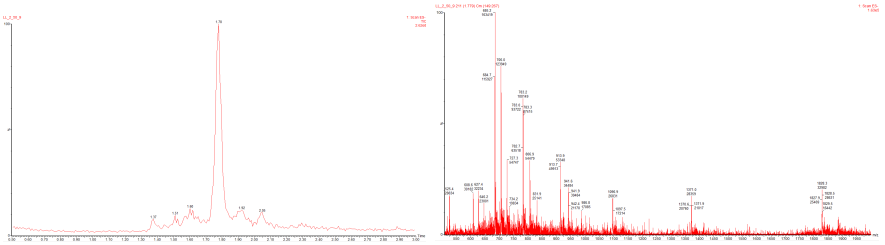
3f
56 %
Molecular weight: 5475.36 g/mol



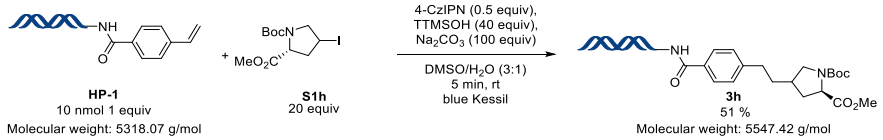


General Procedure II : Compound **3g**, *>95% yield*





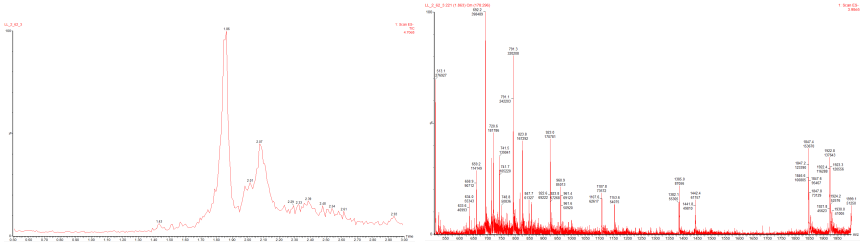
General Procedure II : Compound **3h**, *51% yield*



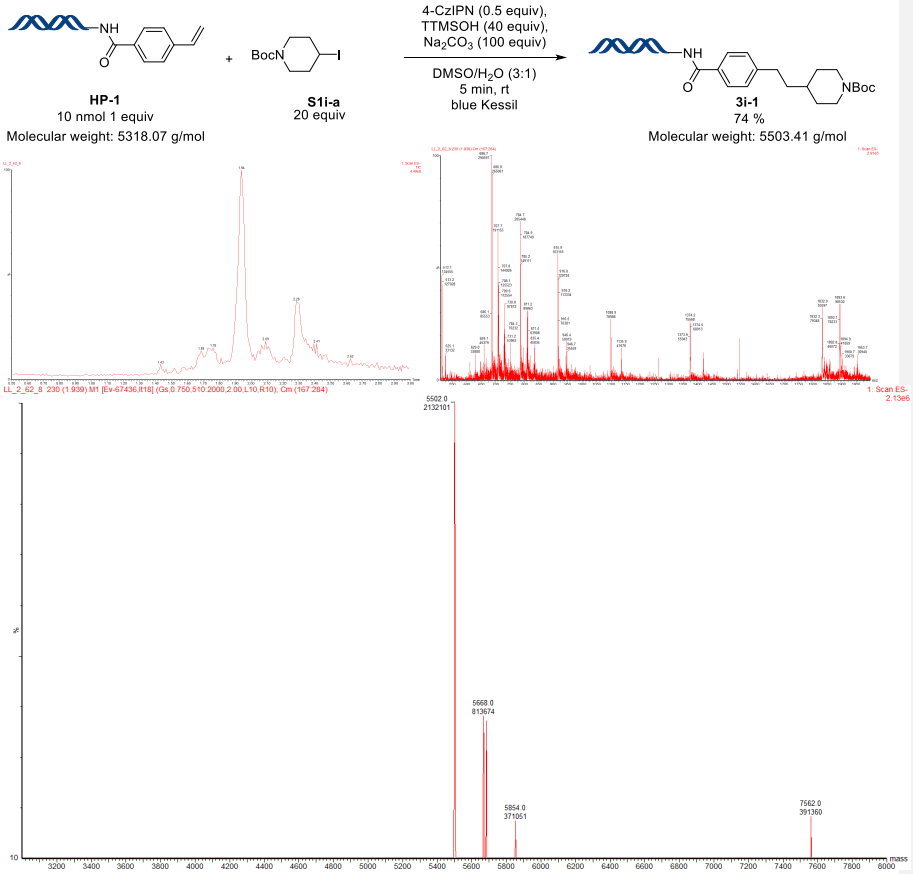
HP-1
10 nmol 1 equiv
Molecular weight: 5318.07 g/mol

S1h
20 equiv

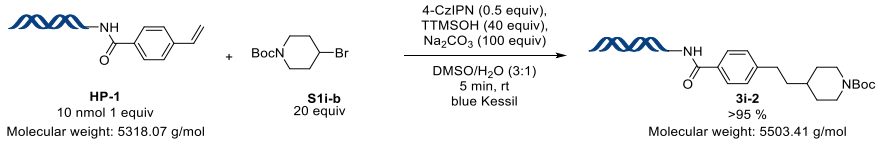
3h
51 %
Molecular weight: 5547.42 g/mol



General Procedure II : Compound **3i**, *74% yield*



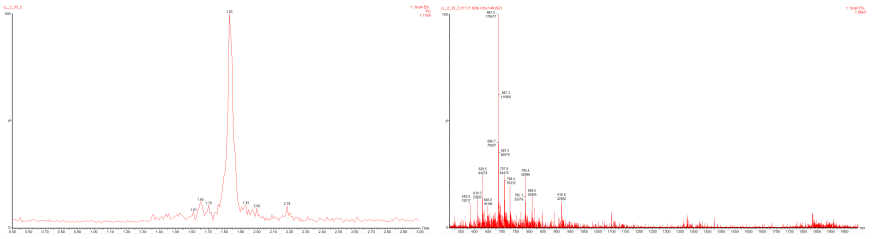
General Procedure II : Compound **3i**, *>95% yield*



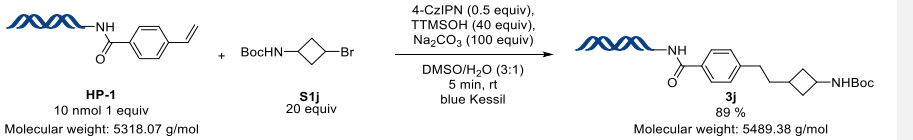
HP-1
10 nmol 1 equiv
Molecular weight: 5318.07 g/mol

S1i-b
20 equiv

3i-2
>95 %
Molecular weight: 5503.41 g/mol



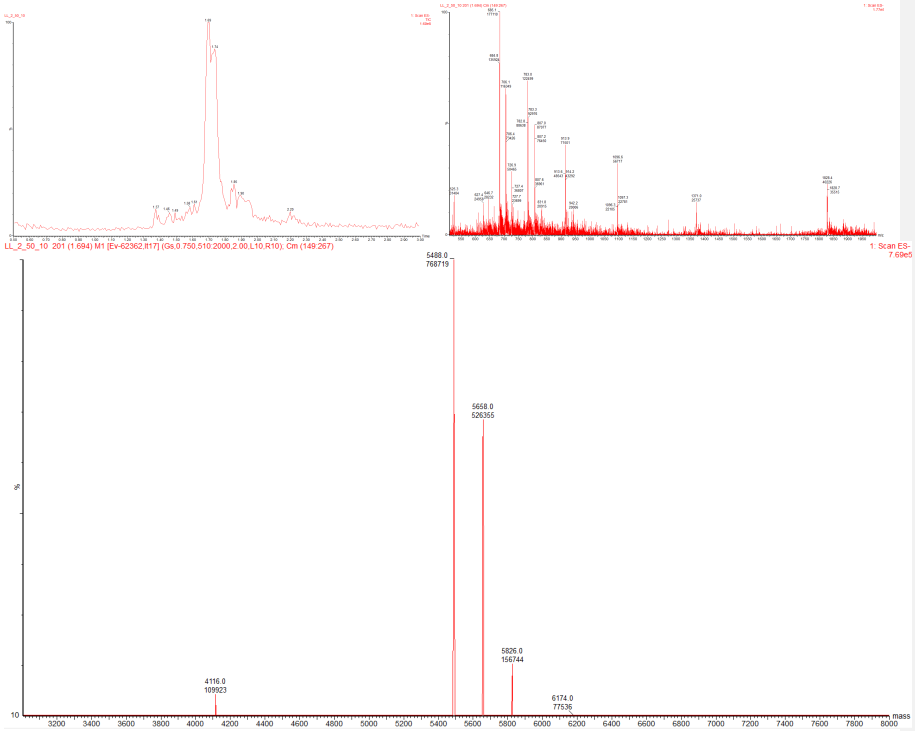
General Procedure II : Compound **3j**, *89% yield*



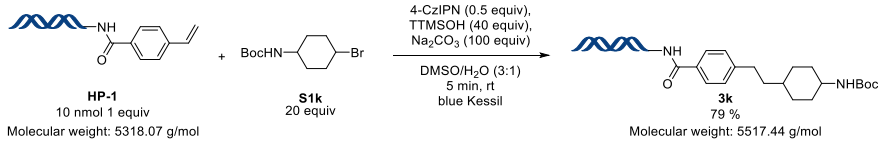
HP-1
10 nmol 1 equiv
Molecular weight: 5318.07 g/mol

S1j
20 equiv

3j
89 %
Molecular weight: 5489.38 g/mol



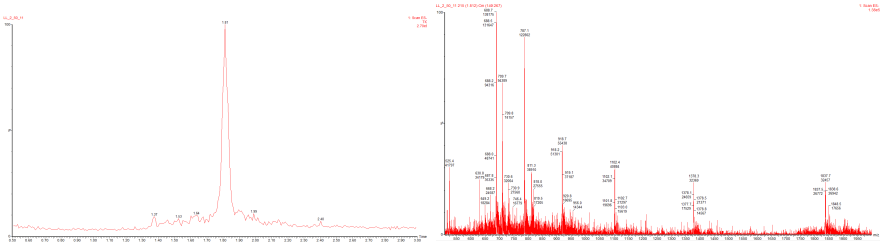
General Procedure II : Compound **3k**, *79% yield*



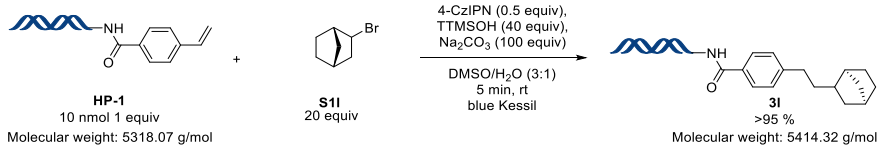
HP-1
10 nmol 1 equiv
Molecular weight: 5318.07 g/mol

S1k
20 equiv

3k
79 %
Molecular weight: 5517.44 g/mol



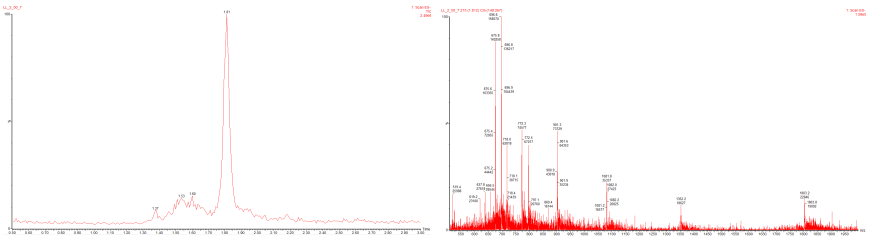
General Procedure II : Compound **3l**, *>95% yield*



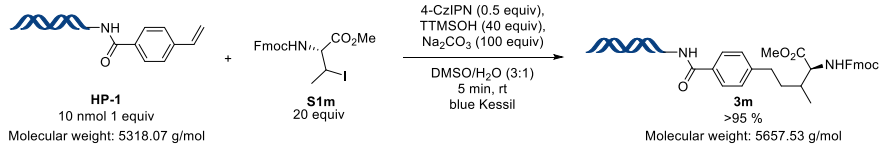
HP-1
10 nmol 1 equiv
Molecular weight: 5318.07 g/mol

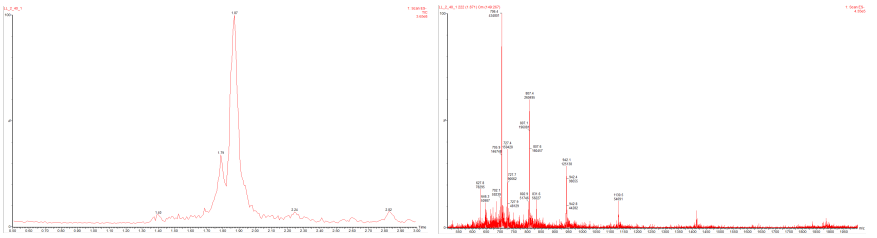
S1l
20 equiv

3l
>95 %
Molecular weight: 5414.32 g/mol

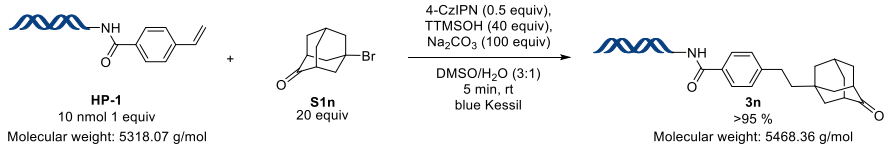


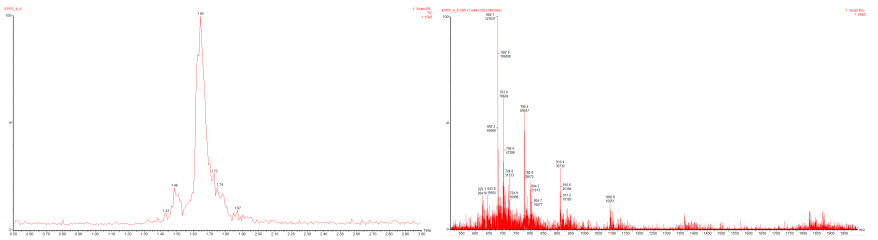
General Procedure II : Compound **3m**, *>95% yield*



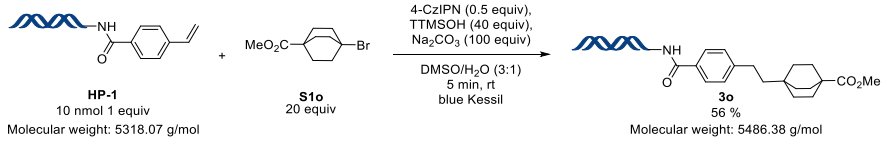


General Procedure II : Compound **3n**, *>95% yield*





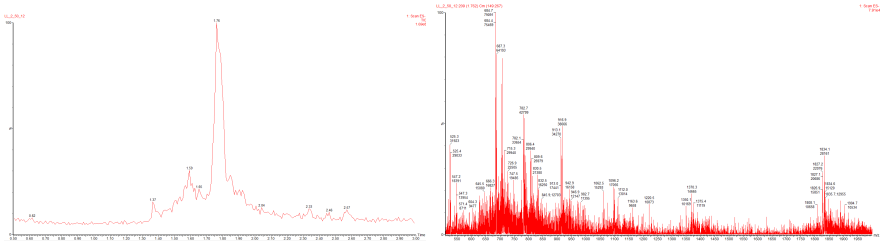
General Procedure II : Compound **3o**, *56% yield*

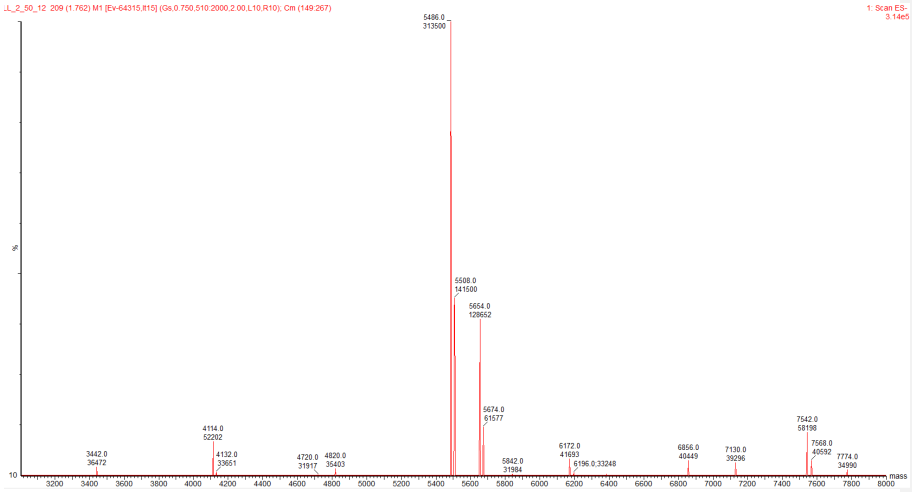


HP-1
10 nmol 1 equiv
Molecular weight: 5318.07 g/mol

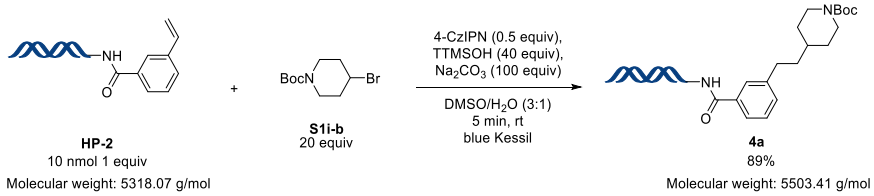
S1o
20 equiv

3o
56 %
Molecular weight: 5486.38 g/mol





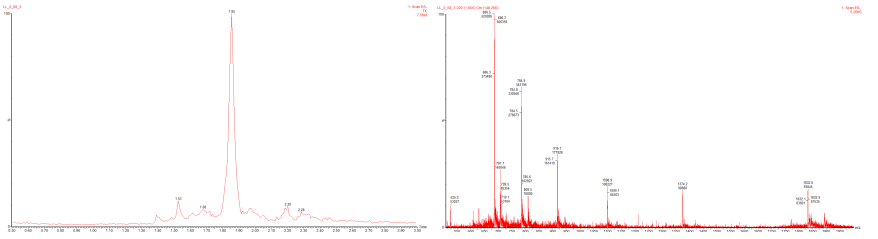
General Procedure II : Compound **4a**, *89% yield*

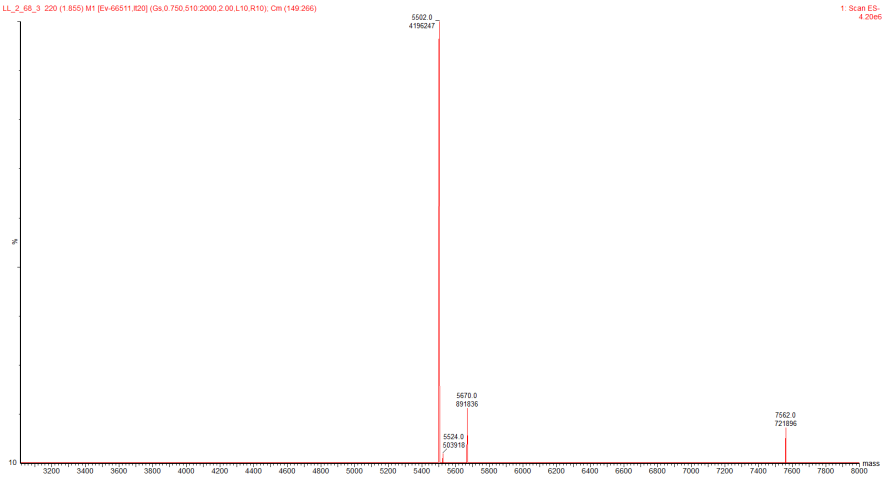


HP-2
10 nmol 1 equiv
Molecular weight: 5318.07 g/mol

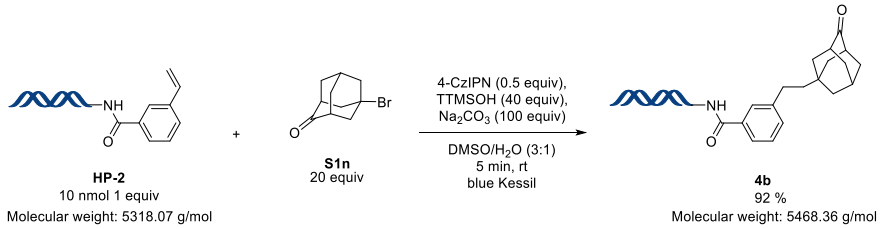
S1i-b
20 equiv

4a
89%
Molecular weight: 5503.41 g/mol





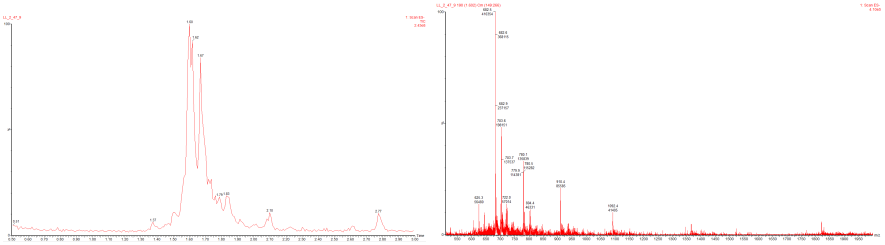
General Procedure II : Compound **4b**, *92% yield*



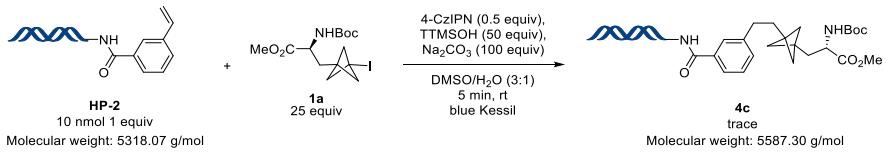
HP-2
10 nmol 1 equiv
Molecular weight: 5318.07 g/mol

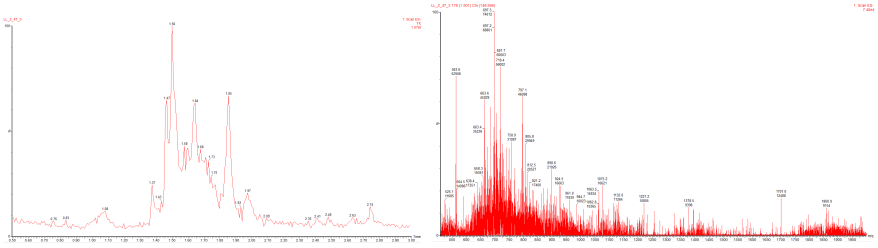
S1n
20 equiv

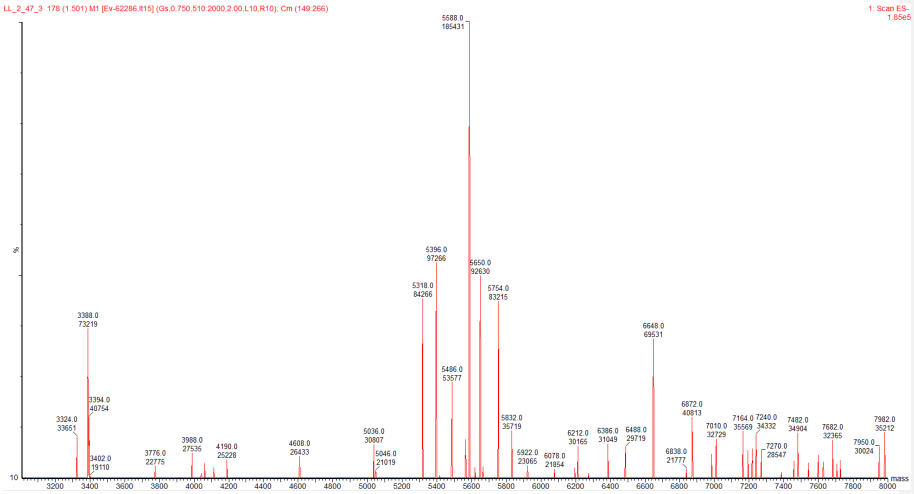
4b
92 %
Molecular weight: 5468.36 g/mol



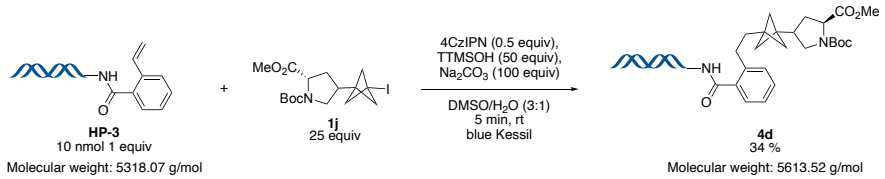
General procedure I : Compound **4c**, *trace*

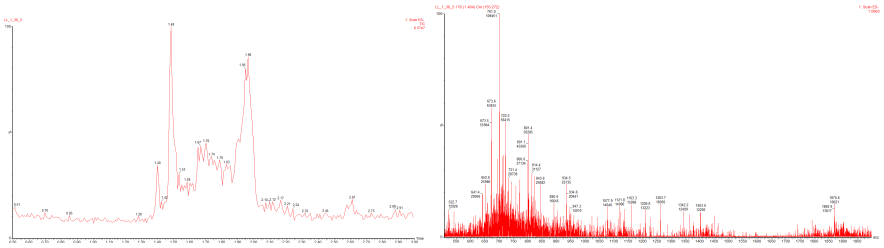


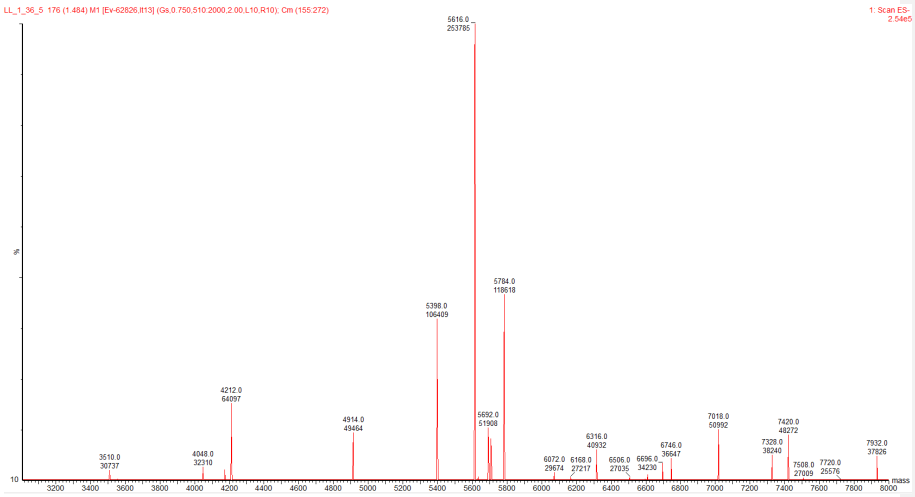




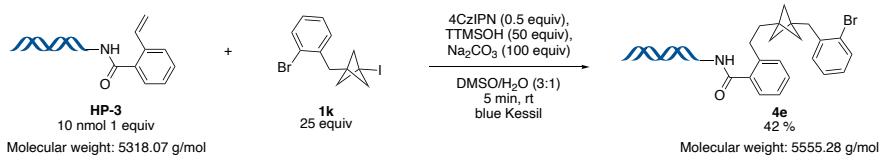
General procedure I : Compound **4d**, *34% yield*







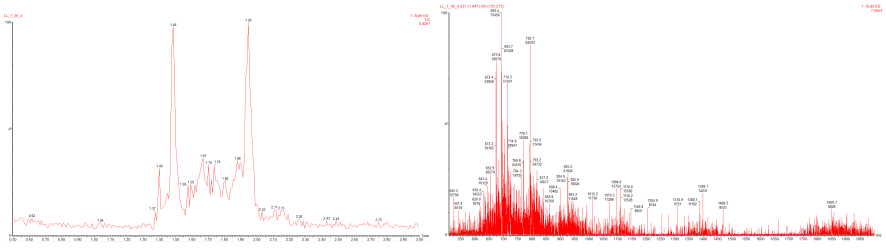
General procedure I : Compound **4e**, *42% yield*



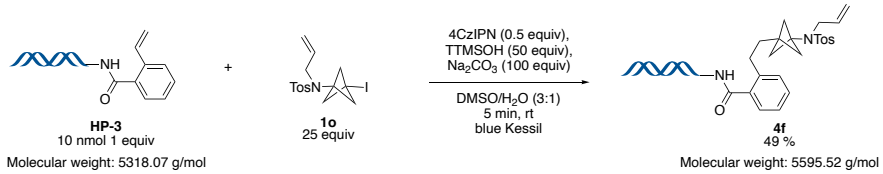
HP-3
10 nmol 1 equiv
Molecular weight: 5318.07 g/mol

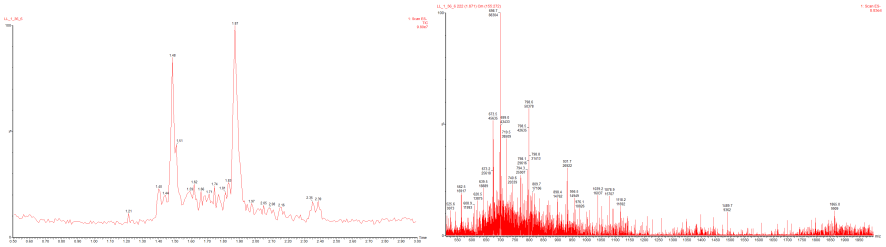
1k
25 equiv

4e
42 %
Molecular weight: 5555.28 g/mol

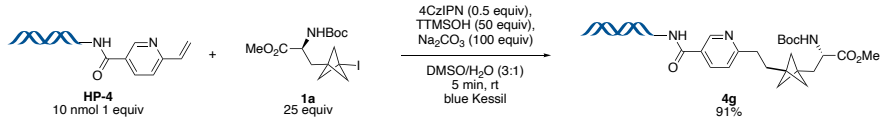


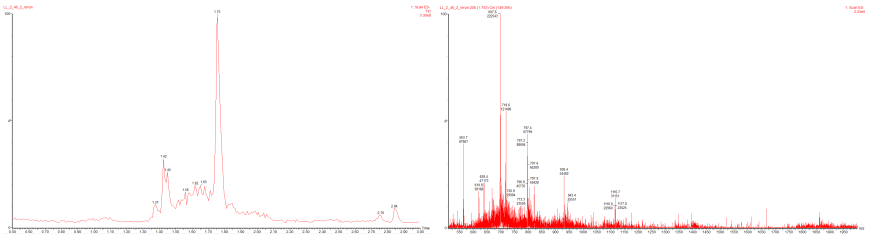
General procedure I : Compound **4f**, *49% yield*



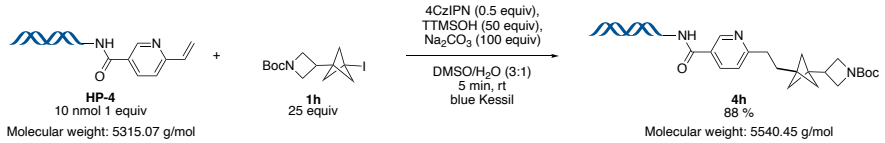


General procedure I : Compound **4g**, *91% yield*





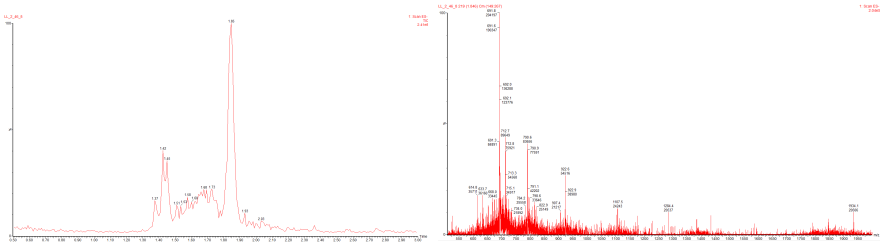
General procedure I : Compound **4h**, *91% yield*

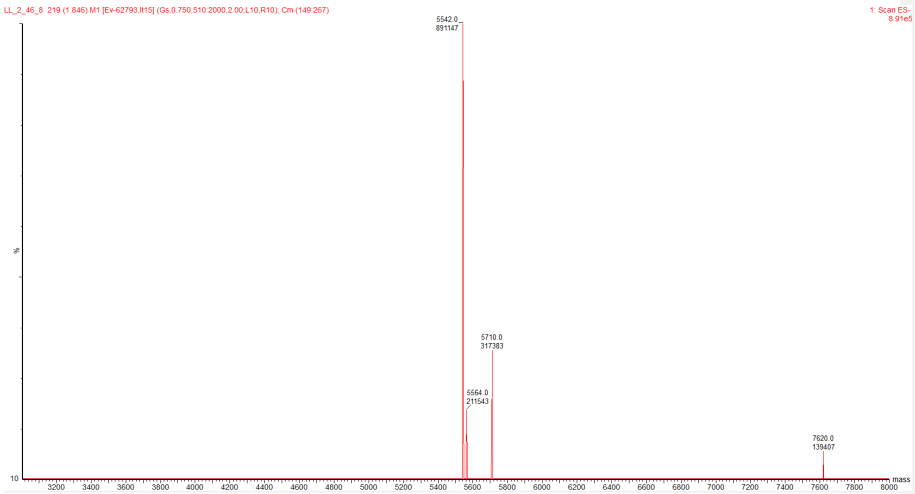


HP-4
10 nmol 1 equiv
Molecular weight: 5315.07 g/mol

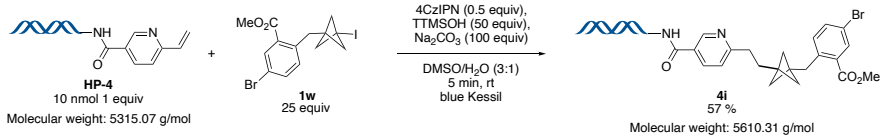
1h
25 equiv

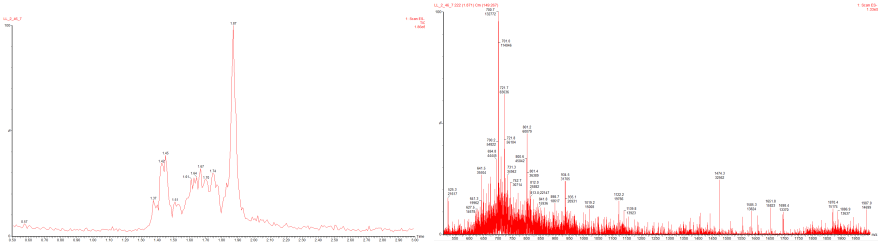
4h
88 %
Molecular weight: 5540.45 g/mol

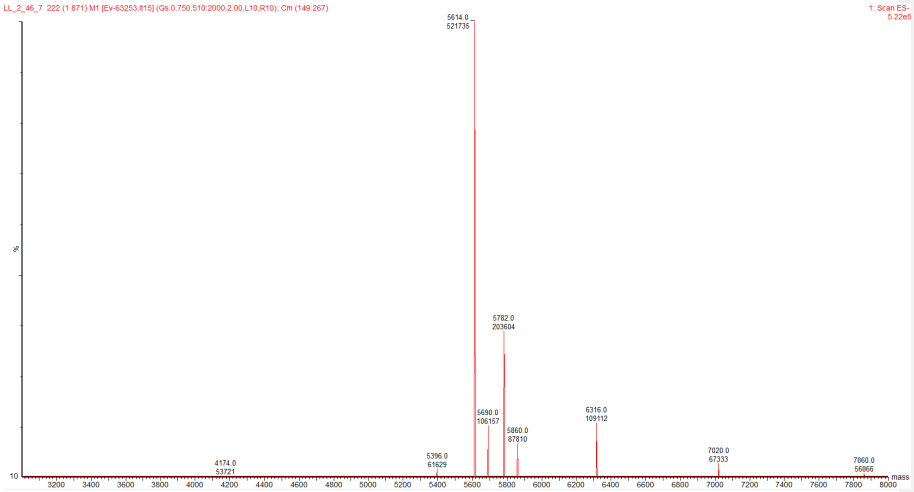




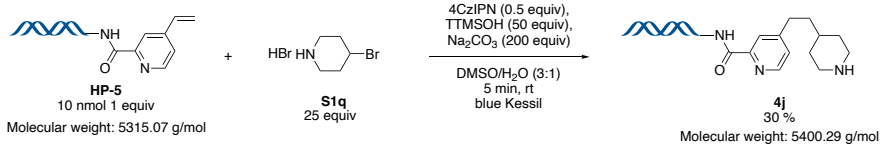
General procedure I : Compound **4i**, *57% yield*







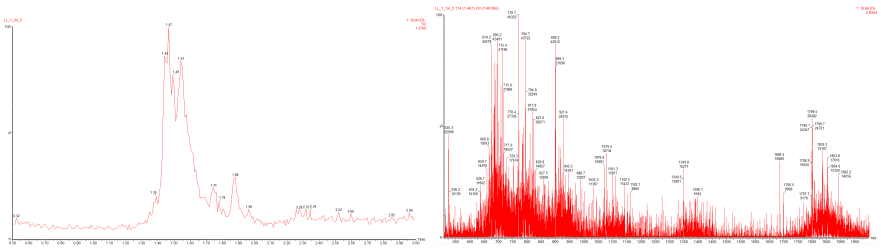
General procedure I : Compound **4j**, *30% yield*

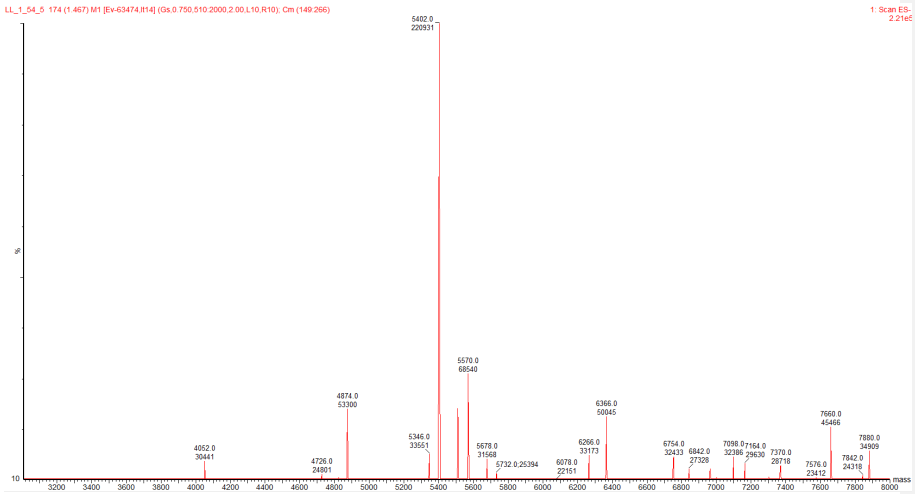


HP-5
10 nmol 1 equiv
Molecular weight: 5315.07 g/mol

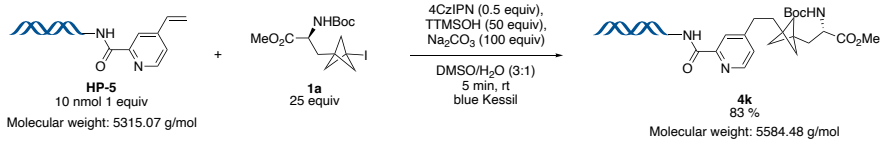
S1q
25 equiv

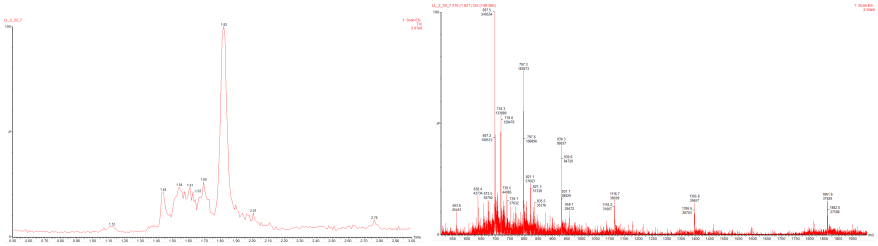
4j
30 %
Molecular weight: 5400.29 g/mol



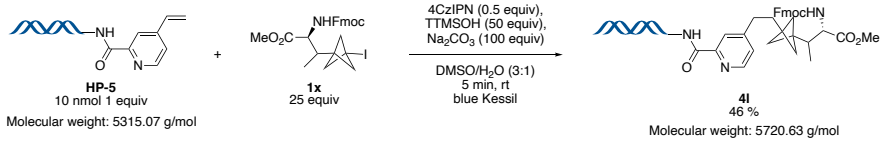


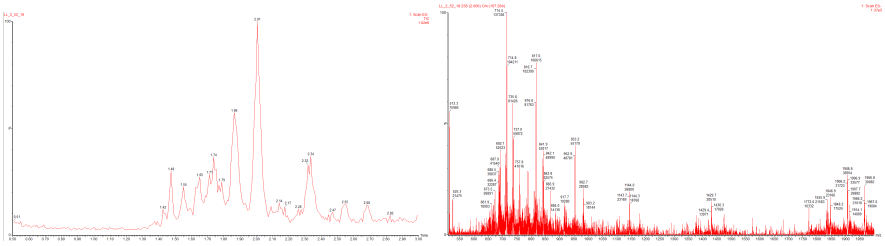
General procedure I : Compound **4k**, *83% yield*

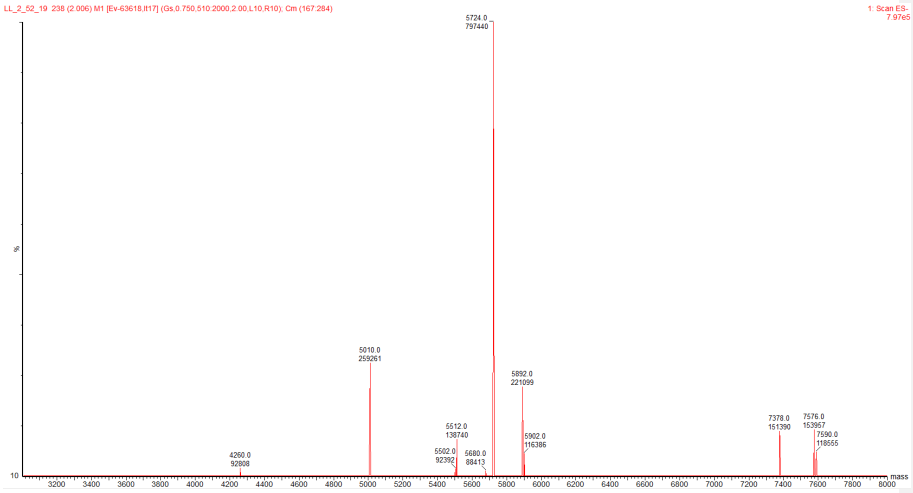




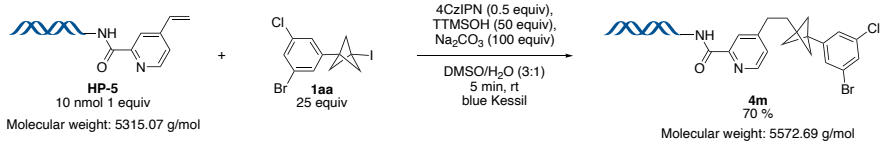
General procedure I : Compound **4l**, *46% yield*

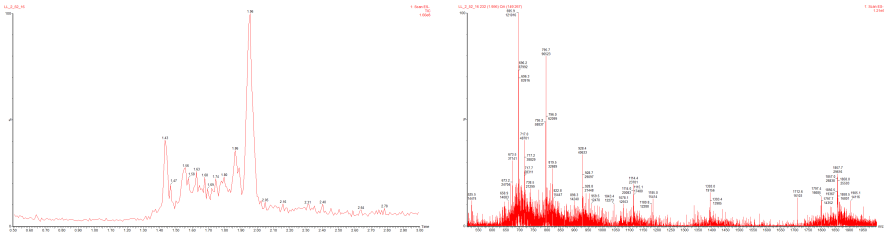




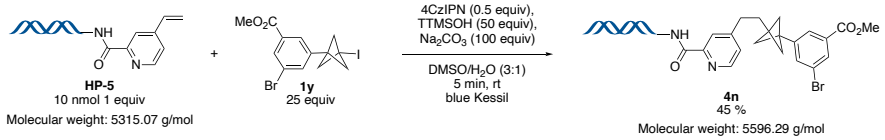


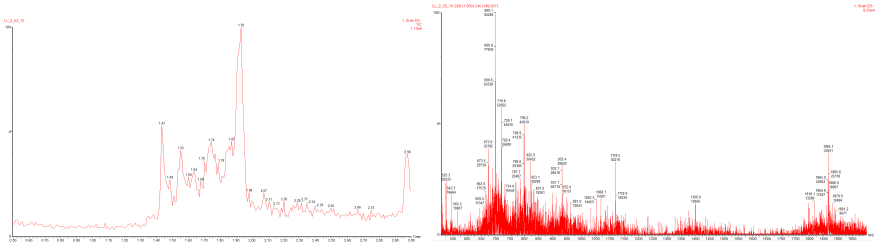
General procedure I : Compound **4m**, *70% yield*

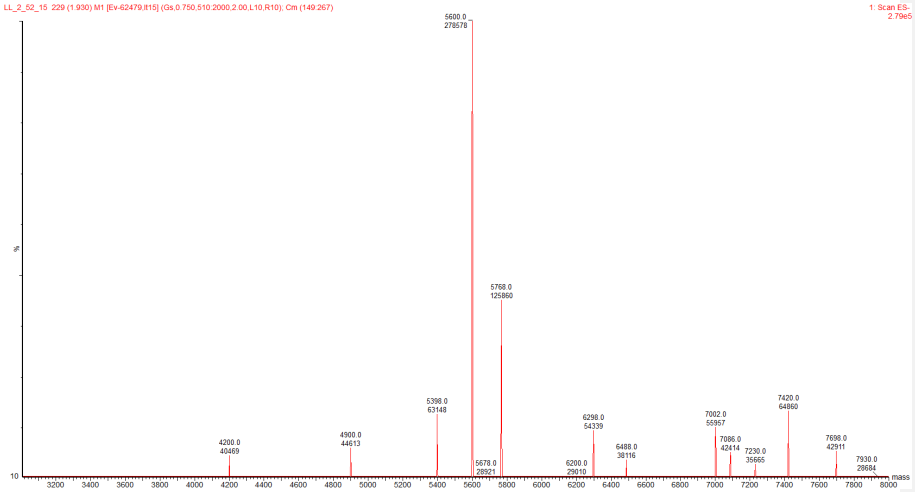




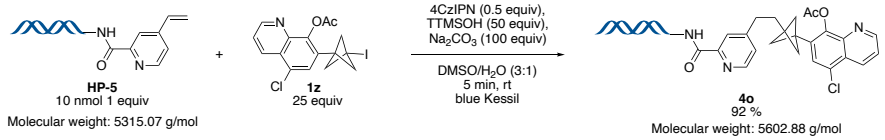
General procedure I : Compound **4n**, *45% yield*

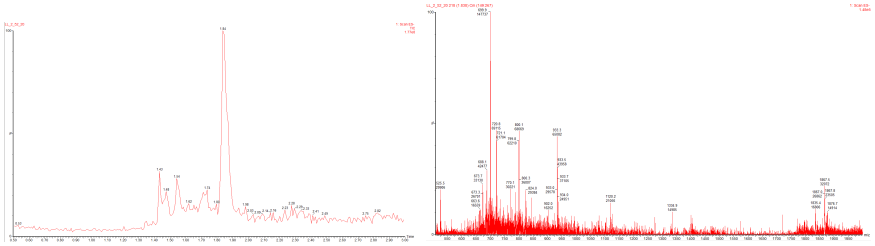




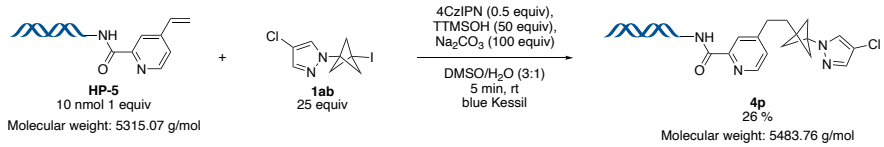


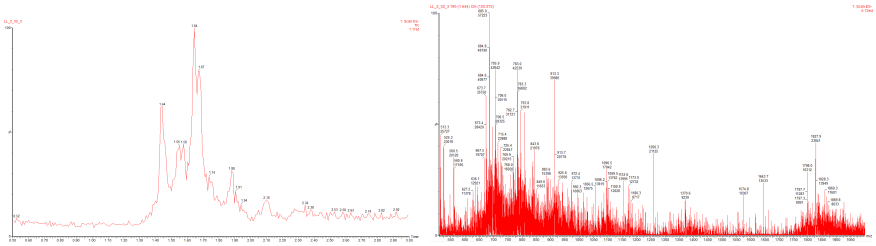
General procedure I : Compound **4o**, *92% yield*

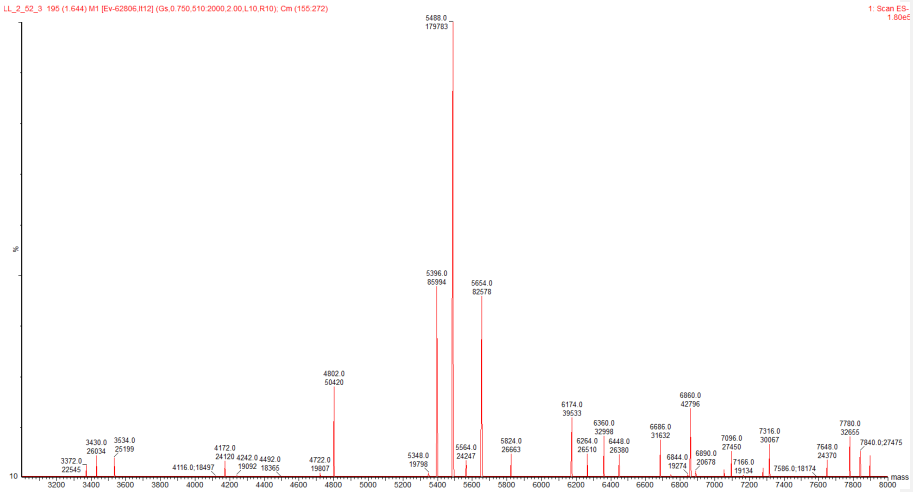




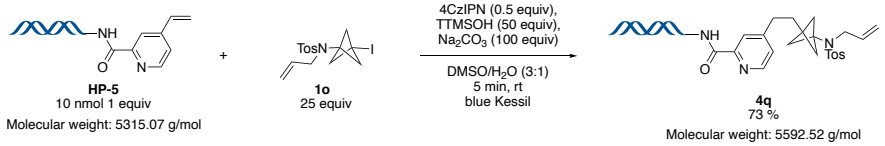
General procedure I : Compound **4p**, *26% yield*

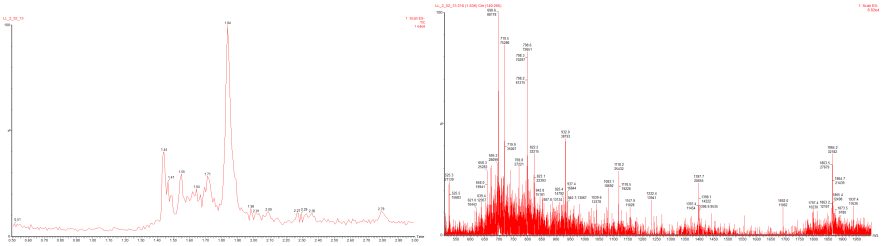


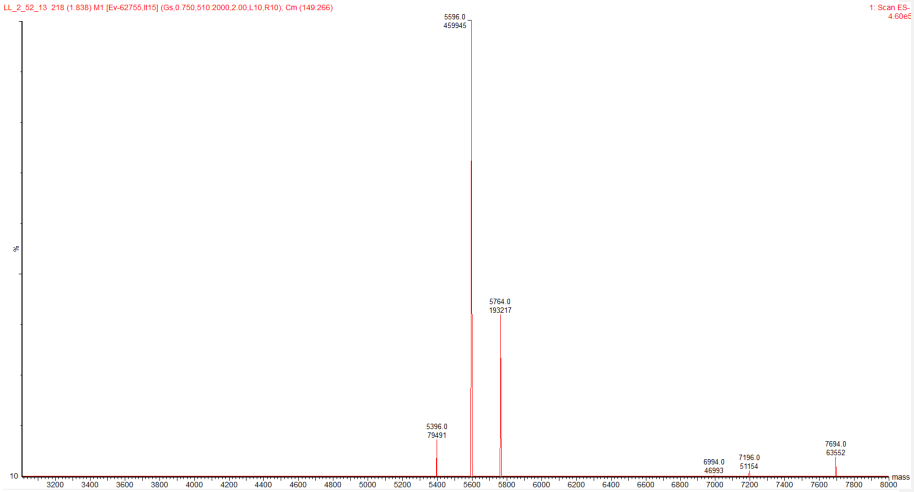




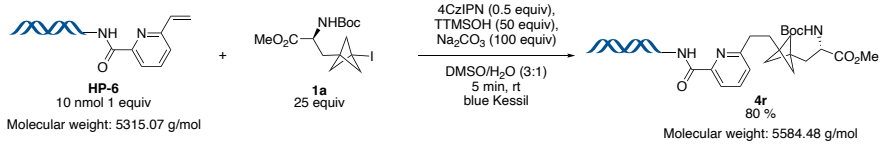
General procedure I : Compound **4q**, *73% yield*

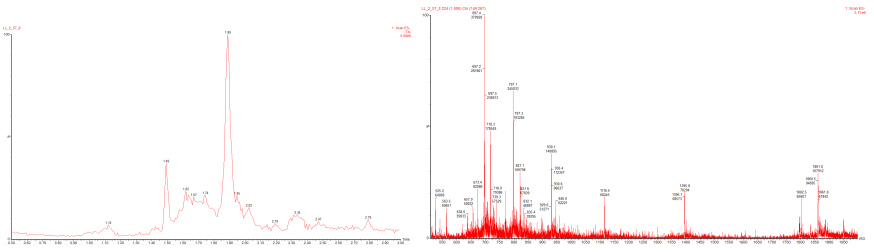




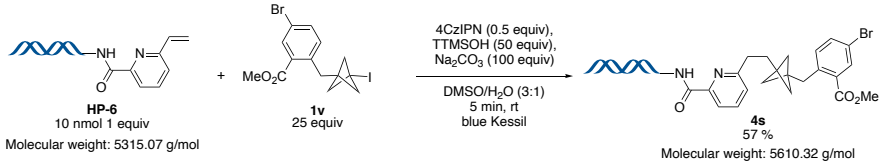


General procedure I : Compound **4r**, *80% yield*





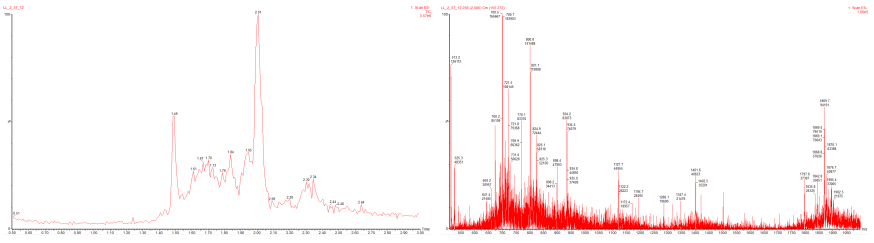
General procedure I : Compound **4s**, *57% yield*



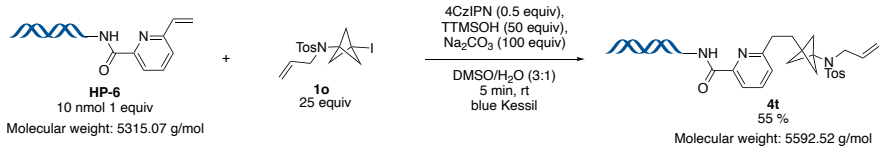
HP-6
10 nmol 1 equiv
Molecular weight: 5315.07 g/mol

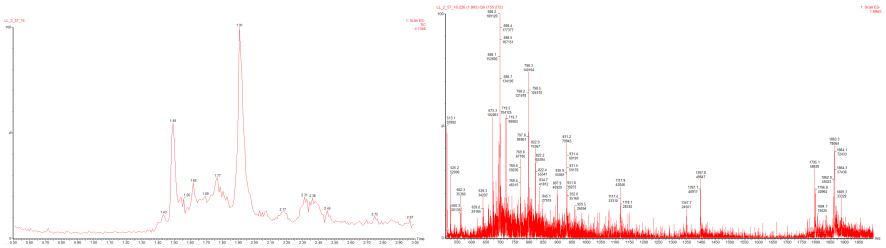
1v
25 equiv

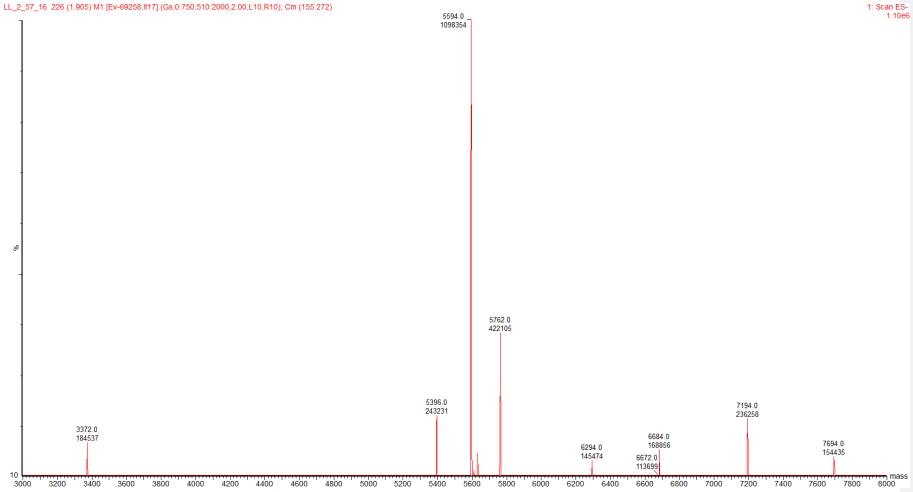
4s
57 %
Molecular weight: 5610.32 g/mol



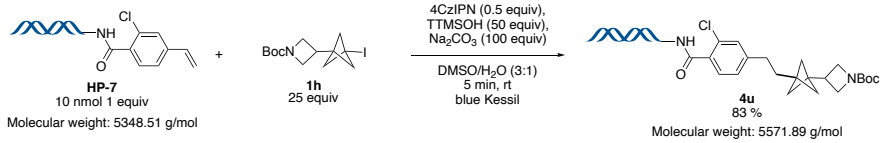
General procedure I : Compound **4t**, *55% yield*

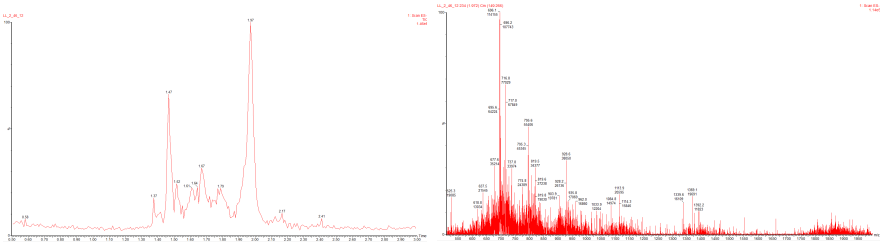


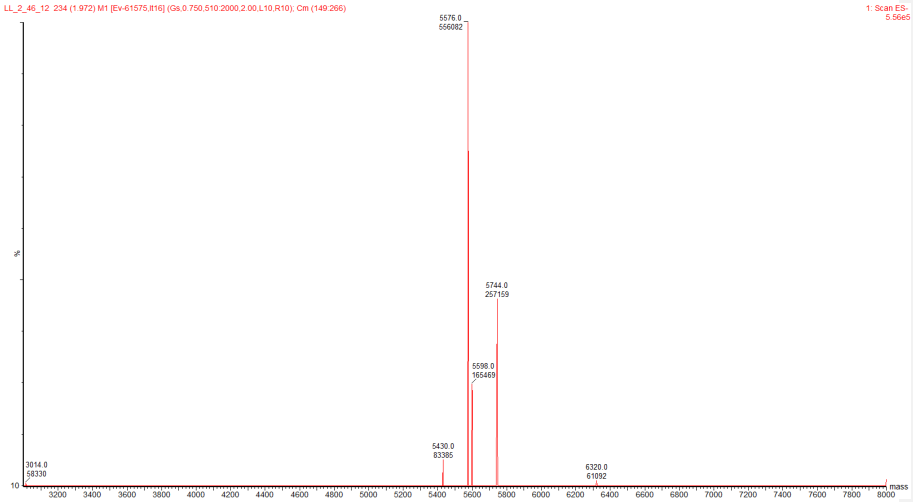




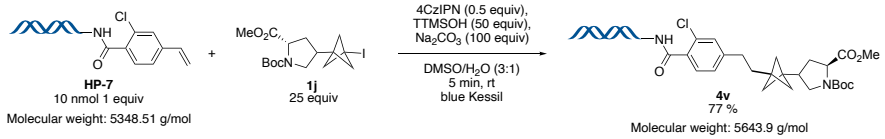
General procedure I : Compound **4u**, *83% yield*

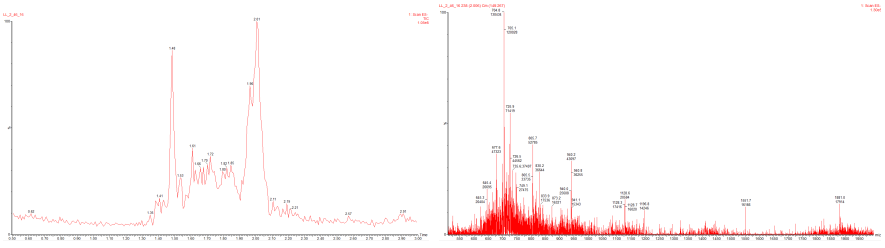


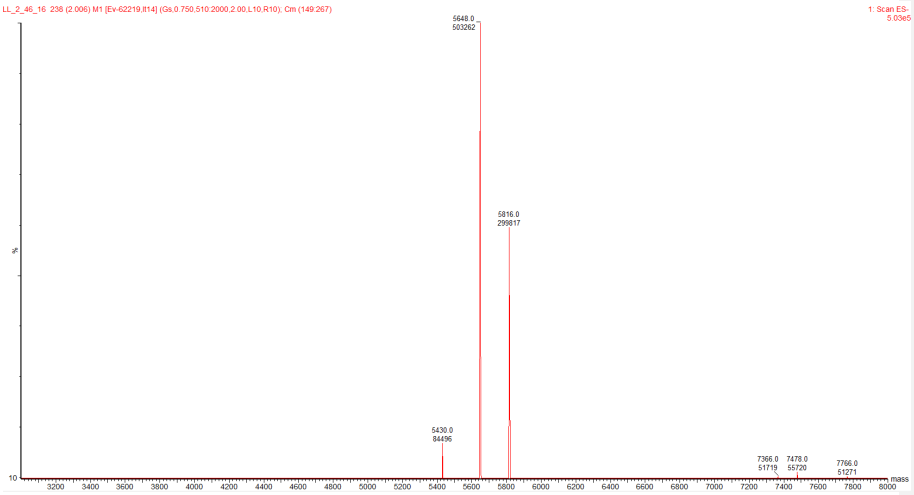




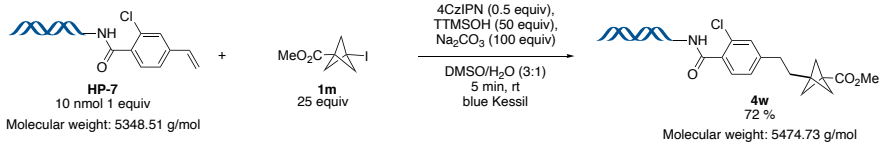
General procedure I : Compound **4v**, *77% yield*







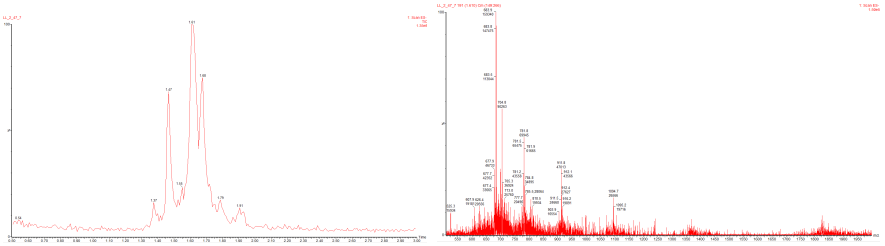
General procedure I : Compound **4w**, *72% yield*

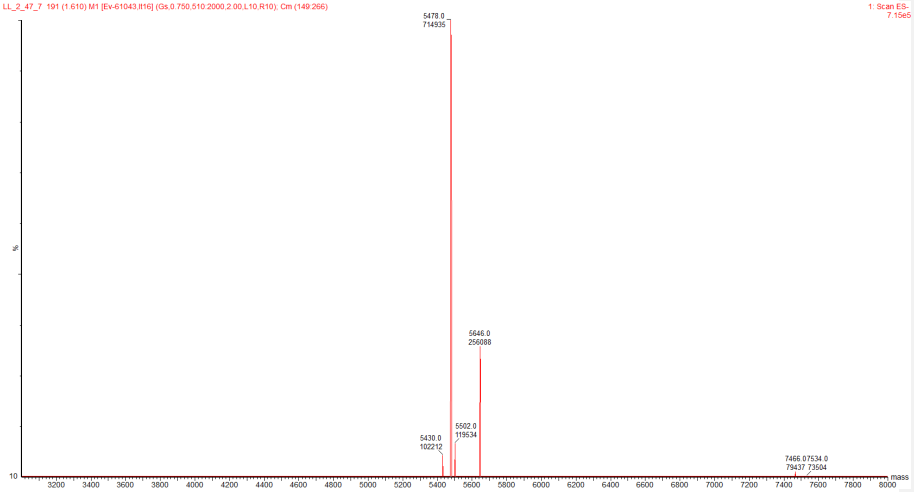


HP-7
10 nmol 1 equiv
Molecular weight: 5348.51 g/mol

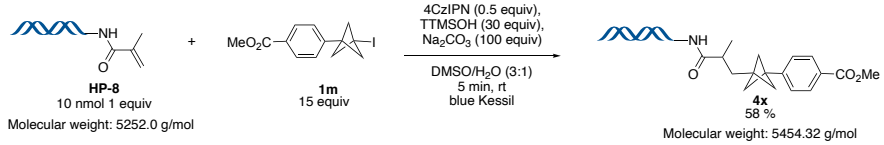
1m
25 equiv

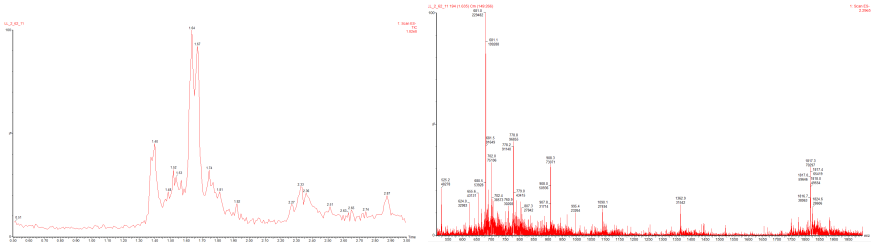
4w
72 %
Molecular weight: 5474.73 g/mol

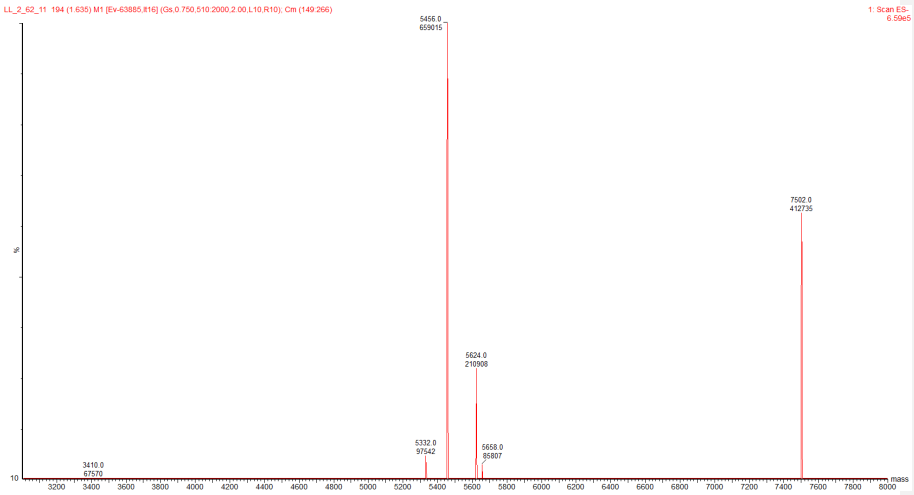




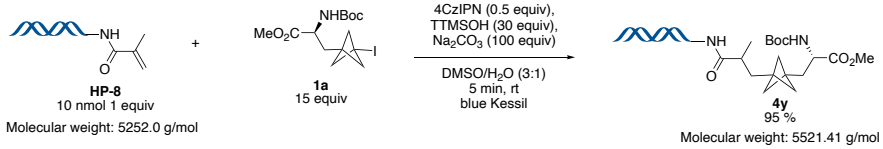
General procedure III : Compound **4x**, *58% yield*

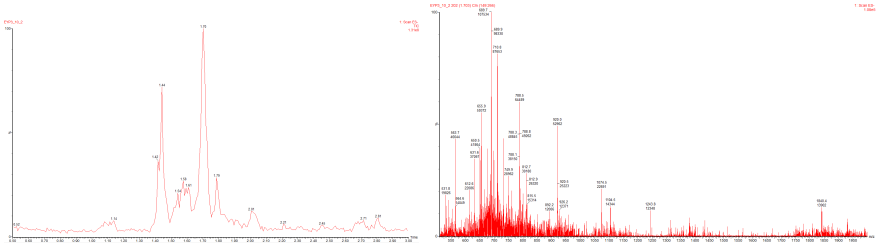




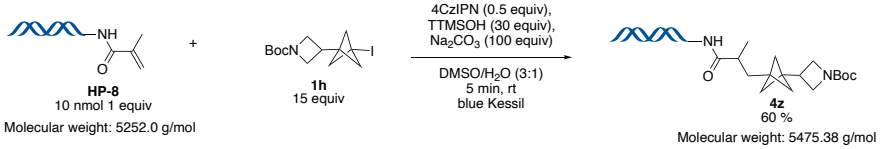


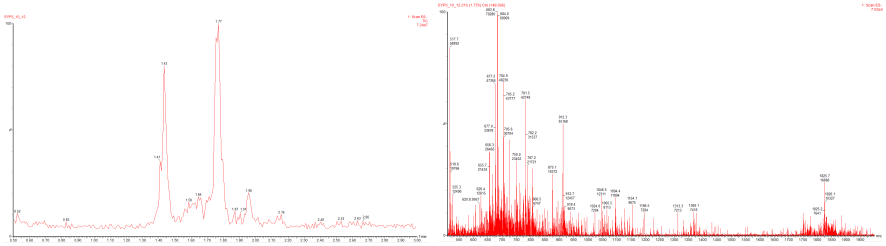
General procedure III : Compound **4y**, *95% yield*



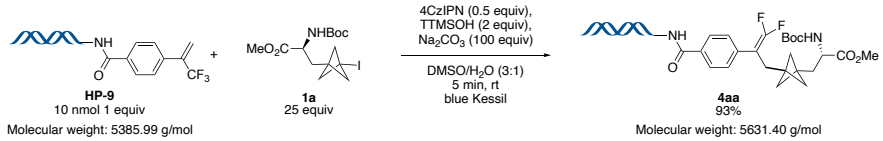


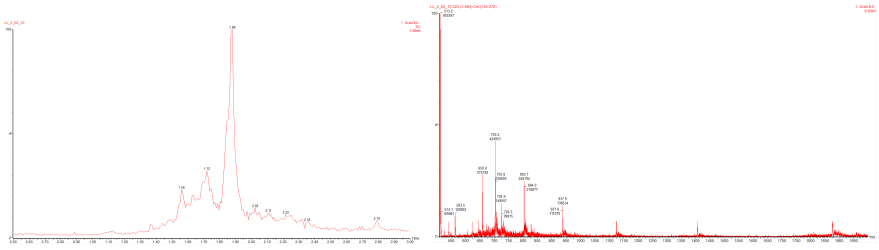
General procedure III : Compound **4z**, *60% yield*



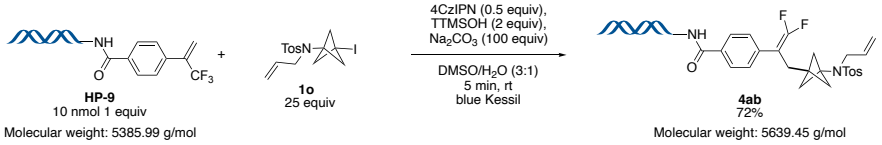


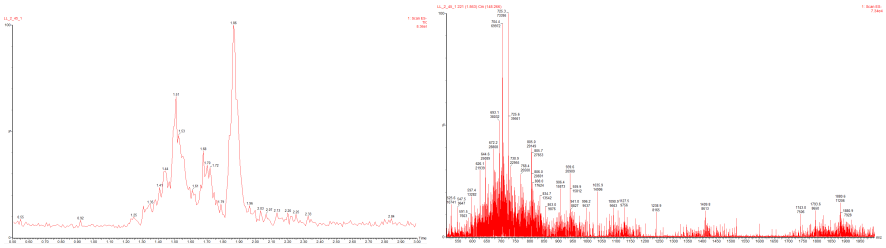
General procedure IV : Compound **4aa**, *93% yield*

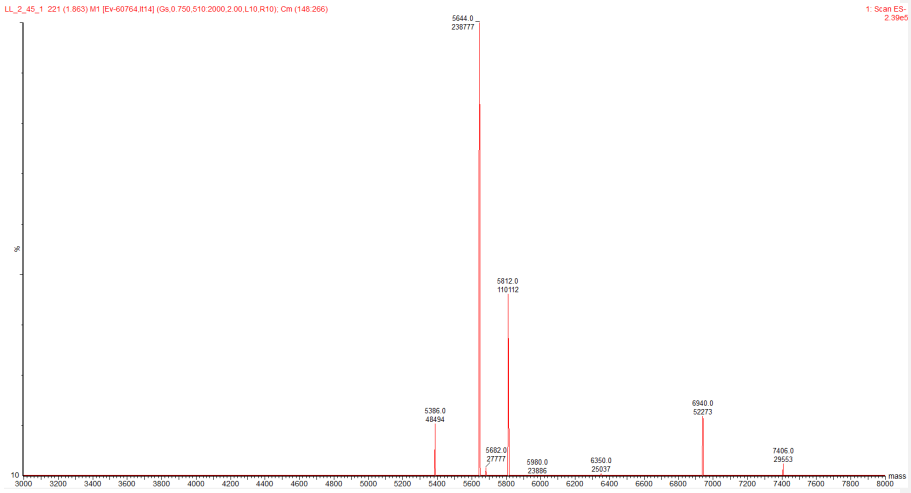




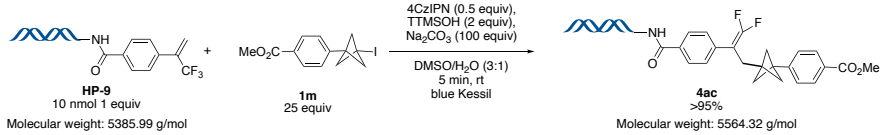
General procedure IV : Compound **4ab**, *72% yield*

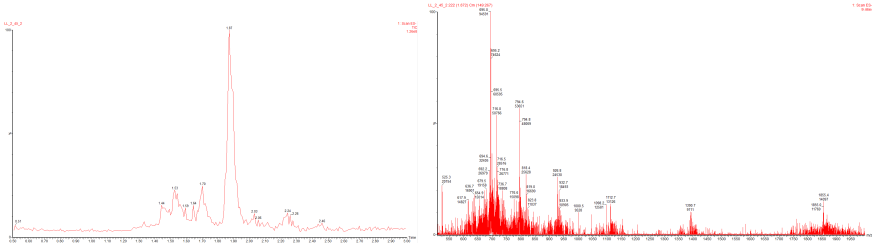




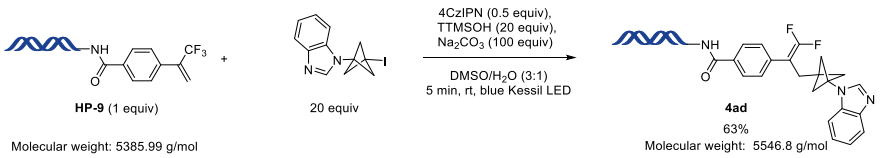


General procedure IV : Compound **4ac**, *>95% yield*





General procedure IV : Compound **4ad**, *63% yield*
*With the following modifications:*TTMSOH 20 equiv, 20 mM in DMSO



HP-9 (1 equiv)

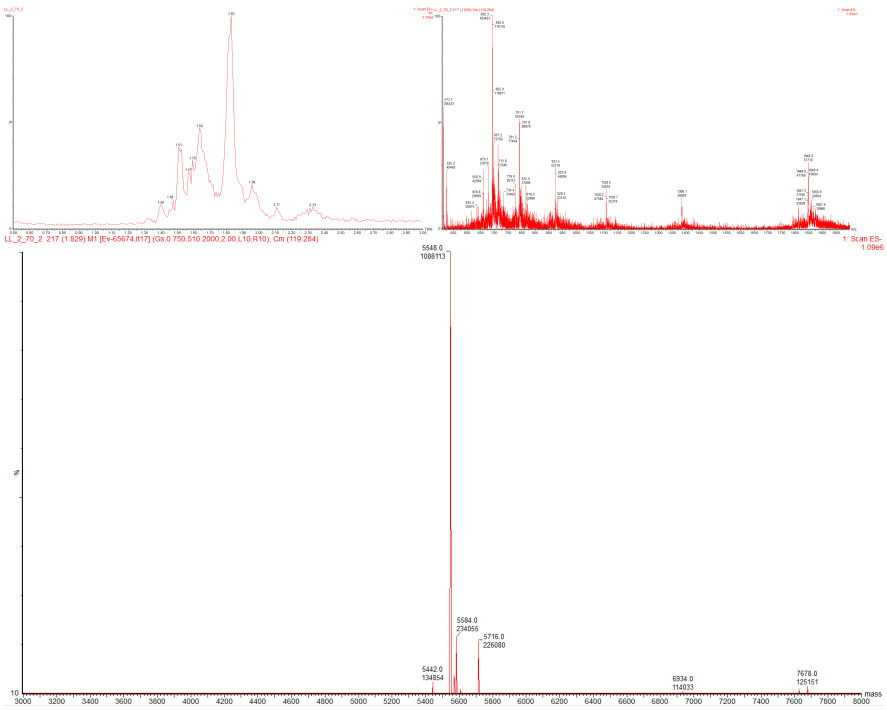
Molecular weight: 5385.99 g/mol

20 equiv

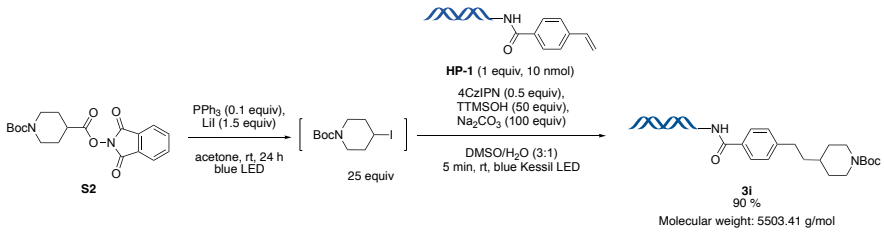
4ad

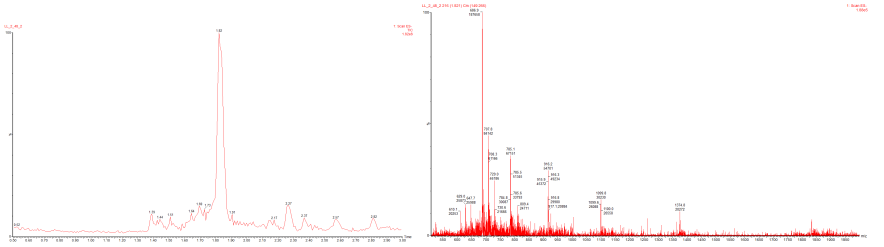
63%

Molecular weight: 5546.8 g/mol

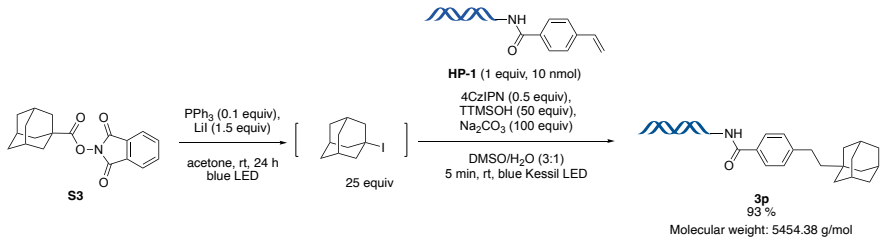


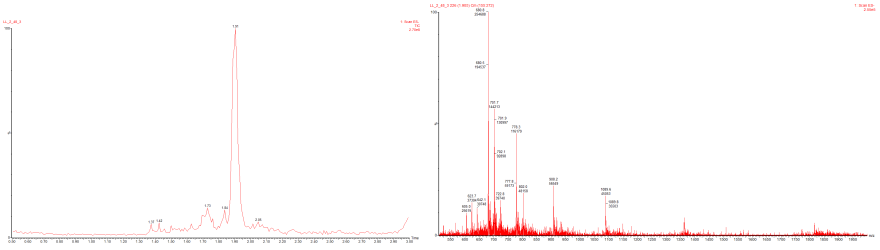
General procedure for telescoped reaction from redox active ester: Compound **3i**, *90% yield*



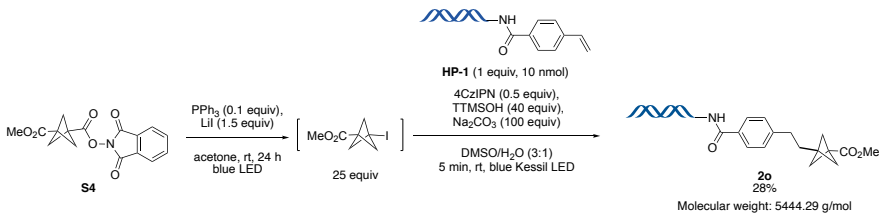


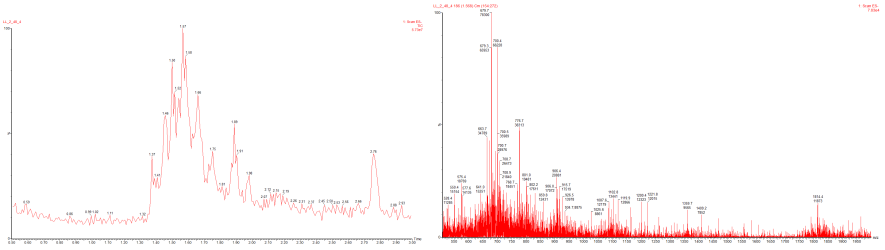
General procedure for telescoped reaction from redox active ester: Compound **3p**, *93% yield*

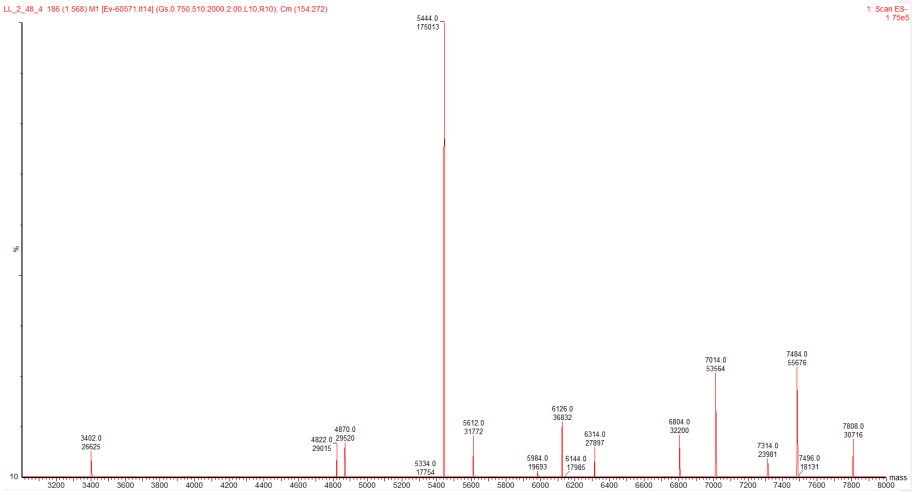




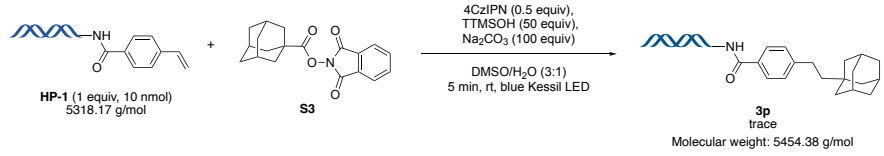
General procedure for telescoped reaction from redox active ester: Compound **2o**, *28% yield*







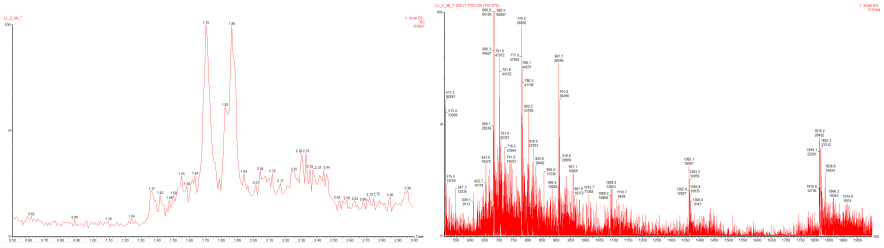
Control

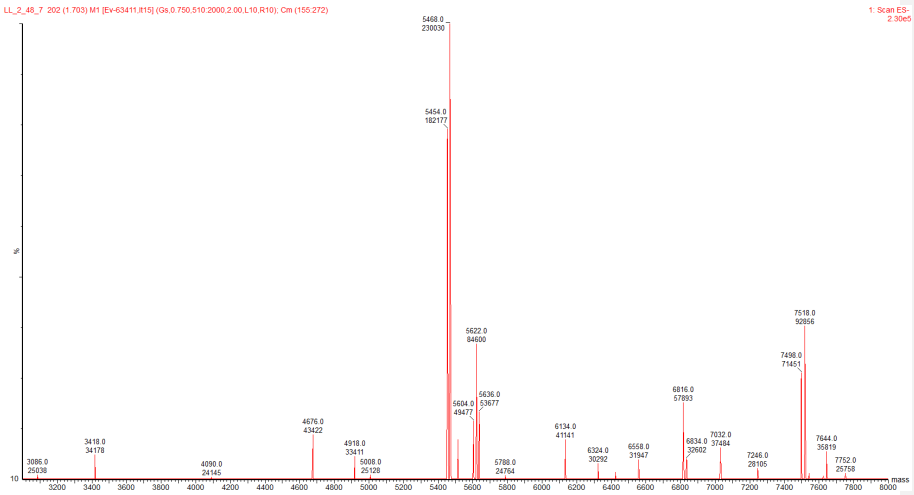


HP-1 (1 equiv, 10 nmol)
5318.17 g/mol

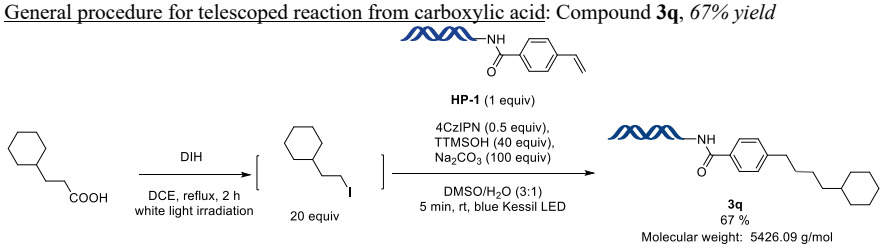
S3

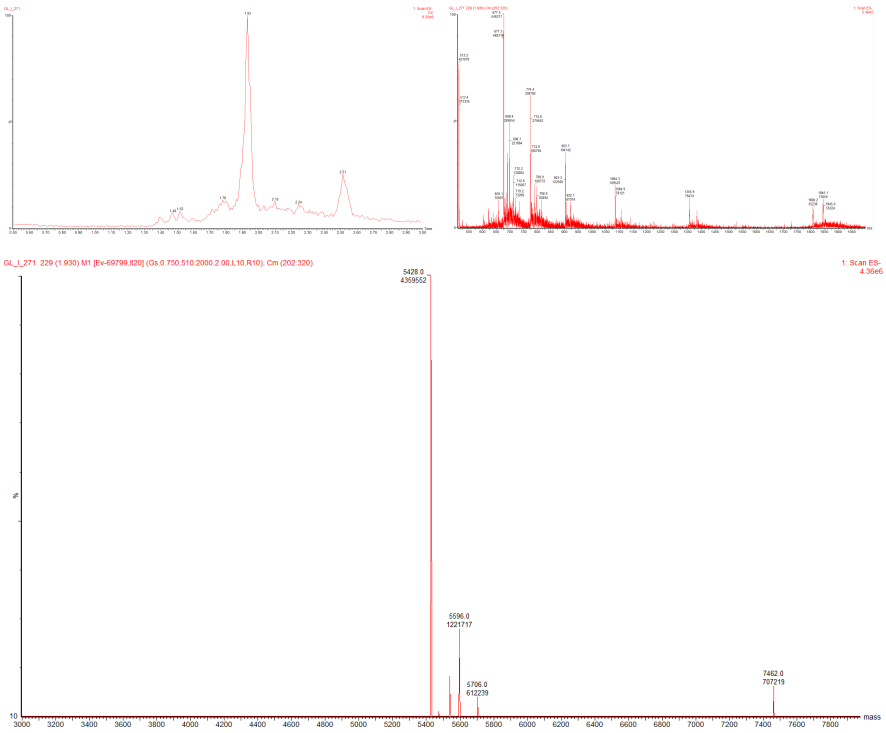
3p
trace
Molecular weight: 5454.38 g/mol



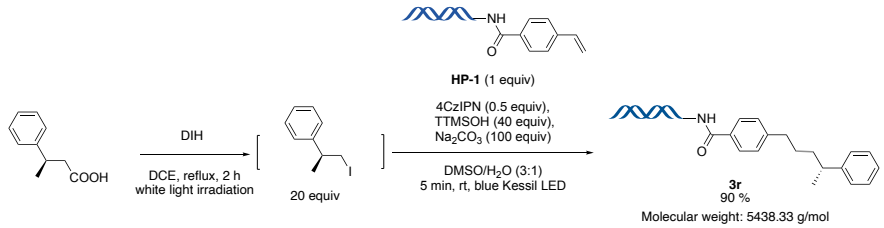


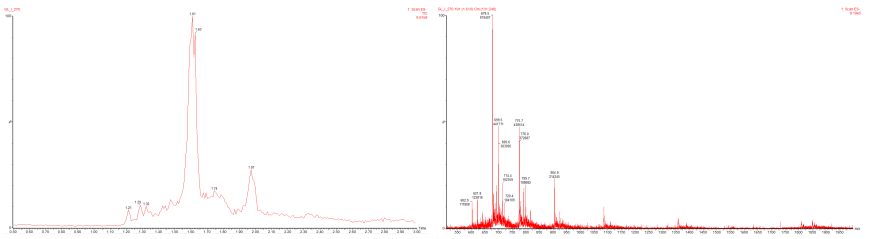
General procedure for telescoped reaction from carboxylic acid: Compound **3q**, *67% yield*



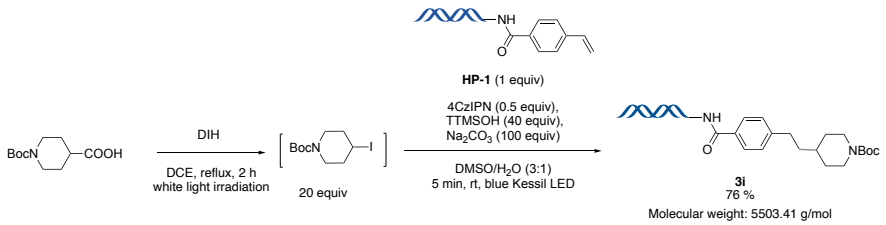


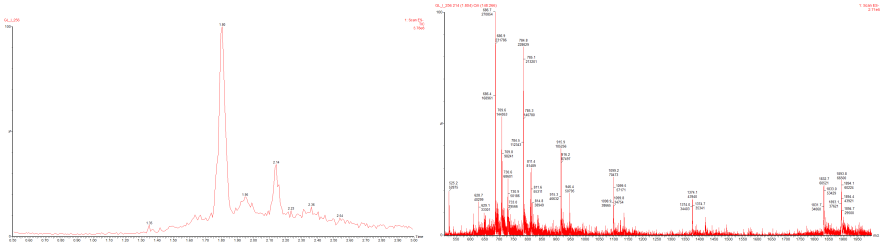
General procedure for telescoped reaction from carboxylic acid: Compound **3r**, *90% yield*

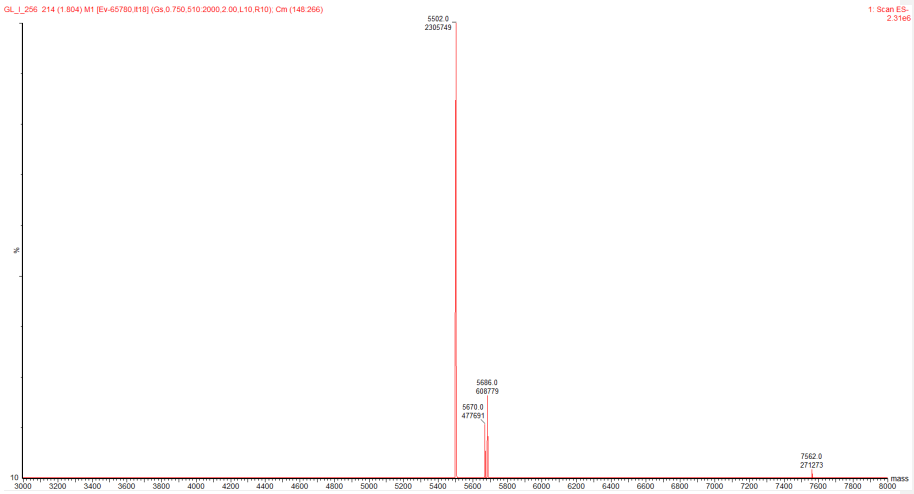




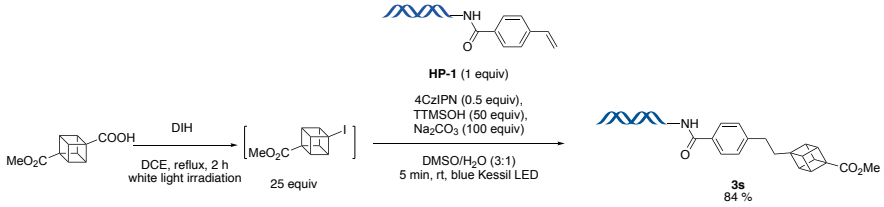
General procedure for telescoped reaction from carboxylic acid: Compound **3i**, *76% yield*

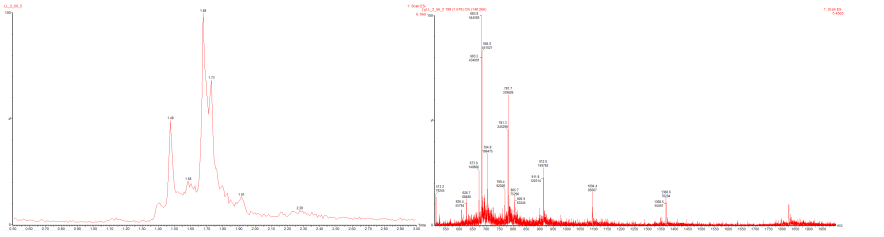


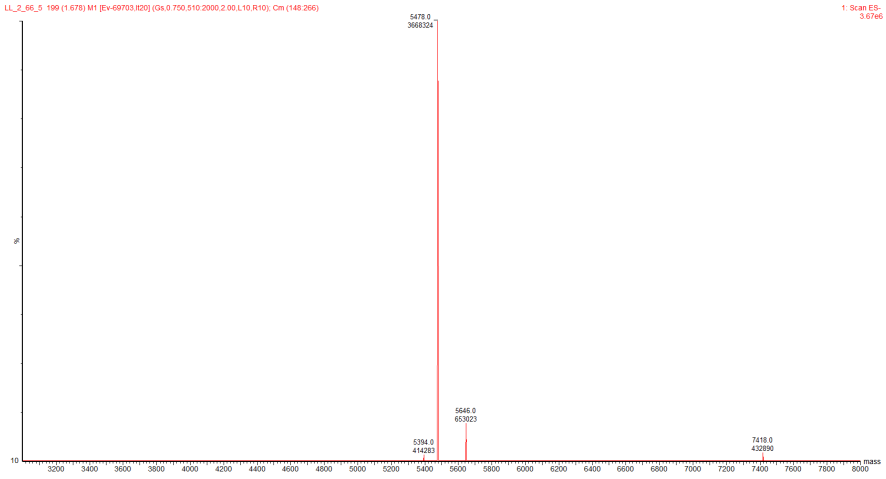




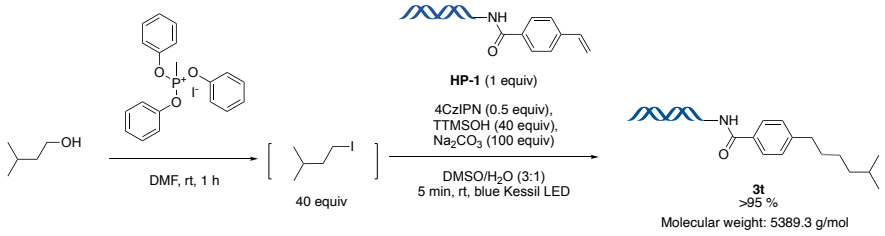
General procedure for telescoped reaction from carboxylic acid: Compound **3s**, *84% yield*

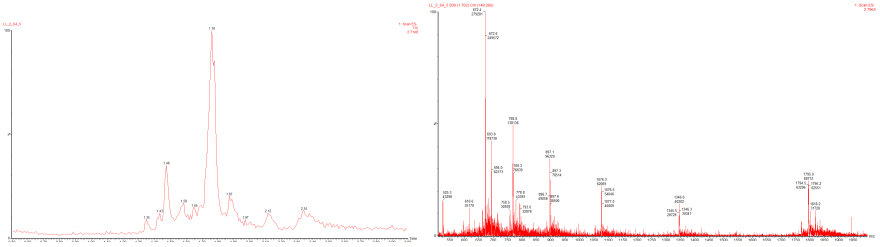




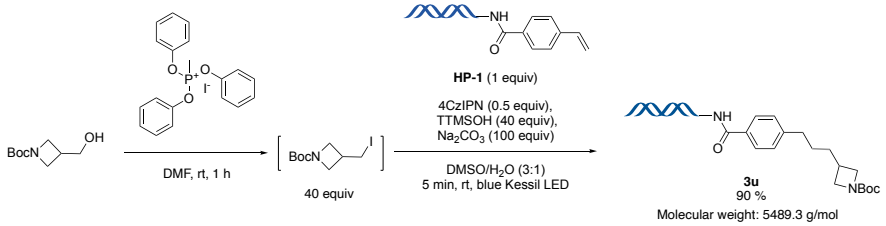


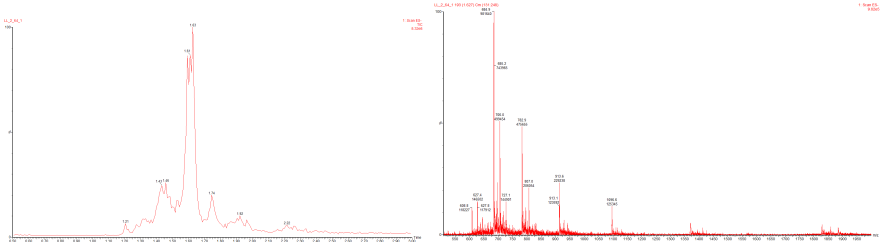
General procedure for telescoped reaction from alcohol: Compound **3t**, *>95% yield*



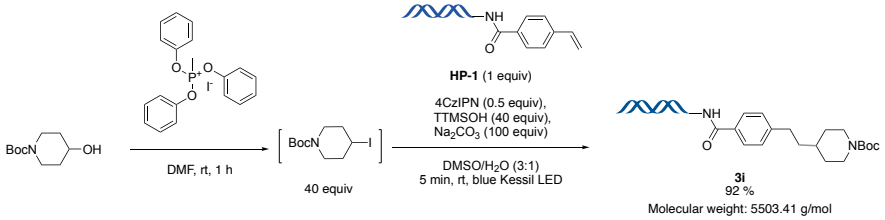


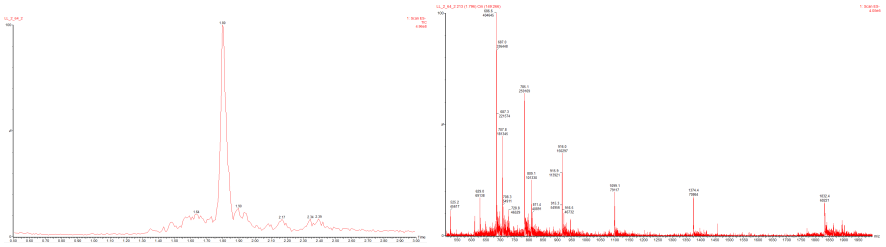
General procedure for telescoped reaction from alcohol: Compound **3u**, *90% yield*



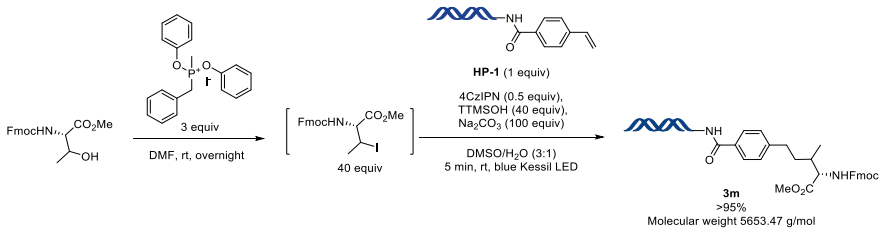


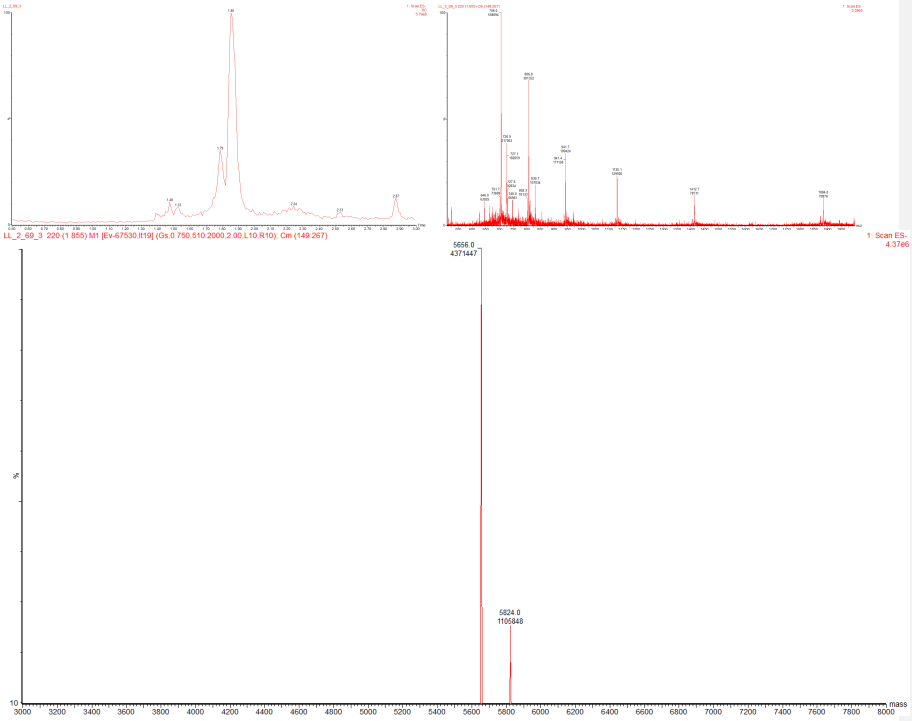
General procedure for telescoped reaction from alcohol: Compound **3i**, *92% yield*





General procedure for telescoped reaction from alcohol: Compound **3m**, *>95% yield*
With the following modification: 3 equiv of [P(OPh)3Me]I





10.DNA Damage Assessment

10.1 Workflow overview

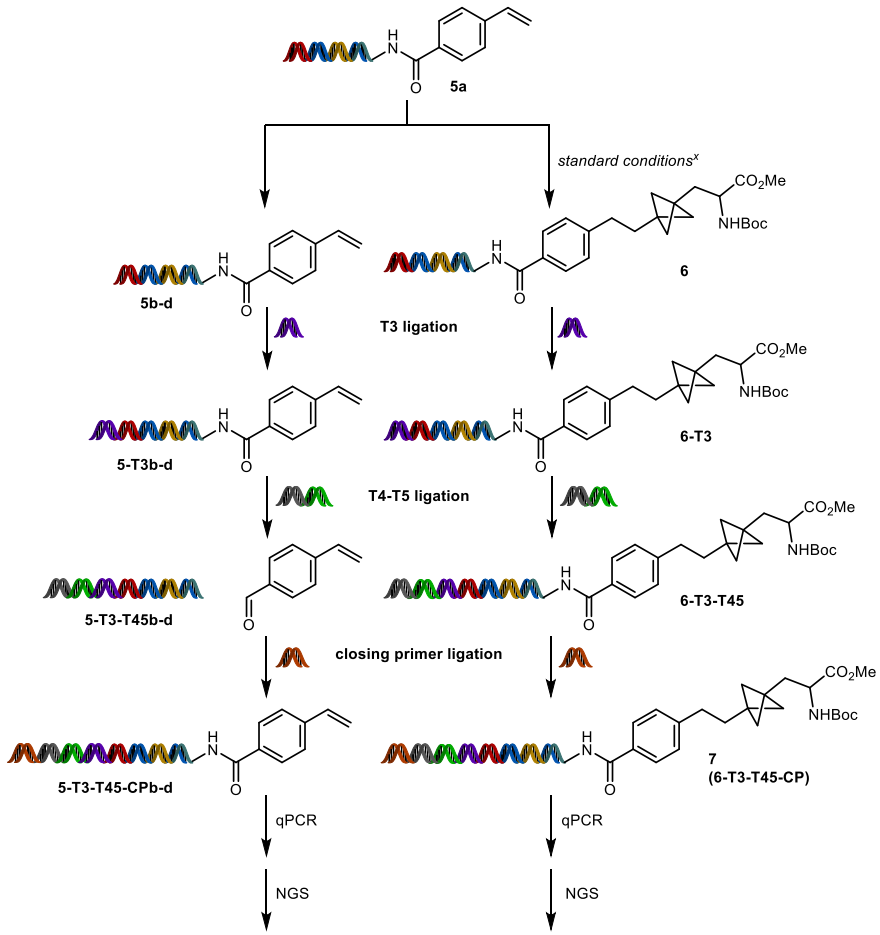
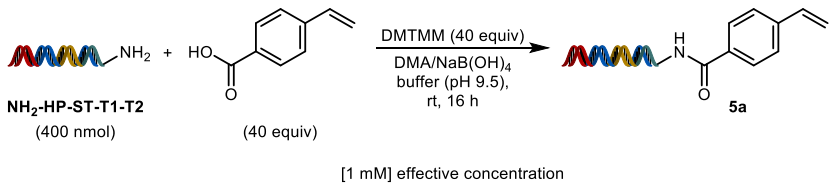


Figure S2: Workflow for the DNA damage assessment.

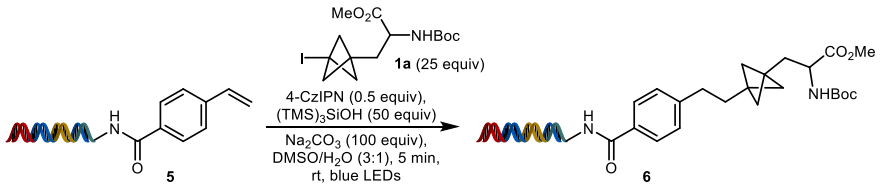
10.2 Preparation of materials



Preparation of 4-vinyl benzamide-capped cycle 2 DNA tag (5a).
To a 1.5 mL PCR was added 400 nmol DNA (NH_2-HP-ST-T1-T2, 80 µL, 5 mM in water, 1 equiv) in water. To this was added 320 µL of sodium borate buffer (pH 9.4), followed by the addition of 80 µL DMTMM (16000 nmol, 200 mM in water, 40 equiv), and 80 µL of 4-vinylbenzoic acid (16000 nmol, 200 mM in DMA, 40 equiv). The reaction was equipped with a stirbar and allowed to stir at room temperature overnight. In the morning, the reaction solution was clear and colorless.

Following the conclusion of the reaction, the reaction sample was subjected to an ethanol precipitation according to General Procedure 1. The DNA pellet was then resuspended in 200 µL of water, and a 1 µL aliquot was taken for LCMS analysis. The DNA solution was then frozen in an acetone/dry ice bath and lyophilized to give the DNA material as a colorless solid.

A sample of the 4-vinyl benzamide capped, elongated DNA was kept for DNA damage analysis without being subjected to the on-DNA photoredox cross-coupling conditions.



[0.3 mM] effective concentration

Synthesis of cycle 2 DNA BCP-coupled product (6).
Reaction conditions A, B, and C were each carried out as 10 x 10 nmol reactions, then pooled to give on 100 nmol sample for qPCR and NGS analysis.

To a 0.2 mL PCR tube was added 5 uL of 4-CzIPN (5 nmol, 1 mM in DMSO, 0.5 equiv), followed by the addition of 10 µL of I-BCP (250 nmol, 25 mM in DMSO, 25 equiv), 10 µL of $(Me_3Si)_3SiOH$ (500 nmol, 50 mM in DMSO, 50 equiv), and 2.5 µL of Na_2CO_3 (1000 nmol, 400 mM in H_2O, 100 equiv). Finally, 4-vinyl functionalized DNA-HP material was added (5 µL, 2 mM in water, 10 nmol) and the solution was vortexed for 30 s. The PCR tube was then suspended about 2 in in front of a 456 nm PR-160 Kessil lamp and irradiated on 100% power for 5 mins. At the conclusion of the reaction time, the reaction solution was clear and colorless in appearance. At the conclusion of the reaction time, the reaction solution was taken up into 100 µL of water. 30 µL of this solution was syringe filtered into a low-volume LM-CS vial, this solution was diluted to 90 µL by the addition of 60 µL of ddH_2O. The reaction sample was then submitted for LC-MS analysis. LC-MS showed 39% yield for the desired product.

Reaction sample 6 were subjected to the normal reaction conditions and irradiated for 5 mins.

Reaction sample 5b were subjected to the reaction conditions but were covered with aluminum foil to avoid irradiation (dark control).

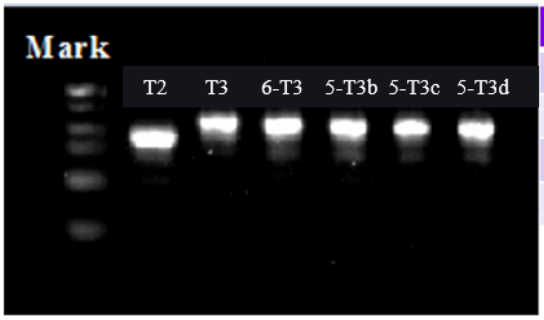
Reaction sample 5c were diluted with appropriate volumes of DMSO and water and irradiated in the absence of reagents.

Reaction sample 5d were not subjected to reagents or irradiation.

At the conclusion of the reaction, the 10 reaction samples were combined for each of the samples and subjected to an ethanol precipitation according to Section 2.2. The precipitated DNA material was taken up into 200 µL of water, frozen in a dry ice/acetone bath and lyophilized in preparation for subsequent ligation steps, followed by qPCR and NGS analysis.

10.3 Ligations

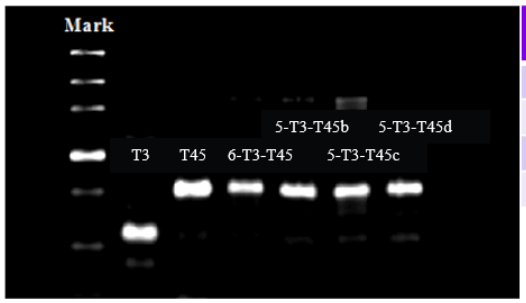
Cycle 3 (T3) ligation (5-T3a-c, 6-T3)
To each tube of **5b-d** and **6** (50 nmol, 1 mM in ddH_2O) was added 1.8 equiv T3 (90 nmol, 1.98 mM in ddH_2O), 10X T4 DNA ligase buffer(20.00 µL), ddH_2O (82.5 µL) and T4 DNA ligase (2 µL, 30 U/ µL). The tubes were vortexed, centrifuged and stood at 16°C for 16 h. After that the samples were subjected to ethanol precipitation and spin filtration with 10K membrane. The ligation efficiency was detected by gel electrophoresis and LC-MS analysis.



Sample	% yield
6-T3	98.97%
5-T3b	97.99%
5-T3c	97.01%
5-T3d	98.48%

Figure S3: Gel image and yield (LC-MS) for the T3 ligation.

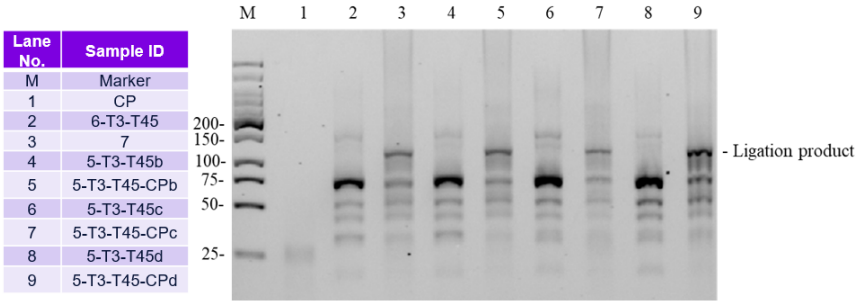
Cycle 4 and 5 (T45, library tag) ligation (5-T3-T45a-c, 6-T3-T45)
To each tube of **5-T3a-c** and **6-T3** (20 nmol, 1 mM in ddH_2O) was added 1.3 equiv. T45 (26 nmol, 1 mM in ddH_2O), 10X T4 DNA ligase buffer (8 µL) , ddH_2O (25 µL) and T4 DNA ligase (1 µL, 30 U/ µL). The tubes were vertexed, centrifuged and stood at 16°C for 16 h. After that the samples were subjected to ethanol precipitation and spin filtration with 30K membrane. The ligation efficiency was detected by gel electrophoresis and LC-MS analysis.



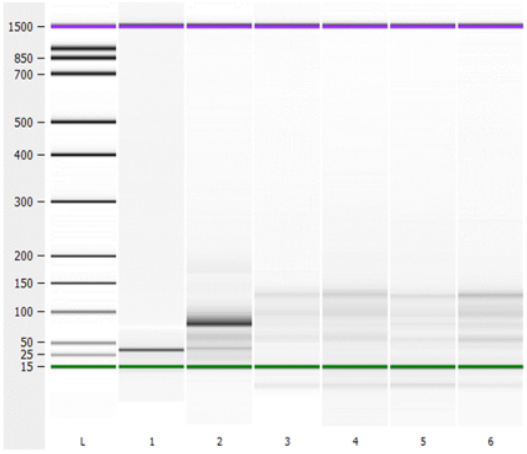
Sample	% yield	Recovery rate
6-T3-T45	100%	79.6%
5-T3-T45b	99.75%	83.7%
5-T3-T45c	99.68%	90.5%
5-T3-T45d	98.88%	84.7%

Figure S4: Gel image and yield (LC-MS) for the cycle 4 and library tag ligation.

Closing tag ligation
To each tube of **5-T3-T45a-c** and **6-T3-T45** (1 nmol, 1 mM in ddH_2O) was added 2 equiv closing tag (2 nmol, 1 mM in ddH_2O), 10X T4 DNA ligase buffer (2 µL), ddH_2O (15.6 µL) and T4 DNA ligase (0.4 µL, 30 U/ µL). The tubes were vortexed, centrifuged and stood at 16°C for 16 h. After that the samples were subjected to ethanol precipitation and gel electrophoresis.



Lane No.	Sample ID
M	Marker
1	CP
2	6-T3-T45
3	7
4	5-T3-T45b
5	5-T3-T45-CPb
6	5-T3-T45c
7	5-T3-T45-CPc
8	5-T3-T45d
9	5-T3-T45-CPd



Lane No.	Sample ID
L	Marker
1	CP
2	6-T3-T45
3	7
4	5-T3-T45-CPb
5	5-T3-T45-CPc
6	5-T3-T45-CPd

- Ligation product
- Ligation by-product

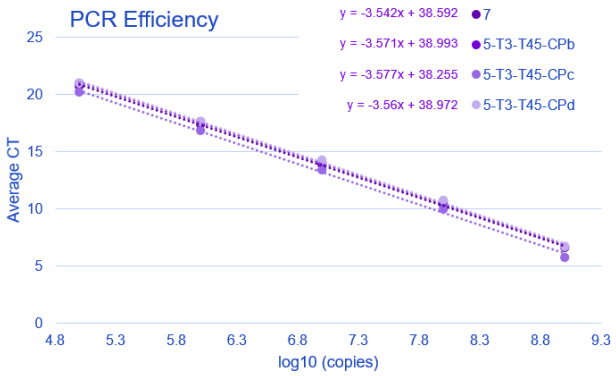
Figure S5: Gel images for the closing tag ligation.

10.4 qPCR and Next Generation Sequencing (NGS)

qPCR procedure
qPCR was performed with the SYBR Green Master Mix kit (Thermo) on a Real-Time PCR System (QuantStudio 7 Flex). All samples were subjected to PCR cycles as follows: 50°C incubation for 2 min, then 95°C heat activation for 5 min followed by 40 cycles of 95°C denaturation (10 seconds each), 55°C annealing (15 seconds each), and 72°C extension (30 seconds each).
To assess the amplification efficiency, the quantity of the full-length DNA templates was first normalized based on the Agilent 2100 Bioanalyzer result and qPCR with serial dilutions was performed. Linear fitting was then calculated respectively based on the CT values. The slope was then used to

determine amplification efficacy, which was found to be comparable between the reaction sample and the controls (~90%).

qPCR results

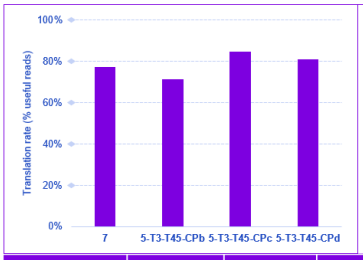


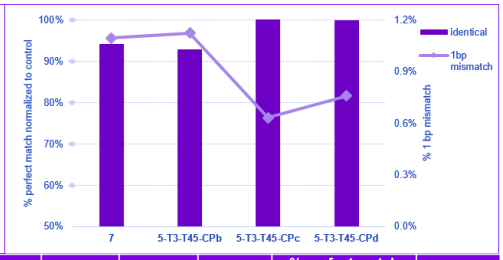
Sample	% PCR Efficiency
7	91.57%
5-T3-T45-CPb	90.56%
5-T3-T45-CPc	90.35%
5-T3-T45-CPd	90.94%

Figure S6: qPCR efficiency.

Next Generation Sequencing (NGS)

Samples were diluted to 1E+7 copies/35 µL as a template for PCR amplification. To a PCR tube was added diluted sample (35.0 µL), 10x high fidelity PCR buffer (5 µL), 50.0 mM $MgSO_4$ (2 µL), 10 mM dNTP mix (1 µL), Platinum Taq DNA Polymerase (0.2 µL), 10 µM forward primer (2 µL), 10 µM reverse primer (2 µL), and nuclease-free water (2.8 µL). The PCR products were purified by the Agencourt AMPure XP Beads method. The purified samples underwent next-generation sequencing (Illumina NovaSeq). Bowtie2 was used to map the sequenced reads to reference sequence (primer + coding region sequence) by local alignment. The detailed mapping identities were extracted from CIGAR string and XM flag in the SAM format. The translation rate of the four samples were found to be comparable and the percentage of the sequences that was a perfect match ranged from 73% for reaction sample **7** to 78% for the control **5-T3-T45-CPd**. When normalized to the control, reaction sample **7** was a 94% perfect sequence match, indicating just 6% mutated sequences.





Sample	Useful reads	Sum of all reads	% Useful reads	perfect match	1bp mismatch	% perfect match	% perfect match normalized to control	% 1bp mismatch
7	56754695	73598543	77.11%	53,800,962	805,879	73.1%	94.16%	1.09%
5-T3-T45-CPb	54420555	76474300	71.17%	55,084,226	859,387	72.0%	92.78%	1.12%
5-T3-T45-CPc	63671722	75302625	84.55%	59,395,697	475,415	78.9%	101.60%	0.63%
5-T3-T45-CPd	64342825	79484212	80.95%	61,705,360	602,798	77.6%	100.00%	0.76%

Figure S7: Results and analysis of the NGS data.