

Merging C(sp³)-H Activation with DNA-Encoding

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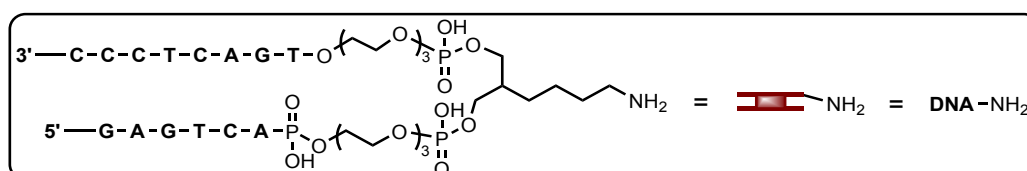
1. General Information

Equipments and chemicals

VWR® modular heating block (64 wells) was used to heat PCR tubes to run the DNA reactions. 10K variable speed mini centrifuge (BT604) was purchased from BTLab Systems. VWR® 9 mm screw-thread polypropylene vials and screw caps were used to submit the samples to HPLC-MS. Hexafluoroisopropanol (HFIP) was purchased from Oakwood. *N,N*-Dimethylacetamide (DMA) was obtained from Honeywell. *N,N*-dimethylformamide (DMF) and acetonitrile (CH₃CN) were obtained by passing the previously degassed solvents through an activated alumina column. Deionized water was used in all the reactions. Pd(OAc)₂ was purchased from Strem Chemicals, Inc. Ag₂CO₃, AgOAc, AgTFA and Ag₃PO₄ were obtained from Sigma-Aldrich. All other reagents were purchased at the highest commercial quality and used without further purification. Ligands were prepared via our previously published protocols except some of them are commercially available. The iodo-substituted heteroaromatic acids were received from Pfizer. Carboxylic acids, amides and ketones bearing directing groups were synthesized via our previously published protocols except some of them are commercially available.

DNA headpiece material

DNA headpiece (5'-/5Phos/GAGTCA/iSp9/iUniAmM/iSp9/TGACTCCC-3', Figure S1) was obtained from Biosearch Technologies, Petaluma, CA. The abbreviated DNA headpiece is shown below.



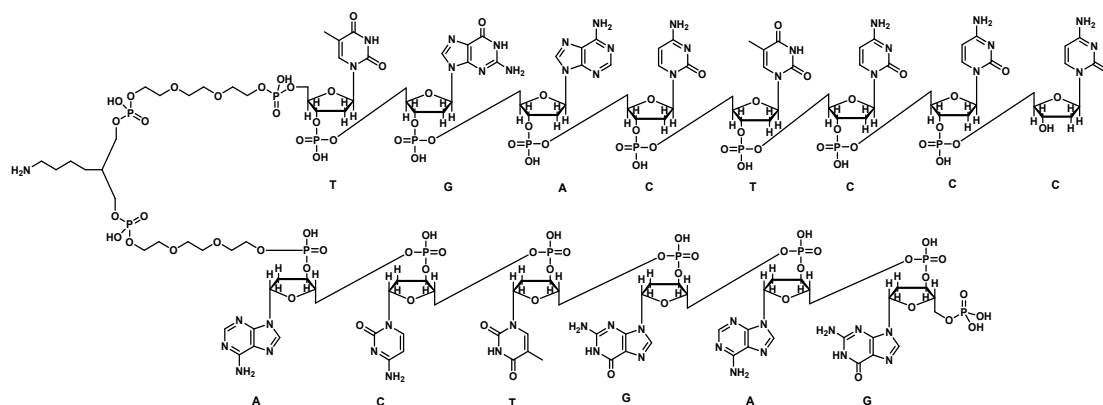


Figure S1. The structure of DNA headpiece.

Analysis of DNA samples

DNA concentration: DNA samples subjected to HPLC-MS analysis were prepared as 0.1 mM in H₂O, assuming 100% of DNA total recovery after reaction.

Analysis: One microliter of the DNA solution was analyzed on a Waters I-Class LC with a Waters BEH C18 column (2.1 × 55 mm, 1.7 μm, 130 Å) using a gradient of 114 mM HFIP and 14 mM Et₃N in water (A) and methanol (B) (0.3 mL/min, 10 - 26% B over 10 minutes) at 60 °C. The yield was determined by calculating the percentage of UV absorbance at 260 nm corresponding to the product peak, ignoring potential UV absorption coefficient differences between DNA products and assuming 100% mass recovery. Peak identities were determined by ESI using the [M]³⁻ ion.

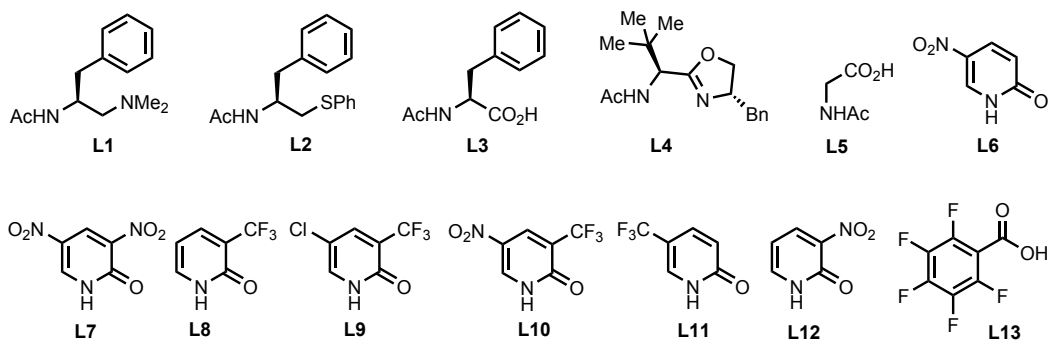
Deconvolution: Data visualization and integration was performed with Mass Lynx V4.1 software.

Yield calculation: Ignoring UV coefficient difference for all DNA products and assuming 100% of DNA total recovery, the yield of DNA products were determined from UV absorbance trace (260 nm) peak area using the equation below:

$$\text{Yield (product, \%)} = \frac{\%UV (\text{product})}{\%UV (\text{DNA starting material before reaction})} \times 100\%$$

MS deconvolution: While multi-charged (negative) mass was observed, triply charged mass was determined to be base peak in all cases. Observed m/z could be calculated as $m/z = [M]/z - 1.00794$.

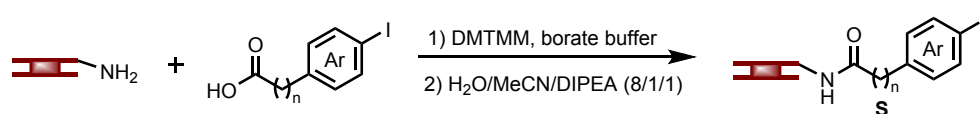
2. Ligand Structures L1-L13



The Ligands **L3**, **L5**, **L6-L13** were purchased from Sigma-Aldrich, Nova Biochem, TCI and Combi-Blocks Inc. The Ligands **L1**,¹ **L2**,² **L4**³ were synthesized according to our previous reports.

3. Preparation of DNA-Conjugated Aryl Iodides

3.1 General Procedure 1 for DNA-Conjugated Aryl Iodides



Materials

Headpiece: 20 mM in H₂O

Sodium carboxylate: 1.0 M in water [1 mmol acid was added into 1.0 mL aqueous NaOH (40 mg) solution]

DMTMM: 1.0 M in water (294.7 mg DMTMM dissolved in 1 mL H₂O)

Borate buffer: 100 mM in H₂O

General Procedure 1

1) To the headpiece solution (400 nmol, 20 μL), was added borate buffer solution (300 μL), sodium carboxylate (100 equiv, 40 μL) and DMTMM (100 equiv, 40 μL). The mixture was vortexed and standed at room temperature for 3 h.

2) To the mixture was added 5 M NaCl solution (40 μL) and cold ethanol (1.2 mL, ethanol stored at -20 °C). The mixture was then stored at a -20 °C freezer for more than 30 minutes.

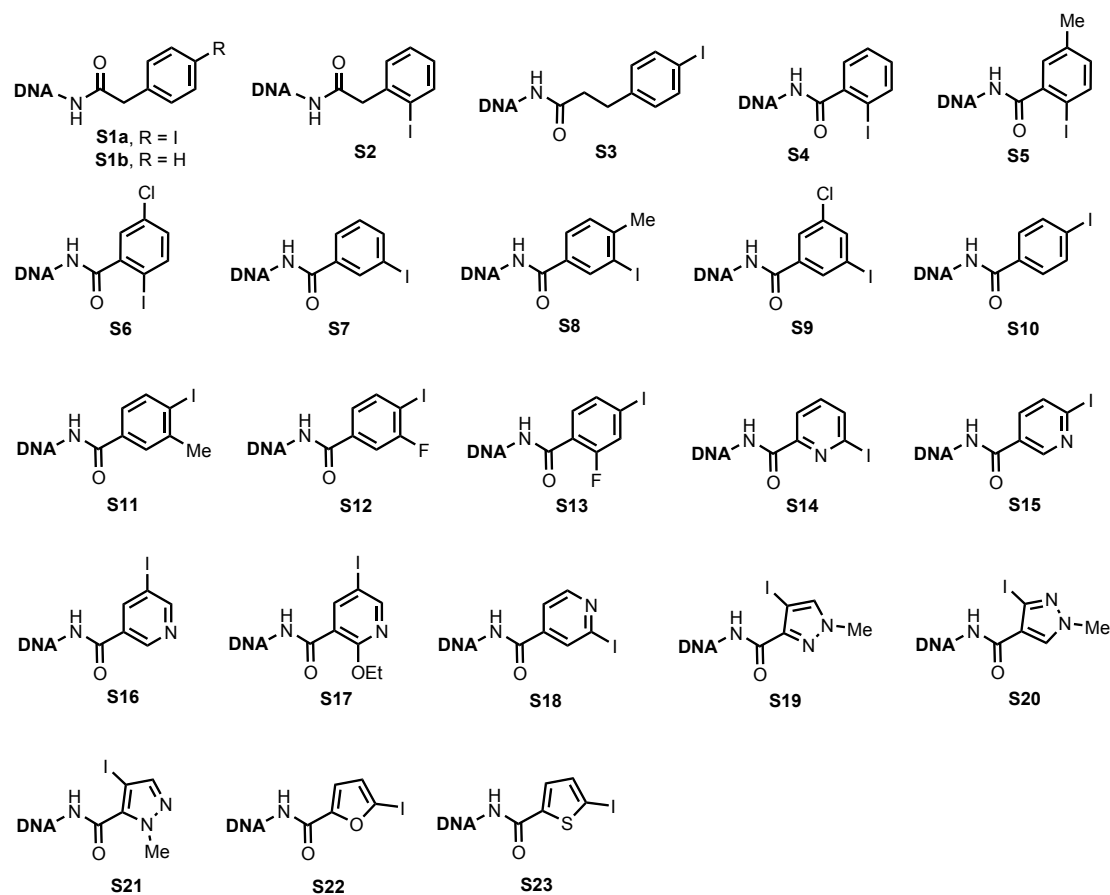
3) Centrifuge the sample for 7 minutes at 4 °C in a microcentrifuge at 10000 rpm. The above supernatant was discarded and the precipitate was dried under vacuum. Then the pellet was dissolved in deionized water (320 μL) and CH₃CN (40 μL) followed by addition of DIPEA (40 μL), heated at 70 °C for 12 h.

4) Cooling to room temperature, 5 M NaCl solution (40 μL) and cold ethanol (1.2 mL) were sequentially added and the resultant mixture was stored at -20 °C for 30 min. The mixture was centrifuged at 4 °C for 7 minutes at 10000 rpm before the resultant supernatant was removed, and the precipitate was dried under vacuum. The pellet was dissolved in deionized water (40 μL, 10 mM), which was used in next experiment without further purification.

5) HPLC-MS analysis: 1 μL of this solution (10 mM) was transferred to a 200 μL

microcentrifuge tube, diluted with 99 μL of H_2O to prepare the testing sample at 0.1 mM concentration.

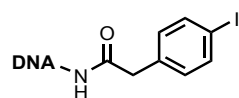
3.2 Structures of S1-S23



The iodo-substituted aromatic acids **S1-S13** were purchased from Sigma-Aldrich, Oakwood, TCI and Combi-Blocks Inc. The heteroaromatic acids **S14-S23** were received from Pfizer.

3.3 LC Trace and Mass Characterization of S1-S23

LC Trace and Mass of S1a

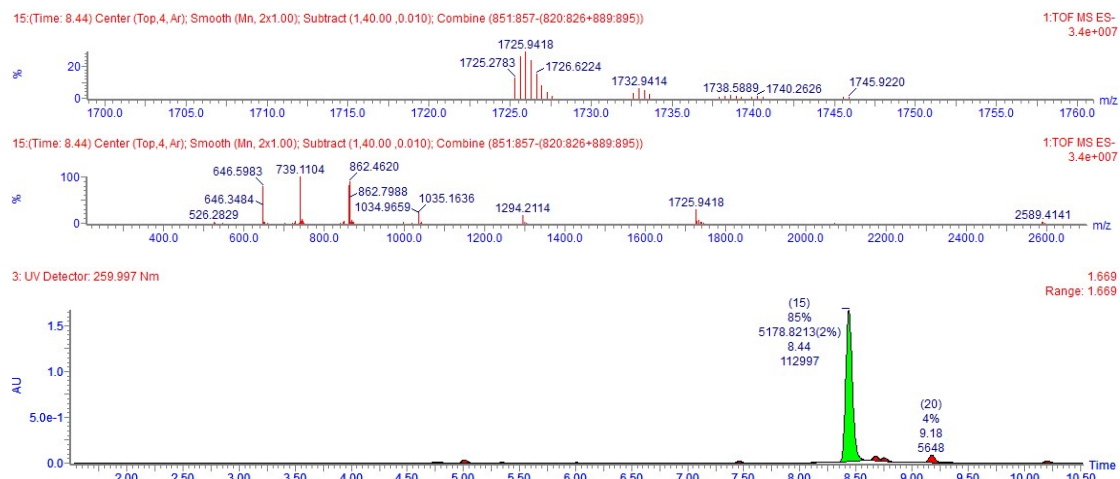


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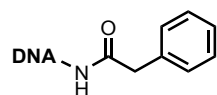
Yield: 85%

Exact mass: 5178.8211

Triply charged mass $[M]/3 - 1.00794$, calculated 1725.2658; observed 1725.2783.



LC Trace and Mass of S1b

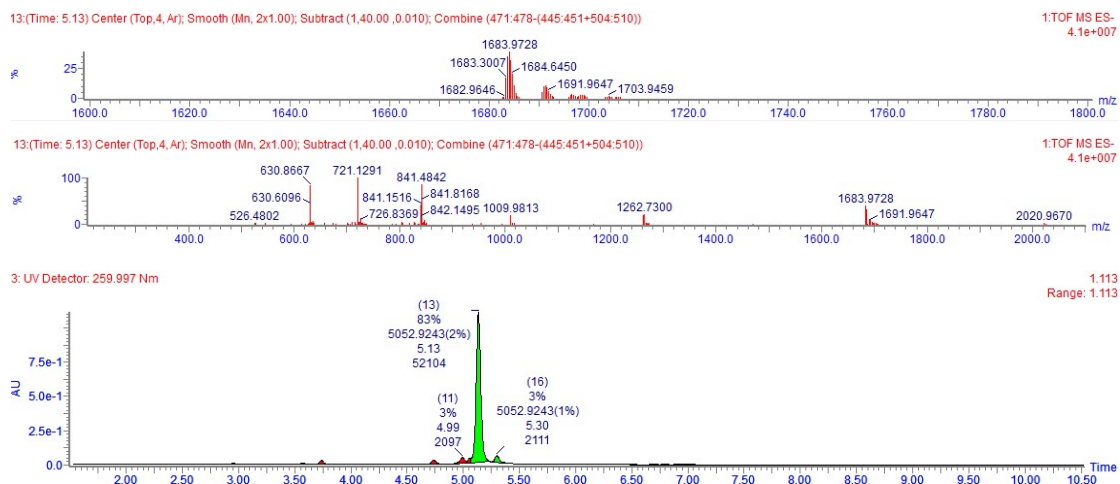


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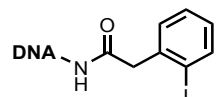
Yield: 83%

Exact mass: 5052.9244

Triply charged mass $[M]/3 - 1.00794$, calculated 1683.3002; observed 1683.3007.



LC Trace and Mass of S2

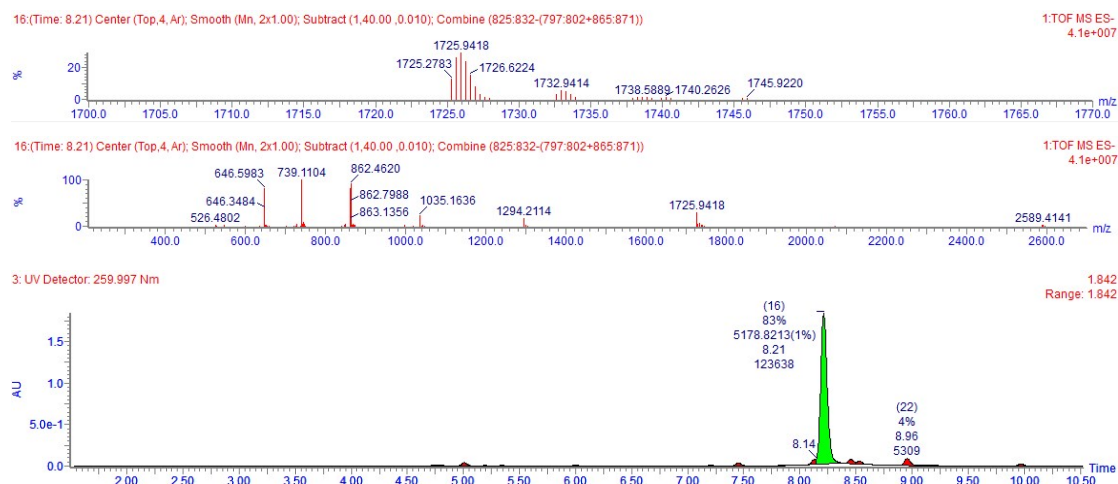


Following General Procedure 1.

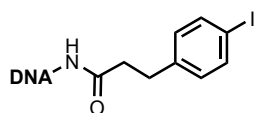
Yield: 83%

Exact mass: 5178.8211

Triply charged mass $[M]/3 - 1.00794$, calculated 1725.2658; observed 1725.2783.



LC Trace and Mass of S3

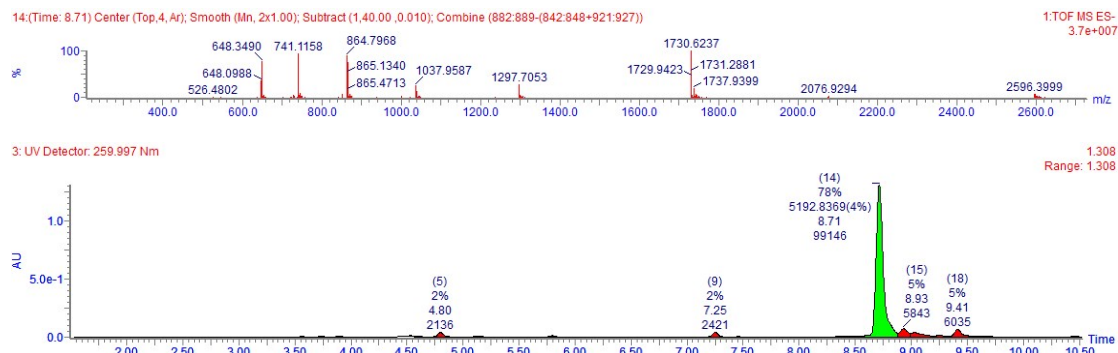


Following General Procedure 1.

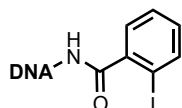
Yield: 78%

Exact mass: 5192.8367

Triply charged mass $[M]/3 - 1.00794$, calculated 1729.9376; observed 1729.9423.



LC Trace and Mass of S4

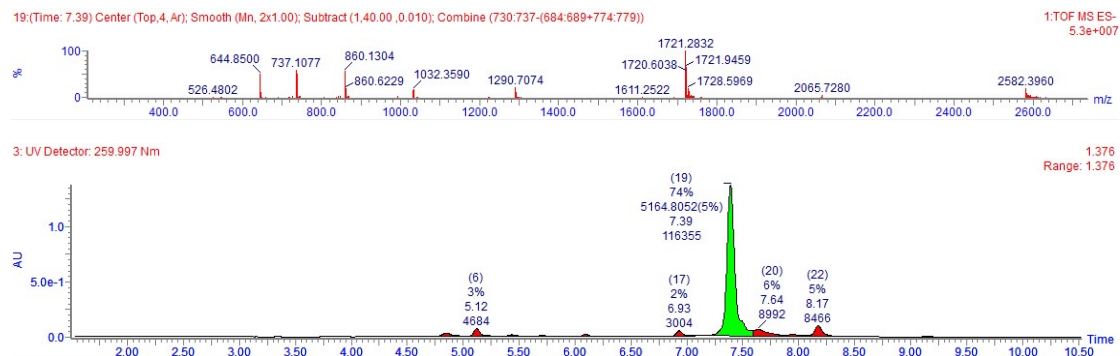


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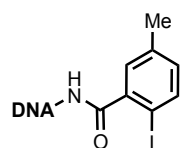
Yield: 74%

Exact mass: 5164.8054

Triply charged mass $[M]/3 - 1.00794$, calculated 1720.5939; observed 1720.6038.



LC Trace and Mass of S5

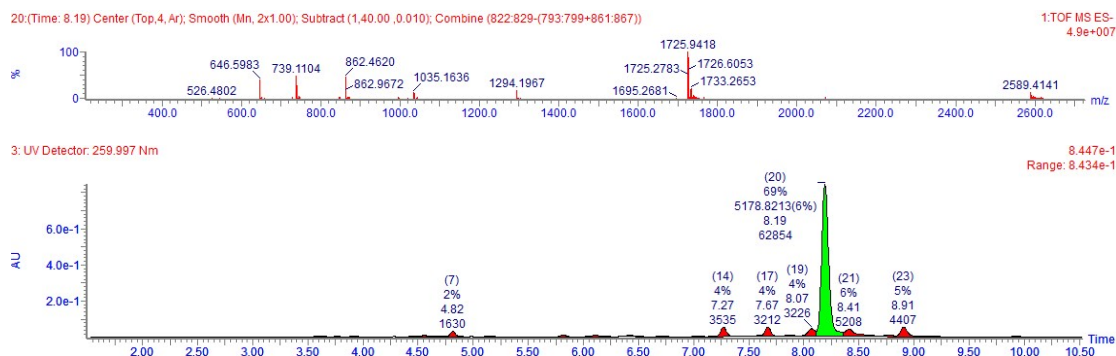


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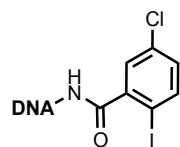
Yield: 69%

Exact mass: 5178.8211

Triply charged mass $[M]/3 - 1.00794$, calculated 1725.2658; observed 1725.2783.



LC Trace and Mass of S6

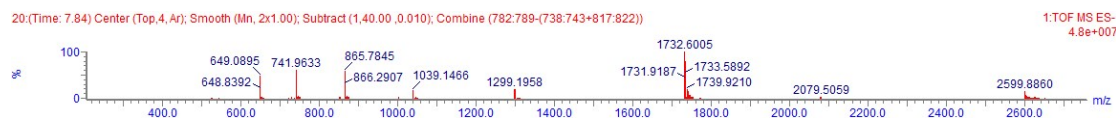


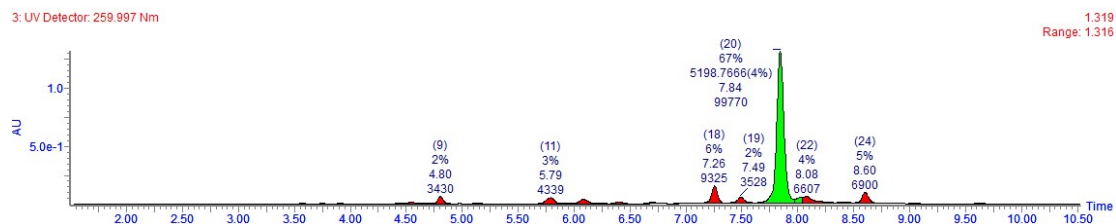
Following General Procedure 1.

Yield: 67%

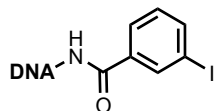
Exact mass: 5198.7664

Triply charged mass $[M]/3 - 1.00794$, calculated 1731.9142; observed 1731.9187.





LC Trace and Mass of S7

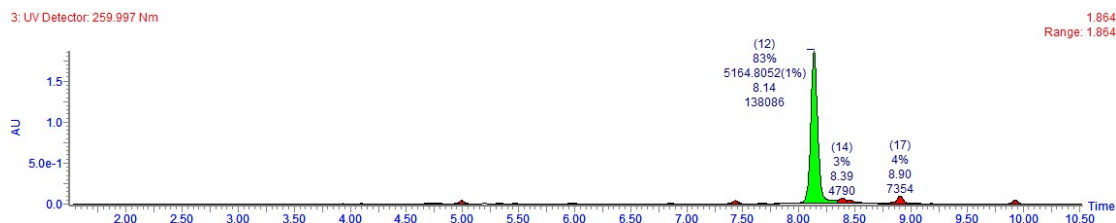
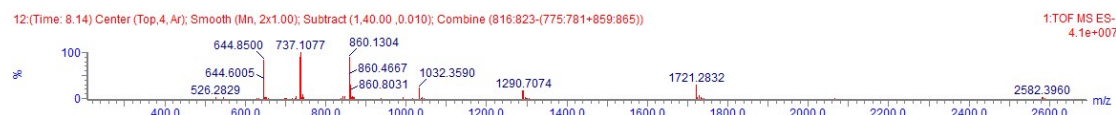
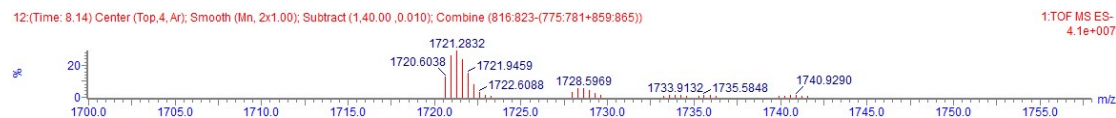


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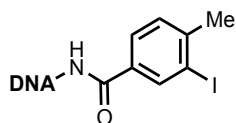
Yield: 83%

Exact mass: 5164.8054

Triply charged mass $[M]/3 - 1.00794$, calculated 1720.5939; observed 1720.6038.



LC Trace and Mass of S8

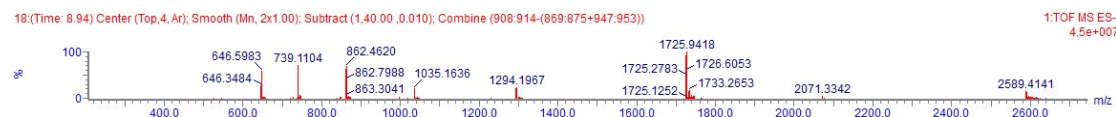


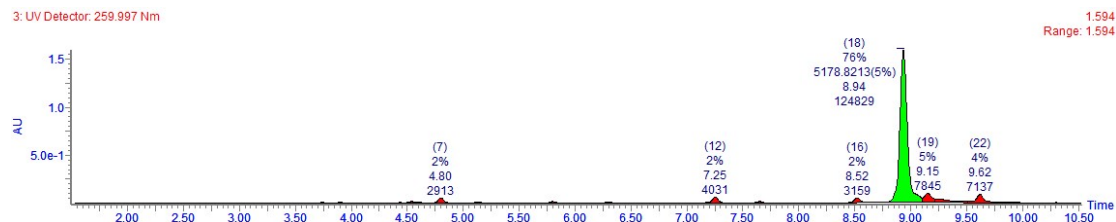
Following General Procedure 1.

Yield: 76%

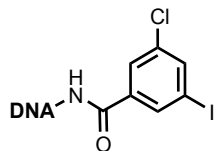
Exact mass: 5178.8211

Triply charged mass $[M]/3 - 1.00794$, calculated 1725.2658; observed 1725.2783.





LC Trace and Mass of S9

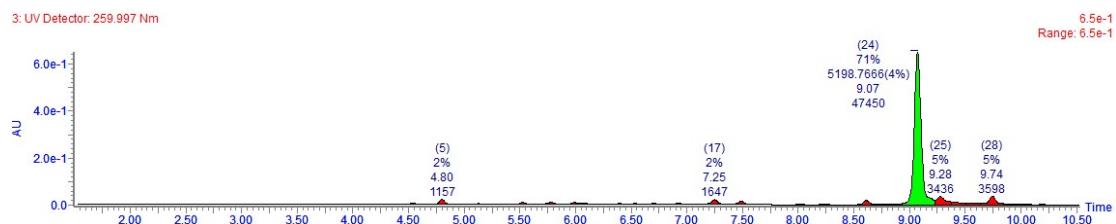


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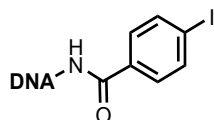
Yield: 71%

Exact mass: 5198.7664

Triply charged mass $[M]/3 - 1.00794$, calculated 1731.9142; observed 1731.9187.



LC Trace and Mass of S10

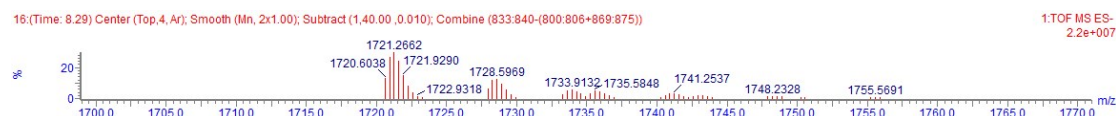


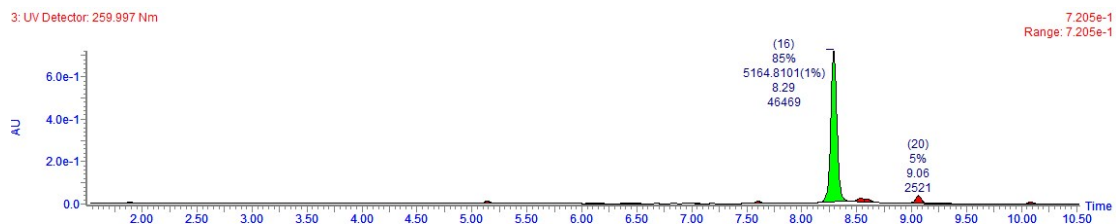
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Yield: 85%

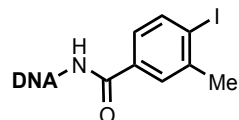
Exact mass: 5164.8054

Triply charged mass $[M]/3 - 1.00794$, calculated 1720.5939; observed 1720.6038.





LC Trace and Mass of S11

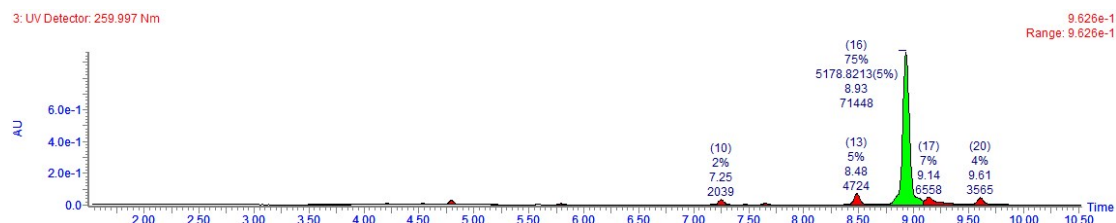
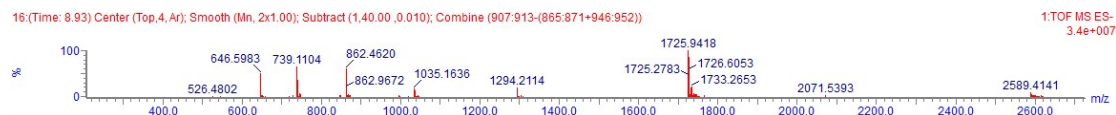


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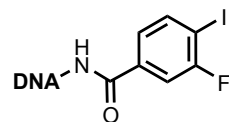
Yield: 75%

Exact mass: 5178.8211

Triply charged mass $[M]/3 - 1.00794$, calculated 1725.2658; observed 1725.2783.



LC Trace and Mass of S12

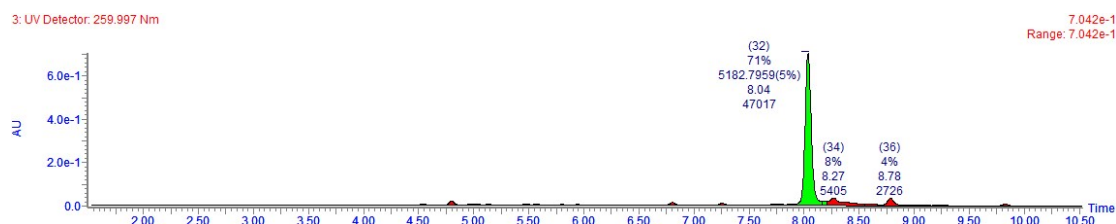
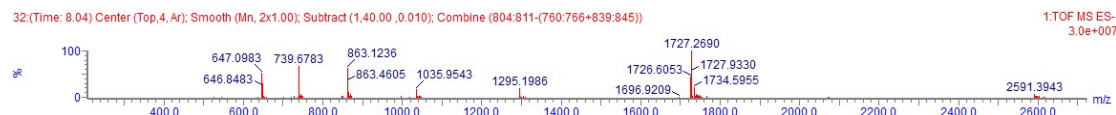


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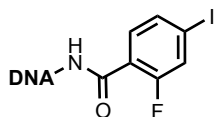
Yield: 71%

Exact mass: 5182.7960

Triply charged mass $[M]/3 - 1.00794$, calculated 1726.5907; observed 1726.6053.



LC Trace and Mass of S13

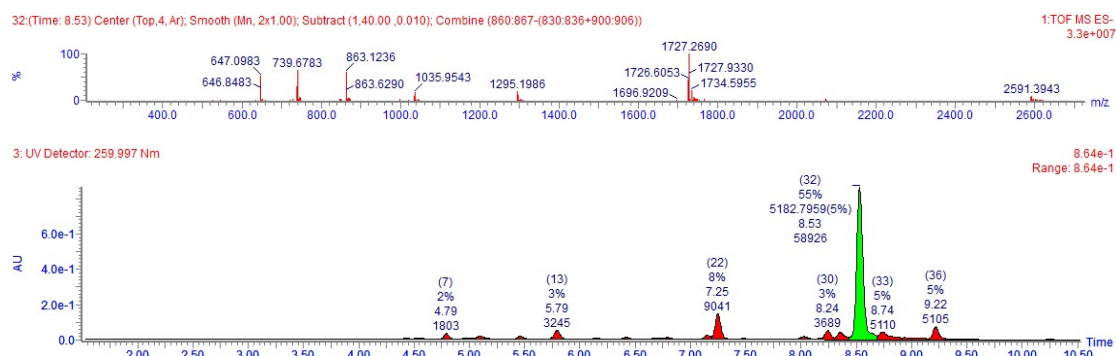


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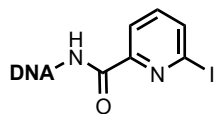
Yield: 55%

Exact mass: 5182.7960

Triply charged mass [M]/3 - 1.00794, calculated 1726.5907; observed 1726.6053.



LC Trace and Mass of S14

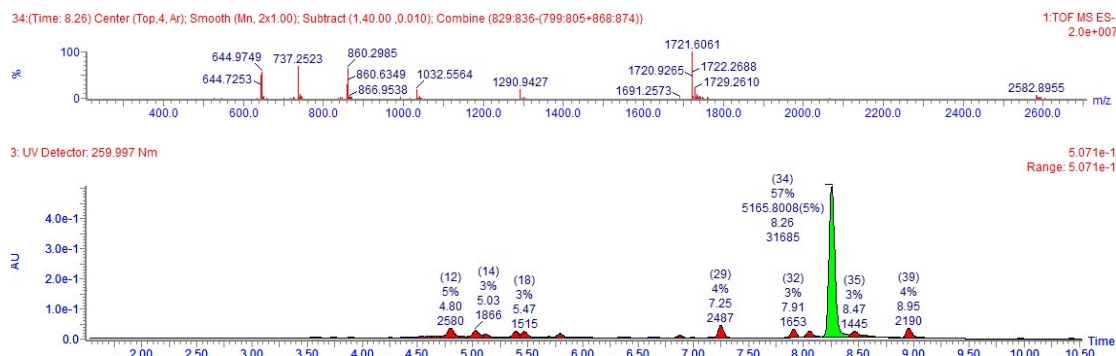


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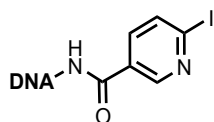
Yield: 57%

Exact mass: 5165.8007

Triply charged mass [M]/3 - 1.00794, calculated 1720.9256; observed 1720.9265.



LC Trace and Mass of S15

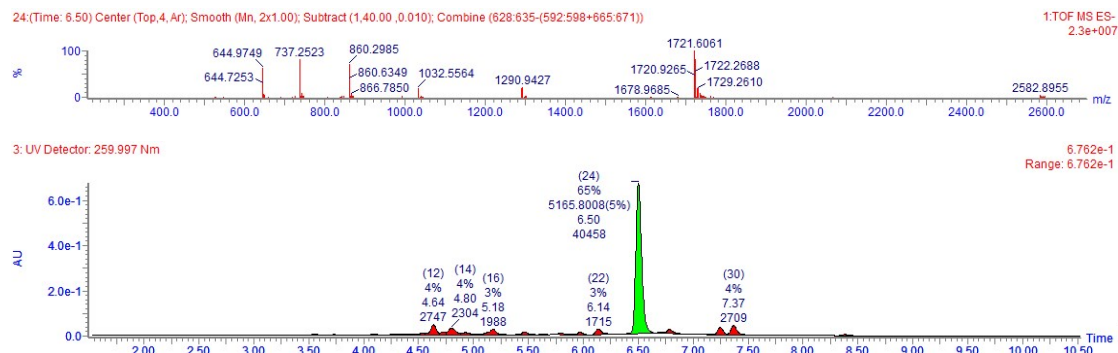


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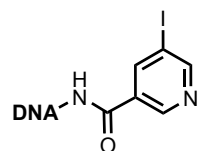
Yield: 65%

Exact mass: 5165.8007

Triply charged mass $[M]/3 - 1.00794$, calculated 1720.9256; observed 1720.9265.



LC Trace and Mass of S16

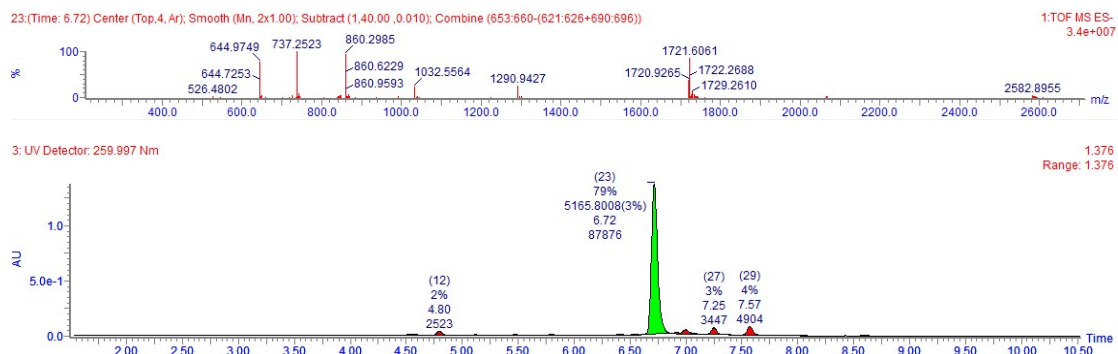


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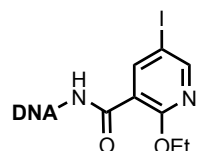
Yield: 79%

Exact mass: 5165.8007

Triply charged mass $[M]/3 - 1.00794$, calculated 1720.9256; observed 1720.9265.



LC Trace and Mass of S17

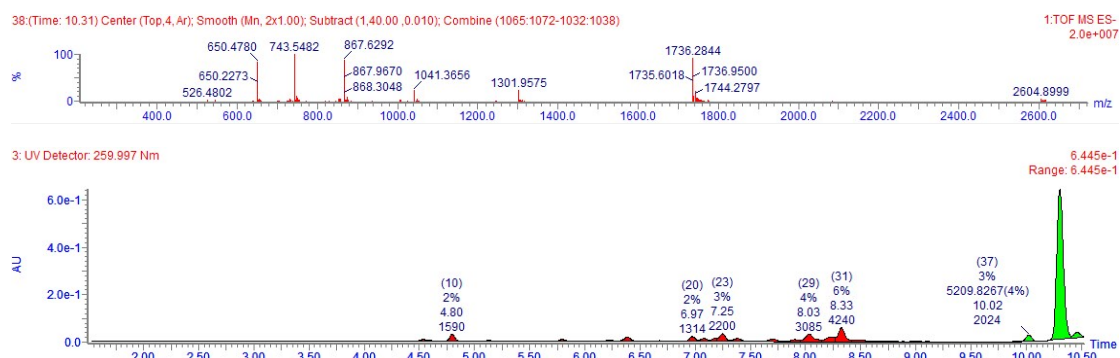


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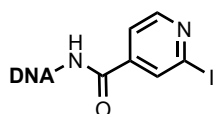
Yield: 59%

Exact mass: 5209.8269

Triply charged mass $[M]/3 - 1.00794$, calculated 1735.6010; observed 1735.6018.



LC Trace and Mass of S18

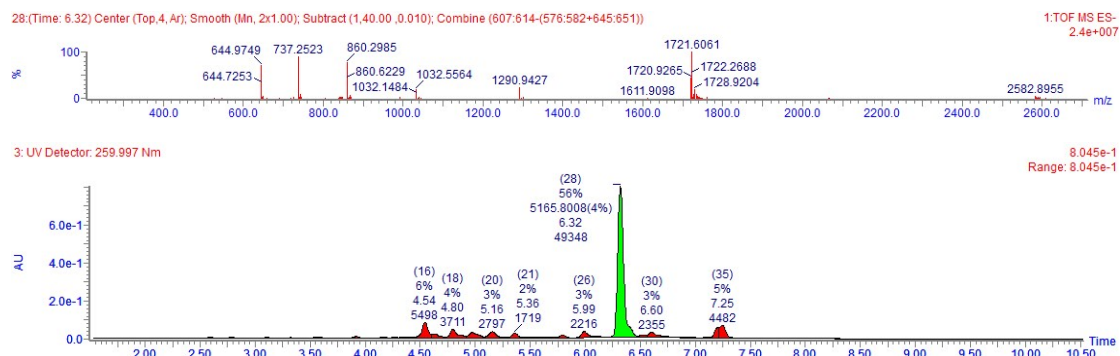


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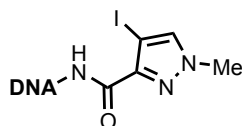
Yield: 56%

Exact mass: 5165.8007

Triply charged mass $[M]/3 - 1.00794$, calculated 1720.9256; observed 1720.9265.



LC Trace and Mass of S19

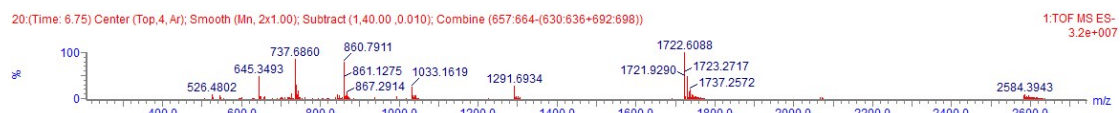


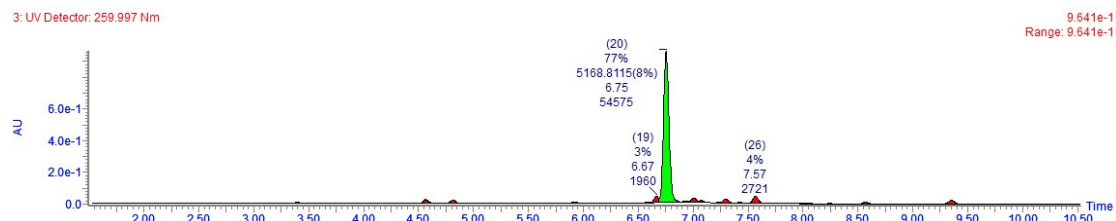
Following General Procedure 1.

Yield: 77%

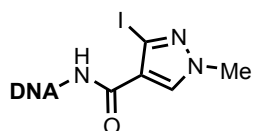
Exact mass: 5168.8116

Triply charged mass $[M]/3 - 1.00794$, calculated 1721.9293; observed 1721.9290.





LC Trace and Mass of S20

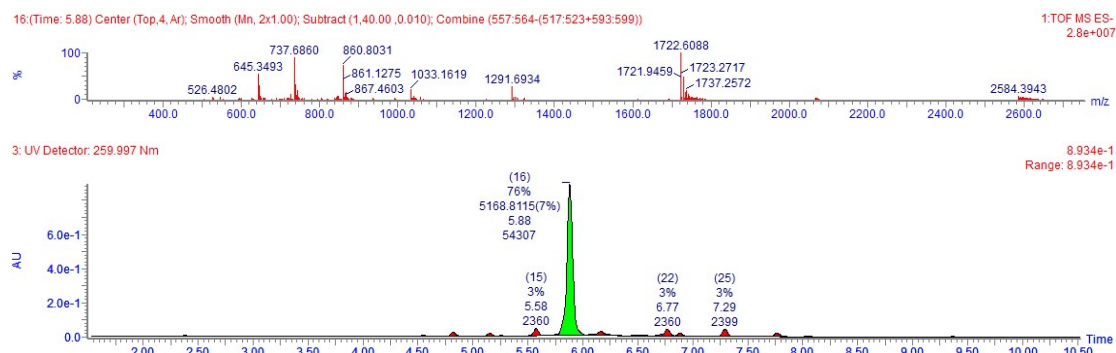


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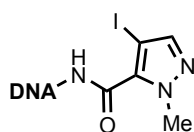
Yield: 76%

Exact mass: 5168.8116

Triply charged mass $[M]/3 - 1.00794$, calculated 1721.9293; observed 1721.9459.



LC Trace and Mass of S21

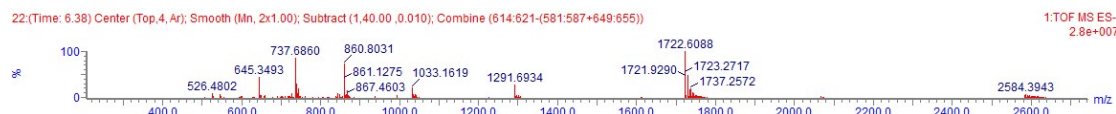


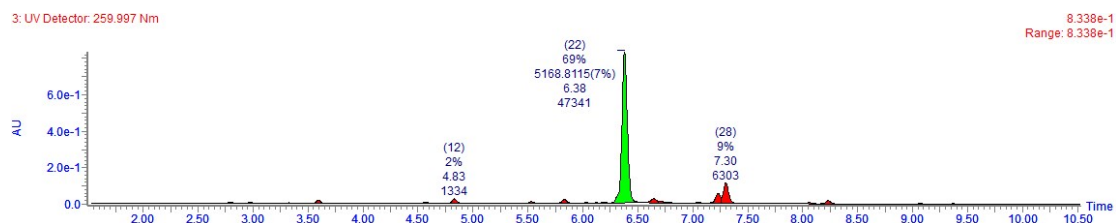
Following General Procedure 1.

Yield: 69%

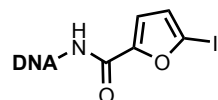
Exact mass: 5168.8116

Triply charged mass $[M]/3 - 1.00794$, calculated 1721.9293; observed 1721.9290.





LC Trace and Mass of S22

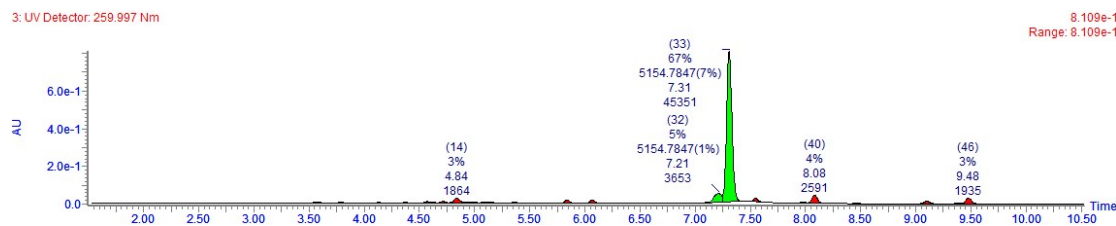
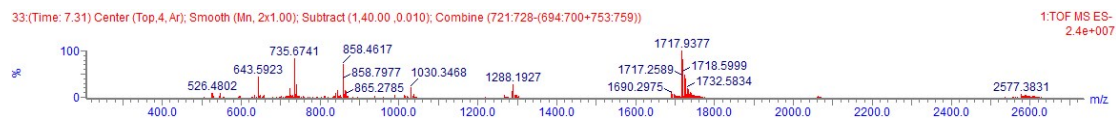


Following General Procedure 1.

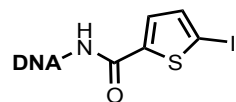
Yield: 67%

Exact mass: 5154.7847

Triply charged mass $[M]/3 - 1.00794$, calculated 1717.2536; observed 1717.2589.



LC Trace and Mass of S23

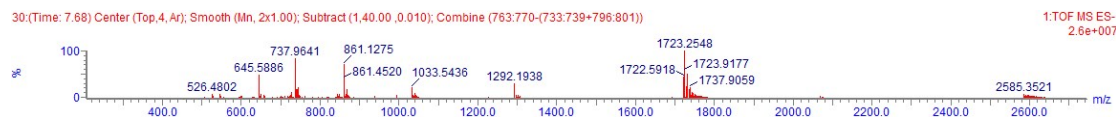


Following General Procedure 1.

Yield: 69%

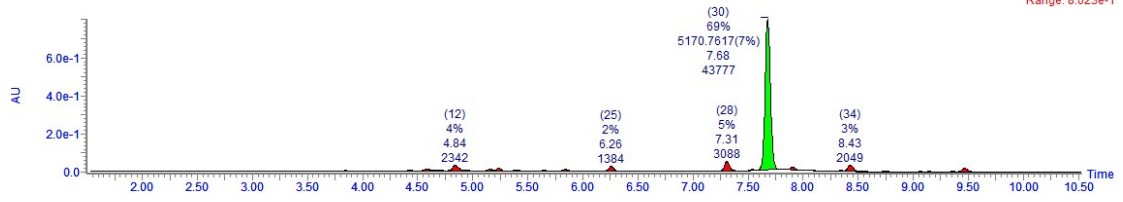
Exact mass: 5170.7618

Triply charged mass $[M]/3 - 1.00794$, calculated 1722.5793; observed 1722.5918.



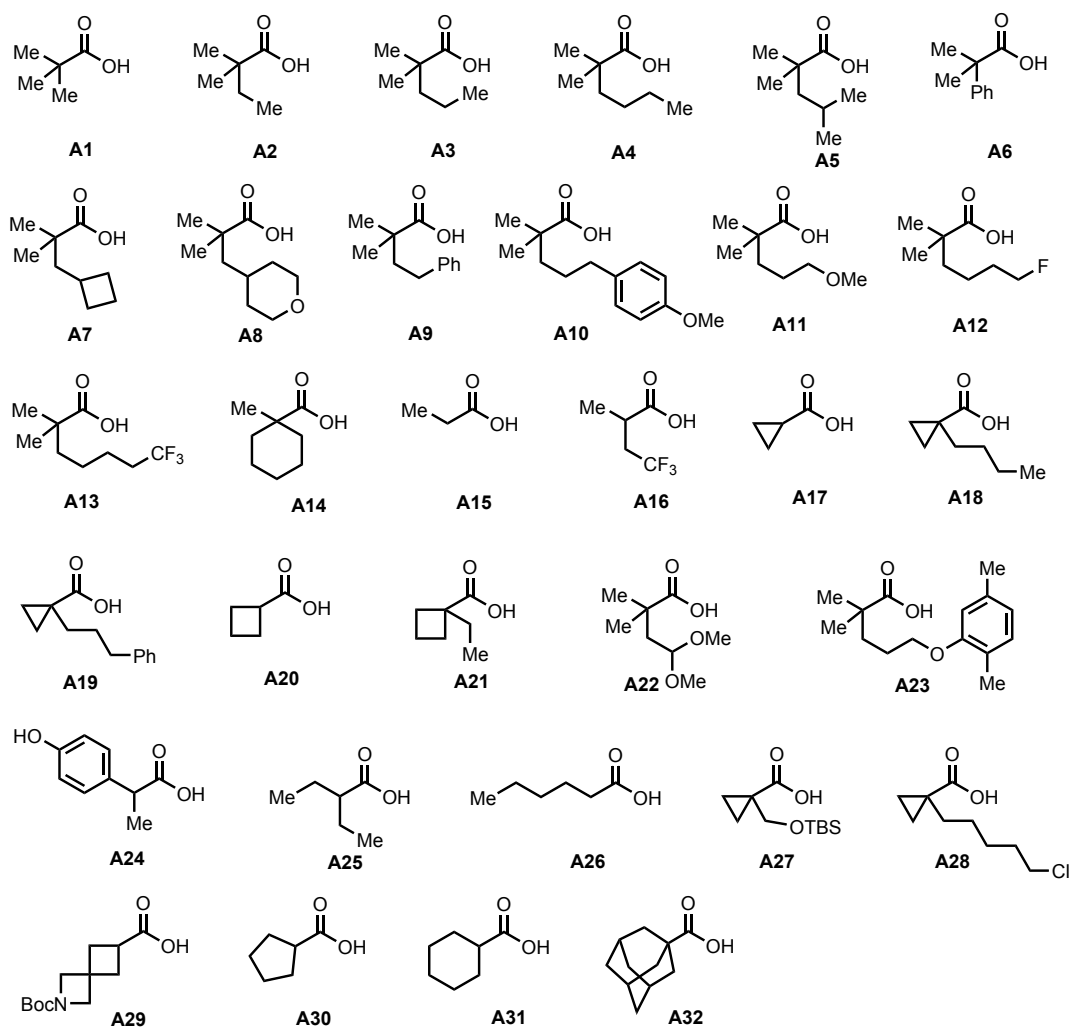
3: UV Detector: 259.997 Nm

8.023e-1
Range: 8.023e-1



4. Experimental Section for on-DNA C-H Arylation of Free Carboxylic Acids

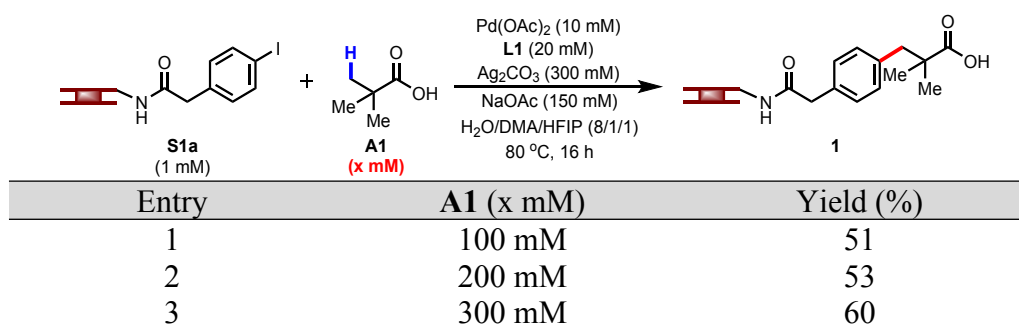
4.1 Substrate Structures of Free Carboxylic Acids A1-A32



Carboxylic acids were obtained from the commercial sources or synthesized following the literature procedures.^{1,4}

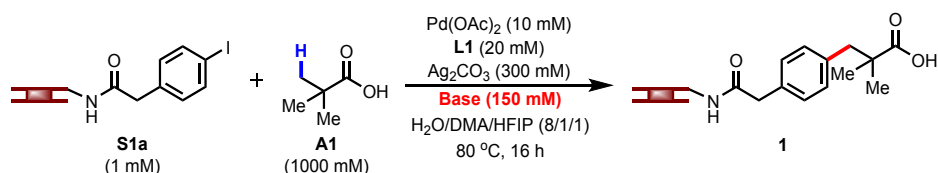
4.2 Condition Optimizations

Table S1. Evaluation of A1 Concentration



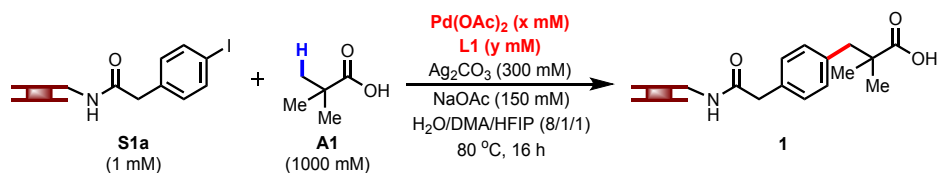
4	500 mM	59
5	800 mM	66
6	1000 mM	78
7	2000 mM	65

Table S2. Evaluation of Base



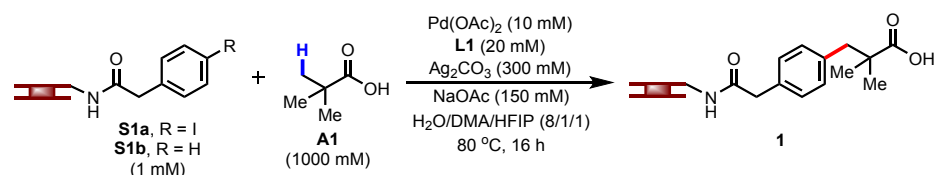
Entry	Base (150 mM)	Yield (%)
1	NaOAc	78
2	KOAc	49
3	Na ₂ CO ₃	47
4	K ₂ CO ₃	65
5	NaHCO ₃	57
6	KHCO ₃	56
7	Na ₂ HPO ₄	57
8	NaH ₂ PO ₄	35
9	Na ₃ PO ₄	48
10	K ₂ HPO ₄	53
11	K ₃ PO ₄	59

Table S3. Evaluation of Pd/L Concentration



Entry	Pd(OAc) ₂ /L1 (x/y)	Yield (%)
1	10/10	67
2	10/15	72
3	10/20	78
4	10/30	49
5	10/40	52
6	5/20	42
7	15/20	60
8	20/20	65

Table S4. Evaluation of Standard Conditions



Entry	Deviation from above	Yield (%)
1	none	78
2	without Pd(OAc) ₂ S20	0

3	without Ag ₂ CO ₃	0
4	without NaOAc	77
5	without L1	56
6	H ₂ O/DMA (9/1) instead of H ₂ O/DMA/HFIP (8/1/1)	76
7	H ₂ O instead of H ₂ O/DMA/HFIP (8/1/1)	76
8	r.t. instead of 80 °C	0
9	L2 instead of L1	74
10	L3 instead of L1	66
11	L4 instead of L1	65
12	L5 instead of L1	54
13	S1b instead of S1a	0 ^a

^aOnly S1b was totally recovered.

4.3 Scavenger Optimization

Assuming no cleavage or depurination of DNA strands, we can use UV absorbance to roughly estimate the total DNA tag recovery after C-H activation reactions. Note that this analytic method is limited to optimize the loadings of scavenger, it cannot be used to evaluate the real DNA degradation after reaction.

The details of procedure are shown as below:

sample 1: 10 nmol DNA-aryl iodide S1a in 100 ul water.

sample 2: product 1 in 100 ul water.

sample 3: 50 ul water and 50 ul sample 2.

sample 4: 50 ul sample 1 and 50 ul sample 2.

note:

a) product 1 was obtained using 10 nmol S1a to run C-H activation.

b) x means the percentage of total DNA recovery.

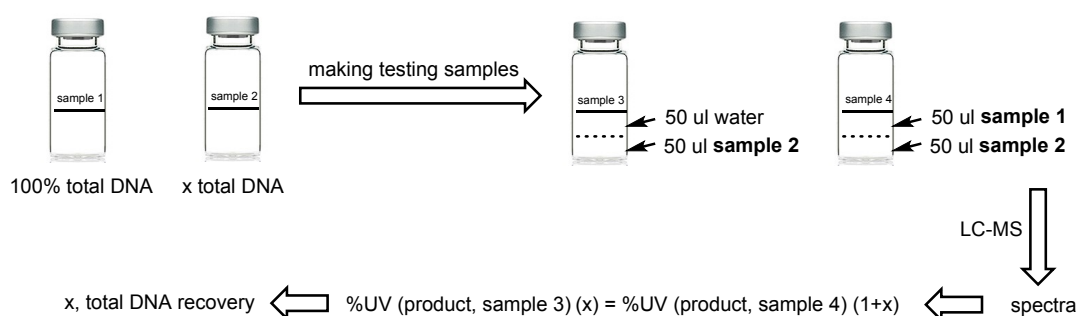
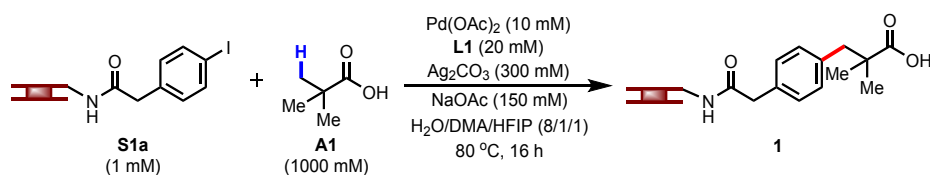


Table S5. Scavenger Optimization



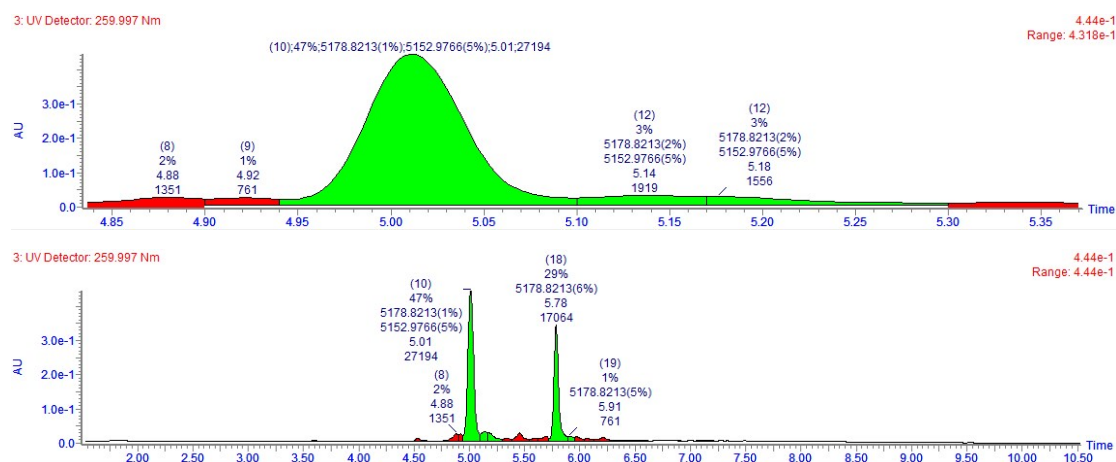
Entry	Scavenger (sodium diethyldithiocarbamate trihydrate)	Total DNA Recovery (%) ^a
1	10 equiv	51
2	50 equiv	76
3	70 equiv	81
4	90 equiv	85
5	100 equiv	70

^aThe total DNA recovery was calculated with **S1a** as the standard.

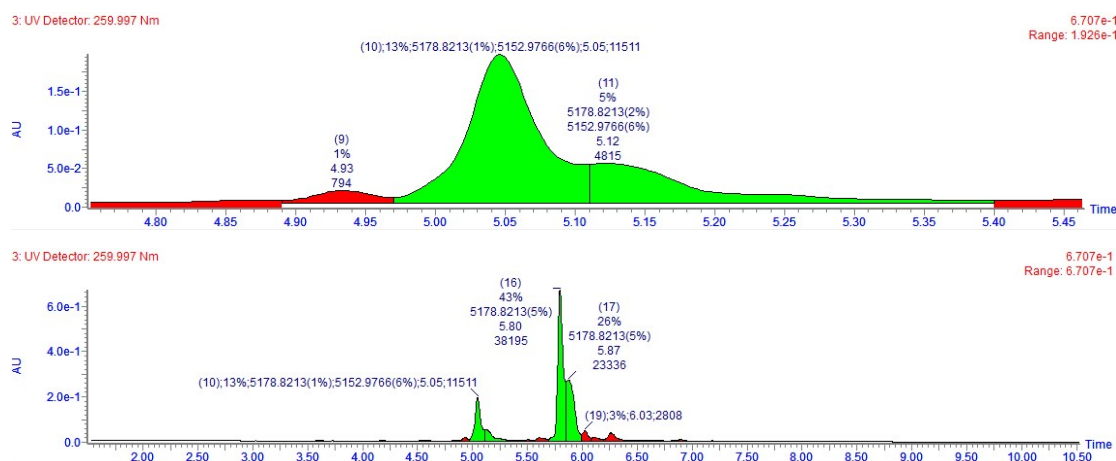
DNA Recovery Calculations of Table S5:

Entry 1: By solving the equation $0.53x = 0.18(1+x)$, it is found that $x = 0.51$. So the total DNA recovery is 51%.

LC trace of **1** in entry 1

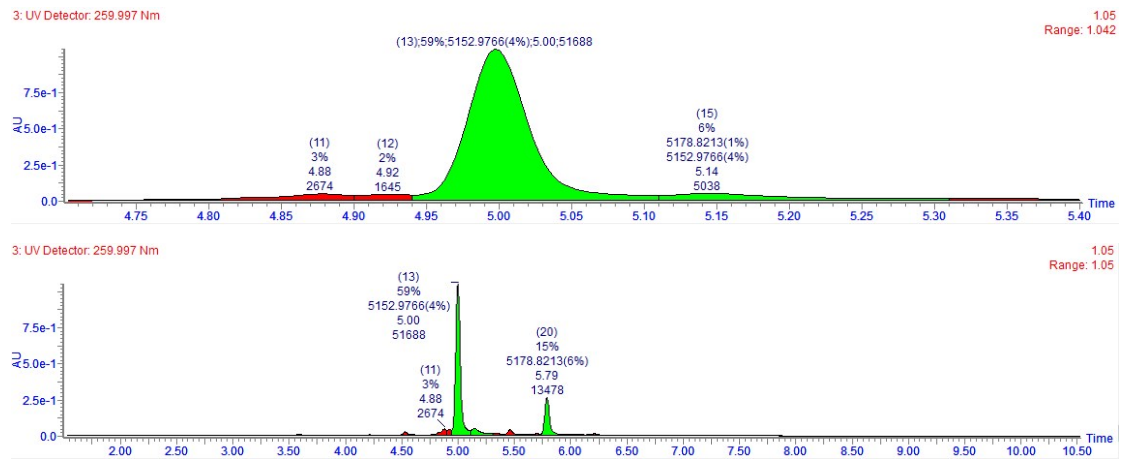


LC trace of **1** in entry 1 in the presence of the standard **S1a**

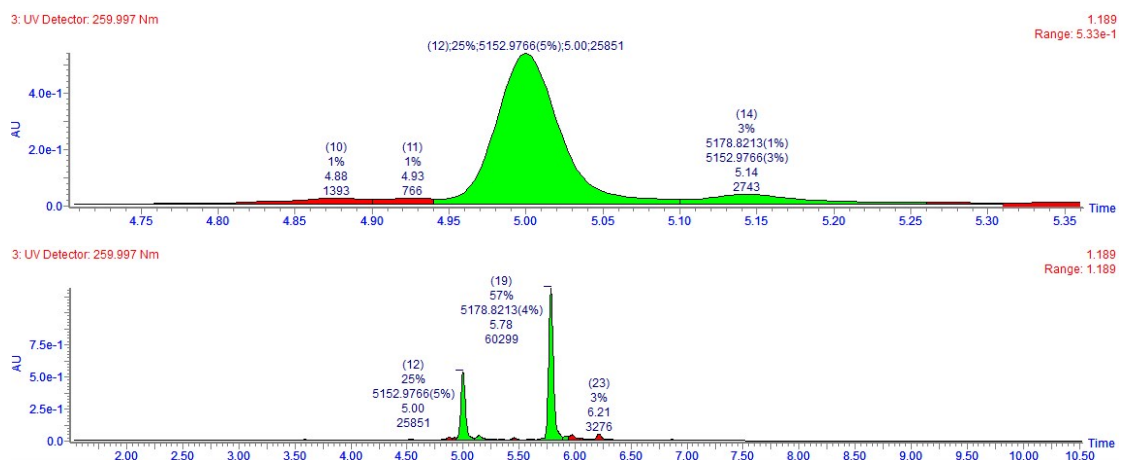


Entry 2: By solving the equation $0.65x = 0.28(1+x)$, it is found that $x = 0.76$. So the total DNA recovery is 76%.

LC trace of **1** in entry 2

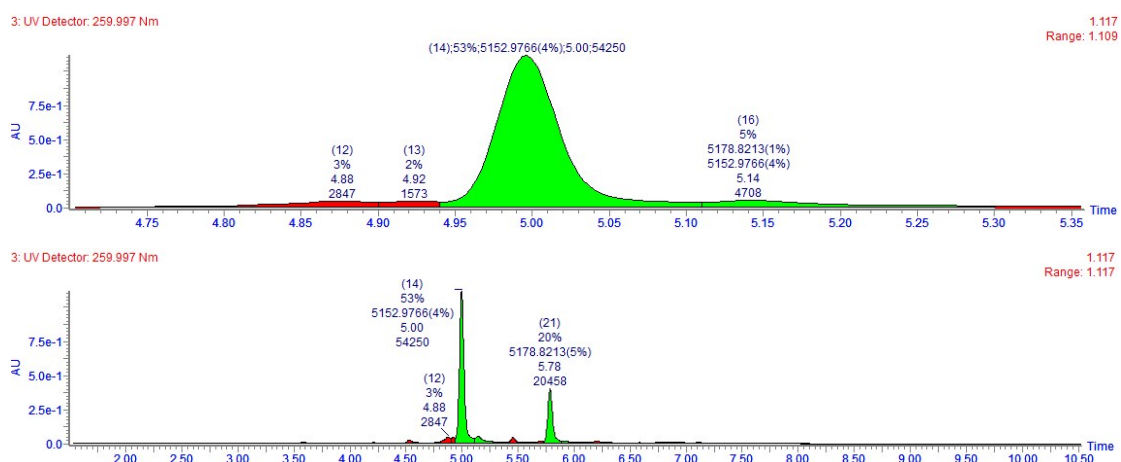


LC trace of **1** in entry 2 in the presence of the standard **S1a**

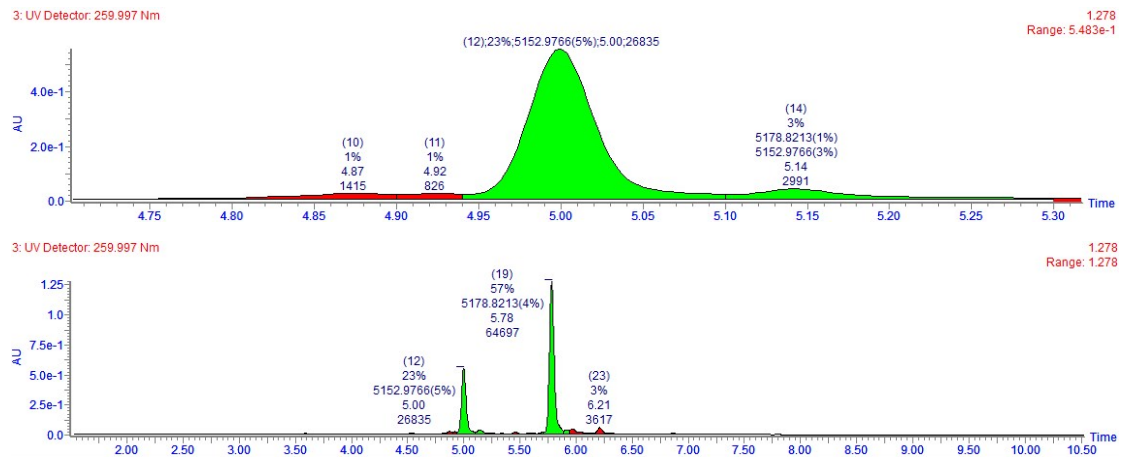


Entry 3: By solving the equation $0.58x = 0.26(1+x)$, it is found that $x = 0.81$. So the total DNA recovery is 81%.

LC trace of **1** in entry 3

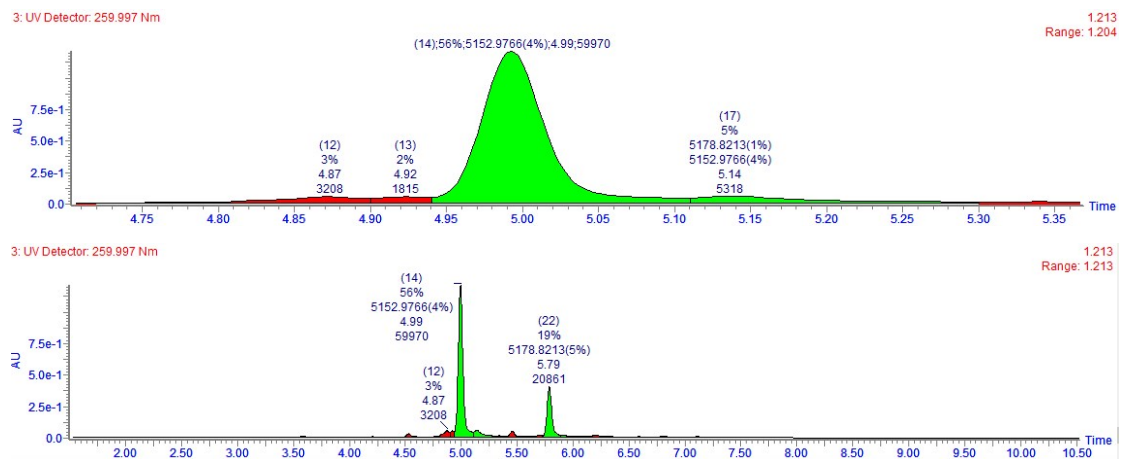


LC trace of **1** in entry 3 in the presence of the standard **S1a**

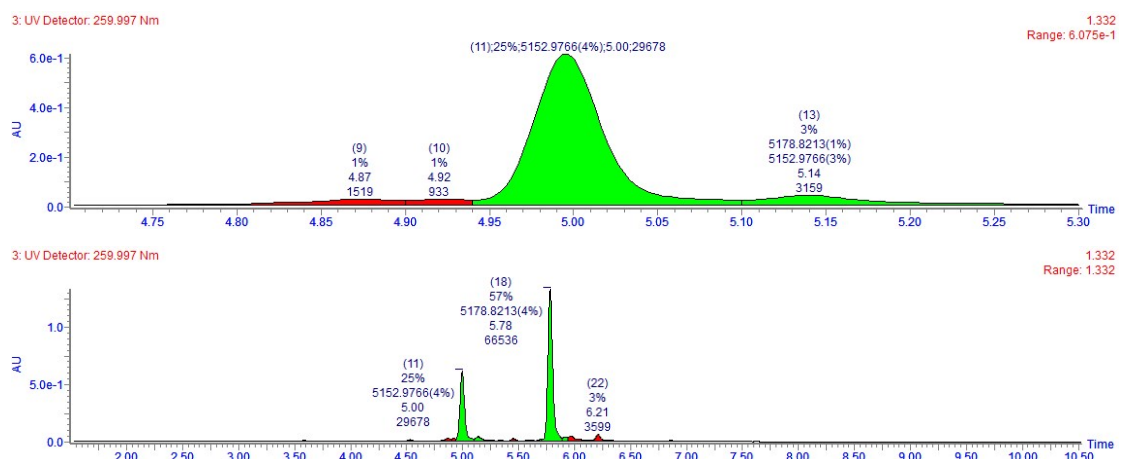


Entry 4: By solving the equation $0.61x = 0.28(1+x)$, it is found that $x = 0.85$. So the total DNA recovery is 85%.

LC trace of **1** in entry 4

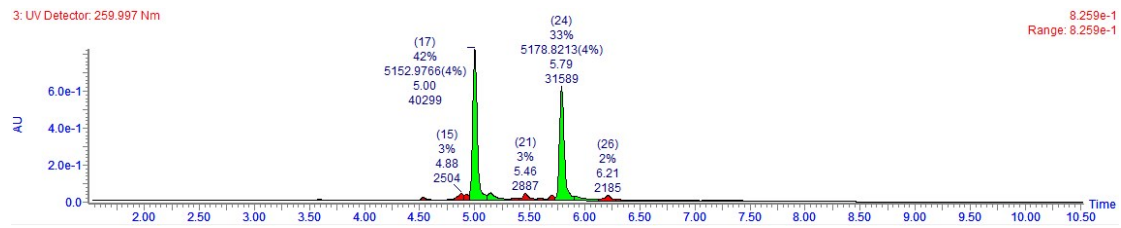
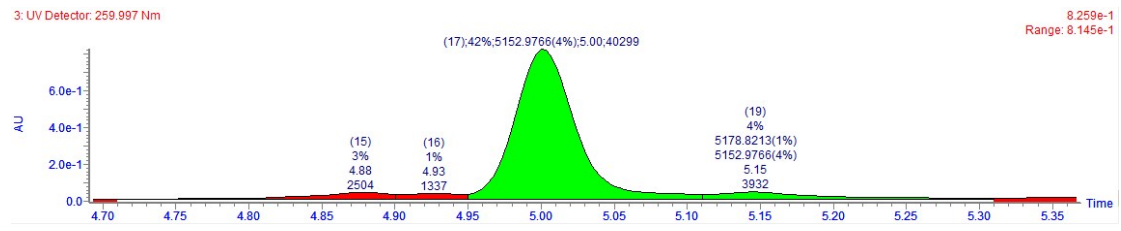


LC trace of **1** in entry 4 in the presence of the standard **S1a**

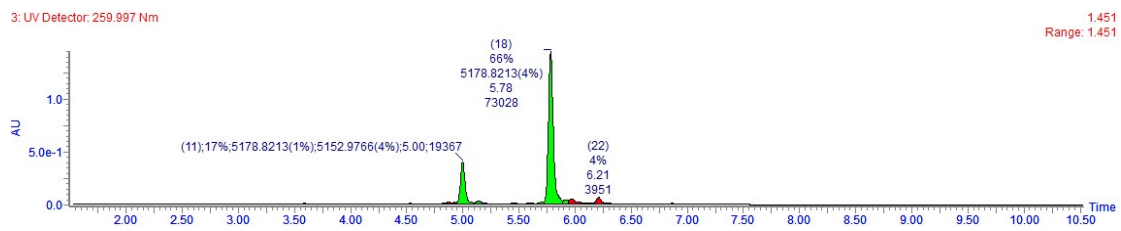
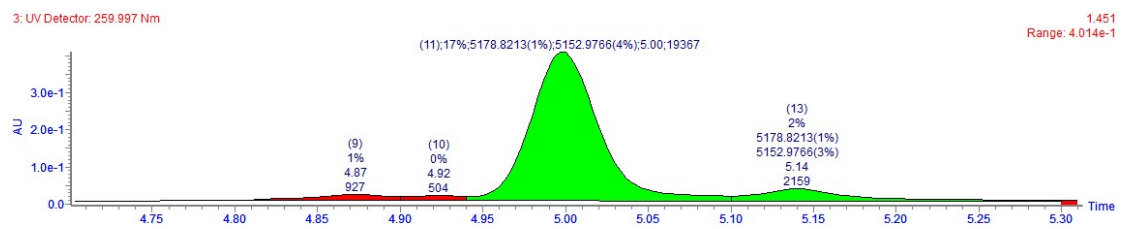


Entry 5: By solving the equation $0.46x = 0.19(1+x)$, it is found that $x = 0.70$. So the total DNA recovery is 70%.

LC trace of **1** in entry 5

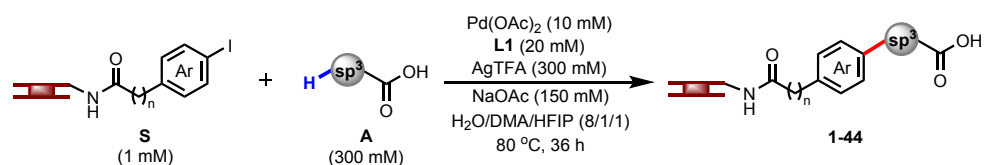


LC trace of 1 in entry 5 in the presence of the standard S1a



4.4 General Procedure 2 for on-DNA C-H Arylation of Free Carboxylic Acids

Condition A:



Materials

DNA-conjugated aryl iodide **S**: 10 mM in H₂O

Carboxylic acid **A**: 3 M in DMA (*Note: the high concentration may increase the total volume*)

L1: 200 mM in HFIP (4.4 mg in 100 μL HFIP)

Pd(OAc)₂: 100 mM in HFIP (2.2 mg in 100 μL HFIP)

NaOAc: 1.5 M in H₂O (12.3 mg in 100 μL H₂O)

Sodium diethyldithiocarbamate trihydrate (scavenger): 1 M in H₂O (225.3 mg in 1.0 mL H₂O)

Procedure

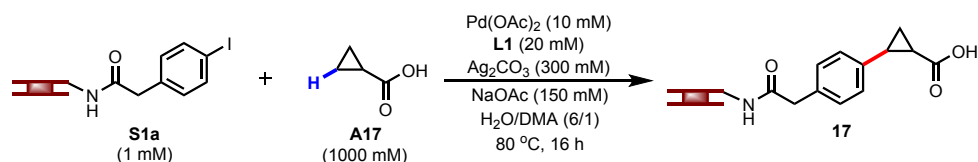
1) To prepared AgTFA (300 equiv, 0.66 mg) was added Pd(OAc)₂ (10 equiv, 1 μL), after air-dry, carboxylic acid **A** (300 equiv, ca. 1.3 μL), DNA-conjugated aryl iodide **S** (10 nmol, 1 μL), NaOAc aqueous solution (150 equiv, 1 μL) and deionized water (6 μL) were added. Finally, **L1** solution (20 equiv, 1 μL) was added. The mixture was vortexed. Heating the reaction mixture at 80 °C for 36 h.

2) Cooling to room temperature, 9.0 μL scavenger was added and reheating the mixture at 80 °C for 30 min.

3) Cooling to room temperature, 5 M NaCl solution (10 % by volume, 1.9 μL) and cold ethanol (3 times by volume, 57 μL). The mixture was stored at a -20 °C freezer for more than 30 minutes.

4) Centrifuge the sample for around 7 minutes in a microcentrifuge at 10000 rpm. The above supernatant was discarded and the precipitate was dried under vacuum. The DNA pellet was redissolved in H₂O (100 μL) and centrifuged for around 2 minutes in a microcentrifuge at 10000 rpm. An aliquot (50 μL) was taken and analyzed via HPLC-MS.

Condition B:



Materials

S1a: 10 mM in H₂O

Cyclopropanecarboxylic acid (**A17**): 3 M in H₂O

L1: 200 mM in HFIP

Pd(OAc)₂: 100 mM in HFIP

NaOAc: 1.5 M in H₂O (12.3 mg in 100 μL H₂O)

Sodium diethyldithiocarbamate trihydrate (scavenger): 1 M in H₂O

Procedure

1) To a 200 μL microcentrifuge tube was added Pd(OAc)₂ (10 equiv, 1 μL) and **L1** solution (20 equiv, 1 μL), after air-dry, Ag₂CO₃ (300 equiv, 0.83 mg) was added, sequentially added **A17** (1000 equiv, 3.3 μL), **S1a** (10 nmol, 1 μL), NaOAc aqueous solution (150 equiv, 1 μL), DMA (1.4 μL) and deionized water (3.3 μL). The mixture was vortexed. Heating the reaction mixture at 80 °C for 16 h.

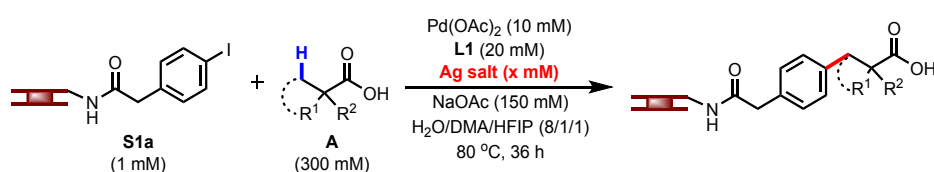
2) Cooling to room temperature, 9.0 μL scavenger was added and reheating the mixture at 80 °C for 30 min.

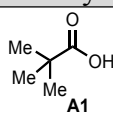
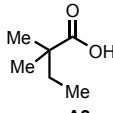
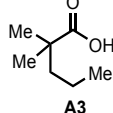
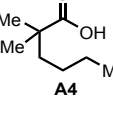
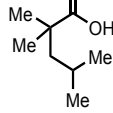
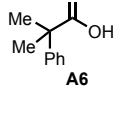
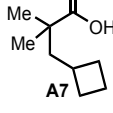
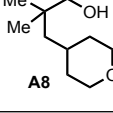
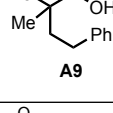
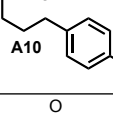
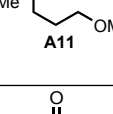
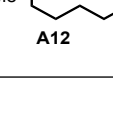
3) Cooling to room temperature, 5 M NaCl solution (10 % by volume, 1.9 μL) and cold ethanol (3 times by volume, 57 μL). The mixture was stored at a -20 °C freezer for more than 30 minutes.

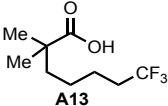
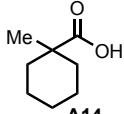
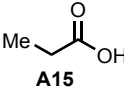
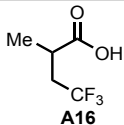

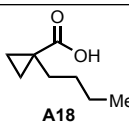
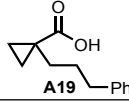
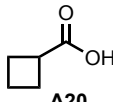
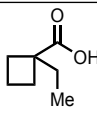
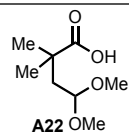
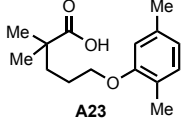
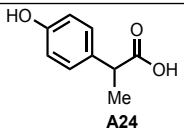
4) Centrifuge the sample for around 7 minutes in a microcentrifuge at 10000 rpm. The above supernatant was discarded and the precipitate was dried under vacuum. The DNA pellet was redissolved in H₂O (100 μL) and centrifuged for around 2 minutes in a microcentrifuge at 10000 rpm. An aliquot (50 μL) was taken and analyzed via HPLC-MS.

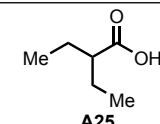
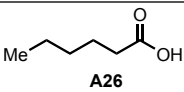
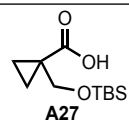
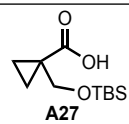
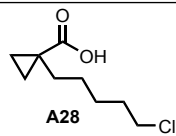
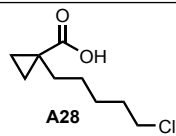
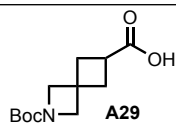
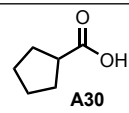
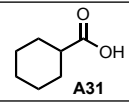
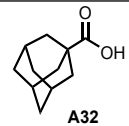
4.5 Scope and Limitations of Free Carboxylic Acids

Table S6. Scope and Limitations of Free Carboxylic Acids



Entry	Free Carboxylic Acid	Ag Salt (x mM)	Yield (%)
1	 <chem>CC(C)(C)C(=O)O</chem> A1	AgTFA (300 mM)	31
2		Ag ₂ CO ₃ (300 mM)	60
3		Ag ₃ PO ₄ (200 mM)	N.D.
4		AgOAc (300 mM)	61
5	 <chem>CC(C)C(C)C(=O)O</chem> A2	AgTFA (300 mM)	46
6		Ag₂CO₃ (300 mM)	49(62)^a
7		Ag ₃ PO ₄ (200 mM)	5
8		AgOAc (300 mM)	22
9	 <chem>CC1(C)CCCCC1C(=O)O</chem> A3	AgTFA (300 mM)	72
10		Ag ₂ CO ₃ (300 mM)	24
11		Ag ₃ PO ₄ (200 mM)	8
12		AgOAc (300 mM)	39
13	 <chem>CC1(C)CCCC(C)C1C(=O)O</chem> A4	AgTFA (300 mM)	56
14		Ag ₂ CO ₃ (300 mM)	9
15		Ag ₃ PO ₄ (200 mM)	8
16		AgOAc (300 mM)	20
17	 <chem>CC1(C)CC(C)CCC1C(=O)O</chem> A5	AgTFA (300 mM)	48
18		Ag ₂ CO ₃ (300 mM)	11
19		Ag ₃ PO ₄ (200 mM)	7
20		AgOAc (300 mM)	35
21	 <chem>CC(C)(C)C(C1=CC=CC=C1)C(=O)O</chem> A6	AgTFA (300 mM)	32
22		Ag ₂ CO ₃ (300 mM)	11
23		Ag ₃ PO ₄ (200 mM)	18
24		AgOAc (300 mM)	20
25	 <chem>CC1(C)CCCC(C2=CC=CC=C2)C1C(=O)O</chem> A7	AgTFA (300 mM)	46
26		Ag ₂ CO ₃ (300 mM)	11
27		Ag ₃ PO ₄ (200 mM)	6
28		AgOAc (300 mM)	13
29	 <chem>CC1(C)CCCC(C2=CC=CC=C2)C1C(=O)O</chem> A8	AgTFA (300 mM)	72
30		Ag ₂ CO ₃ (300 mM)	28
31		Ag ₃ PO ₄ (200 mM)	6
32		AgOAc (300 mM)	20
33	 <chem>CC1(C)CCCC(C2=CC=CC=C2)C1C(=O)O</chem> A9	AgTFA (300 mM)	48
34		Ag ₂ CO ₃ (300 mM)	12
35		Ag ₃ PO ₄ (200 mM)	6
36		AgOAc (300 mM)	16
37	 <chem>CC1(C)CCCC(C2=CC=C(C=C2)OC)C1C(=O)O</chem> A10	AgTFA (300 mM)	46
38		Ag ₂ CO ₃ (300 mM)	4
39		Ag ₃ PO ₄ (200 mM)	4
40		AgOAc (300 mM)	14
41	 <chem>CC1(C)CCCC(COC)C1C(=O)O</chem> A11	AgTFA (300 mM)	61
42		Ag ₂ CO ₃ (300 mM)	20
43		Ag ₃ PO ₄ (200 mM)	N.D.
44		AgOAc (300 mM)	33
45	 <chem>CC1(C)CCCC(CF)C1C(=O)O</chem> A12	AgTFA (300 mM)	64
46		Ag ₂ CO ₃ (300 mM)	39
47		Ag ₃ PO ₄ (200 mM)	7
48		AgOAc (300 mM)	35

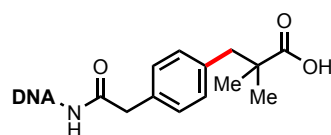
49	 A13	AgTFA (300 mM)	49
50		Ag ₂ CO ₃ (300 mM)	4
51		Ag ₃ PO ₄ (200 mM)	trace
52		AgOAc (300 mM)	5
53	 A14	AgTFA (300 mM)	61
54		Ag ₂ CO ₃ (300 mM)	8
55		Ag ₃ PO ₄ (200 mM)	N.D.
56		AgOAc (300 mM)	11
57	 A15	AgTFA (300 mM)	5
58		Ag ₂ CO ₃ (300 mM)	21
59		Ag₃PO₄ (200 mM)	28
60		AgOAc (300 mM)	22
61	 A16	AgTFA (300 mM)	18
62		Ag ₂ CO ₃ (300 mM)	12
63		Ag ₃ PO ₄ (200 mM)	N.D.
64		AgOTf (300 mM)	26
65	 A17	AgTFA (300 mM)	12
66		Ag₂CO₃ (300 mM)	22(36)^b
67		Ag ₃ PO ₄ (200 mM)	16
68		AgOAc (300 mM)	14
69	 A18	AgTFA (300 mM)	47
70		Ag ₂ CO ₃ (300 mM)	6
71		Ag ₃ PO ₄ (200 mM)	N.D.
72		AgOAc (300 mM)	12
73	 A19	AgTFA (300 mM)	40
74		Ag ₂ CO ₃ (300 mM)	N.D.
75	 A20	AgTFA (300 mM)	20
76		Ag₂CO₃ (300 mM)	16(39)^c
77		Ag ₃ PO ₄ (200 mM)	16
78		AgOAc (300 mM)	19
79	 A21	AgTFA (300 mM)	34
80		Ag₂CO₃ (300 mM)	40
81		Ag ₃ PO ₄ (200 mM)	24
82		AgOAc (300 mM)	25
83	 A22	AgTFA (300 mM)	N.D.
84	 A23	AgTFA (300 mM)	N.D.
85		Ag ₂ CO ₃ (300 mM)	N.D.
86	 A24	AgTFA (300 mM)	N.D.
87		Ag ₂ CO ₃ (300 mM)	Trace

88		AgTFA (300 mM)	N.D.
89		AgTFA (300 mM)	N.D.
90		AgTFA (300 mM)	N.D.
91		Ag ₂ CO ₃ (300 mM)	N.D.
92		AgTFA (300 mM)	N.D.
93		Ag ₂ CO ₃ (300 mM)	N.D.
94		AgTFA (300 mM)	N.D.
95		AgTFA (300 mM)	N.D.
96		AgTFA (300 mM)	N.D.
97		AgTFA (300 mM)	N.D.

^aUsing **A2** (500 mM); ^bCondition B was followed; ^cUsing **A20** (1000 mM), 16 h. N.D. = not detected.

4.6 LC Trace and Mass Characterization of 1-44

LC Trace and Mass of 1



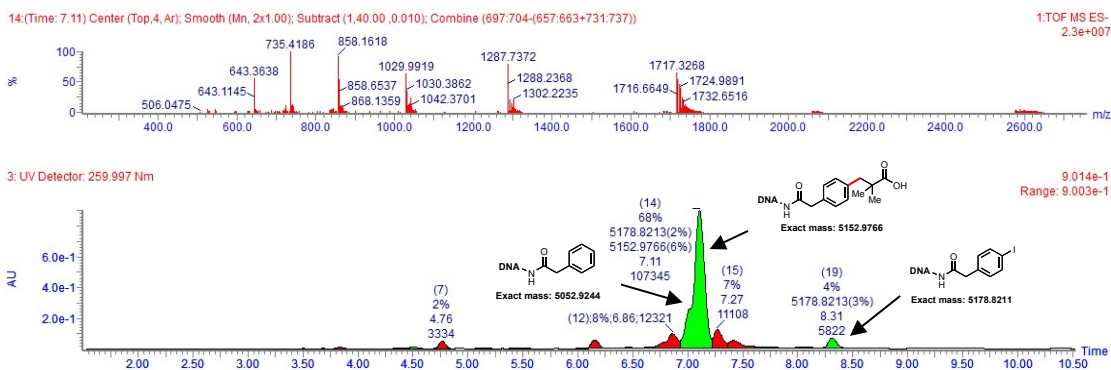
Following General Procedure 2 (Condition A) with **A1** (1000 mM) except for employing Ag₂CO₃ instead of AgTFA.

$$\text{Yield: } \frac{66}{85} \times 100\% = 78\%$$

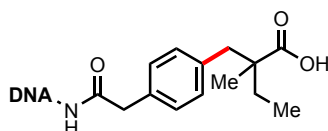
Ratio (product/deiodination/aryl iodide): 66/2/4

Exact mass: 5152.9766

Triply charged mass [M]/3 - 1.00794, calculated 1716.6509; observed 1716.6649.



LC Trace and Mass of 2



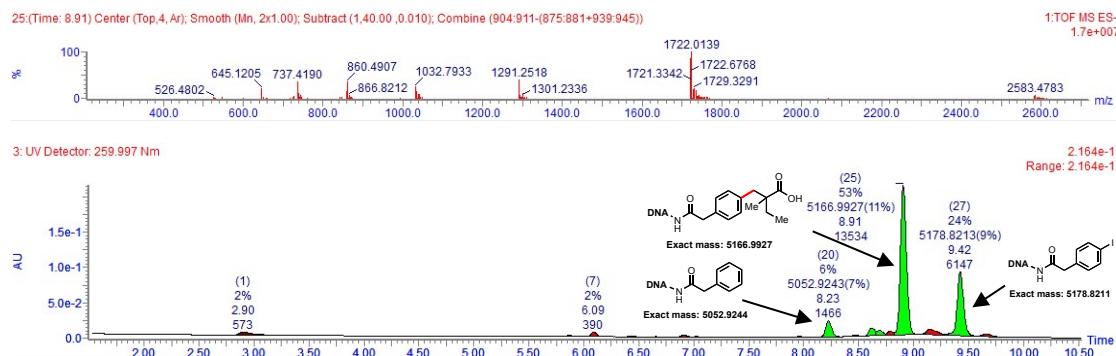
Following General Procedure 2 (Condition A) with **A2** (500 mM) except for employing Ag_2CO_3 instead of AgTFA .

$$\text{Yield: } \frac{53}{85} \times 100\% = 62\%$$

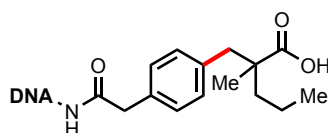
Ratio (product/deiodination/aryl iodide): 53/6/24

Exact mass: 5166.9927

Triply charged mass $[M]/3 - 1.00794$, calculated 1721.3230; observed 1721.3342.



LC Trace and Mass of 3



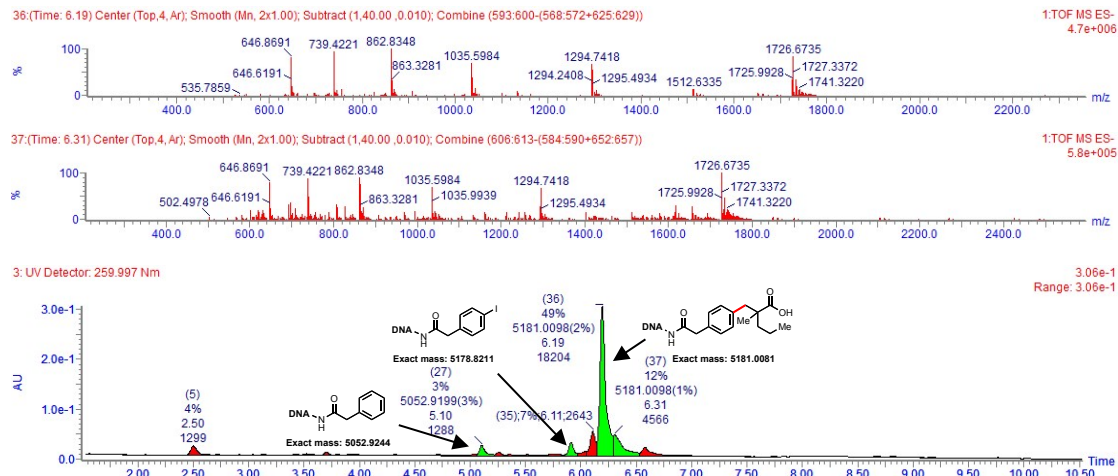
Following General Procedure 2 (Condition A) with **A3**.

$$\text{Yield: } \frac{61}{85} \times 100\% = 72\%$$

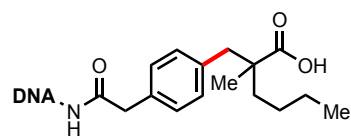
Ratio (product/deiodination/aryl iodide): 61/3/4

Exact mass: 5181.0081

Triply charged mass [M]/3 - 1.00794, calculated 1725.9948; observed 1725.9928.



LC Trace and Mass of 4



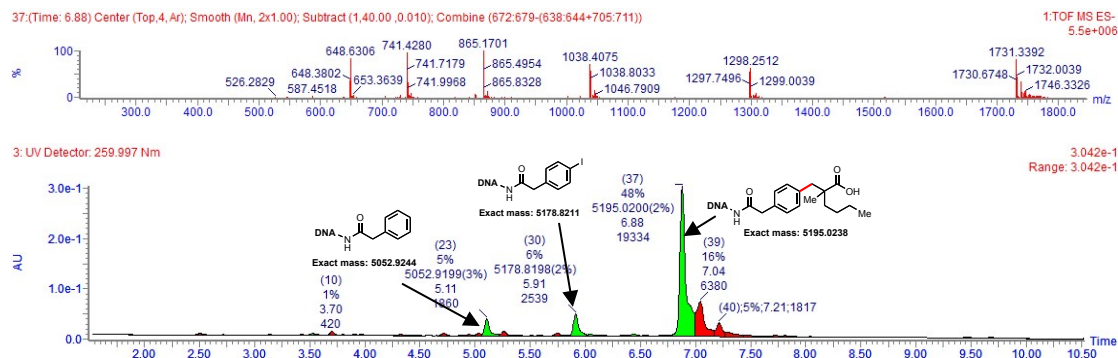
Following General Procedure 2 (Condition A) with A4.

$$\text{Yield: } \frac{48}{85} \times 100\% = 56\%$$

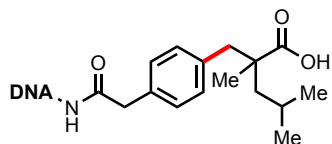
Ratio (product/deiodination/aryl iodide): 48/5/6

Exact mass: 5195.0238

Triply charged mass [M]/3 - 1.00794, calculated 1730.6667; observed 1730.6748.



LC Trace and Mass of 5



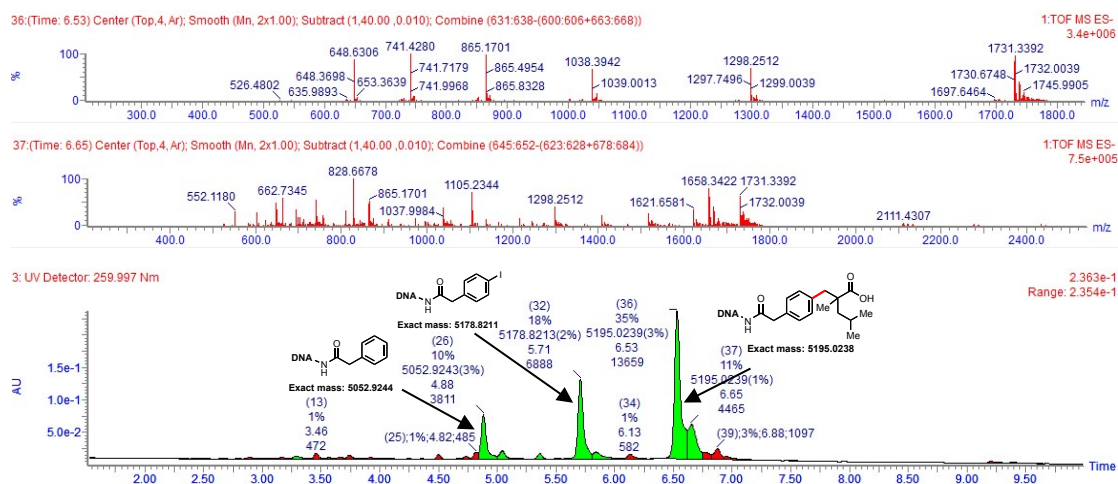
Following General Procedure 2 (Condition A) with **A5**.

$$\text{Yield: } \frac{41}{85} \times 100\% = 48\%$$

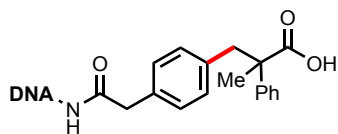
Ratio (product/deiodination/aryl iodide): 41/10/18

Exact mass: 5195.0238

Triply charged mass $[M]/3 - 1.00794$, calculated 1730.6667; observed 1730.6748.



LC Trace and Mass of 6



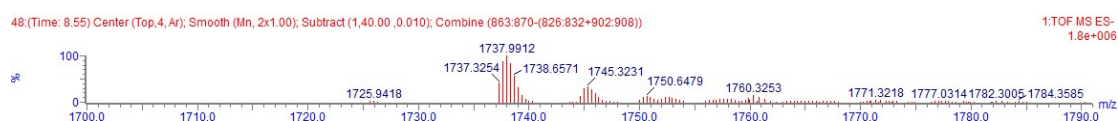
Following General Procedure 2 (Condition A) with **A6**.

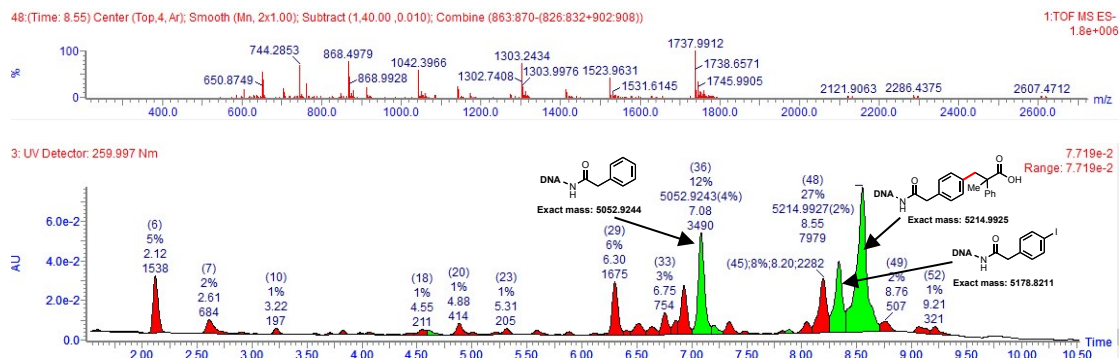
$$\text{Yield: } \frac{27}{85} \times 100\% = 32\%$$

Ratio (product/deiodination/aryl iodide): 27/12/10

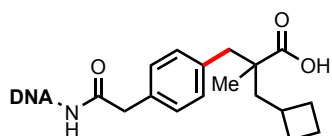
Exact mass: 5214.9925

Triply charged mass $[M]/3 - 1.00794$, calculated 1737.3229; observed 1737.3254.





LC Trace and Mass of 7



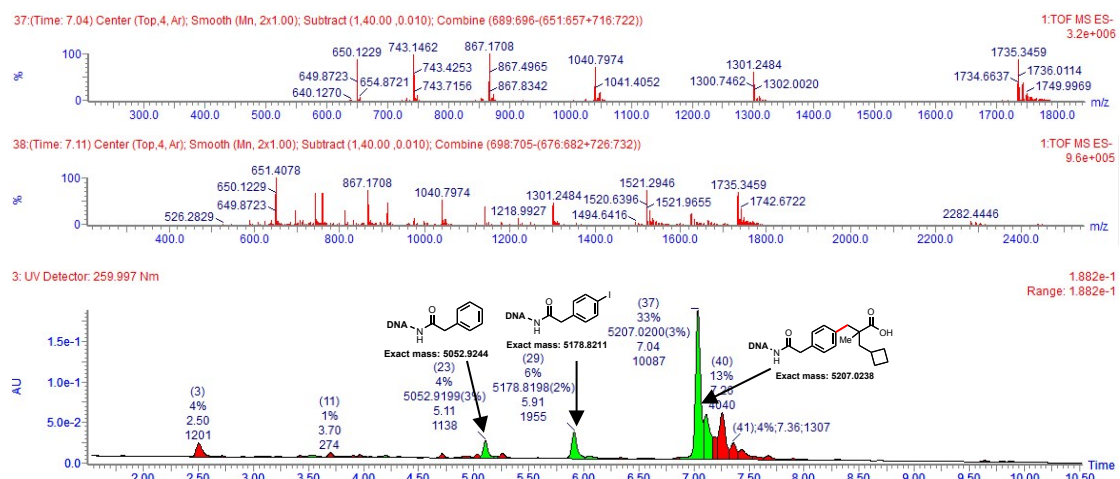
Following General Procedure 2 (Condition A) with A7.

$$\text{Yield: } \frac{39}{85} \times 100\% = 46\%$$

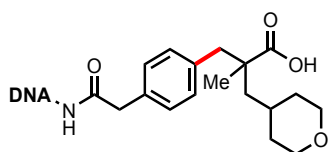
Ratio (product/deiodination/aryl iodide): 39/4/6

Exact mass: 5207.0238

Triply charged mass $[M]/3 - 1.00794$, calculated 1734.6667; observed 1734.6637.



LC Trace and Mass of 8



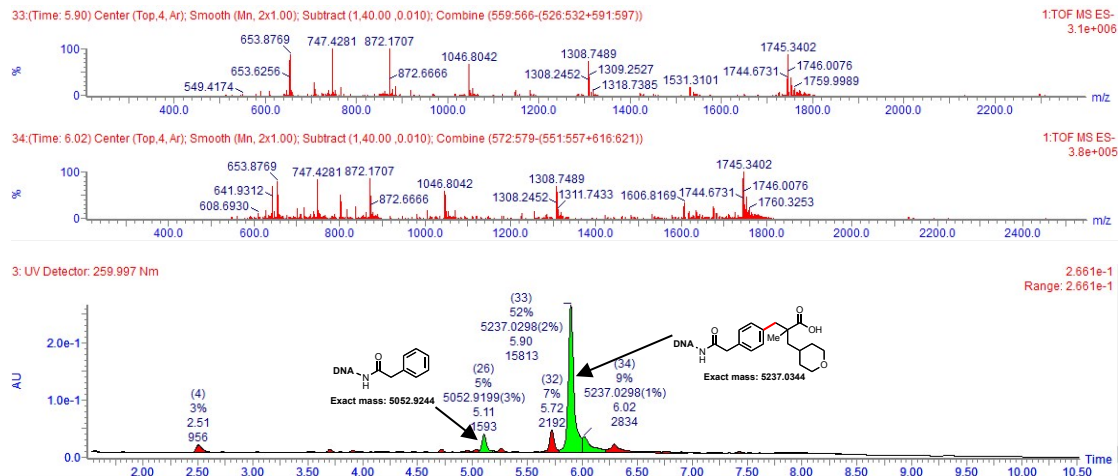
Following General Procedure 2 (Condition A) with A8.

$$\text{Yield: } \frac{61}{85} \times 100\% = 72\%$$

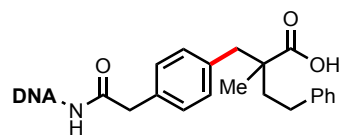
Ratio (product/deiodination/aryl iodide): 61/5/0

Exact mass: 5237.0344

Triply charged mass [M]/3 - 1.00794, calculated 1744.6702; observed 1744.6731.



LC Trace and Mass of 9



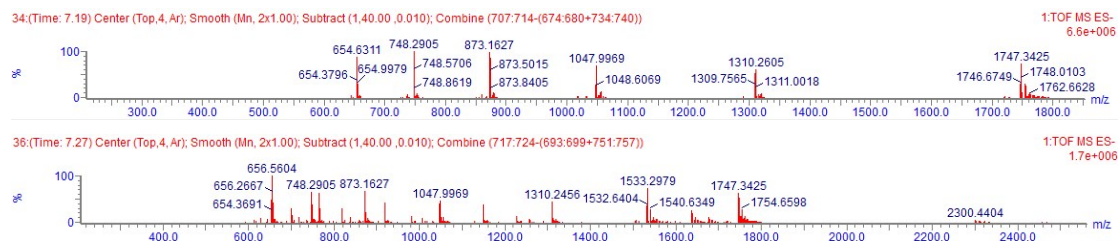
Following General Procedure 2 (Condition A) with A9.

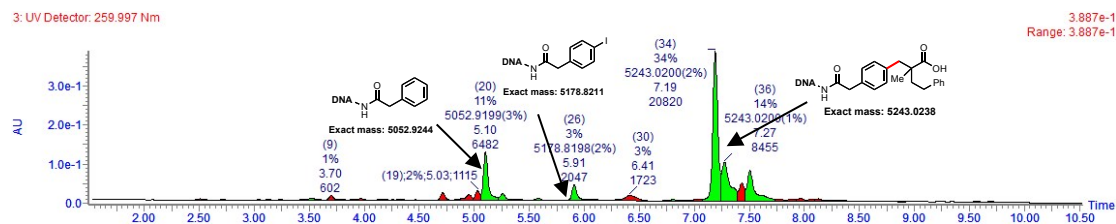
$$\text{Yield: } \frac{41}{85} \times 100\% = 48\%$$

Ratio (product/deiodination/aryl iodide): 41/11/3

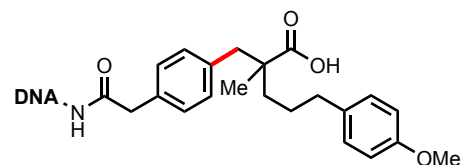
Exact mass: 5243.0238

Triply charged mass [M]/3 - 1.00794, calculated 1746.6667; observed 1746.6749.





LC Trace and Mass of 10



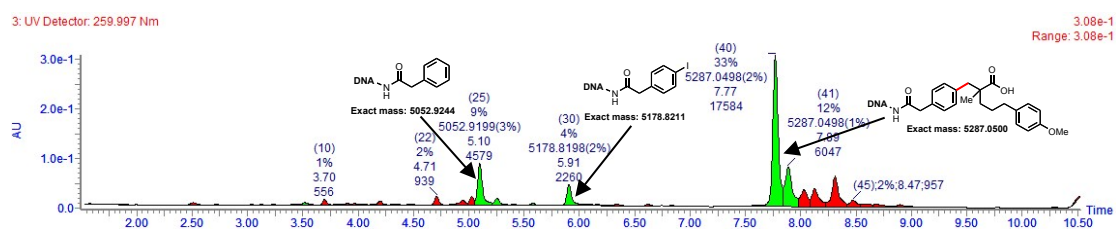
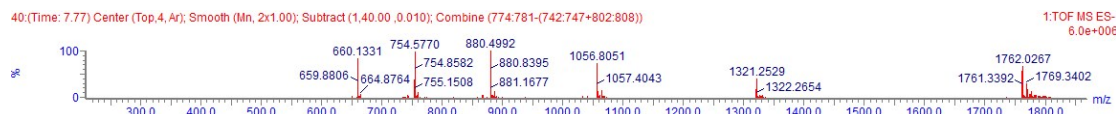
Following General Procedure 2 (Condition A) with **A10**.

$$\text{Yield: } \frac{39}{85} \times 100\% = 46\%$$

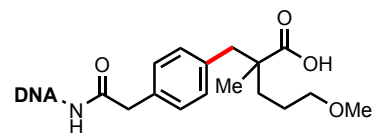
Ratio (product/deiodination/aryl iodide): 39/9/4

Exact mass: 5287.0500

Triply charged mass $[M]/3 - 1.00794$, calculated 1761.3421; observed 1761.3392.



LC Trace and Mass of 11



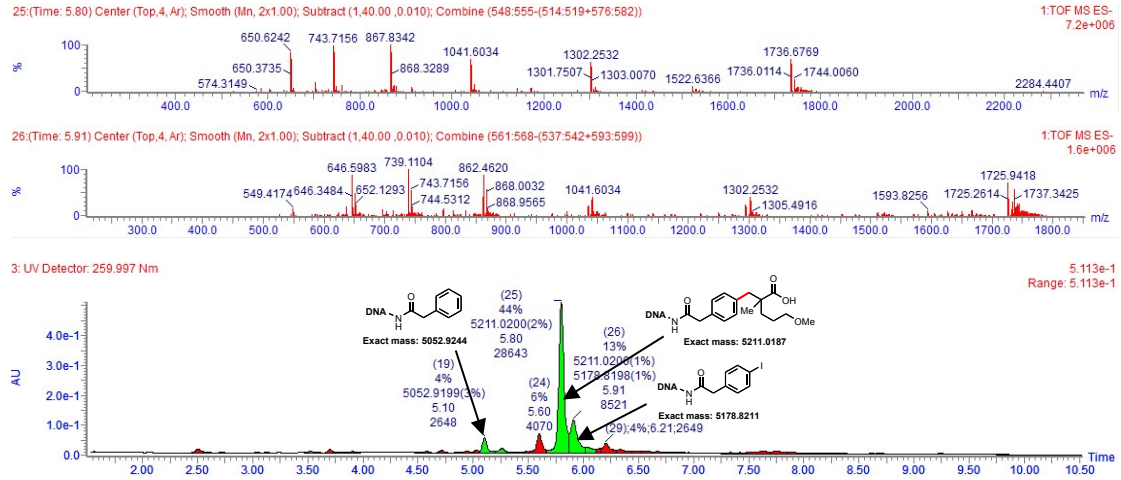
Following General Procedure 2 (Condition A) with **A11**.

$$\text{Yield: } \frac{52}{85} \times 100\% = 61\%$$

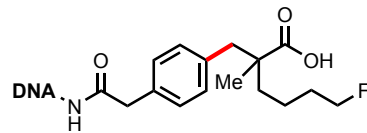
Ratio (product/deiodination/aryl iodide): 52/4/5

Exact mass: 5211.0187

Triply charged mass [M]/3 - 1.00794, calculated 1735.9983; observed 1736.0114.



LC Trace and Mass of 12



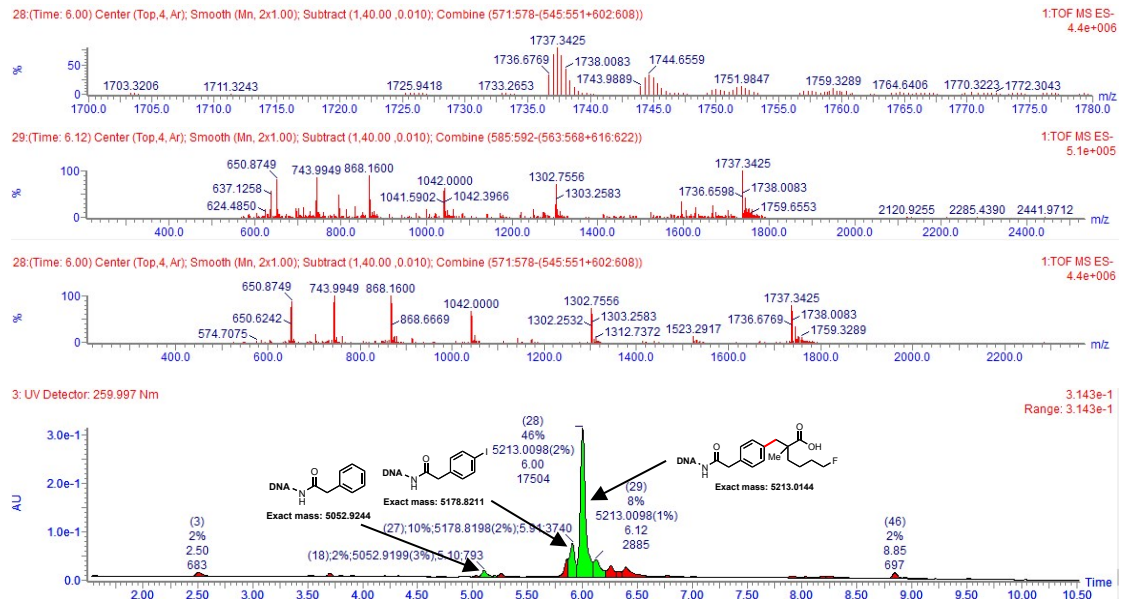
Following General Procedure 2 (Condition A) with **A12**.

$$\text{Yield: } \frac{54}{85} \times 100\% = 64\%$$

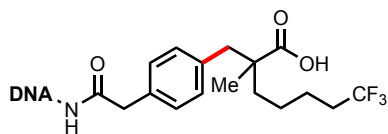
Ratio (product/deiodination/aryl iodide): 54/2/10

Exact mass: 5213.0144

Triply charged mass [M]/3 - 1.00794, calculated 1736.6635; observed 1736.6769.



LC Trace and Mass of 13



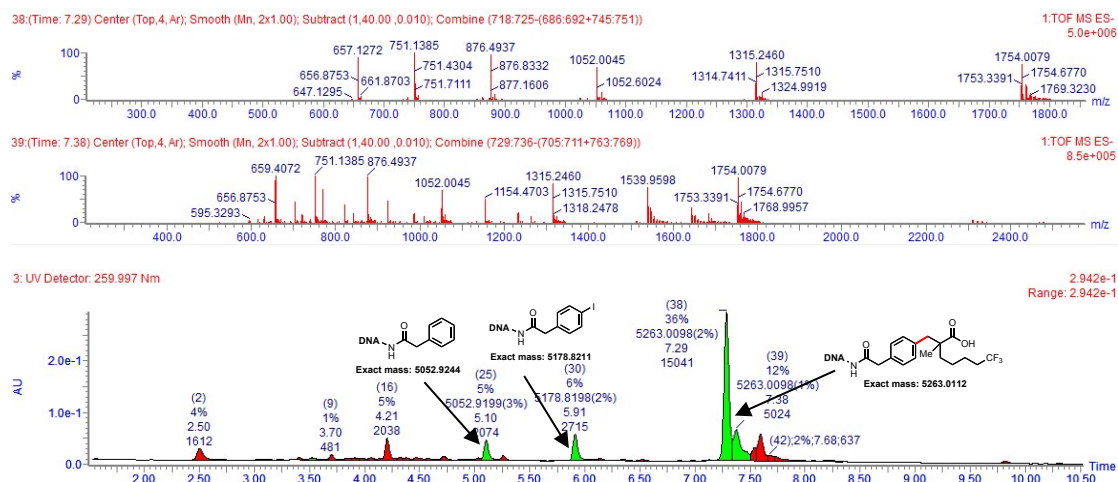
Following General Procedure 2 (Condition A) with **A13**.

$$\text{Yield: } \frac{42}{85} \times 100\% = 49\%$$

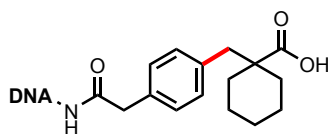
Ratio (product/deiodination/aryl iodide): 42/5/6

Exact mass: 5263.0112

Triply charged mass $[M]/3 - 1.00794$, calculated 1753.3291; observed 1753.3391.



LC Trace and Mass of 14



Following General Procedure 2 (Condition A) with **A14**.

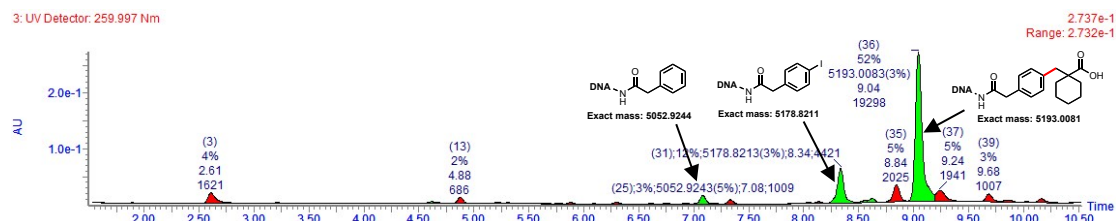
$$\text{Yield: } \frac{52}{85} \times 100\% = 61\%$$

Ratio (product/deiodination/aryl iodide): 52/3/12

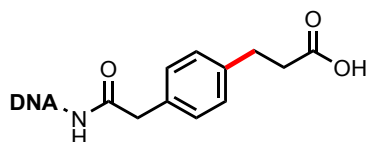
Exact mass: 5193.0081

Triply charged mass $[M]/3 - 1.00794$, calculated 1729.9948; observed 1730.0104.





LC Trace and Mass of 15



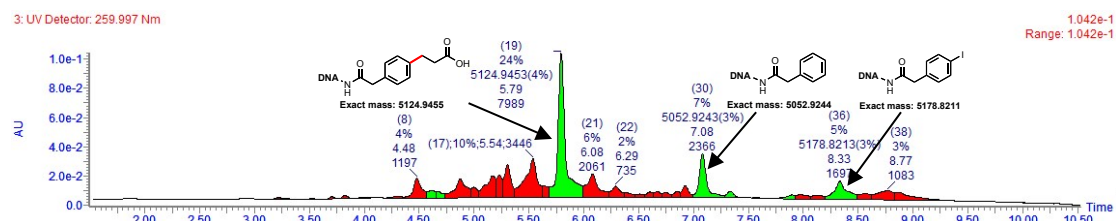
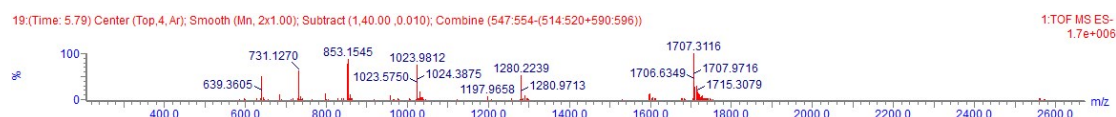
Following General Procedure 2 (Condition A) with **A15** except for employing Ag_3PO_4 instead of AgTFA .

$$\text{Yield: } \frac{24}{85} \times 100\% = 28\%$$

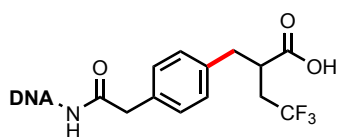
Ratio (product/deiodination/aryl iodide): 24/7/5

Exact mass: 5124.9455

Triply charged mass $[M]/3 - 1.00794$, calculated 1707.3072; observed 1707.3116.



LC Trace and Mass of 16



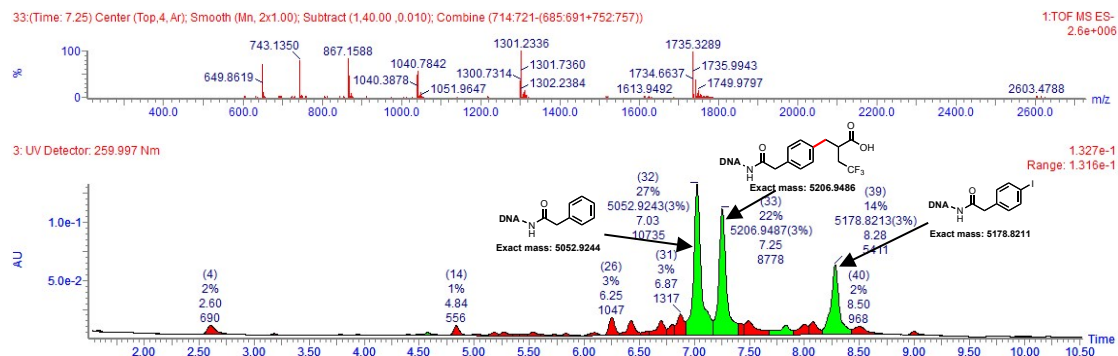
Following General Procedure 2 (Condition A) with **A16** except for employing AgOTf instead of AgTFA .

$$\text{Yield: } \frac{22}{85} \times 100\% = 26\%$$

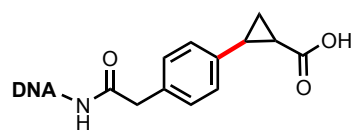
Ratio (product/deiodination/aryl iodide): 22/27/14

Exact mass: 5206.9486

Triply charged mass $[M]/3 - 1.00794$, calculated 1734.6416; observed 1734.6637.



LC Trace and Mass of 17



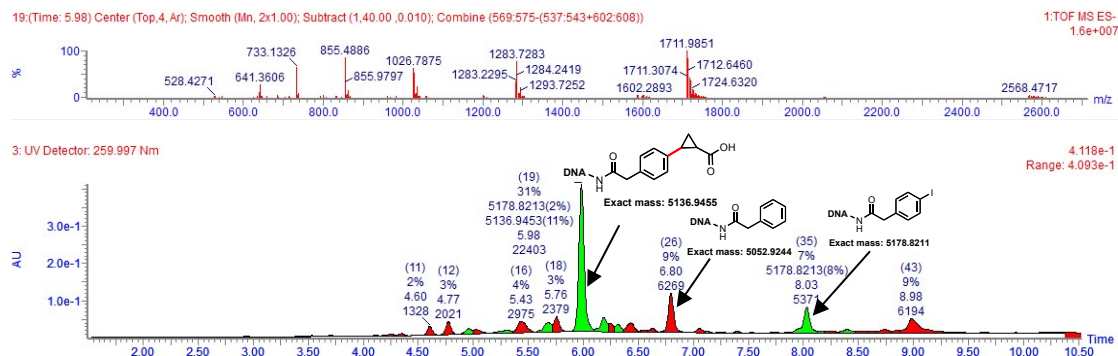
Following General Procedure 2 (Condition B) with A17.

$$\text{Yield: } \frac{31}{85} \times 100\% = 36\%$$

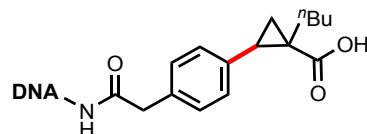
Ratio (product/deiodination/aryl iodide): 31/9/7

Exact mass: 5136.9455

Triply charged mass $[M]/3 - 1.00794$, calculated 1711.3072; observed 1711.3074.



LC Trace and Mass of 18



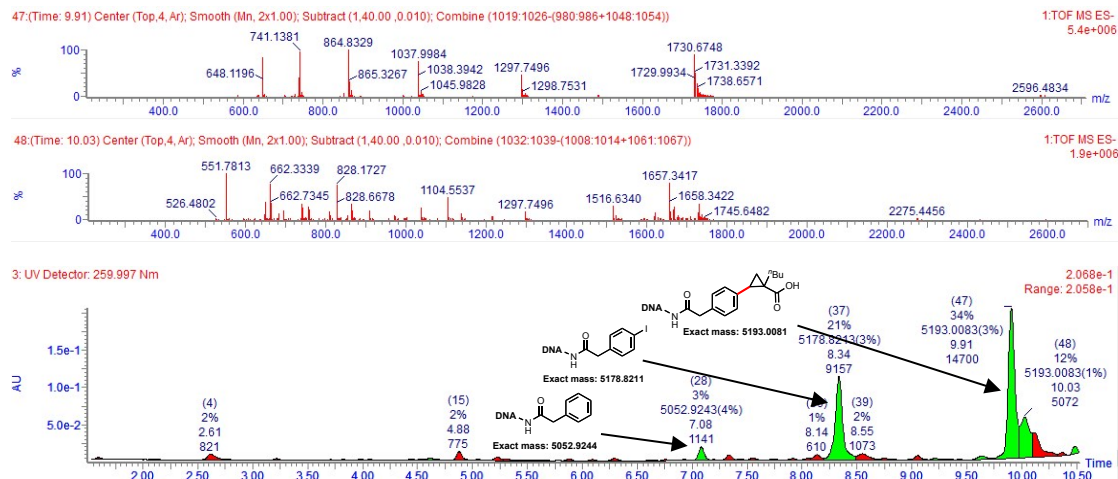
Following General Procedure 2 (Condition A) with A18.

$$\text{Yield: } \frac{40}{85} \times 100\% = 47\%$$

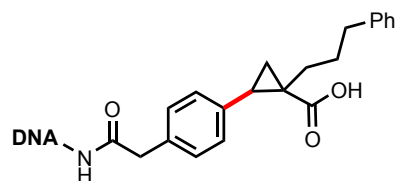
Ratio (product/deiodination/aryl iodide): 40/3/21

Exact mass: 5193.0081

Triply charged mass $[M]/3 - 1.00794$, calculated 1729.9948; observed 1729.9934.



LC Trace and Mass of 19



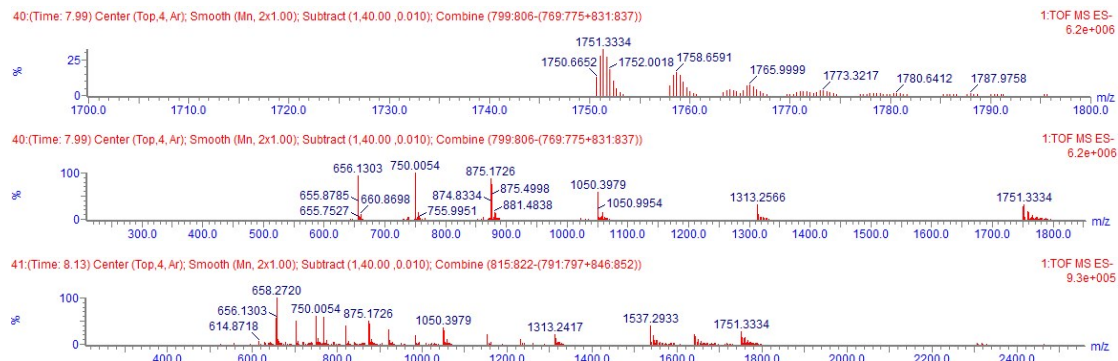
Following General Procedure 2 (Condition A) with A19.

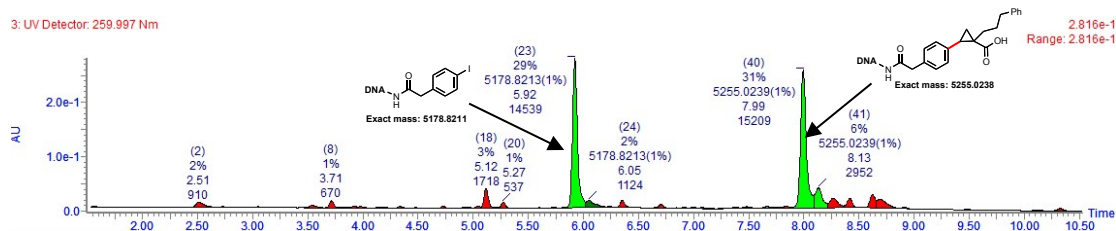
$$\text{Yield: } \frac{34}{85} \times 100\% = 40\%$$

Ratio (product/deiodination/aryl iodide): 34/0/29

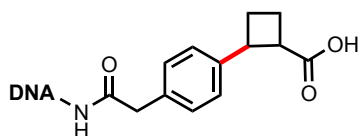
Exact mass: 5255.0238

Triply charged mass $[M]/3 - 1.00794$, calculated 1750.6667; observed 1750.6652.





LC Trace and Mass of 20



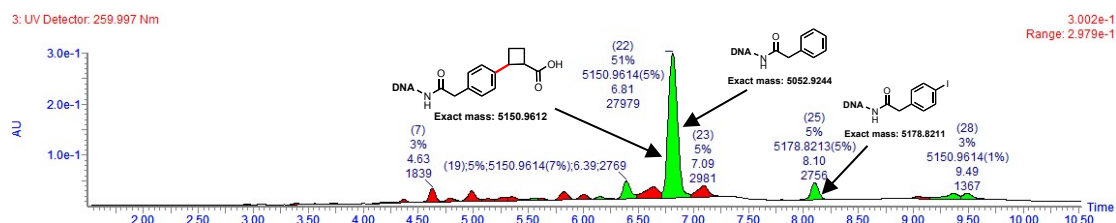
Following General Procedure 2 (Condition A) with **A20** (1000 mM) except for employing Ag_2CO_3 instead of AgTFA .

$$\text{Yield: } \frac{33}{85} \times 100\% = 39\%$$

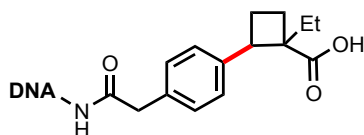
Ratio (product/deiodination/aryl iodide): 33/23/5

Exact mass: 5150.9612

Triply charged mass $[M]/3 - 1.00794$, calculated 1715.9791; observed 1715.9694.



LC Trace and Mass of 21



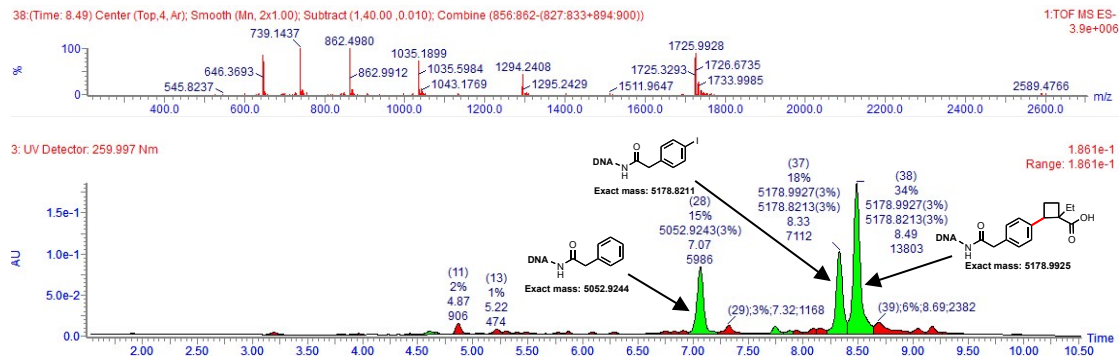
Following General Procedure 2 (Condition A) with **A21** except for employing Ag_2CO_3 instead of AgTFA .

$$\text{Yield: } \frac{34}{85} \times 100\% = 40\%$$

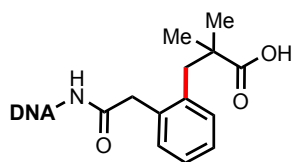
Ratio (product/deiodination/aryl iodide): 34/15/18

Exact mass: 5178.9925

Triply charged mass [M]/3 - 1.00794, calculated 1725.3229; observed 1725.3293.



LC Trace and Mass of 22



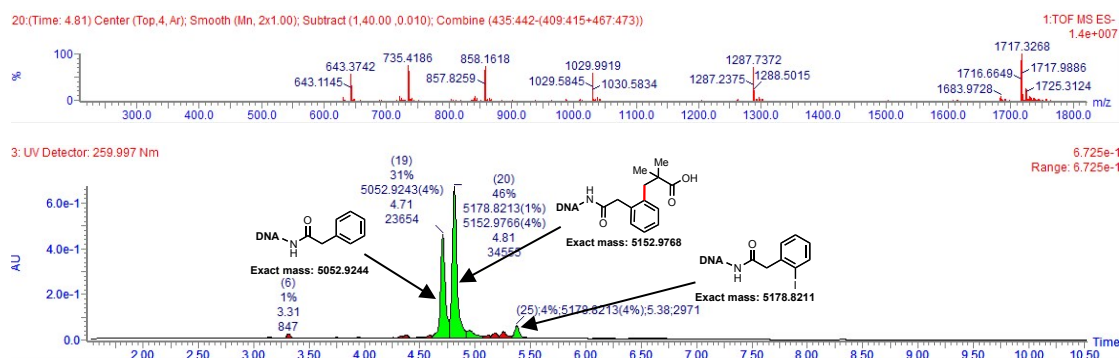
Following General Procedure 2 (Condition A) with **S2** and **A1** (1000 mM) except for employing Ag_2CO_3 instead of AgTFA .

$$\text{Yield: } \frac{46}{83} \times 100\% = 55\%$$

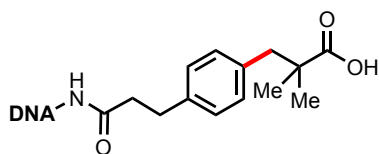
Ratio (product/deiodination/aryl iodide): 46/31/4

Exact mass: 5152.9768

Triply charged mass [M]/3 - 1.00794, calculated 1716.6510; observed 1716.6649.



LC Trace and Mass of 23



Following General Procedure 2 (Condition A) with **S3** and **A1** (1000 mM) except for

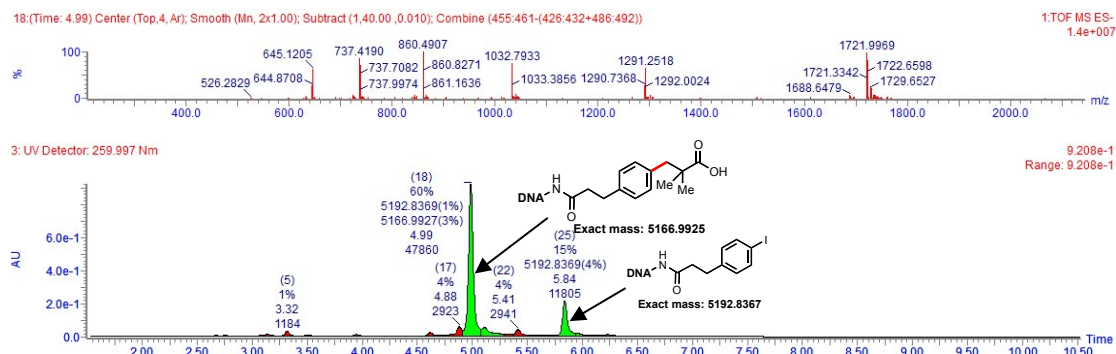
employing Ag_2CO_3 instead of AgTFA .

$$\text{Yield: } \frac{57}{78} \times 100\% = 73\%$$

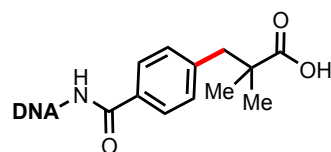
Ratio (product/deiodination/aryl iodide): 57/3/15

Exact mass: 5166.9925

Triply charged mass $[\text{M}]/3 - 1.00794$, calculated 1721.3229; observed 1721.3342.



LC Trace and Mass of 24



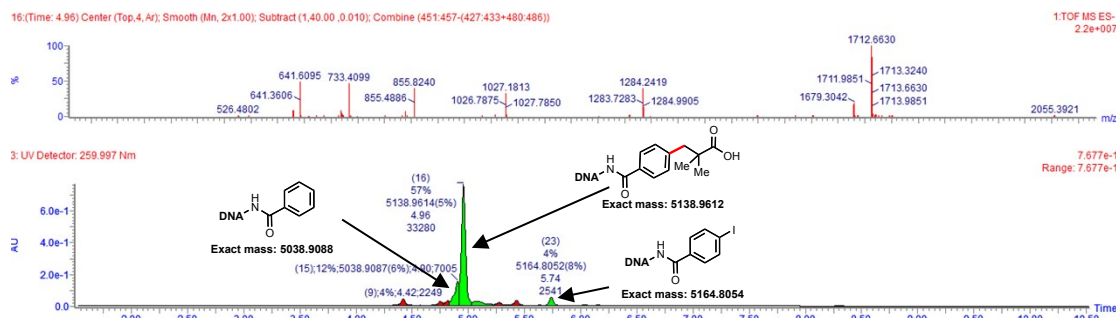
Following General Procedure 2 (Condition A) with **S10** and **A1** (1000 mM) except for employing Ag_2CO_3 instead of AgTFA .

$$\text{Yield: } \frac{57}{85} \times 100\% = 67\%$$

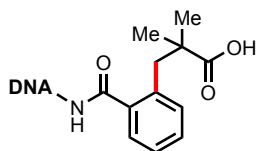
Ratio (product/deiodination/aryl iodide): 57/12/4

Exact mass: 5138.9612

Triply charged mass $[\text{M}]/3 - 1.00794$, calculated 1711.9791; observed 1711.9851.



LC Trace and Mass of 25



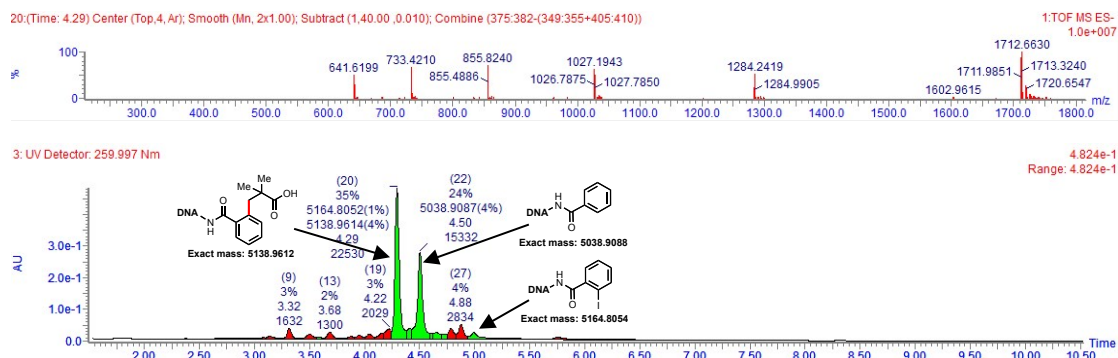
Following General Procedure 2 (Condition A) with **S4** and **A1** (1000 mM) except for employing Ag_2CO_3 instead of AgTFA .

$$\text{Yield: } \frac{35}{74} \times 100\% = 47\%$$

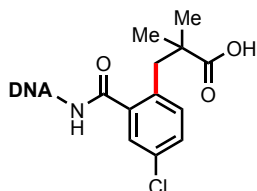
Ratio (product/deiodination/aryl iodide): 35/24/3

Exact mass: 5138.9612

Triply charged mass $[M]/3 - 1.00794$, calculated 1711.9791; observed 1711.9851.



LC Trace and Mass of 26



Following General Procedure 2 (Condition A) with **S6** and **A1** (1000 mM) except for employing Ag_2CO_3 instead of AgTFA .

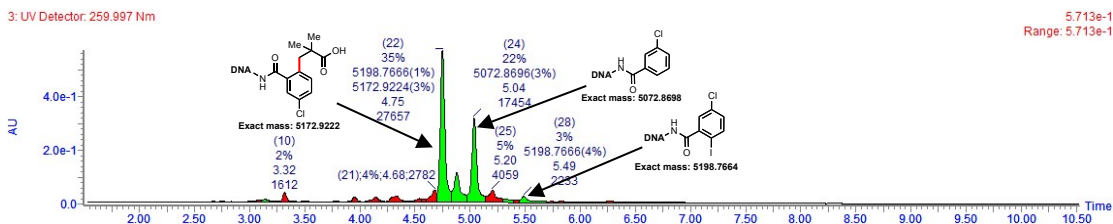
$$\text{Yield: } \frac{35}{67} \times 100\% = 52\%$$

Ratio (product/deiodination/aryl iodide): 35/22/3

Exact mass: 5172.9222

Triply charged mass $[M]/3 - 1.00794$, calculated 1723.2995; observed 1723.3057.





LC Trace and Mass of 27



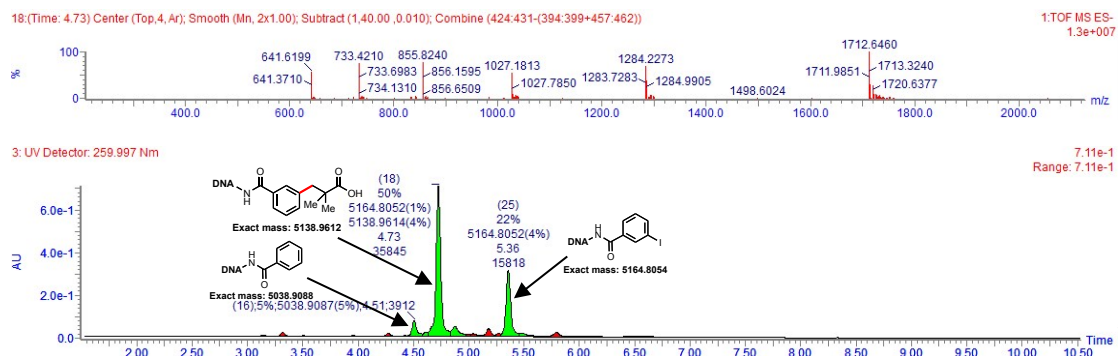
Following General Procedure 2 (Condition A) with **S7** and **A1** (1000 mM) except for employing Ag_2CO_3 instead of AgTFA .

$$\text{Yield: } \frac{50}{83} \times 100\% = 60\%$$

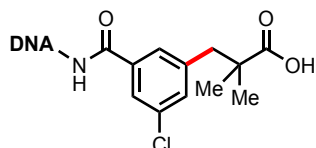
Ratio (product/deiodination/aryl iodide): 50/5/22

Exact mass: 5138.9612

Triply charged mass $[M]/3 - 1.00794$, calculated 1711.9791; observed 1711.9851.



LC Trace and Mass of 28



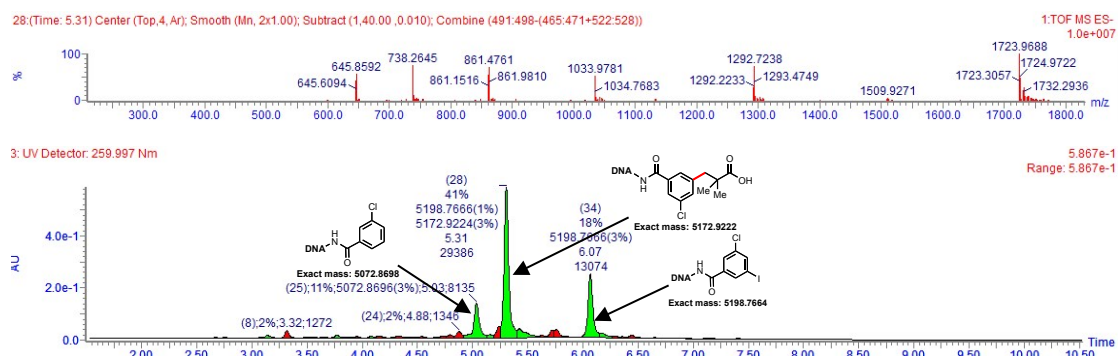
Following General Procedure 2 (Condition A) with **S9** and **A1** (1000 mM) except for employing Ag_2CO_3 instead of AgTFA .

$$\text{Yield: } \frac{41}{71} \times 100\% = 58\%$$

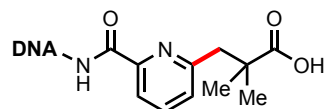
Ratio (product/deiodination/aryl iodide): 41/11/18

Exact mass: 5172.9222

Triply charged mass $[M]/3 - 1.00794$, calculated 1723.2995; observed 1723.3057.



LC Trace and Mass of 29



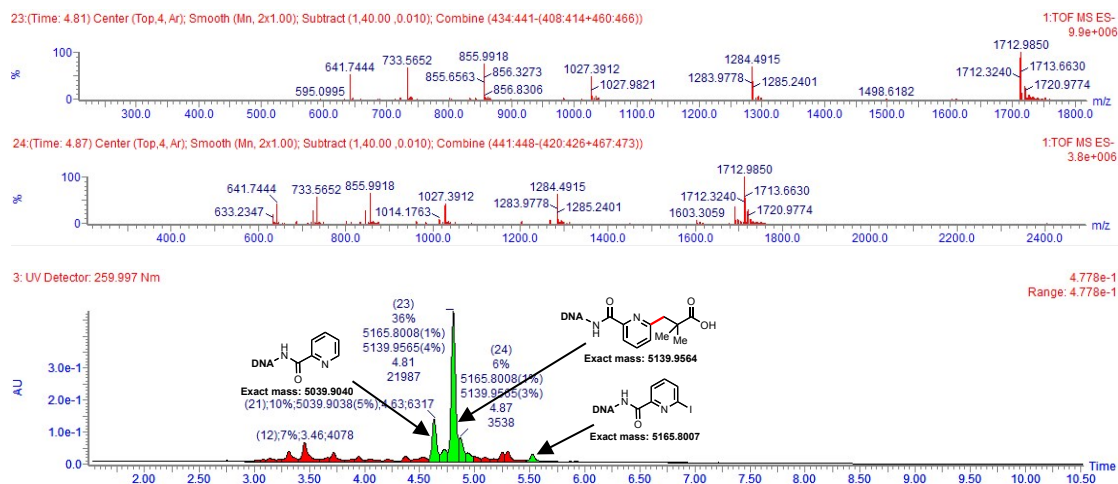
Following General Procedure 2 (Condition A) with **S14** and **A1** (1000 mM) except for employing Ag_2CO_3 instead of AgTFA .

$$\text{Yield: } \frac{42}{57} \times 100\% = 74\%$$

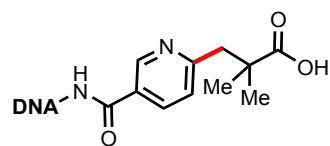
Ratio (product/deiodination/aryl iodide): 42/10/2

Exact mass: 5139.9564

Triply charged mass $[M]/3 - 1.00794$, calculated 1712.3109; observed 1712.3240.



LC Trace and Mass of 30



Following General Procedure 2 (Condition A) with **S15** and **A1** (1000 mM) except for

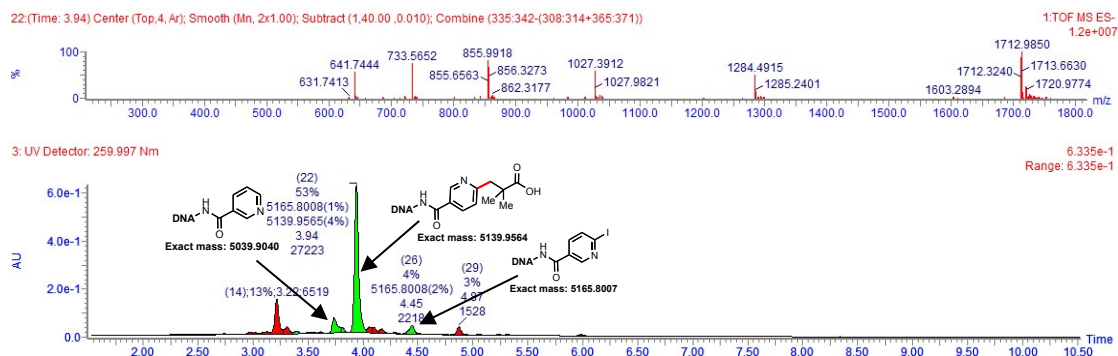
employing Ag_2CO_3 instead of AgTFA .

$$\text{Yield: } \frac{53}{65} \times 100\% = 82\%$$

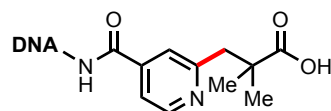
Ratio (product/deiodination/aryl iodide): 53/7/4

Exact mass: 5139.9564

Triply charged mass $[\text{M}]/3 - 1.00794$, calculated 1712.3109; observed 1712.3240.



LC Trace and Mass of 31



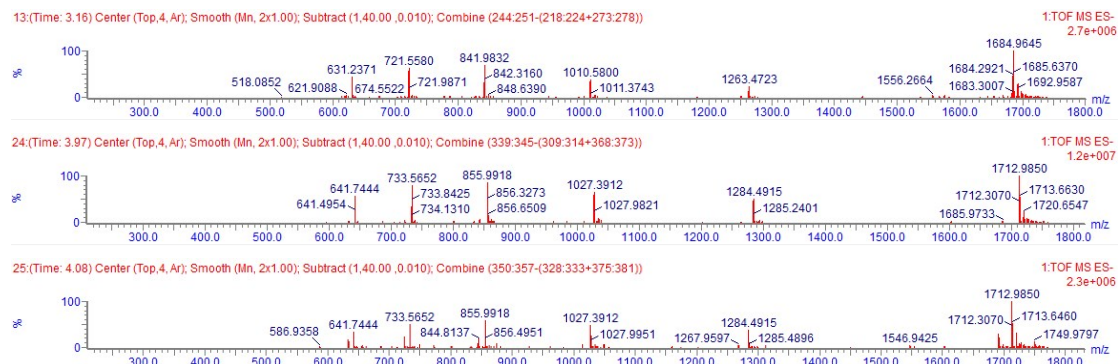
Following General Procedure 2 (Condition A) with **S18** and **A1** (1000 mM) except for employing Ag_2CO_3 instead of AgTFA .

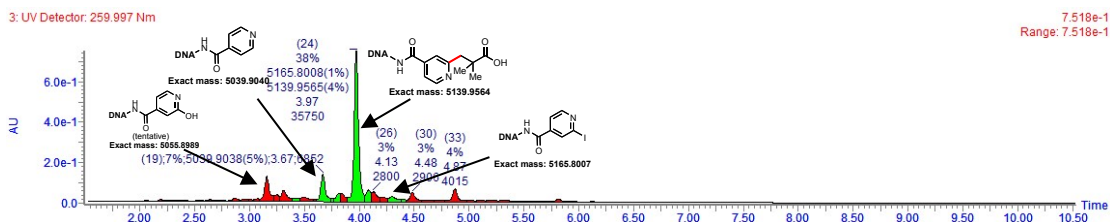
$$\text{Yield: } \frac{41}{56} \times 100\% = 73\%$$

Ratio (product/deiodination/aryl iodide): 41/7/2

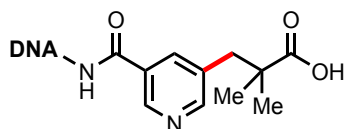
Exact mass: 5139.9564

Triply charged mass $[\text{M}]/3 - 1.00794$, calculated 1712.3109; observed 1712.3070.





LC Trace and Mass of 32



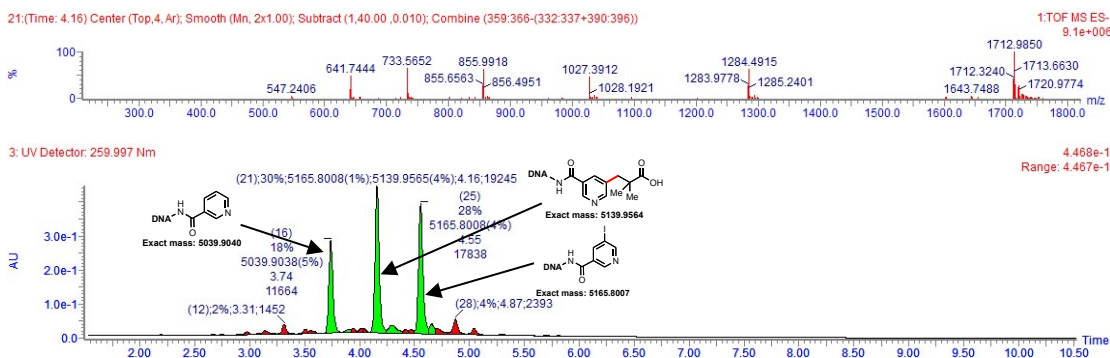
Following General Procedure 2 (Condition A) with **S16** and **A1** (1000 mM) except for employing Ag_2CO_3 instead of AgTFA .

$$\text{Yield: } \frac{30}{79} \times 100\% = 38\%$$

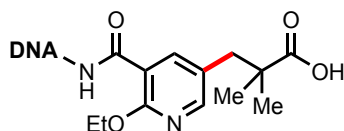
Ratio (product/deiodination/aryl iodide): 30/18/28

Exact mass: 5139.9564

Triply charged mass $[M]/3 - 1.00794$, calculated 1712.3109; observed 1712.3240.



LC Trace and Mass of 33



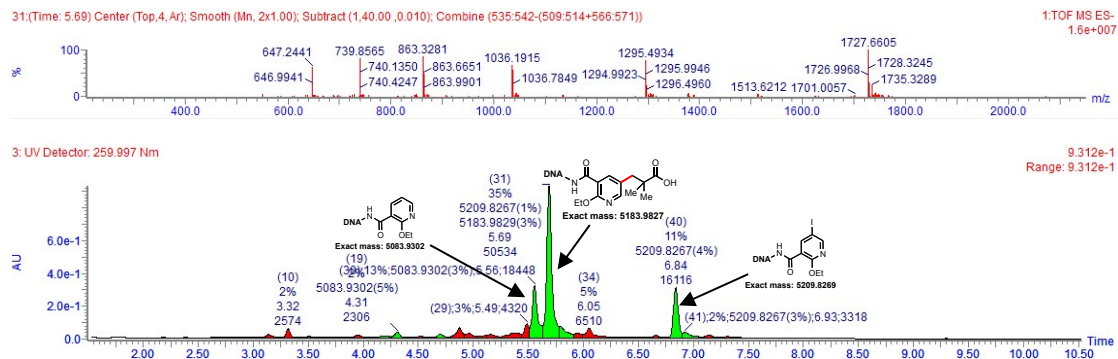
Following General Procedure 2 (Condition A) with **S17** and **A1** (1000 mM) except for employing Ag_2CO_3 instead of AgTFA .

$$\text{Yield: } \frac{35}{59} \times 100\% = 59\%$$

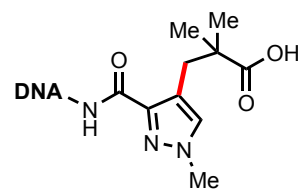
Ratio (product/deiodination/aryl iodide): 35/13/11

Exact mass: 5183.9827

Triply charged mass $[M]/3 - 1.00794$, calculated 1726.9863; observed 1726.9968.



LC Trace and Mass of 34



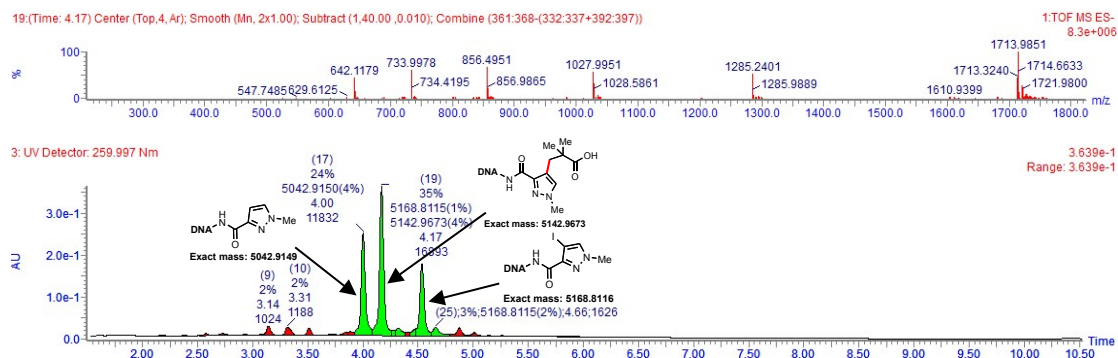
Following General Procedure 2 (Condition A) with **S19** and **A1** (1000 mM) except for employing Ag_2CO_3 instead of AgTFA .

$$\text{Yield: } \frac{35}{77} \times 100\% = 45\%$$

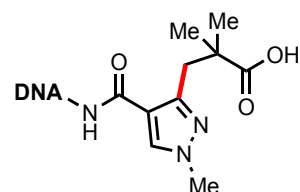
Ratio (product/deiodination/aryl iodide): 35/24/17

Exact mass: 5142.9673

Triply charged mass $[M]/3 - 1.00794$, calculated 1713.3145; observed 1713.3240.



LC Trace and Mass of 35



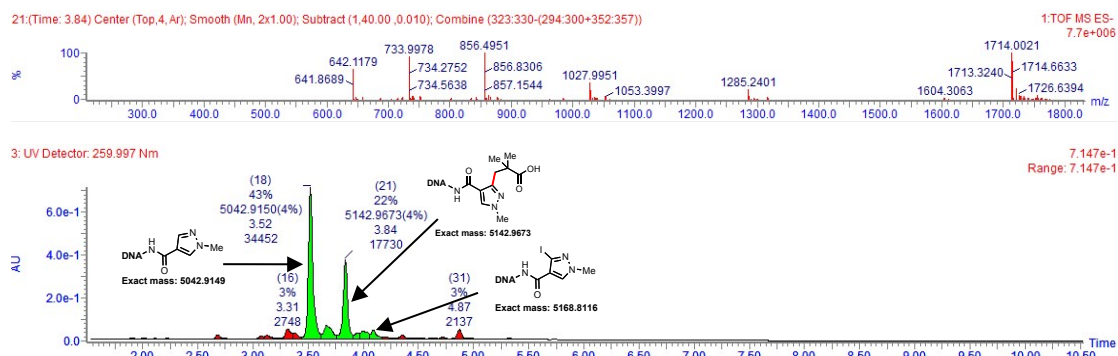
Following General Procedure 2 (Condition A) with **S20** and **A1** (1000 mM) except for employing Ag_2CO_3 instead of AgTFA .

$$\text{Yield: } \frac{22}{76} \times 100\% = 29\%$$

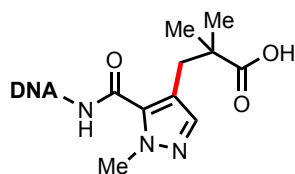
Ratio (product/deiodination/aryl iodide): 22/43/3

Exact mass: 5142.9673

Triply charged mass $[M]/3 - 1.00794$, calculated 1713.3145; observed 1713.3240.



LC Trace and Mass of 36



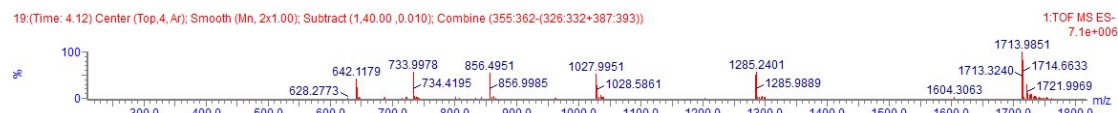
Following General Procedure 2 (Condition A) with **S21** and **A1** (1000 mM) except for employing Ag_2CO_3 instead of AgTFA .

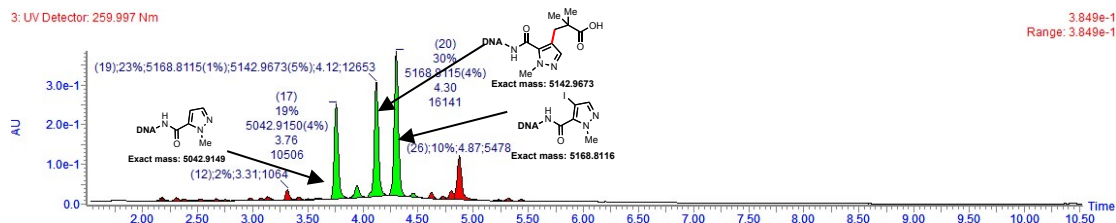
$$\text{Yield: } \frac{23}{69} \times 100\% = 33\%$$

Ratio (product/deiodination/aryl iodide): 23/19/30

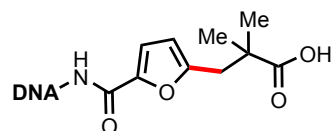
Exact mass: 5142.9673

Triply charged mass $[M]/3 - 1.00794$, calculated 1713.3145; observed 1713.3240.





LC Trace and Mass of 37



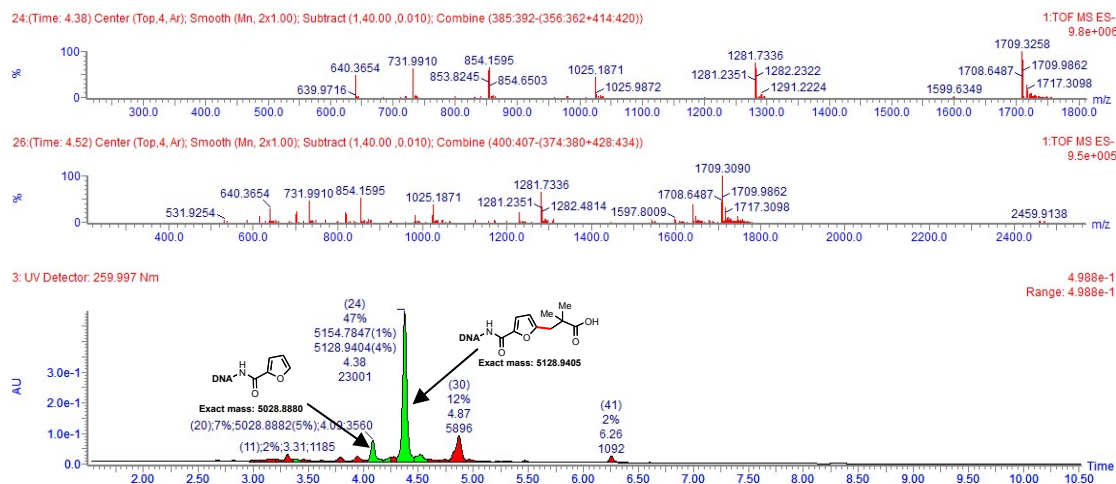
Following General Procedure 2 (Condition A) with **S22** and **A1** (1000 mM) except for employing Ag_2CO_3 instead of AgTFA .

$$\text{Yield: } \frac{51}{67} \times 100\% = 76\%$$

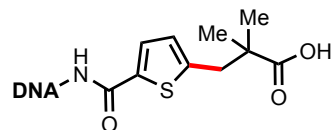
Ratio (product/deiodination/aryl iodide): 51/7/0

Exact mass: 5128.9405

Triply charged mass $[M]/3 - 1.00794$, calculated 1708.6389; observed 1708.6487.



LC Trace and Mass of 38



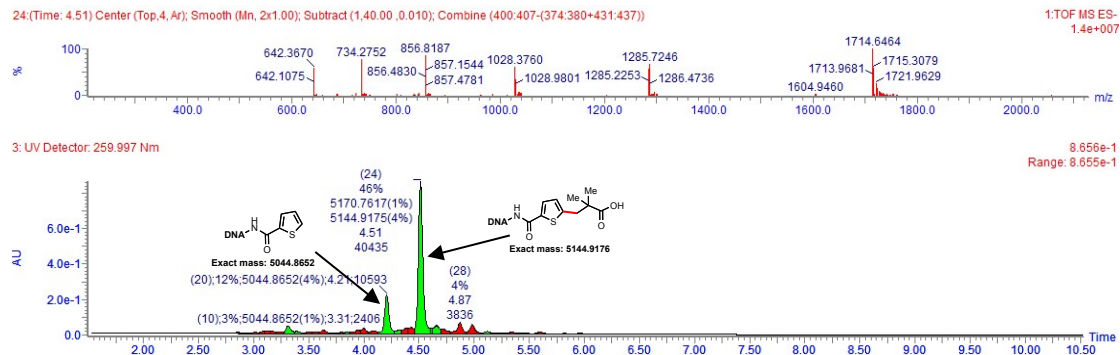
Following General Procedure 2 (Condition A) with **S23** and **A1** (1000 mM) except for employing Ag_2CO_3 instead of AgTFA .

$$\text{Yield: } \frac{46}{69} \times 100\% = 67\%$$

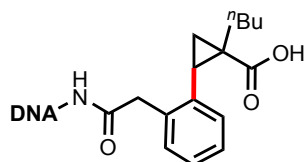
Ratio (product/deiodination/aryl iodide): 46/12/0

Exact mass: 5144.9176

Triply charged mass [M]/3 - 1.00794, calculated 1713.9646; observed 1713.9681.



LC Trace and Mass of 39



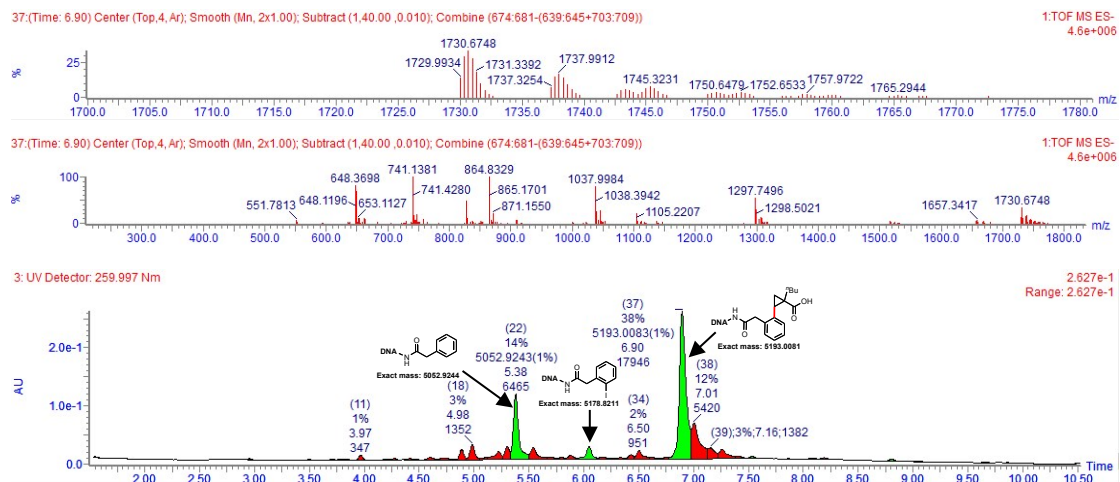
Following General Procedure 2 (Condition A) with **S2** and **A18**.

$$\text{Yield: } \frac{38}{83} \times 100\% = 46\%$$

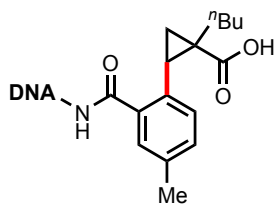
Ratio (product/deiodination/aryl iodide): 38/3/14

Exact mass: 5193.0081

Triply charged mass [M]/3 - 1.00794, calculated 1729.9948; observed 1729.9934.



LC Trace and Mass of 40



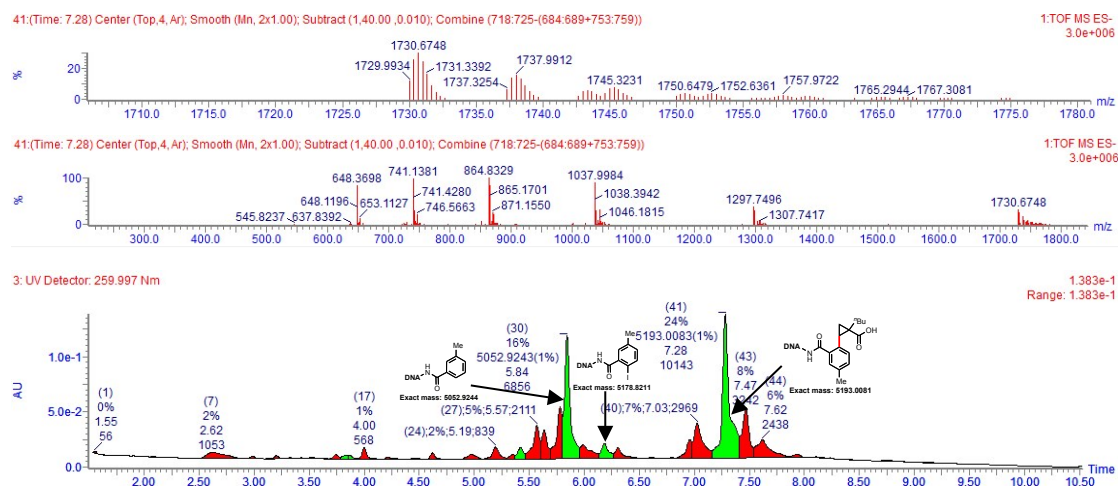
Following General Procedure 2 (Condition A) with **S5** and **A18**.

$$\text{Yield: } \frac{24}{69} \times 100\% = 35\%$$

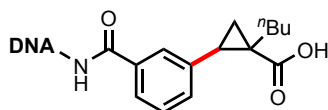
Ratio (product/deiodination/aryl iodide): 24/16/3

Exact mass: 5193.0081

Triply charged mass $[M]/3 - 1.00794$, calculated 1729.9948; observed 1729.9934.



LC Trace and Mass of 41



Following General Procedure 2 (Condition A) with **S7** and **A18**.

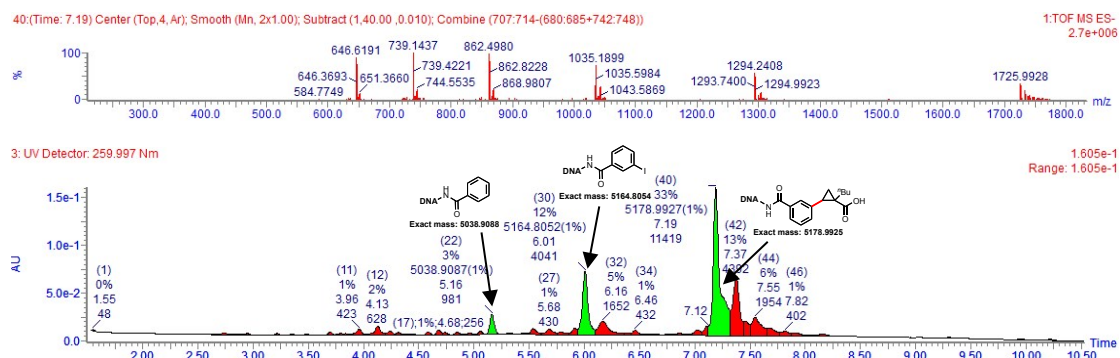
$$\text{Yield: } \frac{33}{83} \times 100\% = 40\%$$

Ratio (product/deiodination/aryl iodide): 33/3/12

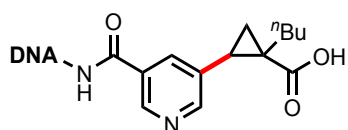
Exact mass: 5178.9925

Triply charged mass $[M]/3 - 1.00794$, calculated 1725.3229; observed 1725.3293.





LC Trace and Mass of 42



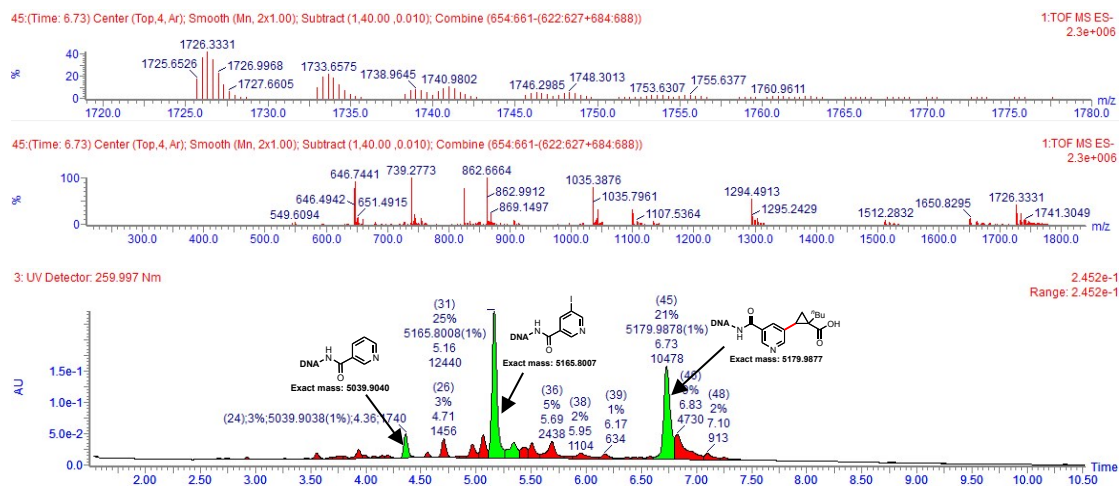
Following General Procedure 2 (Condition A) with **S16** and **A18**.

$$\text{Yield: } \frac{21}{79} \times 100\% = 27\%$$

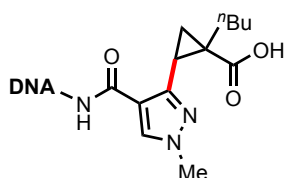
Ratio (product/deiodination/aryl iodide): 21/3/25

Exact mass: 5179.9877

Triply charged mass $[M]/3 - 1.00794$, calculated 1725.6546; observed 1725.6526.



LC Trace and Mass of 43



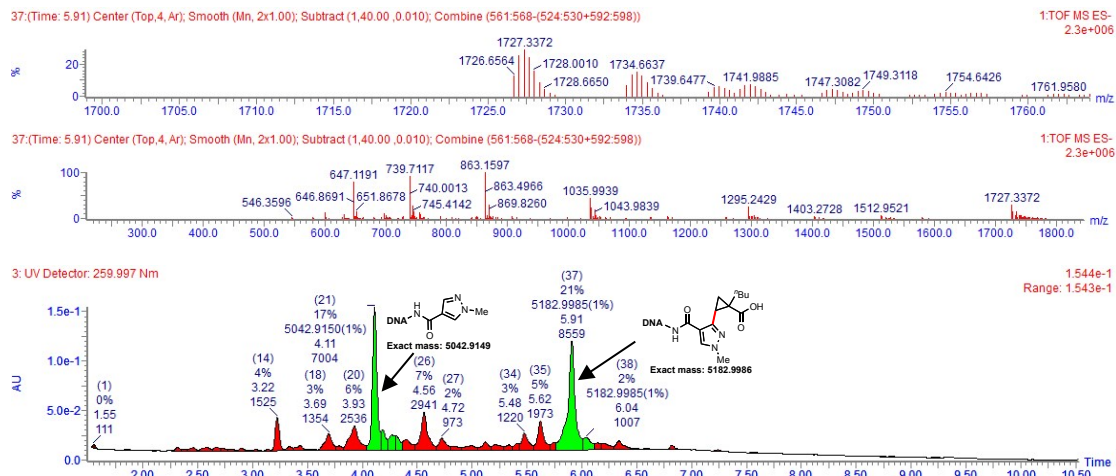
Following General Procedure 2 (Condition A) with **S20** and **A18**.

$$\text{Yield: } \frac{21}{76} \times 100\% = 28\%$$

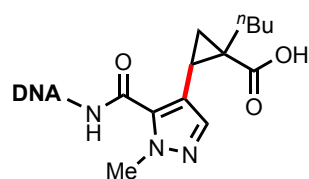
Ratio (product/deiodination/aryl iodide): 21/17/0

Exact mass: 5182.9986

Triply charged mass [M]/3 - 1.00794, calculated 1726.6583; observed 1726.6564.



LC Trace and Mass of 44



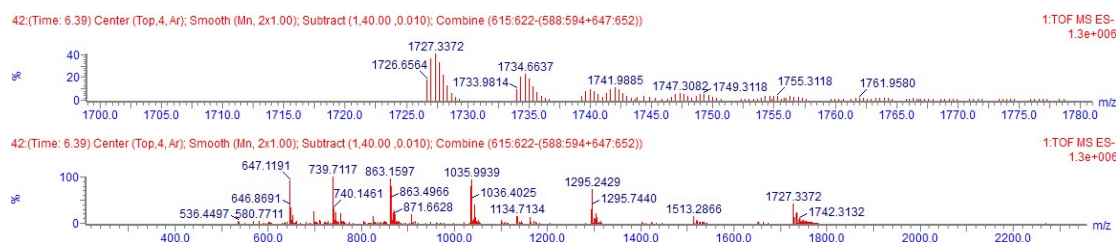
Following General Procedure 2 (Condition A) with **S21** and **A18**.

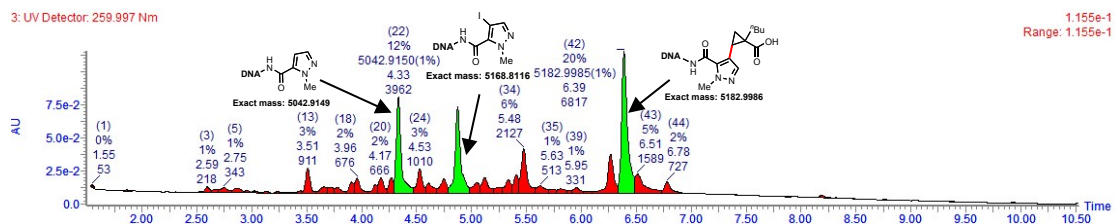
$$\text{Yield: } \frac{20}{69} \times 100\% = 29\%$$

Ratio (product/deiodination/aryl iodide): 20/12/11

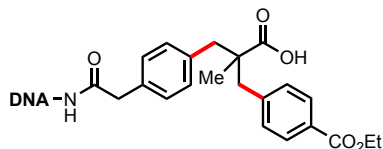
Exact mass: 5182.9986

Triply charged mass [M]/3 - 1.00794, calculated 1726.6583; observed 1726.6564.





LC Trace and Mass of 1'

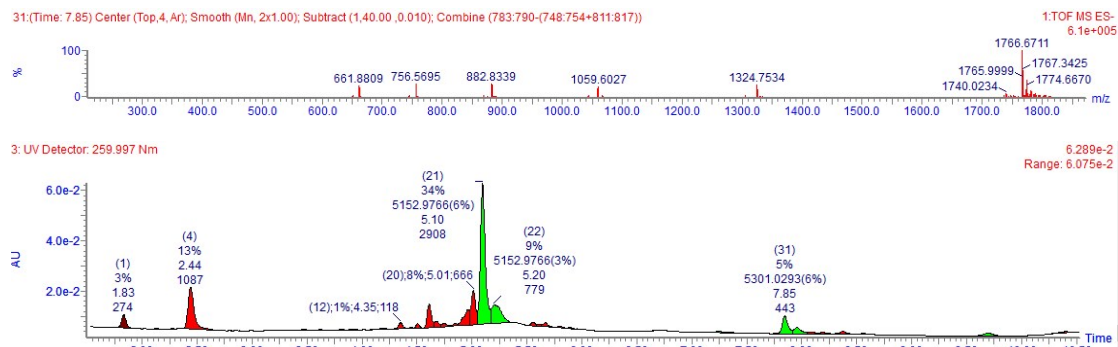


Following General Procedure 2 (Condition A) with **1** (5 nmol), Ethyl 4-iodobenzoate (300 equiv), Pd(OAc)₂ (20 equiv) and KOAc (300 equiv).

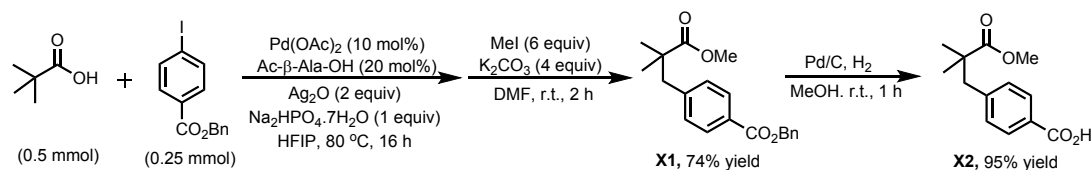
$$\text{Yield: } \frac{5}{66} \times 100\% = 8\%$$

Exact mass: 5301.0293

Triply charged mass [M]/3-1.00794, calculated 1766.0018; observed 1765.9999.

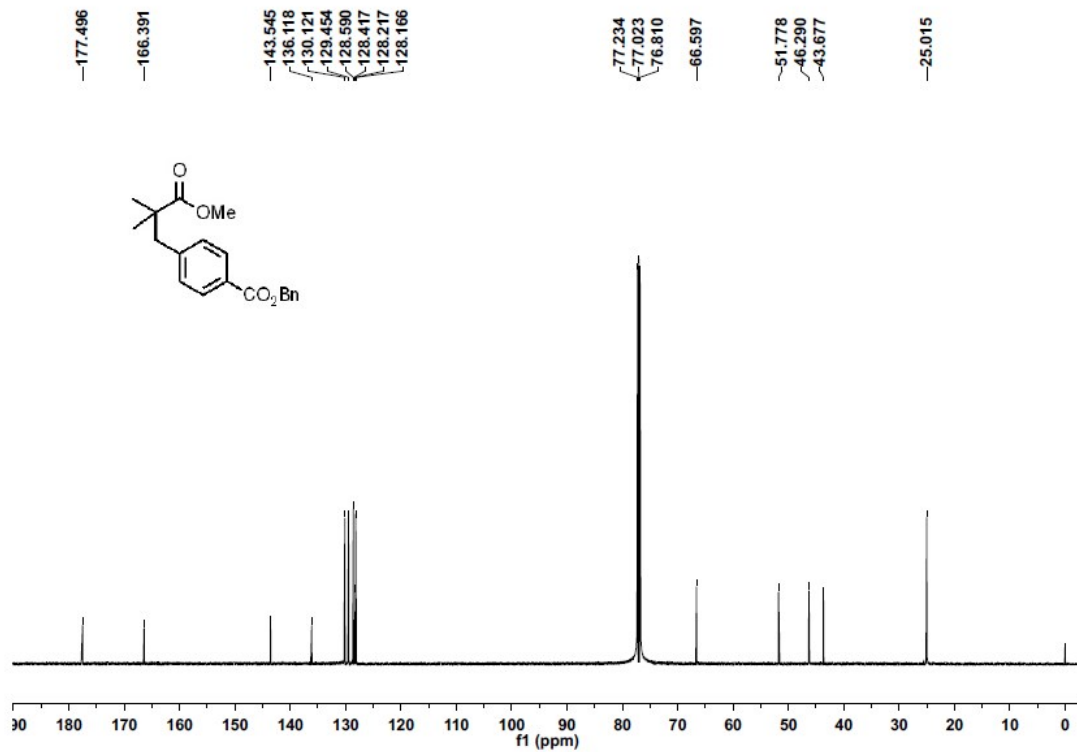
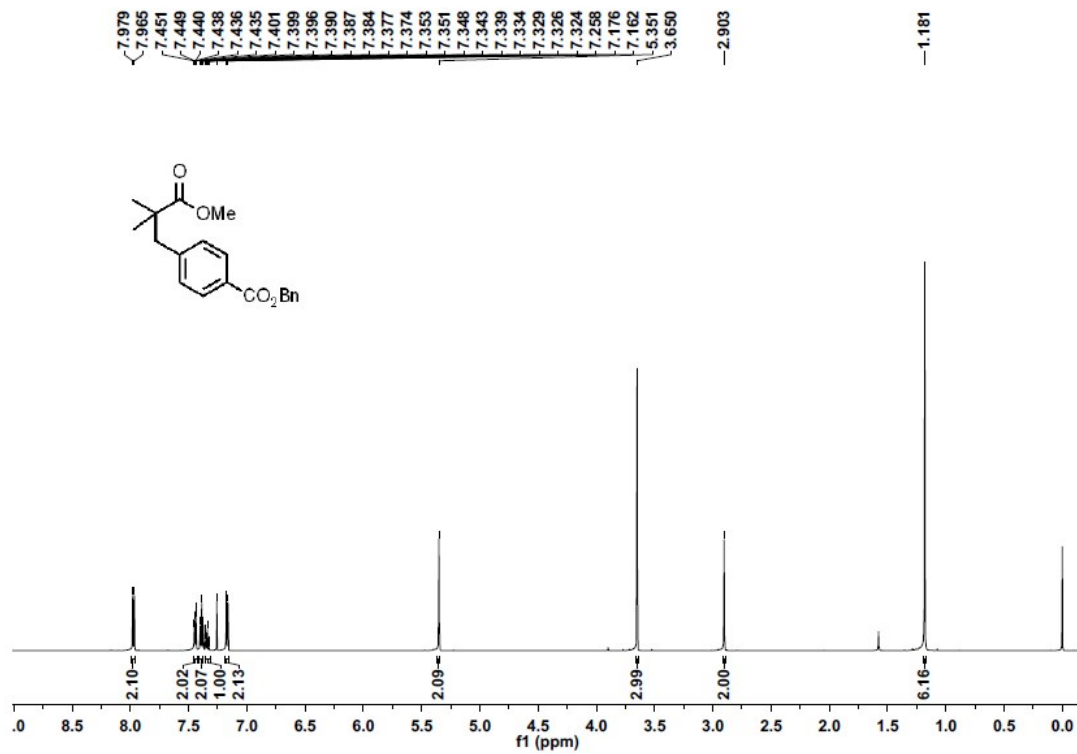


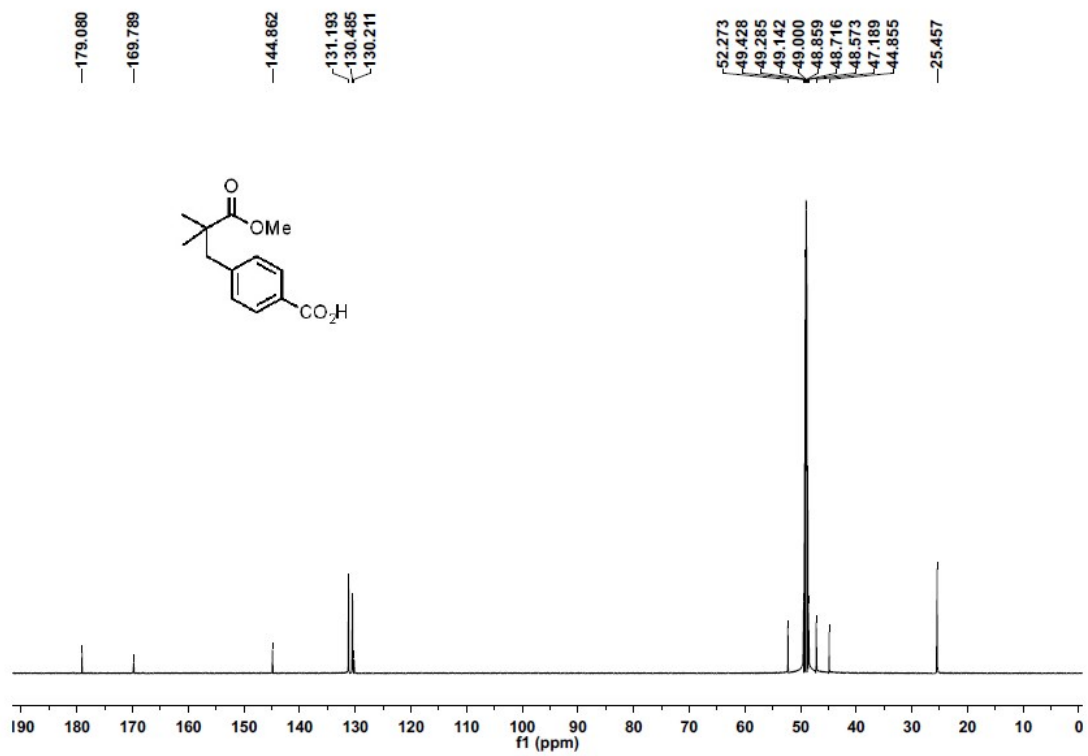
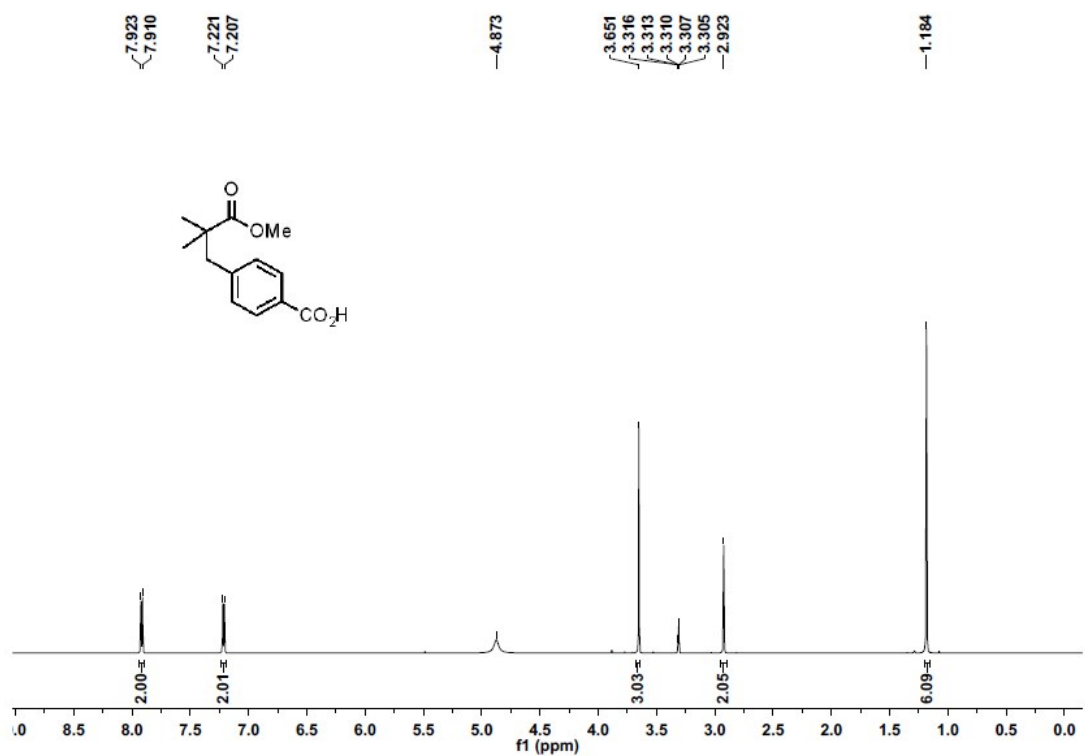
4.7 Off-DNA synthesis of 24

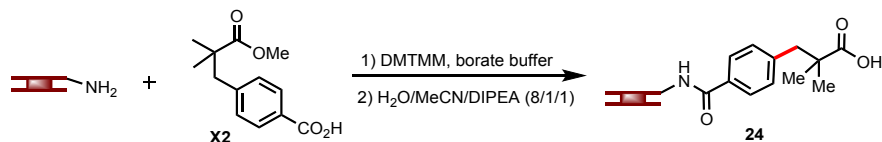


A 5 mL vial was charged with PivOH (51 mg, 0.5 mmol), benzyl 4-iodobenzoate (85 mg, 0.25 mmol), Pd(OAc)₂ (5.6 mg, 10 mol%), Ac-β-Ala-OH (6.5 mg, 20 mol%), Ag₂O (116 mg, 0.5 mmol), Na₂HPO₄·7H₂O (67 mg, 0.25 mmol) in HFIP (2 mL). The vial was heated at 80 °C for 16 h. After cooling to room temperature, the solvent was removed. The mixture was dissolved in trace of DCM and passed through a pad of silica gel with hexane/EA (1:1) as the eluent. The filtrate was concentrated and dissolved in DMF, K₂CO₃ (138 mg) and MeI (93 uL) were added. After 2 hours, water was added to the reaction solution and extracted with EA. The product **X1** was obtained through the purification on pTLC with hexane/EA (5:1). ¹H NMR (600 MHz, CDCl₃) δ 7.97 (d, *J* = 8.3 Hz, 2H), 7.45 – 7.43 (m, 2H), 7.41 – 7.37 (m, 2H), 7.36 – 7.31 (m, 1H), 7.17 (d, *J* = 8.3 Hz, 2H), 5.35 (s, 2H), 3.65 (s, 3H), 2.90 (s, 2H), 1.18 (s, 6H); ¹³C NMR (151 MHz, CDCl₃) δ 177.50, 166.39, 143.55, 136.12, 130.12, 129.45, 128.59, 128.42, 128.22, 128.17, 66.60, 51.78, 46.29, 43.68, 25.01.

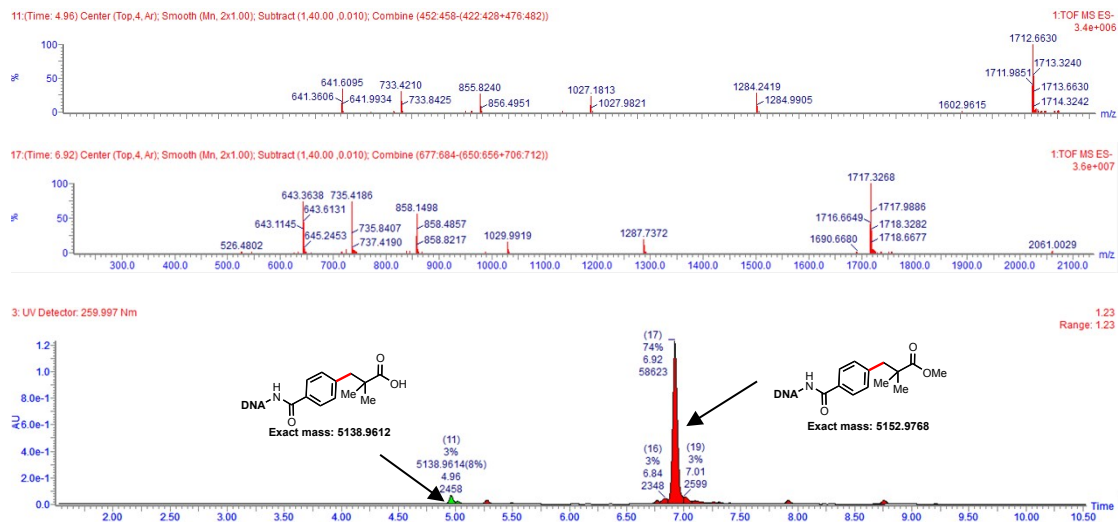
To a solution of **X1** (60 mg) in MeOH (4 mL) was added Pd/C (12 mg). The flask was evacuated briefly under high vacuum and charged with a H₂ balloon. The reaction solution was stirred for 1 h. The solution was passed through a pad of Celite and the filtrate was concentrated. Product **X2** was obtained as a white solid. ¹H NMR (600 MHz, CD₃OD) δ 7.92 (d, *J* = 8.3 Hz, 2H), 7.21 (d, *J* = 8.3 Hz, 2H), 3.65 (s, 3H), 2.92 (s, 2H), 1.18 (s, 6H); ¹³C NMR (151 MHz, CD₃OD) δ 179.08, 169.79, 144.86, 131.19, 130.48, 130.21, 52.27, 47.19, 44.86, 25.46.



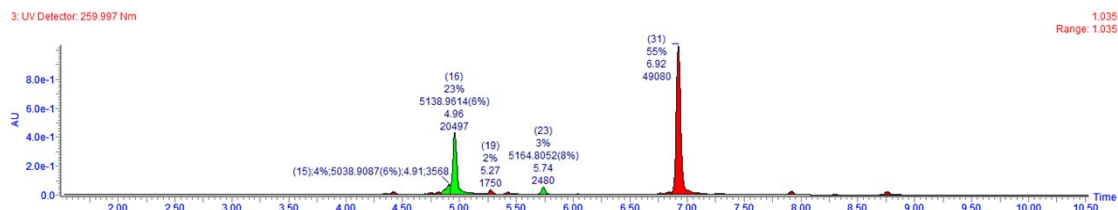




Following General Procedure 1.

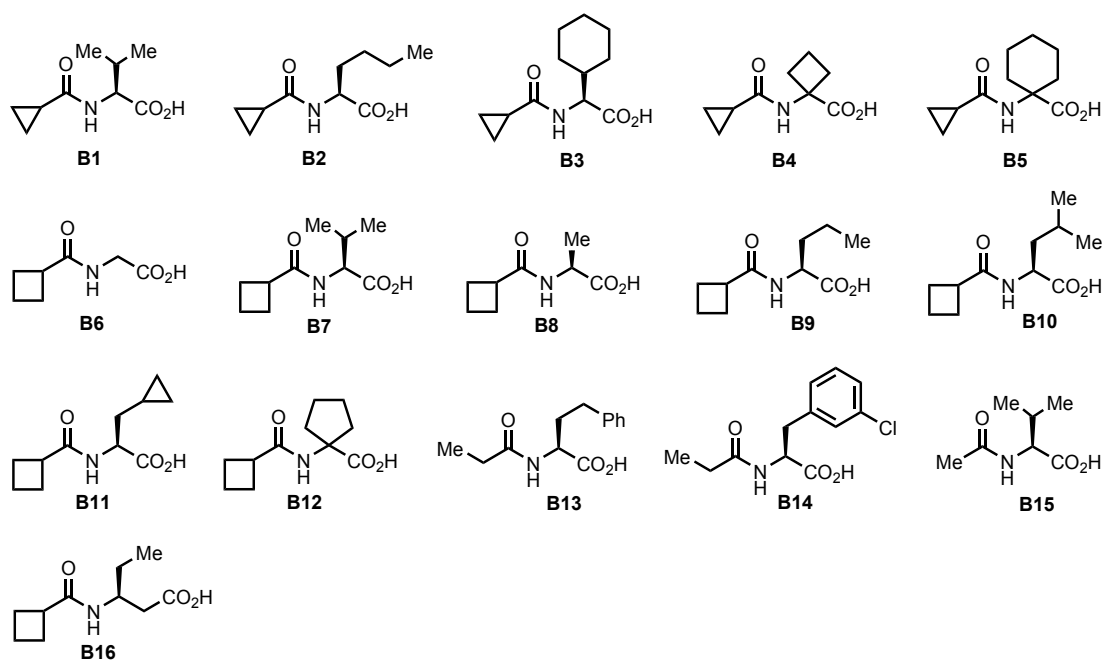


LC trace mixture of 24 through on-DNA and off-DNA synthesis



5. Experimental Section for on-DNA C-H Arylation of Amides

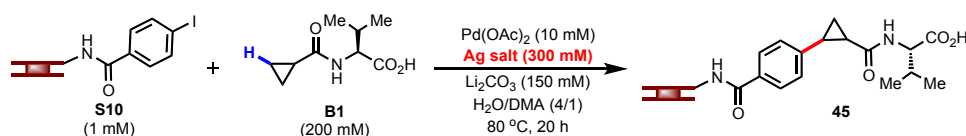
5.1 Substrate Structures of Amides B1-B16



Amides were obtained from the commercial sources or synthesized following the literature procedures.⁵

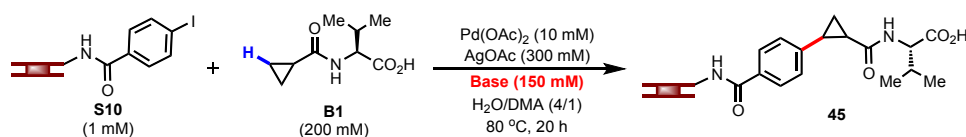
5.2 Condition Optimizations

Table S7. Evaluation of Ag salt



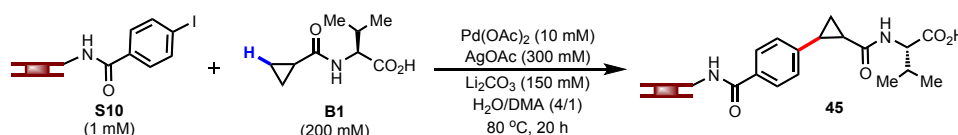
Entry	Ag salt (300 mM)	Yield (%)
1	AgOAc	69
2	AgNO ₃	12
3	AgTFA	46
4	Ag ₂ CO ₃	42
5	AgOTs	35

Table S8. Evaluation of Base



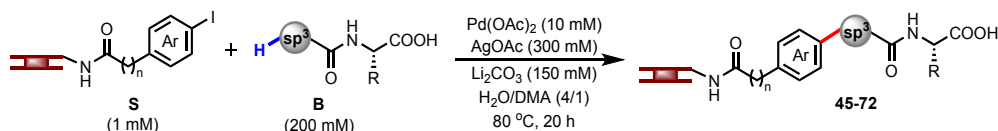
Entry	Base (150 mM)	Yield (%)
1	NaOAc	46
2	Na ₂ CO ₃	55
3	K ₂ CO ₃	41
4	K ₃ PO ₄	31
5	K ₂ HPO ₄ •3H ₂ O	18
6	Li₂CO₃	69
7	Cs ₂ CO ₃	41

Table S9. Evaluation of Standard Conditions



Entry	Deviation from above	Yield (%)
1	none	69
2	without Pd(OAc) ₂	0
3	without AgOAc	24
4	without Li ₂ CO ₃	35
5	r.t. instead of 80 °C	60

5.3 General Procedure 3 for on-DNA C-H Arylation of Amides



Materials

DNA-conjugated aryl iodide **S**: 10 mM in H₂O

Amide **B**: 2 M in DMA

Pd(OAc)₂: 200 mM in HFIP

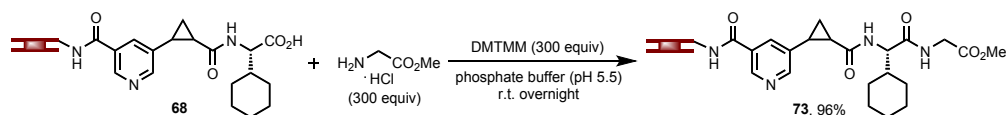
Sodium diethyldithiocarbamate trihydrate (scavenger): 1 M in H₂O

Procedure

1) To a 200 μ L microcentrifuge tube was added Pd(OAc)₂ (10 equiv, 0.5 μ L), after air-dry, AgOAc (300 equiv, 0.5 mg), amide **B** (200 equiv, 1 μ L), DNA-conjugated aryl iodide **S** (10 nmol, 1 μ L), Li₂CO₃ (150 equiv, 0.11 mg), DMA (1 μ L) and deionized water (7 μ L) were added. The mixture was vortexed. Heating the reaction mixture at 80 °C for 20 h.

- 2) Cooling to room temperature, 9.0 μL scavenger was added and reheating the mixture at 80 $^{\circ}\text{C}$ for 30 min.
- 3) Cooling to room temperature, 5 M NaCl solution (10 % by volume, 1.9 μL) and cold ethanol (2.5 times by volume, 47.5 μL). The mixture was stored at a -20 $^{\circ}\text{C}$ freezer for more than 30 minutes.
- 4) Centrifuge the sample for around 10 minutes in a microcentrifuge at 10000 rpm. The above supernatant was discarded and the precipitate was dried under vacuum. The DNA pellet was redissolved in H_2O (100 μL) and centrifuged for around 2 minutes in a microcentrifuge at 10000 rpm. An aliquot (50 μL) was taken and analyzed via HPLC-MS.

5.4 General Procedure 4 for Synthesis of Dipeptides



Materials

68: ca. 5 mM in H_2O

Glycine methyl ester hydrochloride: 1 M in H_2O

DMTMM: 1 M in H_2O

pH 5.5 phosphate buffer: 0.2 M NaH_2PO_4 in H_2O

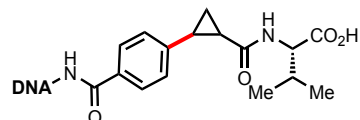
Procedure

- 1) To 2 μL **68** solution was added 22 μL pH 5.5 phosphate buffer, glycine methyl ester hydrochloride (300 equiv, 3 μL) and DMTMM (300 equiv, 3 μL). The mixture was vortexed. Being kept at room temperature for overnight.
- 2) Add 5 M NaCl solution (10 % by volume) and cold ethanol (2.5 times by volume, ethanol stored at -20 $^{\circ}\text{C}$). The mixture was stored at a -20 $^{\circ}\text{C}$ freezer for 1 hour.
- 3) Centrifuge the sample for around 10 minutes in a microcentrifuge at 10000 rpm. The above supernatant was discarded and the precipitate was dried under vacuum. The DNA pellet was redissolved in H_2O (100 μL) and centrifuged for around 2 minutes in a microcentrifuge at 10000 rpm. An aliquot (50 μL) was taken and

analyzed via HPLC-MS.

5.5 LC Trace and Mass Characterization of 45-73

LC Trace and Mass of 45



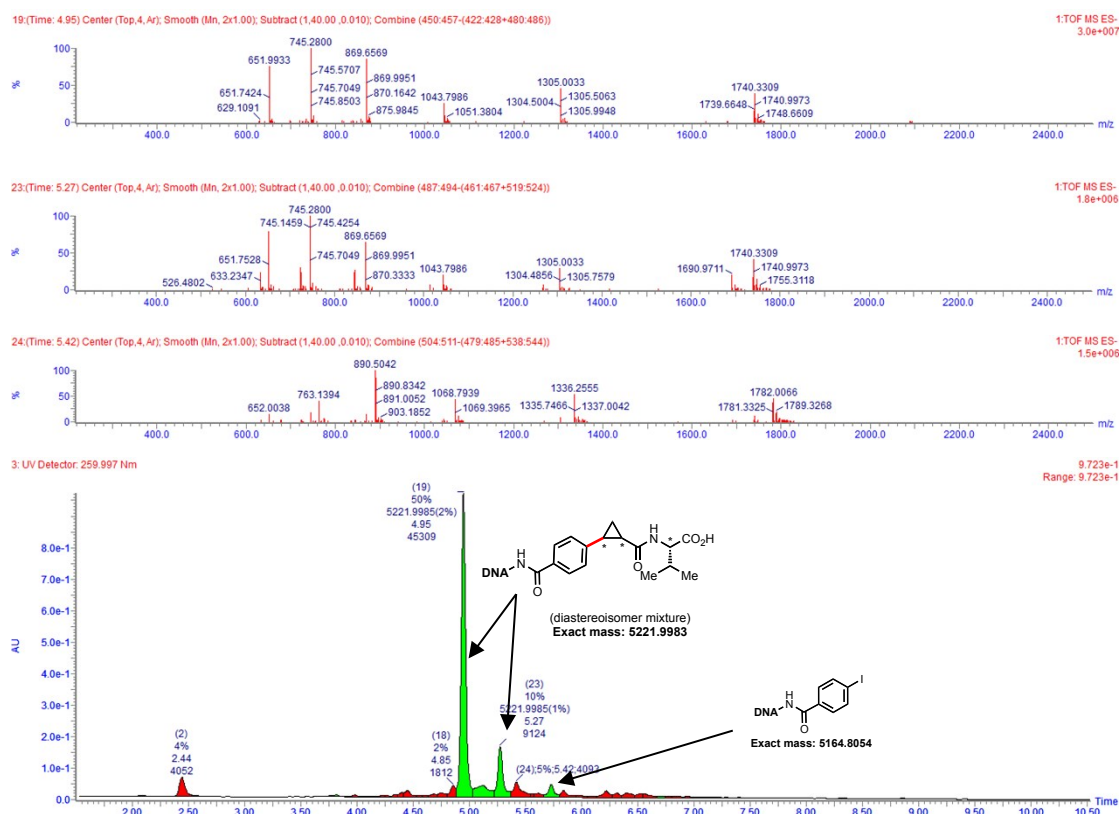
Following General Procedure 3 with **B1**.

$$\text{Yield: } \frac{59}{85} \times 100\% = 69\%$$

Ratio (product/deiodination/aryl iodide): 59/0/3

Exact mass: 5221.9983

Triply charged mass $[M]/3 - 1.00794$, calculated 1739.6582; observed 1739.6648.



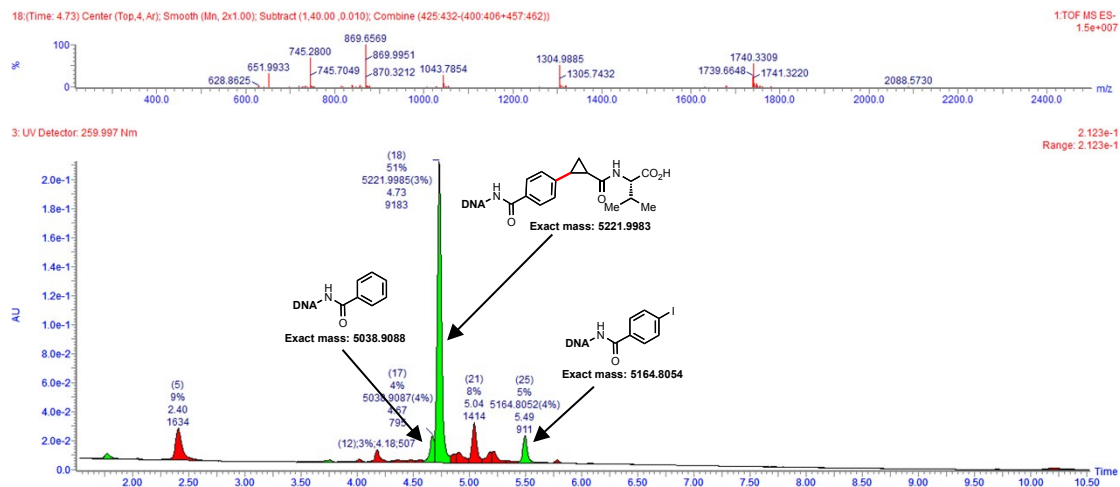
Following General Procedure 3 with **B1** except for running reaction and quenching with scavenger at room temperature.

$$\text{Yield: } \frac{51}{85} \times 100\% = 60\%$$

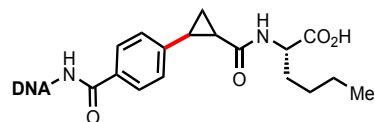
Ratio (product/deiodination/aryl iodide): 51/4/5

Exact mass: 5221.9983

Triply charged mass $[M]/3 - 1.00794$, calculated 1739.6582; observed 1739.6648.



LC Trace and Mass of 46



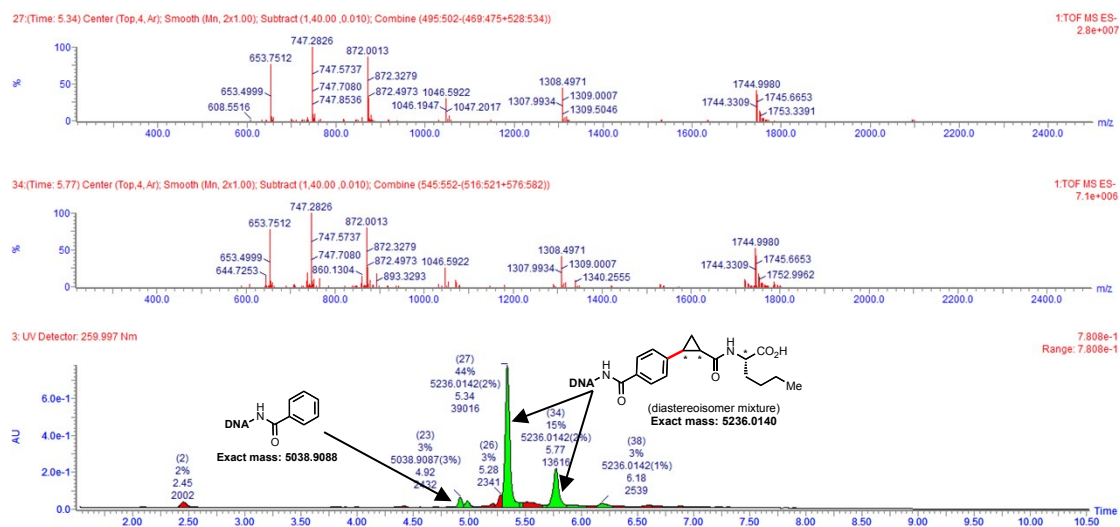
Following General Procedure 3 with **B2**.

$$\text{Yield: } \frac{56}{85} \times 100\% = 66\%$$

Ratio (product/deiodination/aryl iodide): 56/3/0

Exact mass: 5236.0140

Triply charged mass $[M]/3 - 1.00794$, calculated 1744.3301; observed 1744.3309.



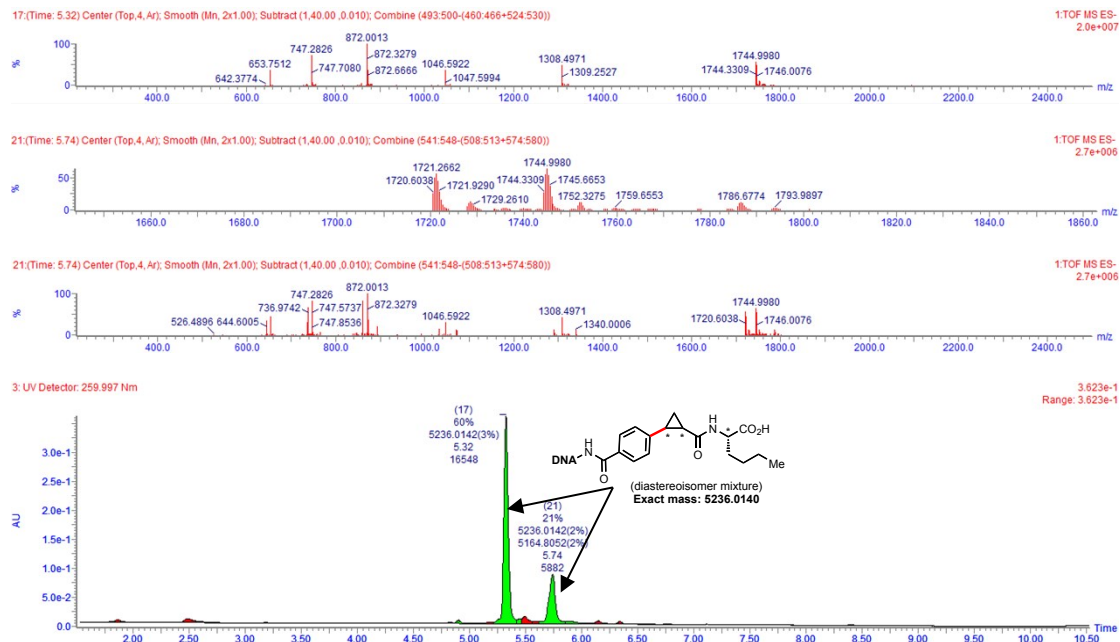
Following General Procedure 3 with **B2** except for running reaction and quenching with scavenger at room temperature.

Yield: $\frac{71}{85} \times 100\% = 84\%$

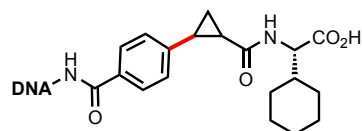
Ratio (product/deiodination/aryl iodide): 71/1/10

Exact mass: 5236.0140

Triply charged mass [M]/3 - 1.00794, calculated 1744.3301; observed 1744.3309.



LC Trace and Mass of 47



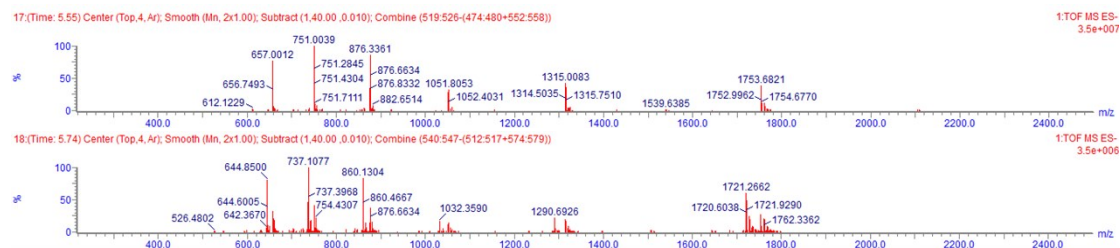
Following General Procedure 3 with **B3**.

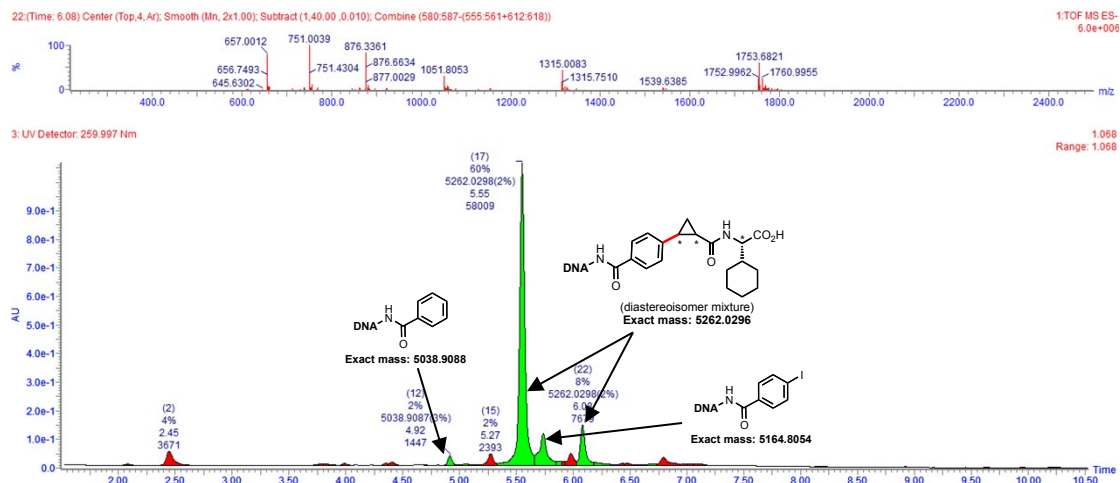
Yield: $\frac{72}{85} \times 100\% = 85\%$

Ratio (product/deiodination/aryl iodide): 72/2/6

Exact mass: 5262.0296

Triply charged mass [M]/3 - 1.00794, calculated 1753.0019; observed 1752.9962.





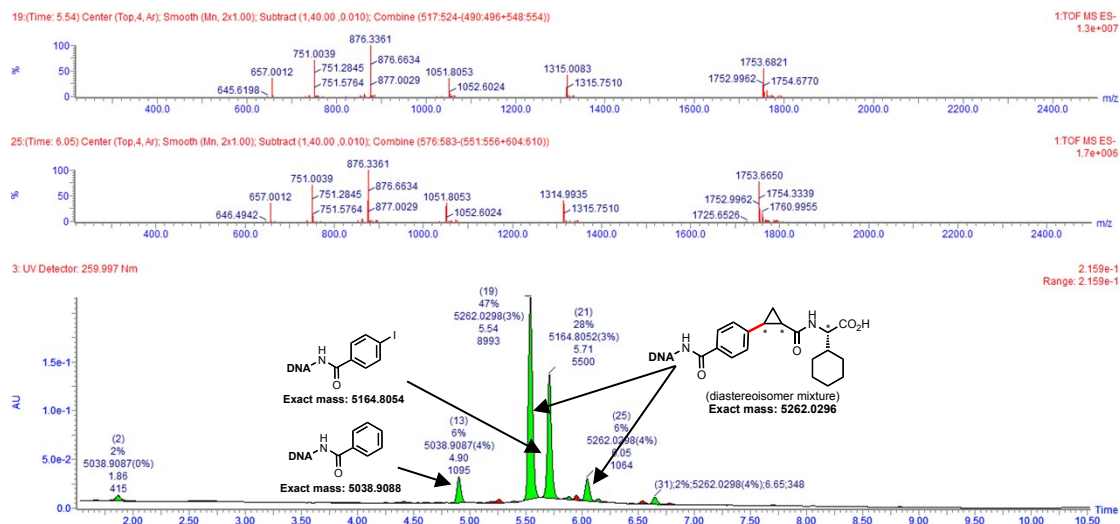
Following General Procedure 3 with **B3** except for running reaction and quenching with scavenger at room temperature.

$$\text{Yield: } \frac{53}{85} \times 100\% = 62\%$$

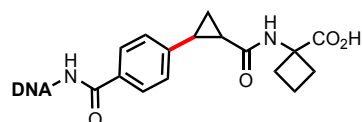
Ratio (product/deiodination/aryl iodide): 53/6/28

Exact mass: 5262.0296

Triply charged mass [M]/3 - 1.00794, calculated 1753.0019; observed 1752.9962.



LC Trace and Mass of 48



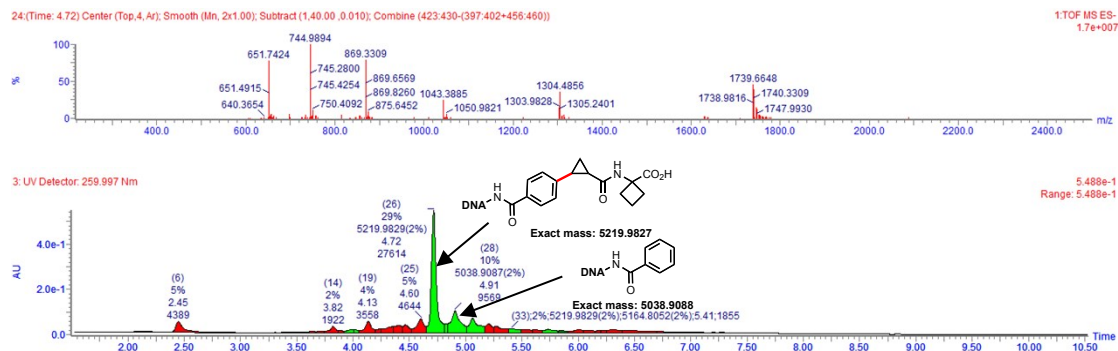
Following General Procedure 3 with **B4**.

$$\text{Yield: } \frac{29}{85} \times 100\% = 34\%$$

Ratio (product/deiodination/aryl iodide): 29/10/0

Exact mass: 5219.9827

Triply charged mass [M]/3 - 1.00794, calculated 1738.9863; observed 1738.9816.



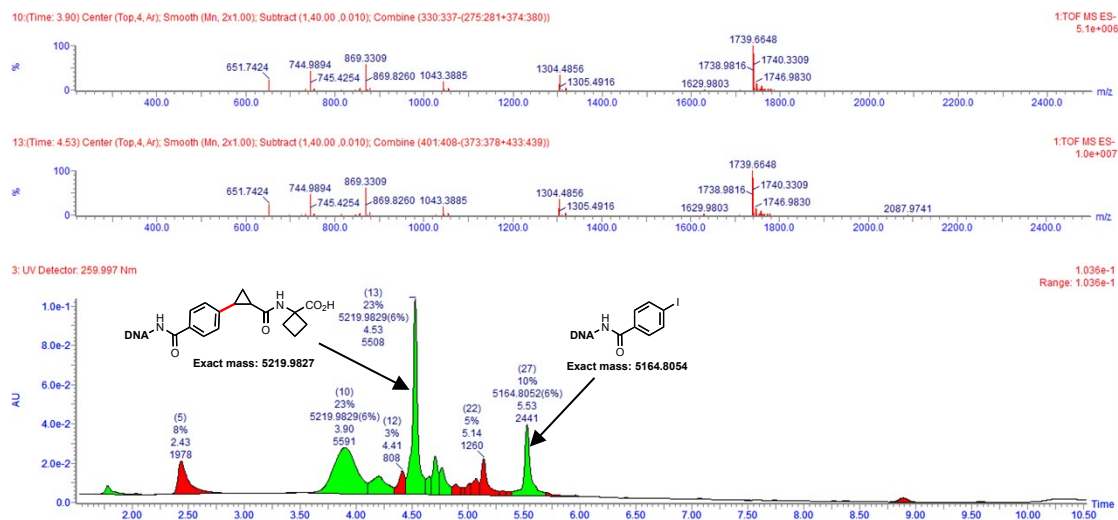
Following General Procedure 3 with **B4** except for running reaction and quenching with scavenger at room temperature.

$$\text{Yield: } \frac{23}{85} \times 100\% = 27\%$$

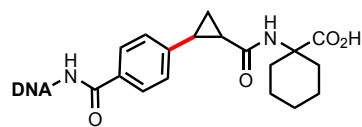
Ratio (product/deiodination/aryl iodide): 23/4/10

Exact mass: 5219.9827

Triply charged mass [M]/3 - 1.00794, calculated 1738.9863; observed 1738.9816.



LC Trace and Mass of 49



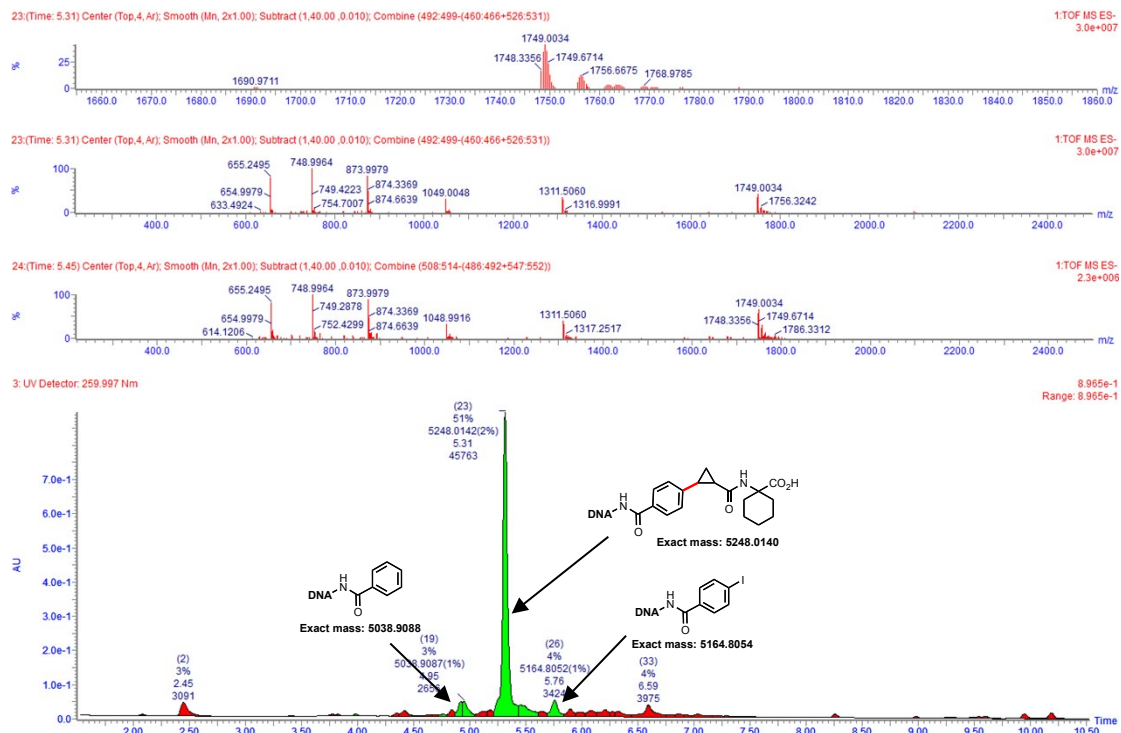
Following General Procedure 3 with **B5**.

$$\text{Yield: } \frac{56}{85} \times 100\% = 66\%$$

Ratio (product/deiodination/aryl iodide): 56/3/4

Exact mass: 5248.0140

Triply charged mass [M]³⁻ - 1.00794, calculated 1748.3301; observed 1748.3356.



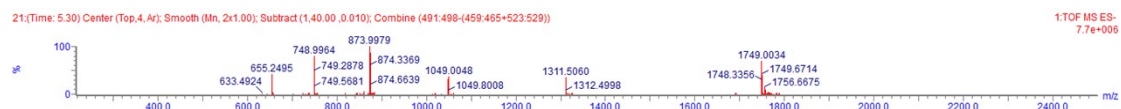
Following General Procedure 3 with **B5** except for running reaction and quenching with scavenger at room temperature.

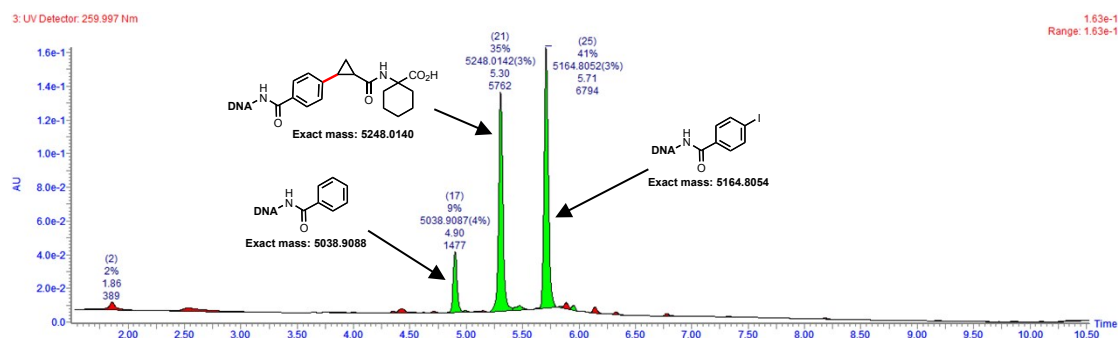
$$\text{Yield: } \frac{35}{85} \times 100\% = 41\%$$

Ratio (product/deiodination/aryl iodide): 35/9/41

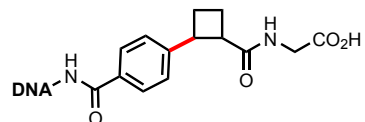
Exact mass: 5248.0140

Triply charged mass [M]³⁻ - 1.00794, calculated 1748.3301; observed 1748.3356.





LC Trace and Mass of 50



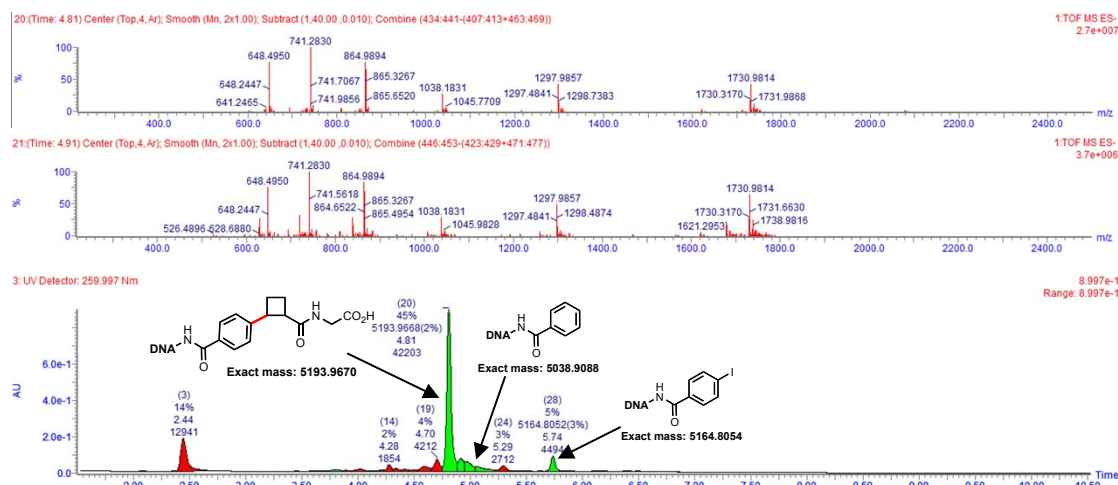
Following General Procedure 3 with **B6**.

$$\text{Yield: } \frac{48}{85} \times 100\% = 56\%$$

Ratio (product/deiodination/aryl iodide): 48/6/5

Exact mass: 5193.9670

Triply charged mass $[M]/3 - 1.00794$, calculated 1730.3144; observed 1730.3170.



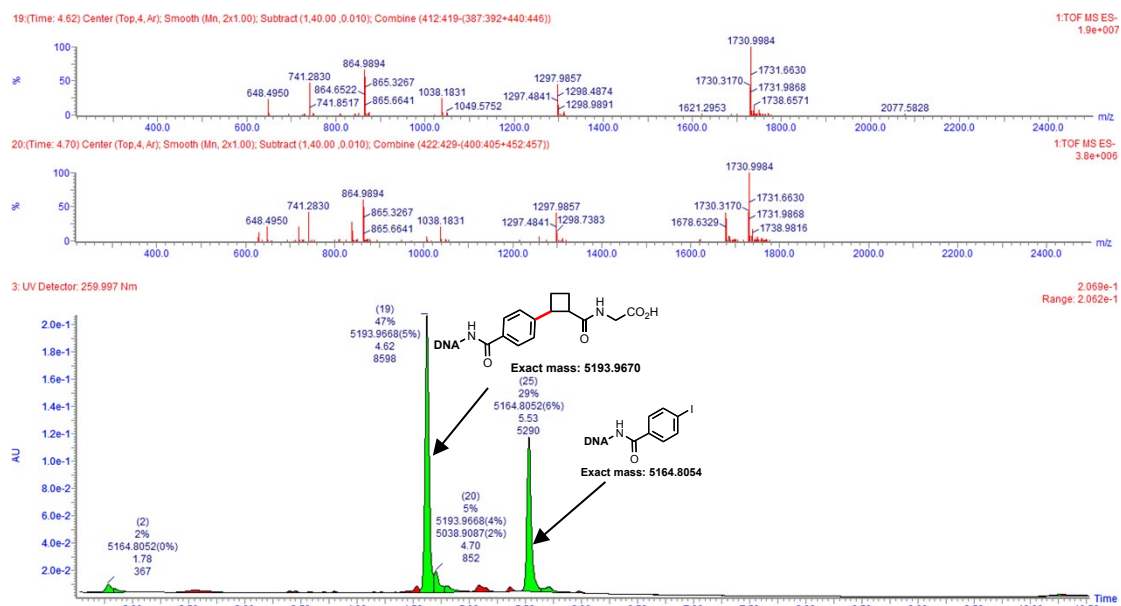
Following General Procedure 3 with **B6** except for running reaction and quenching with scavenger at room temperature.

$$\text{Yield: } \frac{51}{85} \times 100\% = 60\%$$

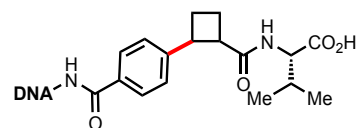
Ratio (product/deiodination/aryl iodide): 51/1/29

Exact mass: 5193.9670

Triply charged mass $[M]/3 - 1.00794$, calculated 1730.3144; observed 1730.3170.



LC Trace and Mass of 51



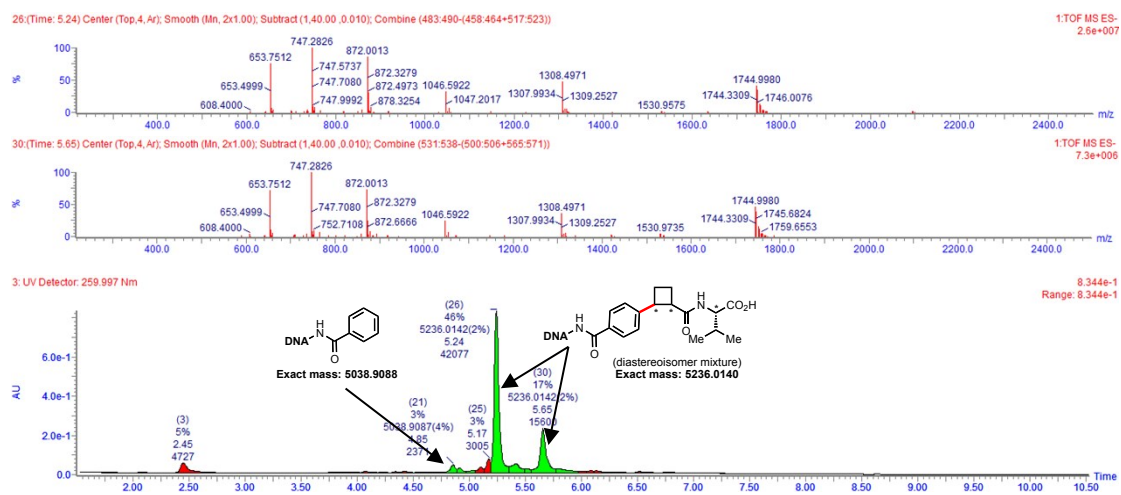
Following General Procedure 3 with **B7**.

$$\text{Yield: } \frac{63}{85} \times 100\% = 74\%$$

Ratio (product/deiodination/aryl iodide): 63/3/0

Exact mass: 5236.0140

Triply charged mass $[M]/3 - 1.00794$, calculated 1744.3301; observed 1744.3309.



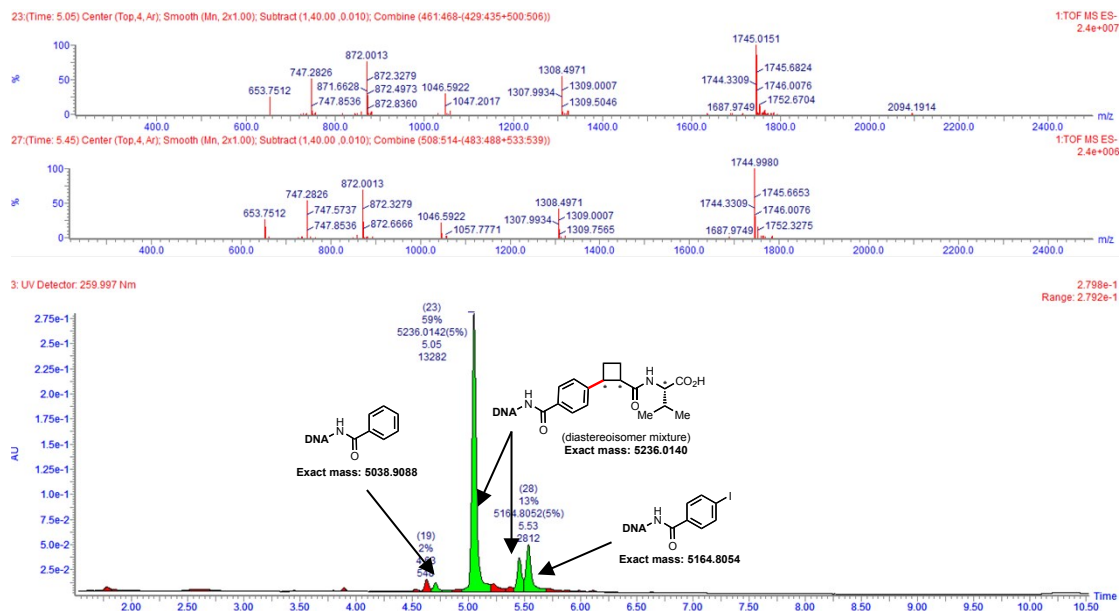
Following General Procedure 3 with **B7** except for running reaction and quenching with scavenger at room temperature.

$$\text{Yield: } \frac{66}{85} \times 100\% = 78\%$$

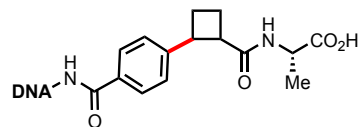
Ratio (product/deiodination/aryl iodide): 66/2/13

Exact mass: 5236.0140

Triply charged mass [M]/3 - 1.00794, calculated 1744.3301; observed 1744.3309.



LC Trace and Mass of 52



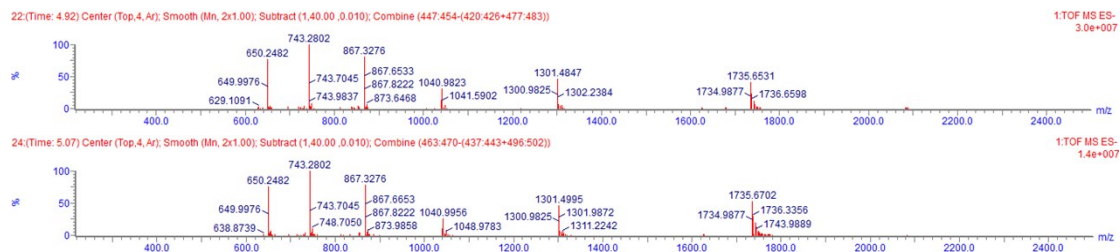
Following General Procedure 3 with **B8**.

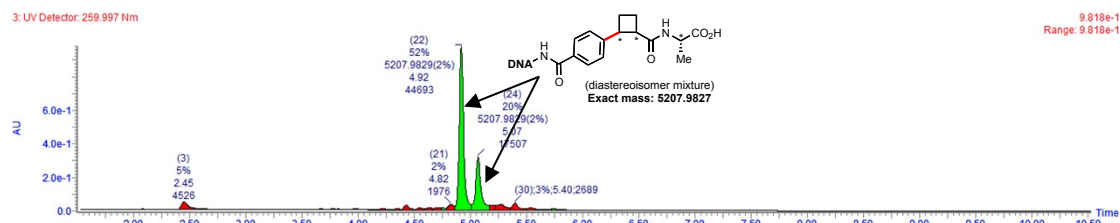
$$\text{Yield: } \frac{72}{85} \times 100\% = 85\%$$

Ratio (product/deiodination/aryl iodide): 72/0/0

Exact mass: 5207.9827

Triply charged mass [M]/3 - 1.00794, calculated 1734.9863; observed 1734.9877.





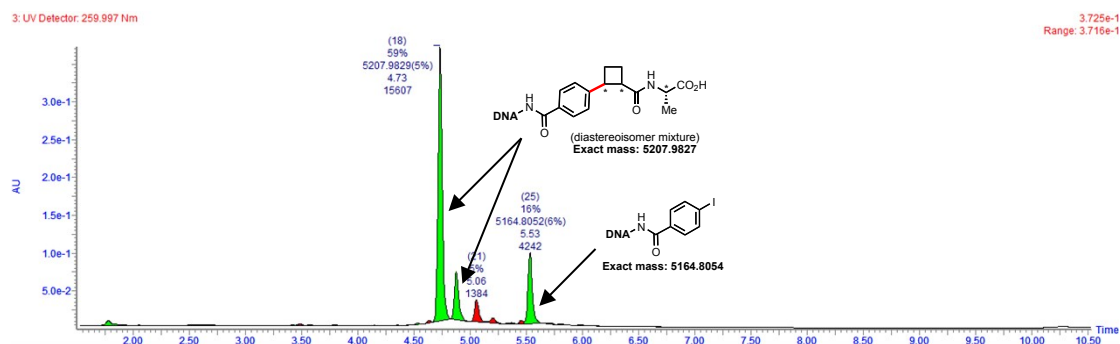
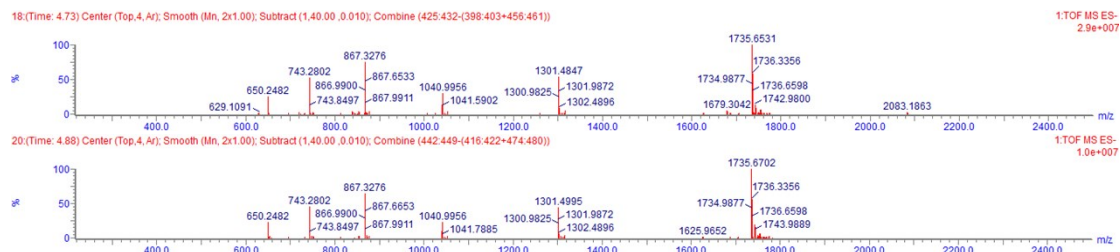
Following General Procedure 3 with **B8** except for running reaction and quenching with scavenger at room temperature.

$$\text{Yield: } \frac{70}{85} \times 100\% = 82\%$$

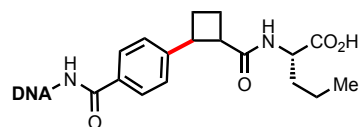
Ratio (product/deiodination/aryl iodide): 70/0/16

Exact mass: 5207.9827

Triply charged mass $[M]/3 - 1.00794$, calculated 1734.9863; observed 1734.9877.



LC Trace and Mass of 53



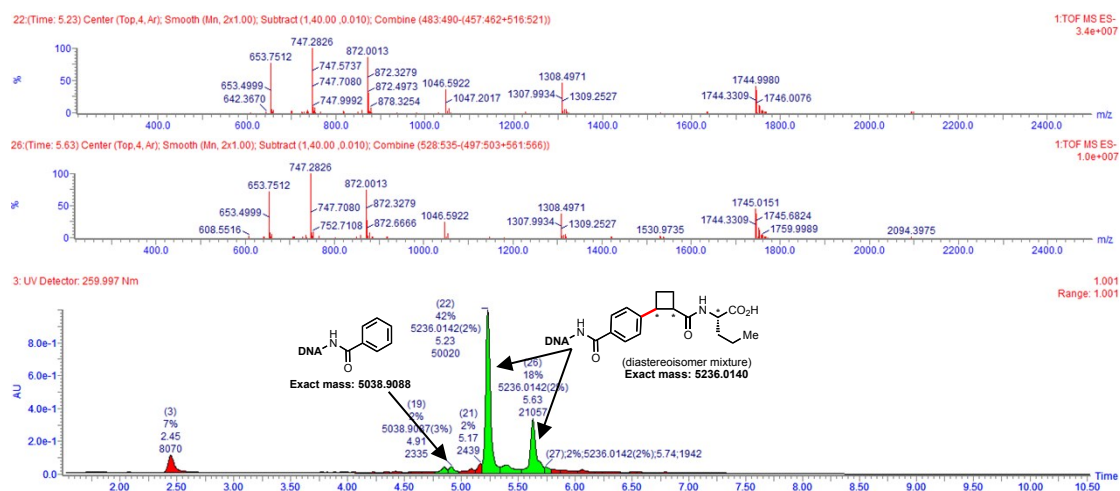
Following General Procedure 3 with **B9**.

$$\text{Yield: } \frac{60}{85} \times 100\% = 71\%$$

Ratio (product/deiodination/aryl iodide): 60/2/0

Exact mass: 5236.0140

Triply charged mass $[M]/3 - 1.00794$, calculated 1744.3301; observed 1744.3309.



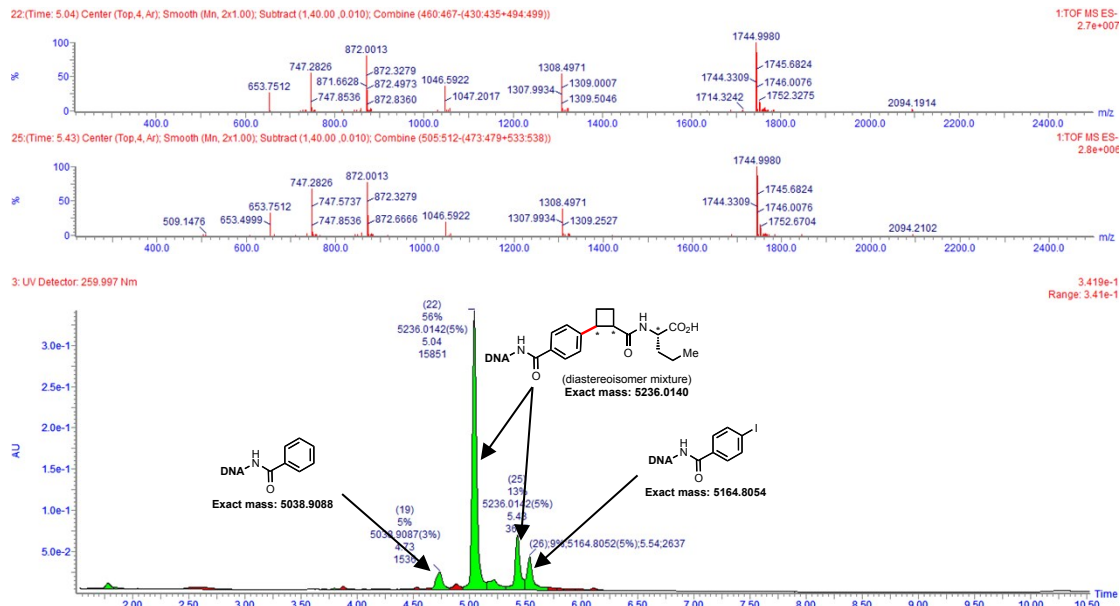
Following General Procedure 3 with **B9** except for running reaction and quenching with scavenger at room temperature.

$$\text{Yield: } \frac{69}{85} \times 100\% = 81\%$$

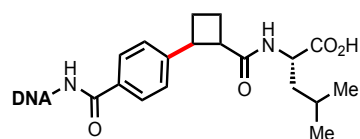
Ratio (product/deiodination/aryl iodide): 69/5/9

Exact mass: 5236.0140

Triply charged mass [M]/3 - 1.00794, calculated 1744.3301; observed 1744.3309.



LC Trace and Mass of 54



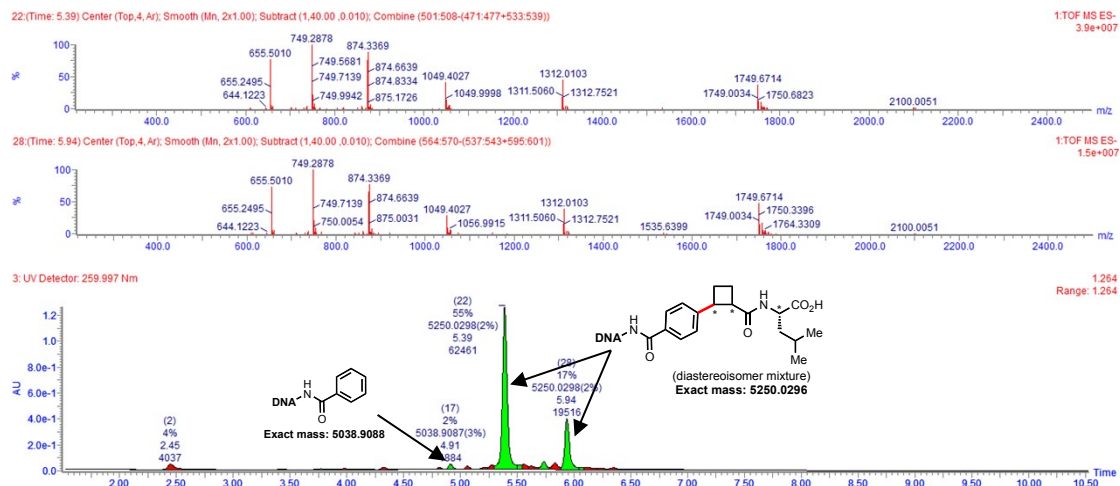
Following General Procedure 3 with **B10**.

$$\text{Yield: } \frac{72}{85} \times 100\% = 85\%$$

Ratio (product/deiodination/aryl iodide): 72/2/3

Exact mass: 5250.0296

Triply charged mass [M]/3 - 1.00794, calculated 1749.0019; observed 1749.0034.



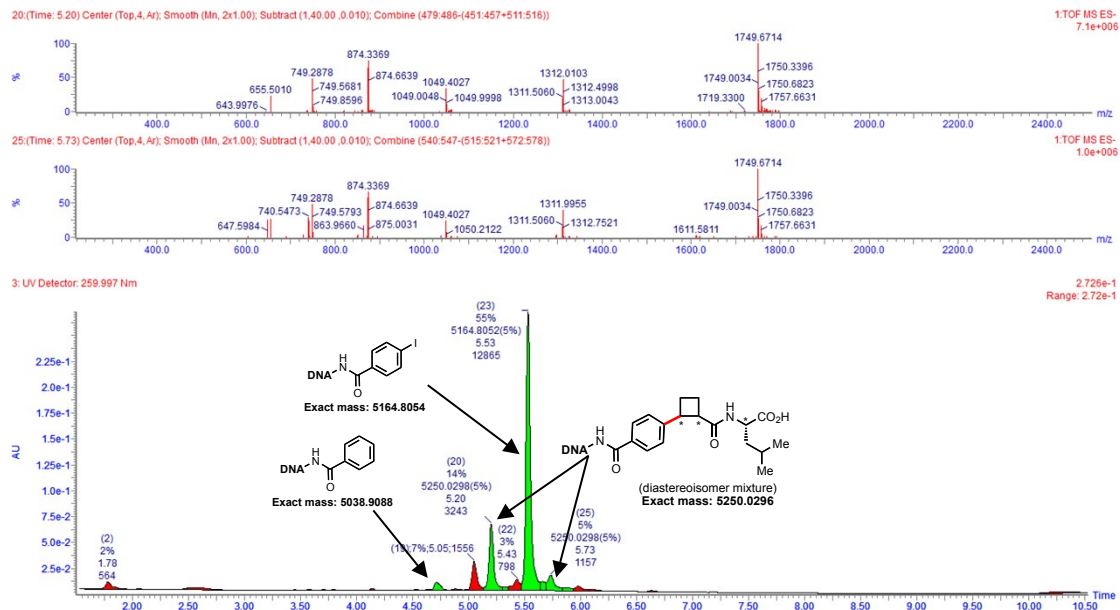
Following General Procedure 3 with **B10** except for running reaction and quenching with scavenger at room temperature.

$$\text{Yield: } \frac{19}{85} \times 100\% = 22\%$$

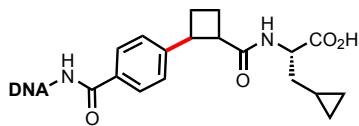
Ratio (product/deiodination/aryl iodide): 19/2/55

Exact mass: 5250.0296

Triply charged mass [M]/3 - 1.00794, calculated 1749.0019; observed 1749.0034.



LC Trace and Mass of 55



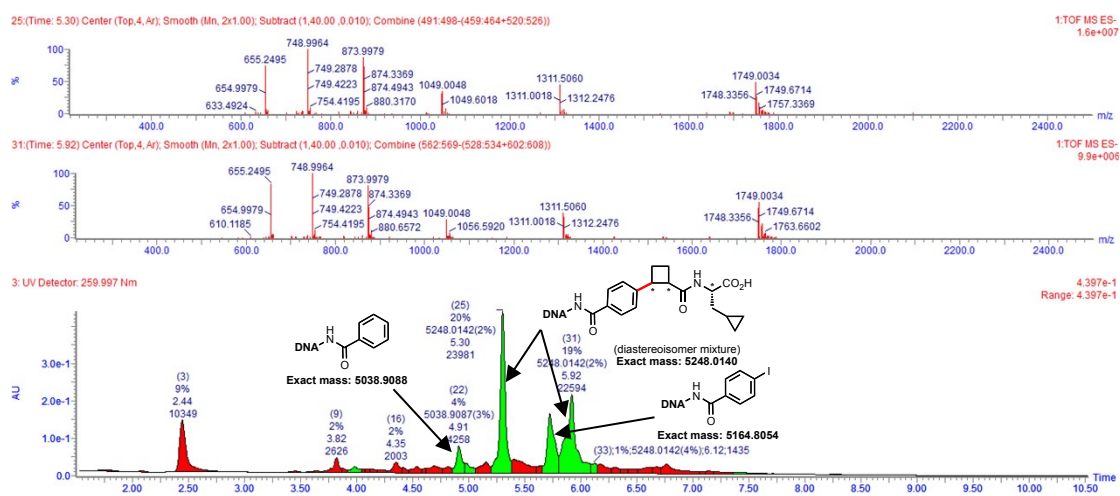
Following General Procedure 3 with **B11**.

$$\text{Yield: } \frac{39}{85} \times 100\% = 46\%$$

Ratio (product/deiodination/aryl iodide): 39/4/5

Exact mass: 5248.0140

Triply charged mass $[M]/3 - 1.00794$, calculated 1748.3301; observed 1748.3356.



Following General Procedure 3 with **B11** except for running reaction and quenching with scavenger at room temperature.

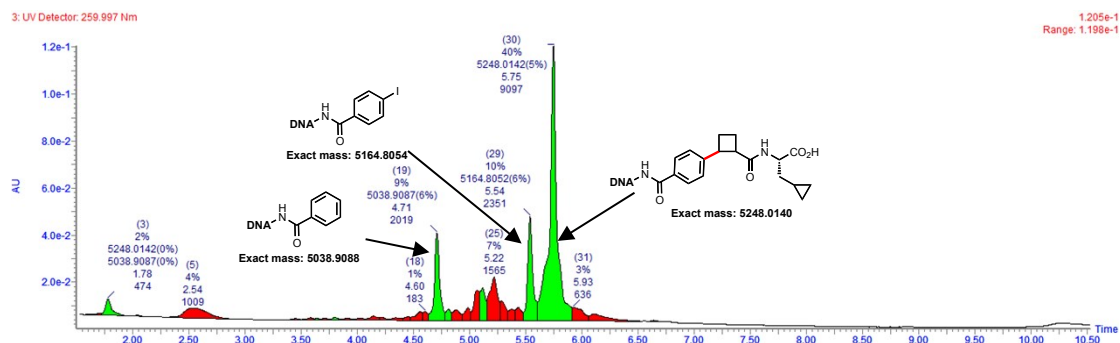
$$\text{Yield: } \frac{40}{85} \times 100\% = 47\%$$

Ratio (product/deiodination/aryl iodide): 40/9/10

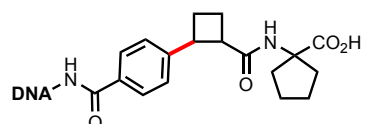
Exact mass: 5248.0140

Triply charged mass $[M]/3 - 1.00794$, calculated 1748.3301; observed 1748.3356.





LC Trace and Mass of 56



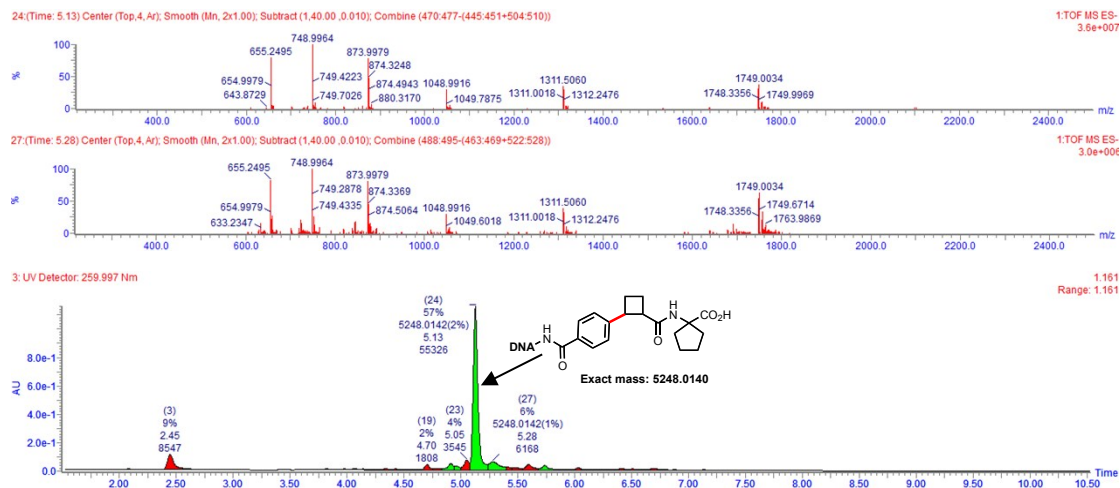
Following General Procedure 3 with **B12**.

$$\text{Yield: } \frac{63}{85} \times 100\% = 74\%$$

Ratio (product/deiodination/aryl iodide): 63/3/2

Exact mass: 5248.0140

Triply charged mass $[M]/3 - 1.00794$, calculated 1748.3301; observed 1748.3356.



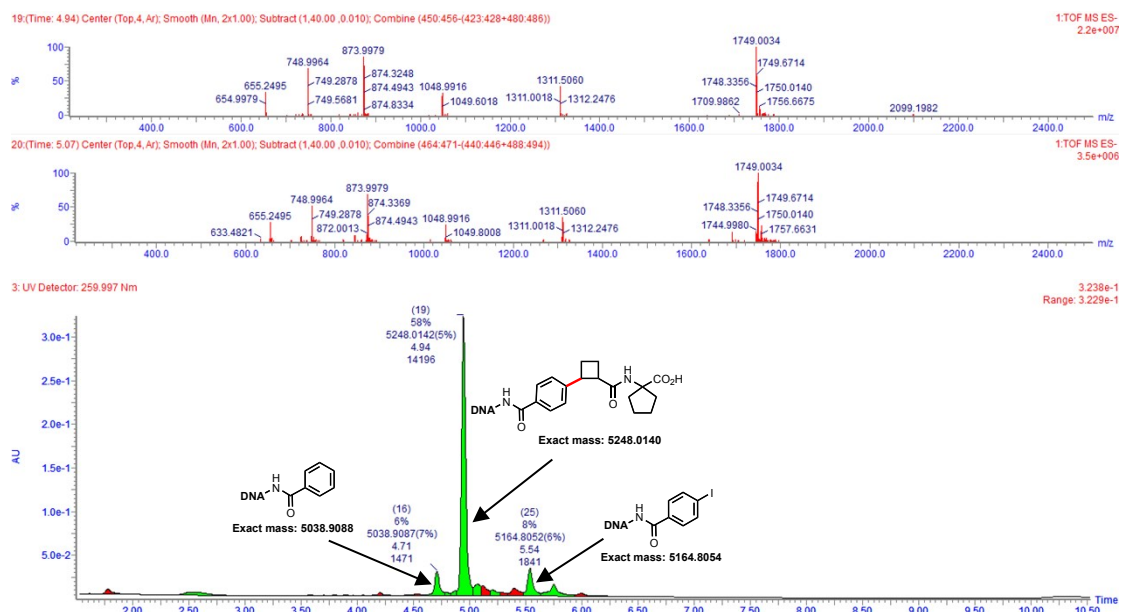
Following General Procedure 3 with **B12** except for running reaction and quenching with scavenger at room temperature.

$$\text{Yield: } \frac{62}{85} \times 100\% = 73\%$$

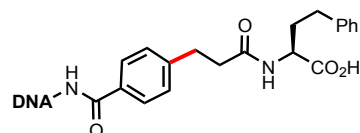
Ratio (product/deiodination/aryl iodide): 68/6/8

Exact mass: 5248.0140

Triply charged mass $[M]/3 - 1.00794$, calculated 1748.3301; observed 1748.3356.



LC Trace and Mass of 57



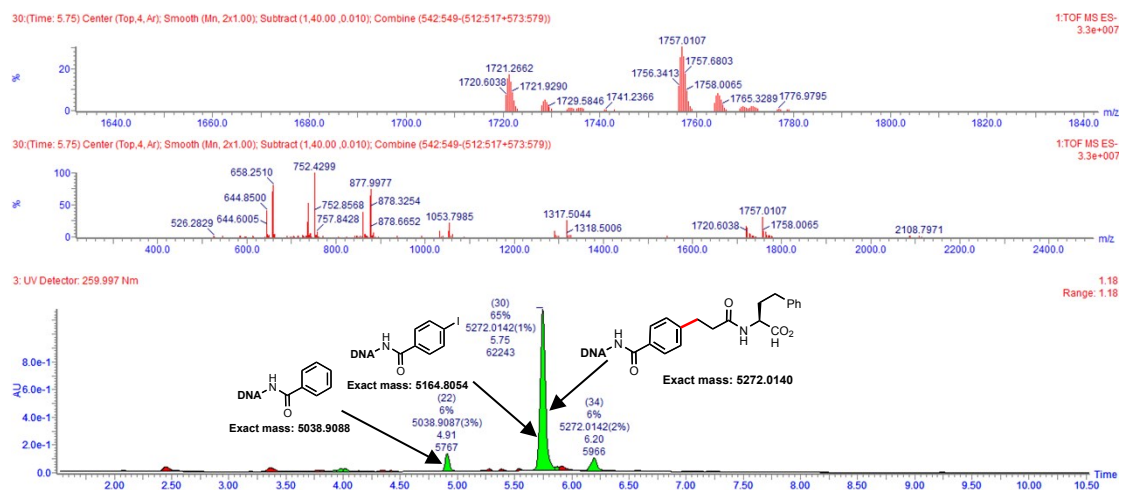
Following General Procedure 3 with **B13**.

Yield: $\frac{43}{85} \times 100\% = 51\%$

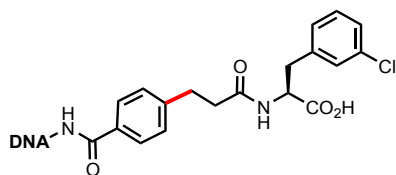
Ratio (product/deiodination/aryl iodide): 43/6/22

Exact mass: 5272.0140

Triply charged mass [M]/3 - 1.00794, calculated 1756.3301; observed 1756.33413.



LC Trace and Mass of 58



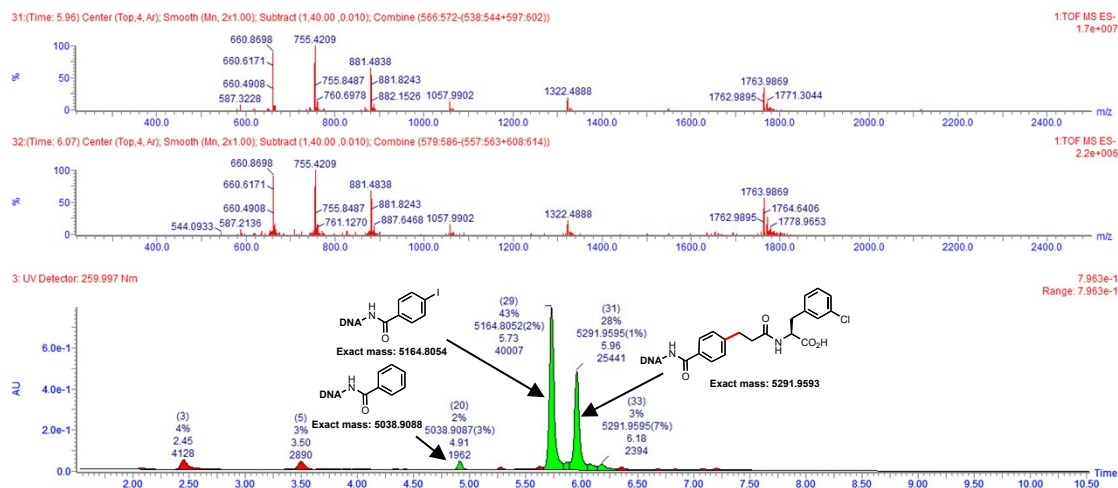
Following General Procedure 3 with **B14**.

$$\text{Yield: } \frac{30}{85} \times 100\% = 35\%$$

Ratio (product/deiodination/aryl iodide): 30/2/43

Exact mass: 5291.9593

Triply charged mass $[M]/3 - 1.00794$, calculated 1762.9785; observed 1762.9895.



Following General Procedure 3 with **B14** except for running reaction and quenching with scavenger at room temperature.

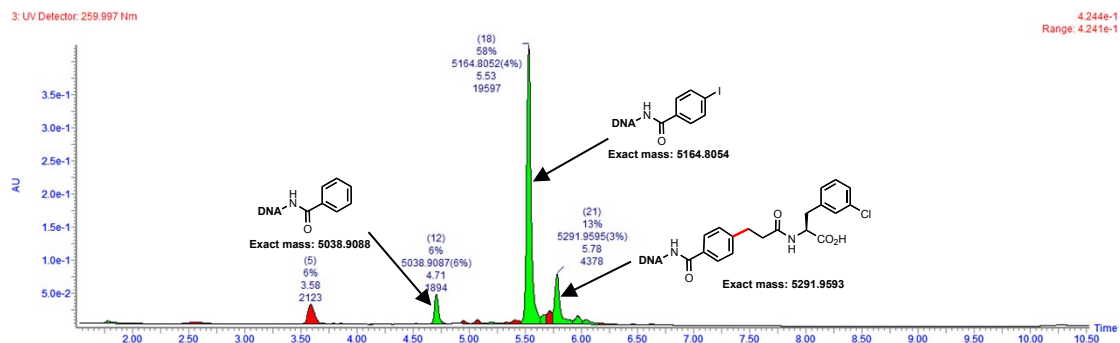
$$\text{Yield: } \frac{13}{85} \times 100\% = 15\%$$

Ratio (product/deiodination/aryl iodide): 13/6/58

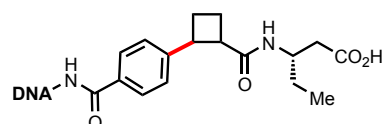
Exact mass: 5291.9593

Triply charged mass $[M]/3 - 1.00794$, calculated 1762.9785; observed 1762.9895.





LC Trace and Mass of 60



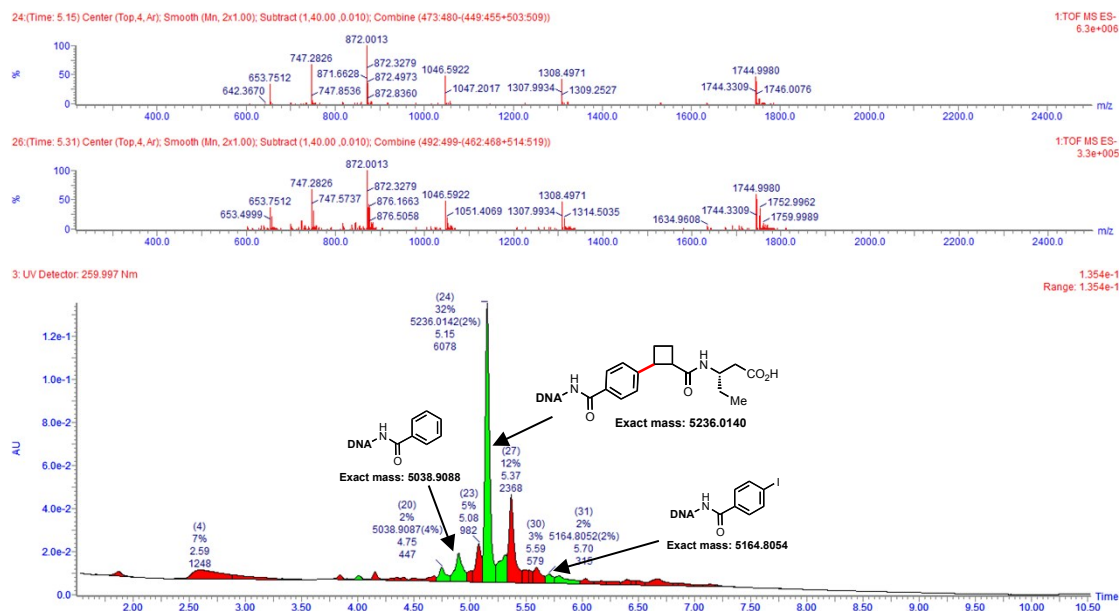
Following General Procedure 3 with **B16**.

$$\text{Yield: } \frac{37}{85} \times 100\% = 44\%$$

Ratio (product/deiodination/aryl iodide): 37/5/2

Exact mass: 5236.0140

Triply charged mass $[M]/3 - 1.00794$, calculated 1744.3301; observed 1744.3309.



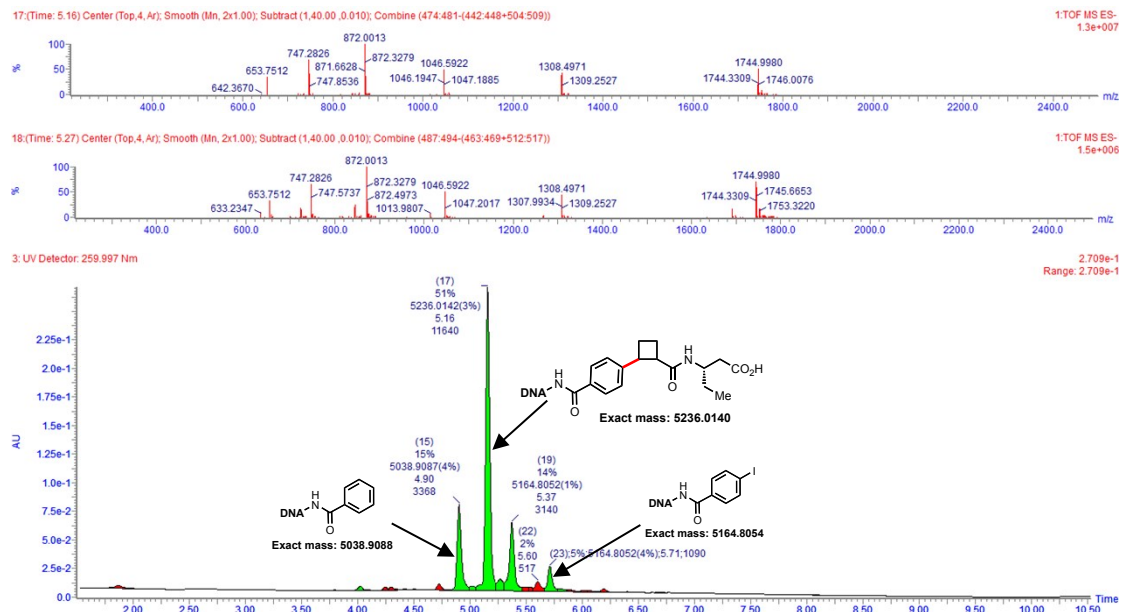
Following General Procedure 3 with **B16** except for running reaction and quenching with scavenger at room temperature.

$$\text{Yield: } \frac{54}{85} \times 100\% = 64\%$$

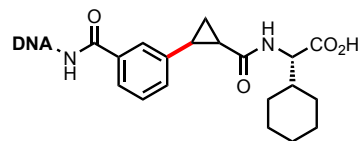
Ratio (product/deiodination/aryl iodide): 54/15/5
S81

Exact mass: 5236.0140

Triply charged mass [M]/3 - 1.00794, calculated 1744.3301; observed 1744.3309.



LC Trace and Mass of 61



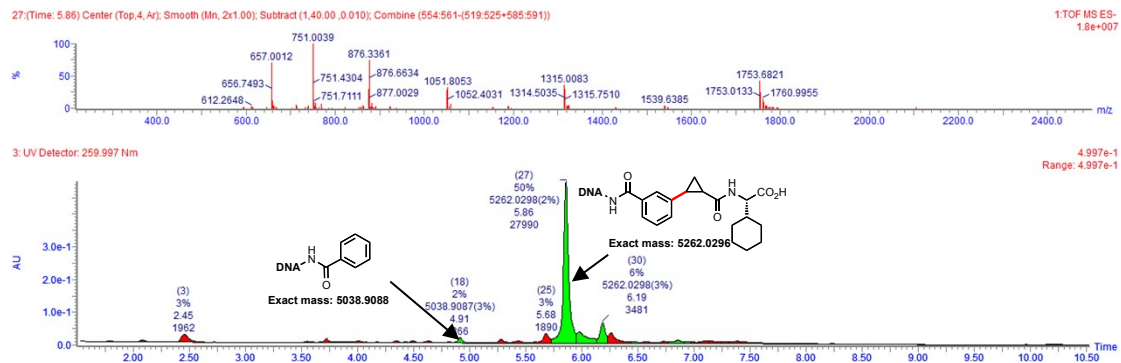
Following General Procedure 3 with **S7** and **B3**.

$$\text{Yield: } \frac{50}{83} \times 100\% = 60\%$$

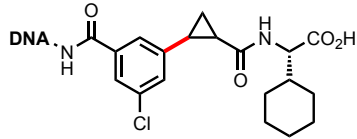
Ratio (product/deiodination/aryl iodide): 50/2/0

Exact mass: 5262.0296

Triply charged mass [M]/3 - 1.00794, calculated 1753.0019; observed 1753.0133.



LC Trace and Mass of 62



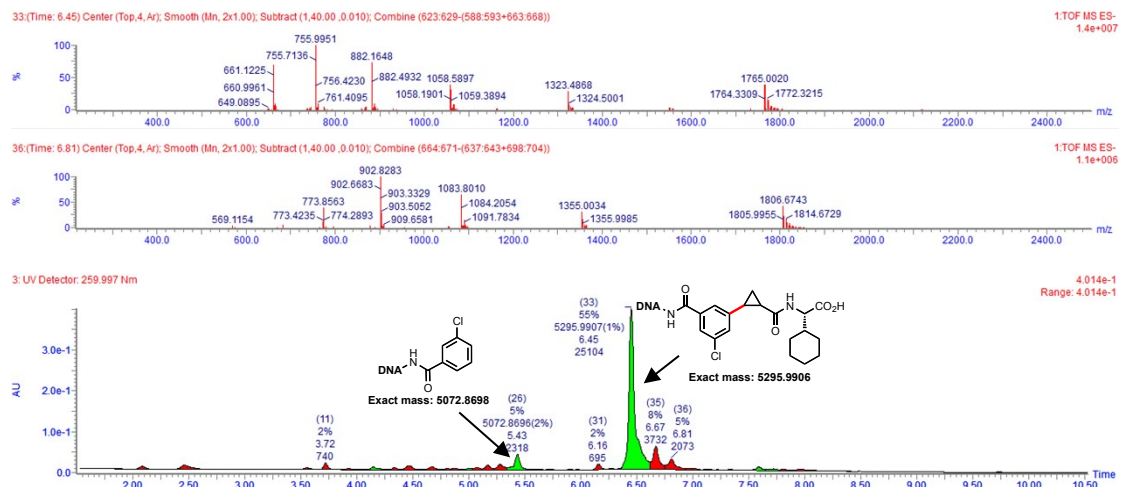
Following General Procedure 3 with **S9** and **B3**.

$$\text{Yield: } \frac{55}{71} \times 100\% = 77\%$$

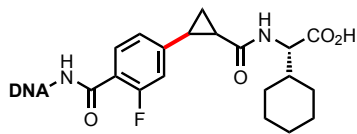
Ratio (product/deiodination/aryl iodide): 55/5/0

Exact mass: 5295.9906

Triply charged mass $[M]/3 - 1.00794$, calculated 1764.3223; observed 1764.3309.



LC Trace and Mass of 63



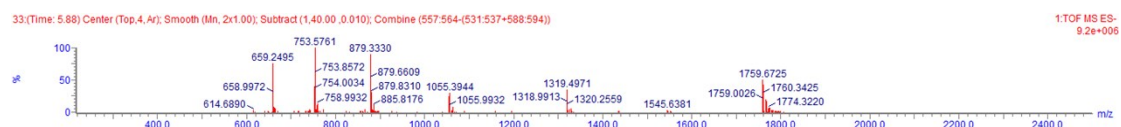
Following General Procedure 3 with **S13** and **B3**.

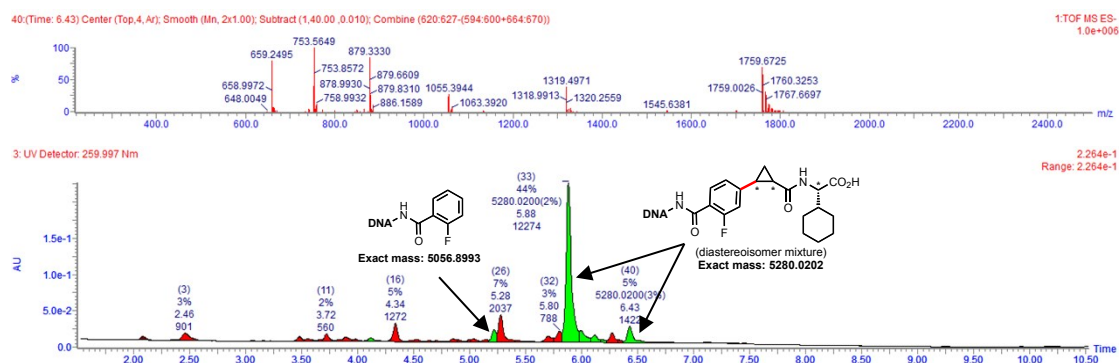
$$\text{Yield: } \frac{49}{55} \times 100\% = 89\%$$

Ratio (product/deiodination/aryl iodide): 49/3/0

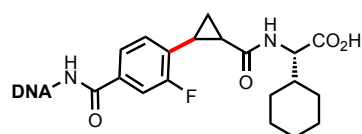
Exact mass: 5280.0202

Triply charged mass $[M]/3 - 1.00794$, calculated 1758.9988; observed 1759.0026.





LC Trace and Mass of 64



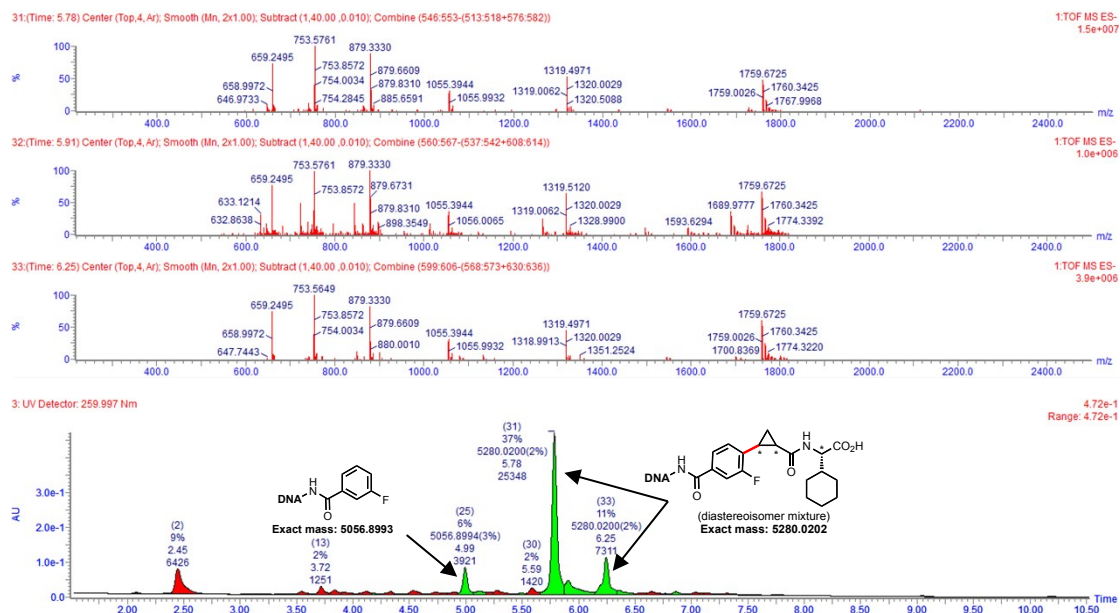
Following General Procedure 3 with **S12** and **B3**.

$$\text{Yield: } \frac{52}{71} \times 100\% = 73\%$$

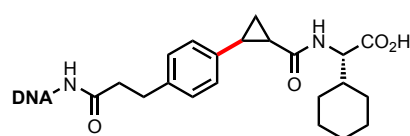
Ratio (product/deiodination/aryl iodide): 52/6/1

Exact mass: 5280.0202

Triply charged mass $[M]/3 - 1.00794$, calculated 1758.9988; observed 1759.0026.



LC Trace and Mass of 65



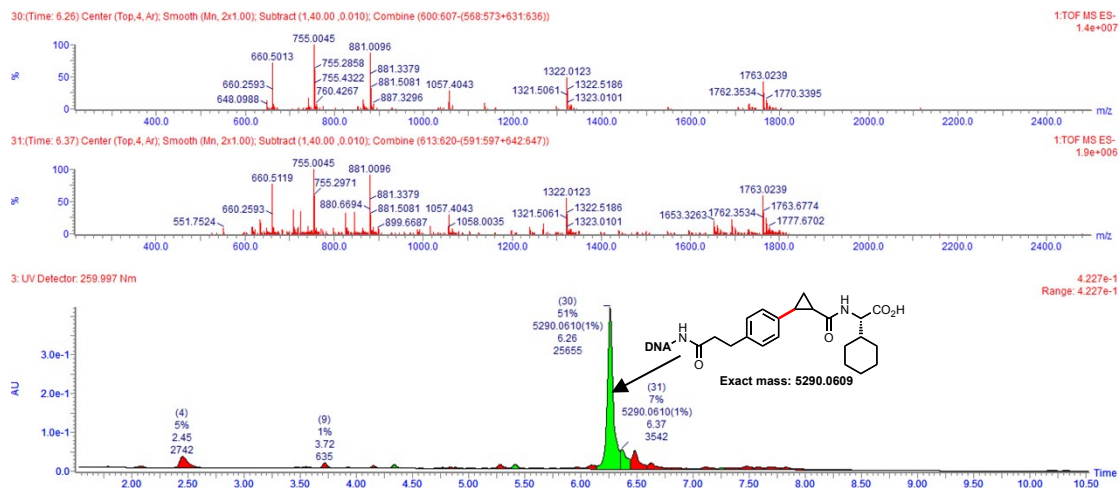
Following General Procedure 3 with **S3** and **B3**.

$$\text{Yield: } \frac{50}{78} \times 100\% = 64\%$$

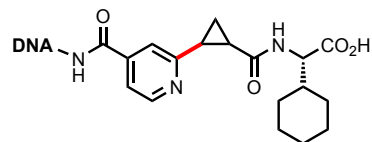
Ratio (product/deiodination/aryl iodide): 50/1/0

Exact mass: 5290.0609

Triply charged mass $[M]/3 - 1.00794$, calculated 1762.3457; observed 1762.3534.



LC Trace and Mass of 66



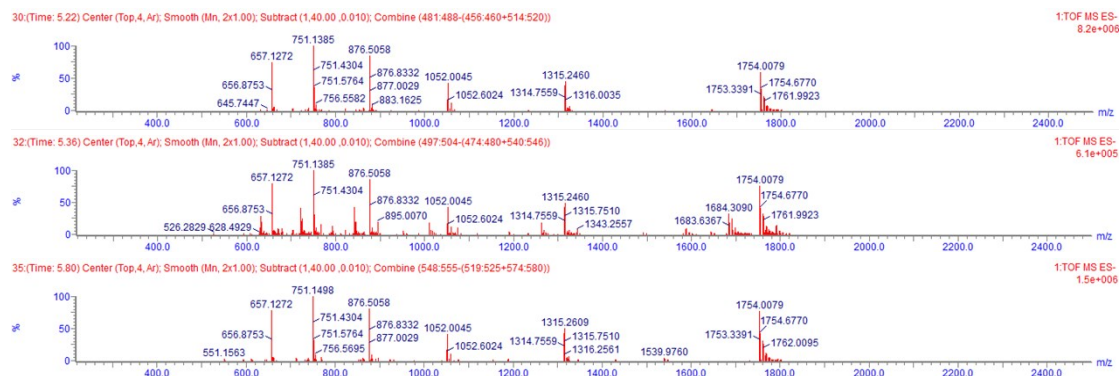
Following General Procedure 3 with **S18** and **B3**.

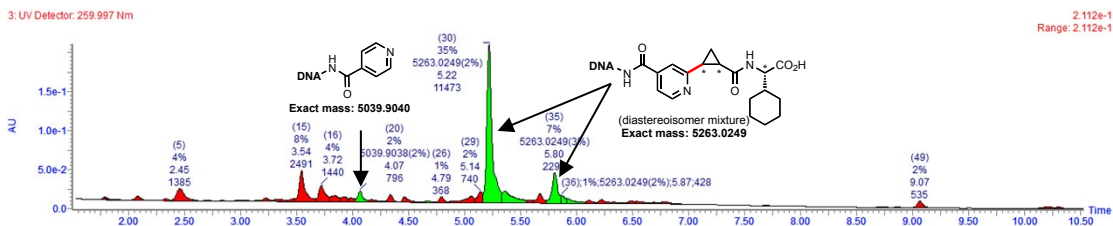
$$\text{Yield: } \frac{45}{56} \times 100\% = 80\%$$

Ratio (product/deiodination/aryl iodide): 45/2/0

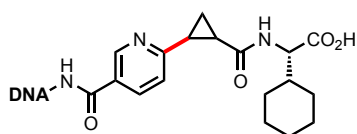
Exact mass: 5263.0249

Triply charged mass $[M]/3 - 1.00794$, calculated 1753.3337; observed 1753.3391.





LC Trace and Mass of 67



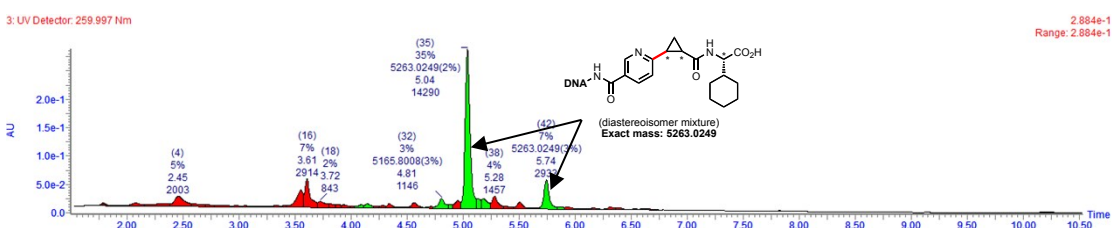
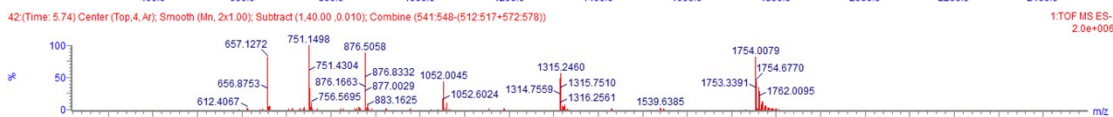
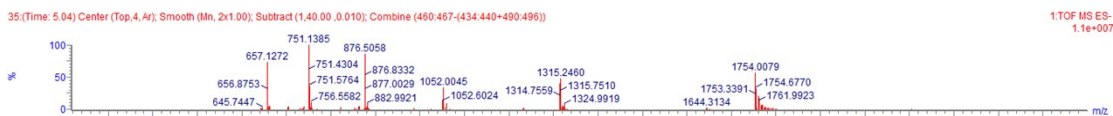
Following General Procedure 3 with **S15** and **B3**.

$$\text{Yield: } \frac{42}{65} \times 100\% = 65\%$$

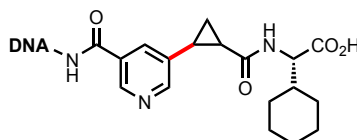
Ratio (product/deiodination/aryl iodide): 42/1/3

Exact mass: 5263.0249

Triply charged mass $[M]/3 - 1.00794$, calculated 1753.3337; observed 1753.3391.



LC Trace and Mass of 68



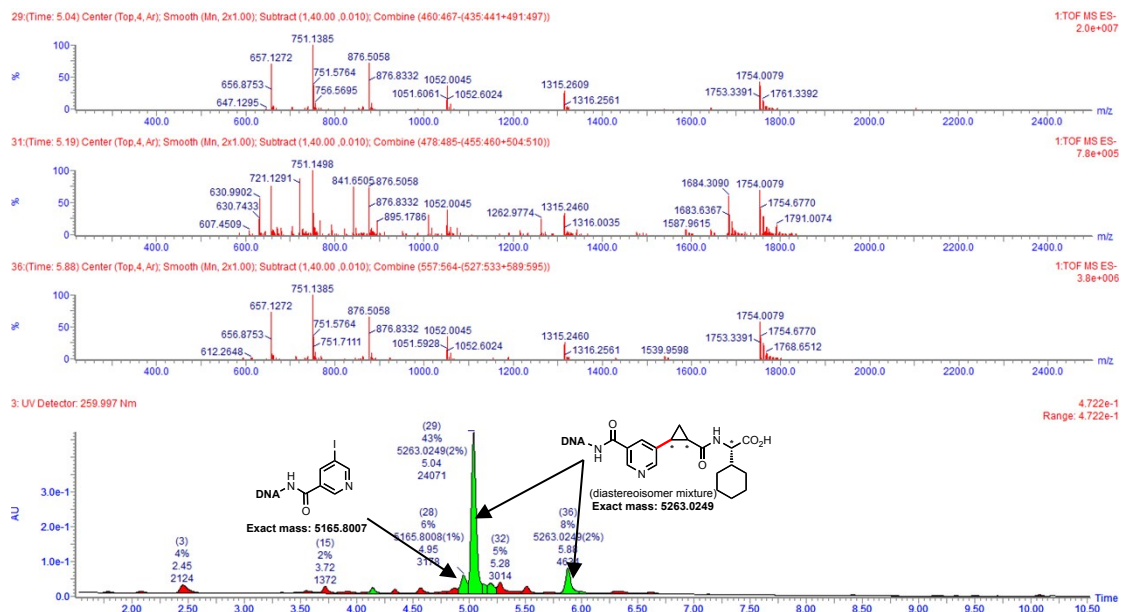
Following General Procedure 3 with **S16** and **B3**.

$$\text{Yield: } \frac{53}{79} \times 100\% = 67\%$$

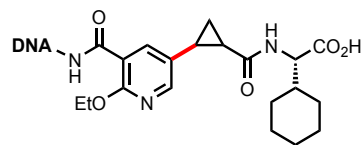
Ratio (product/deiodination/aryl iodide): 53/2/3

Exact mass: 5263.0249

Triply charged mass [M]/3 - 1.00794, calculated 1753.3337; observed 1753.3391.



LC Trace and Mass of 69



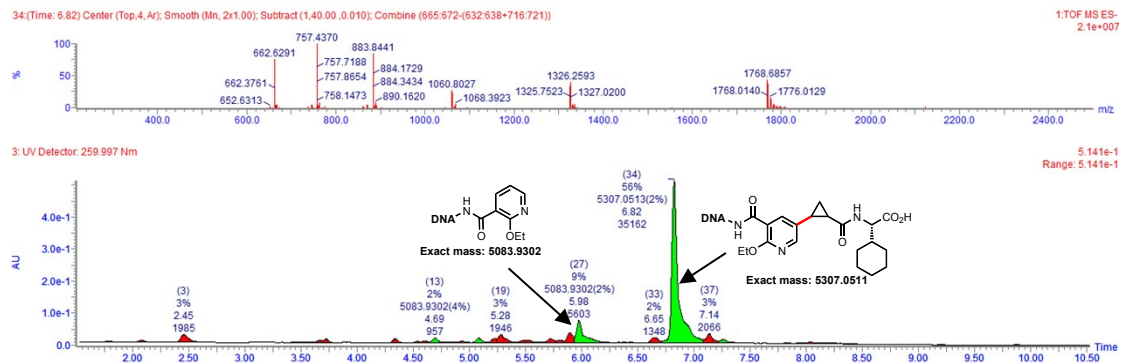
Following General Procedure 3 with **S17** and **B3**.

$$\text{Yield: } \frac{56}{78} \times 100\% = 72\%$$

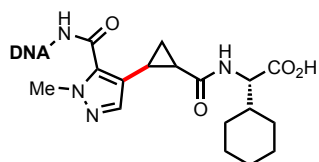
Ratio (product/deiodination/aryl iodide): 56/9/0

Exact mass: 5307.0511

Triply charged mass [M]/3 - 1.00794, calculated 1768.0091; observed 1768.0140.



LC Trace and Mass of 70



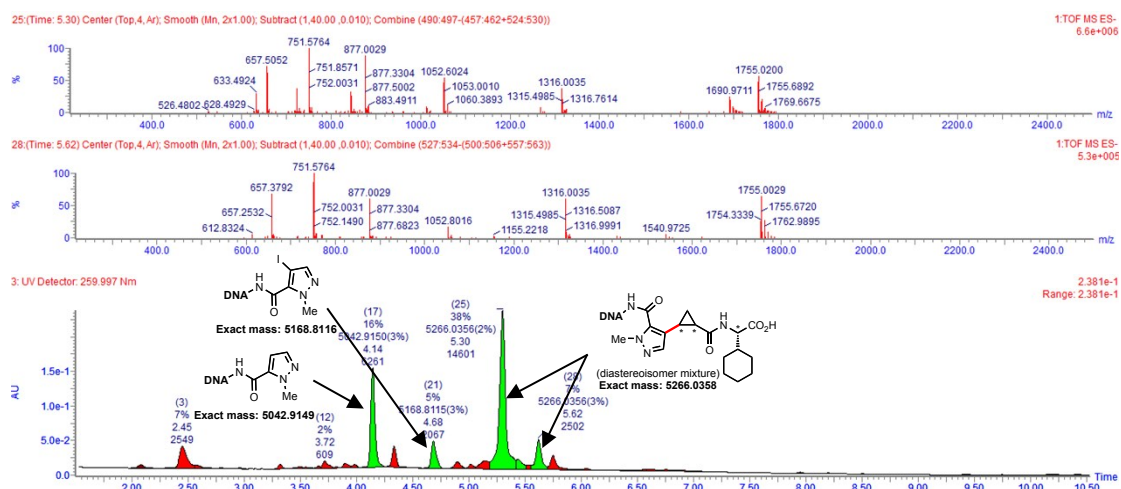
Following General Procedure 3 with **S21** and **B3**.

$$\text{Yield: } \frac{33}{69} \times 100\% = 48\%$$

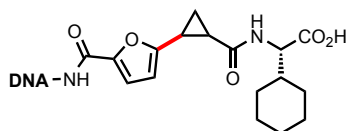
Ratio (product/deiodination/aryl iodide): 33/16/5

Exact mass: 5266.0358

Triply charged mass $[M]/3 - 1.00794$, calculated 1754.3373; observed 1754.3339.



LC Trace and Mass of 71



Following General Procedure 3 with **S22** and **B3**.

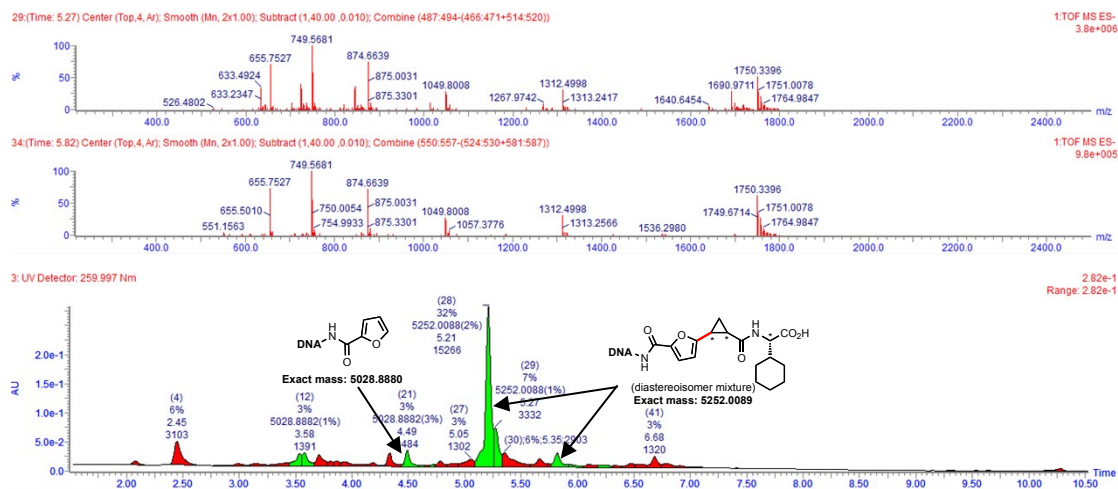
$$\text{Yield: } \frac{39}{67} \times 100\% = 58\%$$

Ratio (product/deiodination/aryl iodide): 39/3/0

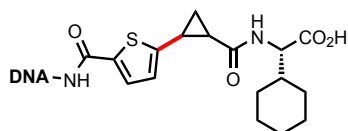
Exact mass: 5252.0089

Triply charged mass $[M]/3 - 1.00794$, calculated 1749.6617; observed 1749.6714.





LC Trace and Mass of 72



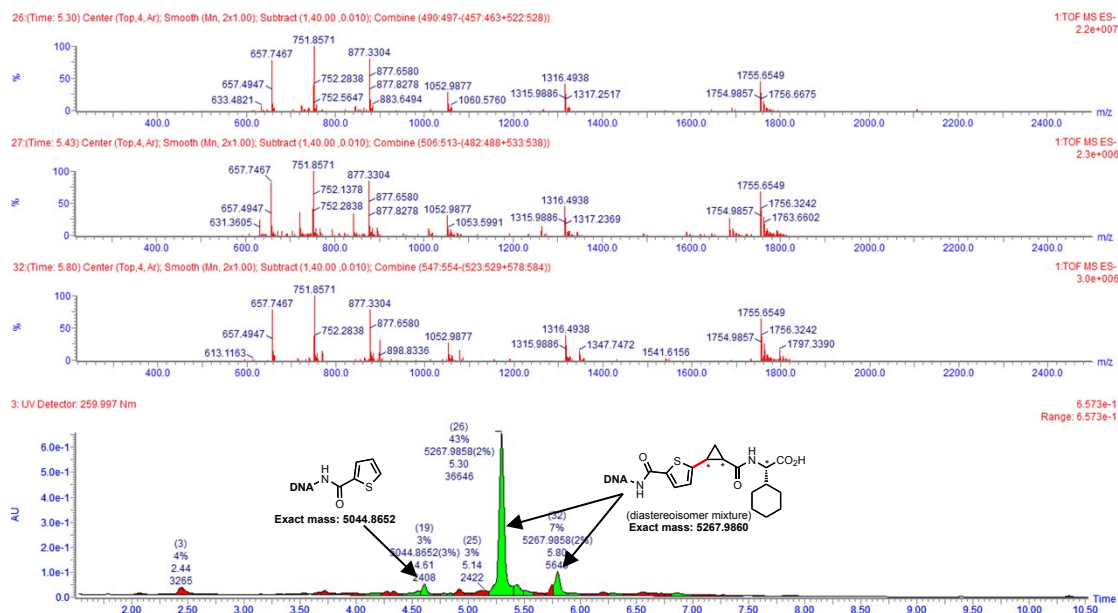
Following General Procedure 3 with **S23** and **B3**.

$$\text{Yield: } \frac{52}{69} \times 100\% = 75\%$$

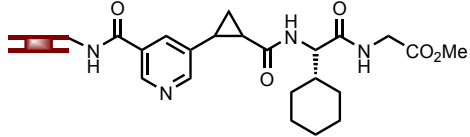
Ratio (product/deiodination/aryl iodide): 52/3/0

Exact mass: 5267.9860

Triply charged mass [M]³⁻ - 1.00794, calculated 1754.9874; observed 1754.9857.



LC Trace and Mass of 73

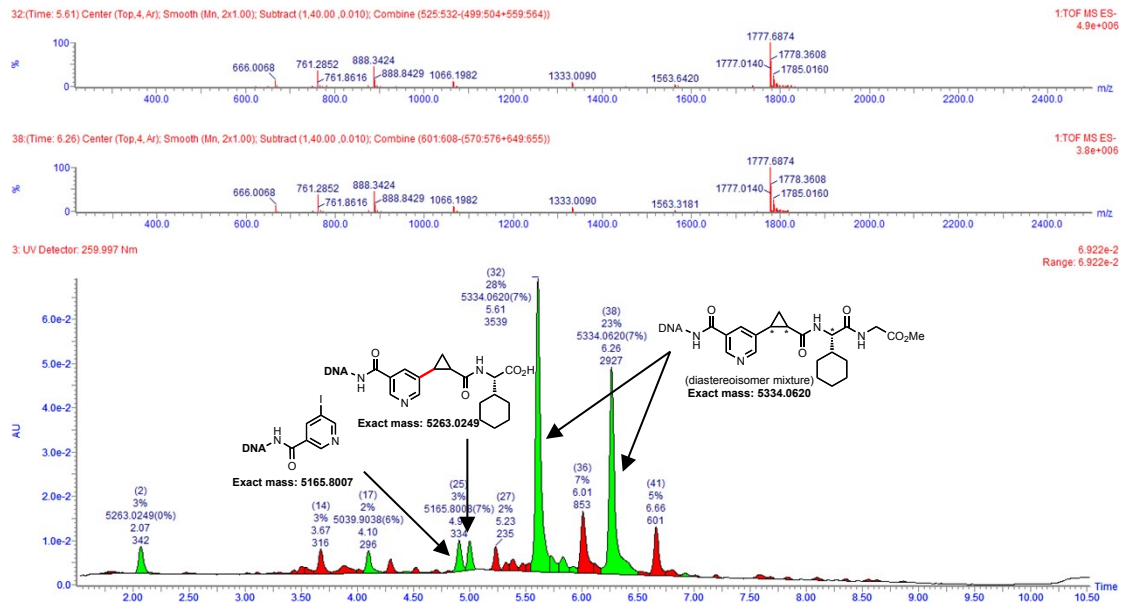


Following General Procedure 4 with **68**.

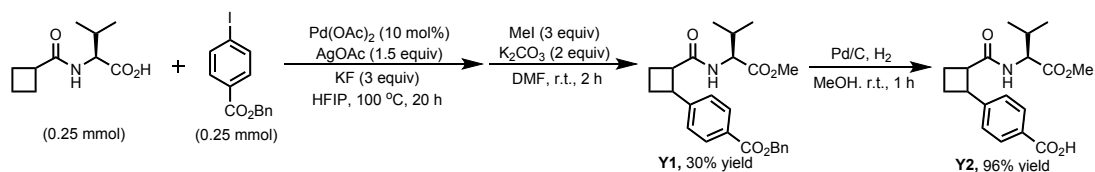
$$\text{Yield: } \frac{51}{53} \times 100\% = 96\%$$

Exact mass: 5334.0620

Triply charged mass $[M]/3 - 1.00794$, calculated 1777.0127; observed 1777.0140.



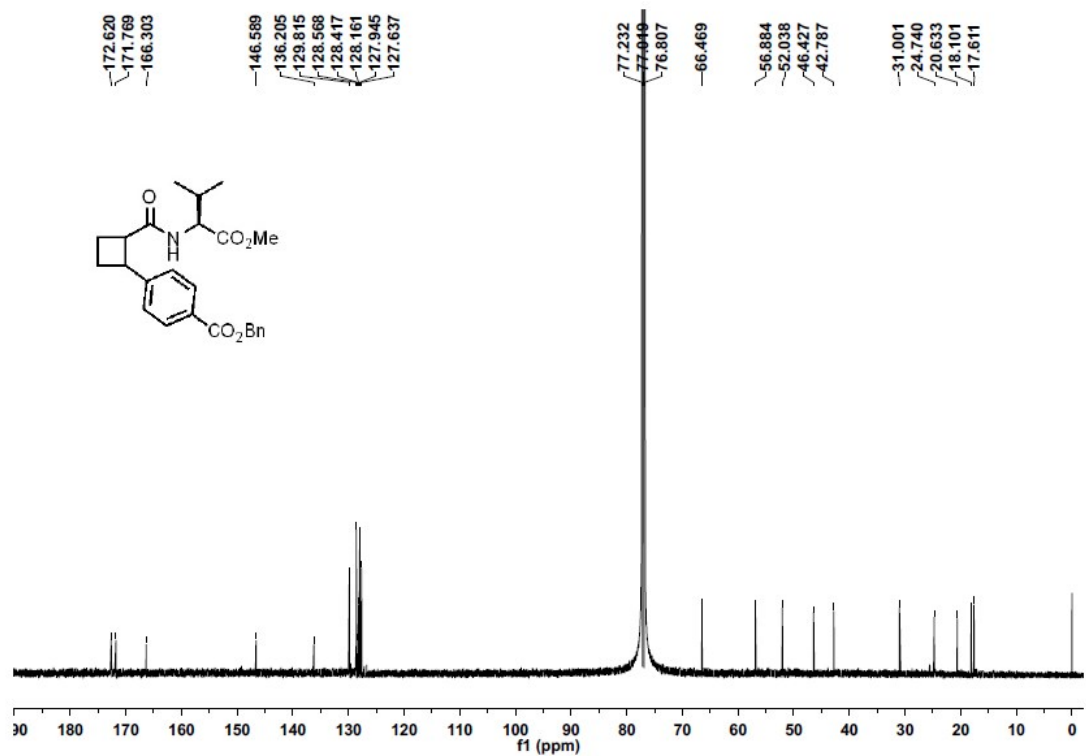
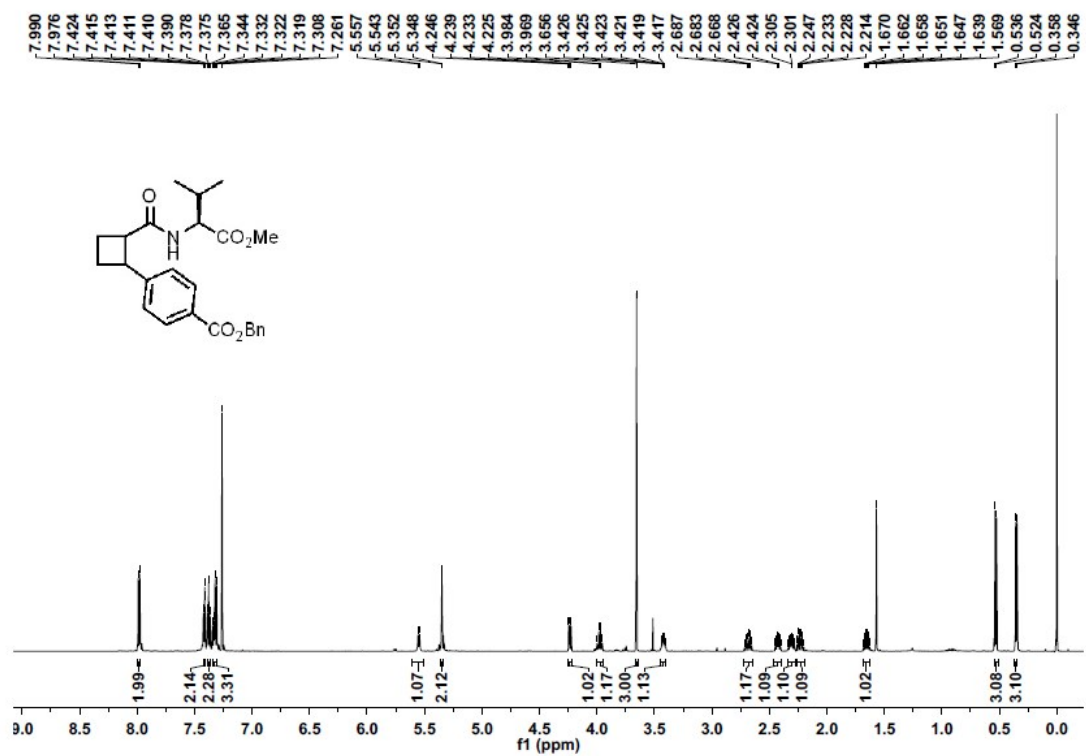
5.6 Off-DNA synthesis of 51

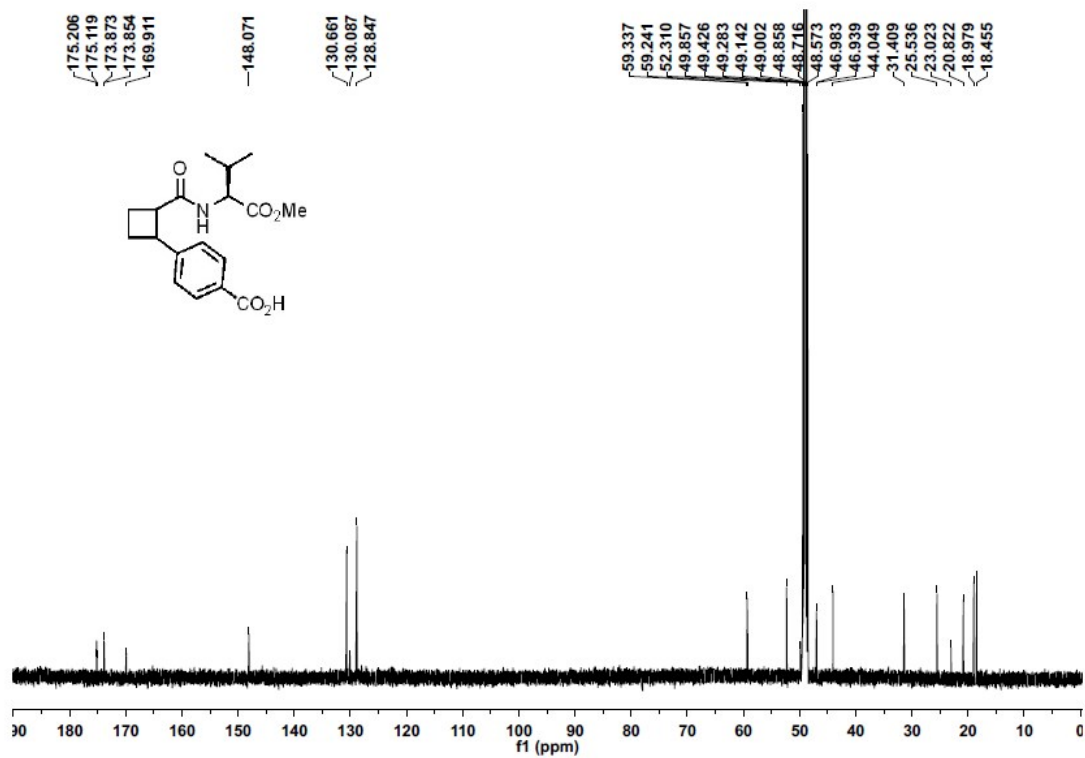
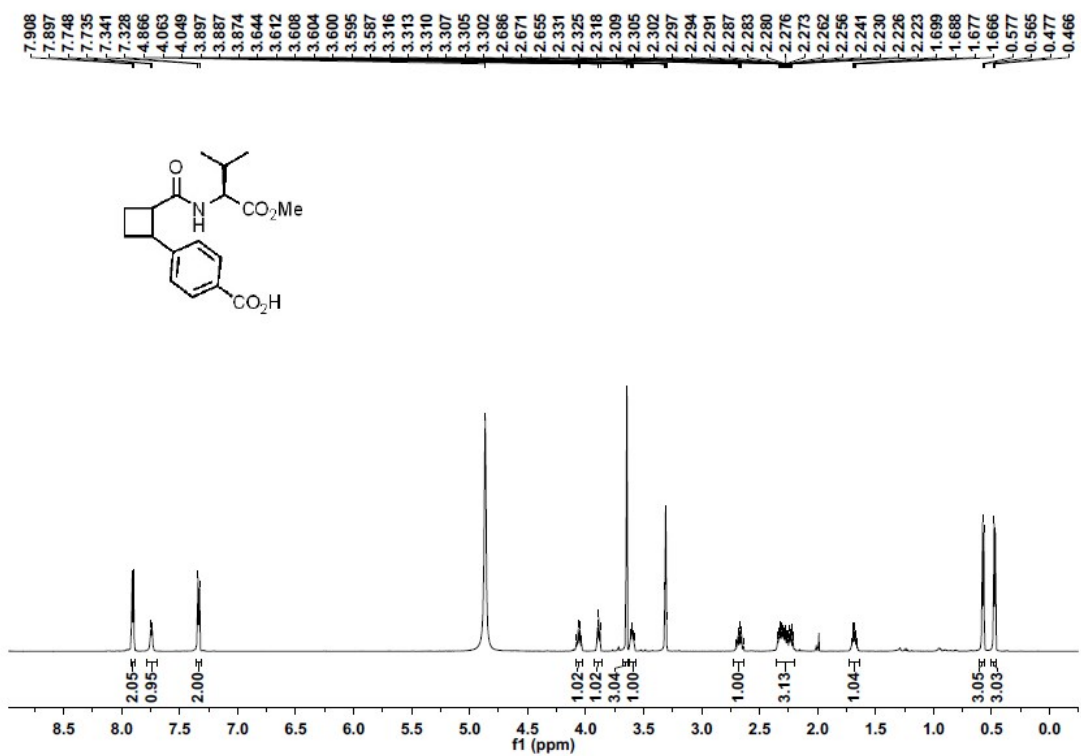


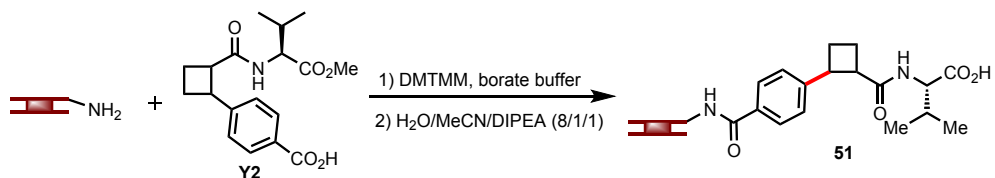
(cyclobutanecarbonyl)-L-valine (50 mg, 0.25 mmol), benzyl 4-iodobenzoate (85 mg, 0.25 mmol), Pd(OAc)₂ (5.6 mg, 10 mol%), KF (44 mg, 3 equiv), AgOAc (63 mg, 1.5 equiv) were added in HFIP (2 mL). The mixture was heated at 100 °C for 20 h. After the solvent was removed. The mixture was dissolved in trace of DCM and passed through a pad of silica gel with hexane/EA (1:1) as the eluent. The filtrate was concentrated and dissolved in DMF, K₂CO₃ (69 mg) and MeI (46 uL) were added. After 2 hours, water was added to the reaction solution and extracted with EA. The product **Y1** was obtain through the purification on pTLC with hexane/EA (2:1). ¹H NMR (600 MHz, CDCl₃) δ 7.98 (d, *J* = 8.4 Hz, 2H), 7.43 – 7.41 (m, 2H), 7.38 (dd, *J* = 8.3, 6.5 Hz, 2H), 7.33 (dd, *J* = 13.7, 7.7 Hz, 3H), 5.55 (d, *J* = 8.3 Hz, 1H), 5.35 (d, *J* = 2.4 Hz, 2H), 4.24 (dd, *J* = 8.3, 4.6 Hz, 1H), 4.00 – 3.95 (m, 1H), 3.66 (s, 3H), 3.45 – 3.40 (m, 1H), 2.72 – 2.64 (m, 1H), 2.46 – 2.40 (m, 1H), 2.31 (dtdt, *J* = 10.9, 6.3, 4.3, 2.1 Hz, 1H), 2.23 (dq, *J* = 11.5, 8.4 Hz, 1H), 1.68 – 1.63 (m, 1H), 0.53 (d, *J* = 6.9 Hz, 3H), 0.35 (d, *J* = 6.9 Hz, 3H); ¹³C NMR (151 MHz, CDCl₃) δ 172.62, 171.77, 166.30, 146.59, 136.20, 129.81, 128.57, 128.42, 128.16, 127.94, 127.64, 66.47, 56.88, 52.04, 46.43, 42.79, 31.00, 24.74, 20.63, 18.10, 17.61.

To a solution of **Y1** (32 mg) in MeOH (2 mL), then added Pd/C (6 mg), the flask was evacuated briefly under high vacuum and charged with a H₂ balloon. The reaction solution was stirred for 1 h. The solution was passed through a pad of Celite and the filtrate was concentrated. Product **Y2** was obtained as a white solid. ¹H NMR (600 MHz, CD₃OD) δ 7.90 (d, *J* = 6.6 Hz, 2H), 7.74 (d, *J* = 7.8 Hz, 1H), 7.33 (d, *J* = 8.1 Hz, 2H), 4.06 (q, *J* = 9.2 Hz, 1H), 3.92 – 3.86 (m, 1H), 3.64 (s, 3H), 3.60 (tt, *J* = 7.0, 2.6 Hz, 1H), 2.68 (q, *J* = 11.3, 9.8 Hz, 1H), 2.36 – 2.20 (m, 3H), 1.68 (h, *J* = 6.7 Hz, 1H), 0.57 (d, *J* = 6.9 Hz, 3H), 0.47 (d, *J* = 7.0 Hz, 3H); ¹³C NMR (151 MHz, CD₃OD) δ 175.20, 175.12, 173.87, 173.85, 169.91, 148.07, 130.66, 130.09, 128.85, 59.34,

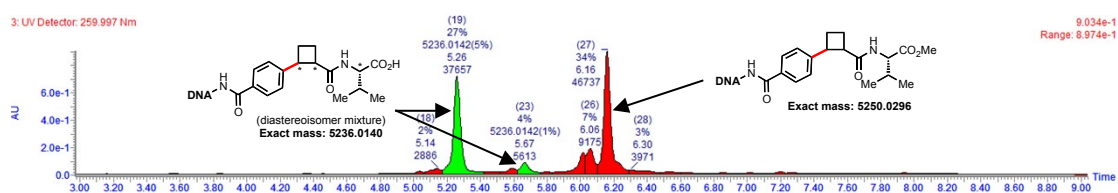
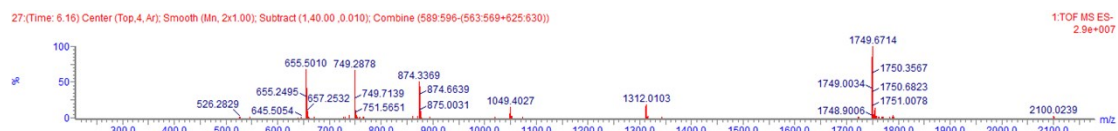
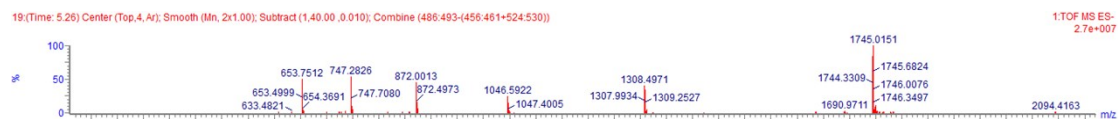
59.24, 52.31, 49.86, 46.98, 46.94, 44.05, 31.41, 31.39, 25.54, 23.02, 20.82, 18.98, 18.45.



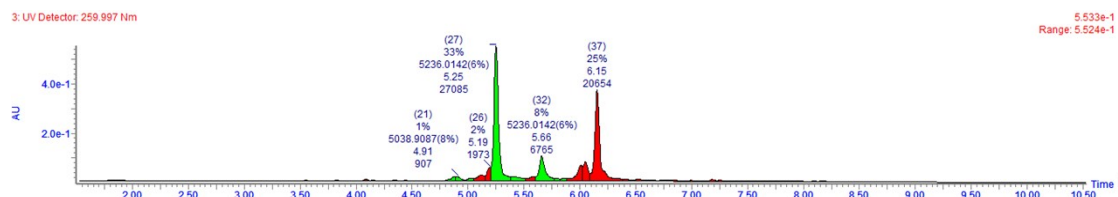




Following General Procedure 1.

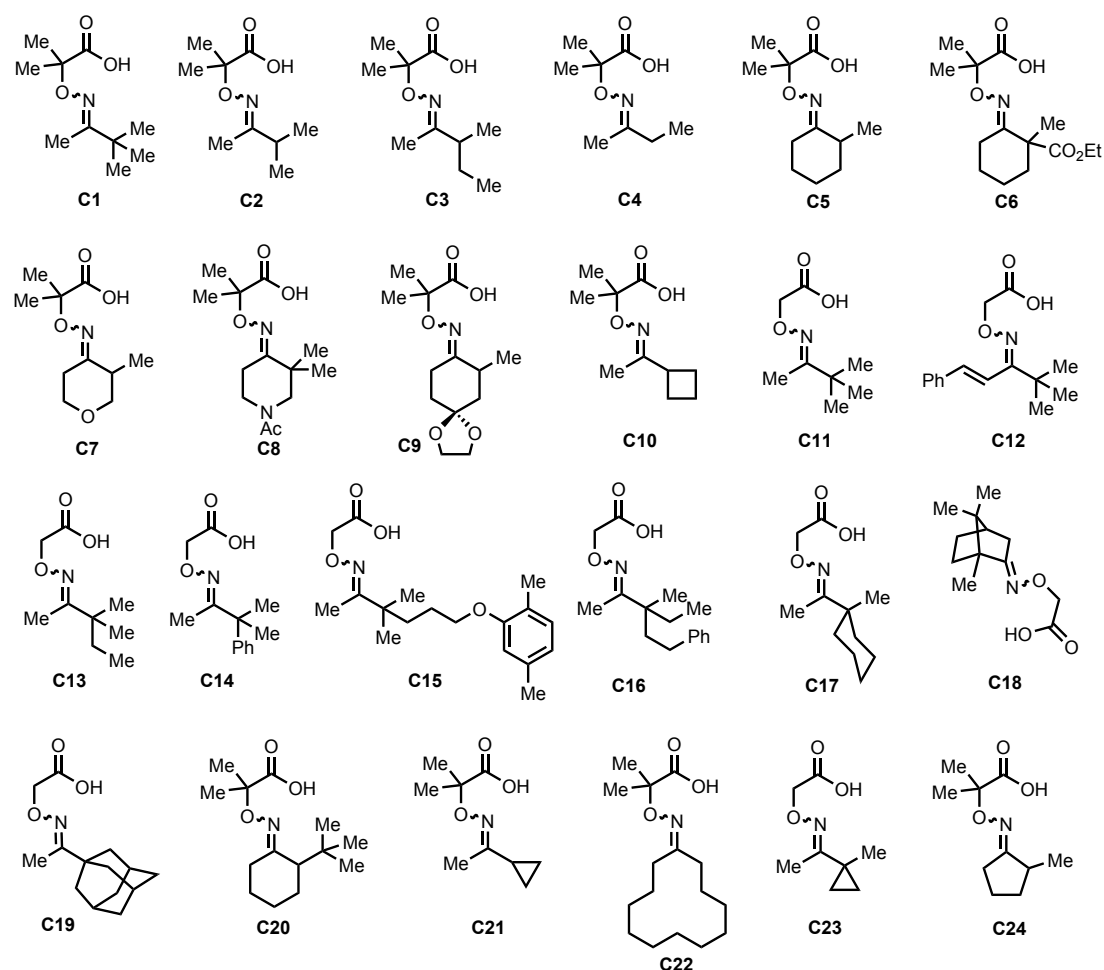


LC trace mixture of 51 through on-DNA and off-DNA synthesis



6. Experimental Section for on-DNA C-H Arylation of Ketones

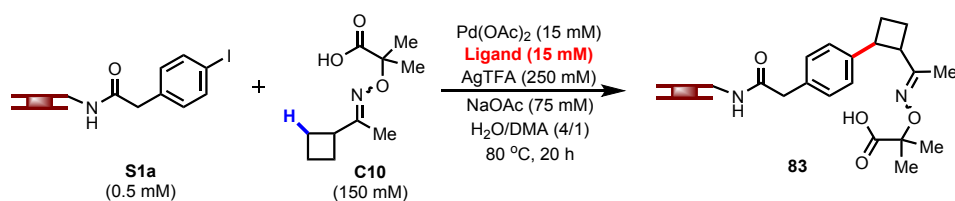
6.1 Substrate Structures of Ketones Containing Directing Groups (DGs) C1-C24



Ketones containing directing groups C1-C24 were synthesized following our previous report.⁶

6.2 Condition Optimizations

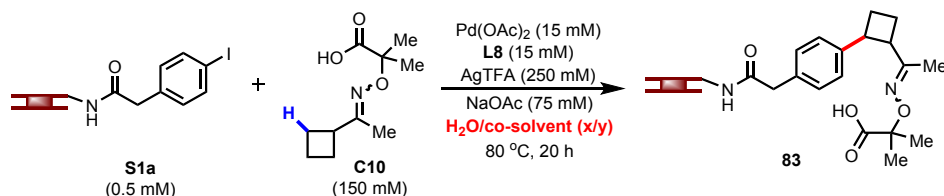
Table S10. Ligand Optimization



Entry	Ligand (15 mM)	Yield (%)
1	L6	16
2	L7	32
3	L8	38
4	L9	36
	S95	

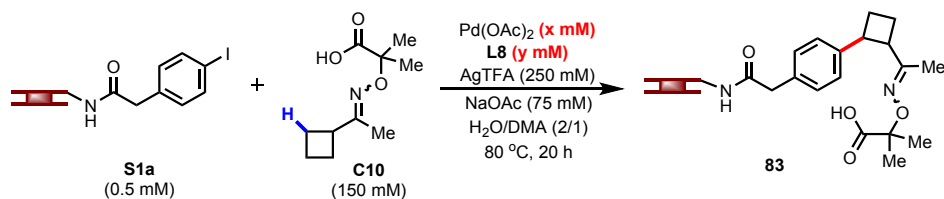
5	L10	32
6	L11	33
7	L12	37
8	L13	27

Table S11. Co-solvent Optimization



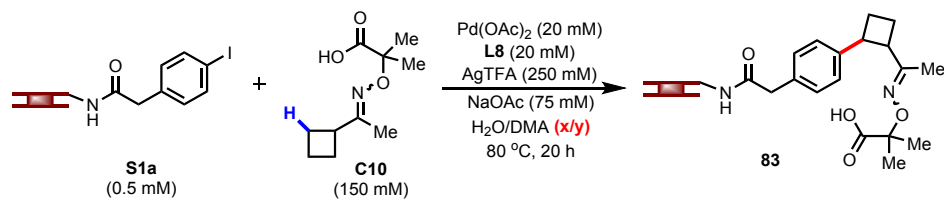
Entry	H ₂ O/Co-solvent (x/y)	Yield (%)
1	H ₂ O/DMA (1/1)	28
2	H₂O/DMA (2/1)	39
3	H ₂ O/DMF (2/1)	35
4	H ₂ O/DMSO (2/1)	26

Table S12. Pd/L8 Concentration Optimization



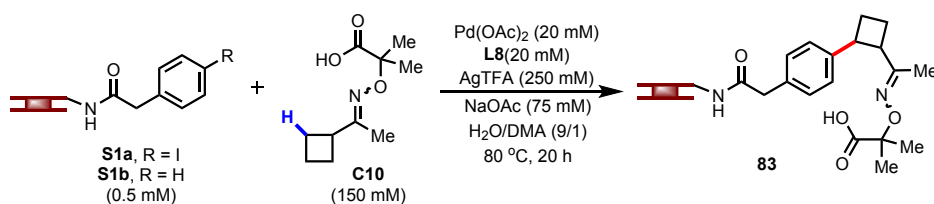
Entry	Pd/L8 (x/y)	Yield (%)
1	20/10	33
2	20/15	48
3	20/20	48

Table S13. Solvent Ratio Optimization



Entry	H ₂ O/DMA (x/y)	Yield (%)
1	4/1	51
2	9/1	62

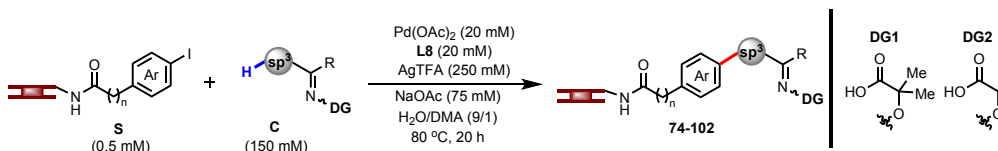
Table S14. Evaluation of Standard Conditions



Entry	Deviation from above	Yield (%)
1	none	62
2	without Pd(OAc) ₂	0
3	without AgTFA	4
4	without NaOAc	55
5	without L8	51
6	r.t instead of 80 °C	0
7	Ag ₂ CO ₃ (150 mM) instead of AgTFA (250 mM)	25
8	AgOAc (250 mM) instead of AgTFA (250 mM)	32
9	C10 (100 mM) instead of 150 mM	61
10	C10 (200 mM) instead of 150 mM	53
11	C10 (250 mM) instead of 150 mM	54
12	L1 instead of L8	48
13	L5 instead of L8	45
14	Pd(OAc) ₂ / L8 (15/15) instead of 20/20	49
15	S1b instead of S1a	0 ^a

^aOnly **S1b** was totally recovered.

6.3 General Procedure 5 for on-DNA C-H Arylation of Ketones



Materials

DNA-conjugated aryl iodide **S**: 10 mM in H₂O

Ketone **C**: 3 M in DMA (*Note: the high concentration may increase the total volume*)

L8: 400 mM in DMA (6.5 mg in 100 μL DMA)

Pd(OAc)₂: 400 mM in HFIP (9 mg in 100 μL HFIP)

NaOAc: 1.5 M in H₂O (12.3 mg in 100 μL H₂O)

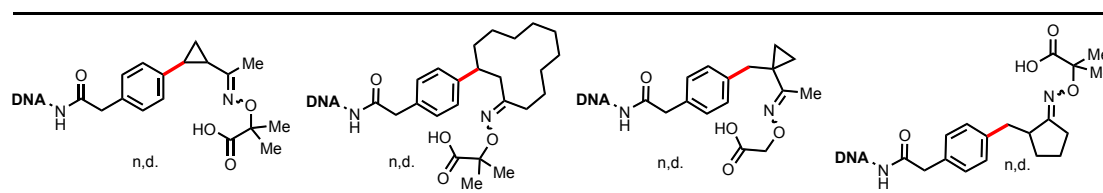
Sodium diethyldithiocarbamate trihydrate (scavenger): 1 M in H₂O

Procedure

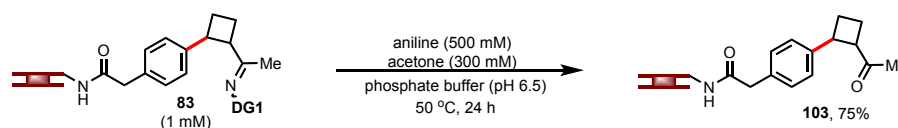
1) To prepared AgTFA (500 equiv, 1.1 mg) was added Pd(OAc)₂ (40 equiv, 1 μL), after air-dry, ketone **C** (300 equiv, ca. 1.3 μL), DNA-conjugated aryl iodide **S** (10 nmol, 1 μL), **L8** (40 equiv, 1 μL), NaOAc aqueous solution (150 equiv, 1 μL) and deionized water (16 μL) were added. The mixture was vortexed. Heating the reaction mixture at 80 °C for 20 h.

- 2) Cooling to room temperature, 9.0 μL scavenger was added and reheating the mixture at 80 $^{\circ}\text{C}$ for 30 min.
- 3) Cooling to room temperature, 5 M NaCl solution (10 % by volume, 2.9 μL) and cold ethanol (3 times by volume, 87 μL). The mixture was stored at a -20 $^{\circ}\text{C}$ freezer for more than 30 minutes.
- 4) Centrifuge the sample for around 7 minutes in a microcentrifuge at 10000 rpm. The above supernatant was discarded and the precipitate was dried under vacuum. The DNA pellet was redissolved in H_2O (100 μL) and centrifuged for around 2 minutes in a microcentrifuge at 10000 rpm. An aliquot (50 μL) was taken and analyzed via HPLC-MS.

6.4 Limitations of Ketones



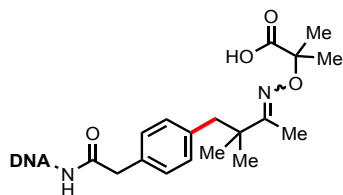
6.5 General Procedure 6 for Removal of DG



- 1) Aniline (0.45 μL , 5 μmol , 500 equiv) and acetone (0.22 μL , 3 μmol , 300 equiv) were added to a solution of the DNA substrate **83** (ca. 10 nmol) in pH 6.5 phosphate buffer (20 μL). The reaction mixture was subsequently heated at 50 $^{\circ}\text{C}$ for 24 h.
- 2) Cooling to room temperature, 5 M NaCl solution (3 μL) and cold ethanol (200 μL). The mixture was stored at a -20 $^{\circ}\text{C}$ freezer for more than 30 minutes.
- 3) Centrifuge the sample for around 7 minutes in a microcentrifuge at 10000 rpm. The above supernatant was discarded and the precipitate was dried under vacuum. The DNA pellet was redissolved in H_2O (100 μL) and centrifuged for around 2 minutes in a microcentrifuge at 10000 rpm. An aliquot (50 μL) was taken and analyzed via HPLC-MS.

6.6 LC Trace and Mass Characterization of 74-103

LC Trace and Mass of 74



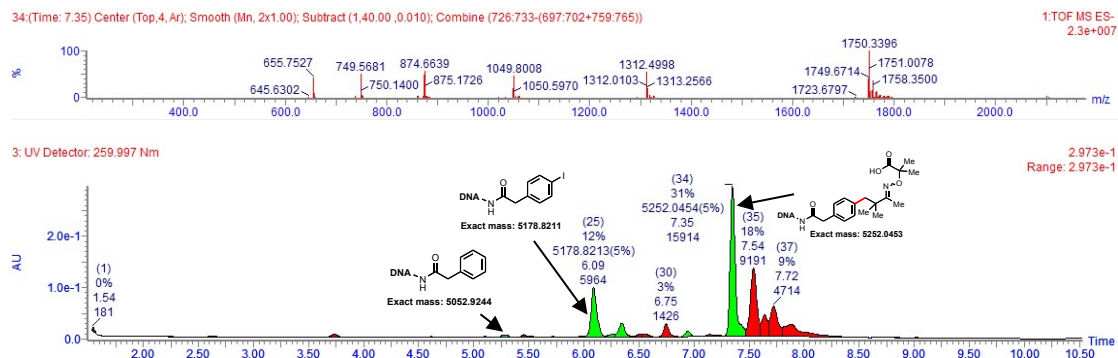
Following General Procedure 5 with C1.

$$\text{Yield: } \frac{31}{85} \times 100\% = 36\%$$

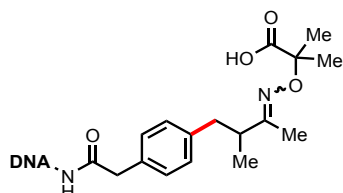
Ratio (product/deiodination/aryl iodide): 31/1/12

Exact mass: 5252.0453

Triply charged mass $[M]/3 - 1.00794$, calculated 1749.6738; observed 1749.6714.



LC Trace and Mass of 75



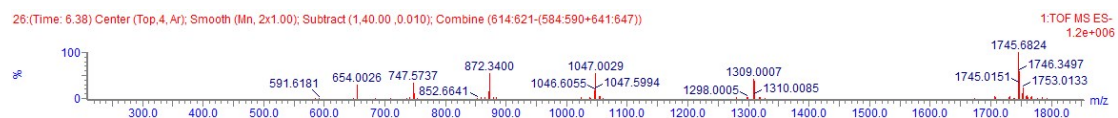
Following General Procedure 5 with C2.

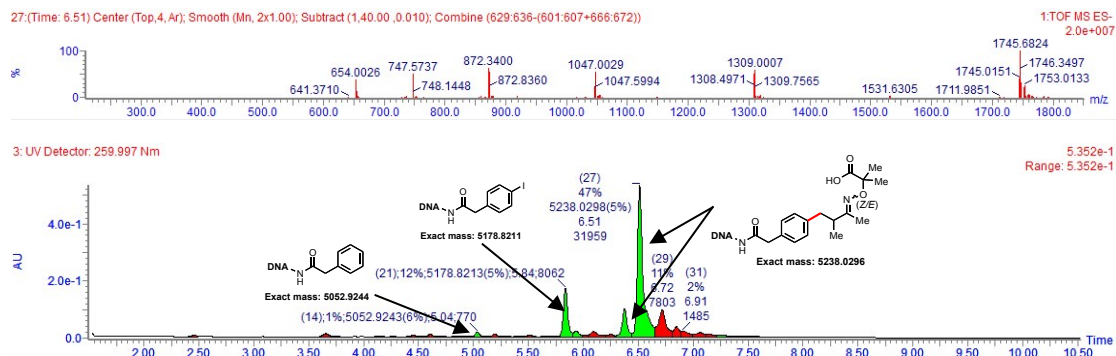
$$\text{Yield: } \frac{55}{85} \times 100\% = 65\%$$

Ratio (product/deiodination/aryl iodide): 55/1/12

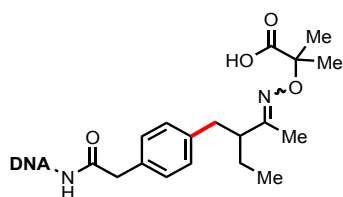
Exact mass: 5238.0296

Triply charged mass $[M]/3 - 1.00794$, calculated 1745.0019; observed 1745.0151.





LC Trace and Mass of 76



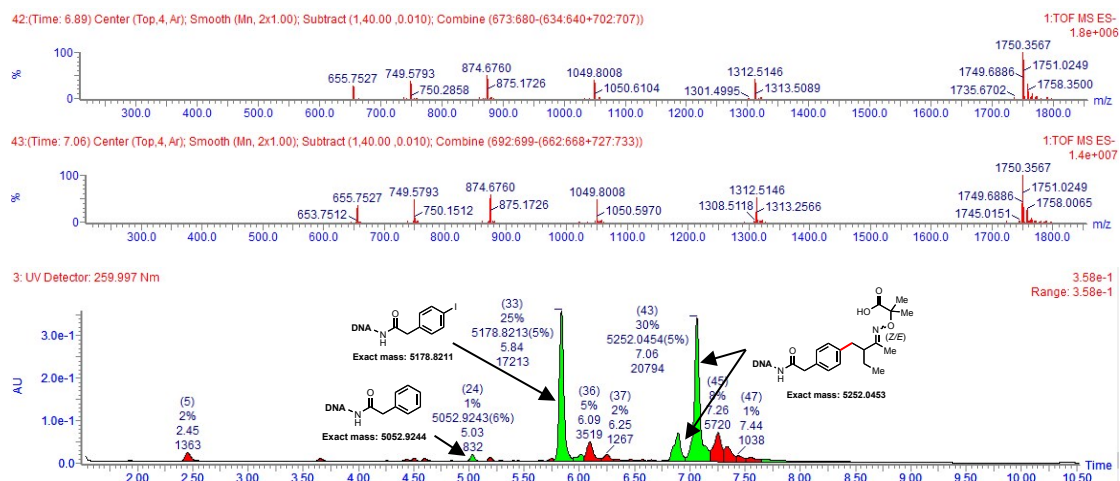
Following General Procedure 5 with C3.

$$\text{Yield: } \frac{38}{85} \times 100\% = 45\%$$

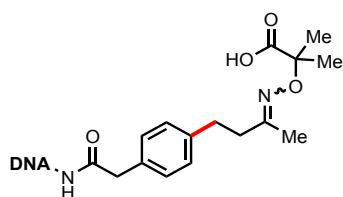
Ratio (product/deiodination/aryl iodide): 38/1/25

Exact mass: 5252.0453

Triply charged mass $[M]/3 - 1.00794$, calculated 1749.6738; observed 1749.6886.



LC Trace and Mass of 77



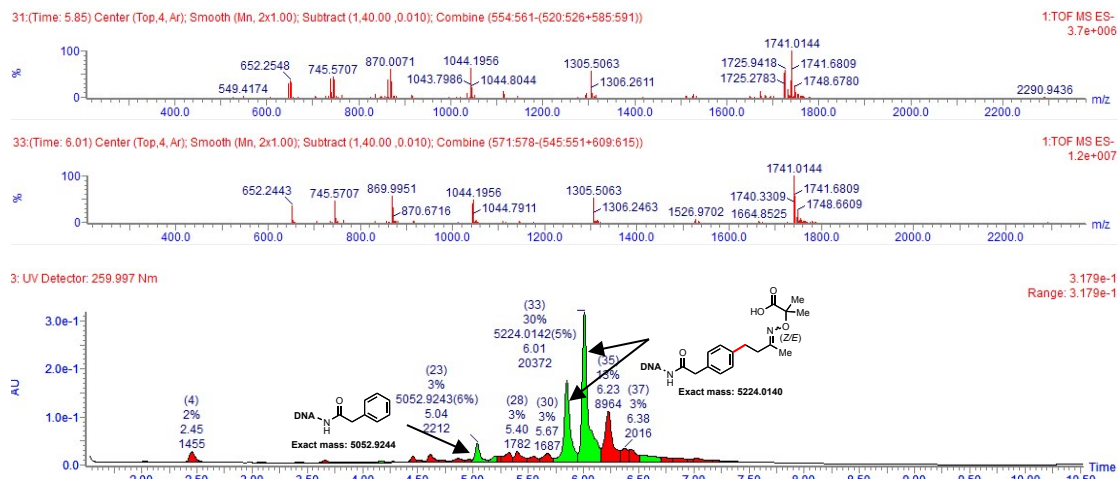
Following General Procedure 5 with C4.

$$\text{Yield: } \frac{47}{85} \times 100\% = 55\%$$

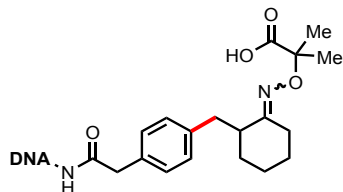
Ratio (product/deiodination/aryl iodide): 47/3/0

Exact mass: 5224.0140

Triply charged mass [M]/3 - 1.00794, calculated 1740.3301; observed 1740.3309.



LC Trace and Mass of 78



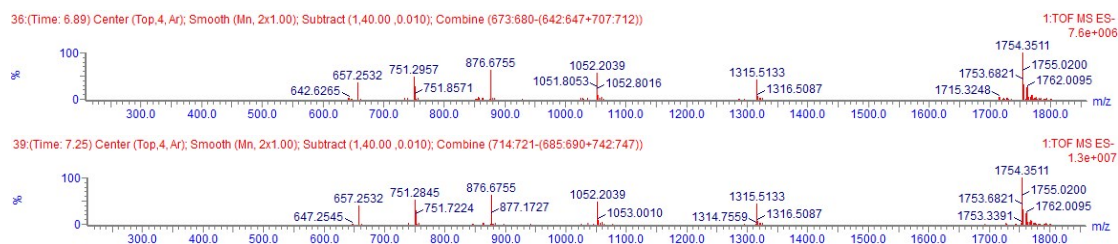
Following General Procedure 5 with C5.

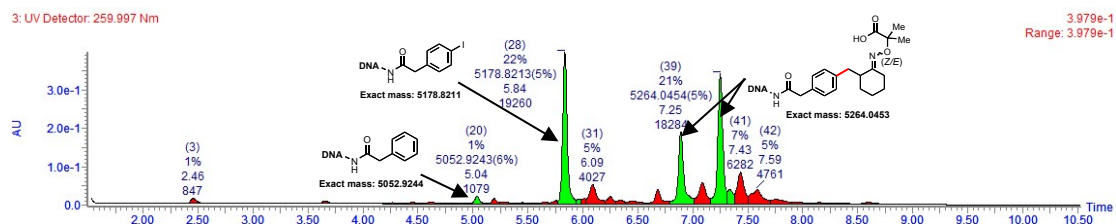
$$\text{Yield: } \frac{34}{85} \times 100\% = 40\%$$

Ratio (product/deiodination/aryl iodide): 34/1/22

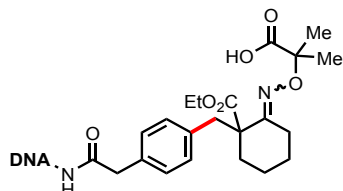
Exact mass: 5264.0453

Triply charged mass [M]/3 - 1.00794, calculated 1753.6738; observed 1753.6821.





LC Trace and Mass of 79



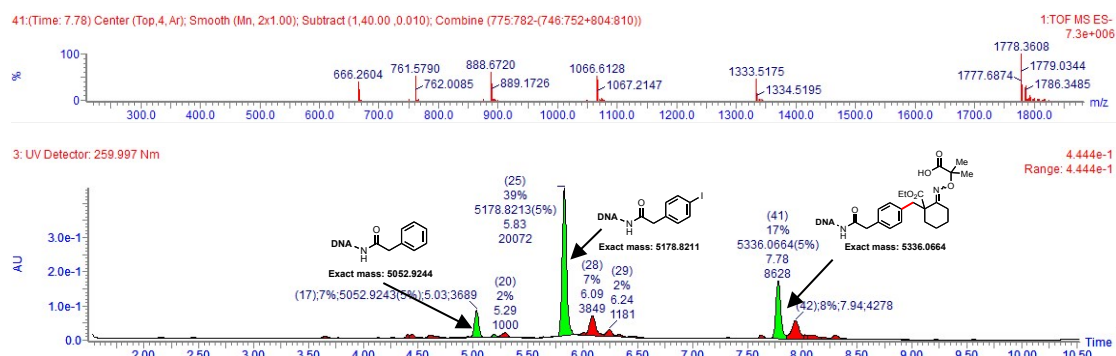
Following General Procedure 5 with C6.

$$\text{Yield: } \frac{17}{85} \times 100\% = 20\%$$

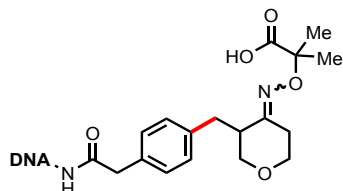
Ratio (product/deiodination/aryl iodide): 17/7/39

Exact mass: 5336.0664

Triply charged mass $[M]/3 - 1.00794$, calculated 1777.6809; observed 1777.6874.



LC Trace and Mass of 80



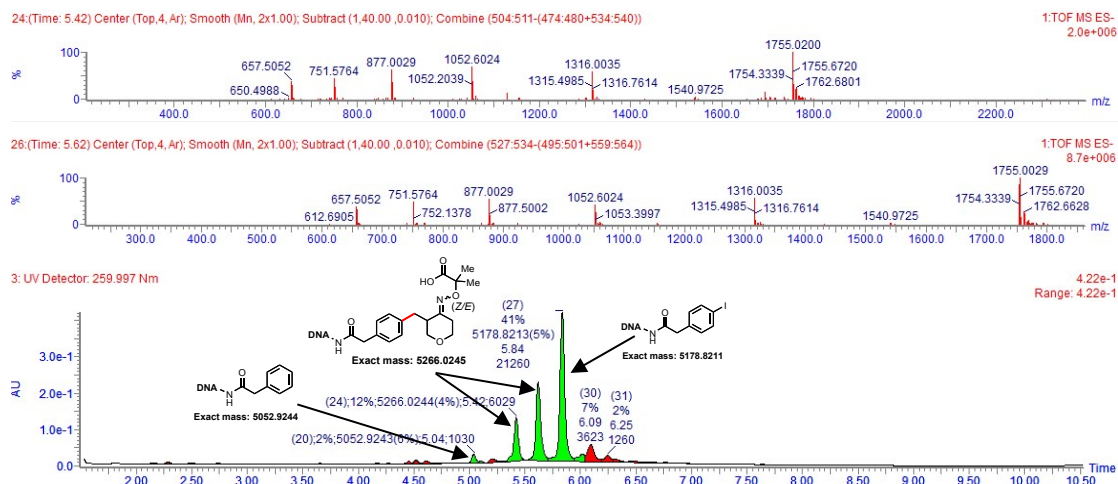
Following General Procedure 5 with C7.

$$\text{Yield: } \frac{34}{85} \times 100\% = 40\%$$

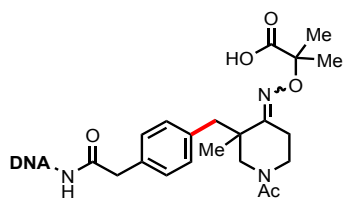
Ratio (product/deiodination/aryl iodide): 34/2/41

Exact mass: 5266.0245

Triply charged mass $[M]/3 - 1.00794$, calculated 1754.3336; observed 1754.3339.



LC Trace and Mass of 81



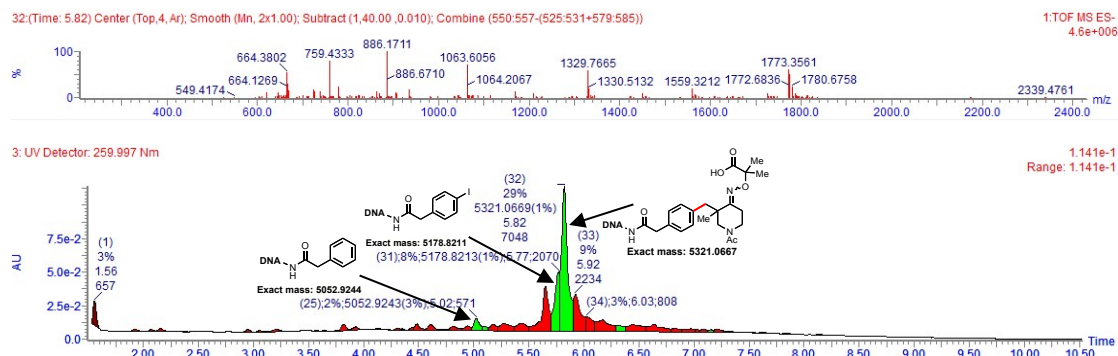
Following General Procedure 5 with **C8**.

$$\text{Yield: } \frac{29}{85} \times 100\% = 34\%$$

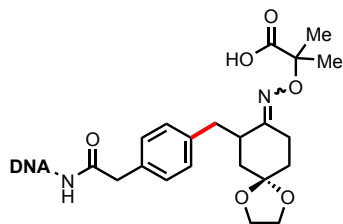
Ratio (product/deiodination/aryl iodide): 29/2/8

Exact mass: 5321.0667

Triply charged mass $[M]/3 - 1.00794$, calculated 1772.6810; observed 1772.6836.



LC Trace and Mass of 82



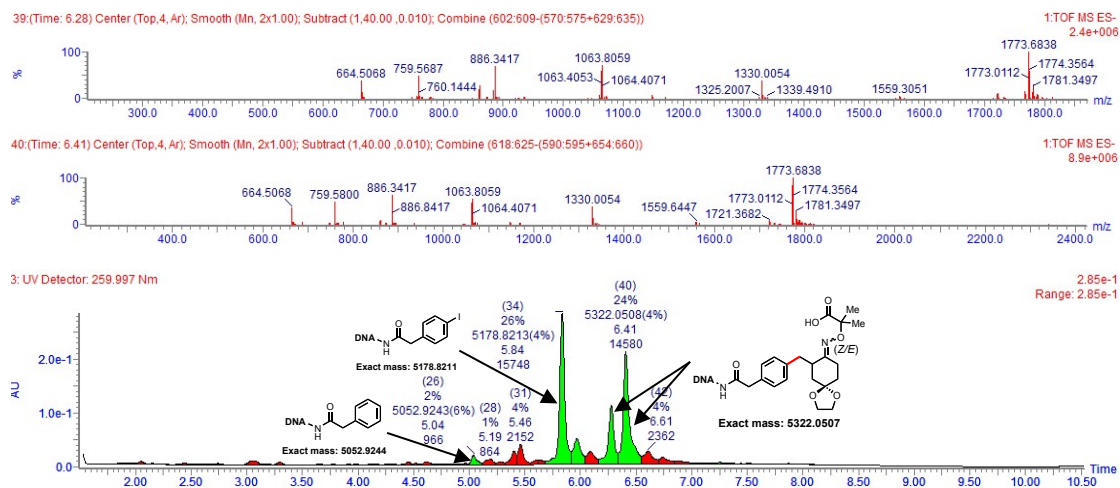
Following General Procedure 5 with **C9**.

$$\text{Yield: } \frac{36}{85} \times 100\% = 42\%$$

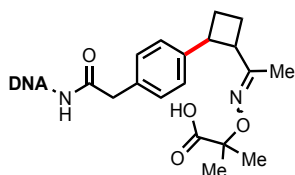
Ratio (product/deiodination/aryl iodide): 36/2/26

Exact mass: 5322.0507

Triply charged mass $[M]/3 - 1.00794$, calculated 1773.0090; observed 1773.0112.



LC Trace and Mass of 83



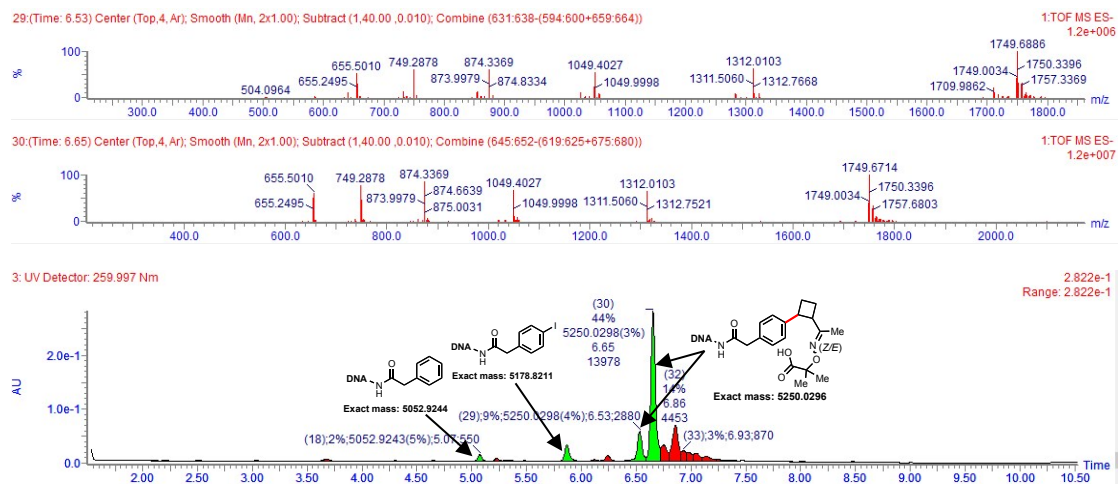
Following General Procedure 5 with **C10**.

$$\text{Yield: } \frac{53}{85} \times 100\% = 62\%$$

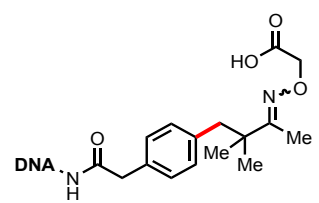
Ratio (product/deiodination/aryl iodide): 53/2/5

Exact mass: 5250.0296

Triply charged mass $[M]/3 - 1.00794$, calculated 1749.0019; observed 1749.0034.



LC Trace and Mass of 84



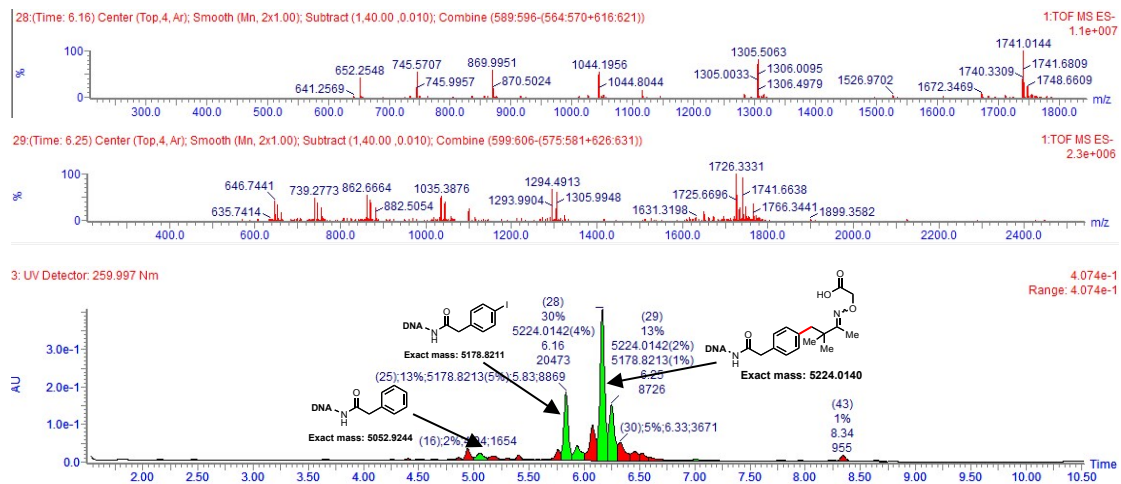
Following General Procedure 5 with C11.

Yield: $\frac{36}{85} \times 100\% = 42\%$

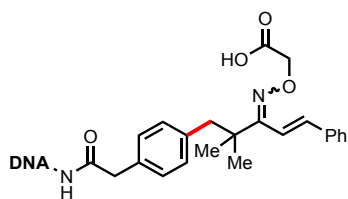
Ratio (product/deiodination/aryl iodide): 36/2/13

Exact mass: 5224.0140

Triply charged mass [M]/3 - 1.00794, calculated 1740.3301; observed 1740.3309.



LC Trace and Mass of 85



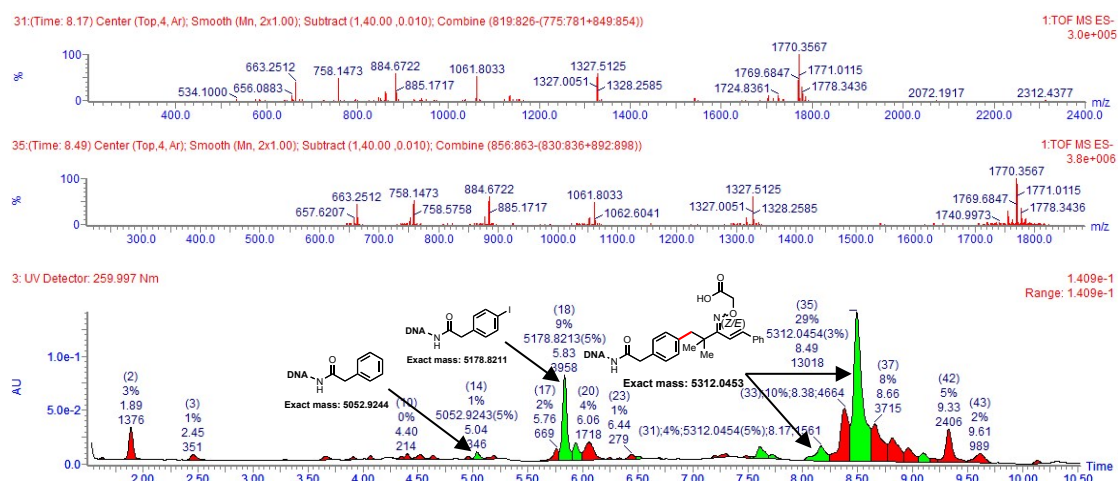
Following General Procedure 5 with **C12**.

$$\text{Yield: } \frac{33}{85} \times 100\% = 39\%$$

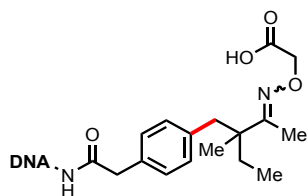
Ratio (product/deiodination/aryl iodide): 33/1/9

Exact mass: 5312.0453

Triply charged mass $[M]/3 - 1.00794$, calculated 1769.6738; observed 1769.6847.



LC Trace and Mass of 86



Following General Procedure 5 with **C13**.

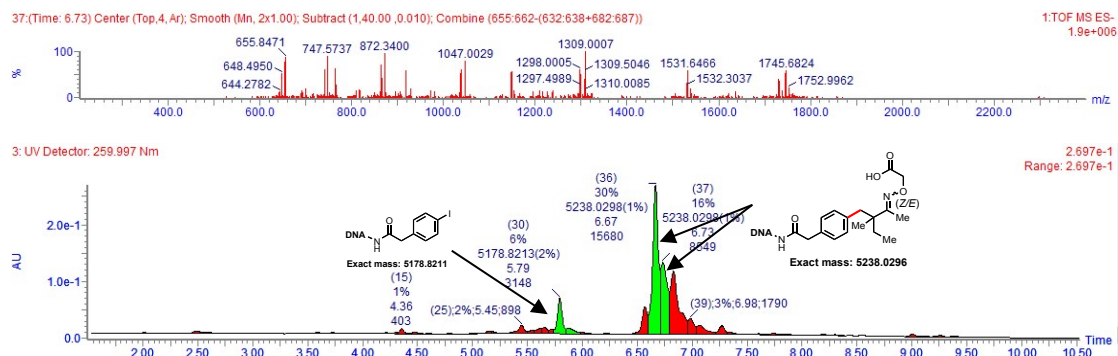
$$\text{Yield: } \frac{38}{85} \times 100\% = 45\%$$

Ratio (product/deiodination/aryl iodide): 38/0/6

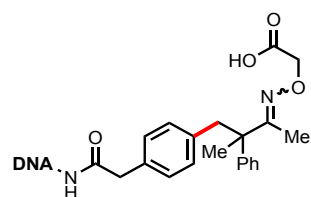
Exact mass: 5238.0296

Triply charged mass $[M]/3 - 1.00794$, calculated 1745.0019; observed 1744.9980.





LC Trace and Mass of 87



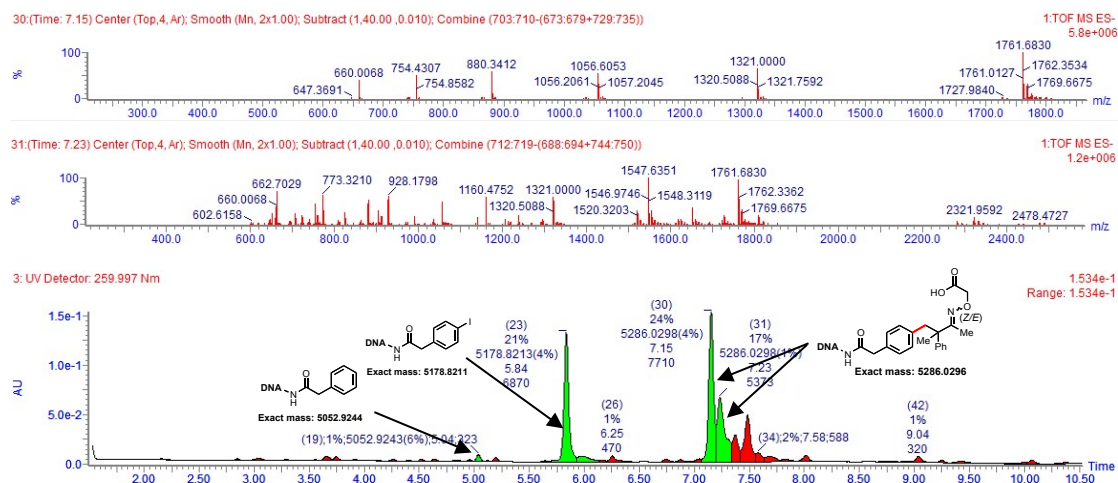
Following General Procedure 5 with C14.

$$\text{Yield: } \frac{32}{85} \times 100\% = 38\%$$

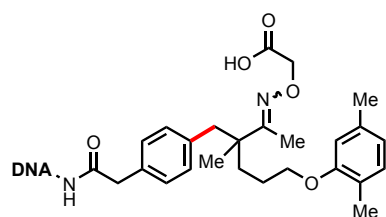
Ratio (product/deiodination/aryl iodide): 32/1/21

Exact mass: 5286.0296

Triply charged mass $[M]/3 - 1.00794$, calculated 1761.0019; observed 1761.0127.



LC Trace and Mass of 88



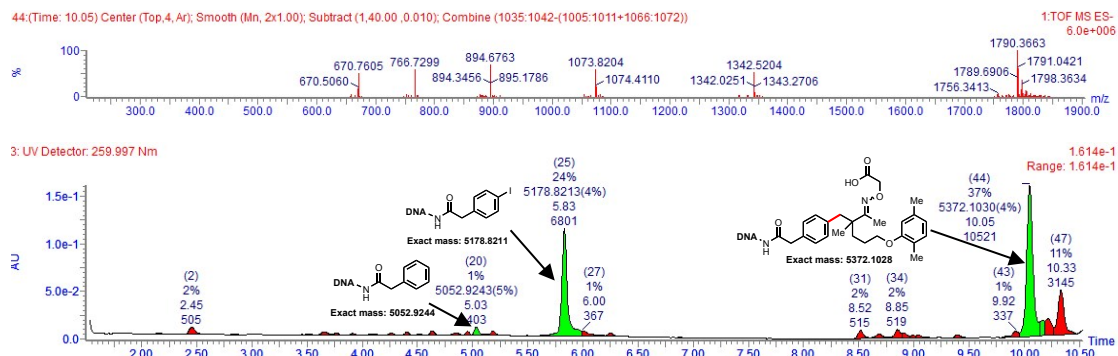
Following General Procedure 5 with **C15**.

$$\text{Yield: } \frac{37}{85} \times 100\% = 44\%$$

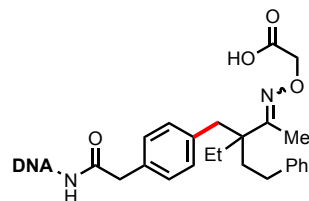
Ratio (product/deiodination/aryl iodide): 37/1/24

Exact mass: 5372.1028

Triply charged mass [M]/3 - 1.00794, calculated 1789.6930; observed 1789.6906.



LC Trace and Mass of 89



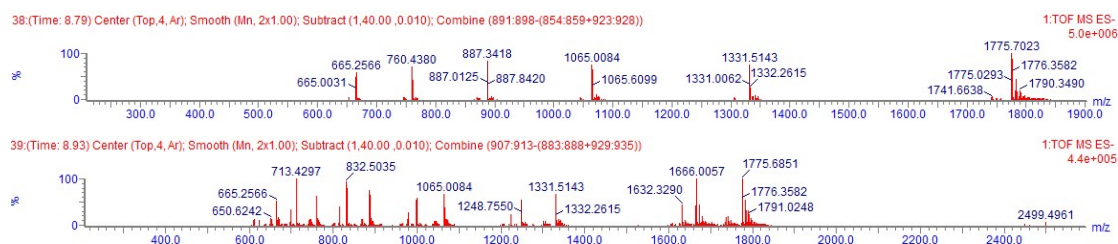
Following General Procedure 5 with **D16** except for employing Pd(OAc)₂ (15 mM) and **L8** (15 mM) in H₂O/DMA (2/1).

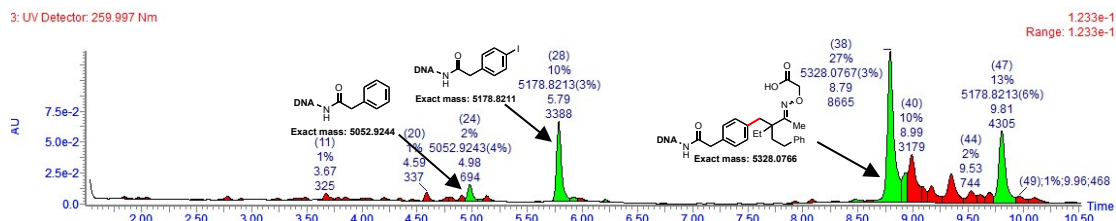
$$\text{Yield: } \frac{29}{85} \times 100\% = 34\%$$

Ratio (product/deiodination/aryl iodide): 29/2/10

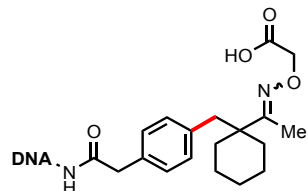
Exact mass: 5328.0766

Triply charged mass [M]/3 - 1.00794, calculated 1775.0176; observed 1775.0293.





LC Trace and Mass of 90



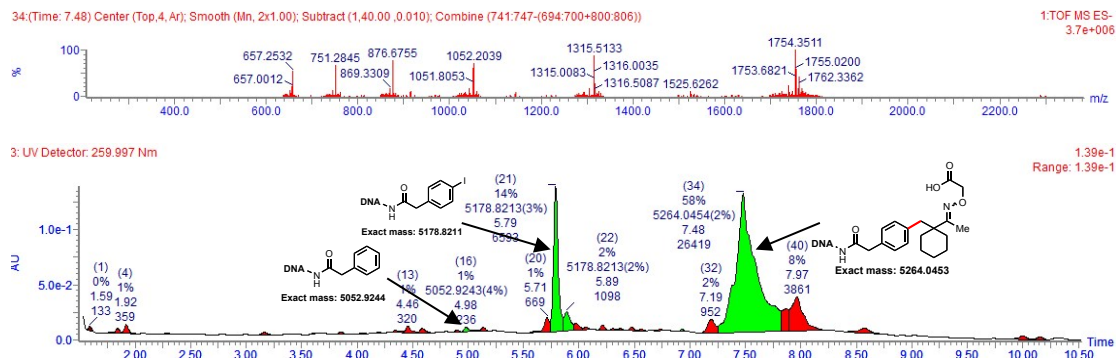
Following General Procedure 5 with **C17** except for employing Pd(OAc)₂ (15 mM) and **L8** (15 mM) in H₂O/DMA (2/1).

$$\text{Yield: } \frac{58}{85} \times 100\% = 68\%$$

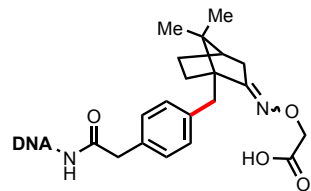
Ratio (product/deiodination/aryl iodide): 58/1/14

Exact mass: 5264.0453

Triply charged mass [M]/3 - 1.00794, calculated 1753.6738; observed 1753.6821.



LC Trace and Mass of 91



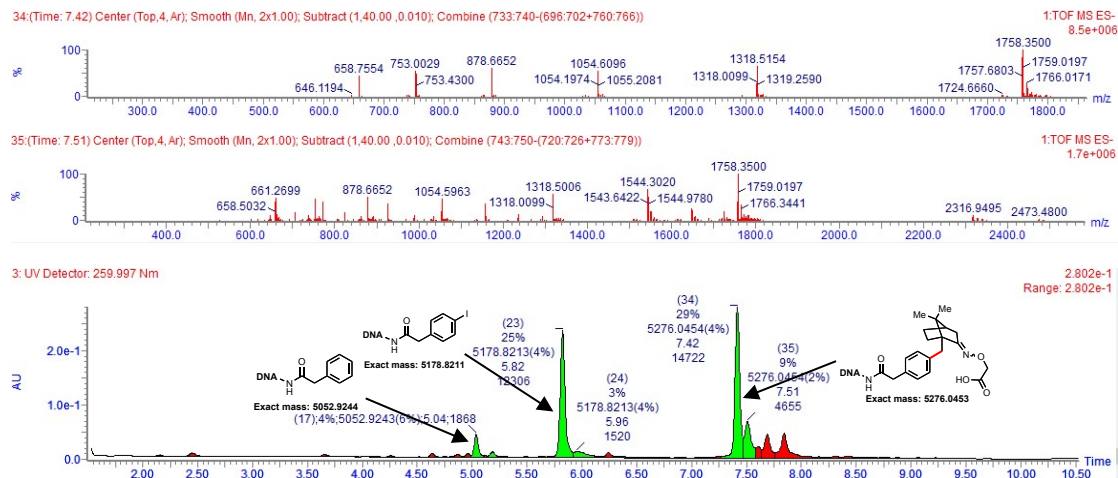
Following General Procedure 5 with **C18**.

$$\text{Yield: } \frac{34}{85} \times 100\% = 40\%$$

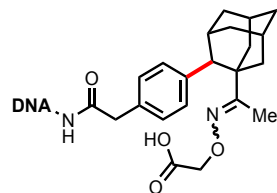
Ratio (product/deiodination/aryl iodide): 34/4/25

Exact mass: 5276.0453

Triply charged mass $[M]/3 - 1.00794$, calculated 1757.6738; observed 1757.6803.



LC Trace and Mass of 92



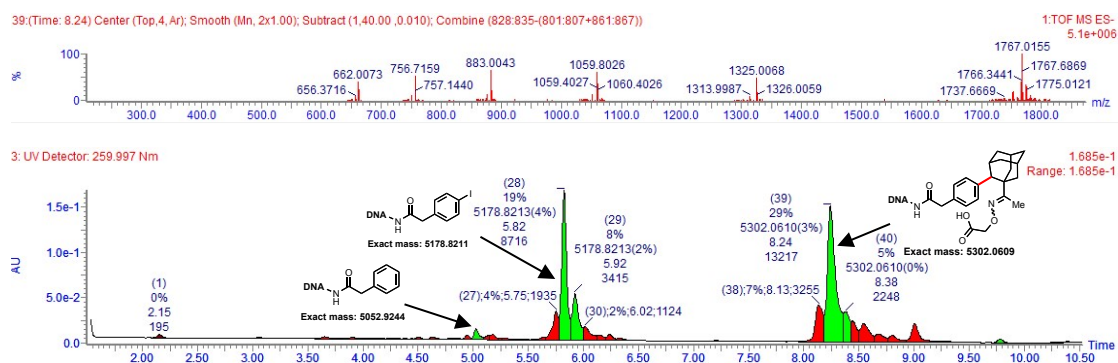
Following General Procedure 5 with C19.

$$\text{Yield: } \frac{29}{85} \times 100\% = 34\%$$

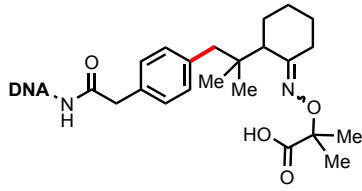
Ratio (product/deiodination/aryl iodide): 29/1/19

Exact mass: 5302.0609

Triply charged mass $[M]/3 - 1.00794$, calculated 1766.3457; observed 1766.3441.



LC Trace and Mass of 93



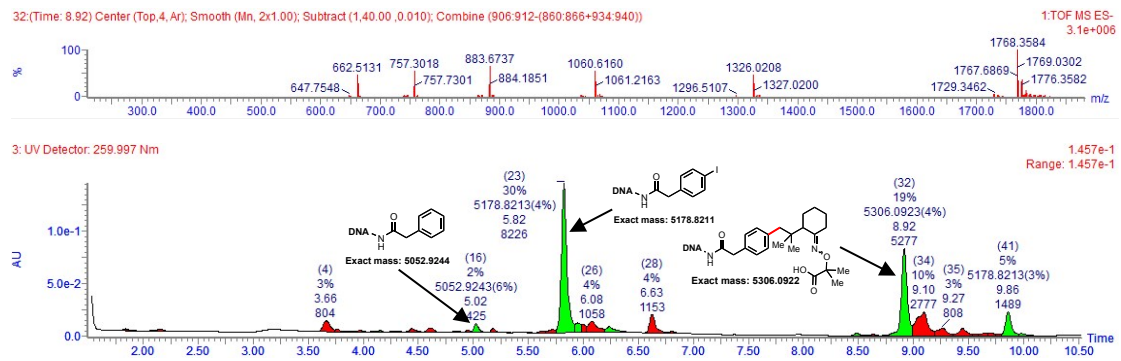
Following General Procedure 5 with **C20**.

Yield: $\frac{19}{85} \times 100\% = 22\%$

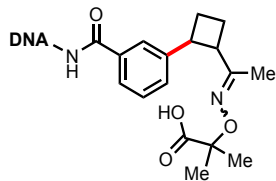
Ratio (product/deiodination/aryl iodide): 19/2/30

Exact mass: 5306.0922

Triply charged mass $[M]/3 - 1.00794$, calculated 1767.6895; observed 1767.6869.



LC Trace and Mass of 94



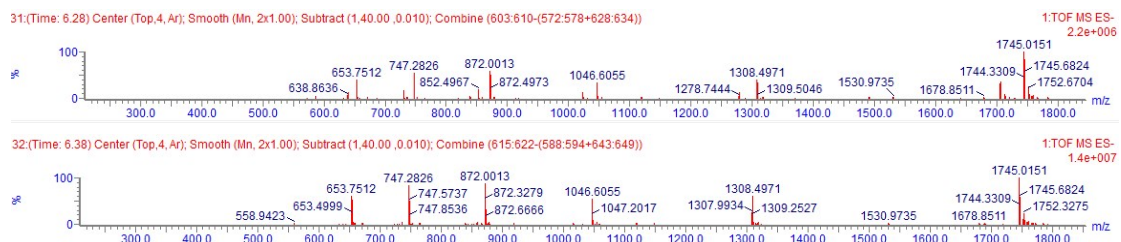
Following General Procedure 5 with **S7** and **C10**.

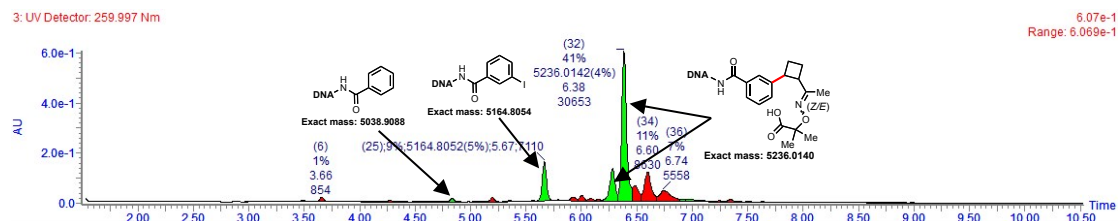
Yield: $\frac{51}{83} \times 100\% = 61\%$

Ratio (product/deiodination/aryl iodide): 51/1/9

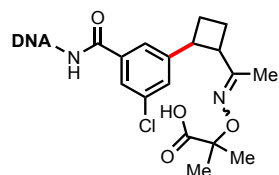
Exact mass: 5236.0140

Triply charged mass $[M]/3 - 1.00794$, calculated 1744.3301; observed 1744.3309.





LC Trace and Mass of 95



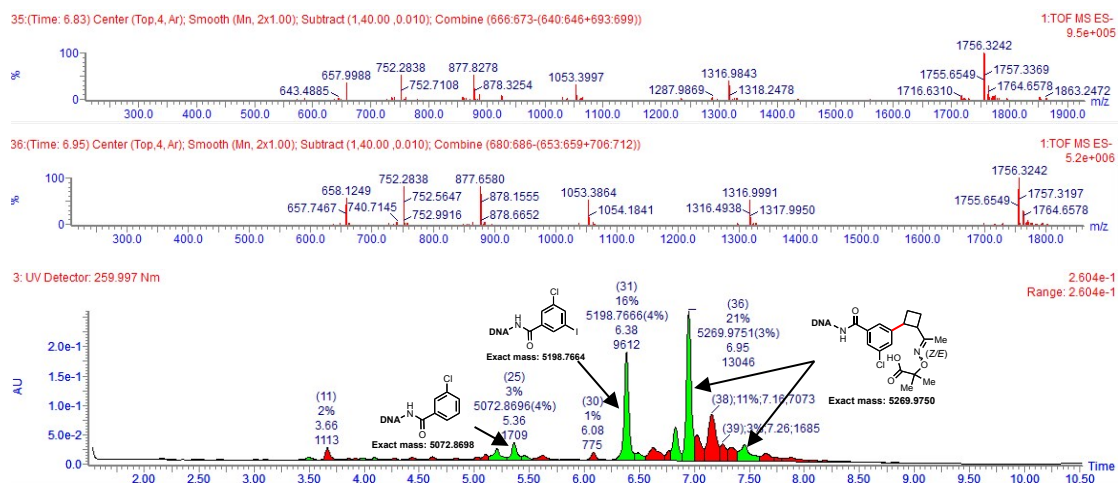
Following General Procedure 5 with **S9** and **C10**.

$$\text{Yield: } \frac{26}{71} \times 100\% = 37\%$$

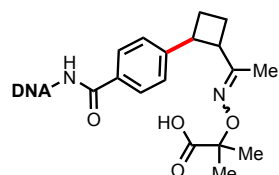
Ratio (product/deiodination/aryl iodide): 26/3/16

Exact mass: 5269.9750

Triply charged mass $[M]/3 - 1.00794$, calculated 1755.6504; observed 1755.6549.



LC Trace and Mass of 96



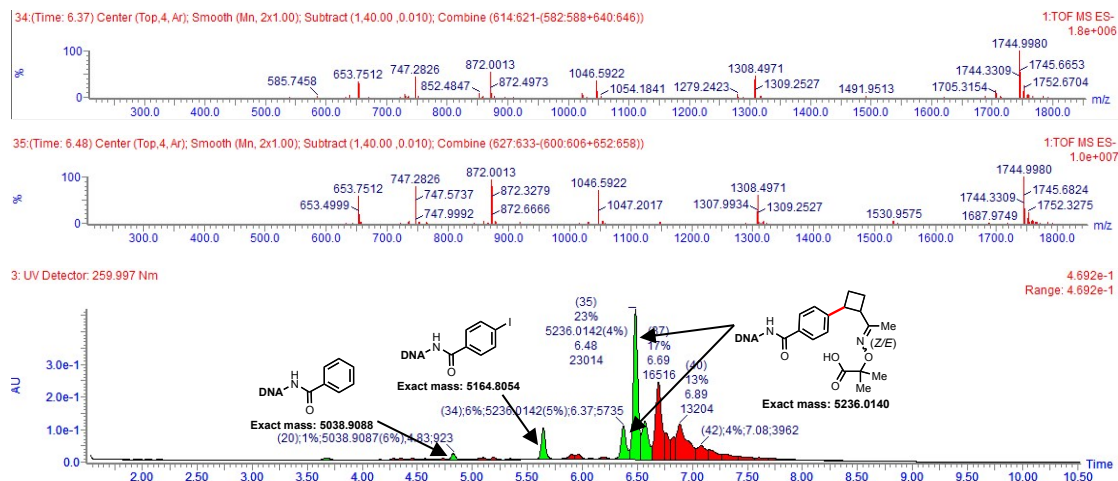
Following General Procedure 5 with **S10** and **C10**.

$$\text{Yield: } \frac{29}{85} \times 100\% = 34\%$$

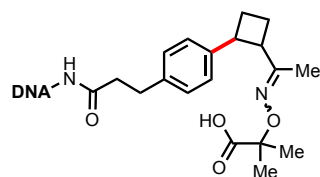
Ratio (product/deiodination/aryl iodide): 29/1/4

Exact mass: 5236.0140

Triply charged mass $[M]/3 - 1.00794$, calculated 1744.3301; observed 1744.3309.



LC Trace and Mass of 97



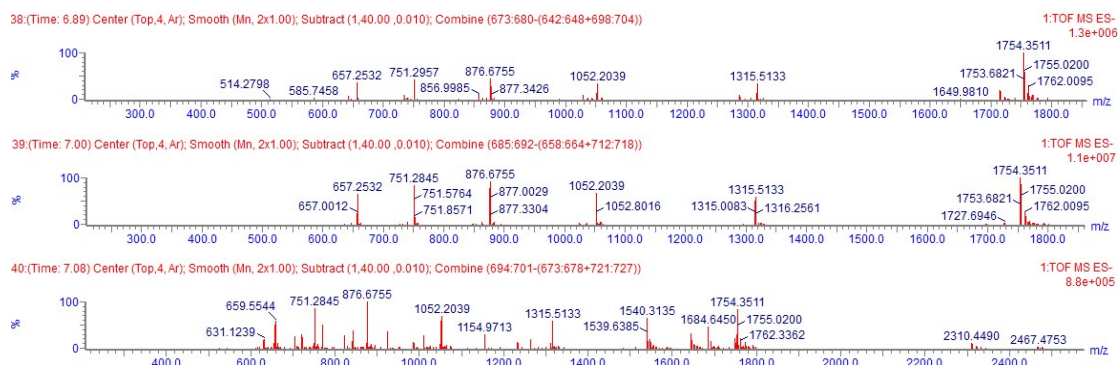
Following General Procedure 5 with **S3** and **C10**.

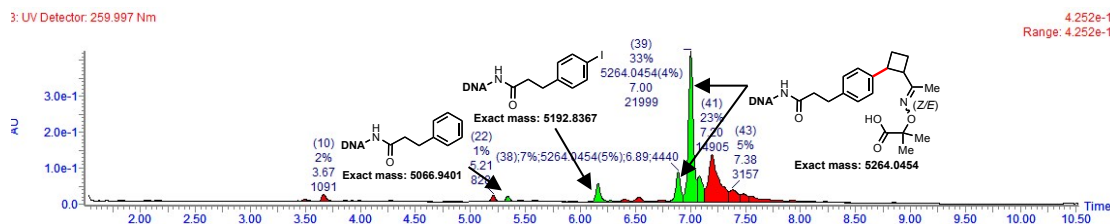
$$\text{Yield: } \frac{43}{78} \times 100\% = 55\%$$

Ratio (product/deiodination/aryl iodide): 43/1/4

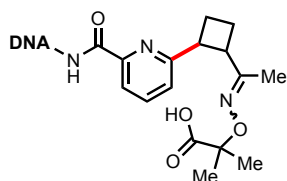
Exact mass: 5264.0454

Triply charged mass $[M]/3 - 1.00794$, calculated 1753.6739; observed 1753.6821.





LC Trace and Mass of 98



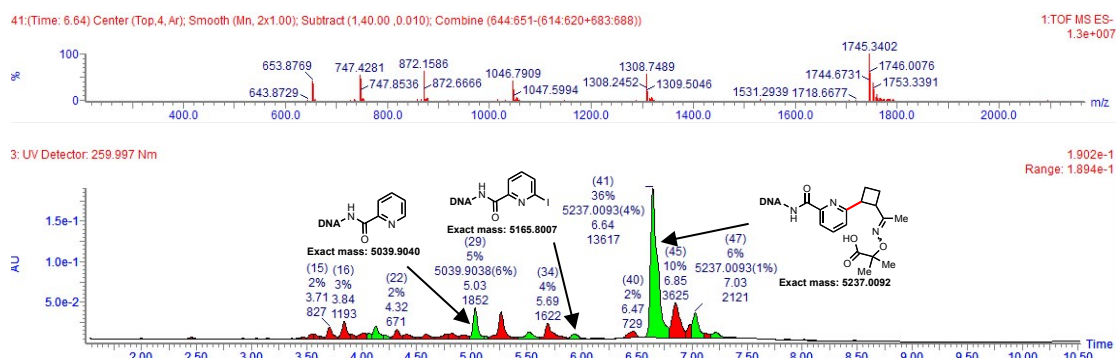
Following General Procedure 5 with **S14** and **C10**.

$$\text{Yield: } \frac{36}{57} \times 100\% = 63\%$$

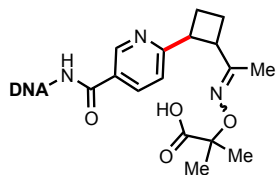
Ratio (product/deiodination/aryl iodide): 36/5/1

Exact mass: 5237.0092

Triply charged mass $[M]/3 - 1.00794$, calculated 1744.6618; observed 1744.6731.



LC Trace and Mass of 99



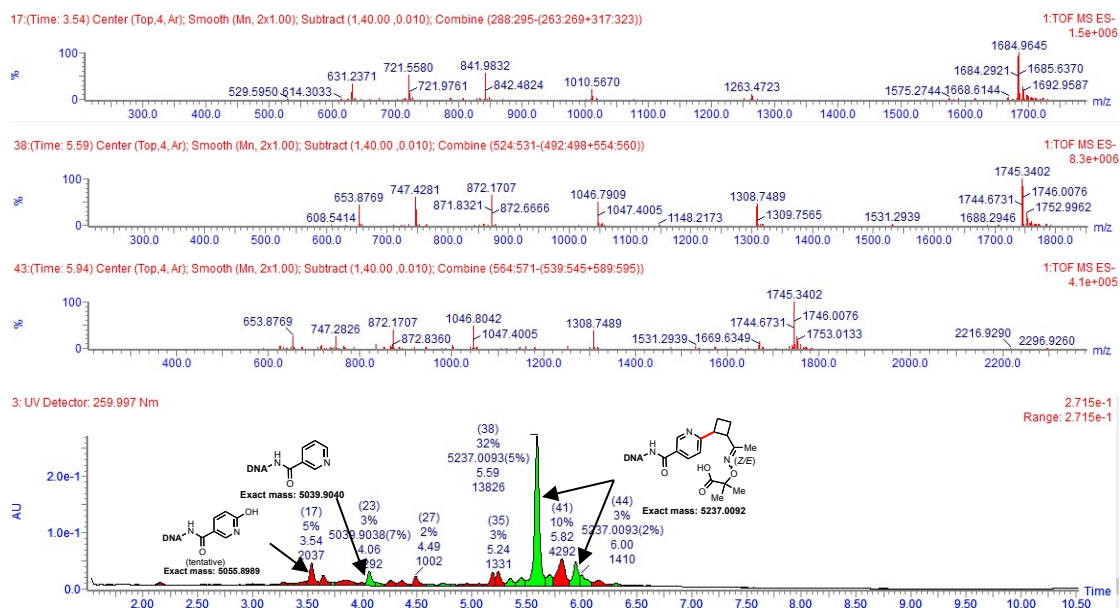
Following General Procedure 5 with **S15** and **C10**.

$$\text{Yield: } \frac{38}{65} \times 100\% = 58\%$$

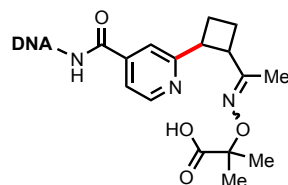
Ratio (product/deiodination/aryl iodide): 38/3/0

Exact mass: 5237.0092

Triply charged mass $[M]/3 - 1.00794$, calculated 1744.6618; observed 1744.6731.



LC Trace and Mass of 100



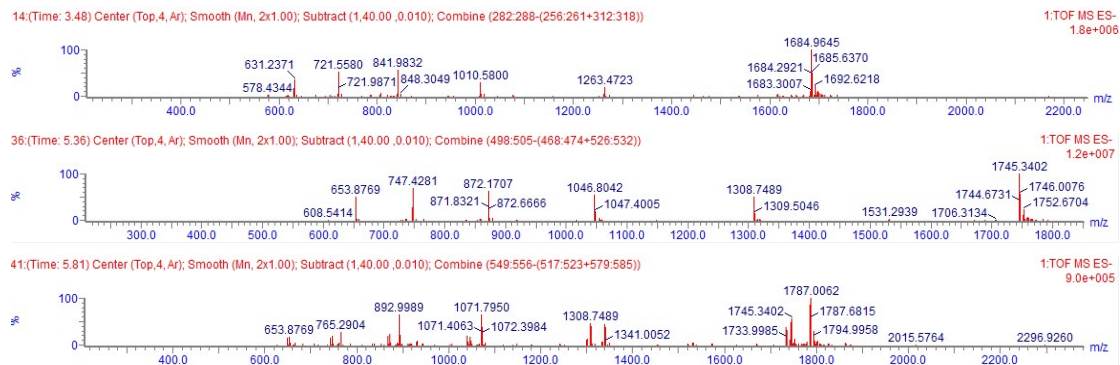
Following General Procedure 5 with **S18** and **C10**.

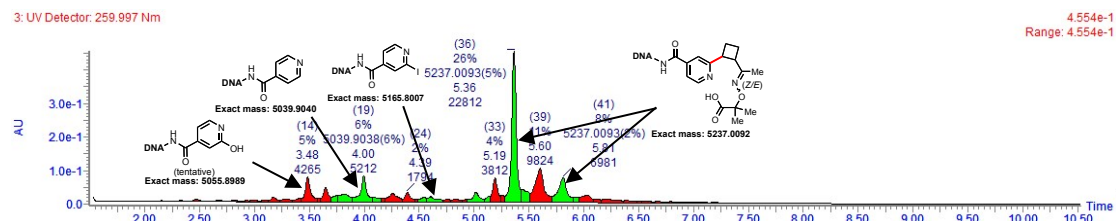
$$\text{Yield: } \frac{29}{56} \times 100\% = 52\%$$

Ratio (product/deiodination/aryl iodide): 29/6/2

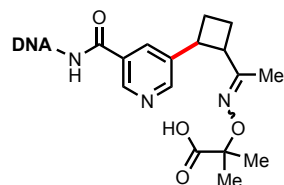
Exact mass: 5237.0092

Triply charged mass $[M]/3 - 1.00794$, calculated 1744.6618; observed 1744.6731.





LC Trace and Mass of 101



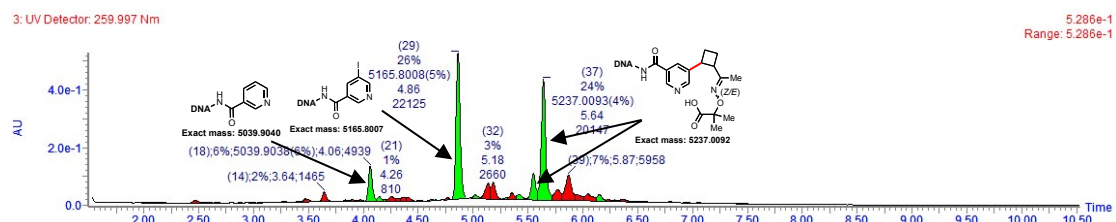
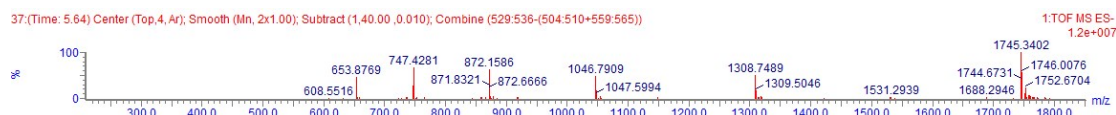
Following General Procedure 5 with **S16** and **C10**.

$$\text{Yield: } \frac{29}{79} \times 100\% = 37\%$$

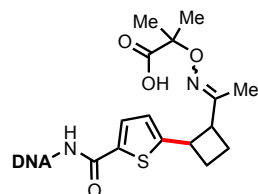
Ratio (product/deiodination/aryl iodide): 29/6/26

Exact mass: 5237.0092

Triply charged mass $[M]/3 - 1.00794$, calculated 1744.6618; observed 1744.6731.



LC Trace and Mass of 102



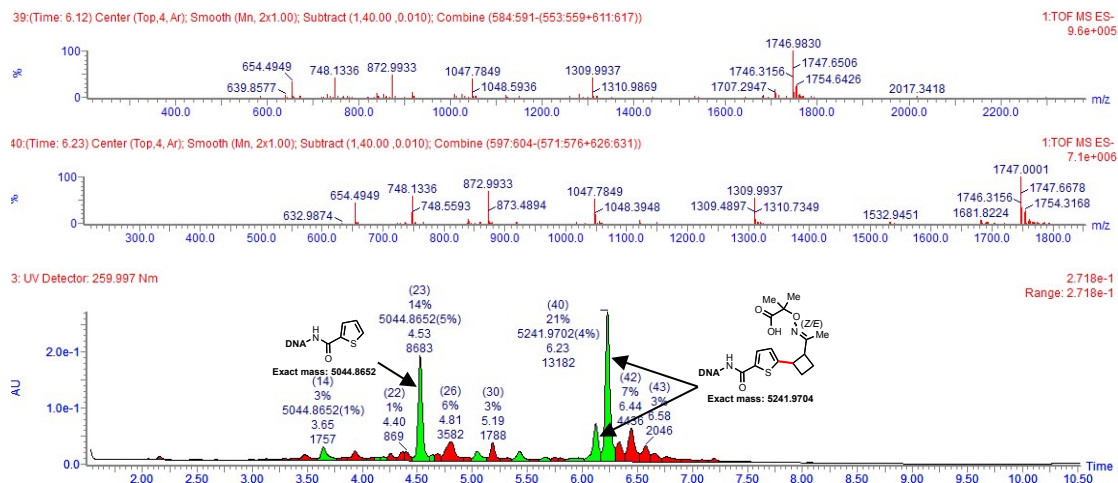
Following General Procedure 5 with **S23** and **C10**.

$$\text{Yield: } \frac{28}{69} \times 100\% = 41\%$$

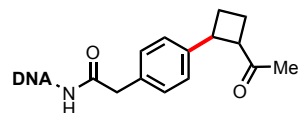
Ratio (product/deiodination/aryl iodide): 28/14/0

Exact mass: 5241.9704

Triply charged mass $[M]/3 - 1.00794$, calculated 1746.3155; observed 1746.3156.



LC Trace and Mass of 103

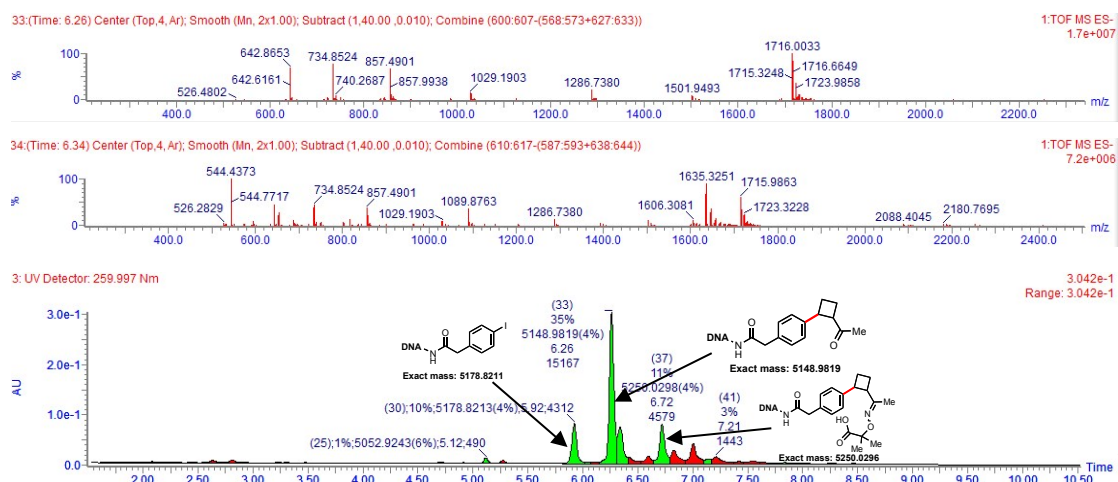


Following General Procedure 6 with **83**.

$$\text{Yield: } \frac{40}{53} \times 100\% = 75\%$$

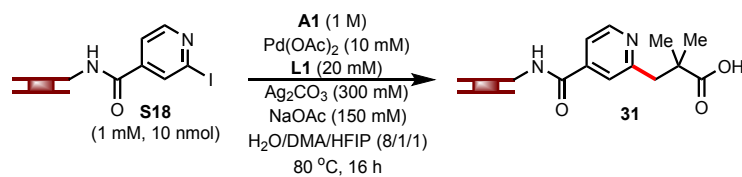
Exact mass: 5148.9819

Triply charged mass $[M]/3 - 1.00794$, calculated 1715.3194; observed 1715.3248.



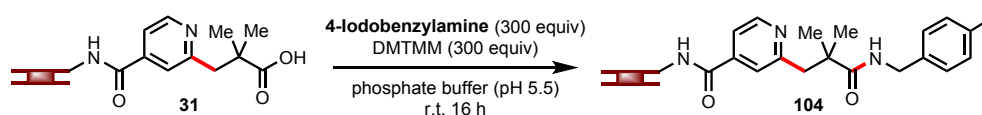
7. Representative Synthesis of 105

Step 1: 1st C(sp³)-H activation



LC Trace and Mass of 31, see above.

Step 2: amidation



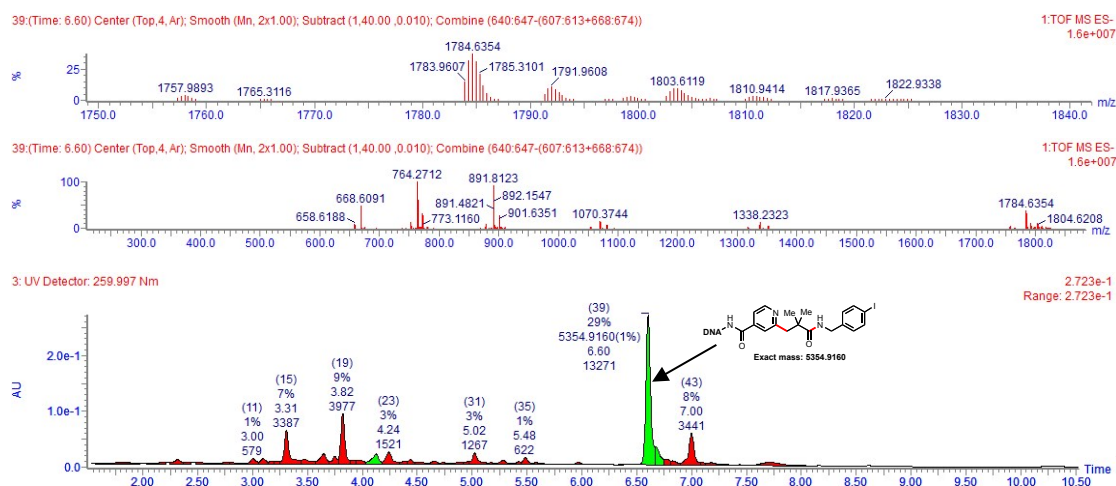
LC Trace and Mass of 104

Following General Procedure 4 with **31** and 4-iodobenzylamine.

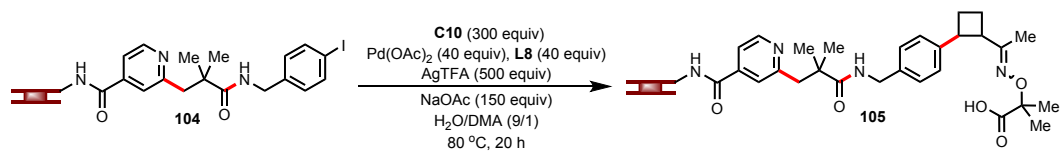
$$\text{Yield: } \frac{29}{41} \times 100\% = 71\%$$

Exact mass: 5354.9160

Triply charged mass $[M]/3 - 1.00794$, calculated 1783.9641; observed 1783.9607.



Step 3: 2nd C(sp³)-H activation



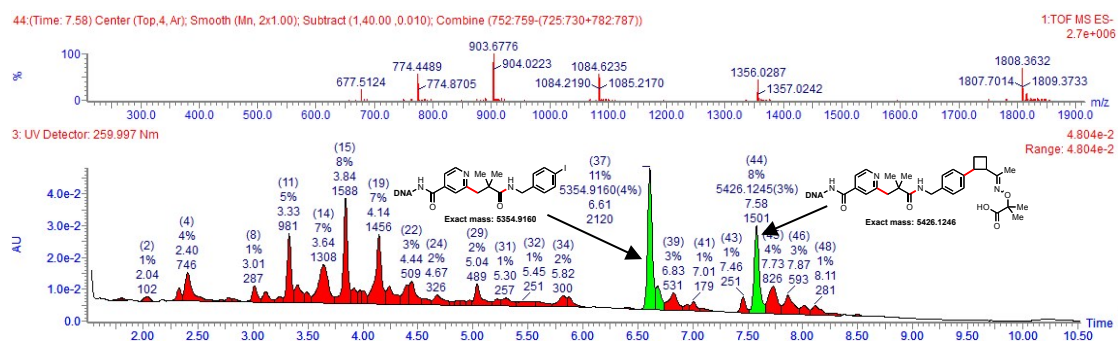
LC Trace and Mass of 105

Following General Procedure 5 with **104** and **C10**.

$$\text{Yield: } \frac{8}{29} \times 100\% = 28\%$$

Exact mass: 5426.1246

Triply charged mass [M]/3 - 1.00794, calculated 1807.7003; observed 1807.7014.



8. Evaluation of the DNA Tags Degradation

General Procedure 7

65-mer DNA Tag: ‘TOP’ and ‘BOTTOM’ ssDNA oligonucleotides purchased from IDT were dissolved in annealing buffer (10 mM Tris, 1 mM EDTA, 50 mM NaCl, pH 8.0), heated to 95 °C for 5 minutes, and then allowed to cool to RT over the course of 20 minutes.

DNA Ligation: To each 2 µL DNA-pellets (1 mM) was added 4 µL 10x ligation buffer, 32 µL annealed 65-mer DNA tag (100 µM solution in annealing buffer), and 2 µL T4 DNA ligase (400 U/µL, NEB). The ligations were incubated for 90 minutes at RT. Analysis via gel electrophoresis indicated that the ligations had completed. The product was purified with a Zymo DNA spin column. The purified products were analyzed with 6% native PAGE and stained with SYBR gold.

PCR Amplification: PCR of ligated DNA was performed in a mixture containing 200 µM each of dNTPs, 0.02 U/µl Q5 DNA Polymerase, 0.5 µM each of Forward Primer and Reverse Primer, and 1 nM template (ligated DNA) were mixed in 1× Q5 reaction buffer. The PCR reaction was carried out with the following thermocycling program: 98 °C, 120 s; 14 cycles of (98 °C, 10 s; 64 °C, 30 s; 72 °C, 30 s); 72 °C, 2 min. PCR products were assayed with 6% native PAGE, stained with SYBR gold and imaged using a Molecular Imager Gel Doc XR+ equipped with a 520DF30 filter (Bio-Rad).

DNA Sequencing: To detect the amplification is successful or not, designed primers were installed part of the adapters required for Illumina next-generation DNA sequencing. Then submitting the PCR products to GENEWIZ for Sanger sequencing with the following primer (5' → 3'): AGT TCA GAC GTG TGC TCT TCC. This primer was chosen to get reliable data for the region of the barcode that was present during the C-H activation reaction.

qPCR: Quantitative PCR experiments was performed on a Real Time PCR system with SYBR Green as the detection dye. qPCR was performed in a mixture containing 200 µM each of dNTPs, 0.02 U/µl Q5 DNA Polymerase, 0.5 µM each of Forward

Primer and Reverse Primer, and 1 nM template (ligated DNA) were mixed in 1× Q5 reaction buffer. The PCR reaction was carried out with the following thermocycling program: 98 °C, 120 s; 30 cycles of (98 °C, 10 s; 64 °C, 30 s; 72 °C, 30 s); 72 °C, 2 min. Calibration plots for each templated were generated with different concentrations of standard nucleic acid samples in 30 μL PCR system under standard conditions. The log of initial template concentration was plotted vs. the threshold cycle and a linear function was fitted to the data. Meanwhile, 10⁵ dilution of each samples was used in a 30 μL qPCR system as templates for quantification using calibration plot acquired above.

Table S15. ssDNA Oligonucleotides and PCR Primers Used to Amplify DNA

Barcode	
Name	Sequence (5' → 3')
“Top”	/5Phos/AAA TCG ATG TGG TCA GGA AGC AGG TTC GTC TGC TGT GAC ATC GTG TTC AGA CAA GCT TCA CCT GC
“Bottom”	/5Phos/GCA GGT GAA GCT TGT CTG AAC ACG ATG TCA CAG CAG ACG AAC CTG CTT CCT GAC CAC ATC GAT TTG G
Forward	5'-ACA CTC TTT CCC TAC ACG ACG CTC TTC CGA TCT NNN NTG ACT CCC AAA TCG ATG TG
Reverse	5'-TGG AGT TCA GAC GTG TGC TCT TCC GAT CTG CAG GTG AAG CTT GTC TG

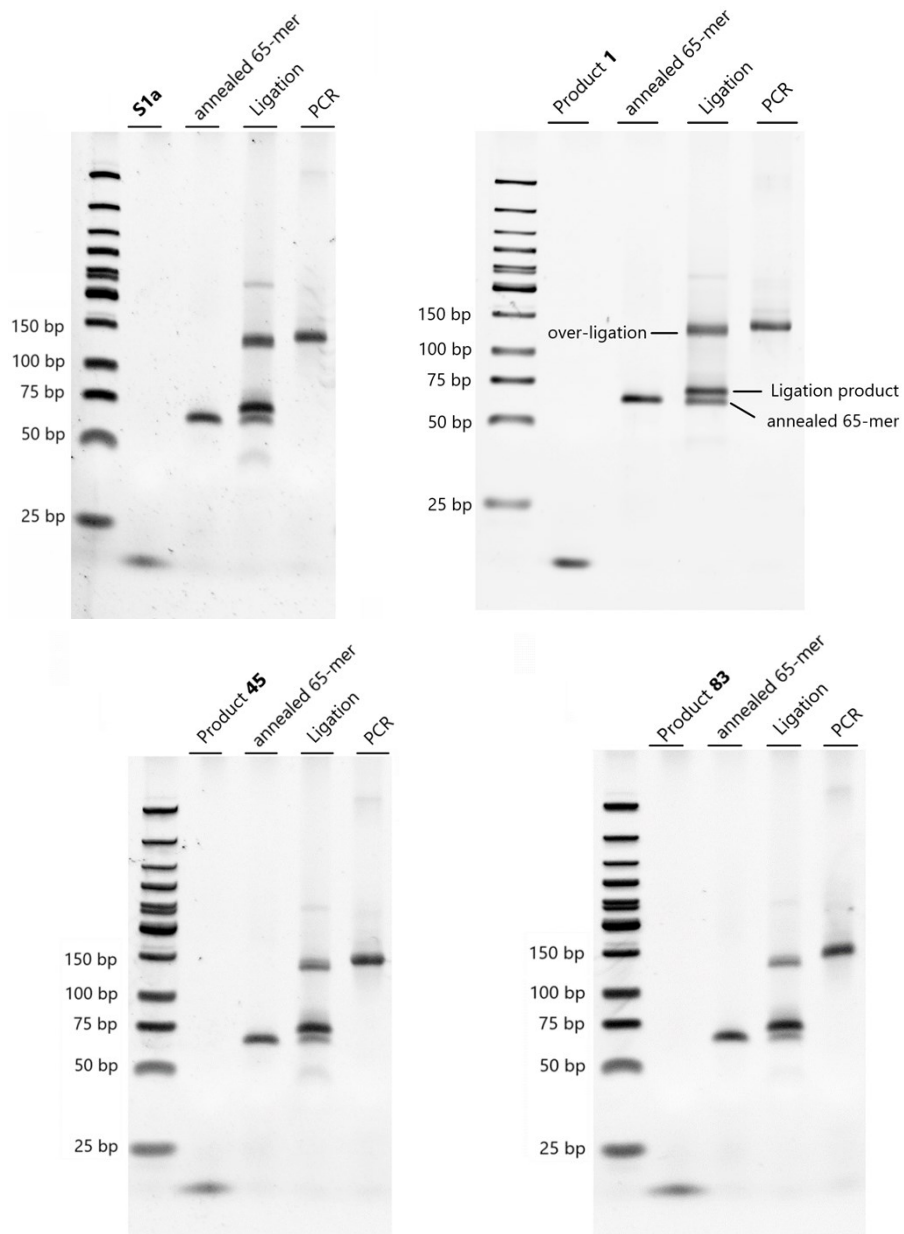
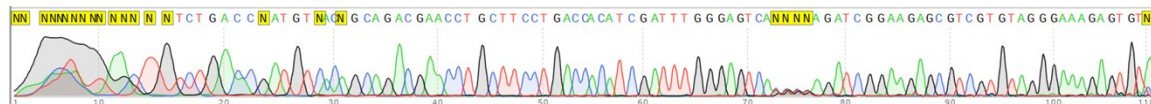


Figure S2. Assessment of DNA ligation and PCR amplification via gel electrophoresis (6% native PAGE)

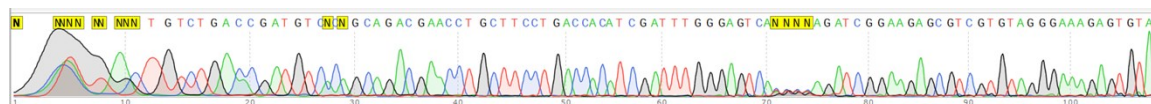
Expected sequence: AGA CGA ACC TGC TTC CTG ACC ACA TCG ATT **TGG GAG TCA NNN NAG ATC GGA AGA GCG TCG TGT AGG GAA AGA GTG T**

1



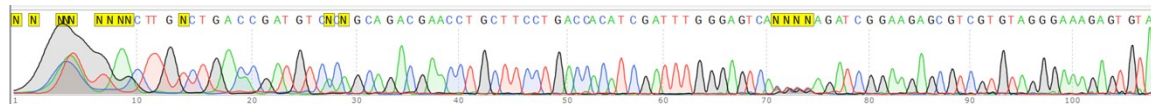
Observed sequence (34-109): AGA CGA ACC TGC TTC CTG ACC ACA TCG ATT **TGG GAG TCA NNN NAG ATC GGA AGA GCG TCG TGT AGG GAA AGA GTG T**

45



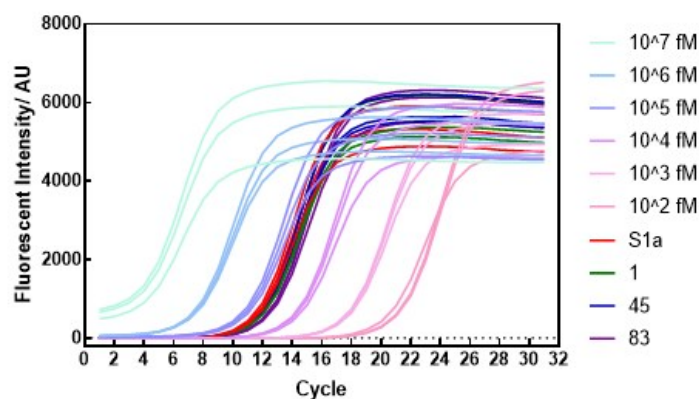
Observed sequence (32-107): AGA CGA ACC TGC TTC CTG ACC ACA TCG ATT **TGG GAG TCA NNN NAG ATC GGA AGA GCG TCG TGT AGG GAA AGA GTG T**

83



Observed sequence (32-107): AGA CGA ACC TGC TTC CTG ACC ACA TCG ATT **TGG GAG TCA NNN NAG ATC GGA AGA GCG TCG TGT AGG GAA AGA GTG T**

Figure S3. Sanger sequencing results of PCR-amplified products; sequence present during C-H activation bolded



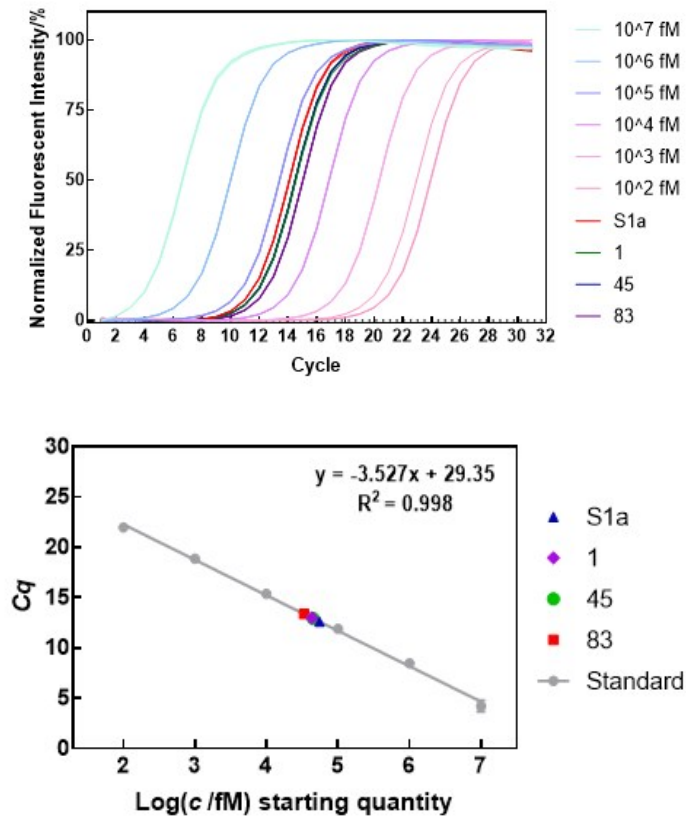


Figure S4. qPCR analysis of samples. Amplification curve and calibration curve of qPCR analysis. Starting from the same amount of HP, the recovery ratio of **1** to **S1a** was 78.16% (SD = ± 0.0877); the recovery ratio of **45** to **S1a** was 81.27% (SD = ± 0.0843); the recovery ratio of **83** to **S1a** was 60.81% (SD = ± 0.1126).

9. References

- 1 Shen, P.-X., Hu, L., Shao, Q., Hong, K. & Yu, J.-Q. Pd(II)-catalyzed enantioselective C(sp³)-H arylation of free carboxylic acids. *J. Am. Chem. Soc.* **140**, 6545-6549 (2018).
- 2 Zhuang, Z. *et al.* Ligand-enabled β -C(sp³)-H olefination of free carboxylic acids. *J. Am. Chem. Soc.* **140**, 10363-10367 (2018).
- 3 Wu, Q.-F. *et al.* Formation of α -chiral centers by asymmetric β -C(sp³)-H arylation, alkenylation, and alkynylation. *Science* **355**, 499-503 (2017).
- 4 Park, H., Chekshin, N., Shen, P.-X. & Yu, J.-Q. Ligand-enabled, palladium-catalyzed β -C(sp³)-H arylation of Weinreb amides. *ACS Catal.* **8**, 9292-9297 (2018).
- 5 Dydio, P., Rubay, C., Gadzikwa, T., Lutz, M. & Reek, J. N. H. 'Cofactor'-controlled enantioselective catalysis. *J. Am. Chem. Soc.* **133**, 17176-17179 (2011).
- 6 Zhu, R.-Y. *et al.* Versatile alkylation of (hetero)aryl iodides with ketones via β -C(sp³)-H activation. *J. Am. Chem. Soc.* **139**, 16080-16083 (2017).