

## Two-Step Synthesis of $\alpha$ -Aryl- $\alpha$ -diazoamides as Modular Bioreversible Labels

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## I. General Information

Compounds **2a–2j**, **3a–3l**, and **4a–4e** were synthesized by the routes shown in **Scheme 1**, **Scheme 2**, and **Figure 2**. All reactions were performed in a reaction vial fitted with TFE-silicone septa under an atmosphere of N<sub>2</sub>(g) using standard Schlenk-line techniques. Reactions carried out at low temperature were cooled by cooling agents in a Dewar vessel (water-ice bath at 0 °C), while reactions performed above room temperature were heated on the IKA RCT basic plate. All reactions were magnetically stirred and monitored by liquid chromatography–mass spectrometry (LC–MS) and by analytical thin-layer chromatography (TLC). Purification was performed by flash column chromatography using silica gel or a Biotage Isolera One system unless indicated otherwise. Note: Diazoamide compounds (**3a–3l**, **4a–4e**) were purified manually by column chromatography to avoid any exposure of UV light from the UV detector in the Biotage. For the same reason, purification by high-performance liquid chromatography (HPLC) is also not recommended. Organic solutions were concentrated *in vacuo* using a Buchi rotary evaporator (model R-210).

*Materials.* Reagents and solvents were from Sigma–Aldrich (Milwaukee, WI) and were used without further purification unless indicated otherwise. 4-Iodotoluene, 3-iodobenzotrifluoride, 3-iodoanisole, 4-iodobenzotrifluoride, and 4-iodopyridine were from Alfa Aesar (Tewksbury, MA). 4-Iodoanisole was from ACROS Organics (Morris Plains, NJ). 2-(4-Iodophenyl)acetic acid was from Chem-Impex International (Wood Dale, IL). Azido-PEG4-Amine was from BroadPharm (San Diego, CA). Tri(2-furyl)phosphine was from TCI America (Portland, OR). Rink amide ProTide Resin was from CEM Corporation (Matthews, NC). Reagent-grade solvents (dichloromethane (DCM), tetrahydrofuran (THF), triethylamine (Et<sub>3</sub>N), acetonitrile (MeCN), methanol (MeOH) and *N,N*-dimethylformamide (DMF)) were dried over a column of alumina and removed from a dry still under an inert atmosphere. Anhydrous ethyl acetate (EtOAc) was from ACROS Organics. Flash column chromatography was performed with Silicycle 40–63 Å silica (230–400 mesh), and thin-layer chromatography (TLC) was performed with EMD 250 μm silica gel 60 F254 plates. 40-mL reaction vials (Item No. CG-4909-05) and 8-mL reaction vials (Item No. CG-4909-03) with green open top cap (TFE Septa) were from Chemglass Life Sciences (Vineland, NJ).

*Conditions.* All procedures were performed under a positive pressure of N<sub>2</sub>(g) at ambient temperature (~22 °C) and pressure (1.0 atm) unless indicated otherwise.

*Solvent Removal.* The phrase “concentrated under reduced pressure” refers to the removal of solvents and other volatile materials using a rotary evaporator (<20 Torr) while maintaining a water bath at ambient temperature (~22 °C). Residual solvent was removed from samples at high vacuum (<0.1 Torr).

*Nuclear magnetic resonance (NMR) Spectroscopy.* <sup>1</sup>H and <sup>13</sup>C NMR spectra were acquired with a Bruker Avance Neo 400 MHz or Bruker Avance Neo 500 MHz spectrometer at the Department of Chemistry Instrumentation Facility at MIT (DCIF). Proton chemical shifts are reported in parts per million (ppm, δ scale) and are relative to residual protons

in the deuterated solvent ( $\text{CDCl}_3$ :  $\delta$  7.26;  $\text{D}_2\text{O}-d_2$ :  $\delta$  4.79;  $\text{CD}_3\text{CN}-d_3$ :  $\delta$  1.94;  $\text{DMSO}-d_6$ :  $\delta$  2.50;  $\text{THF}-d_8$ :  $\delta$  1.72). Carbon chemical shifts are reported in parts per million (ppm,  $\delta$  scale) and are relative to the carbon resonance of the solvent ( $\text{CDCl}_3$ :  $\delta$  77.16;  $\text{CD}_3\text{CN}-d_3$ :  $\delta$  1.32;  $\text{THF}-d_8$ :  $\delta$  25.37).  $\text{CDCl}_3$  containing 0.03% (v/v) TMS (AC209561000) was supplied by ACROS Organics.  $\text{D}_2\text{O}-d_2$ ,  $\text{CD}_3\text{CN}-d_3$ , and  $\text{THF}-d_8$ , and  $\text{DMSO}-d_6$  containing 0.03% (v/v) TMS were purchased from Sigma Aldrich. Multiplicities are abbreviated as: s (singlet), br (broad), d (doublet), t (triplet), q (quartet), and m (multiplet).  $^{13}\text{C}$  signal corresponding to diazo carbon ( $\text{C}=\text{N}=\text{N}$ ) is missing in most of the spectra, possibly due to a T1 relaxation effect. Because this quaternary carbon is highly shielded by nitrogen, a high number of scans and long relaxation time ( $d_1 > 1.5$  s) are required. Despite its being a quaternary carbon, the chemical shift of a diazo carbon is generally reported to be in the 55–65 ppm region.<sup>10</sup> Similarly, we have validated diazo carbon peaks of selected compounds using HMBC (**2a**, **2b**, **2f**, **2g**, and **3j**) and HSQC (**3j**) experiments.

*Mass Spectrometry.* Mass spectra of small molecules were acquired with an LCT electrospray ionization (ESI) instrument from Agilent (1260 infinity II) and a LC–MS column (Agilent, Poroshell 120, SB  $\text{C}_{18}$ -reverse-phase, length 50 mm, internal diameter: 2.1 mm, particle size: 2.7 micron) with a gradient of 10–95% v/v MeCN (0.1% v/v formic acid) in water (0.1% v/v formic acid) over 10 min (**Figure S5**). To minimize the fragmentation of diazo moieties, the MSD parameters were set as following: capillary voltage, 3000 V; drying gas temperature, 350 °C; gas flow, 13/min; fragmentor voltage, 30; nebulizer pressure, 35 psig; and cycle time, 0.83 s/cycle. High-resolution mass spectra (HRMS) were obtained with a Jeol Accu-ToF (AccuTOF-DART) instrument.

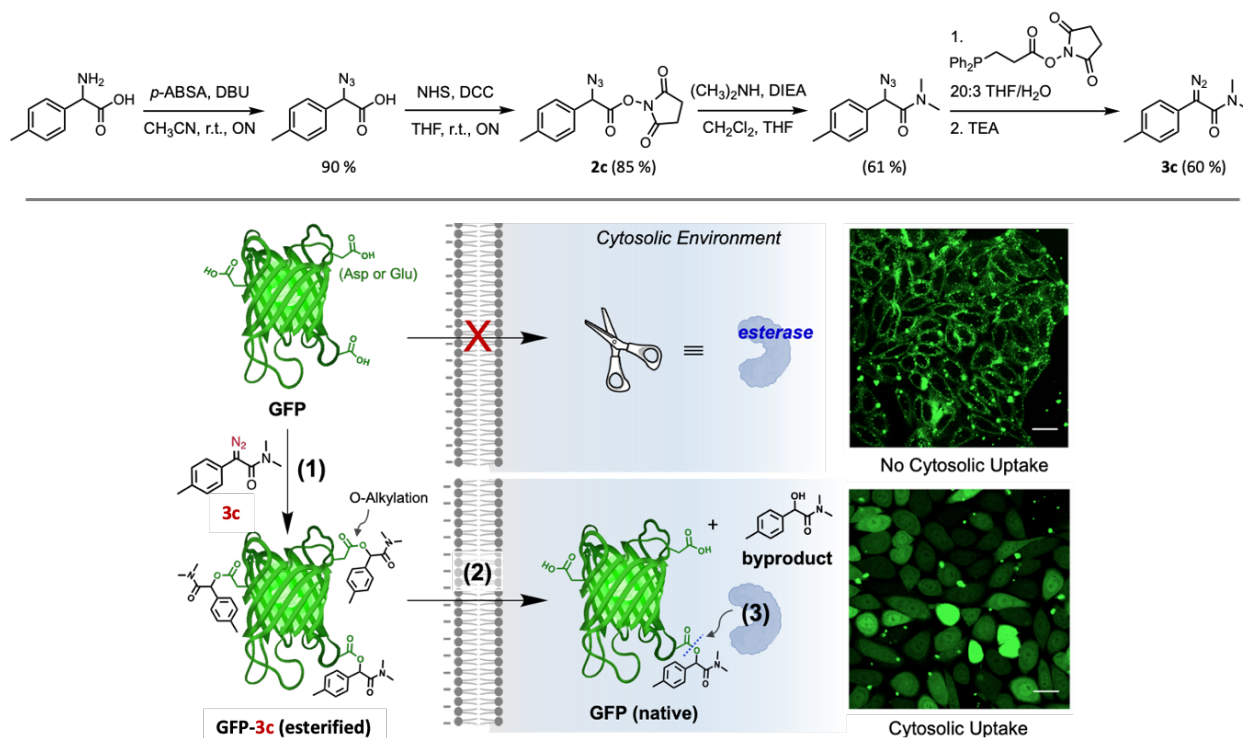
*Compound Purity.* The purity of all compounds was judged to be  $\geq 95\%$ , as assessed by  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectroscopy, mass spectrometry, and reversed-phase high performance liquid chromatography (HPLC) using an LC–MS column and gradient of 10–95% v/v MeCN (0.1% v/v formic acid) in water (0.1% v/v formic acid) over 10 min (**Figure S5**) unless indicated otherwise.

*Infrared Spectroscopy.* IR spectra were obtained with a Bruker Alpha II FTIR spectrometer with a diamond crystal attenuated total reflectance (ATR) accessory. IR spectra were acquired by dissolving a small amount of compound in dichloromethane to mount the sample (neat samples) and representative bands (e.g., the diazo  $\text{N}=\text{N}$  stretching at  $\sim 2100\text{ cm}^{-1}$ ) are reported in terms of wavenumbers in  $\text{cm}^{-1}$ .

*Safety.* \***Caution**\* Although we never experienced any problems, diazo compounds are potentially explosive upon exposure to heat, light, pressure, and shock.<sup>1</sup> They should be stored at  $\leq 0$  °C in a location away from light, pressure, and shock. *N*-Succinimidyl 2-diazoacetate (**1**)<sup>2</sup> and *N*-phthalimidoyl 2-diazoacetate (**NHPI-DA**, **S4**)<sup>3</sup> are reported to be bench-stable and can be isolated in gram amounts as a crystalline solid. Moreover, structurally similar  $\alpha$ -aryl- $\alpha$ -diazoesters have been shown to have  $T_{\text{onset}}$ , which reports on thermostability, ranging from 80 °C (*p*-OMe) to 130 °C (*p*-NO<sub>2</sub>), depending on the aryl substituents.<sup>1</sup> Our synthetic routes (**Scheme 1**, **Figure 2**) do not require any heat and are done on a small scale (<500 mg). Still, a blast shield should be placed around the reaction vessels containing the

diazo compounds for synthesis on a multi-gram scale.

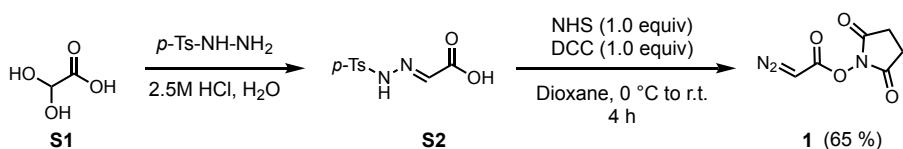
## II. Application of Diazo Compounds in Chemical Biology<sup>4</sup>



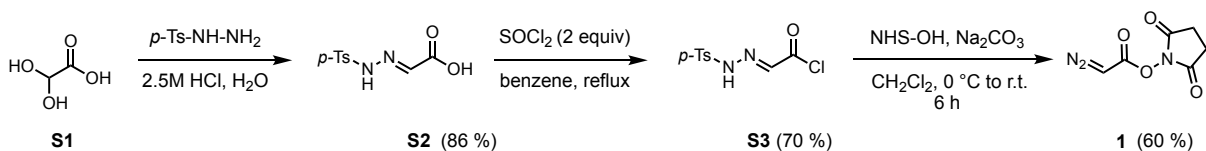
**Figure S1.** Top) Previously reported synthetic route of  $\alpha$ -aryl- $\alpha$ -diazoamide **3c**.<sup>5,4</sup> Bottom) its application in “bioreversible” esterification of green fluorescent protein (GFP) for cytosolic delivery (bottom).<sup>4</sup> (1) Esterification of **GFP** was done by incubating with **1** (4 equiv) in bis-TRIS buffer (pH 6.5, 20% v/v MeCN) for 4 h at 37 °C to generate **GFP-3c**. (2) Membrane permeability was analyzed by confocal images of **GFP** and **GFP-3c** in CHO-K1 cells ( $\lambda_{\text{ex}}$ ,  $\lambda_{\text{em}}$ : 488 nm, 525 nm).<sup>4</sup> Cells were incubated with protein (15  $\mu\text{M}$ ) for 2 h at 37 °C. Scale bars are 25  $\mu\text{m}$ . Lastly, (3) intracellular esterases are anticipated to cleave the pendant ester bond, releasing the byproduct, to unmask the native protein.

## III. Synthesis of the Key Precursor (*N*-Succinimidyl 2-Diazoacetate, **1**)

### Reported Synthesis I (Ouihia *et al.*)<sup>2</sup>

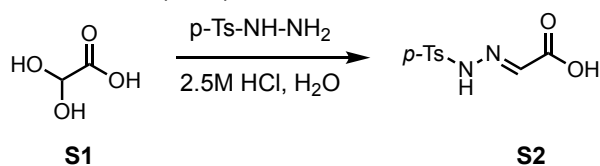


### Reported Synthesis II (Gupta and Yin *et al.*)<sup>6</sup>



**Figure S2.** Previously reported synthetic routes and yields of diazo compound **1**. The synthesis of **1** was adapted from

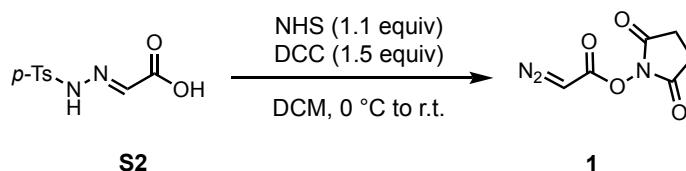
Ouihia *et al.* (1993) and Gupta and Yin *et al.* (2019).<sup>2,6</sup>



**2-(2-tosylhydrazono) acetic acid (S2):** Glyoxylic acid monohydrate **S1** (23.2 g, 250 mmol) was dissolved in water (250 mL) and heated to 65 °C until **S1** was dissolved fully. In a separate round bottom flask, *p*-toluenesulfonylhydrazide (46.6 g, 250 mmol) in 2.5 M aqueous hydrochloric acid (150 mL) was heated at 65 °C. The resulting solution of *p*-toluenesulfonylhydrazide was then added to the glyoxylic acid solution, and the reaction mixture was heated at 65 °C for 15 min. The reaction mixture was allowed to warm to room temperature and was kept in the refrigerator overnight to induce precipitation. The precipitated crude product was collected by filtration, washed with cold water (70 mL), and dried in the open air for 2 days to remove water. The crude product was then recrystallized using hot EtOAc and hexanes. The product was filtered and washed with ice-cold 33% v/v EtOAc in hexanes to afford compound **S2** as a white solid (52.2 g, 215 mmol, 86%).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, δ): 8.47 (s, 1H), 7.83–7.80 (m, 2H), 7.38 (d, *J* = 8.1 Hz, 2H), 7.13 (s, 1H), 2.46 (s, 3H)

Note: The <sup>1</sup>H NMR spectrum of **S2** matched with the literature except for the exchanging protons.<sup>2,6</sup>

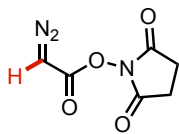
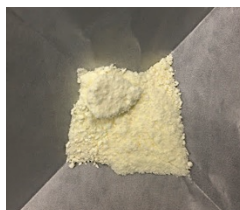
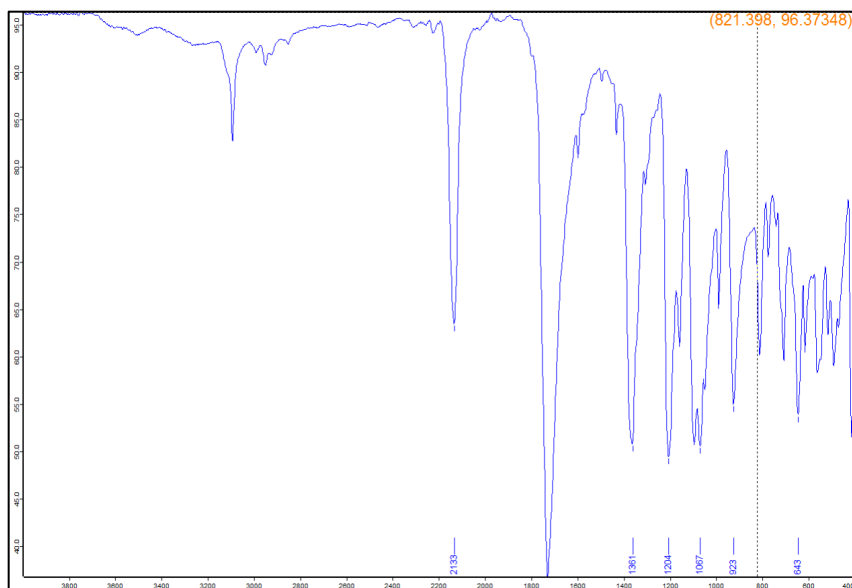
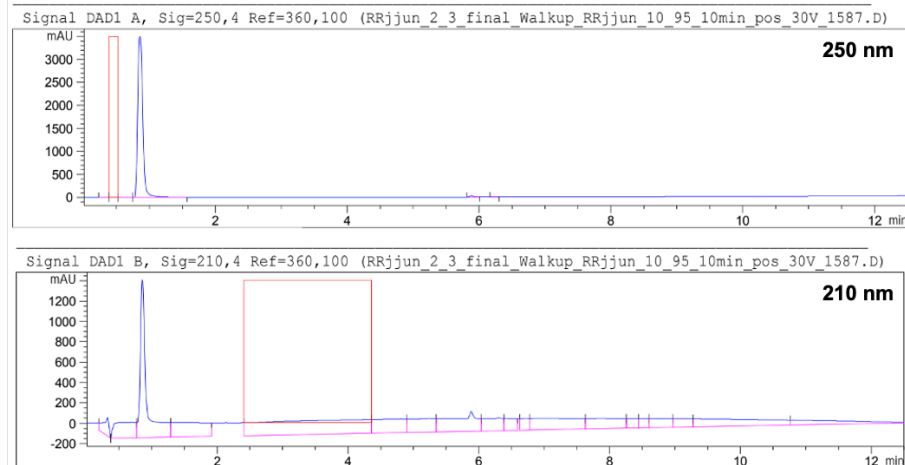


**N-Succinimidyl 2-Diazoacetate (1):** Compound **S2** (9.7 g, 40 mmol, 1.0 equiv) and *N*-hydroxysuccinimide (5.1 g, 44 mmol, 1.1 equiv) were dissolved in anhydrous DCM (400 mL), and the reaction mixture was cooled to 0 °C. A solution of *N,N'*-dicyclohexylcarbodiimide (DCC) (60 mmol, 1.5 equiv) in anhydrous DCM (1.0 M solution) was then added dropwise to the reaction mixture, and stirred at 0 °C for 1 h. The reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction was quenched by filtering out the byproduct, dicyclohexylurea, and the filtrate was concentrated under reduced pressure. The reaction mixture was then extracted with EtOAc (200 mL × 3) and washed with saturated aqueous NaHCO<sub>3</sub> (200 mL × 3), followed by brine (200 mL). The organic layer was separated, dried with Na<sub>2</sub>SO<sub>4</sub>(s), and filtered. The solvent was removed under reduced pressure, and the crude product was purified by chromatography on silica gel (6:4:1 hexanes/EtOAc/DCM) to yield the product as a pale yellow crystalline solid (4.9 g, 27 mmol, 67%).

Note: The <sup>1</sup>H NMR, <sup>13</sup>C NMR, and IR spectra of **1** match those previously reported for this compound.<sup>2</sup>



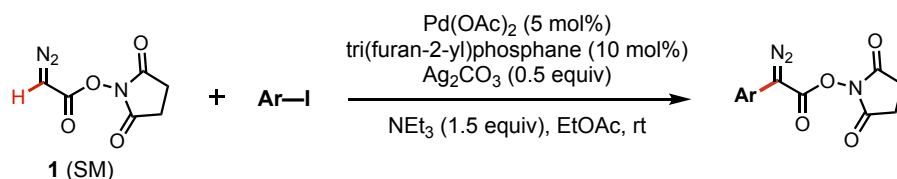
#### IV. Characterization Data for *N*-Succinimidyl 2-Diazoacetate (**1**)

**1****Physical State:** pale yellow solid**TLC:** *R<sub>f</sub>* = 0.32 (1:1 pentane/EtOAc) Stained red with vanillin**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, δ):** 5.11 (s, 1H), 2.85 (s, 4H)**<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>, δ):** 169.43, 168.64, 45.11, 25.45**HRMS (ESI-TOF):** calc'd for C<sub>6</sub>H<sub>5</sub>N<sub>3</sub>O<sub>4</sub>Na [M + Na]<sup>+</sup>, 206.0172; found, 206.0171**IR (neat):** 2133 (diazo), 1361, 1204, 1067, 923, 643 cm<sup>-1</sup>**Analytical HPLC:** 10–95% v/v MeCN (0.1% v/v formic acid) in water (0.1% v/v formic acid) over 10 min (**Figure S5**)

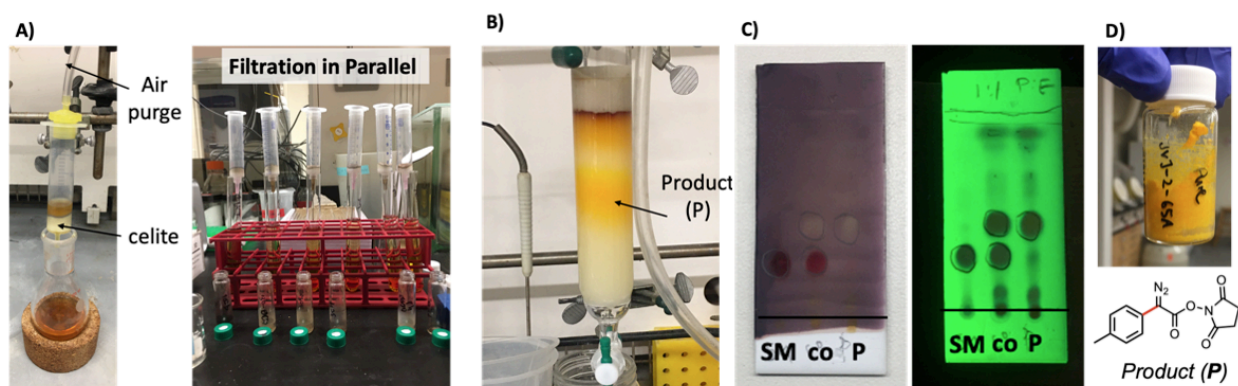
## V. Experimental Procedure for the Pd-Catalyzed C—H Arylation

### V-1. C—H Arylation of **1**

**General Procedure A.** The C—H arylation of **1** to synthesize *N*-succinimidyl 2-aryl-2-diazoacetates **2a–2j**



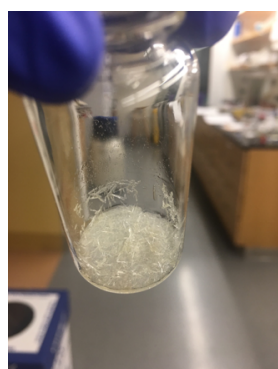
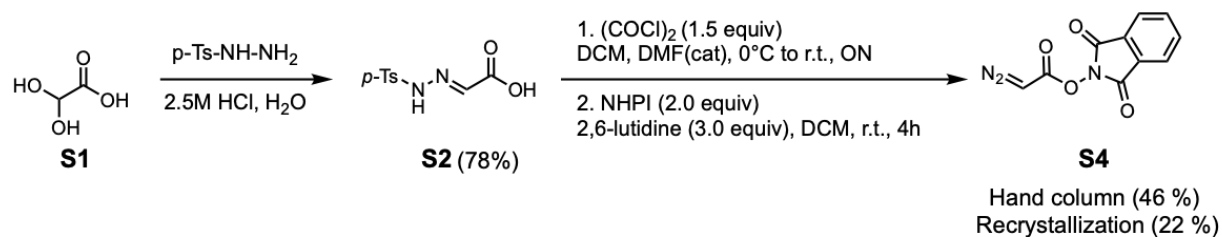
The cross-coupling reaction condition was adapted from the original procedure by Yu *et al.*<sup>4</sup> Aryl iodide (1.62 mmol, 1.5 equiv), tri(furan-2-yl)phosphane (25 mg, 0.11 mmol, 10 mol%), Pd(OAc)<sub>2</sub> (12 mg, 0.054 mmol, 5 mol%), and Ag<sub>2</sub>CO<sub>3</sub> (151 mg, 0.54 mmol, 0.50 equiv) were added to a 40-mL reaction vial with a TFE septa cap, which was then evacuated and backfilled with N<sub>2</sub>(g). Subsequently, compound **1** (200 mg, 1.08 mmol, 1.0 equiv) and Et<sub>3</sub>N (166 mg, 1.62 mmol, 1.5 equiv) in EtOAc (22 mL, 0.05M) was added in one portion to the reaction vial. The reaction mixture was stirred at room temperature for 6 h under N<sub>2</sub>(g). The progress of the reaction was monitored by TLC (**Figure S3**). The reaction mixture was filtered through a Celite pad using fitted syringe and washed with EtOAc to remove insoluble catalysts and silver salts. The filtrate was concentrated under reduced pressure and purified by silica gel chromatography to get desired product unless otherwise specified.



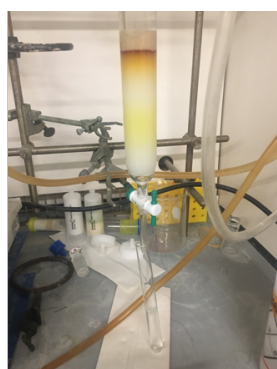
**Figure S3.** General purification procedure to obtain the arylated product (**P**). (A) Filtration using fitted syringe, (B) column chromatography with yellow product band, (C) TLC stained with vanillin stain (left) and TLC under a hand-held UV lamp (254 nm), and (D) purified product and its structure.

## V-2. C—H Arylation of NHPI-DA (S4)

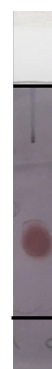
**Synthesis of NHPI-DA (S4):** Prepared according to the literature procedure.<sup>3</sup>



recrystallization

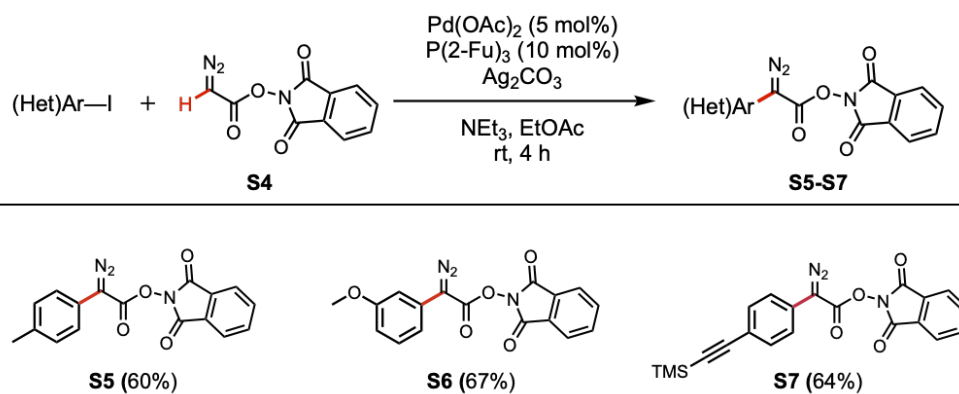


Column (2DCM: 1EA: 7Hex)



TLC (Vanillin Stain)

**Synthesis of aryl diazoacetate (S5–S7):** Prepared according to the literature procedure.<sup>3</sup>



**S5** represents the standard substrate that will lead to reported bioreversible aryl diazoamide reagent **3c** (Figure S1)

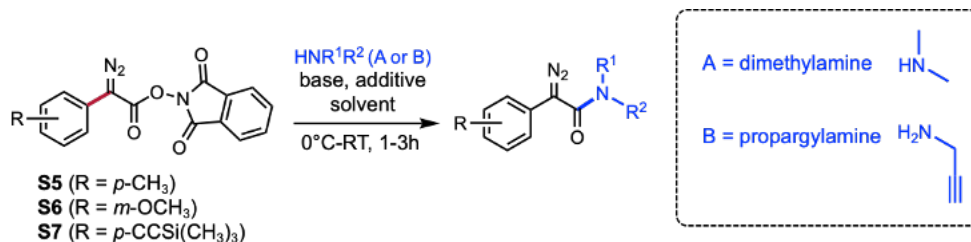
**S6** represents 3-position substituted aryl group

**S7** represents the substrate with a site for bioconjugation

## VI. Experimental Procedure for Aminolysis

VI-1. Aminolysis of *N*-Phthalimidyl 2-Aryl-2-Diazoacetates (S5–S7)

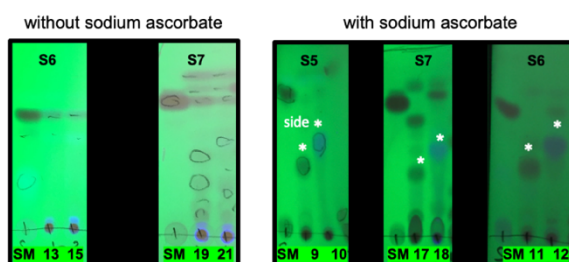
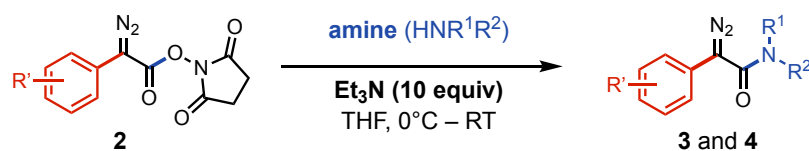
Table S1. Optimization of Aminolysis



entry	mmol	Ar-NHPI	HNR <sup>1</sup> R <sup>2</sup>	equiv	base	equiv	additive	solvent	yield
1	0.02	<b>S5</b>	-	0.0 equiv	Et <sub>3</sub> N	100 equiv	-	THF	no reaction
2	0.02	<b>S5</b>	A	10 equiv	-	0.0 equiv	-	THF	degradation
3	0.02	<b>S5</b>	A	1.2 equiv	Et <sub>3</sub> N	3.0 equiv	-	THF	0
4	0.02	<b>S5</b>	A	1.2 equiv	DIEA	3.0 equiv	-	THF	0
5	0.02	<b>S5</b>	A	1.2 equiv	Et <sub>3</sub> N	3.0 equiv	-	EA	0
6	0.02	<b>S5</b>	A	1.2 equiv	DIEA	3.0 equiv	-	EA	0
7	0.01	<b>S5</b>	A	1.2 equiv	Et <sub>3</sub> N	10 equiv	-	THF	trace
8	0.01	<b>S5</b>	B	1.2 equiv	Et <sub>3</sub> N	10 equiv	-	THF	trace
9	0.02	<b>S5</b>	A	5.0 equiv	Et <sub>3</sub> N	10 equiv	Na ascorbate	THF	trace
10	0.02	<b>S5</b>	B	5.0 equiv	Et <sub>3</sub> N	10 equiv	Na ascorbate	THF	trace
11	0.02	<b>S6</b>	A	5.0 equiv	Et <sub>3</sub> N	10 equiv	Na ascorbate	THF	trace
12	0.02	<b>S6</b>	B	5.0 equiv	Et <sub>3</sub> N	10 equiv	Na ascorbate	THF	trace
13	0.01	<b>S6</b>	B	1.0 equiv	Et <sub>3</sub> N	10 equiv	-	THF	trace
14	0.01	<b>S6</b>	B	1.0 equiv	Et <sub>3</sub> N	10 equiv	Na ascorbate	THF	trace
15	0.01	<b>S6</b>	B	1.0 equiv	Et <sub>3</sub> N	10 equiv	-	MeCN	trace
16	0.01	<b>S6</b>	B	1.0 equiv	Et <sub>3</sub> N	10 equiv	Na ascorbate	MeCN	trace
17	0.02	<b>S7</b>	A	5.0 equiv	Et <sub>3</sub> N	10 equiv	Na ascorbate	THF	trace
18	0.02	<b>S7</b>	B	5.0 equiv	Et <sub>3</sub> N	10 equiv	Na ascorbate	THF	trace
19	0.01	<b>S7</b>	B	1.0 equiv	Et <sub>3</sub> N	10 equiv	-	THF	trace, SM left
20	0.01	<b>S7</b>	B	1.0 equiv	Et <sub>3</sub> N	10 equiv	Na ascorbate	THF	trace, SM left
21	0.01	<b>S7</b>	B	1.0 equiv	Et <sub>3</sub> N	10 equiv	-	MeCN	trace, SM left
22	0.01	<b>S7</b>	B	1.0 equiv	Et <sub>3</sub> N	10 equiv	Na ascorbate	MeCN	trace, SM left

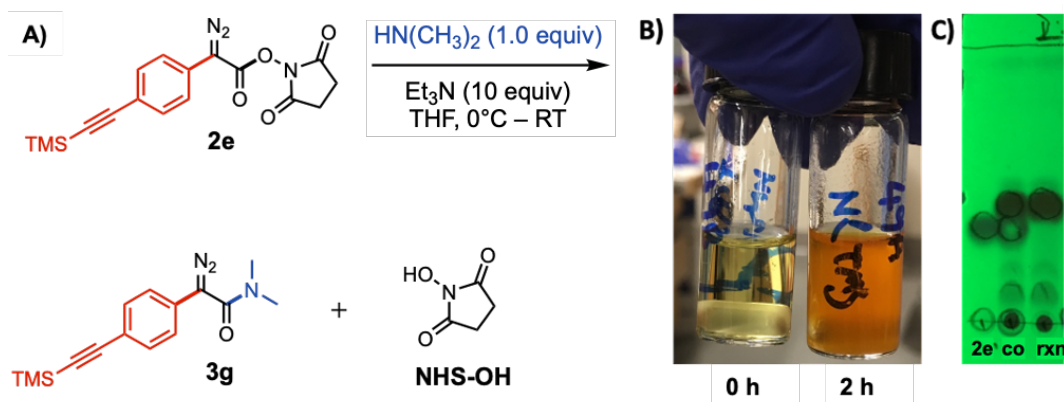
Each reaction was analyzed by LC–MS and TLC to determine the production formation and the conversion of starting material. Sodium ascorbate was added to minimize the degradation of redox-active NHPI ester.

## TLC of selected reactions from Table S1:

VI-2. Aminolysis of *N*-Succinimidyl 2-Aryl-2-DiazoacetateGeneral Procedure B. Aminolysis of *N*-succinimidyl 2-aryl-2-diazoacetate (**2**)

Adapting literature procedures,<sup>6,7</sup> an 8-mL scintillation vial was charged with a magnetic stir bar, aryl diazoester **2** (0.17 mmol, 1.0 equiv), and Et<sub>3</sub>N (0.85 mmol, 5.0 equiv) in dry THF (1.7 mL), and cooled to 0 °C in an ice bath. A solution of amine (0.85 mmol, 5.0 equiv) and Et<sub>3</sub>N (0.85 mmol, 5.0 equiv) in dry THF (1.7 mL) was then added dropwise to a final concentration of 0.05 M. The reaction mixture was stirred at 0 °C for 1 h and allowed to warm to room temperature for an additional 2 h. The progress of the reaction was monitored by TLC, and product formation was indicated by the precipitation of *N*-hydroxysuccinimide (**NHS-OH**) as well as the color of solution changing from yellowish to darker orange (**Figure S4**). The reaction mixture was concentrated under reduced pressure and purified by column chromatography (50% v/v EtOAc in hexanes) to afford the desired α-aryl-α-diazoamide.

*Note: Using 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) or sodium hydride (NaH) instead of Et<sub>3</sub>N led to degradation or no product formation, respectively.*

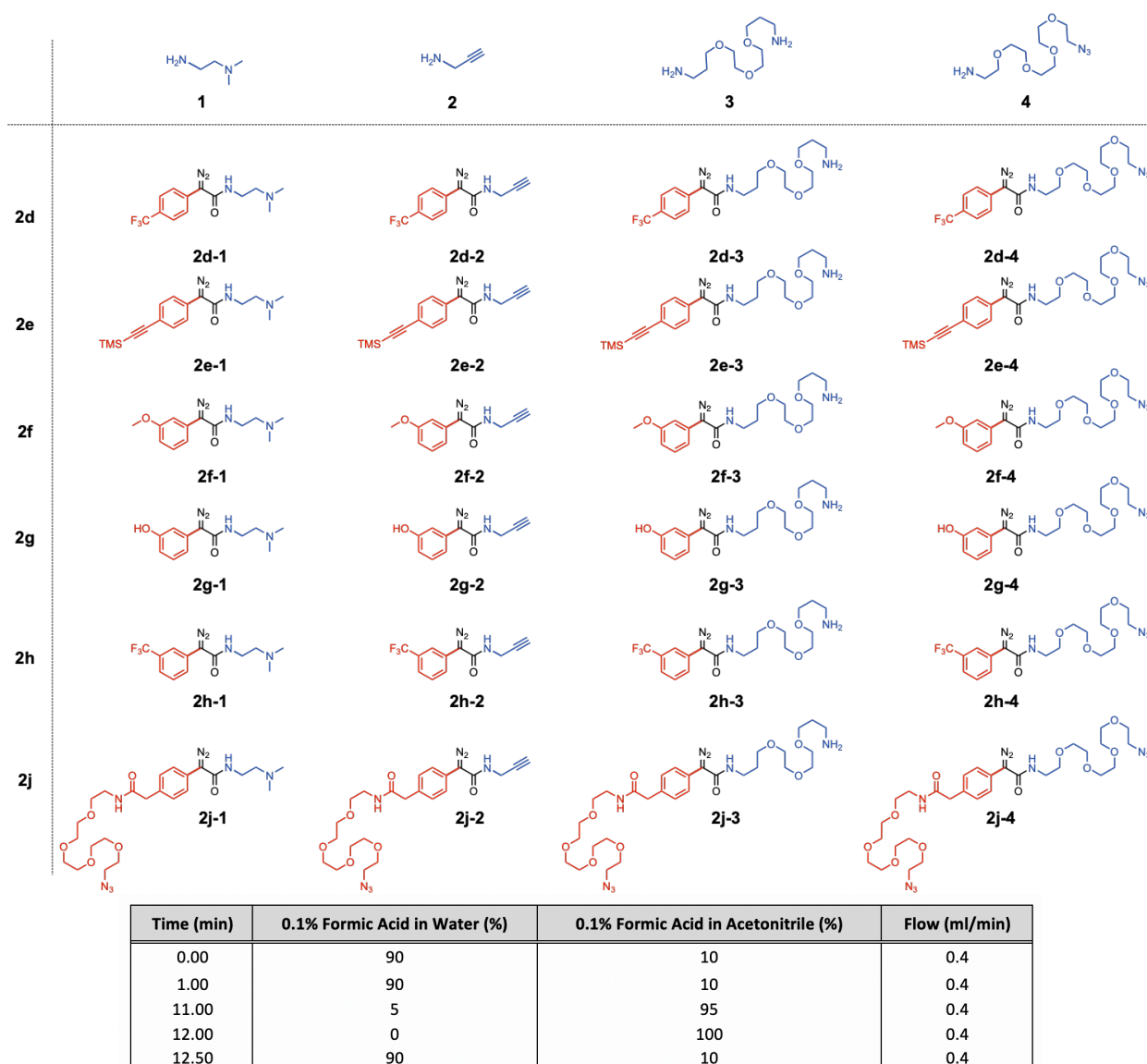


**Figure S4.** (A) Aminolysis of **2e**, (B) color change and precipitation upon product (**3g**) and **NHS-OH** formation, respectively, and (C) TLC of starting material (**2e**), crude reaction (**rxn**), and co-staining (**co**) in 33% v/v EtOAc in hexanes.

## VII. Aminolysis with Primary Amines

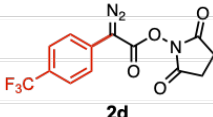
The scope of the aminolysis was analyzed *via* LC–MS using six aryl diazoesters (**2d**, **2e**, **2f**, **2g**, **2h**, and **2j**) and four primary amines (**1–4**). Reaction conditions for screening were adopted from General Procedure B on a small scale (0.15 mmol/reaction). Each reaction was done with a final concentration of 0.01 M in THF (1.5 mL). After stirring overnight (17 h), the reaction mixture was concentrated under pressure and redissolved in 1 mL of MeCN. 100  $\mu$ L of the reaction solution was added to 900  $\mu$ L of 50% v/v MeCN in H<sub>2</sub>O for LC–MS analysis with the gradient shown in **Figure S5**. The product distribution was analyzed by the total ion count (TIC) and UV absorbance plots at 210 nm, 250 nm, and 280 nm. Generally, ionized mass with the loss of N<sub>2</sub> was observed.

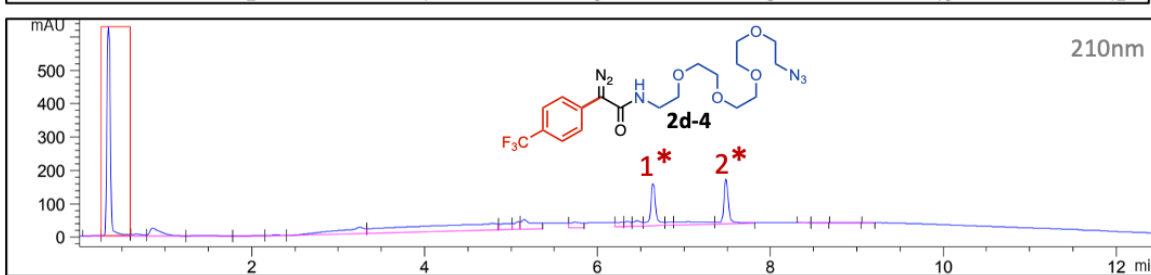
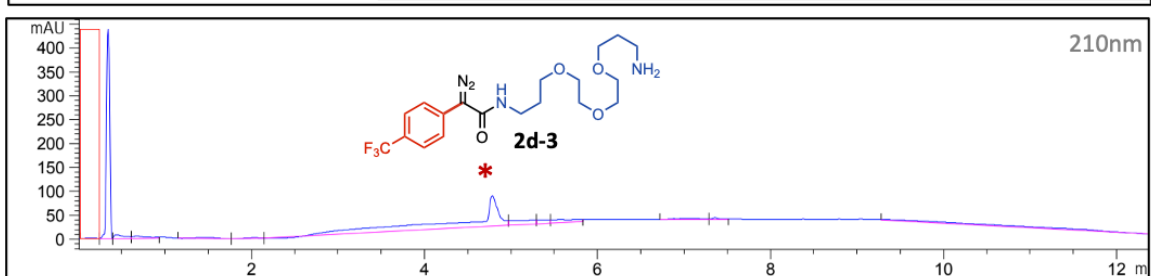
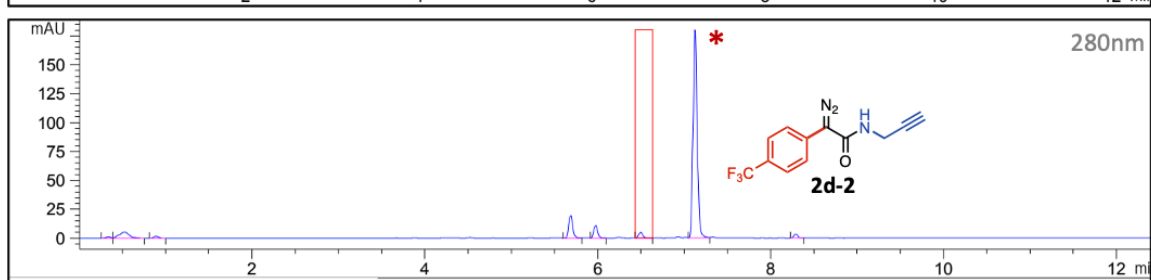
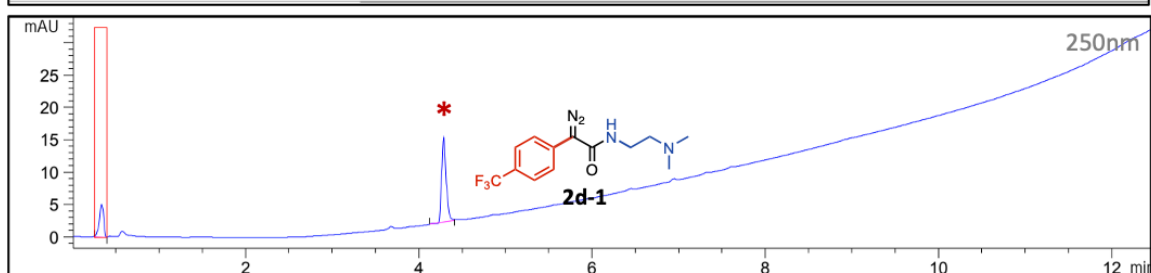
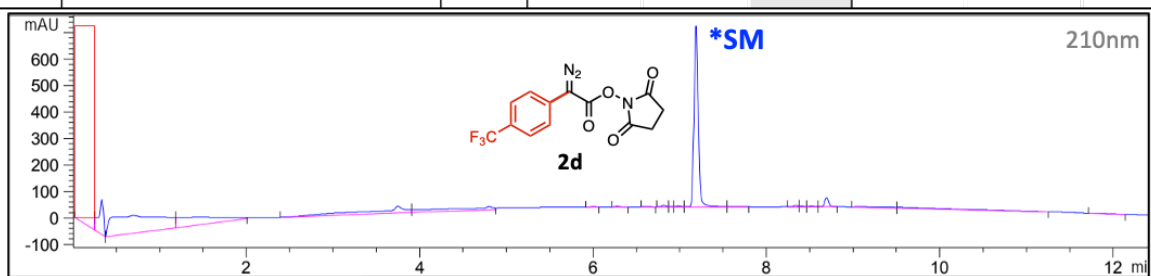
**Scheme S1. The Predicted Structure of Diazoamides upon Aminolysis**

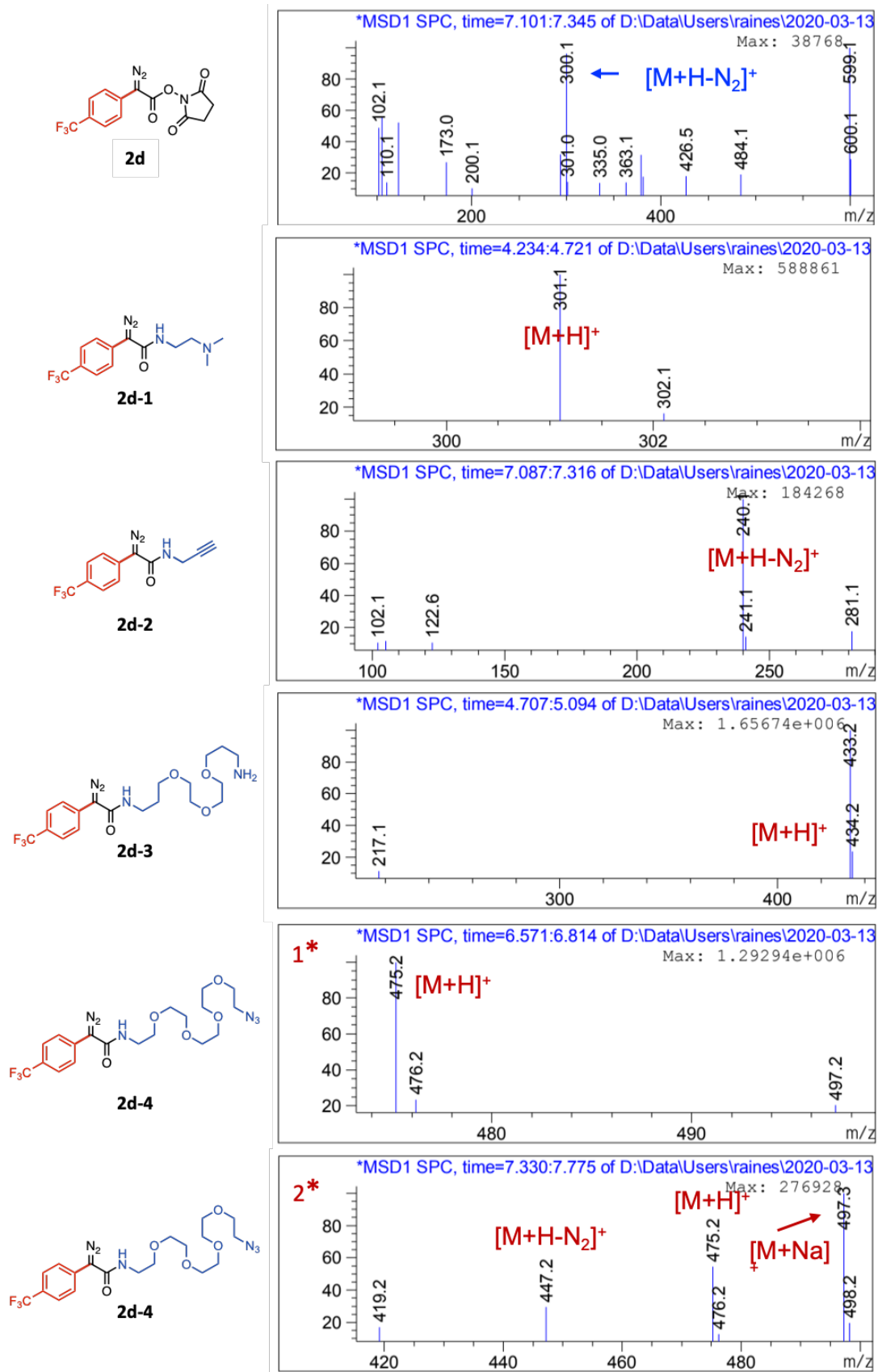


**Figure S5.** LC–MS Gradient. 10–95% v/v MeCN (0.1% v/v formic acid) in water (0.1% v/v formic acid) over 10 min.

## VII-1. Aminolysis of 2d

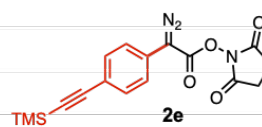
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			Ar-NHS	amine	product	[M+H] <sup>+</sup>	[M+Na] <sup>+</sup>	[M+H-N <sub>2</sub> ] <sup>+</sup>
2d-1	 <chem>Cc1ccc(cc1)C(=O)ON2C(=O)CCC2=N</chem>	1	327.2	88.2	300.3	301.3	323.3	273.3
2d-2		2	327.2	55.1	267.2	268.2	290.2	240.2
2d-3		3	327.2	220.3	432.4	433.4	455.4	405.4
2d-4		4	327.2	262.3	474.4	475.4	497.4	447.4

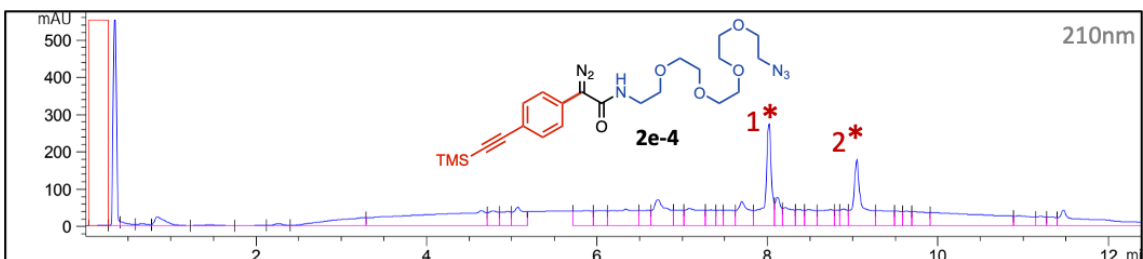
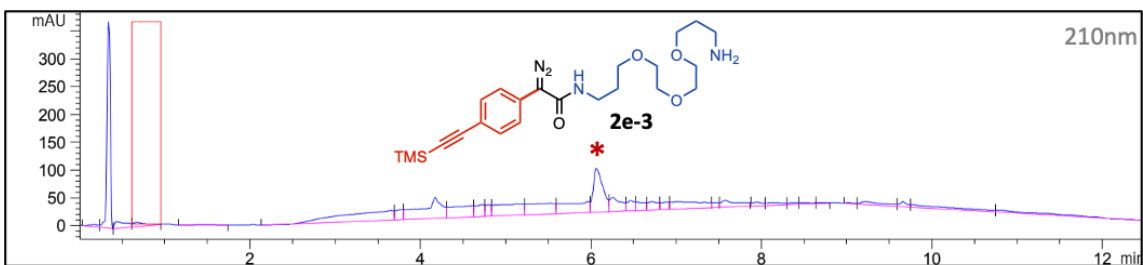
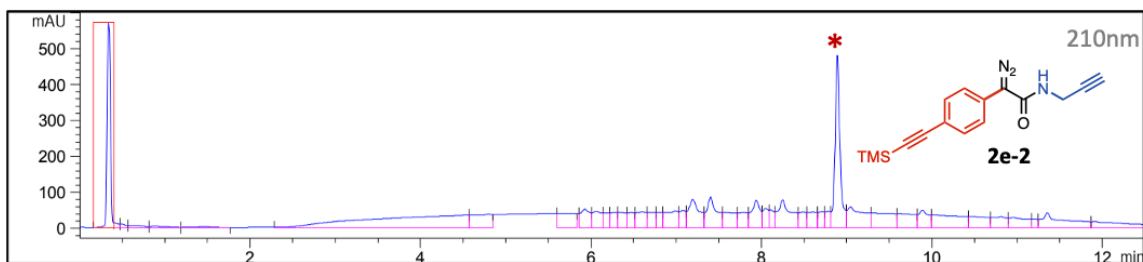
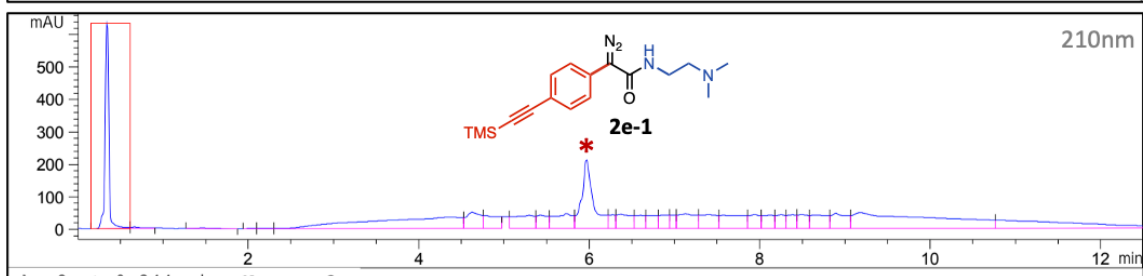
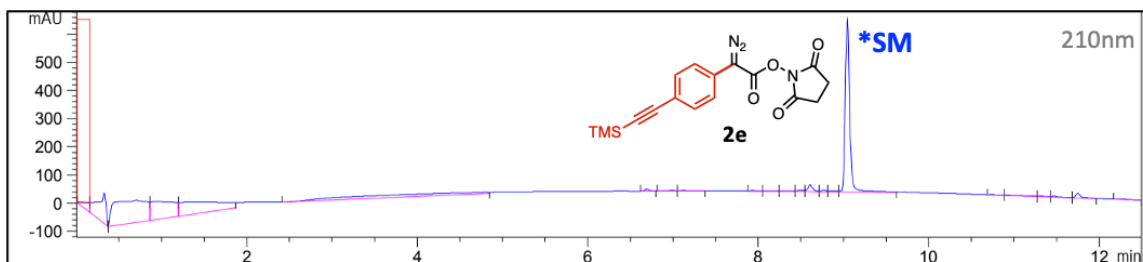


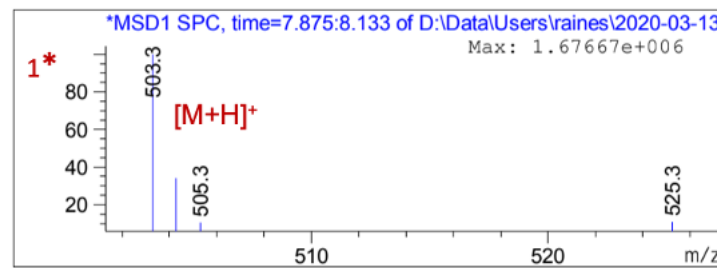
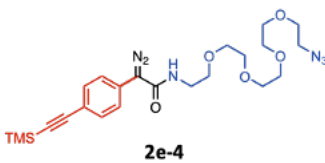
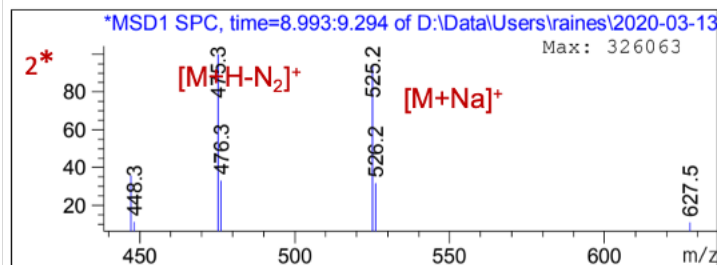
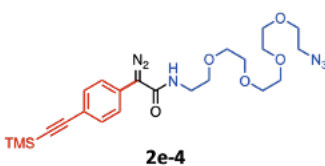
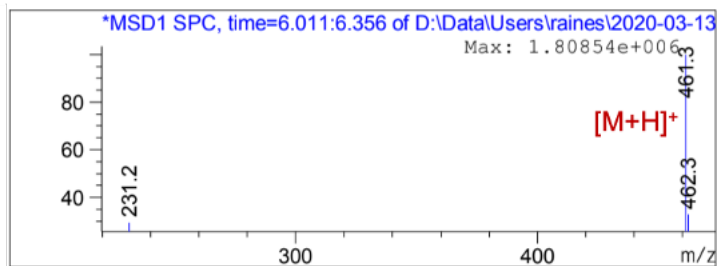
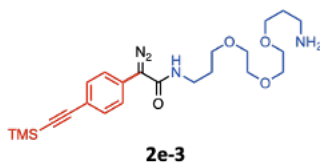
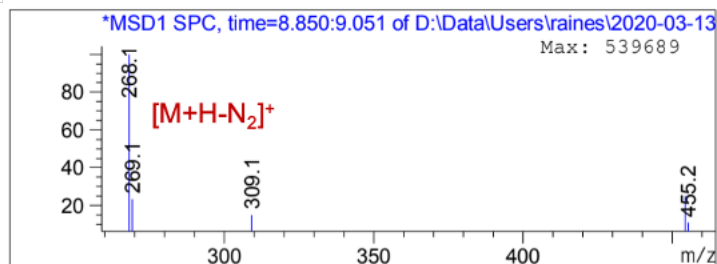
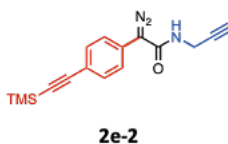
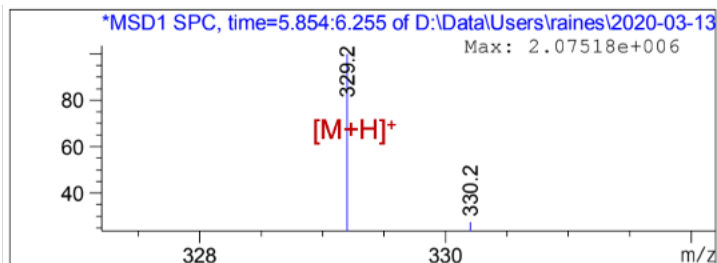
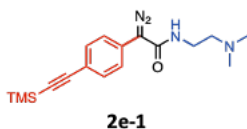
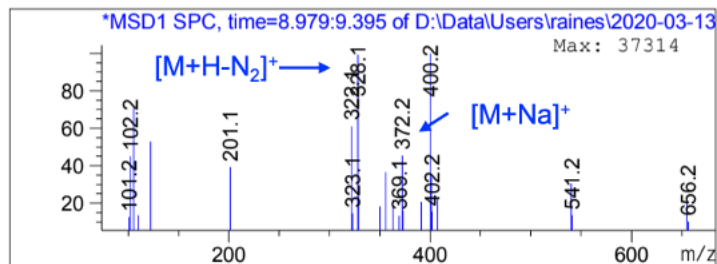
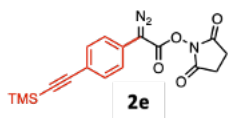




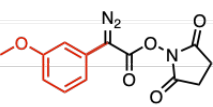
## VII-2. Aminolysis of 2e

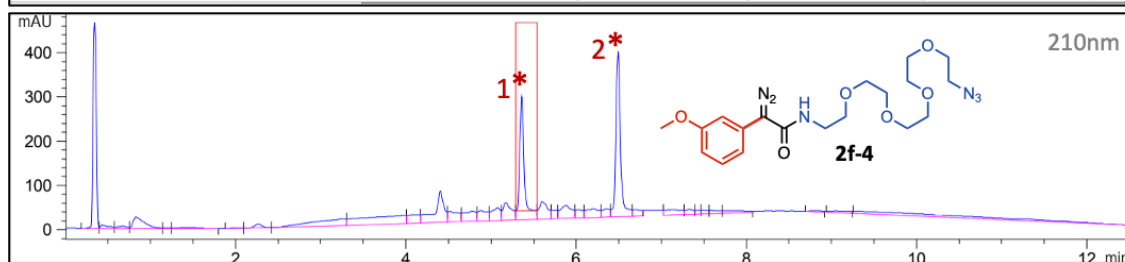
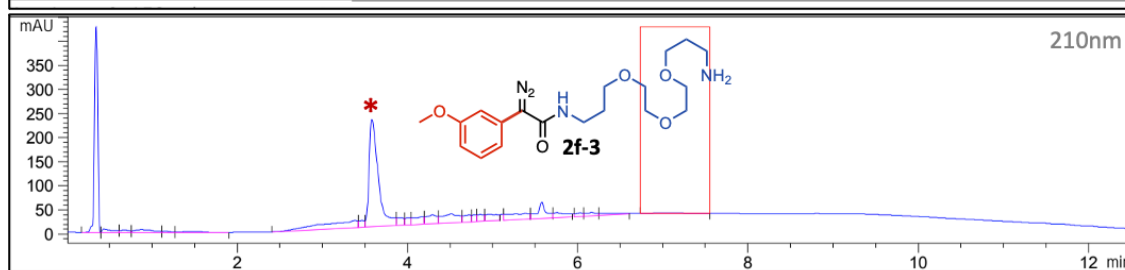
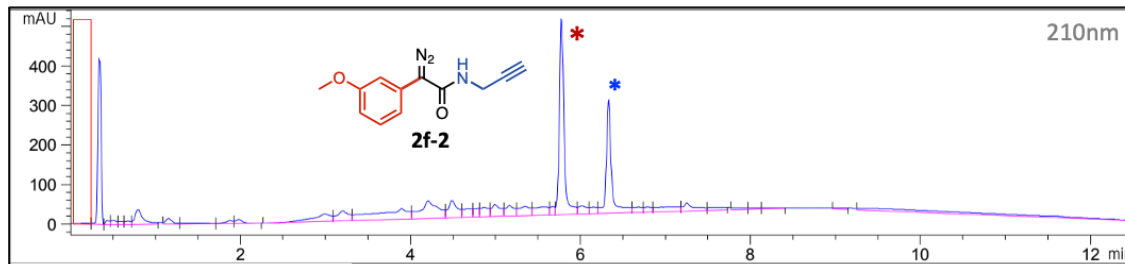
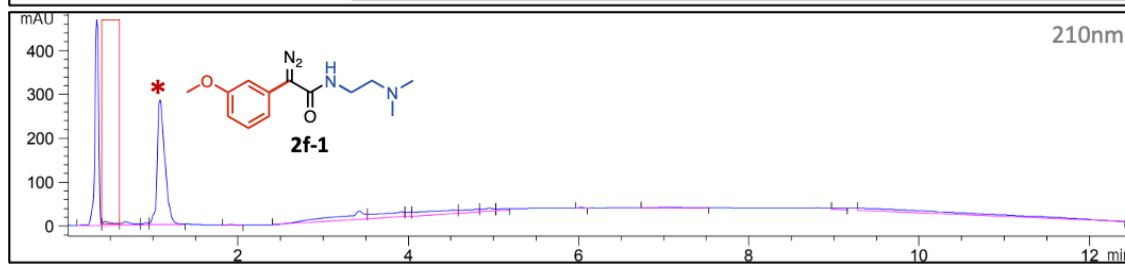
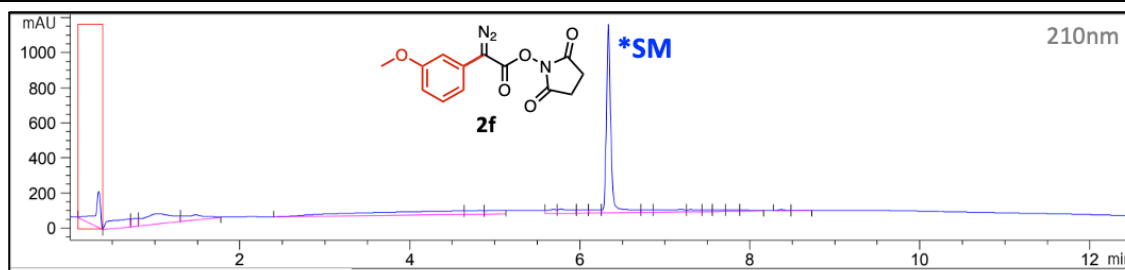
cmpd	Ar-NHS	amine	Molecular Weight			LCMS (m/z)		
			Ar-NHS	amine	product	[M+H] <sup>+</sup>	[M+Na] <sup>+</sup>	[M+H-N <sub>2</sub> ] <sup>+</sup>
2e-1		1	355.4	88.2	328.5	329.5	351.5	301.5
2e-2		2	355.4	55.1	295.4	296.4	318.4	268.4
2e-3		3	355.4	220.3	460.7	461.7	483.7	433.7
2e-4		4	355.4	262.3	502.6	503.6	525.6	475.6

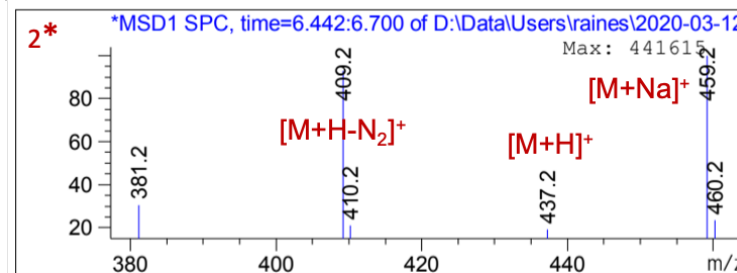
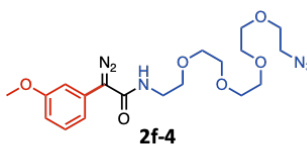
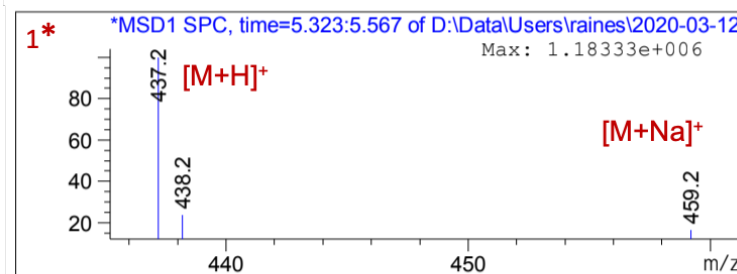
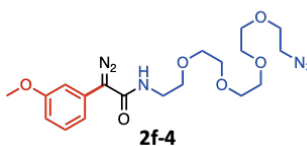
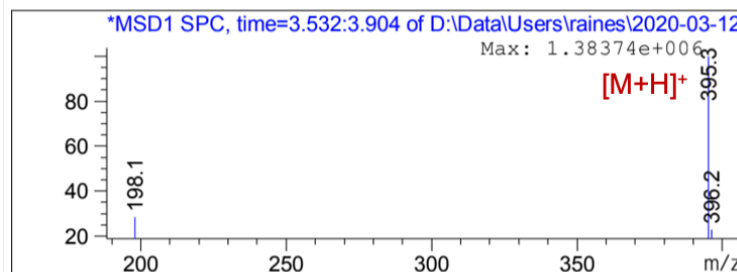
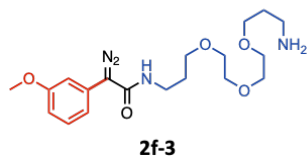
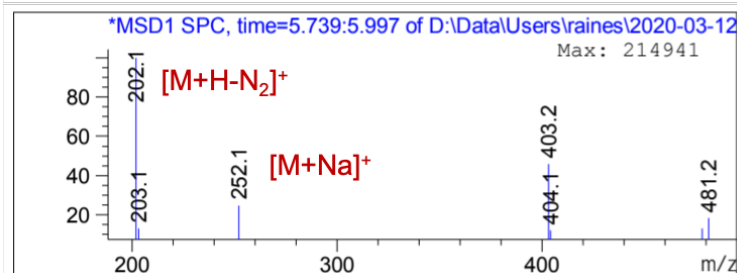
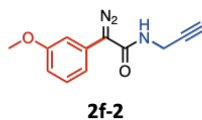
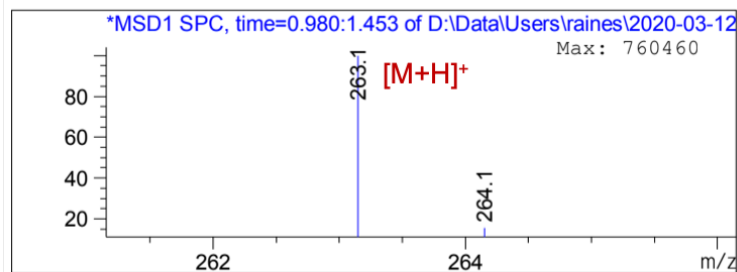
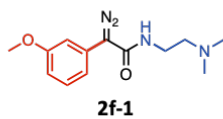
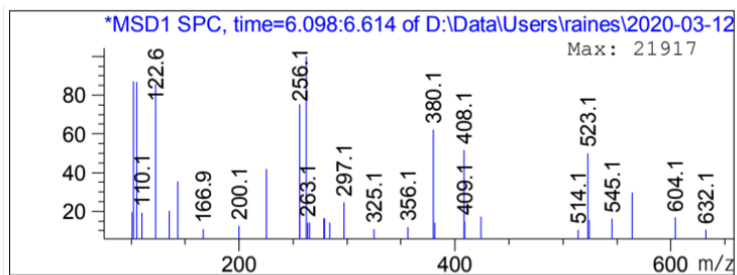
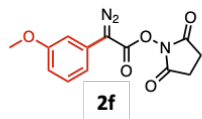




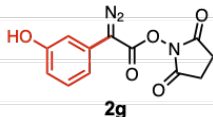
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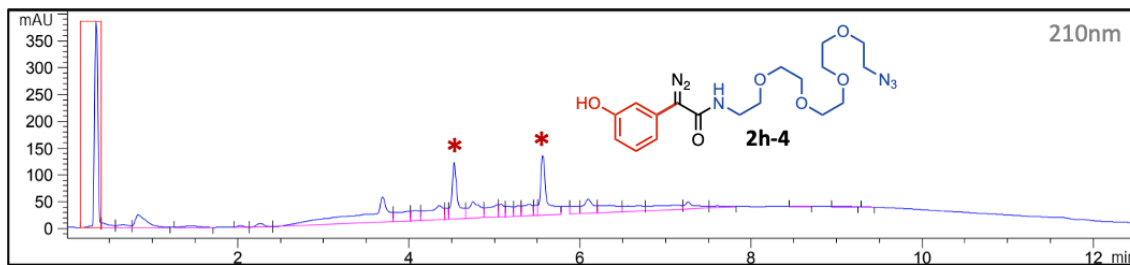
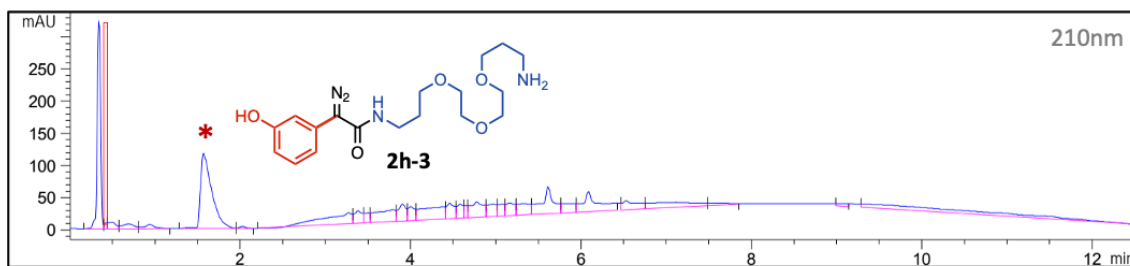
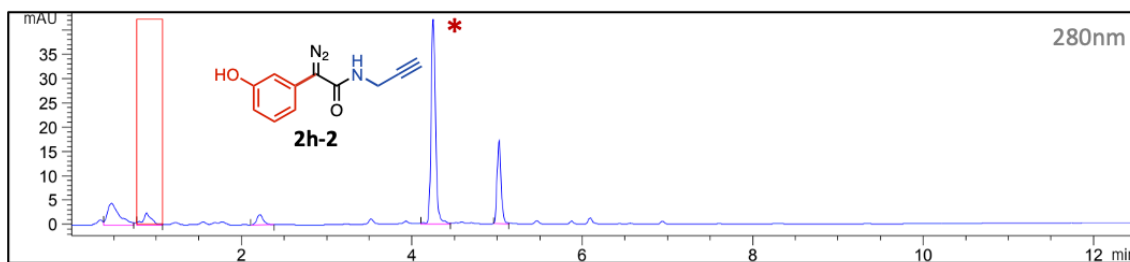
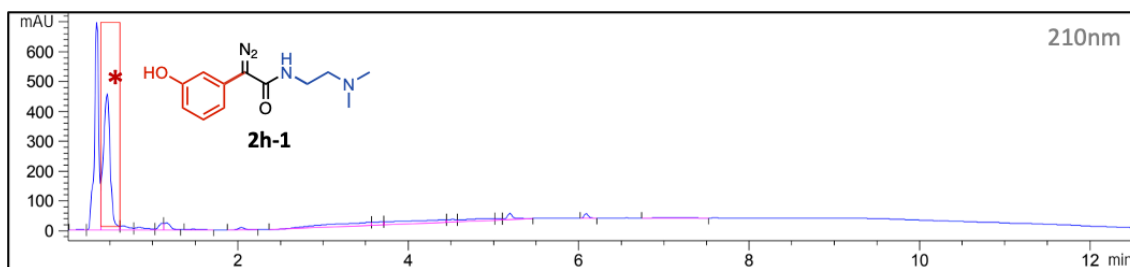
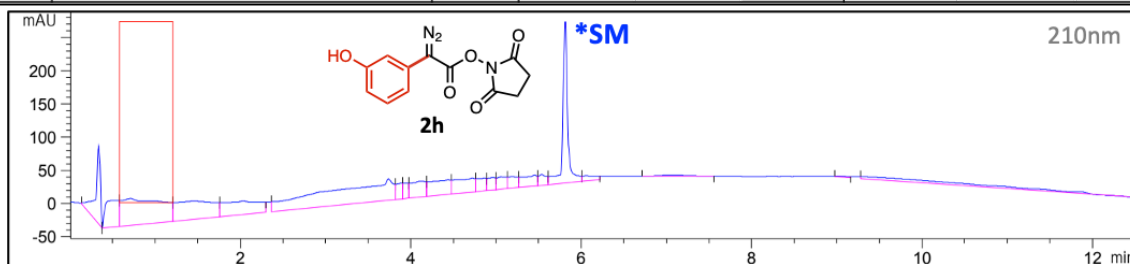
cmpd	Ar-NHS	amine	Molecular Weight			LCMS (m/z)		
			Ar-NHS	amine	product	[M+H] <sup>+</sup>	[M+Na] <sup>+</sup>	[M+H-N <sub>2</sub> ] <sup>+</sup>
2f-1	 2f	1	289.2	88.2	262.3	263.3	285.3	235.3
2f-2		2	289.2	55.1	229.2	230.2	252.2	202.2
2f-3		3	289.2	220.3	394.5	395.5	417.5	367.5
2f-4		4	289.2	262.3	436.5	437.5	459.5	409.5

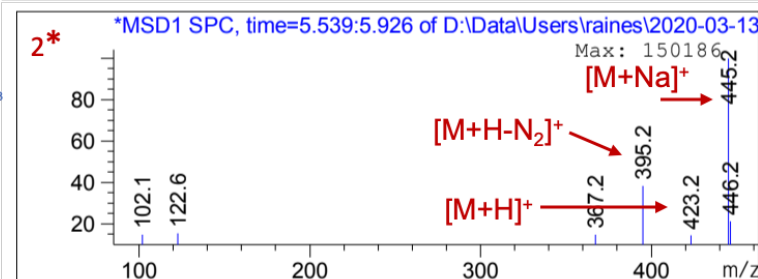
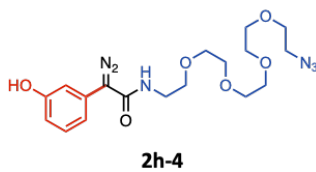
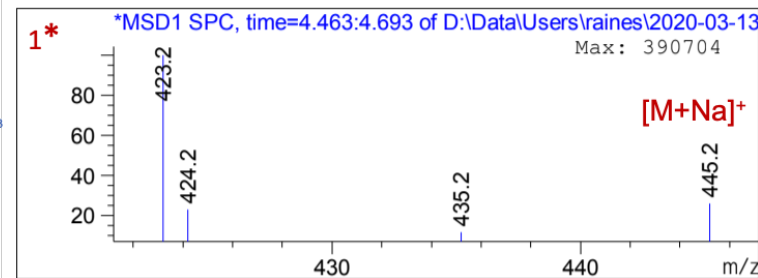
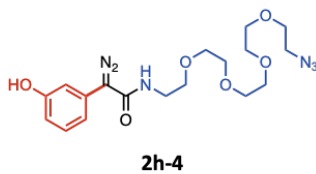
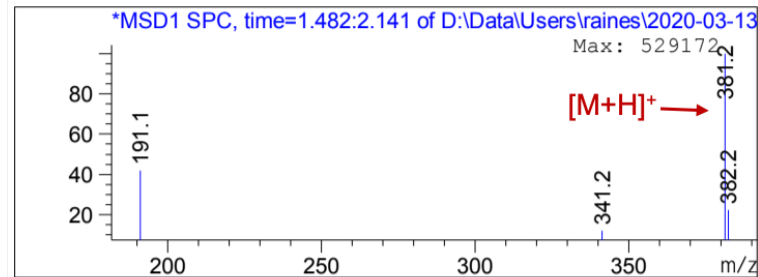
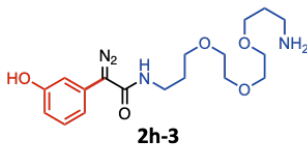
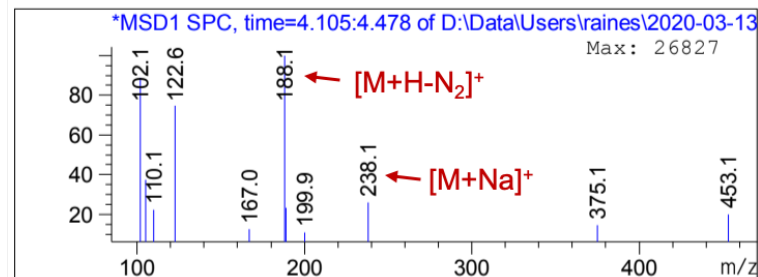
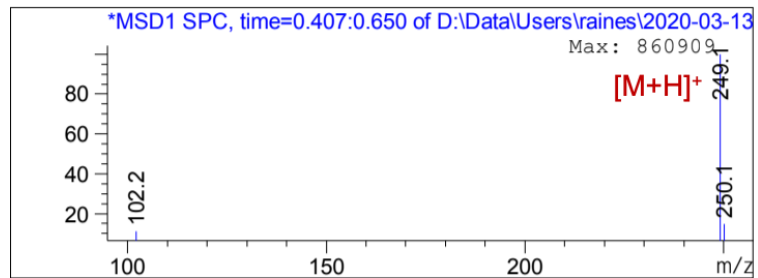
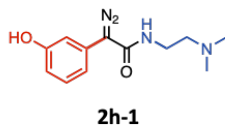
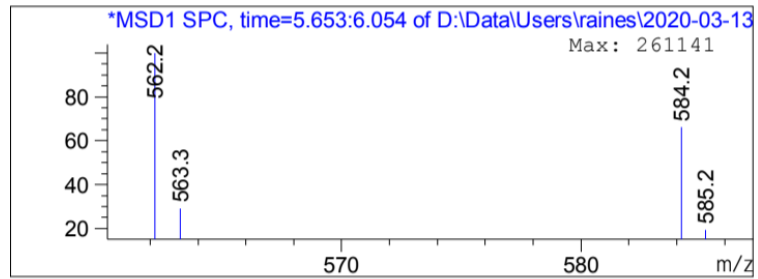
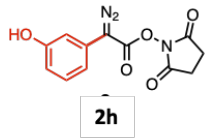




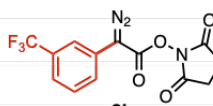
## VII-4. Aminolysis of 2g

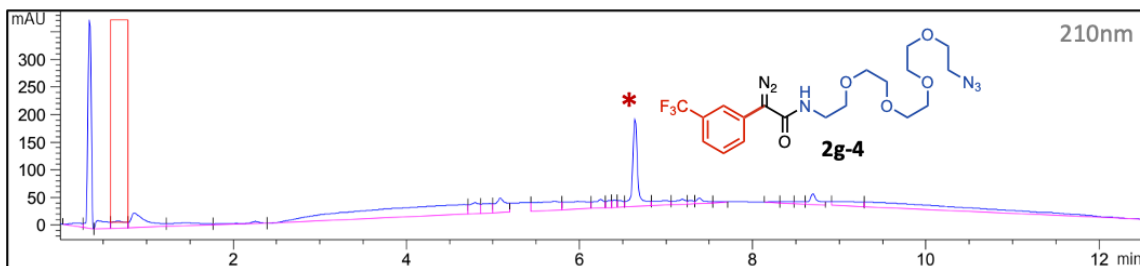
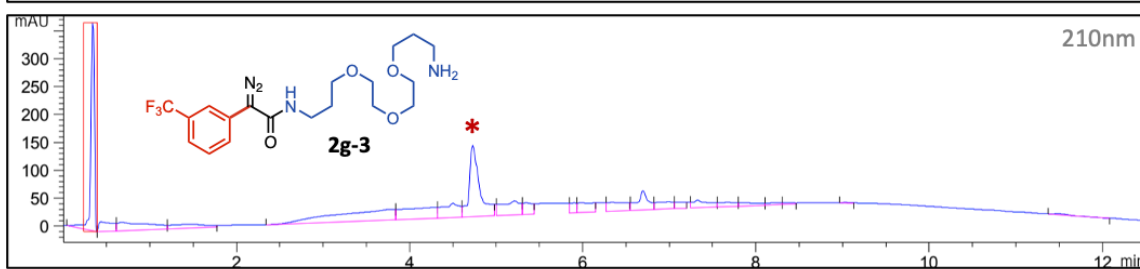
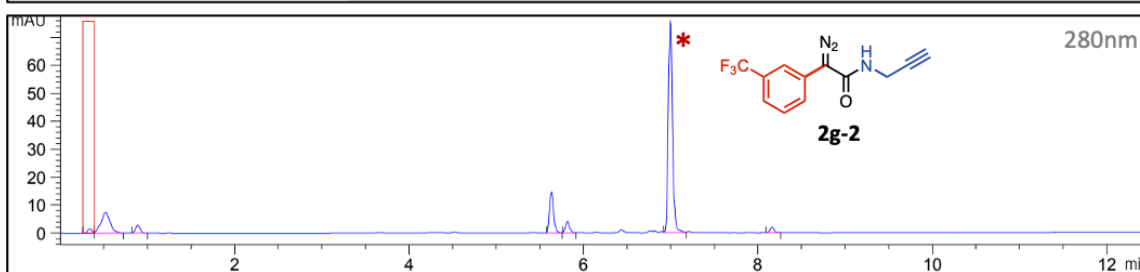
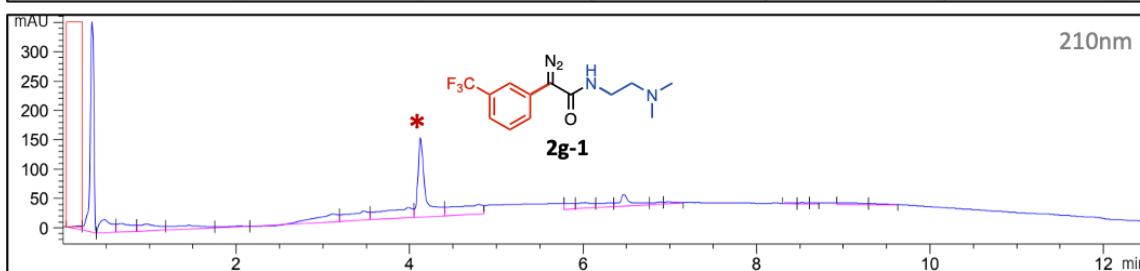
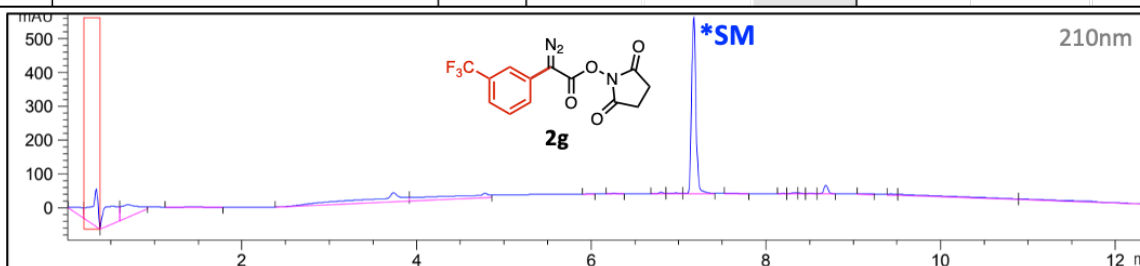
cmpd	Ar-NHS	amine	Molecular Weight			LCMS (m/z)		
			Ar-NHS	amine	product	[M+H] <sup>+</sup>	[M+Na] <sup>+</sup>	[M+H-N <sub>2</sub> ] <sup>+</sup>
2g-1	 2g	1	275.2	88.2	248.3	249.3	271.3	221.3
2g-2		2	275.2	55.1	215.2	216.2	238.2	188.2
2g-3		3	275.2	220.3	380.4	381.4	403.4	353.4
2g-4		4	275.2	262.3	422.4	423.4	445.4	395.4

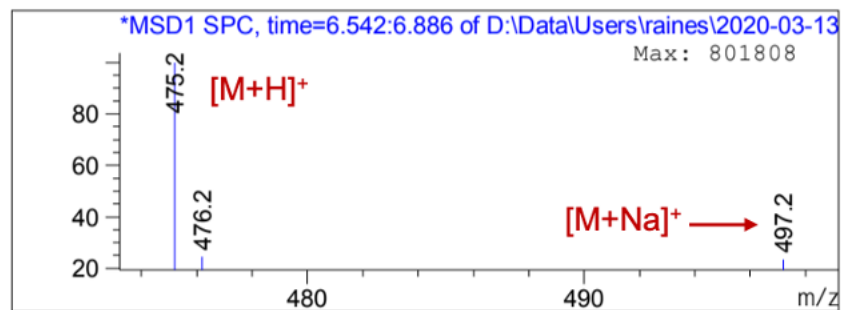
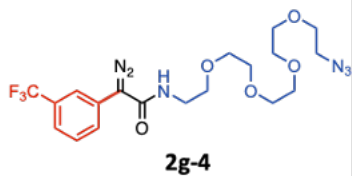
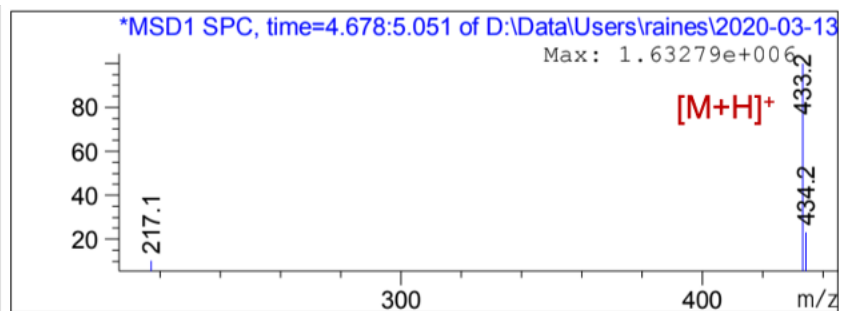
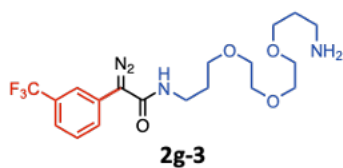
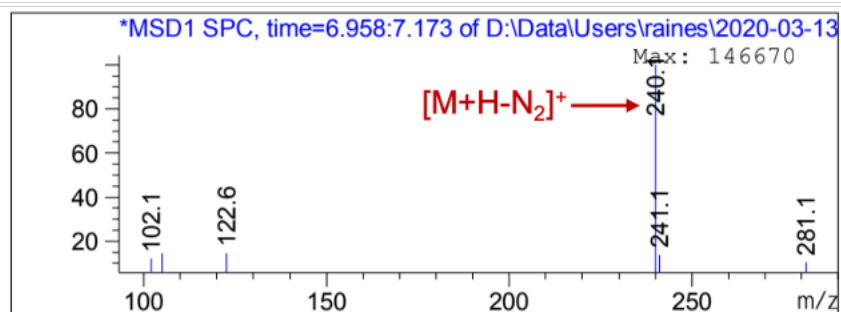
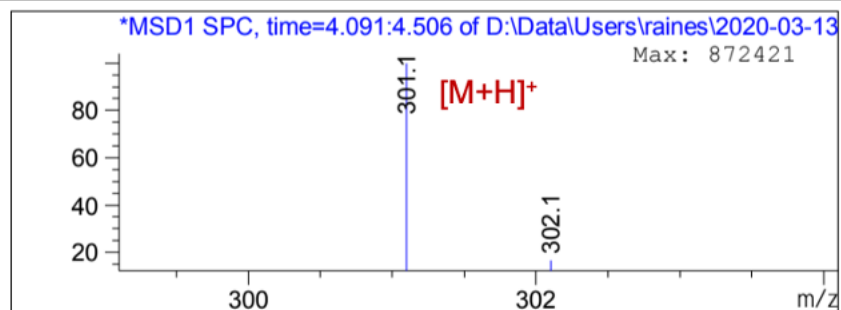
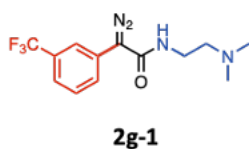
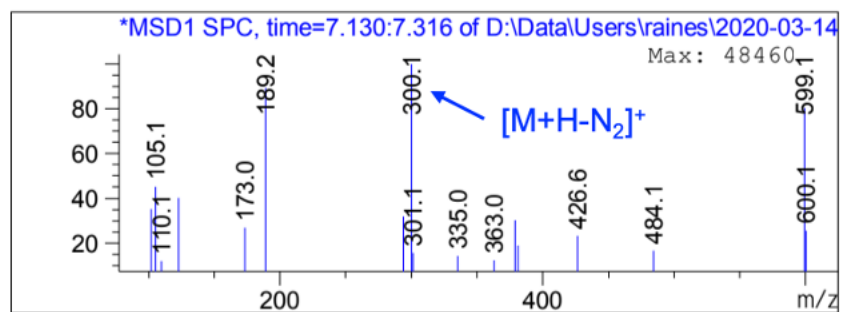
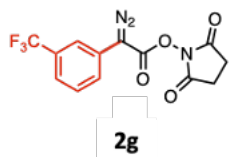




## VII-5. Aminolysis of 2h

cmpd	Ar-NHS	amine	Molecular Weight			LCMS (m/z)		
			Ar-NHS	amine	product	[M+H] <sup>+</sup>	[M+Na] <sup>+</sup>	[M+H-N <sub>2</sub> ] <sup>+</sup>
2h-1	 2h	1	327.2	88.2	300.3	301.3	323.3	273.3
2h-2		2	327.2	55.1	267.2	268.2	290.2	240.2
2h-3		3	327.2	220.3	432.4	433.4	455.4	405.4
2h-4		4	327.2	262.3	474.4	475.4	497.4	447.4

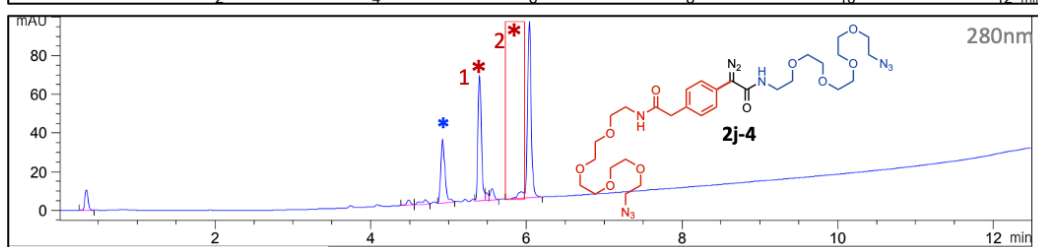
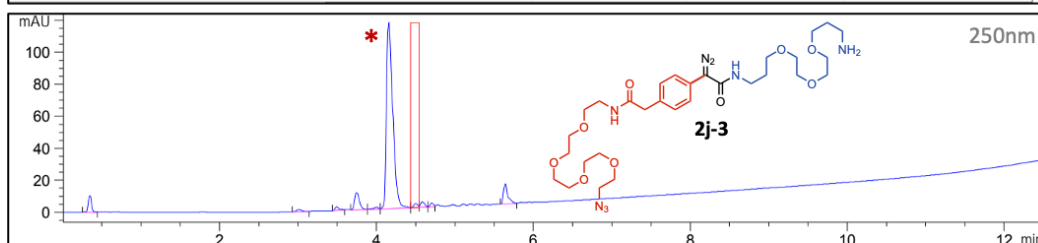
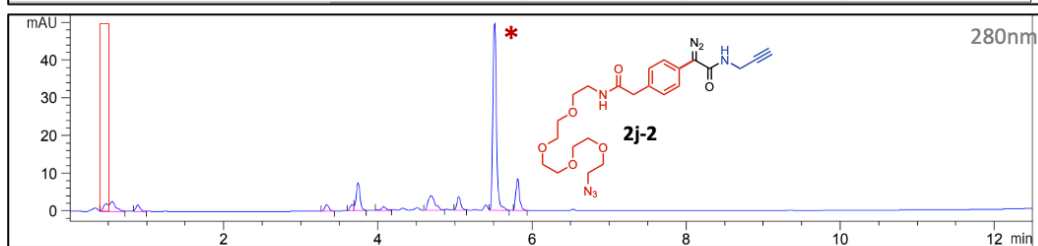
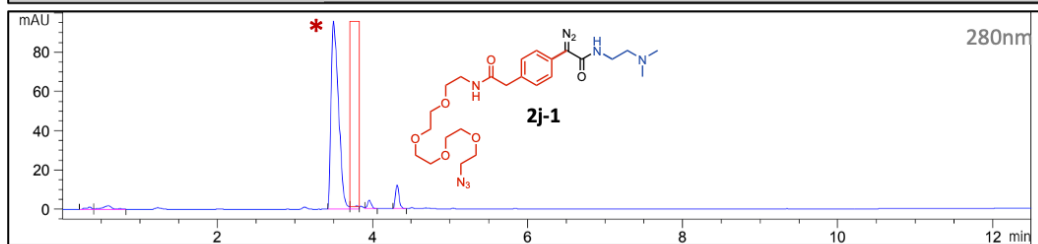
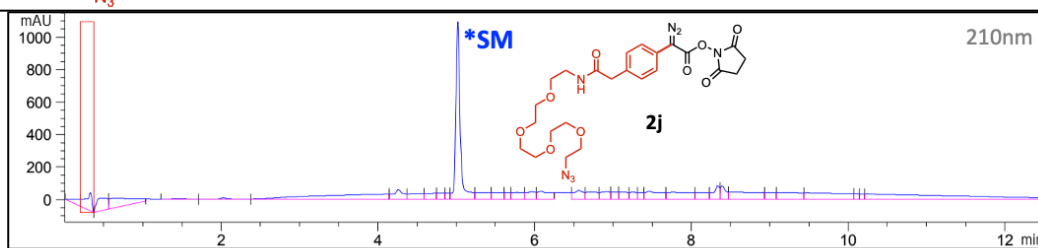


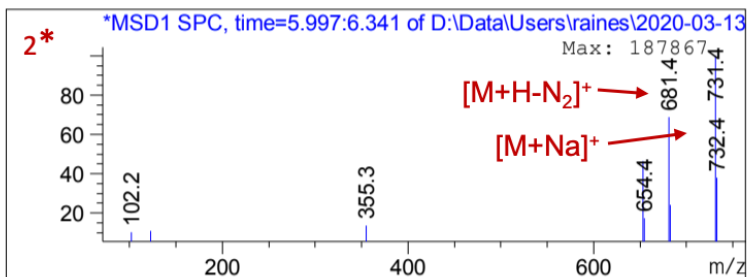
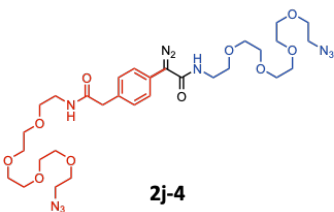
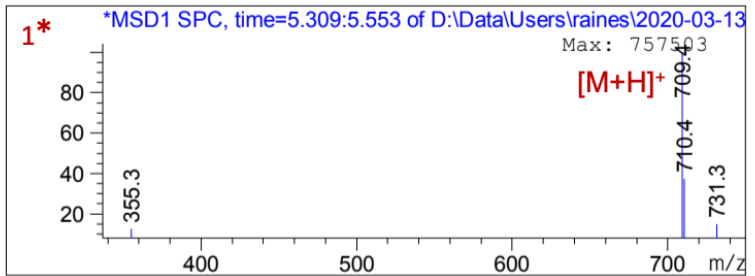
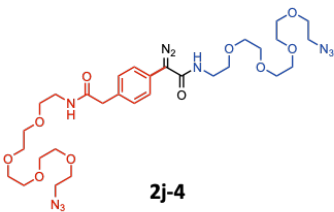
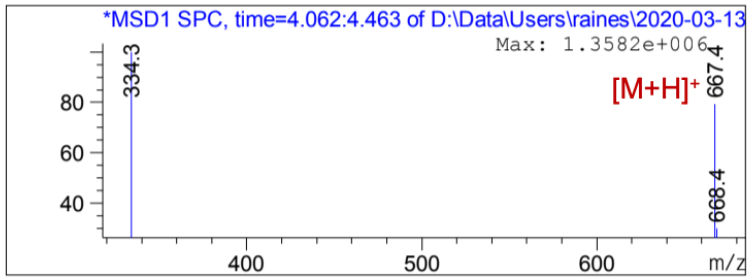
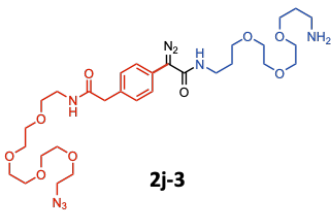
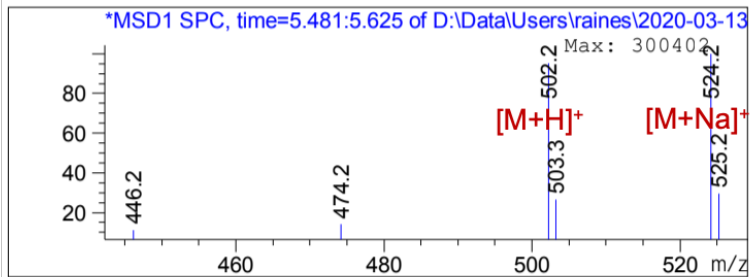
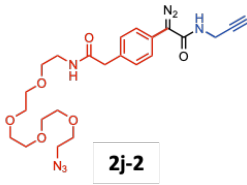
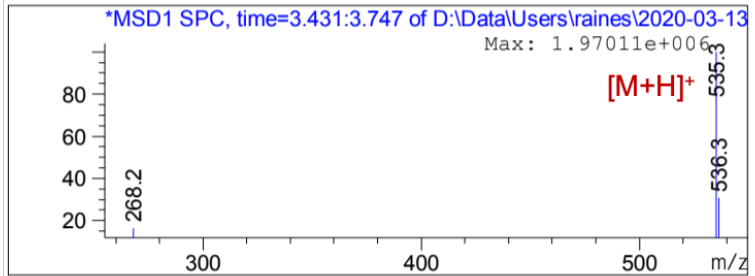
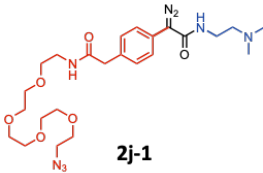
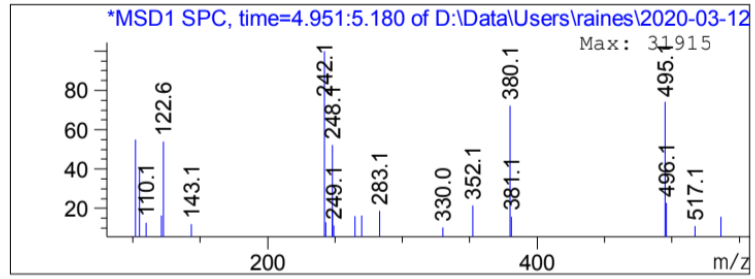
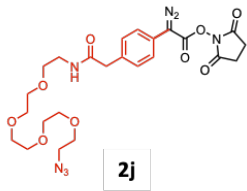




## VII-6. Aminolysis of 2j

cmpd	Ar-NHS	amine	Molecular Weight			LCMS (m/z)		
			Ar-NHS	amine	product	[M+H] <sup>+</sup>	[M+Na] <sup>+</sup>	[M+H-N <sub>2</sub> ] <sup>+</sup>
2j-1		1	561.6	88.2	534.6	535.6	557.6	507.6
2j-2		2	561.6	55.1	501.5	502.5	524.5	474.5
2j-3		3	561.6	220.3	666.8	667.8	689.8	639.8
2j-4		4	561.6	262.3	708.8	709.8	731.8	681.8

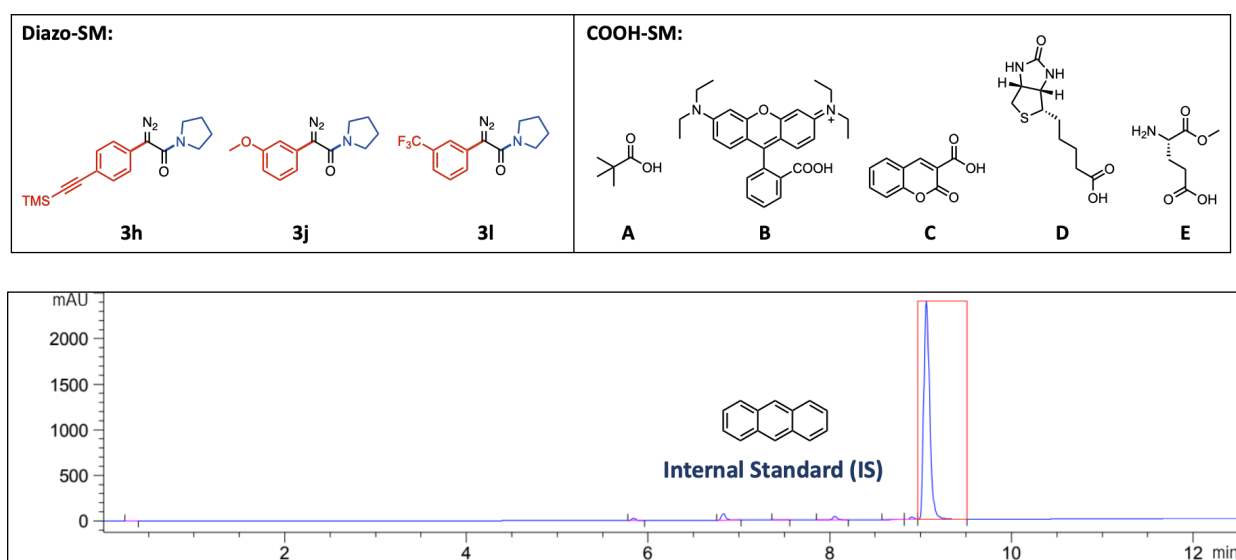




### VIII. Esterification of Aryl $\alpha$ -Diazoamides

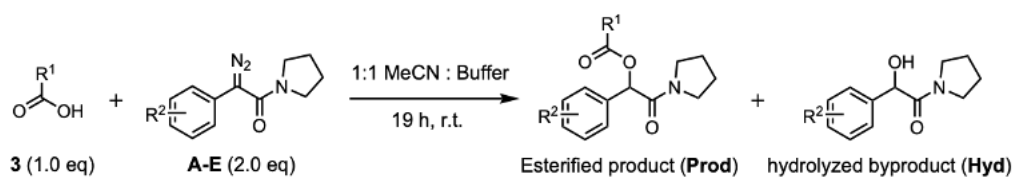
Pivalic acid (**A**,  $pK_a$  5.03), rhodamine B (**B**,  $pK_a$  4.2),<sup>8</sup> coumarin-3-carboxylic acid (**C**), biotin (**D**, alkyl carboxylate  $pK_a$   $\sim$ 5), and L-glutamic acid  $\alpha$ -methyl ester/HGluOMe (**E**,  $pK_a$   $\sim$ 4.2) are chosen to represent sterically versatile and biologically relevant substrates. For diazo compounds, **3h** is selected to represent the reagent suitable for bioconjugation, **3j** to represent 3-position-substituted with an electron-donating group, and **3i** to represent 3-position-substituted with an electron-withdrawing group. Stock solutions of small molecules containing a carboxylic acid (**A–E**) in 100 mM MES–NaOH buffer, pH 6.0, and diazo compound (**3h**, **3j**, and **3i**) in MeCN (50 mM) were prepared. To a 4-mL reaction vial, the stock solution of one carboxylic acid (300  $\mu$ L) and that of one diazo compound (300  $\mu$ L) were mixed to have 50% v/v MeCN in the MES–NaOH buffer (final volume: 3 mL). The reaction mixture was stirred on the Titer plate shaker (speed 1) at room temperature for 19 h (overnight). Each reaction was analyzed by LC–MS using anthracene (0.04 mM in 1/1 MeCN:H<sub>2</sub>O) as an internal standard (**IS**). To a solution with internal standard (900  $\mu$ L), the reaction mixture (100  $\mu$ L) was added and analyzed by LC–MS using the standard gradient (**Figure S5–S6**). The distribution of esterified product (**Prod**) and hydrolyzed byproduct (**Hyd**) is shown in **Table S2**.

*Note: Some carboxylic acid stock solutions in aqueous buffer was not fully soluble. For those stock solutions, the equal volume of slurry was added to the reaction vial.*



**Figure S6.** Top) chemical structures of diazoamide starting materials (**Diazo-SM**) and carboxylic acid starting materials (**COOH-SM**). Bottom) the UV trace (210 nm) of internal standard (anthracene).

Table S2. Product Distribution of Esterification

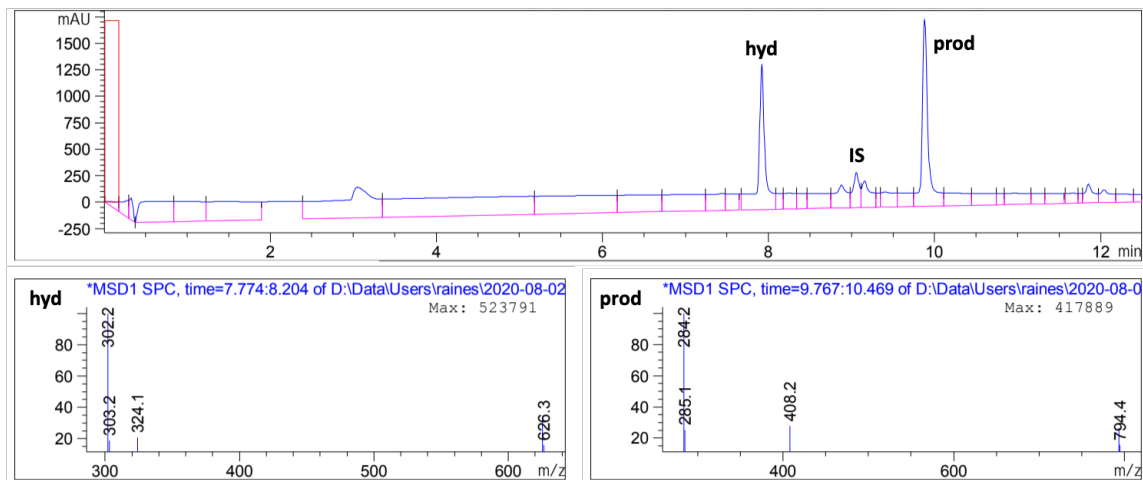
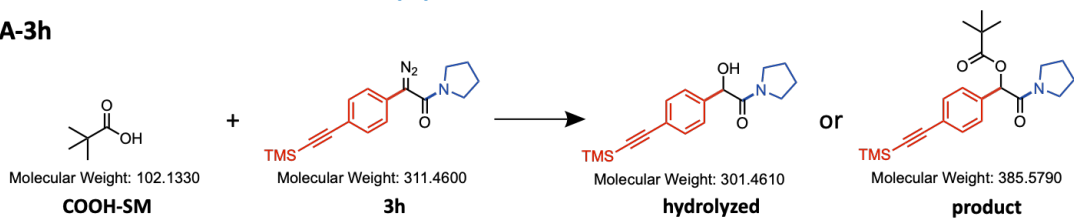


	IS	Diazo-SM	Hydrolyzed	Product	Hyd / IS	Prod / IS	% Hyd	% Prod	Prod / Hyd
<b>A-3h</b>	11243.2	0.0	8024.6	9105.6	0.7	0.8	47	<b>53</b>	1.1
<b>A-3j</b>	10834.1	0.0	4858.1	5678.2	0.4	0.5	46	<b>54</b>	1.2
<b>A-3l</b>	10858.7	0.0	3769.3	4401.7	0.3	0.4	46	<b>54</b>	1.2
<b>B-3h</b>	6892.5	0.0	529.1	1909.8	0.1	0.3	22	<b>78</b>	3.6
<b>B-3j</b>	5537.7	0.0	1799.4	1738.7	0.3	0.3	51	<b>49</b>	1.0
<b>B-3l</b>	5555.5	0.0	290.7	1181.4	0.1	0.2	20	<b>80</b>	4.1
<b>C-3h</b>	5090.5	0.0	3921.2	6390.3	0.8	1.3	38	<b>62</b>	1.6
<b>C-3j</b>	5118.5	0.0	1464.5	3376.5	0.3	0.7	30	<b>70</b>	2.3
<b>C-3l</b>	5719.5	0.0	2790.7	5228.6	0.5	0.9	35	<b>65</b>	1.9
<b>D-3h</b>	5194.4	0.0	2501.2	4056.2	0.5	0.8	38	<b>62</b>	1.6
<b>D-3j</b>	5129.2	0.0	3151.4	2994.7	0.6	0.6	51	<b>49</b>	1.0
<b>D-3l</b>	5153.0	0.0	2066.1	2349.6	0.4	0.5	47	<b>53</b>	1.1
<b>E-3h</b>	5199.5	0.0	2498.7	1157.2	0.5	0.2	68	<b>32</b>	0.5
<b>E-3j</b>	5167.9	0.0	3603.2	1449.7	0.7	0.3	71	<b>29</b>	0.4
<b>E-3l</b>	5138.7	0.0	1351.3	627.5	0.3	0.1	68	<b>32</b>	0.5

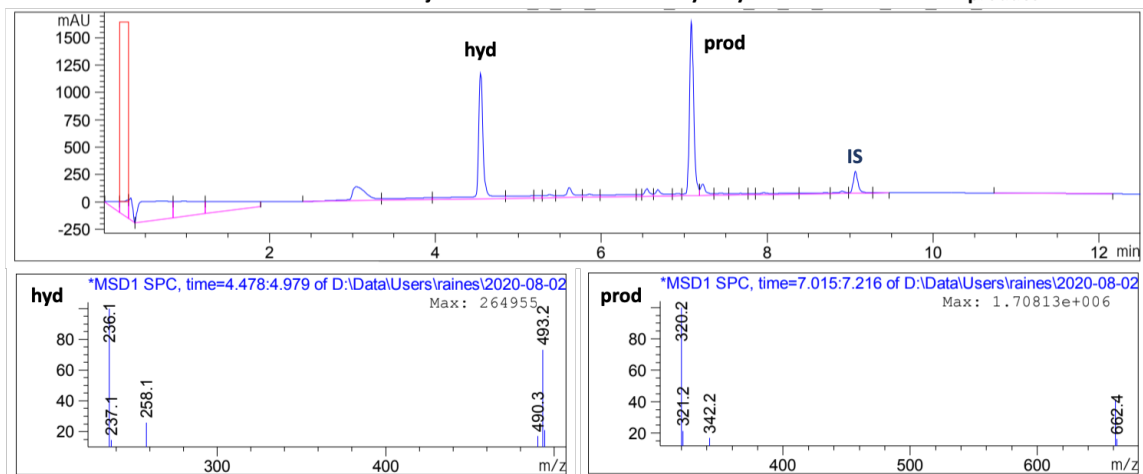
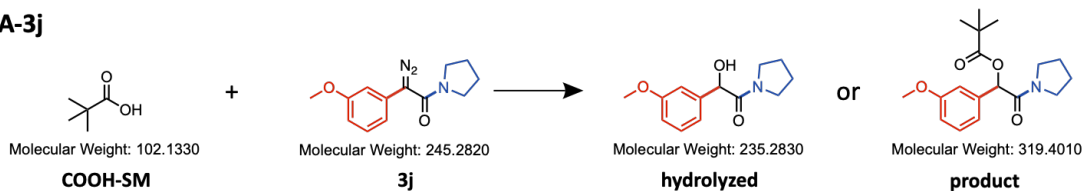
From left to right, the area of internal standard (at 210 nm), diazo starting material, hydrolyzed product, and esterified product are shown. Assuming the area of starting material + product + hydrolyzed = 100%, the normalized yield (**Hyd/IS**, **Prod/IS**), % yield (**% Hyd**, **% Prod**), and the ratio of carboxylic acid over water selectivity (**Prod/Hyd**) are shown.

## VIII-1. Esterification of Pivalic Acid (A)

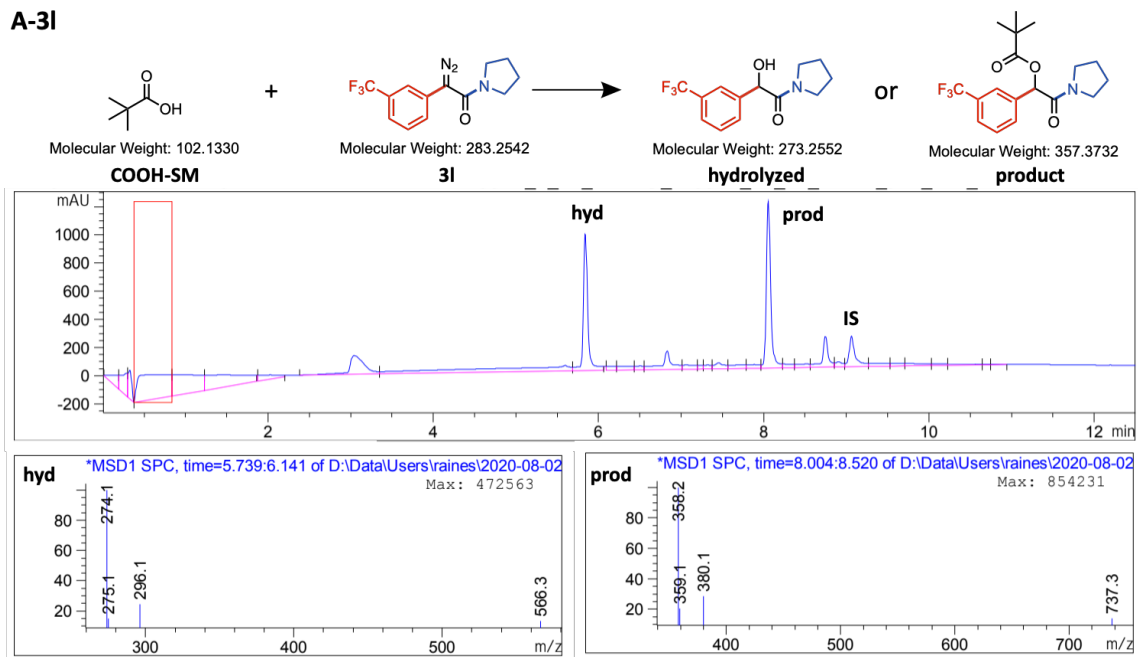
A-3h



A-3j

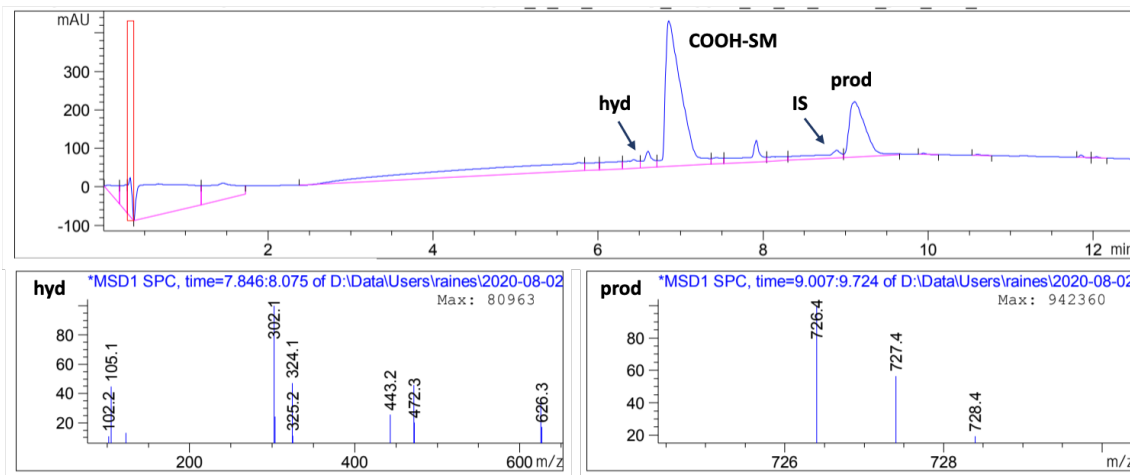
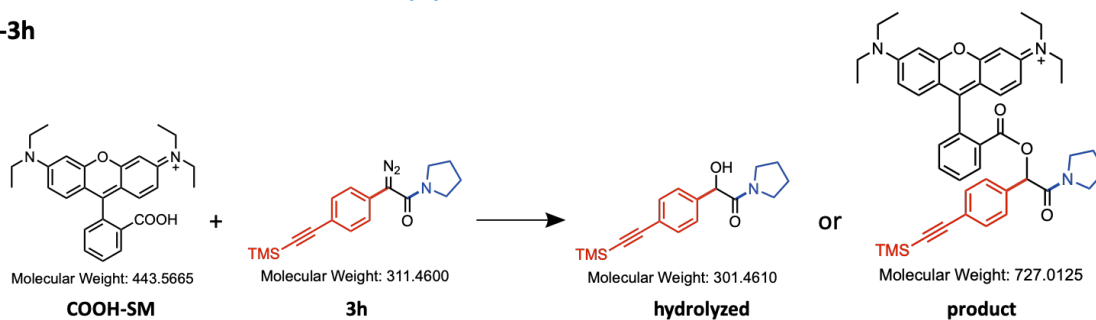


## A-31

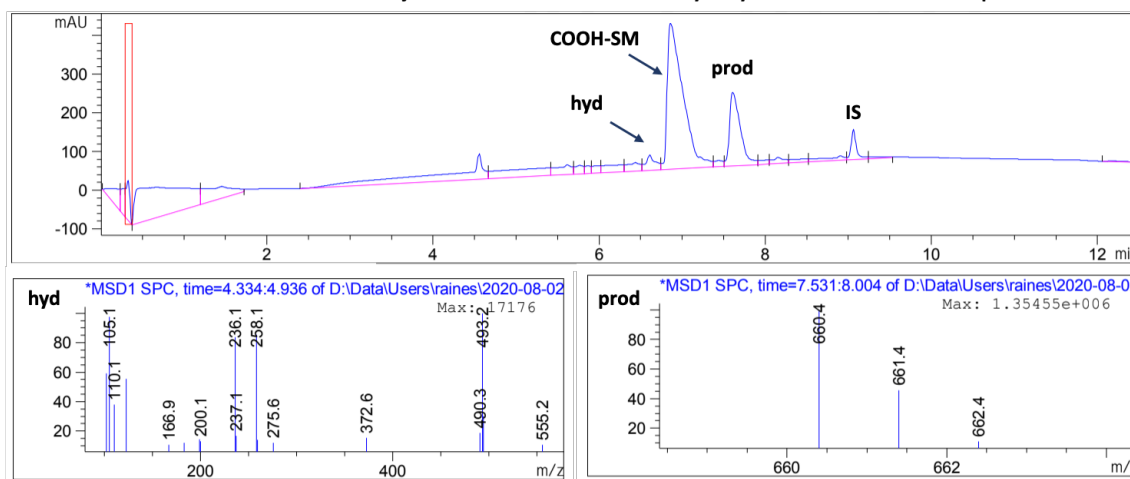
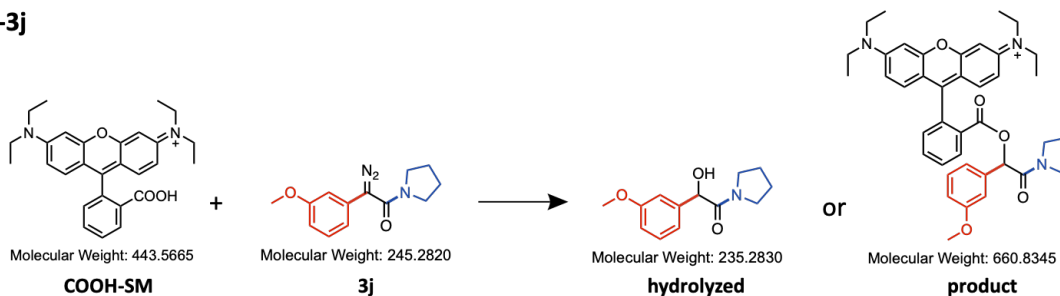


## VIII-2. Esterification of Rhodamine B (B)

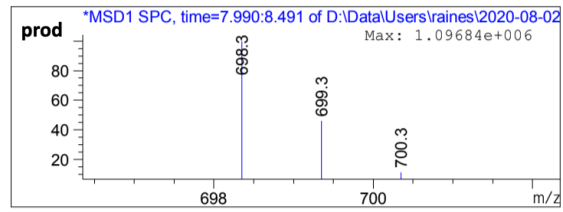
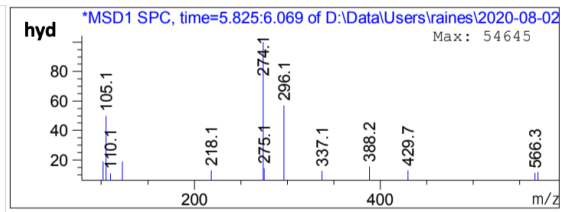
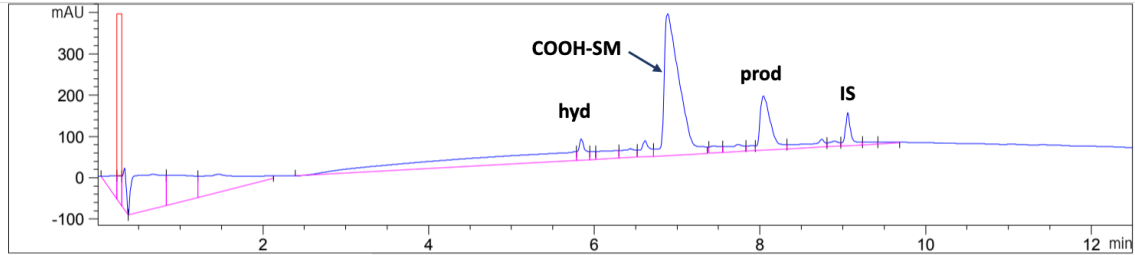
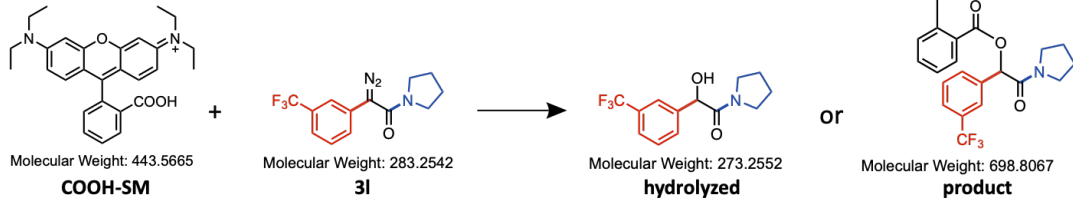
## B-3h



## B-3j



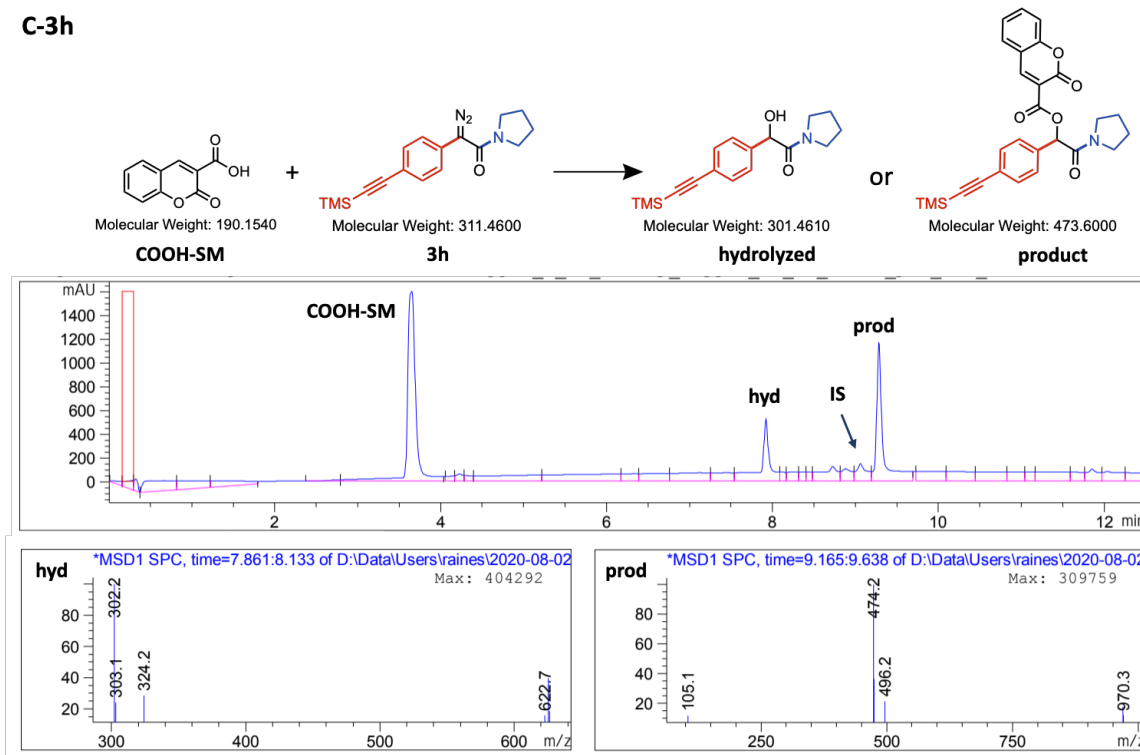
**B-3I**



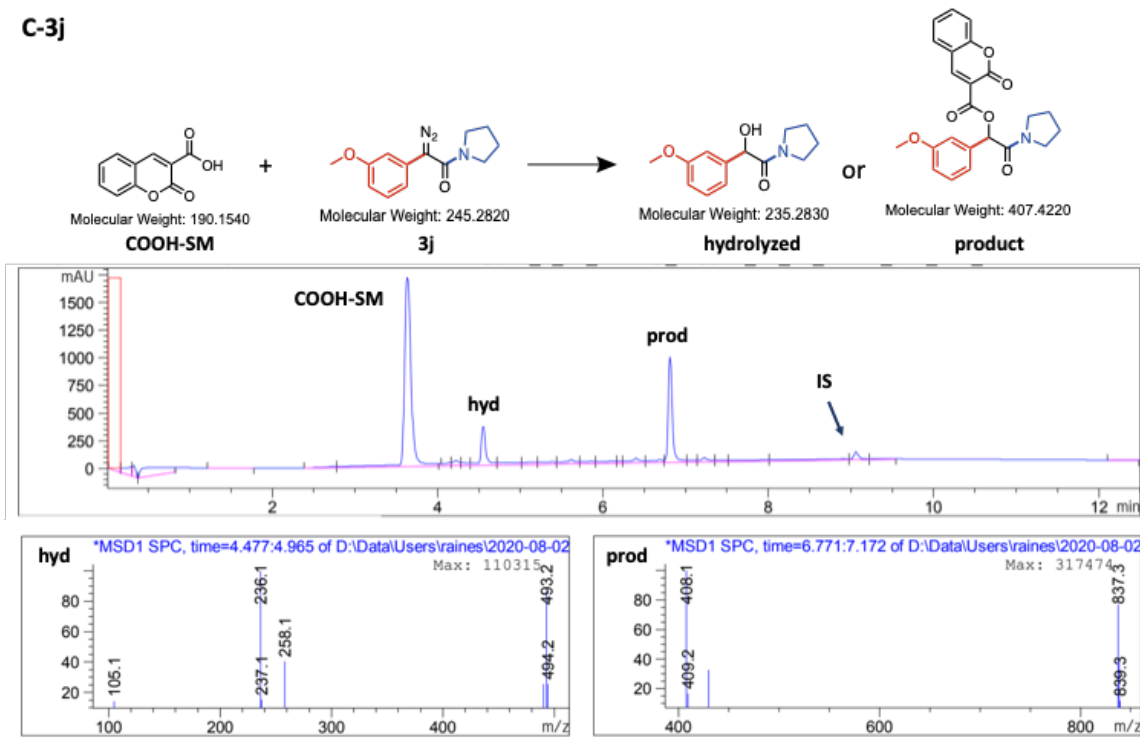


## VIII-3. Esterification of Coumarin-3-carboxylic acid (C)

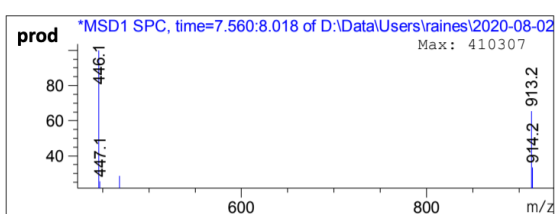
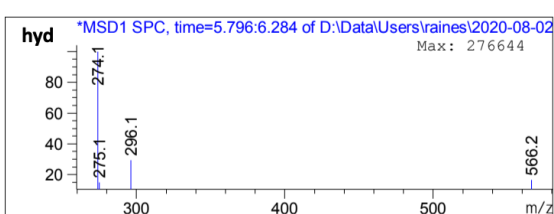
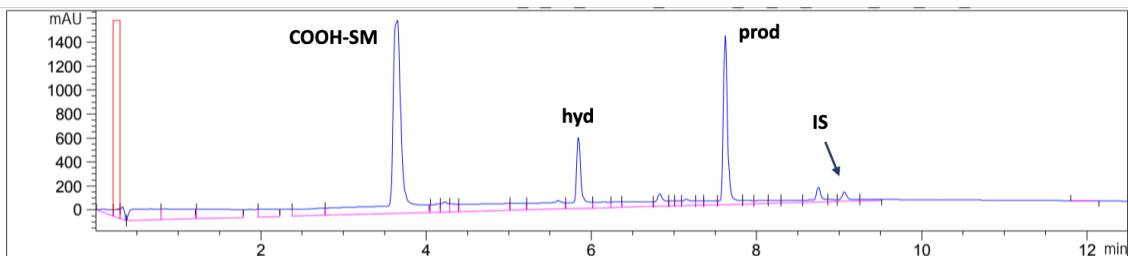
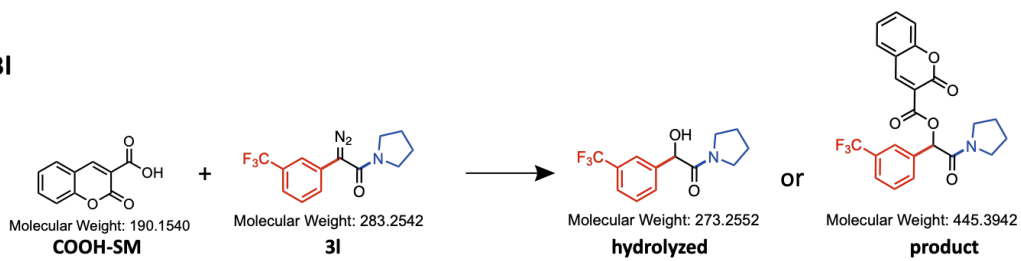
C-3h



C-3j

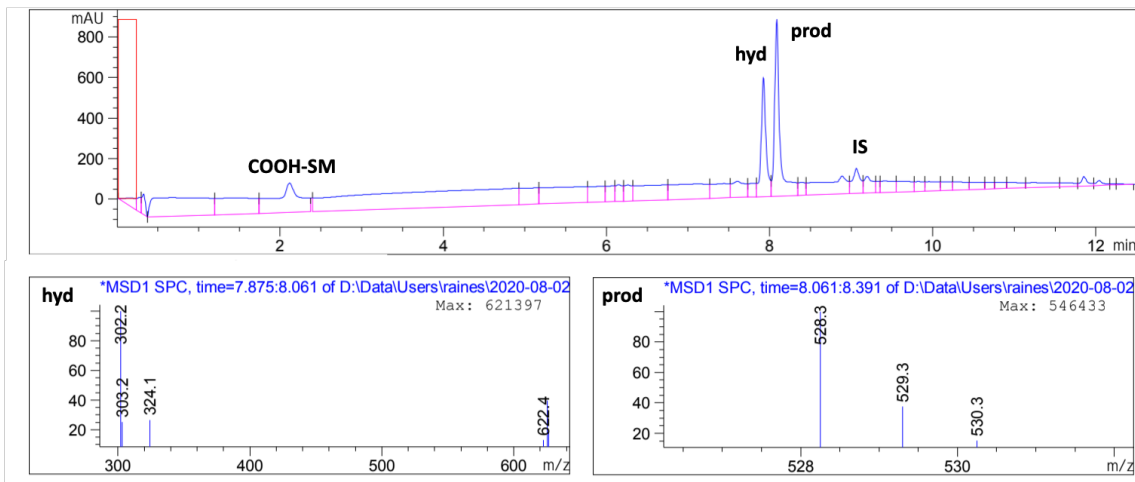
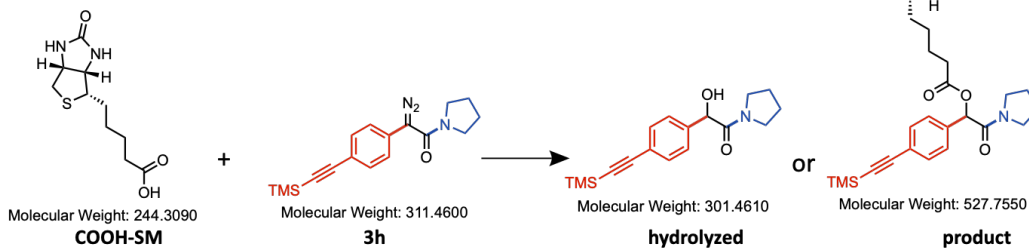


## C-31

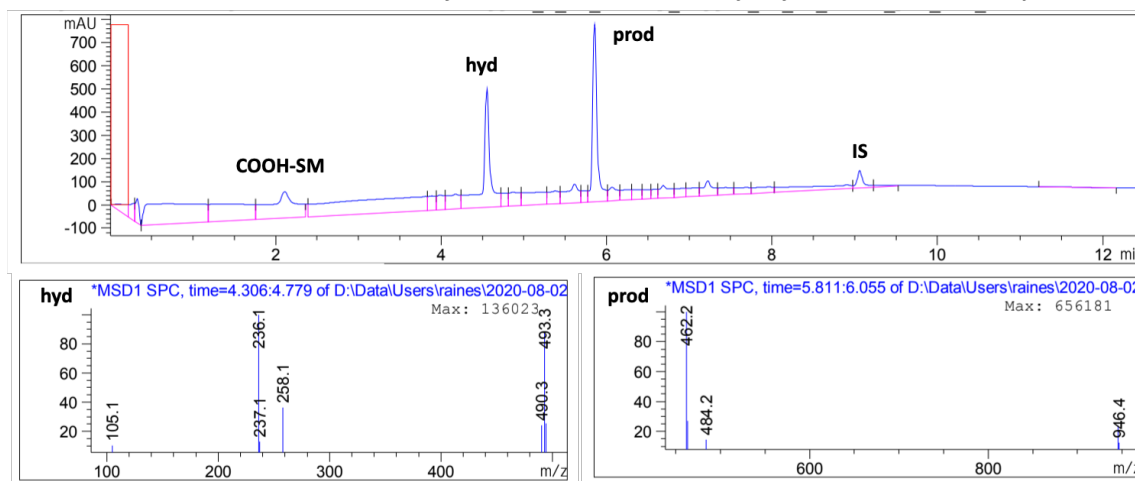
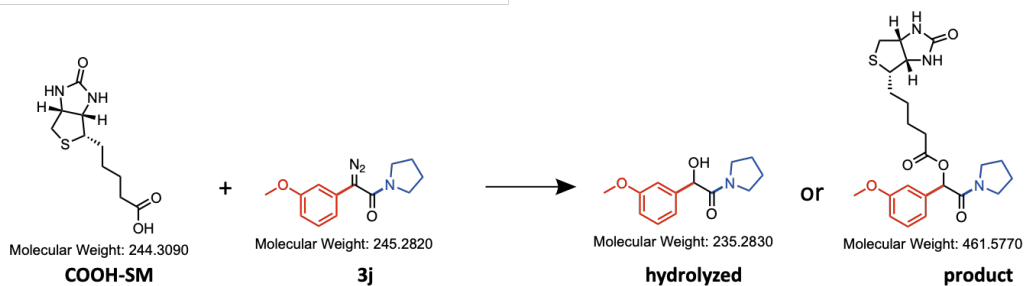


## VIII-4. Esterification of Biotin (D)

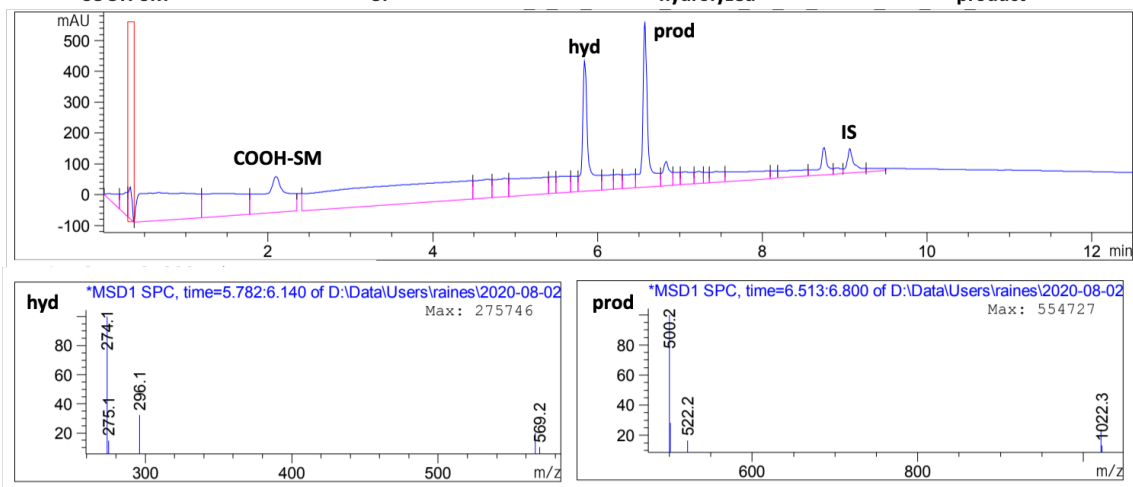
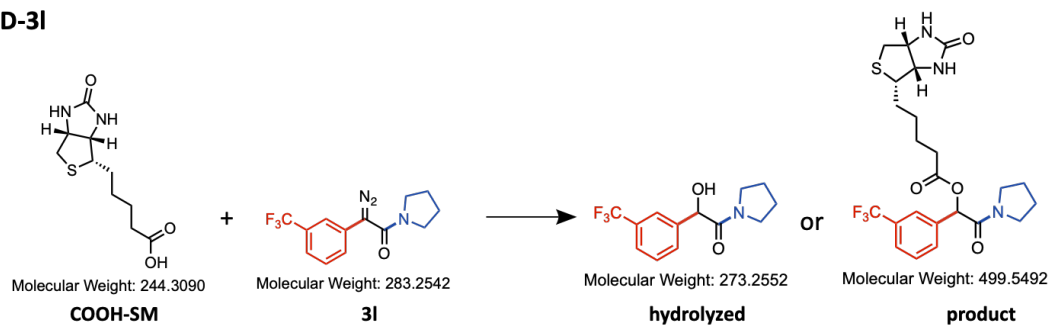
D-3h



D-3j

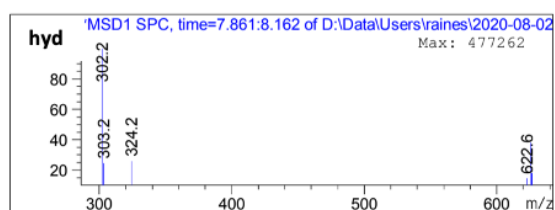
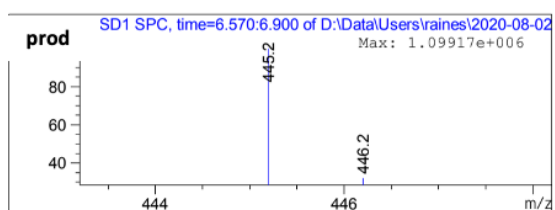
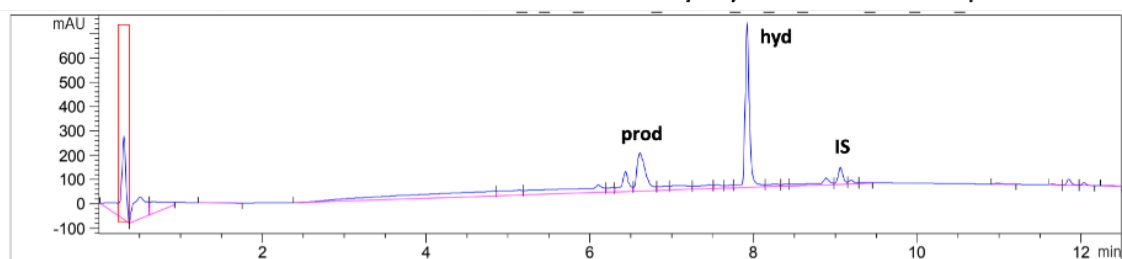
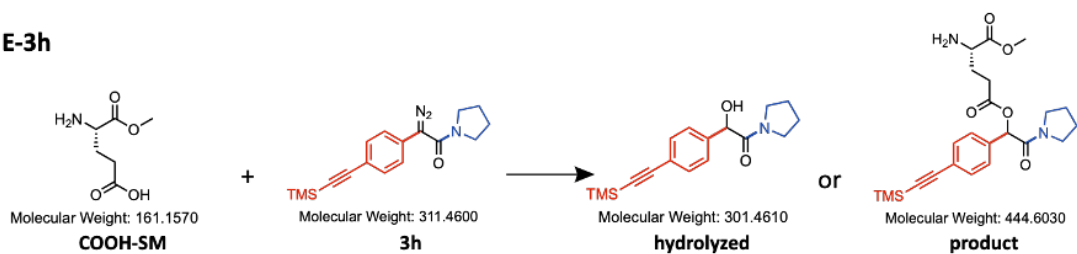


## D-31

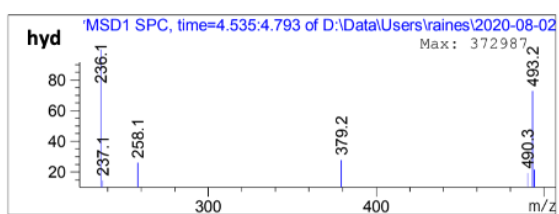
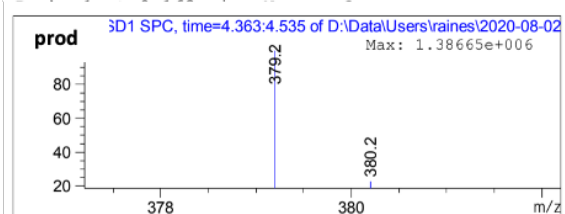
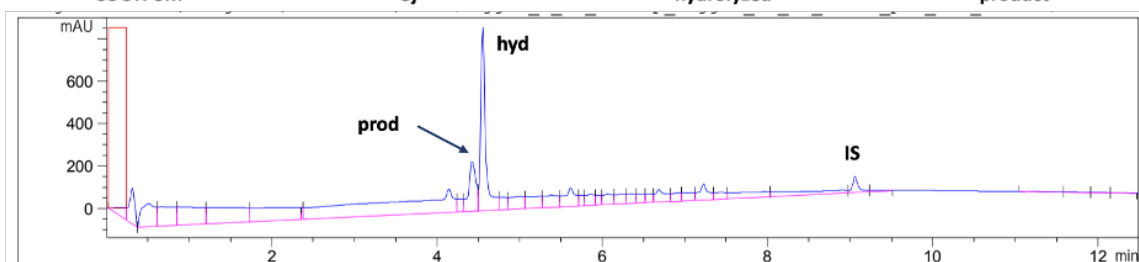
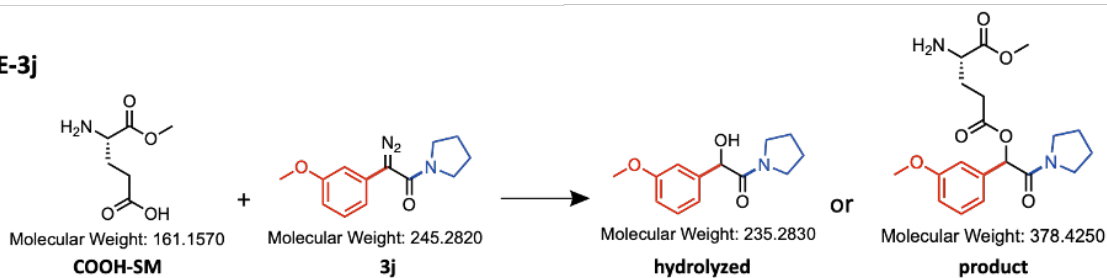


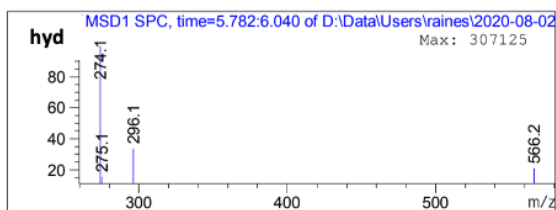
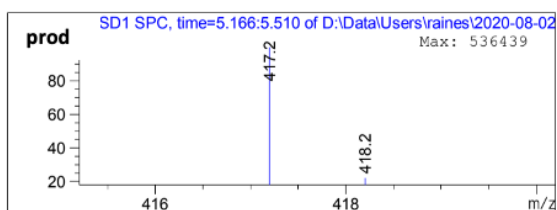
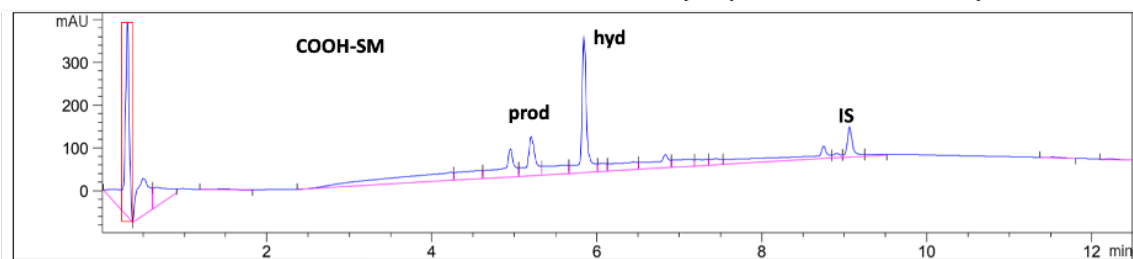
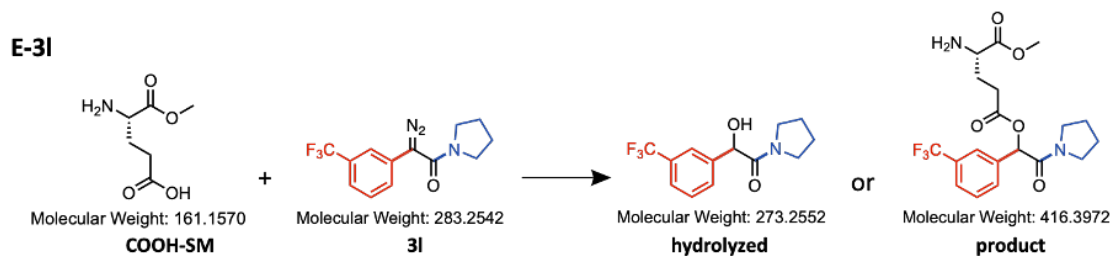
## VIII-5. Esterification of HGLuOMe (E)

E-3h



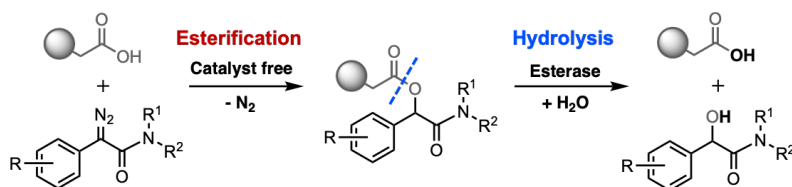
E-3j





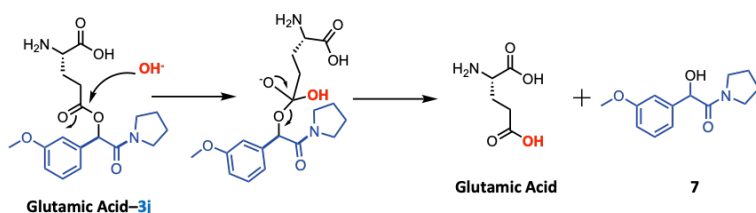
## IX. Experimental Procedure for Hydrolysis

In order to study bioreversibility of aryl diazoamide compounds, the small molecule model system is designed to test the hydrolytic cleavage of pendant ester bond formed by **3j**.

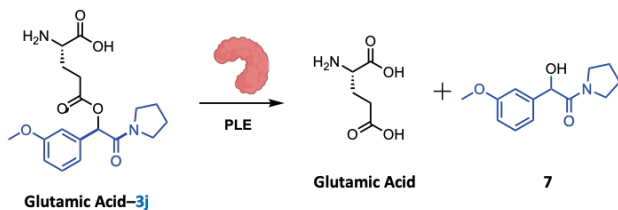


### IX-1. Designing the Model Compound AcGluNH<sub>2</sub> (**5**)

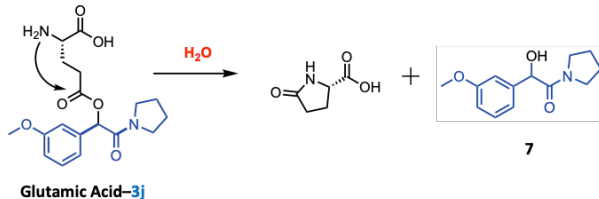
#### □ General Hydrolysis



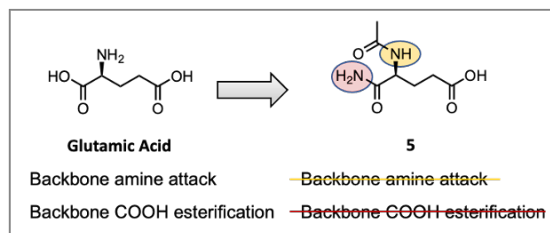
#### □ Esterase Cleavage



#### □ Backbone Amine Attack

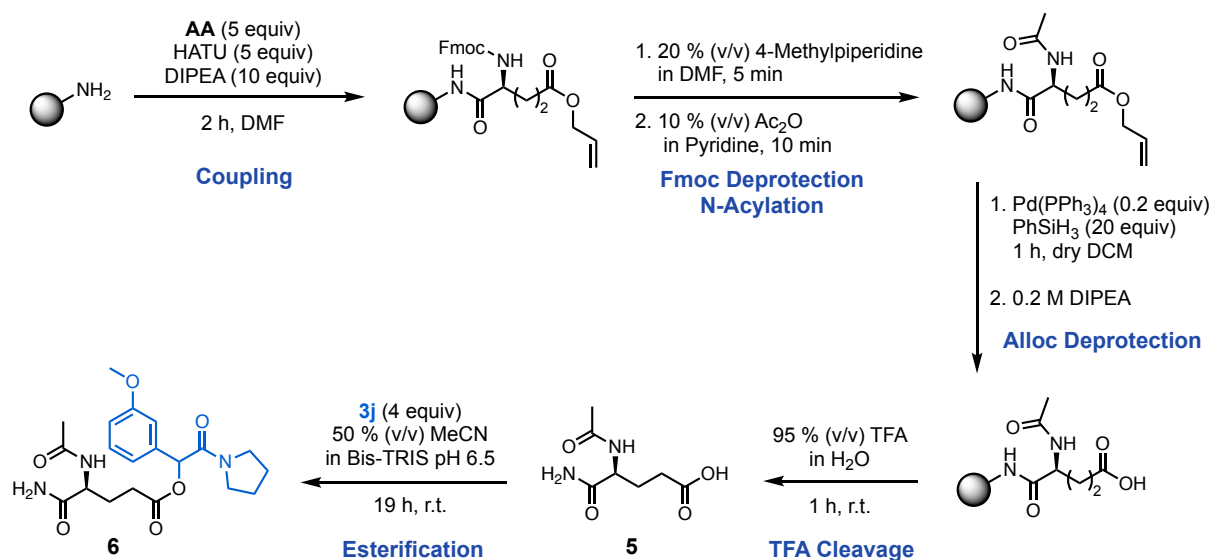


#### Designing the Model Compound



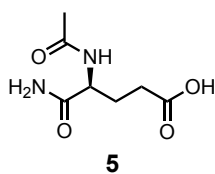
**Scheme S2.** The model compound **5** was designed to study the bioreversibility of esterification by aryl diazoamide **3j**. Because glutamic acid itself can lead to three possible routes to yield alcohol **7**, compound **5** was designed to block backbone amine attack and backbone carboxylic acid esterification.

## IX-2. Synthesis and Characterization of Compound 5–7



**Figure S7.** Solid-Phase Synthesis and Esterification. **AA** is Fmoc-Glu(OAll)-OH (CAS Number 133464-46-7), HATU (CAS Number 148893-10-1) is a peptide coupling reagent, Ac<sub>2</sub>O is acetic anhydride, DIPEA is *N,N*-diisopropylethylamine, and TFA is trifluoroacetic acid.



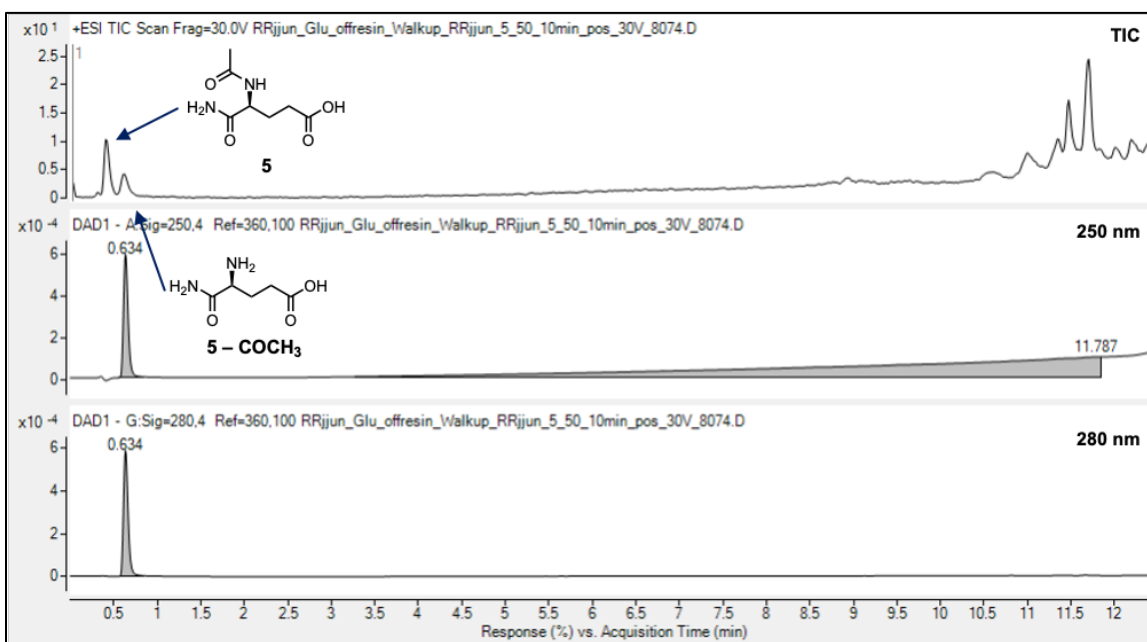


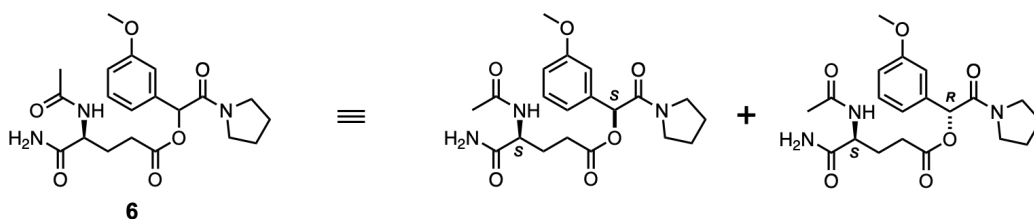
**AcGluNH<sub>2</sub> (Compound 5):** Adapting the literature procedure,<sup>9</sup> the synthesis of **5** was entirely performed on solid phase, using Rink Amide resin (ProTide). Coupling Fmoc-Glu(OAll)-OH (**AA**) onto the resin, Fmoc group elimination, acetylation of N<sup>α</sup>, removal of the Alloc-protecting group, and resin cleavage led to **5**. Washing between coupling, deprotection, and subsequent capping steps were carried out with DMF (3 mL × 5) and DCM (3 mL × 5).

*Note: This compound (AcGluNH<sub>2</sub> / acetyl-L-glutamic acid α-amide, CAS: 25460-87-1) is commercially available from AK Scientific.*

**HRMS (ESI-TOF):** calc'd for C<sub>7</sub>H<sub>13</sub>N<sub>2</sub>O<sub>4</sub> [M + H]<sup>+</sup>, 189.0870; found, 189.0870

**Analytical LC-MS (crude reaction):** 5–50% v/v MeCN in 10 min (**Figure S8**)





**Compound 6:** 500  $\mu$ L of compound **5** (50 mM in Bis-TRIS buffer, pH 6.5) and 500  $\mu$ L of diazo compound **3j** (200 mM in MeCN) were added to a 4-mL vial, and the reaction mixture was stirred overnight. The product was purified by reverse phase HPLC (30–80% v/v MeCN (0.1% v/v TFA) in H<sub>2</sub>O (0.1% v/v TFA) over 40 min). The desired product eluted around 60% v/v MeCN in H<sub>2</sub>O.

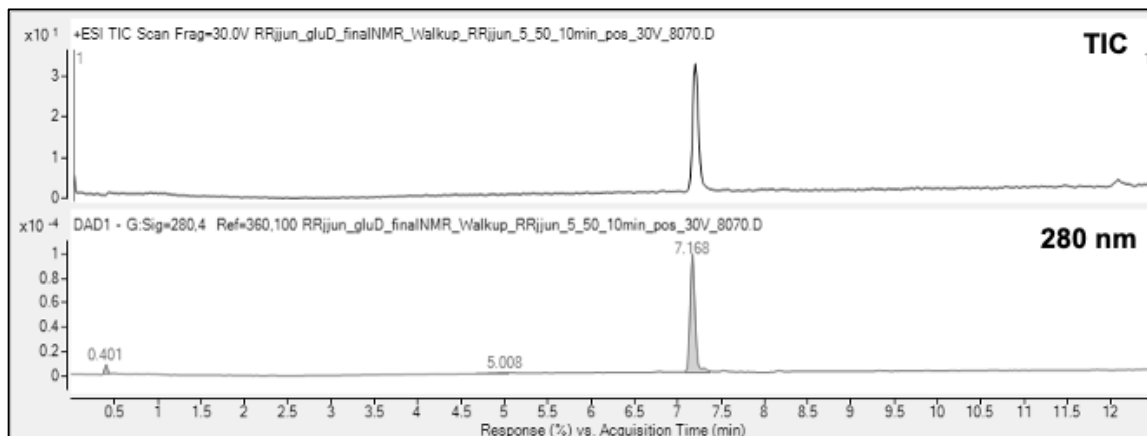
**Physical State:** white solid

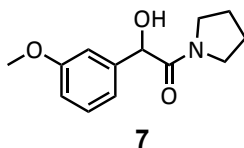
**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>,  $\delta$ ):** 7.92 (s, 1H), 7.32 (t,  $J$  = 7.7 Hz, 2H), 7.12 (s, 1H), 7.07–6.91 (m, 4H), 6.57 (d,  $J$  = 7.8 Hz, 1H), 6.09 (s, 1H), 5.98 (s, 1H), 5.77 (d,  $J$  = 29.5 Hz, 2H), 4.81 (q,  $J$  = 3.3 Hz, 1H), 4.59 (d,  $J$  = 7.3 Hz, 1H), 3.82 (d,  $J$  = 7.0 Hz, 4H), 3.66–3.34 (m, 6H), 3.15–3.02 (m, 2H), 2.71–2.62 (m, 1H), 2.62–2.45 (m, 2H), 2.43–2.23 (m, 2H), 2.10 (d,  $J$  = 6.5 Hz, 2H), 2.03 (d,  $J$  = 3.5 Hz, 4H), 2.01–1.69 (m, 6H)

**<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>,  $\delta$ ):** 172.5, 172.2, 171.7, 170.6, 167.1, 166.9, 160.3, 160.2, 134.8, 134.4, 130.4, 130.3, 121.2, 121.1, 115.4, 115.1, 114.5, 114.4, 74.9, 74.5, 55.6, 55.5, 52.6, 51.7, 46.8, 46.7, 46.2, 31.5, 30.8, 29.2, 27.1, 26.2, 23.9, 23.9, 23.2, 22.9

**HRMS (ESI-TOF):** calc'd for C<sub>20</sub>H<sub>27</sub>N<sub>3</sub>O<sub>6</sub> [M + H]<sup>+</sup>, 406.1973; found, 406.1974

**Analytical LC-MS:** 5–50% v/v MeCN in 10 min (**Figure S8**)





**Compound 7:** Compound **7** was obtained by purifying the byproduct from the esterification reaction above. The desired product was purified by reverse phase HPLC (30–80% v/v MeCN (0.1% v/v TFA) in H<sub>2</sub>O (0.1% v/v TFA) over 40 min), eluting around 40% v/v MeCN in H<sub>2</sub>O.

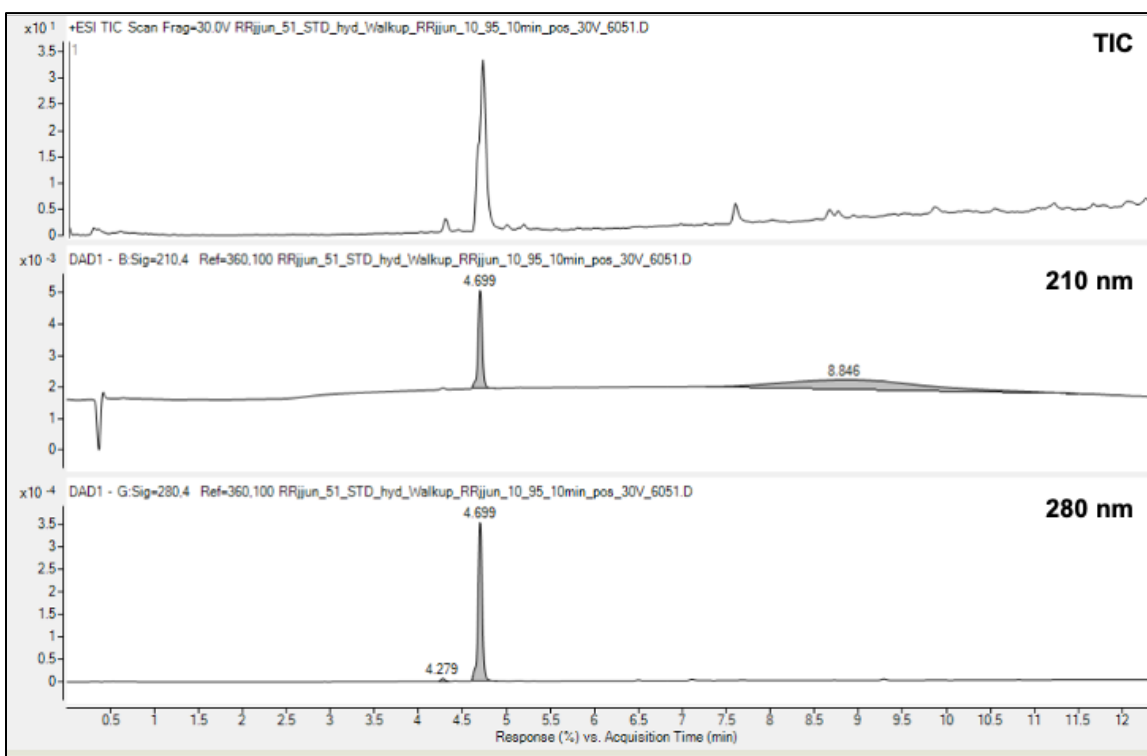
**Physical State:** white solid

**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>, δ):** 7.28 (d, *J* = 7.7 Hz, 1H), 6.98–6.80 (m, 3H), 5.01 (s, 1H), 3.80 (s, 3H), 3.61 (d, *J* = 5.2 Hz, 1H), 3.49 (d, *J* = 4.8 Hz, 1H), 3.38 (dd, *J* = 6.4, 3.6 Hz, 1H), 2.94–2.87 (m, 1H), 1.90–1.72 (m, 4H)

**<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>, δ):** 170.7, 160.2, 140.5, 130.1, 120.3, 114.4, 113.2, 72.7, 55.5, 46.8, 46.0, 26.0, 24.0

**HRMS (ESI-TOF):** calc'd for C<sub>13</sub>H<sub>18</sub>NO<sub>3</sub> [M + H]<sup>+</sup>, 236.1281; found, 236.1274

**Analytical LC-MS:** 10–95% v/v MeCN in H<sub>2</sub>O over 10 min (**Figure S5**)



### IX-3. Hydrolytic Cleavage of Compound 6

A 1-mM stock solution of compound **6** was prepared in water. 10.8 mg of pig liver esterase (PLE, 15 U/mg) was dissolved in 578  $\mu$ L of 100 mM sodium phosphate buffer, pH 7.2, to have 28 U (activity unit) per 100  $\mu$ L. 100  $\mu$ L of compound **6** (0.14  $\mu$ mole, 1 equiv) was added to each reaction vial containing 100  $\mu$ L of buffer solution with or without PLE (**Table S3**). Phosphate buffer (100 mM) solutions of physiologically relevant pH (pH 5.8, 7.2, and 8.0) were prepared to measure the background hydrolysis without PLE. The progress of hydrolysis was analyzed by LC–MS. For the samples with PLE, PLE was removed by spin filtration (Amicon Ultra 0.5-mL centrifugal filters, MWCO 10 kDa) prior to LC–MS analysis.

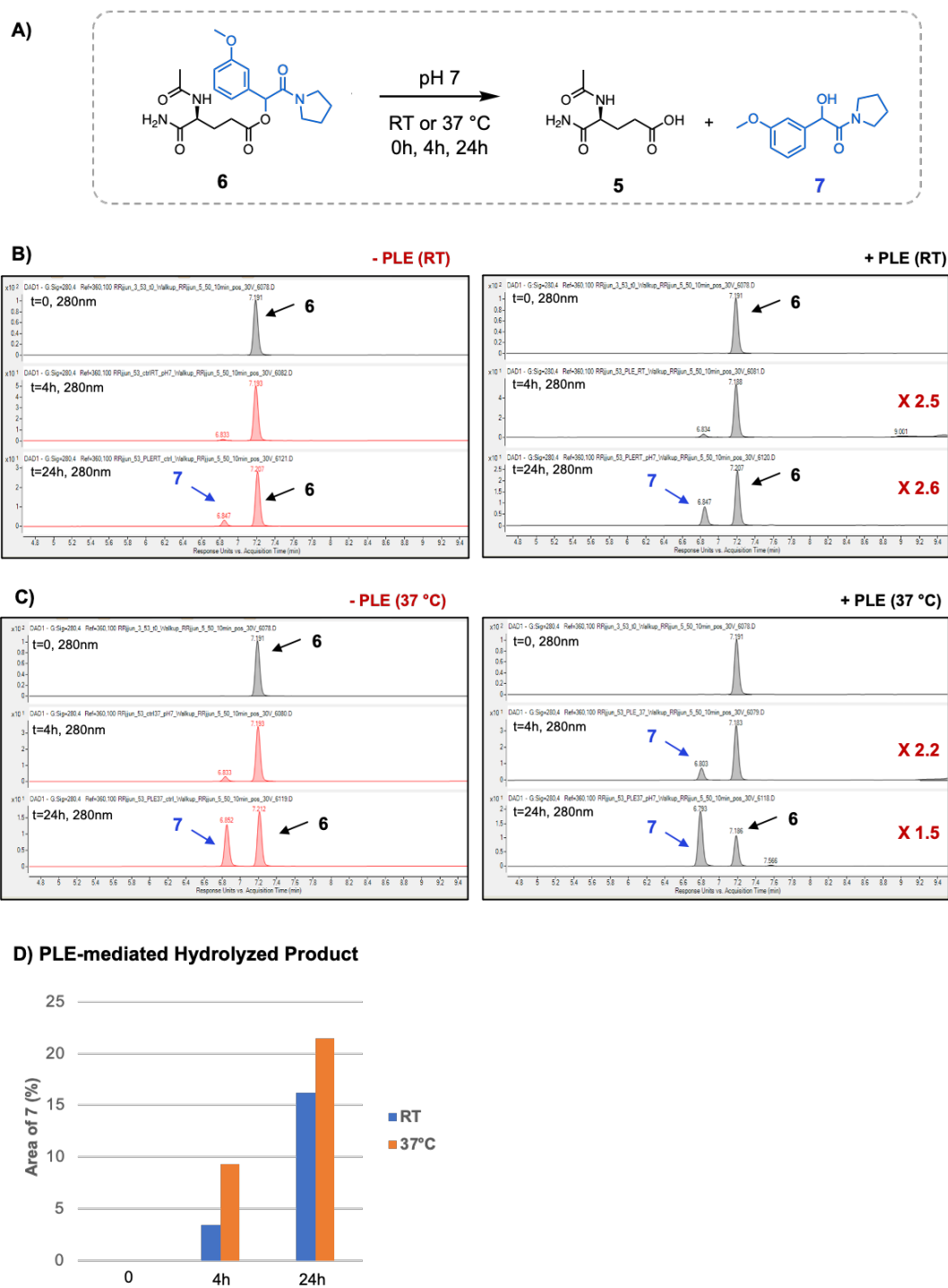
**Table S3. Hydrolysis Conditions**

condition	1	2	3	4	5	6
compound <b>6</b>	Yes	Yes	Yes	Yes	Yes	Yes
buffer	pH 7.2	pH 7.2	pH 7.2	pH 7.2	pH 7.2	pH 8.0
PLE	Yes	No	Yes	No	No	No
temp	room temp	room temp	37 °C	37 °C	37 °C	37 °C

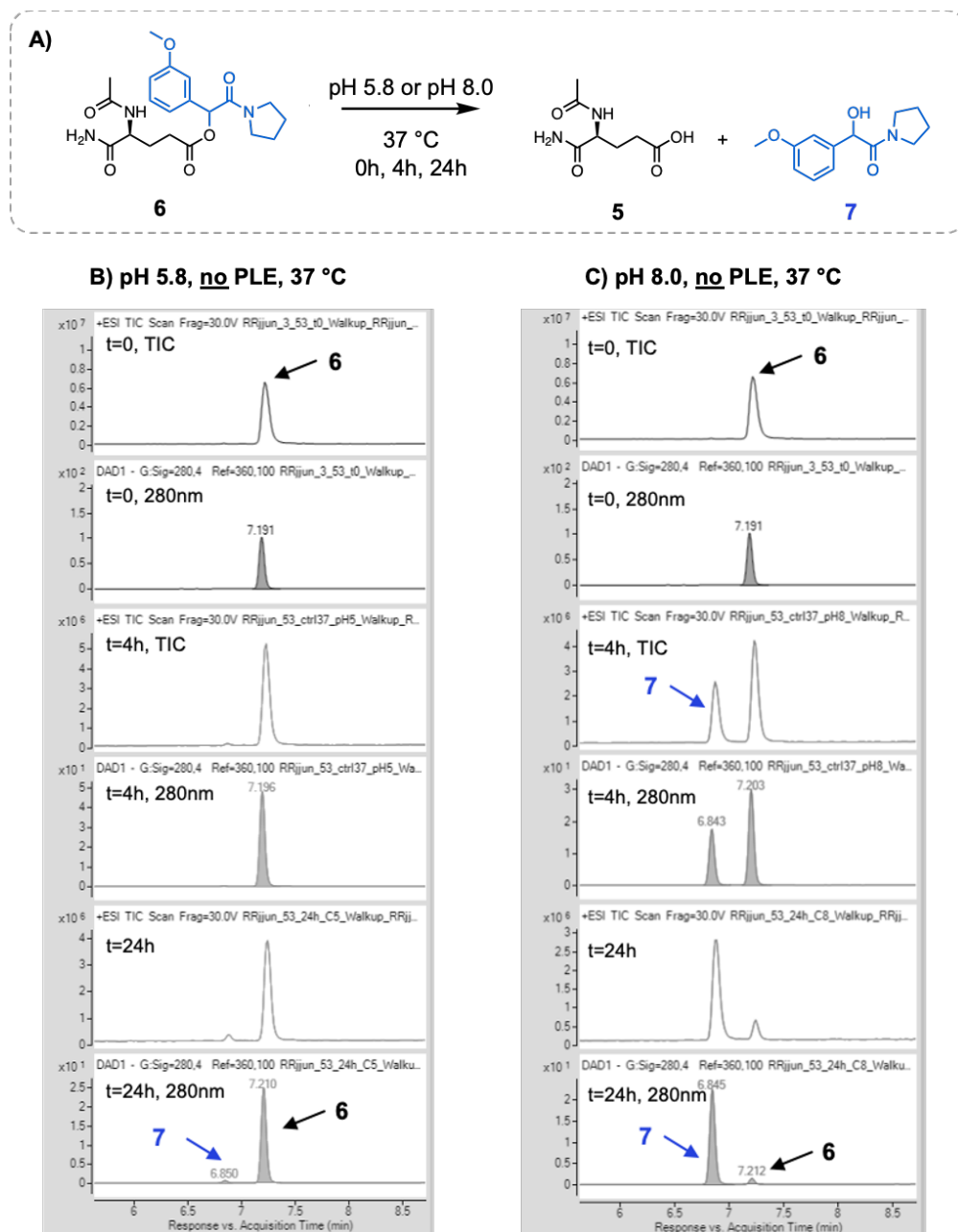
**LC–MS Condition for Polar Substrates:**

Time (min)	0.1 % Formic Acid in Water (%)	0.1 % Formic Acid in MeCN (%)	Flow (mL/min)
0.00	95	5	0.4
1.00	95	5	0.4
11.00	50	50	0.4
12.00	0	100	0.4
12.50	95	5	0.4

**Figure S8.** LC–MS gradient for polar compounds. 5 to 50% v/v MeCN in water over 10 min.

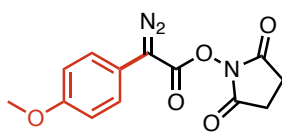


**Figure S9.** Hydrolysis Condition 1–4. (A) Reaction scheme, (B) crude LC–MS data (UV trace at 280 nm) for reactions done at room temperature, (C) crude LC–MS data (UV trace at 280 nm) for reactions done at 37 °C, and (D) background subtracted hydrolyzed product **7** at three different time points. Area of **7** from condition 2 (or 4) was subtracted from that from condition 1 (or 3) to represent the amount of hydrolysis achieved by PLE.



**Figure S10.** Hydrolysis Condition 5–6. (A) Reaction scheme, (B) crude LC–MS data (TIC and UV trace at 280 nm) for reactions done at pH 5.8, and (C) at pH 8.0.

## X. Characterization Data for 2a–2j

**2a**

**2,5-Dioxopyrrolidin-1-yl 2-diazo-2-(4-methoxyphenyl)acetate (2a):** General Procedure A was applied using **1** (200 mg, 1.09 mmol) and 1-iodo-4-methoxybenzene (383 mg, 1.64 mmol). Pd(OAc)<sub>2</sub> (24 mg, 0.11 mmol, 10 mol%) and P(2-Fu)<sub>3</sub> (51 mg, 0.22 mmol, 20 mol%) were used to afford higher product yield. The reaction was quenched after 6 h. The crude product was purified by column chromatography (20% v/v EtOAc in pentane) to afford compound **2a** as an orange solid (250 mg, 0.86 mmol, 79% yield). The compound is recommended to use within one to three days.

**Physical State:** orange solid

**TLC:** R<sub>f</sub> = 0.5 (1:1 pentane/EtOAc)

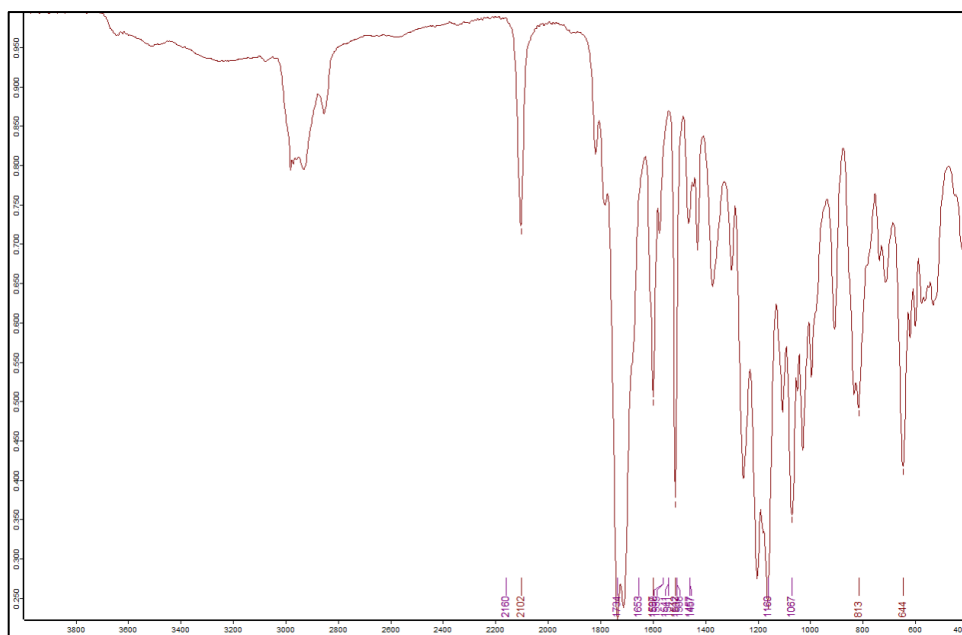
**<sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>CN, δ):** 7.41 (d, *J* = 8.9 Hz, 2H), 7.02 (d, *J* = 8.9 Hz, 2H), 3.80 (s, 3H), 2.80 (s, 4H)

**<sup>13</sup>C NMR (126 MHz, CD<sub>3</sub>CN, δ):** 171.3, 160.1, 128.1, 115.9, 115.8, 60.9 (diazo carbon, validated by HMBC), 56.1, 26.4

*Note: The diazo carbon (C=N=N) signal is not observed in <sup>13</sup>C NMR as mentioned in General Information (page S6).<sup>10</sup>*

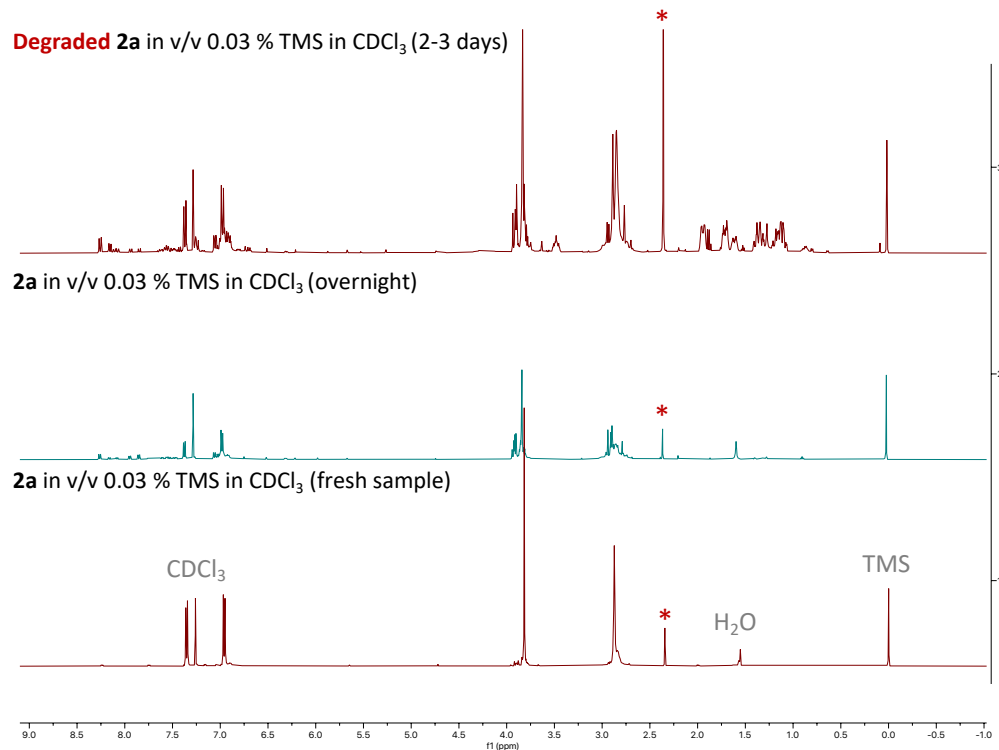
**HRMS (ESI-TOF):** calc'd for C<sub>13</sub>H<sub>12</sub>NO<sub>5</sub> [M + H - N<sub>2</sub>]<sup>+</sup>, 262.0710; found, 262.0707

**IR (neat):** 2102 (diazo), 1734, 1508, 1160, 1067, 813, 644 cm<sup>-1</sup>

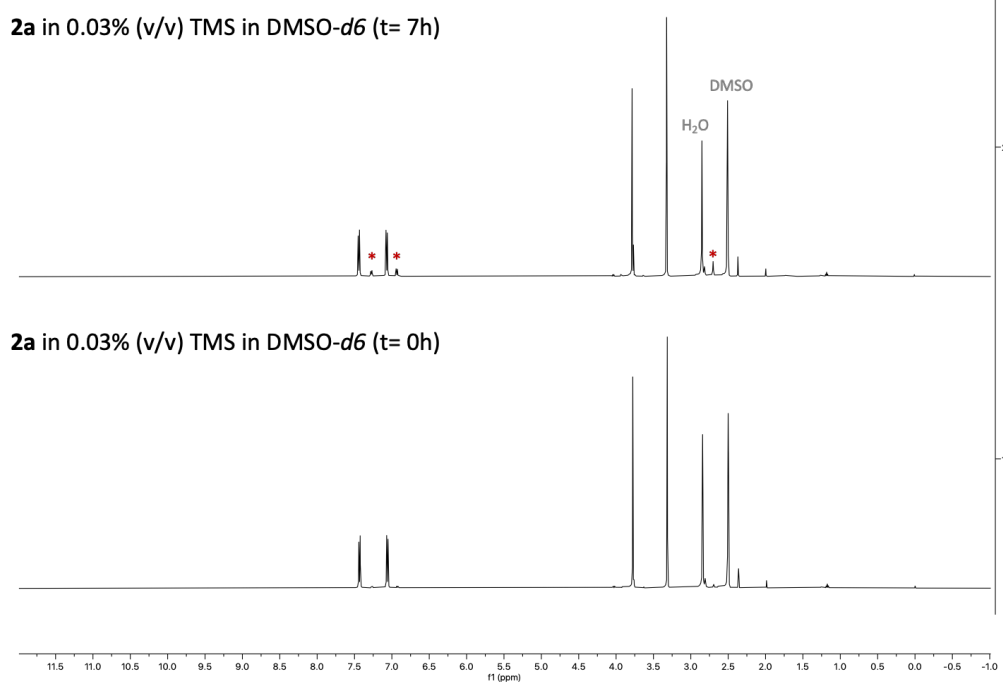


**Stability of 2a:** Based on NMR analysis, the slow degradation of compound **2a** in weakly acidic organic solvents (chloroform, dichloromethane, etc.) was observed. Hence, we recommend using this compound within 1–3 days. Storing the compound as solid in a  $-20\text{ }^{\circ}\text{C}$  freezer can slow down the degradation.

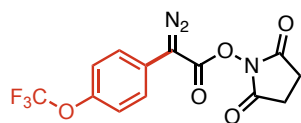
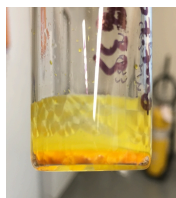
**Degradation peaks (\*) observed in  $\text{CDCl}_3/\text{TMS}$**



**Degradation peaks (\*) observed in  $\text{DMSO}/\text{TMS}$**





**2b**

**2,5-Dioxopyrrolidin-1-yl 2-diazo-2-(4-(trifluoromethoxy)phenyl)acetate (2b):** General Procedure A was applied using **1** (37 mg, 0.2 mmol) and 1-iodo-4-(trifluoromethoxy)benzene (86 mg, 0.3 mmol, 1.5 equiv). Pd(OAc)<sub>2</sub> (4 mg, 0.02 mmol, 10 mol%) and P(2-Fu)<sub>3</sub> (9 mg, 0.4 mmol, 20 mol%) were used to afford higher product yield. The reaction was quenched after 6 h. The crude product was purified using Biotage (10–80% over 20 min; product eluted at 35–55% v/v EtOAc in hexanes) to yield the title compound (45 mg, 65% yield).

**Physical State:** yellow solid

**TLC: R<sub>f</sub>** = 0.5 (1:1 pentane/EtOAc)

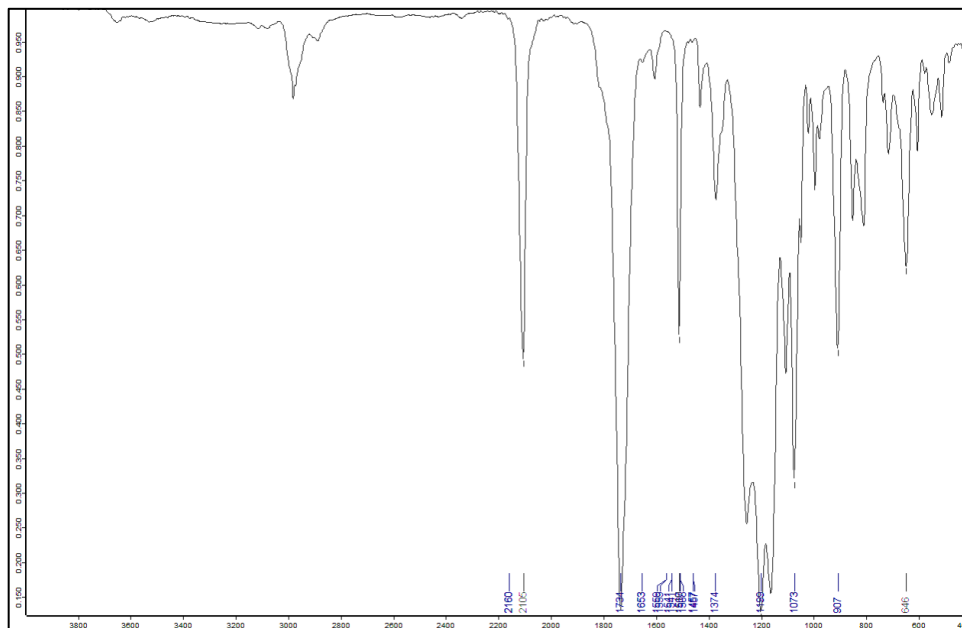
**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>, δ):** 7.54–7.45 (*m*, 2H), 7.33–7.25 (*m*, 2H), 2.88 (*s*, 4H)

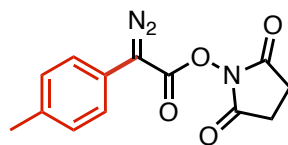
**<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>, δ):** 169.4, 160.2, 148.0, 125.9, 123.9 (q, *J*<sub>CF</sub> = 258.3 Hz), 122.3, 121.9, 121.5 (q, *J*<sub>CF</sub> = 258.3 Hz), 119.46 (q, *J*<sub>CF</sub> = 258.3 Hz), 117.4 (q, *J*<sub>CF</sub> = 258.3 Hz), 61.3 (diazo carbon validated by HMBC), 25.6

**<sup>19</sup>F NMR (471 MHz, CDCl<sub>3</sub>, δ):** –57.98

**HRMS (ESI–TOF):** calc'd for C<sub>13</sub>H<sub>9</sub>F<sub>3</sub>NO<sub>5</sub> [M + H – N<sub>2</sub>]<sup>+</sup>, 316.0427; found, 316.0427

**IR (neat):** 2105 (diazo), 1734, 1457, 1374, 1189, 1073, 907, 646 cm<sup>–1</sup>



**2c**

**2,5-Dioxopyrrolidin-1-yl 2-diazo-2-(*p*-tolyl)acetate (2c):** General Procedure A was applied using **1** (200 mg, 1.09 mmol, 1.0 equiv) and 1-iodo-4-methylbenzene (356 mg, 1.64 mmol, 1.5 equiv). The reaction was quenched after 6 h. The crude product was purified by column chromatography (25% v/v EtOAc in pentane) to yield the title compound (229 mg, 77% yield).

**Physical State:** yellowish orange solid

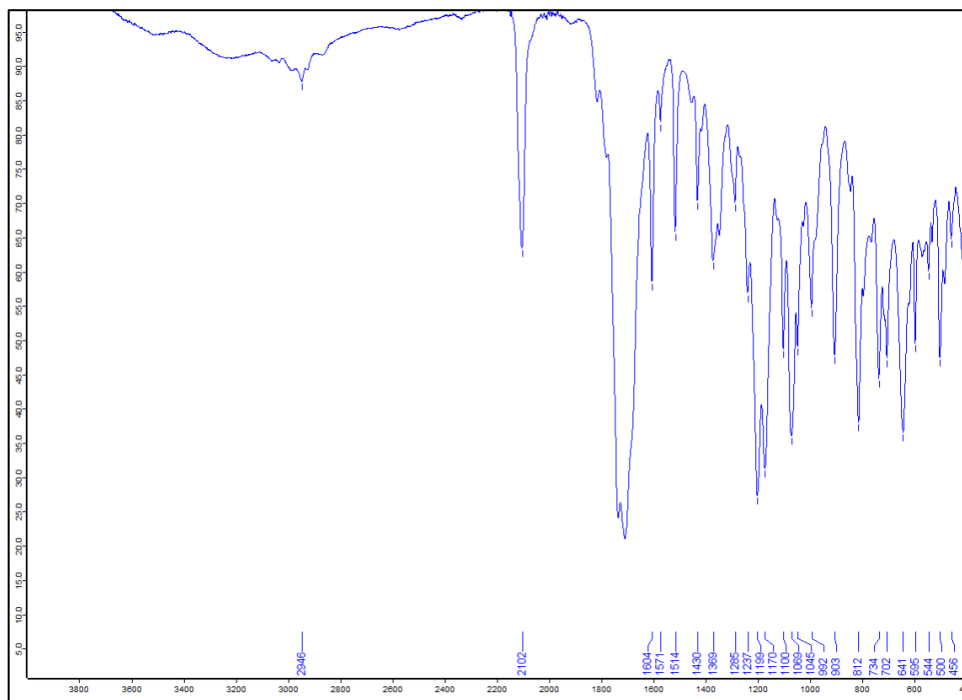
**TLC:** *R<sub>f</sub>* = 0.6 (1:1 EtOAc/pentane)

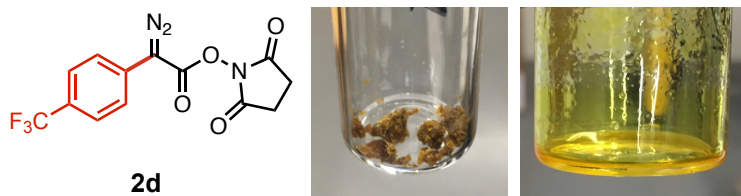
**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, δ):** 7.32 (d, *J* = 8.4 Hz, 2H), 7.22 (d, *J* = 8.1 Hz, 2H), 2.88 (s, 4H), 2.35 (s, 3H)

<sup>1</sup>H NMR spectrum of **3c** matched with the literature.<sup>4</sup>

**HRMS (ESI-TOF):** calc'd for C<sub>13</sub>H<sub>12</sub>NO<sub>4</sub> [M + H - N<sub>2</sub>]<sup>+</sup>, 246.0761; found, 246.0753

**IR (neat):** 2946, 2102 (diazo), 1604, 1571, 1514, 1430, 1369, 1285, 1237, 1199, 1170, 1100, 1069, 1045, 992, 903, 812, 734, 702, 641, 595, 544, 500, 456 cm<sup>-1</sup>





**2,5-Dioxopyrrolidin-1-yl 2-diazo-2-(4-(trifluoromethyl)phenyl)acetate (2d):** General Procedure A was applied using **1** (335 mg, 1.83 mmol) and 1-iodo-4-(trifluoromethyl)benzene (996 mg, 3.66 mmol, 2.0 equiv). Pd(OAc)<sub>2</sub> (41 mg, 0.18 mmol, 10 mol%) and P(2-Fu)<sub>3</sub> (85 mg, 0.37 mmol, 20 mol%) were used to afford higher product yield. The reaction was quenched after 6 h. The crude product was purified by column chromatography (40% v/v EtOAc in pentane) to yield the title compound (531 mg, 89% yield).

**Physical State:** dark yellow, brownish solid or yellow amorphous solid

**TLC:** R<sub>f</sub> = 0.4 (1:1 EtOAc/pentane)

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, δ):** 7.64 (d, *J* = 8.5 Hz, 2H), 7.54 (d, *J* = 8.4 Hz, 2H), 2.86 (s, 4H)

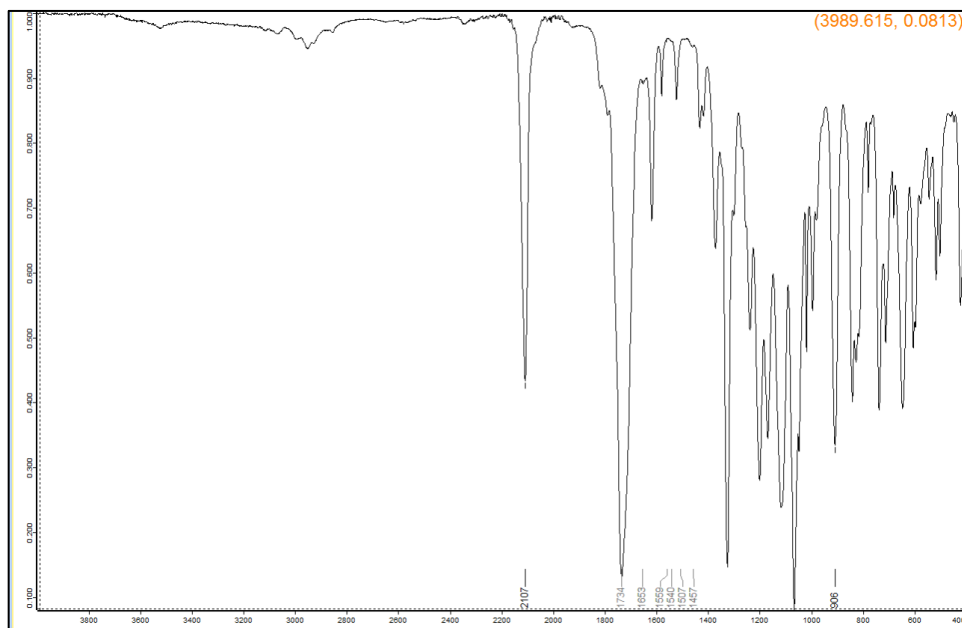
**<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>, δ):** 169.3, 159.7, 128.8, 128.5, 127.9 (m), 126.1 (q, *J* = 3.8 Hz), 125.2, 123.9, 122.5, 25.5

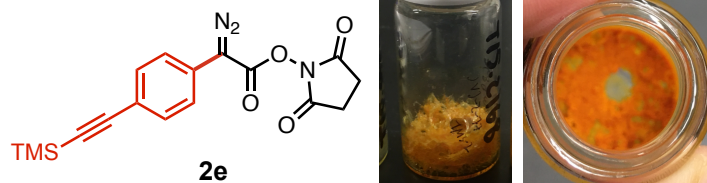
*Note: The diazo carbon (C=N=N) signal is not observed as mentioned in General Information (page S6).*<sup>10</sup>

**<sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>, δ):** -62.65

**HRMS (ESI-TOF):** calc'd for C<sub>13</sub>H<sub>8</sub>F<sub>3</sub>N<sub>3</sub>O<sub>4</sub>Na [M + Na]<sup>+</sup>, 350.0359; found, 350.0361

**IR (neat):** 2107 (diazo), 1734, 1653, 1558, 1540, 1507, 1457, 906 cm<sup>-1</sup>





**2,5-Dioxopyrrolidin-1-yl 2-diazo-2-(4-((trimethylsilyl)ethynyl)phenyl)acetate (2e):** General Procedure A was applied using **1** (200 mg, 1.09 mmol) and ((4-iodophenyl)ethynyl)trimethylsilane (491 mg, 1.64 mmol, 1.5 equiv). The reaction was quenched after 6 h. The crude product was purified by column chromatography (25% v/v EtOAc in pentane) to yield the title compound (368 mg, 95% yield).

**Physical State:** sticky reddish orange solid

**TLC:** R<sub>f</sub> = 0.64 (1:1 EtOAc/pentane)

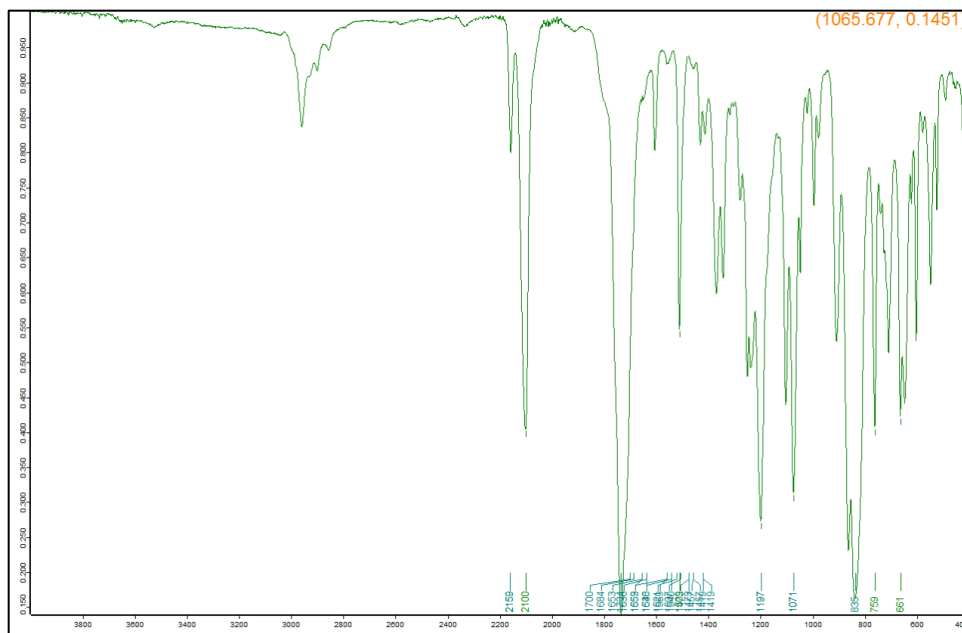
**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, δ):** 7.49 (d, *J* = 8.5 Hz, 2H), 7.36 (d, *J* = 8.3 Hz, 2H), 2.87 (s, 4H), 0.24 (s, 9H)

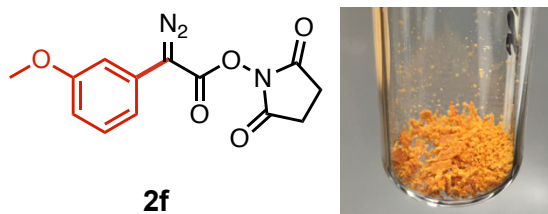
**<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>, δ):** 169.4, 160.0, 132.9, 123.7, 123.5, 121.7, 104.4, 95.5, 25.7, 0.0

*Note: The diazo carbon (C=N=N) signal is not observed as mentioned in General Information (page S6).<sup>10</sup>*

**HRMS (ESI-TOF):** calc'd for C<sub>17</sub>H<sub>18</sub>N<sub>3</sub>O<sub>4</sub>Si [M + H]<sup>+</sup>, 356.1061; found, 356.1066

**IR (neat):** 2159, 2100 (diazo), 1700, 1197, 1071, 853, 759, 661 cm<sup>-1</sup>





**2,5-Dioxopyrrolidin-1-yl 2-diazo-2-(3-methoxyphenyl)acetate (2f):** General Procedure A was applied using **1** (260 mg, 1.4 mmol) 1-iodo-3-methoxybenzene (498 mg, 2.13 mmol, 1.5 equiv). The reaction was quenched after 6 h. The crude product was purified by column chromatography (20% v/v EtOAc in pentane) to yield the title compound (342 mg, 83% yield).

**Physical State:** orange solid

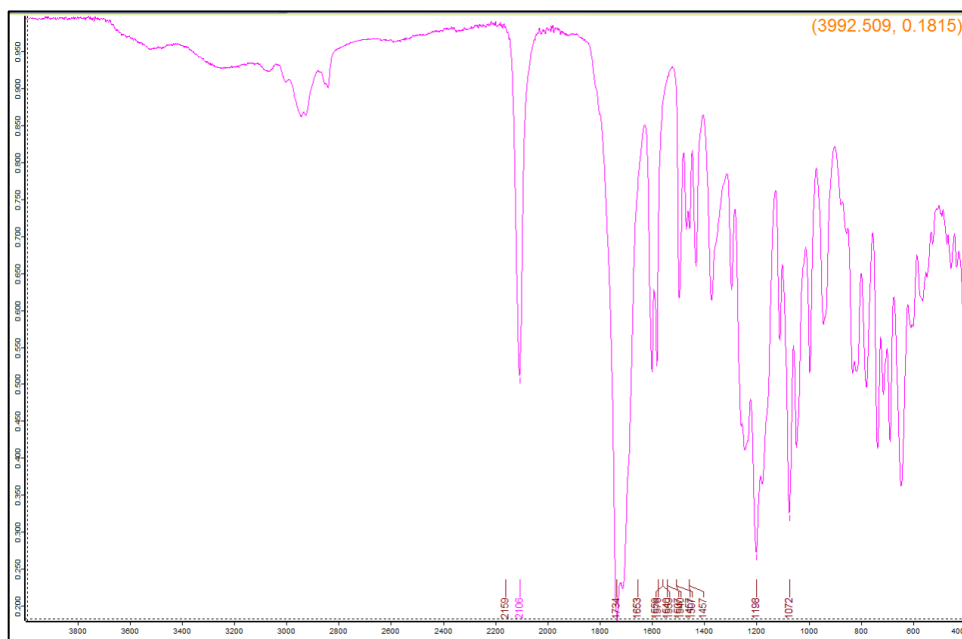
**TLC:** R<sub>f</sub> = 0.5 (1:1 EtOAc/pentane)

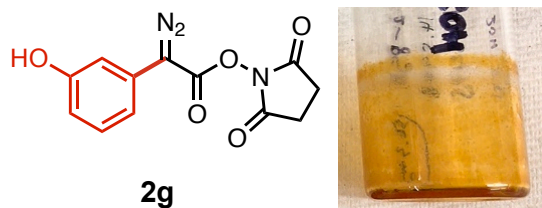
**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>, δ):** 7.31 (t, J = 8.1 Hz, 1H), 7.05 (t, J = 2.2 Hz, 1H), 6.94 (dd, J = 7.9, 1.8 Hz, 1H), 6.78 (dd, J = 8.4, 2.5 Hz, 1H), 3.79 (s, 3H), 2.84 (s, 4H)

**<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>, δ):** 169.4, 160.2, 130.2, 124.6, 116.3, 112.6, 110.1, 61.7 (diazo carbon, verified by HMBC and HSQC), 55.3, 25.5

**HRMS (ESI-TOF):** calc'd for C<sub>13</sub>H<sub>11</sub>N<sub>3</sub>O<sub>5</sub>Na [M + Na]<sup>+</sup>, 312.0591; found, 312.0586

**IR (neat):** 2106 (diazo), 1734, 1653, 1198, 1072 cm<sup>-1</sup>



**2g**

**2,5-Dioxopyrrolidin-1-yl 2-diazo-2-(3-hydroxyphenyl)acetate (2g):** General Procedure A was applied using **1** (37 mg, 0.2 mmol) and 3-iodophenol (66 mg, 0.3 mmol, 1.5 equiv). Pd(OAc)<sub>2</sub> (4 mg, 0.02 mmol, 10 mol%) and P(2-Fu)<sub>3</sub> (9 mg, 0.04 mmol, 20 mol%) were used to afford higher product yield. The reaction was quenched after 6 h. The crude product was purified by column chromatography (40% v/v EtOAc in pentane) to yield the title compound (50 mg, 90% yield).

**Physical State:** reddish film

**TLC:** R<sub>f</sub> = 0.4 (1:1 EtOAc/pentane)

**<sup>1</sup>H NMR (500 MHz, THF-*d*<sub>8</sub>, δ):** 8.42 (s, 1H), 7.14 (t, J = 8.0 Hz, 1H), 6.91 (t, J = 2.2 Hz, 1H), 6.88–6.80 (m, 1H), 6.58 (dd, J = 8.1, 2.4 Hz, 1H), 2.74 (s, 4H)

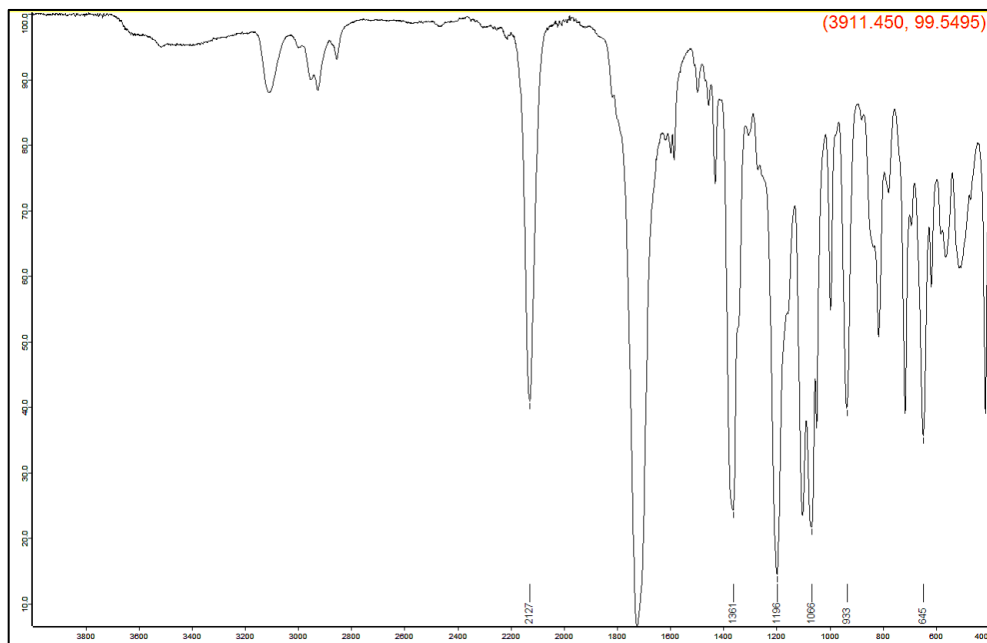
**<sup>13</sup>C NMR (126 MHz, THF-*d*<sub>8</sub>, δ):** 170.1, 161.2, 159.4, 130.9, 125.8, 115.8, 114.7, 112.1, 61.4 (diazo carbon, validated by HMBC), 26.2

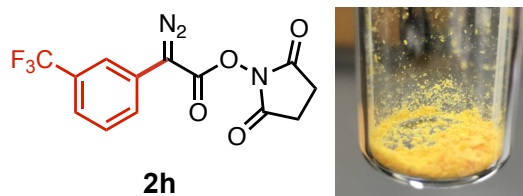
*Note: The diazo carbon (C=N=N) signal is not observed as mentioned in General Information (page S6).<sup>10</sup>*

**HRMS (ESI-TOF):** calc'd for C<sub>12</sub>H<sub>10</sub>NO<sub>5</sub> [M + H - N<sub>2</sub>]<sup>+</sup>, 248.0553; found, 248.0558

calc'd for C<sub>12</sub>H<sub>9</sub>N<sub>3</sub>O<sub>5</sub>Na [M + Na - N<sub>2</sub>]<sup>+</sup>, 298.0434; found, 298.0451

**IR (neat):** 2127 (diazo), 1700, 1361, 1196, 1066, 944, 645 cm<sup>-1</sup>





**2,5-Dioxopyrrolidin-1-yl 2-diazo-2-(3-(trifluoromethyl)phenyl)acetate (2h):** General Procedure A was applied using **1** (200 mg, 1.09 mmol) and 1-iodo-3-(trifluoromethyl)benzene (445 mg, 1.64 mmol, 1.5 equiv). The reaction was quenched after 6 h. The crude product was purified by column chromatography (40% v/v EtOAc in pentane) to yield the title compound (292 mg, 82% yield).

**Physical State:** yellow solid

**TLC:**  $R_f$  = 0.4 (1:1 EtOAc/pentane)

**$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ,  $\delta$ ):** 7.75 (s, 1H), 7.59–7.45 (m, 3H), 2.86 (s, 4H)

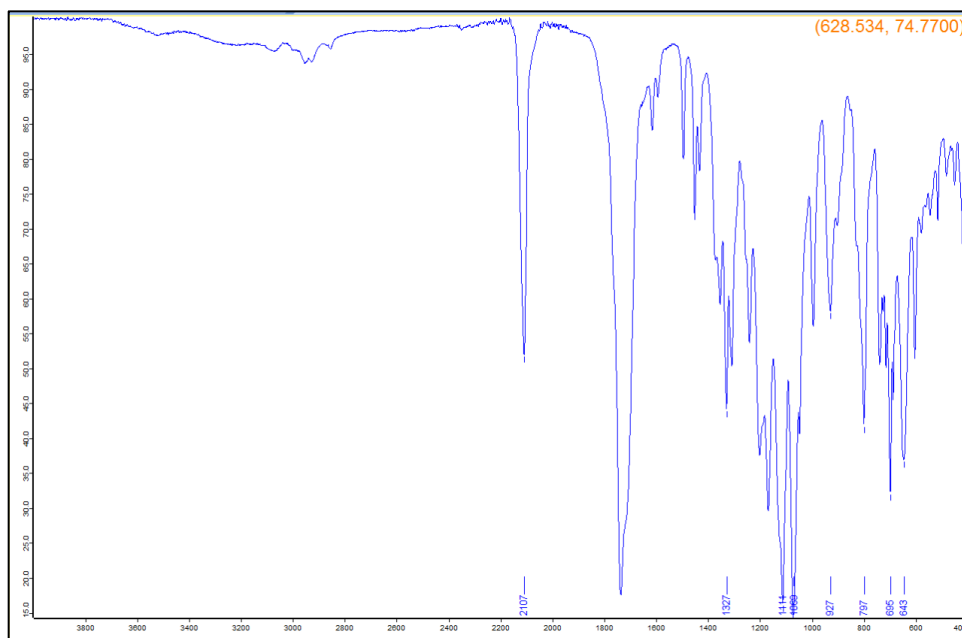
**$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ ,  $\delta$ ):** 169.4, 159.9, 131.5 (q,  $J$  = 32.6 Hz), 129.7, 126.9, 124.9, 123.5 (q,  $J$  = 3.7 Hz), 122.4, 120.7 (q,  $J$  = 3.9 Hz), 25.5

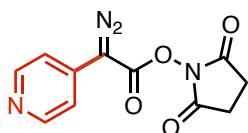
*Note: The diazo carbon ( $\text{C}=\text{N}=\text{N}$ ) signal is not observed as mentioned in General Information (page S6).<sup>10</sup>*

**$^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ ,  $\delta$ ):** -62.95

**HRMS (ESI-TOF):**  $\text{C}_{13}\text{H}_8\text{F}_3\text{N}_3\text{O}_4\text{Na}$  [ $\text{M} + \text{Na}$ ]<sup>+</sup>, 350.0359; found, 350.0349

**IR (neat):** 2107(diazo), 1700, 1327, 1411, 1080, 927, 797, 695, 643  $\text{cm}^{-1}$



**2i**

**2,5-Dioxopyrrolidin-1-yl 2-diazo-2-(pyridin-4-yl)acetate (2i):** General Procedure A was applied using **1** (200 mg, 1.09 mmol) and 1-iodo-4-methylbenzene (447 mg, 2.18 mmol, 2.0 equiv). The reaction was quenched after 6 h. The crude product was purified by column chromatography (1:1 EtOAc/pentane with 2.5% v/v MeOH) to yield the title compound (228 mg, 80% yield).

**Physical State:** light orange solid

**TLC:**  $R_f$  = 0.22 (1:1 pentane/EtOAc with 2.5% v/v MeOH)

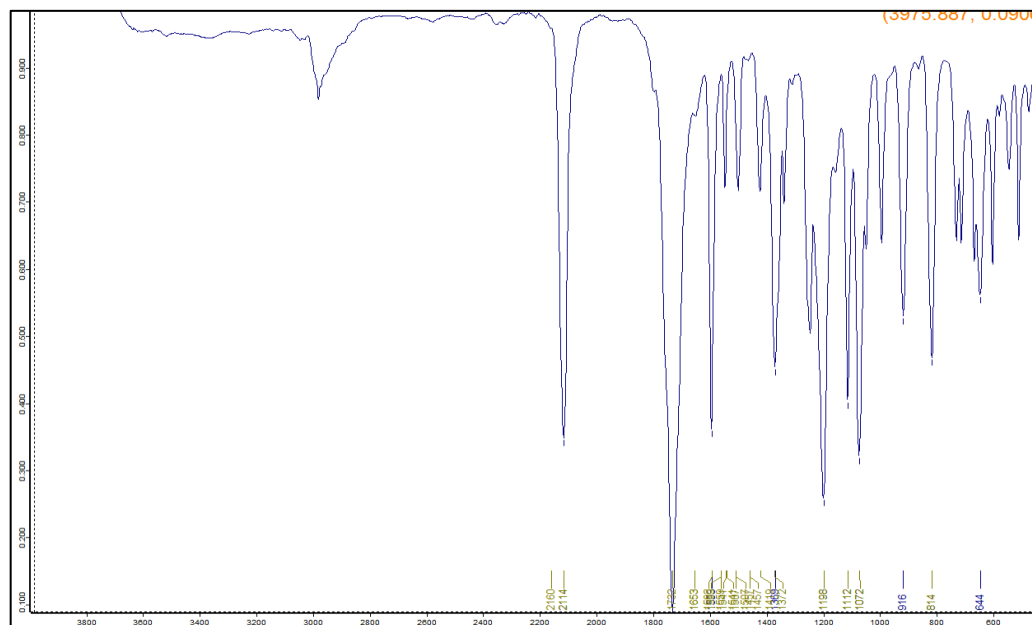
**$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ,  $\delta$ ):** 8.70–8.43 (m, 2H), 7.50–7.28 (m, 2H), 2.90 (s, 4H)

**$^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ ,  $\delta$ ):** 169.2, 158.9, 150.3, 133.6, 117.5, 25.7

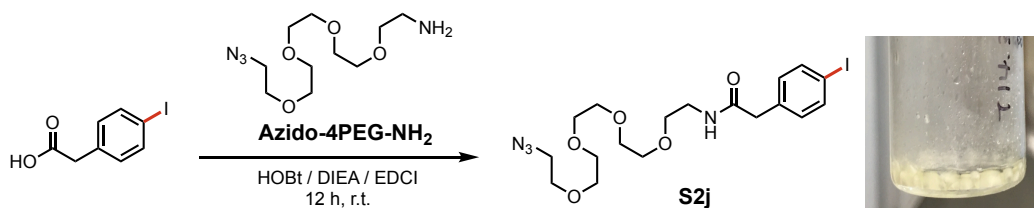
*Note: The diazo carbon ( $\text{C}=\text{N}=\text{N}$ ) signal is not observed as mentioned in General Information (page S6).<sup>10</sup>*

**HRMS (ESI-TOF):** calc'd for  $\text{C}_{11}\text{H}_9\text{N}_4\text{O}_4$  [ $\text{M} + \text{H}$ ]<sup>+</sup>, 261.0618; found, 261.0615

**IR (neat):** 2114 (diazo), 1722, 1583, 1457, 1372, 1198, 1072, 814, 644  $\text{cm}^{-1}$







***N*-(14-Azido-3,6,9,12-tetraoxatetradecyl)-2-(4-iodophenyl)acetamide (S2j):** To a solution of 2-(4-iodophenyl)acetic acid (100 mg, 0.38 mmol, 1 equiv) and azido-4PEG-NH<sub>2</sub> (120 mg, 0.42 mmol, 1.1 equiv) in DCM (5.75 mL), hydroxybenzotriazole (HOBT) (65 mg, 0.46 mmol, 1.2 equiv) and *N,N*-diisopropylethylamine (DIEA) (199  $\mu$ L, 1.14 mmol, 3 equiv) were added. The reaction mixture was cooled down to 0 °C and *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (EDCI) (88 mg, 0.46 mmol, 1.2 equiv) was added. After stirring at room temperature for 12 h, the reaction mixture was quenched by adding water at 0 °C. The reaction solution was then extracted with EtOAc and organic layer was concentrated under reduced pressure. The residue was purified by silica chromatography (5% v/v MeOH in DCM) to afford the title compound in 76% yield. (146.8 mg, 0.29 mmol).

**Physical State:** white solid

**TLC:** *R<sub>f</sub>* = 0.38 (5% v/v MeOH in DCM) Staining of azide is done by PPh<sub>3</sub>/ninhydrin stain.<sup>11</sup>

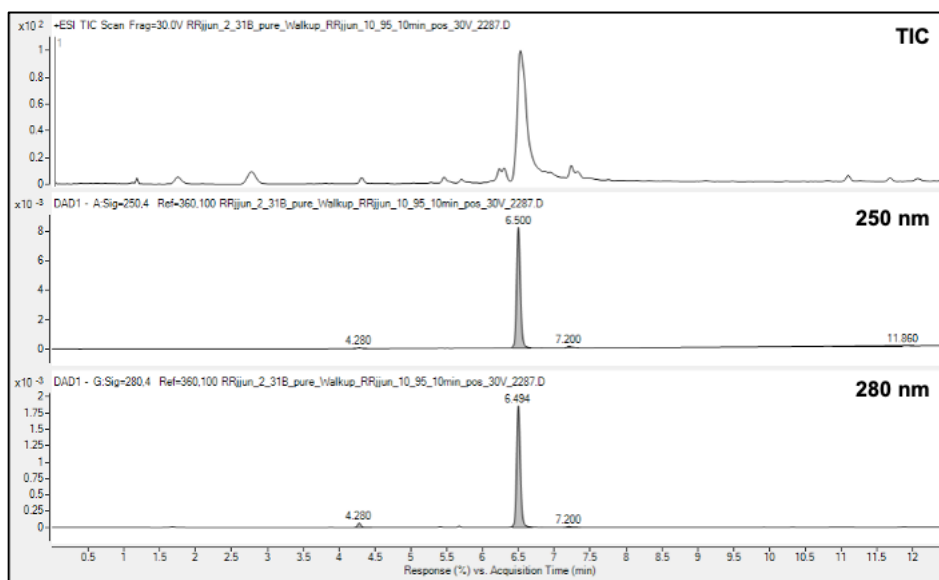
**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>,  $\delta$ ):** 7.46 (d, *J* = 8.2 Hz, 2H), 6.87 (d, *J* = 8.2 Hz, 2H), 6.53 (s, 1H), 3.53–3.39 (m, 14H), 3.35 (t, *J* = 5.3 Hz, 2H), 3.29 (s, 2H), 3.26–3.17 (m, 4H)

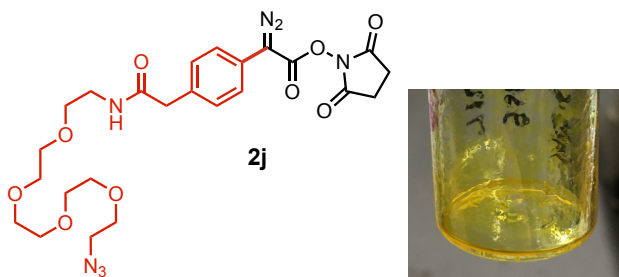
**<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>,  $\delta$ ):** 170.0, 137.1, 134.7, 130.9, 92.0, 77.5, 77.2, 76.8, 70.1, 70.1, 70.0, 67.0, 69.7, 69.5, 69.1, 50.1, 42.3, 39.0

*Note: The diazo carbon (C=N=N) signal is not observed as mentioned in General Information (page S6).*<sup>10</sup>

**HRMS (ESI-TOF):** calc'd for C<sub>18</sub>H<sub>27</sub>N<sub>4</sub>O<sub>5</sub> [M + H]<sup>+</sup>, 507.1099; found, 507.1100

**Analytical LC-MS:** 10–95% v/v MeCN in 10 min (Figure S5)





**2,5-Dioxopyrrolidin-1-yl 2-(4-(17-azido-2-oxo-6,9,12,15-tetraoxa-3-azaheptadecyl)phenyl)-2-diazoacetate (2j):** General Procedure A was applied using **1** (37 mg, 0.2 mmol, 1.0 equiv) and **S2j** (152 mg, 0.3 mmol, 1.2 equiv). Pd(OAc)<sub>2</sub> (4 mg, 0.02 mmol, 10 mol%) and P(2-Fu)<sub>3</sub> (9 mg, 0.04 mmol, 20 mol%) were used to afford higher product yield. The reaction was quenched after 6 h. The crude product was purified by column chromatography (4:8:2 pentane/EtOAc/MeOH) to yield the title compound (74 mg, 66% yield).

**Physical State:** yellow film

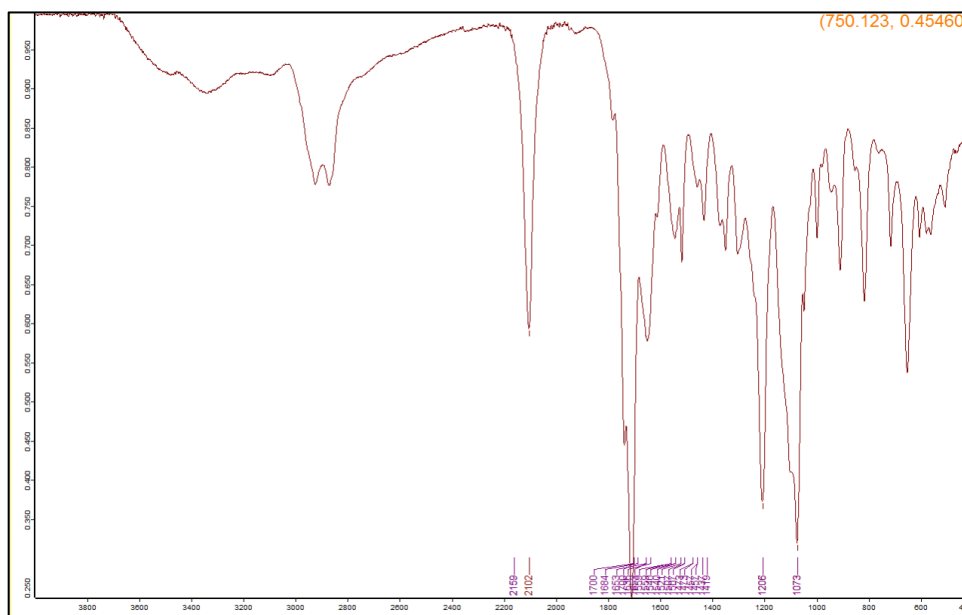
**TLC:** R<sub>f</sub> = 0.32 (4:8:2 pentane/EtOAc/MeOH) Staining of azide was done by PPh<sub>3</sub>/ninhydrin stain.<sup>11</sup>

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, δ):** 7.40 (d, *J* = 8.4 Hz, 2H), 7.34 (d, *J* = 8.3 Hz, 2H), 6.29 (s, 1H), 3.58–3.51 (m, 10H), 3.60–3.49 (m, 8H), 3.40 (m, 4H), 2.88 (s, 4H)

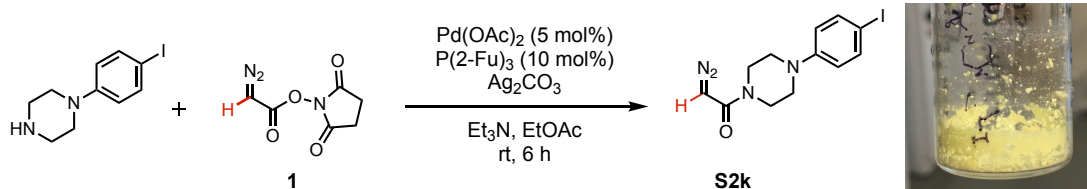
**<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>, δ):** 172.2, 170.7, 169.4, 160.3, 134.2, 130.2, 124.8, 122.1, 70.7, 70.6, 70.6, 70.5, 70.2, 70.0, 69.7, 50.7, 43.0, 39.5, 25.6

**HRMS (ESI-TOF):** calc'd for C<sub>24</sub>H<sub>31</sub>N<sub>7</sub>O<sub>9</sub>Na [M + Na]<sup>+</sup>, 584.2075; found, 584.2070

**IR (neat):** 2102 (diazo), 1700, 1206, 1073 cm<sup>-1</sup>



## XI. Characterization Data for S2k



**Figure S11.** C–H arylation of **1** with nucleophilic amine (1-(4-iodophenyl)piperazine)

**2-Diazo-1-(4-(4-iodophenyl)piperazin-1-yl)ethan-1-one (S2k):** General Procedure A was applied using **1** (200 mg, 1.09 mmol) and 1-(4-iodophenyl)piperazine (314 mg, 1.1 mmol, 1 equiv). The reaction was quenched after 6 h. The crude product was purified by column chromatography (33% v/v EtOAc in pentane) to yield the title compound (91 mg, 23% yield).

**Physical State:** light yellow solid

**TLC:** R<sub>f</sub> = 0.16 (1:1 pentane/EtOAc)

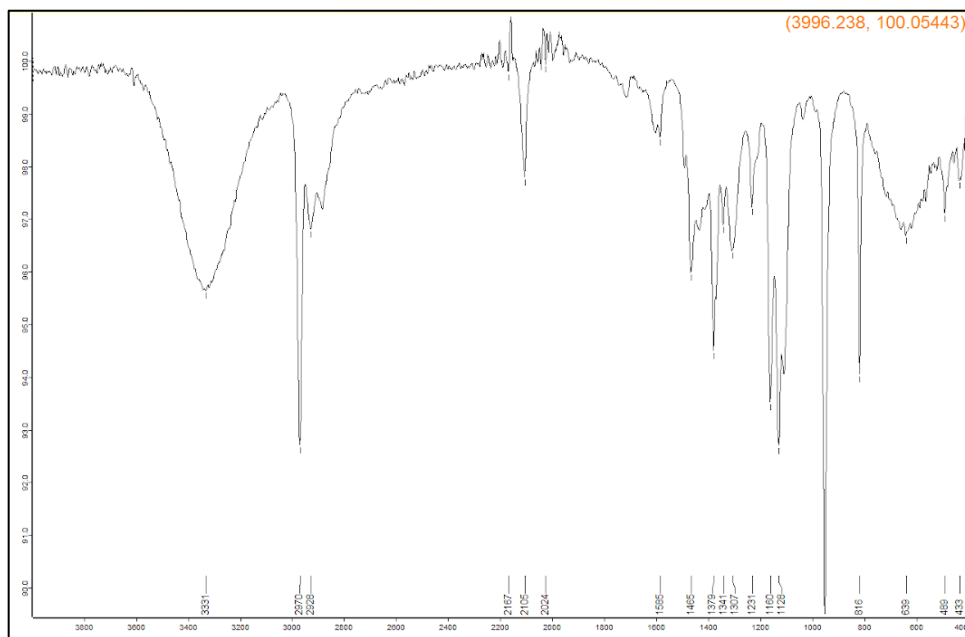
**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, δ):** 7.53 (d, *J* = 8.9 Hz, 2H), 6.67 (d, *J* = 8.9 Hz, 2H), 5.07 (s, 1H), 3.56 (s, 4H), 3.14 (dd, *J* = 6.2, 4.2 Hz, 4H)

**<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>, δ):** 164.9, 150.5, 138.0, 118.6, 82.4, 48.9, 46.6

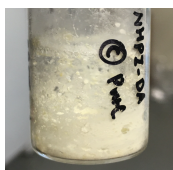
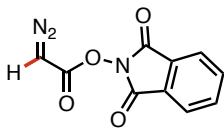
*Note: The diazo carbon (C=N=N) signal is not observed as mentioned in General Information (page S6).<sup>10</sup>*

**HRMS (ESI–TOF):** calc'd for C<sub>12</sub>H<sub>13</sub>N<sub>4</sub>O [M + H]<sup>+</sup>, 357.0207; found, 357.0206

**IR (neat):** 2970, 2928, 2105 (diazo), 1585m 1465m 1379, 1231, 1160, 816, 489, 433 cm<sup>-1</sup>



## XII. Characterization Data for S4–S7



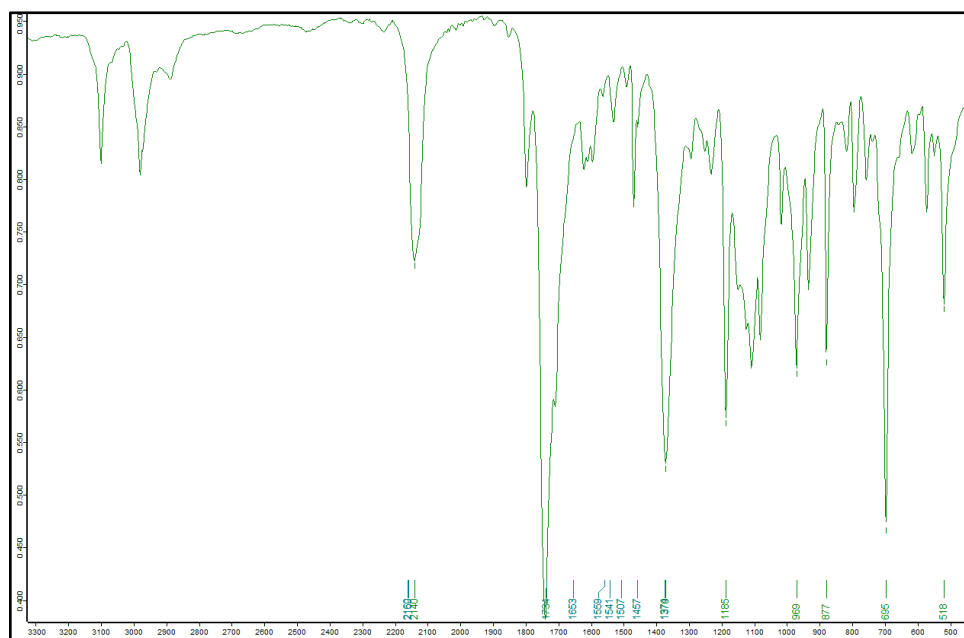
**N-Phthalimidoyl 2-diazoacetate (NHPI-DA, S4):** Synthesized as previously reported procedure.<sup>10b</sup>

**Physical State:** pale yellow white solid

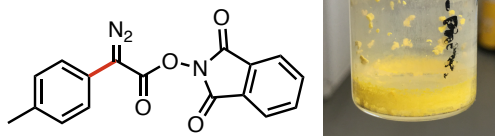
**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>, δ):** 7.91–7.89 (m, 2H), 7.81–7.79 (m, 2H), 5.17 (br s, 1 H) ppm

<sup>1</sup>H NMR spectrum of S4 matched with the literature.<sup>10b</sup>

**IR (neat):** 2140 (diazo), 1734, 1653, 1370, 1185, 969, 877, 695, 518 cm<sup>-1</sup>



*Note: NHPI-DA S4 can be obtained from Key Organics (SO-3001, CAS 816437-80-6).*



**Compound S5:** Synthesized as previously reported procedure.<sup>3</sup>

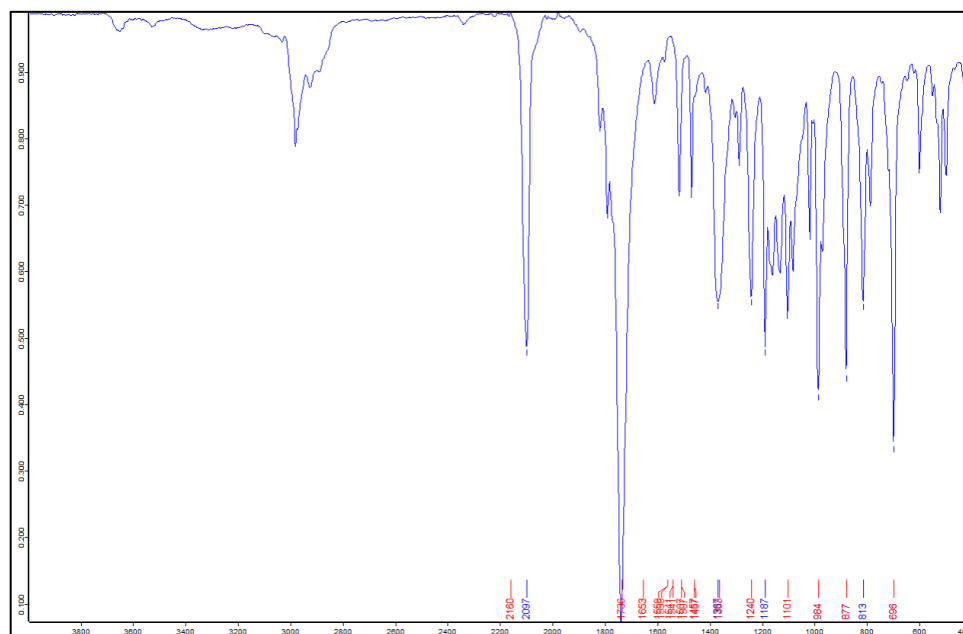
**Physical State:** yellow solid

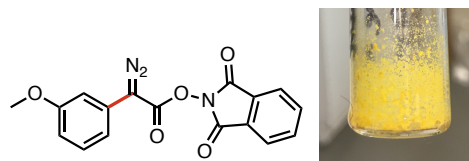
**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>, δ):** 7.91 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.80 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.34 (d, *J* = 8.4 Hz, 2H), 7.22 (d, *J* = 8.1 Hz, 2H), 2.35 (s, 3H)

**<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>, δ):** 162.3, 161.6, 137.1, 135.0, 130.1, 129.0, 125.6, 124.2, 120.1, 21.2

<sup>1</sup>H and <sup>13</sup>C NMR spectra of S5 were matched with the literature.<sup>3</sup>

**IR (neat):** 2097 (diazo), 1700, 1367, 1187, 1240, 1187, 1101, 984, 813, 696 cm<sup>-1</sup>





**Compound S6:** Synthesized as previously reported procedure.<sup>3</sup>

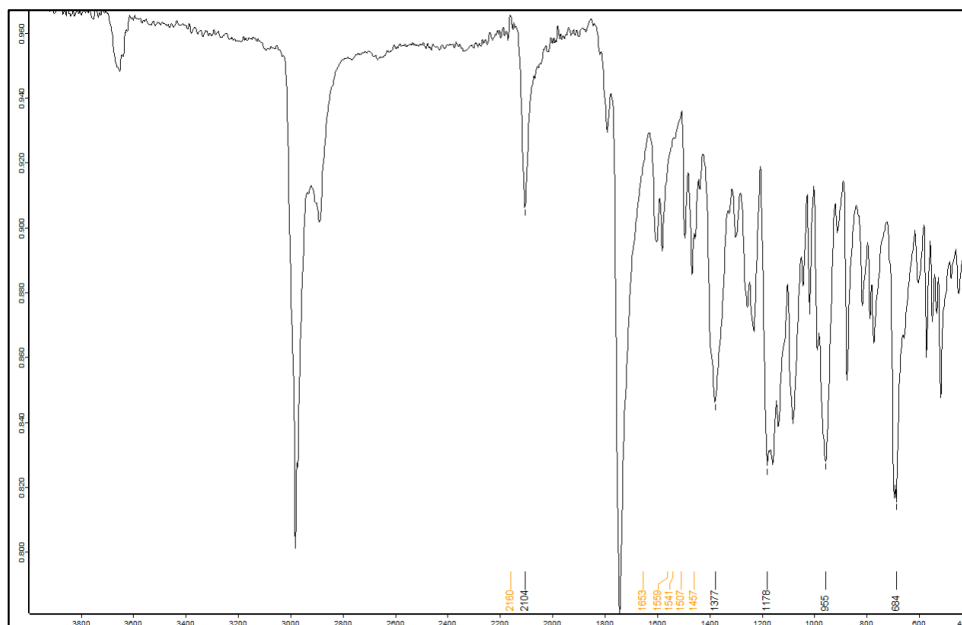
**Physical State:** yellow solid

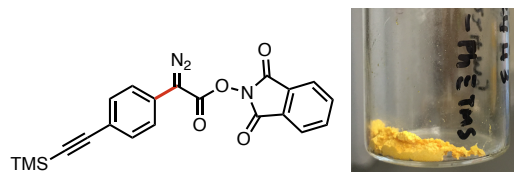
**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>, δ):** 7.90 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.79 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.53–7.43 (m, 2H), 7.39 (d, *J* = 8.6 Hz, 2H), 0.24 (s, 9H)

**<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>, δ):** 162.2, 160.9, 135.0, 132.8, 128.9, 124.2, 123.7, 123.6, 121.6, 104.4, 95.4

<sup>1</sup>H and <sup>13</sup>C NMR spectra of S6 were matched with the literature.<sup>3</sup>

**IR (neat):** 2104 (diazo), 1700, 1377, 1178, 955, 684 cm<sup>-1</sup>





**Compound S7:** Synthesized as previously reported procedure.<sup>3</sup>

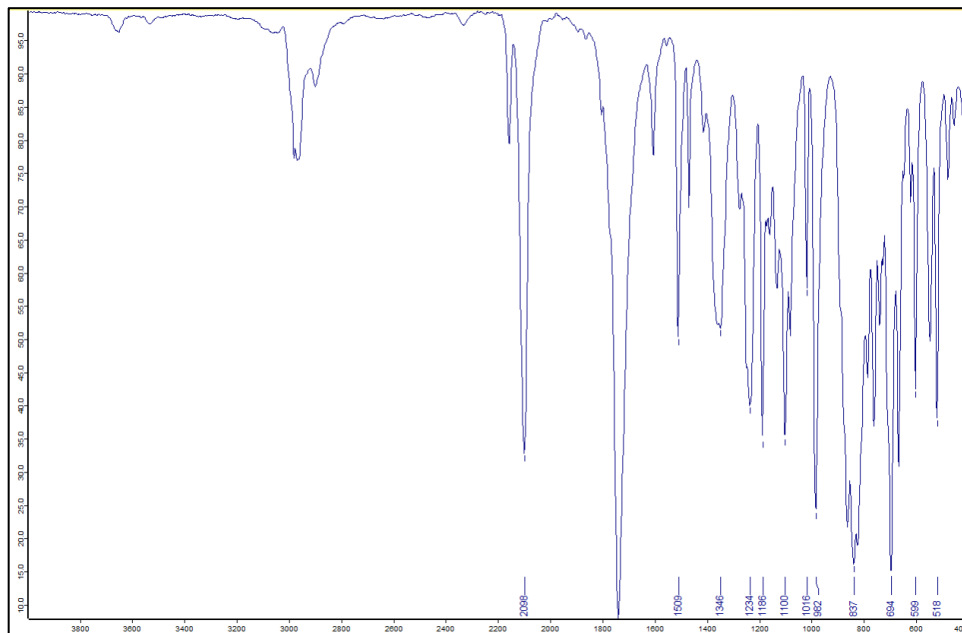
**Physical State:** yellow solid

**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>, δ):** 7.90 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.79 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.53–7.43 (m, 2H), 7.39 (d, *J* = 8.6 Hz, 2H), 0.24 (s, 9H)

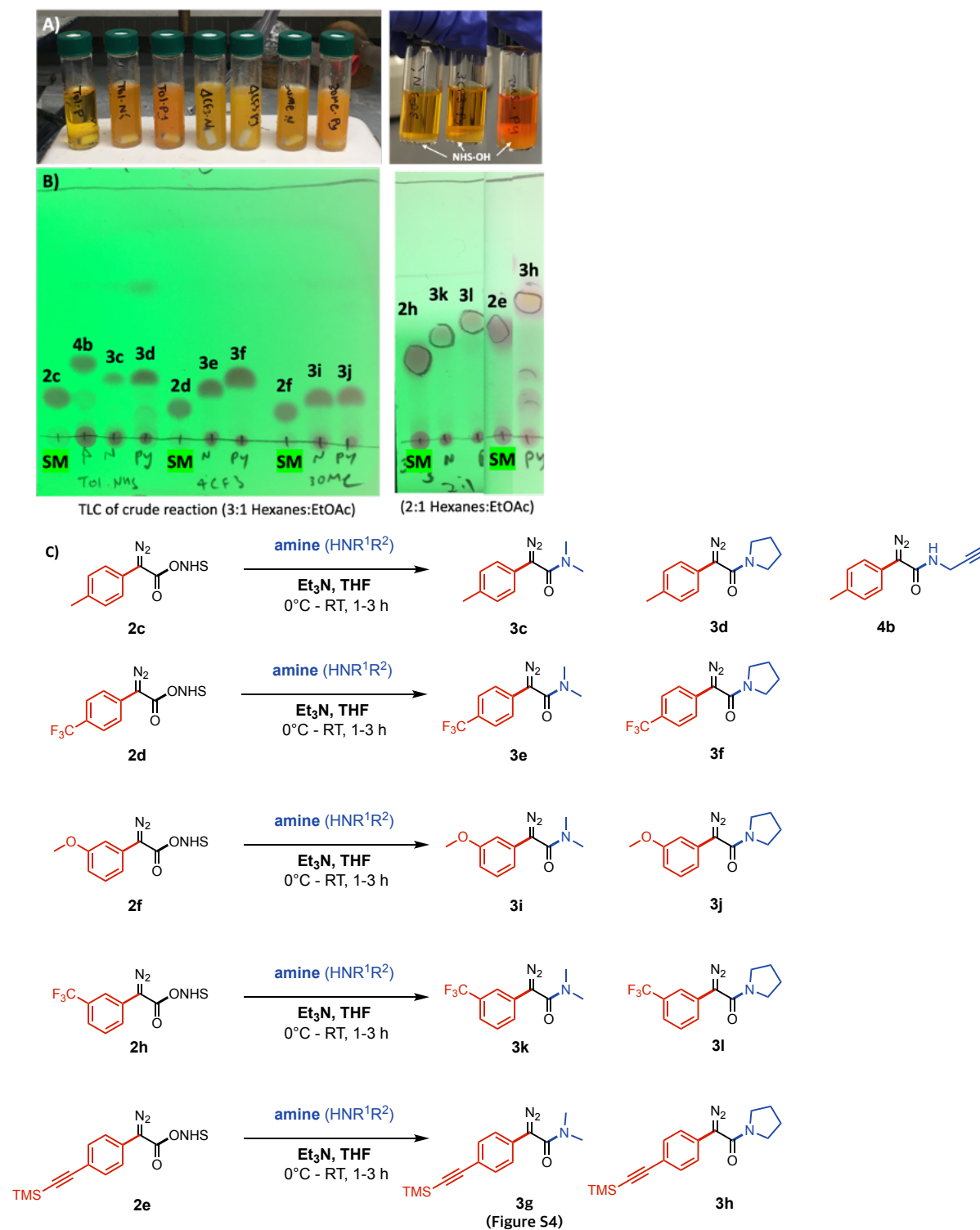
**<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>, δ):** 162.2, 161.0, 135.0, 132.8, 128.9, 124.2, 123.7, 123.6, 121.6, 104.4, 95.4, 77.4, 77.2, 76.9, 0.0

<sup>1</sup>H and <sup>13</sup>C NMR spectra of **S7** were matched with the literature.<sup>3</sup>

**IR (neat):** 2098 (diazo), 1700, 1509, 1346, 1234, 1186, 1100, 1016, 982, 837, 694, 599, 518 cm<sup>-1</sup>

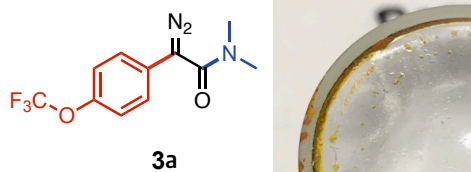


## XIII. Characterization Data for 3a–3l



**Figure S12.** Examples of aminolysis. (A) Parallel synthesis of diazoamides. The product formation is indicated by precipitation of **NHS-OH**. (B) TLC analysis of crude reaction mixtures. The reaction yield is generally quantitative, but the isolated yield is low possibly due to product degradation during silica column purification. (C) Chemical structures of each reaction shown in TLC.





**2-Diazo-*N,N*-dimethyl-2-(4-(trifluoromethoxy)phenyl)acetamide (3a):** General Procedure B was applied using **2b** (22 mg, 0.08 mmol, 1.0 equiv) and dimethylamine solution (2.0 M) in THF (0.2 mL, 0.4 mmol, 5.0 equiv). The reaction was quenched after 1 h. The crude product was purified by column chromatography (20% v/v EtOAc in hexanes) to yield the title compound (5.6 mg, 25% yield).

**Physical State:** orange oil

**TLC:** *R<sub>f</sub>* = 0.31 (1:2 EtOAc/hexanes)

**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>, δ):** 7.28–7.26 (m, 2H), 7.25–7.20 (m, 2H), 3.00 (s, 6H)

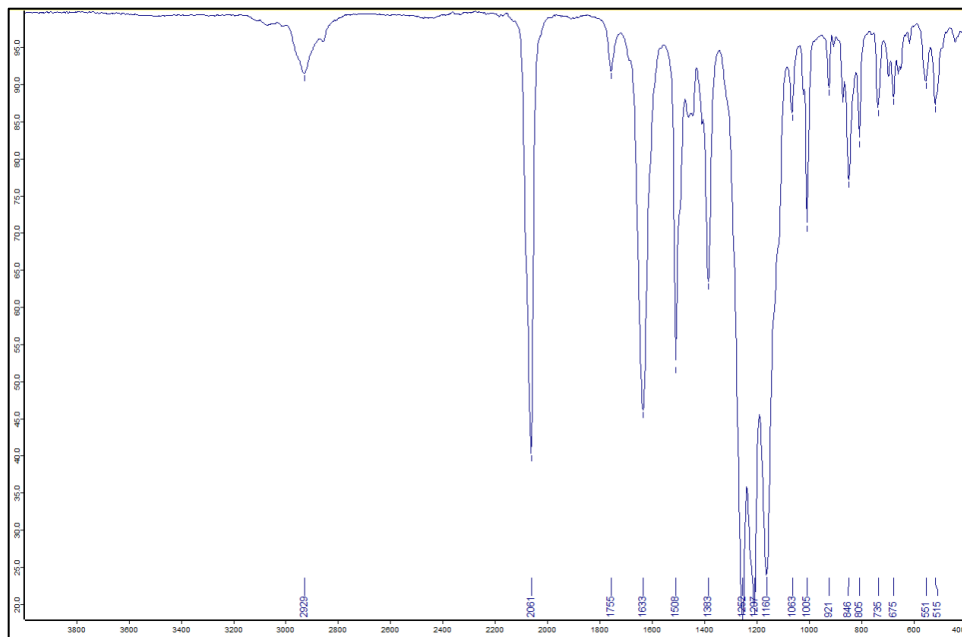
**<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>, δ):** 165.3, 130.4, 126.7, 125.6, 121.9, 121.2, 37.8

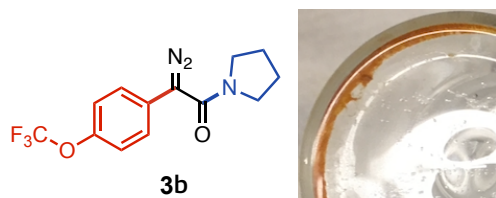
*Note: The diazo carbon (C=N=N) signal is not observed as mentioned in General Information (page S6).<sup>10</sup>*

**HRMS (ESI-TOF):** calc'd for C<sub>11</sub>H<sub>11</sub>F<sub>3</sub>N<sub>3</sub>O<sub>2</sub> [M + H]<sup>+</sup>, 274.0798; found, 274.0807

calc'd for C<sub>11</sub>H<sub>10</sub>F<sub>3</sub>N<sub>3</sub>O<sub>2</sub>Na [M + Na]<sup>+</sup>, 296.0617; found, 296.0618

**IR (neat):** 2929, 2061 (diazo), 1755, 1633, 1508, 1383, 1252, 1207, 1160, 1063, 1005, 921, 846, 805, 735, 675 cm<sup>-1</sup>





**2-Diazo-1-(pyrrolidin-1-yl)-2-(4-(trifluoromethoxy)phenyl)ethan-1-one (3b):** General Procedure B was applied using **2b** (22 mg, 0.08 mmol, 1.0 equiv) and pyrrolidine (28 mg, 0.4 mmol, 5.0 equiv). The reaction was quenched after 1 h. The crude product was purified by column chromatography (33% v/v EtOAc in hexanes) to yield the title compound (16.6 mg, 69% yield).

**Physical State:** dark orange solid

**TLC:**  $R_f$  = 0.33 (1:1 EtOAc/hexanes)

**$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ,  $\delta$ ):** 7.36 (d,  $J$  = 8.8 Hz, 2H), 7.23–7.19 (m, 2H), 3.49–3.40 (m, 4H), 1.96–1.89 (m, 4H)

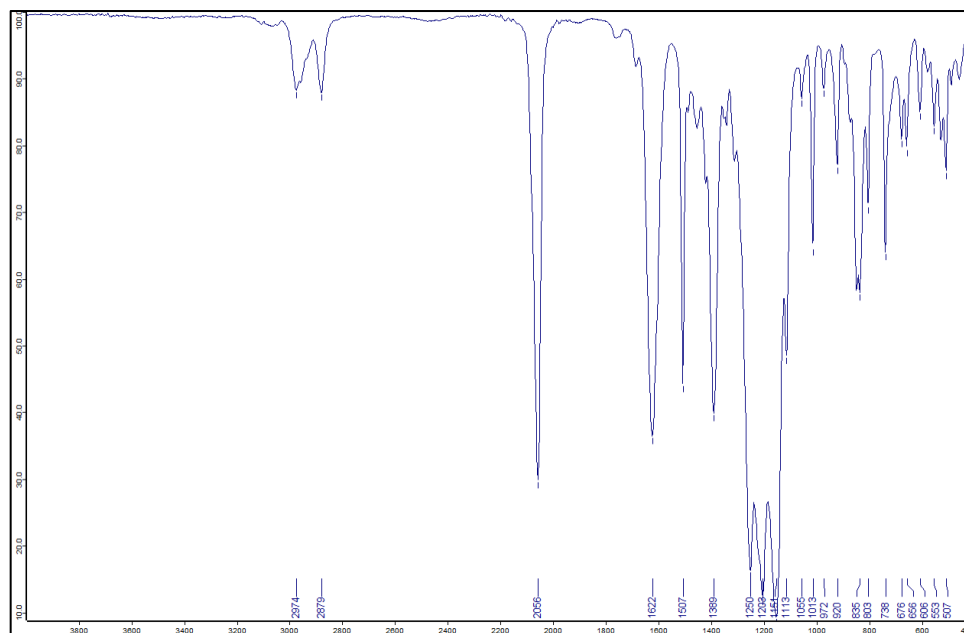
**$^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ ,  $\delta$ ):** 163.2, 147.1 (q,  $J$  = 2.2 Hz), 132.3, 130.4, 126.3, 126.2, 121.8, 47.9, 25.5

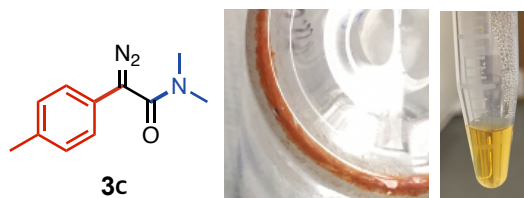
*Note: The diazo carbon ( $\text{C}=\text{N}=\text{N}$ ) signal is not observed as mentioned in General Information (page S6).<sup>10</sup>*

**$^{19}\text{F}$  NMR (471 MHz,  $\text{CDCl}_3$ ,  $\delta$ ):** -57.98

**HRMS (ESI-TOF):** calc'd for  $\text{C}_{13}\text{H}_{13}\text{F}_3\text{N}_3\text{O}_2$  [ $\text{M} + \text{H}$ ]<sup>+</sup>, 300.0954; found, 300.0954

**IR (neat):** 2974, 2879, 2056 (diazo), 1622, 1507, 1389, 1250, 1203, 1151, 1113, 1055, 1013, 972, 835, 738, 656  $\text{cm}^{-1}$





**2-Diazo-*N,N*-dimethyl-2-(*p*-tolyl)acetamide (3c):** General Procedure B was applied using **2c** (48 mg, 0.17 mmol, 1.0 equiv) and dimethylamine solution (2.0 M) in THF (0.43 mL, 0.85 mmol, 5.0 equiv). The reaction was quenched after 3 h. The crude product was purified by column chromatography (20% v/v EtOAc in hexanes) to yield the title compound (12 mg, 34% yield).

**Physical State:** red solid (orange solution in MeCN)

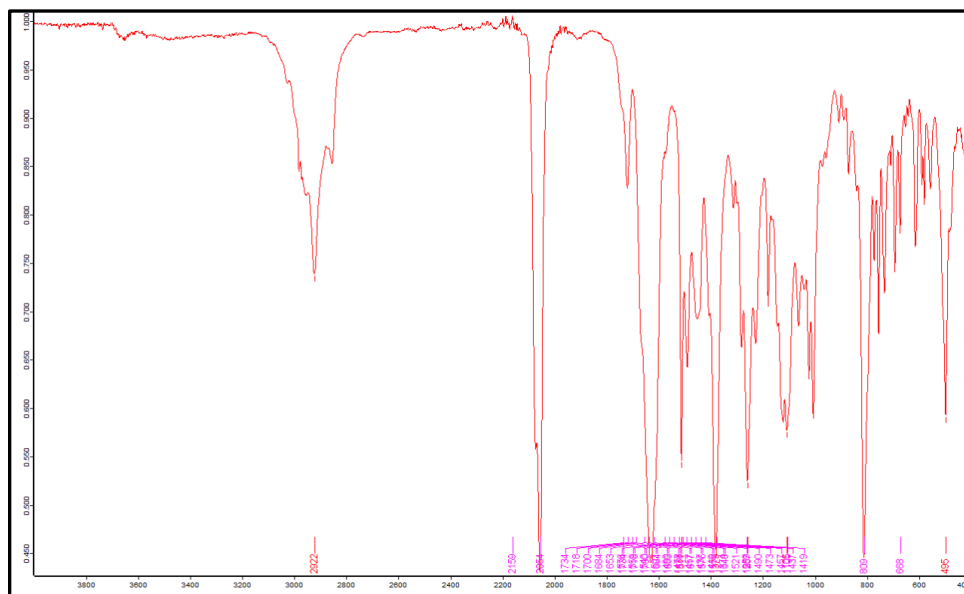
**TLC:** *R<sub>f</sub>* = 0.24 (3:1 hexanes/EtOAc)

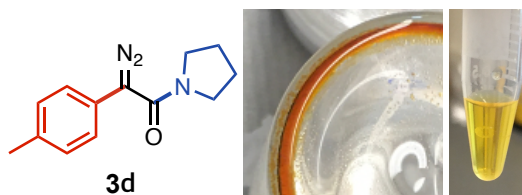
**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, δ):** 7.18 (d, *J* = 8.2 Hz, 2H), 7.10 (d, *J* = 8.2 Hz, 2H), 2.95 (s, 6H), 2.33 (s, 3H)

<sup>1</sup>H NMR spectrum of **3c** matched with the literature.<sup>4</sup>

**HRMS (ESI-TOF):** calc'd for C<sub>11</sub>H<sub>14</sub>NO [M + H-N<sub>2</sub>]<sup>+</sup>, 262.0710; found, 262.0707

**IR (neat):** 2922, 2054 (diazo), 1648, 1521, 1490, 1473, 1419, 809, 668, 495 cm<sup>-1</sup>





**2-Diazo-1-(pyrrolidin-1-yl)-2-(*p*-tolyl)ethan-1-one (3d):** General Procedure B was applied using **2c** (48 mg, 0.17 mmol, 1.0 equiv) and pyrrolidine (60 mg, 0.85 mmol, 5.0 equiv). The reaction was quenched after 1 h. The crude product was purified by column chromatography (20% v/v EtOAc in hexanes) to yield the title compound (27 mg, 69% yield).

**Physical State:** reddish orange amorphous solid (yellow solution in MeCN)

**TLC:** *R<sub>f</sub>* = 0.25 (3:1 hexanes/EtOAc)

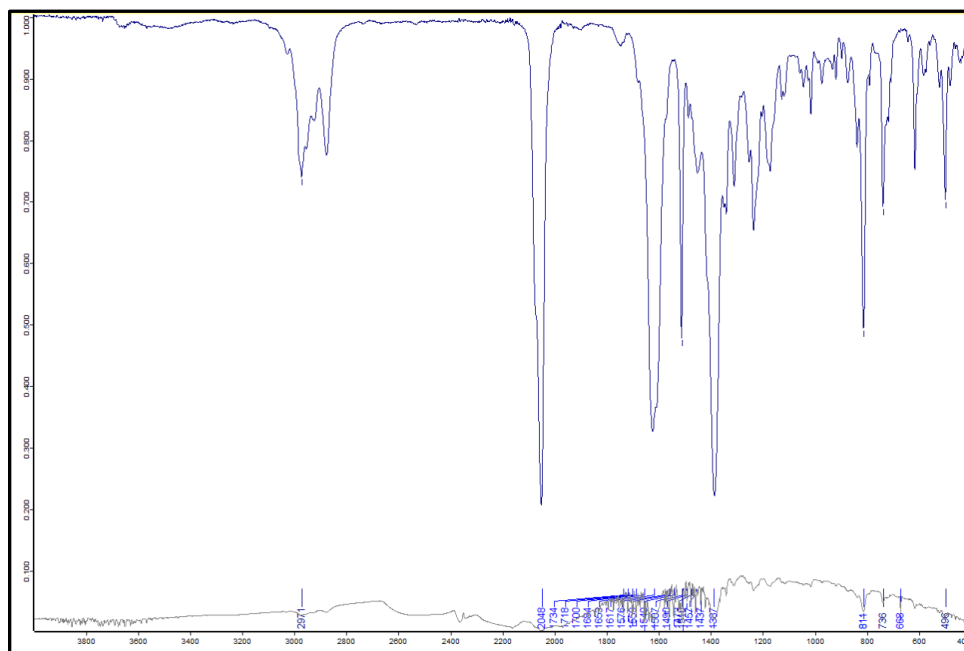
**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, δ):** 7.23–7.13 (m, 4H), 3.40 (s, 4H), 2.33 (s, 3H), 1.93–1.83 (m, 4H)

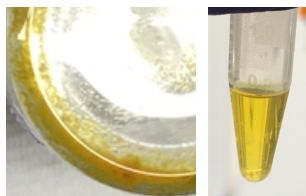
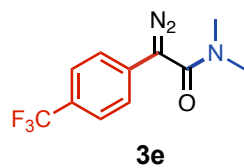
**<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>, δ):** 164.1, 136.0, 129.8, 125.6, 124.1, 47.9, 29.8, 25.5, 21.2

*Note: The diazo carbon (C=N=N) signal is not observed as mentioned in General Information (page S6).<sup>10</sup>*

**HRMS (ESI-TOF):** calc'd for C<sub>13</sub>H<sub>26</sub>N<sub>3</sub>O [M + H]<sup>+</sup> 230.1288; found, 230.1291

**IR (neat):** 2971, 2048 (diazo), 1617, 1387, 814, 736, 668, 496 cm<sup>-1</sup>





**2-Diazo-*N,N*-dimethyl-2-(4-(trifluoromethyl)phenyl)acetamide (3e):** General Procedure B was applied using **2d** (57 mg, 0.17 mmol, 1.0 equiv) and dimethylamine solution (2.0 M) in THF (0.43 mL, 0.85 mmol, 5.0 equiv). The reaction was quenched after 3 h. The crude product was purified by column chromatography (20% v/v EtOAc in hexanes) to yield the title compound (17 mg, 38% yield).

**Physical State:** yellow amorphous solid

**TLC:** *R<sub>f</sub>* = 0.28 (2:1 hexanes/EtOAc)

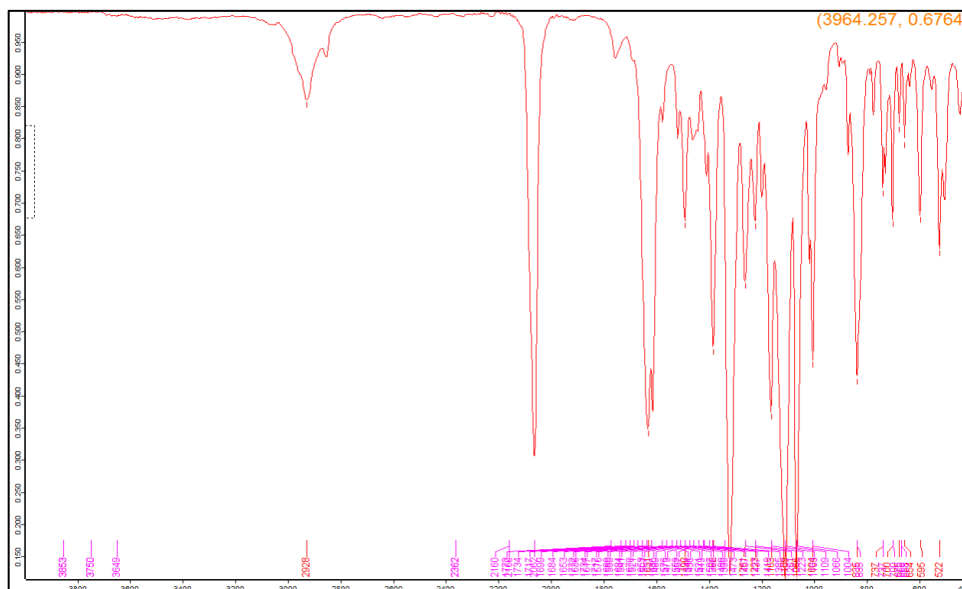
**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>, δ):** 7.59 (d, *J* = 8.3 Hz, 2H), 7.32 (d, *J* = 8.3 Hz, 2H), 3.02 (s, 6H)

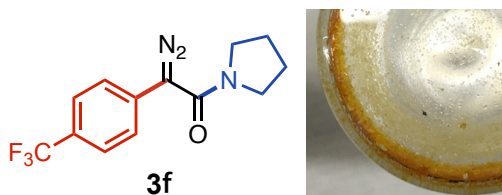
**<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>, δ):** 164.8, 132.2, 129.5, 126.1 (q, *J* = 3.8 Hz), 123.9, 37.8

*Note: The diazo carbon (C=N=N) signal is not observed as mentioned in General Information (page S6).<sup>10</sup>*

**HRMS (ESI-TOF):** calc'd for C<sub>11</sub>H<sub>11</sub>F<sub>3</sub>NO [M + H - N<sub>2</sub>]<sup>+</sup>, 230.0787; found, 230.0790

**IR (neat):** 2928, 2062 (diazo), 1670, 1576, 737, 595, 522 cm<sup>-1</sup>





**2-Diazo-1-(pyrrolidin-1-yl)-2-(4-(trifluoromethyl)phenyl)ethan-1-one (3f):** General Procedure B was applied using **2d** (57 mg, 0.17 mmol, 1.0 equiv) and pyrrolidine (60 mg, 0.85 mmol, 5.0 equiv). reaction was quenched after 3 h. The crude product was purified by column chromatography (20% v/v EtOAc in hexanes) to yield the title compound (36 mg, 74% yield).

**Physical State:** orange amorphous solid

**TLC:** R<sub>f</sub> = 0.26 (3:1 hexanes/EtOAc)

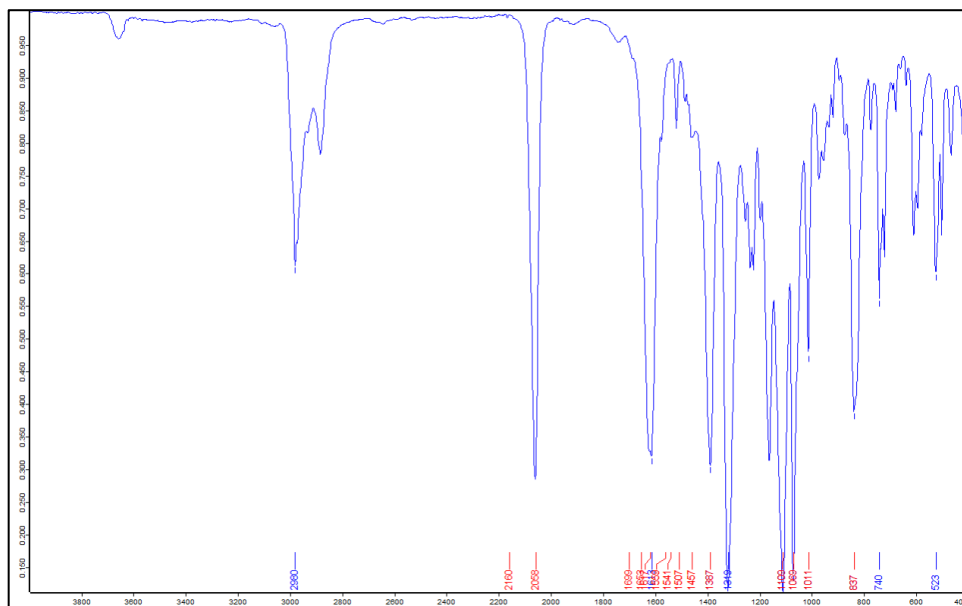
**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>, δ):** 7.58 (d, *J* = 8.2 Hz, 2H), 7.43 (d, *J* = 8.4 Hz, 2H), 3.47 (s, 4H), 2.04–1.80 (m, 4H)

**<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>, δ):** 162.6, 131.9, 129.5, 125.9 (q, *J* = 3.8 Hz), 124.3, 47.9, 25.5

*Note: The diazo carbon (C=N=N) signal is not observed as mentioned in General Information (page S6).<sup>10</sup>*

**HRMS (ESI-TOF):** calc'd for C<sub>13</sub>H<sub>13</sub>F<sub>3</sub>N<sub>3</sub>O [M + H]<sup>+</sup>, 284.1005; found, 284.1008

**IR (neat):** 2980, 2058 (diazo), 1613, 1319, 1109, 1069, 1011 cm<sup>-1</sup>





**2-Diazo-*N,N*-dimethyl-2-(4-((trimethylsilyl)ethynyl)phenyl)acetamide (3g)** General Procedure B was applied using **2e** (60 mg, 0.17 mmol, 1.0 equiv) and dimethylamine solution (2.0 M) in THF (0.43 mL, 0.85 mmol, 5.0 equiv). The reaction was quenched after 3 h. The crude product was purified by column chromatography (20% v/v EtOAc in hexanes) to yield the title compound (36.5 mg, 75% yield). Also see **Figure S4** for additional information.

**Physical State:** orange oil (orange solution in MeCN)

**TLC:** *R<sub>f</sub>* = 0.41 (2:1 hexanes/EtOAc)

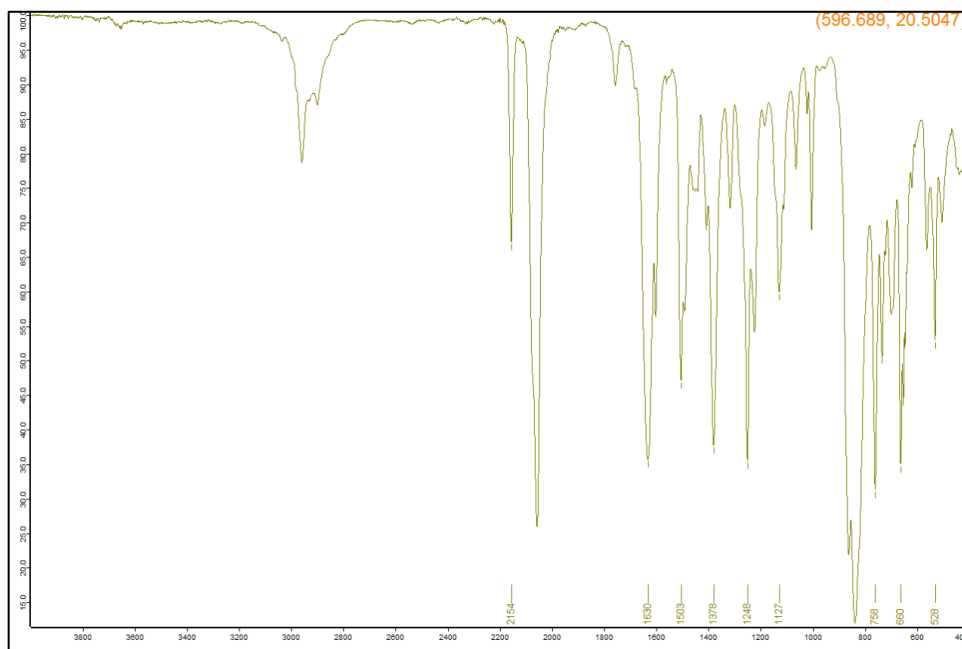
**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, δ):** 7.50–7.38 (m, 2H), 7.20–7.01 (m, 2H), 2.97 (s, 6H), 0.24 (s, 9H)

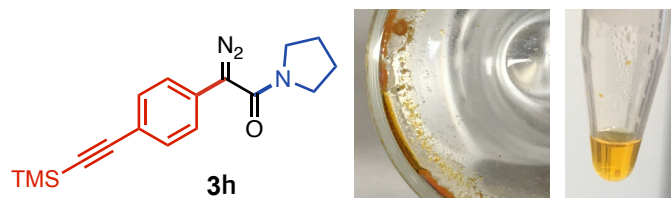
**<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>, δ):** 165.3, 132.8, 128.0, 123.8, 120.2, 104.9, 94.7, 37.8, 0.1

*Note: The diazo carbon (C=N=N) signal is not observed as mentioned in General Information (page S6).*<sup>10</sup>

**HRMS (ESI-TOF):** calc'd for C<sub>15</sub>H<sub>19</sub>N<sub>3</sub>OSiNa [M + Na]<sup>+</sup>, 308.1190; found, 308.1189

**IR (neat):** 2154, 2055 (diazo), 1630, 1503, 1378, 1248, 1127, 758, 660, 528 cm<sup>-1</sup>





**2-Diazo-1-(pyrrolidin-1-yl)-2-(4-((trimethylsilyl)ethynyl)phenyl)ethan-1-one (3h):** General Procedure B was applied using **2e** (60 mg, 0.17 mmol, 1.0 equiv) and pyrrolidine (60 mg, 0.85 mmol, 5.0 equiv). The reaction was quenched after 3 h. The crude product was purified by column chromatography (33% v/v EtOAc in hexanes) to yield the title compound (37mg, 70% yield).

**Physical State:** orange amorphous solid

**TLC:**  $R_f$  = 0.52 (2:1 hexanes/EtOAc)

**$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ,  $\delta$ ):** 7.47 (d,  $J$  = 8.5 Hz, 2H), 7.27 (d,  $J$  = 8.6 Hz, 2H), 3.46 (s, 4H), 1.99–1.88 (m, 4H), 0.27 (s, 9H)

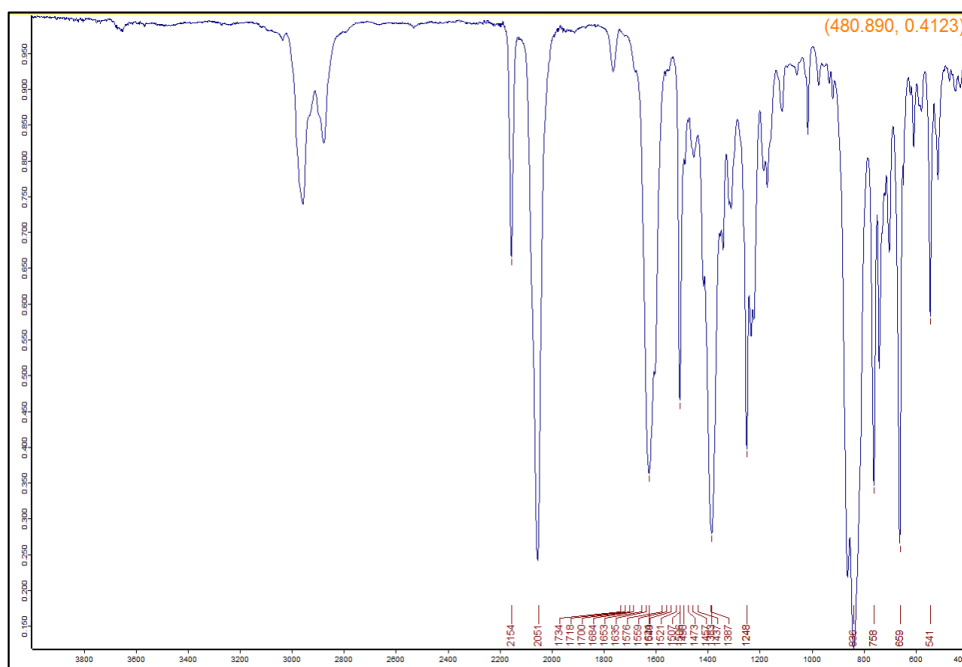
**$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ ,  $\delta$ ):** 163.2, 132.6, 127.7, 124.3, 120.3, 105.0, 94.6, 47.9, 25.5, 0.1

*Note: The diazo carbon ( $\text{C}=\text{N}=\text{N}$ ) signal is not observed as mentioned in General Information (page S6).<sup>10</sup>*

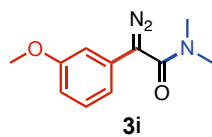
**HRMS (ESI-TOF):** calc'd for  $\text{C}_{17}\text{H}_{22}\text{N}_3\text{OSi}$  [ $\text{M} + \text{H}$ ]<sup>+</sup>, 312.1527; found, 312.1527

calc'd for  $\text{C}_{17}\text{H}_{21}\text{N}_3\text{OSiNa}$  [ $\text{M} + \text{Na}$ ]<sup>+</sup>, 334.1346; found, 334.1346

**IR (neat):** 2154, 2051 (diazo), 1734, 1387, 1248, 835, 758, 659, 541  $\text{cm}^{-1}$







**2-Diazo-2-(3-methoxyphenyl)-*N,N*-dimethylacetamide (3i):** General Procedure B was applied using **2f** (50 mg, 0.17 mmol, 1.0 equiv) and dimethylamine solution (2.0 M) in THF (0.43 mL, 0.85 mmol, 5.0 equiv). The reaction was quenched after 1 h. No precipitation was observed. The crude product was purified by column chromatography (25% v/v EtOAc in hexanes) to yield the title compound (12 mg, 31% yield).

**Physical State:** yellow amorphous solid

**TLC:** *R<sub>f</sub>* = 0.18 (3:1 hexanes/EtOAc)

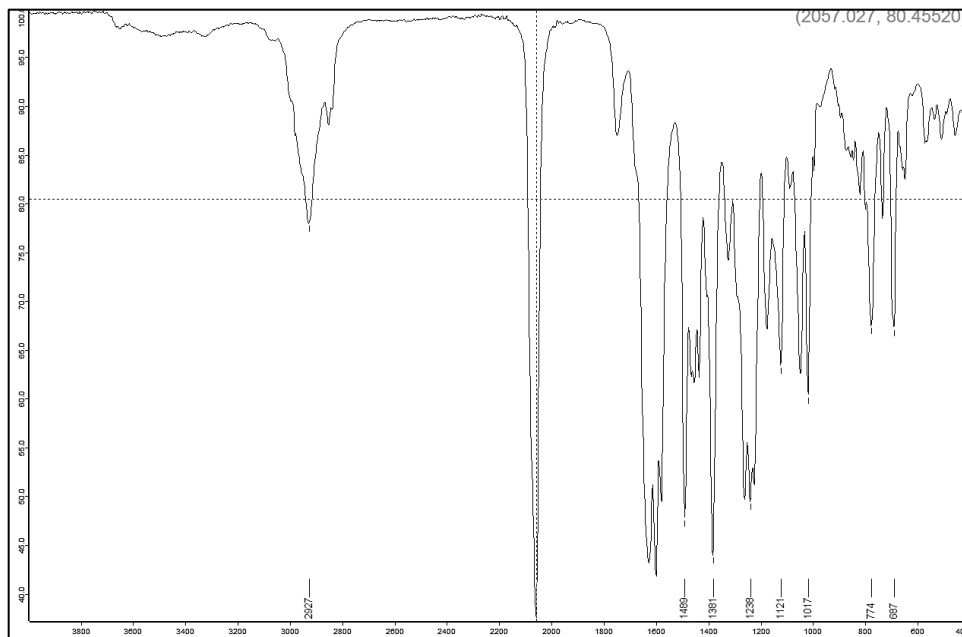
**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>, δ):** 7.30–7.26 (m, 1H), 6.84–6.72 (m, 2H), 6.71 (ddd, *J* = 8.3, 2.5, 0.9 Hz, 1H), 3.80 (s, 3H), 2.97 (s, 6H)

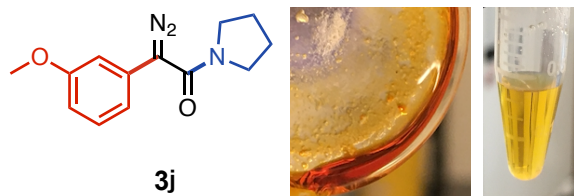
**<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>, δ):** 165.8, 160.3, 130.2, 129.3, 117.0, 111.4, 110.3, 55.4, 37.9

*Note: The diazo carbon (C=N=N) signal is not observed as mentioned in General Information (page S6).<sup>10</sup>*

**HRMS (ESI-TOF):** calc'd for C<sub>11</sub>H<sub>14</sub>NO<sub>2</sub> [M + H - N<sub>2</sub>]<sup>+</sup>, 192.1019; found, 192.1010

**IR (neat):** 2927, 2056 (diazo), 1489, 1381, 1238, 1121, 1017, 774, 687 cm<sup>-1</sup>





**2-Diazo-2-(3-methoxyphenyl)-1-(pyrrolidin-1-yl)ethan-1-one (3j):** General Procedure B was applied using **2f** (50 mg, 0.17 mmol, 1.0 equiv) and pyrrolidine (60 mg, 0.85 mmol, 5.0 equiv). The reaction was quenched after 1 h. The crude product was purified by column chromatography (25%v/v EtOAc in hexanes) to yield the title compound (33 mg, 76% yield).

**Physical State:** red film

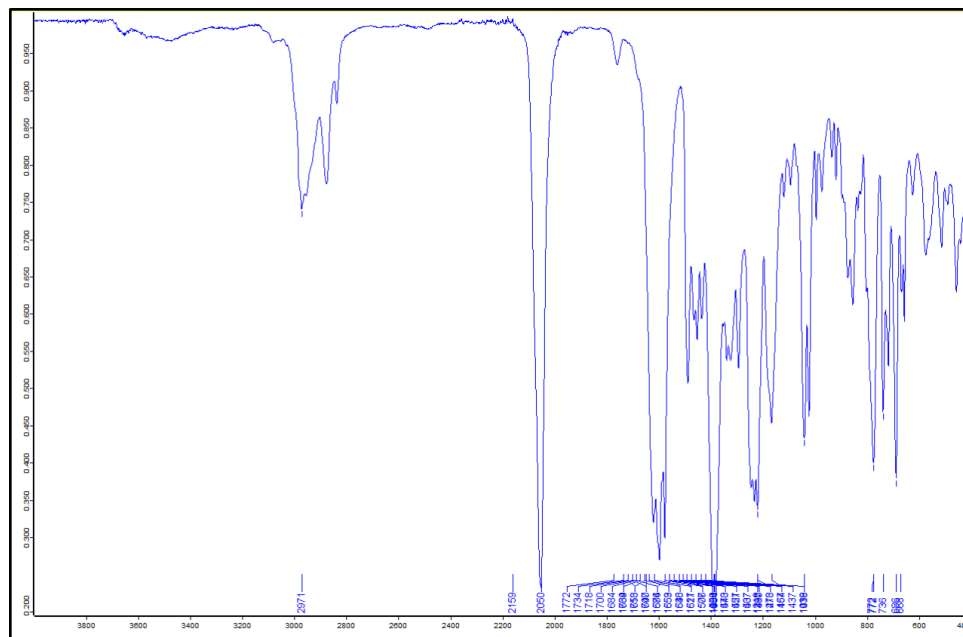
**TLC:** *R<sub>f</sub>* = 0.19 (3:1 hexanes/EtOAc)

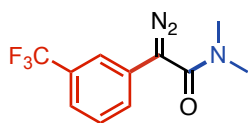
**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>, δ):** 7.27 (t, *J* = 8.0 Hz, 1H), 6.93 (s, 1H), 6.86 (dd, *J* = 7.8, 1.7 Hz, 1H), 6.72 (dd, *J* = 8.3, 2.5 Hz, 1H), 3.80 (s, 4H), 3.43 (m, 4H), 1.93–1.87 (m, 4H)

**<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>, δ):** 163.7, 160.2, 130.0, 128.8, 117.5, 111.7, 110.8, 63.1 (diazo carbon, verified by HBMC and HSQC), 55.4, 47.9, 25.5

**HRMS (ESI-TOF):** calc'd for C<sub>13</sub>H<sub>16</sub>N<sub>3</sub>O<sub>2</sub> [M + H]<sup>+</sup>, 246.1237; found, 246.1226

**IR (neat):** 2971, 2050 (diazo), 1627, 1278, 1038 cm<sup>-1</sup>



**3k**

**2-Diazo-*N,N*-dimethyl-2-(3-(trifluoromethyl)phenyl)acetamide (3k):** General Procedure B was applied using **2h** (59 mg, 0.18 mmol, 1.0 equiv) and dimethylamine solution (2.0 M) in THF (0.45 mL, 0.9 mmol, 5.0 equiv). The reaction was quenched after 3 h. The crude product was purified by column chromatography (20% v/v EtOAc in hexanes) to yield the title compound (17 mg, 37% yield).

**Physical State:** orange film

**TLC:**  $R_f = 0.39$  (2:1 hexanes/EtOAc)

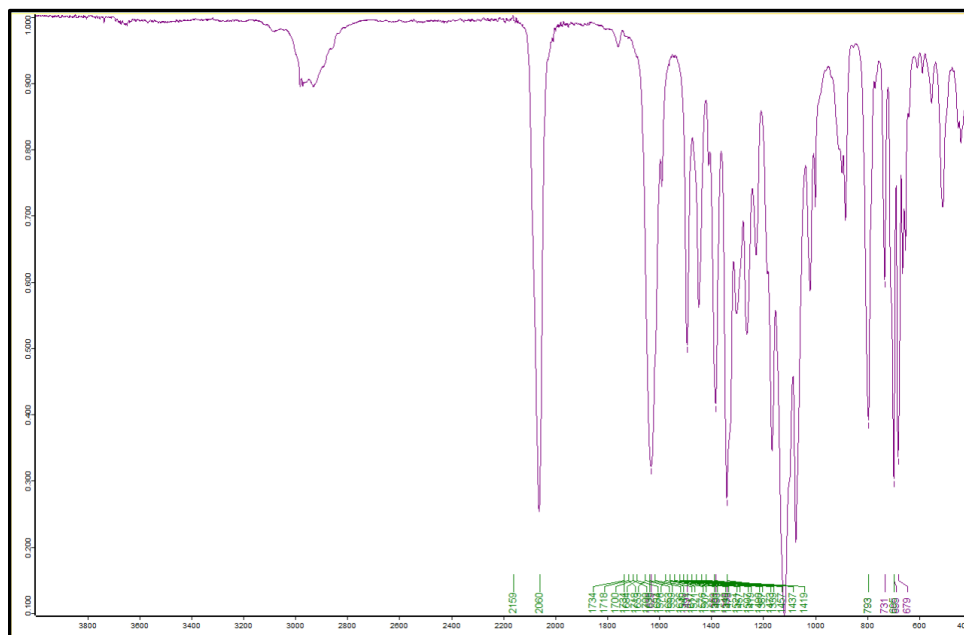
**$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ,  $\delta$ ):** 7.50 (d,  $J = 1.7$  Hz, 1H), 7.49–7.36 (m, 3H), 3.01 (s, 6H)

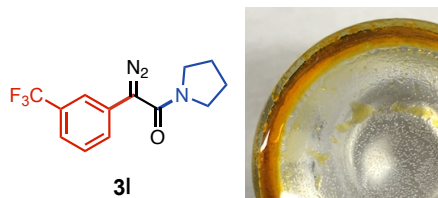
**$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ ,  $\delta$ ):** 164.9, 129.6, 129.2, 127.1, 122.3 (q,  $J = 3.8$  Hz), 120.8 (q,  $J = 3.9$  Hz), 37.8

*Note: The diazo carbon ( $\text{C}=\text{N}=\text{N}$ ) signal is not observed as mentioned in General Information (page S6).<sup>10</sup>*

**HRMS (ESI-TOF):** calc'd for  $\text{C}_{11}\text{H}_{11}\text{F}_3\text{N}_3\text{O}$  [ $\text{M} + \text{H}$ ]<sup>+</sup>, 258.0849; found, 258.0841

**IR (neat):** 2060 (diazo), 1734, 1659, 1419, 793, 679  $\text{cm}^{-1}$





**2-Diazo-1-(pyrrolidin-1-yl)-2-(3-(trifluoromethyl)phenyl)ethan-1-one (3I):** General Procedure B was applied using **2h** (59 mg, 0.18 mmol, 1.0 equiv) and pyrrolidine (0.45 mL, 0.9 mmol, 5.0 equiv). reaction was quenched after 6 h. The crude product was purified by column chromatography (20% v/v EtOAc in hexanes) to yield the title compound (33 mg, 65% yield).

**Physical State:** orange film

**TLC:** R<sub>f</sub> = 0.41 (2:1 hexanes/EtOAc)

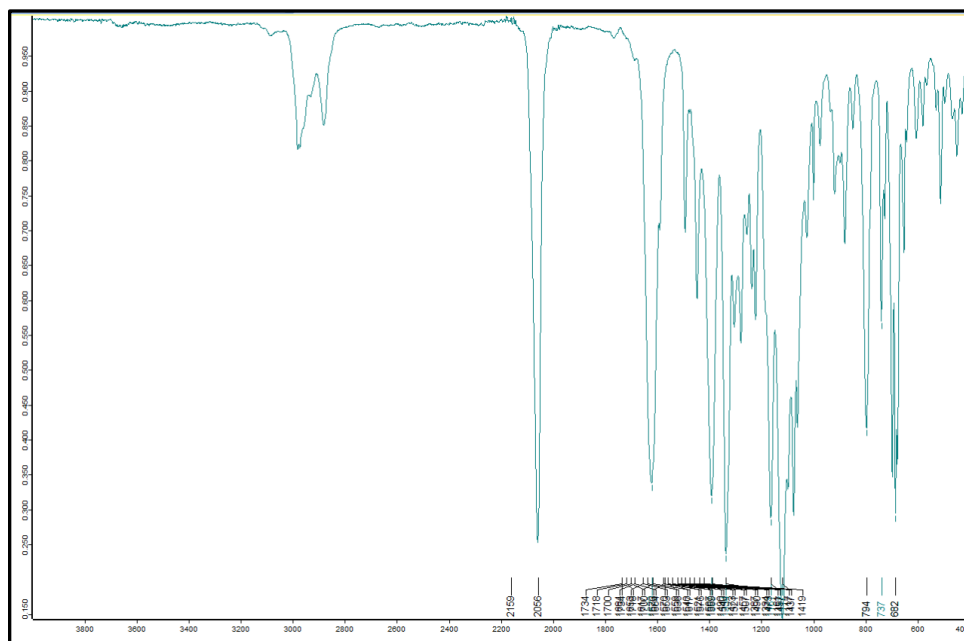
**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, δ):** 7.61 (d, *J* = 2.2 Hz, 1H), 7.53–7.36 (m, 3H), 3.47 (d, *J* = 6.2 Hz, 4H), 1.98–1.88 (m, 4H)

**<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>, δ):** 162.8, 129.4, 128.8, 127.6, 122.3 (q, *J* = 3.7 Hz), 121.3 (q, *J* = 3.9 Hz), 47.9, 25.4

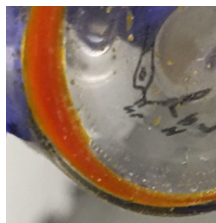
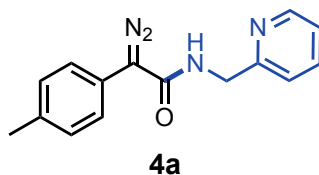
*Note: The diazo carbon (C=N=N) signal is not observed as mentioned in General Information (page S6).<sup>10</sup>*

**HRMS (ESI-TOF):** calc'd for C<sub>13</sub>H<sub>13</sub>F<sub>3</sub>N<sub>3</sub>O [M + H]<sup>+</sup>, 284.1005; found, 284.1005

**IR (neat):** 2056 (diazo), 1734, 1700, 1647, 1419, 794, 682 cm<sup>-1</sup>



#### XIV. Characterization Data for 4a–4e



**2-Diazo-*N*-(pyridin-2-ylmethyl)-2-(*p*-tolyl)acetamide (4a):** General Procedure B was applied using **2c** (30 mg, 0.11 mmol, 1.0 equiv) and 2-picolyamine (36 mg, 0.33 mmol, 3.0 equiv). The reaction was quenched after 1.5 h. The crude product was purified by column chromatography (50% v/v EtOAc in hexanes) to yield the title compound (19 mg, 65% isolated yield).

**Physical State:** orange amorphous solid

**TLC:** *R<sub>f</sub>* = 0.17 (1:1 EtOAc/hexanes)

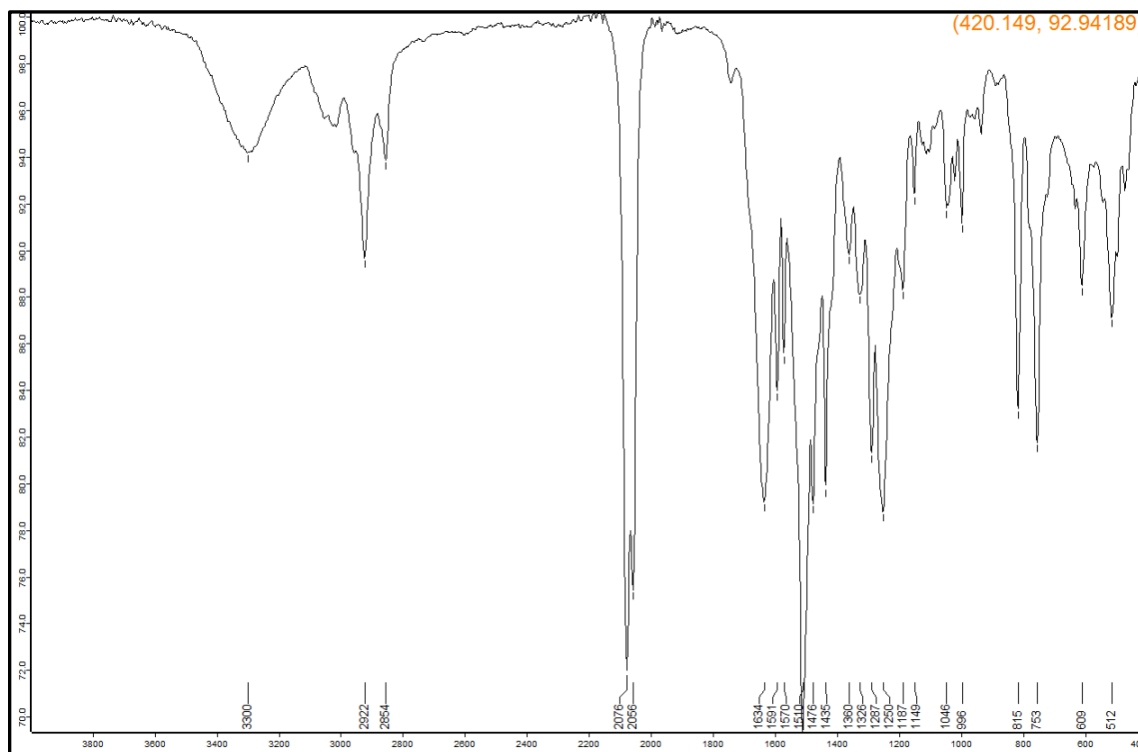
**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>, δ):** 8.50 (dt, *J* = 4.8, 1.4 Hz, 1H), 7.68 (td, *J* = 7.7, 1.8 Hz, 1H), 7.33–7.31 (m, 2H), 7.27 (d, *J* = 8.0 Hz, 2H), 7.22–7.17 (m, 1H), 6.74 (d, *J* = 5.3 Hz, 1H), 4.68 (d, *J* = 5.1 Hz, 2H), 2.39 (s, 3H)

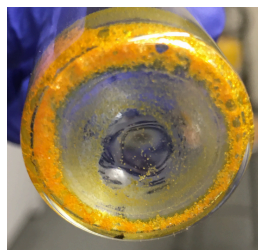
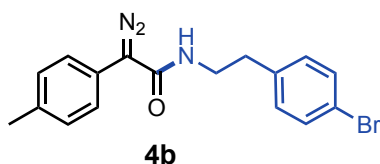
**<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>, δ):** 165.2, 156.7, 149.3, 137.8, 136.9, 130.5, 130.5, 127.6, 123.2, 122.5, 122.2, 45.2, 29.8, 21.3

*Note: The diazo carbon (C=N=N) signal is not observed as mentioned in General Information (page S6).<sup>10</sup>*

**HRMS (ESI-TOF):** calc'd for C<sub>15</sub>H<sub>15</sub>N<sub>4</sub>O [M + H]<sup>+</sup>, 267.1240; found, 267.1243

**IR (neat):** 2922, 2854, 2076 (diazo), 2056, 1634, 1591, 1510, 1250, 815, 753, 512 cm<sup>-1</sup>





**N-(4-Bromophenethyl)-2-diazo-2-(p-tolyl)acetamide (4b):** General Procedure B was applied using **2c** (30 mg, 0.11 mmol, 1.0 equiv) and 4-bromophenethylamine (66 mg, 0.33 mmol, 3.0 equiv). The reaction was quenched after 1.5 h. The crude product was purified by column chromatography (1:6 EtOAc/pentane) to yield the title compound (31 mg, 78% isolated yield).

**Physical State:** yellow amorphous solid

**TLC:**  $R_f = 0.5$  (1:2 EtOAc/pentane)

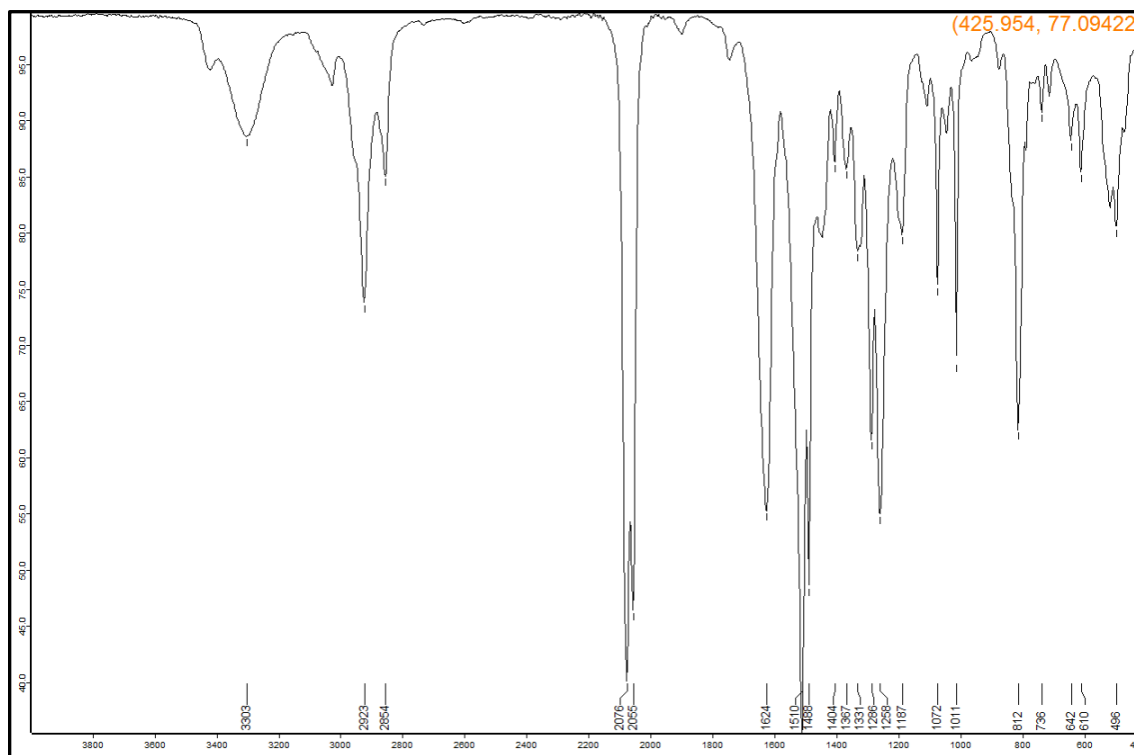
**$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ,  $\delta$ ):** 7.47–7.36 (m, 2H), 7.19 (d,  $J = 8.1$  Hz, 2H), 7.11–7.06 (m, 2H), 7.06–7.03 (m, 2H), 5.36 (t,  $J = 5.9$  Hz, 1H), 3.56 (td,  $J = 6.9, 5.8$  Hz, 2H), 2.80 (t,  $J = 7.0$  Hz, 2H), 2.36 (s, 3H)

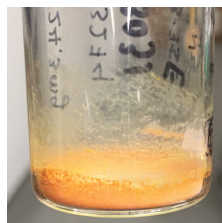
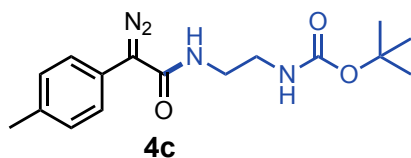
**$^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ ,  $\delta$ ):** 165.0, 138.1, 137.8, 131.7, 130.5, 130.4, 127.8, 122.9, 120.4, 41.9, 35.3, 21.2

*Note: The diazo carbon ( $\text{C}=\text{N}=\text{N}$ ) signal is not observed as mentioned in General Information (page S6).<sup>10</sup>*

**HRMS (ESI-TOF):** calc'd for  $\text{C}_{17}\text{H}_{17}\text{BrN}_3\text{O}$  [ $\text{M} + \text{H}$ ]<sup>+</sup>, 358.0531; found, 358.0548

**IR (neat):** 2923, 2854, 2076 (diazo), 2055, 1624, 1510, 1258, 1011, 812  $\text{cm}^{-1}$





**tert-Butyl-(2-(2-diazo-2-(*p*-tolyl)acetamido)ethyl)carbamate (4c):** General Procedure B was applied using **2c** (30 mg, 0.11 mmol, 1.0 equiv) and *N*-*boc*-ethylenediamine (53 mg, 0.33 mmol, 3.0 equiv). The reaction was quenched after 1.5 h. The crude product was purified by column chromatography (33% v/v EtOAc in hexanes) to yield the title compound (24 mg, 69% isolated yield).

**Physical State:** light orange solid

**TLC:** *R<sub>f</sub>* = 0.33 (1:1 EtOAc/hexanes)

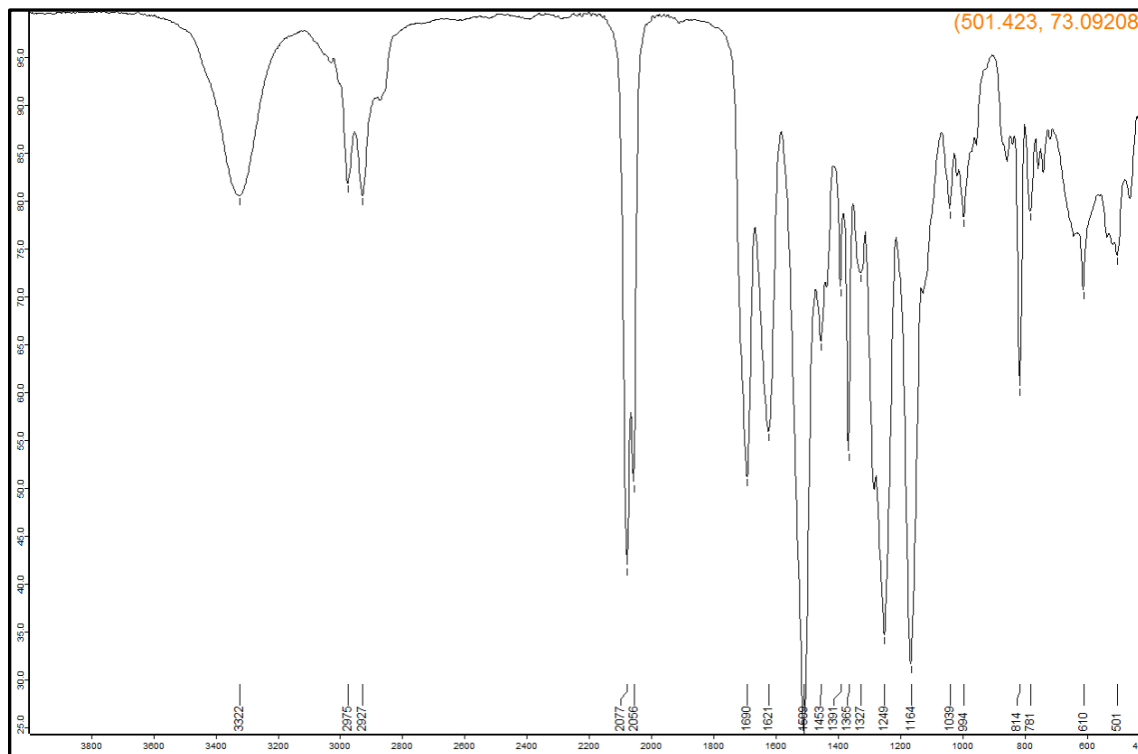
**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>, δ):** 7.24 (d, *J* = 2.0 Hz, 4H), 6.09–5.97 (m, 1H), 4.98 (t, *J* = 6.3 Hz, 1H), 3.44 (t, *J* = 5.8 Hz, 2H), 3.27 (q, *J* = 5.9 Hz, 2H), 2.36 (s, 3H), 1.39 (s, 9H)

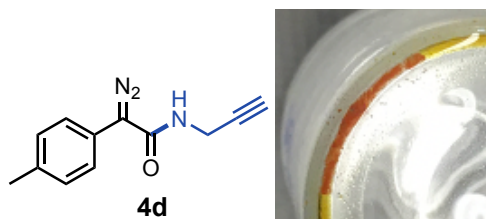
**<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>, δ):** 165.8, 156.9, 137.9, 130.5, 127.8, 123.0, 79.8, 41.4, 40.7, 28.4, 21.3

*Note: The diazo carbon (C=N=N) signal is not observed as mentioned in General Information (page S6).<sup>10</sup>*

**HRMS (ESI-TOF):** calc'd for C<sub>16</sub>H<sub>23</sub>N<sub>4</sub>O<sub>3</sub> [M + H]<sup>+</sup>, 319.1765; found, 319.1762

**IR (neat):** 3322, 2975, 2927, 2077 (diazo), 2056, 1690, 1621, 1509, 1391, 1249, 1164, 781, 610 cm<sup>-1</sup>





**2-Diazo-N-(prop-2-yn-1-yl)-2-(p-tolyl)acetamide (4d):** General Procedure B was applied using **2c** (48 mg, 0.17 mmol, 1.0 equiv) and propargylamine (48 mg, 0.87 mmol, 5.0 equiv). The reaction was quenched after 3 h. The crude product was purified by column chromatography (1:5 EtOAc/hexanes) to yield the title compound (21 mg, 57% yield).

**Physical State:** red orange solid

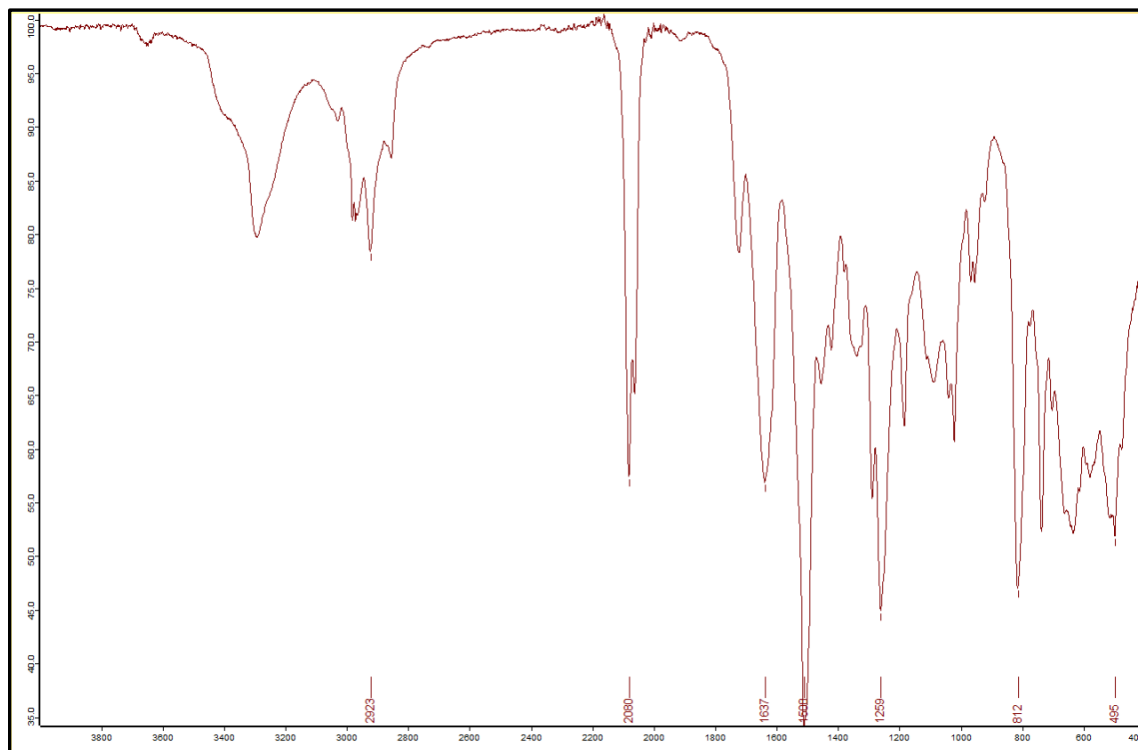
**TLC:**  $R_f$  = 0.29 (1:3 EtOAc/hexanes)

**$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ ,  $\delta$ ):** 7.28 (m, 4H), 5.53 (s, 1H), 4.17 (dd,  $J$  = 5.4, 2.6 Hz, 2H), 2.41 (s, 3H)

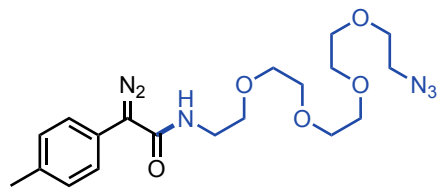
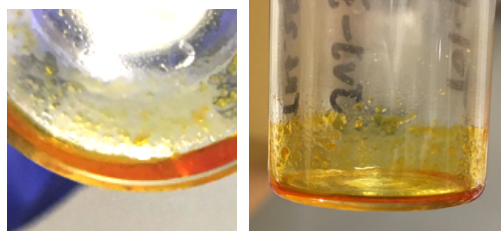
$^1\text{H NMR}$  spectrum of **4d** matched with the literature.<sup>4</sup>

**HRMS (ESI-TOF):** calc'd for  $\text{C}_{12}\text{H}_{12}\text{N}_3\text{O}$  [ $\text{M} + \text{H}$ ]<sup>+</sup>, 214.0975 ; found, 214.0974

**IR (neat):** 2923, 2080 (diazo), 1637, 1508, 1259, 812, 495  $\text{cm}^{-1}$





**4e**

**N-(14-Azido-3,6,9,12-tetraoxatetradecyl)-2-diazo-2-(*p*-tolyl)acetamide (4e):** General Procedure B was applied using **2c** (30 mg, 0.11 mmol, 1.0 equiv) and 14-azido-3,6,9,12-tetraoxatetradecan-1-amine (29 mg, 0.11 mmol, 1.0 equiv). The reaction was quenched after 3 h. The crude product was purified by column chromatography (4:8:1 pentane/EtOAc/MeOH) to yield the title compound (42 mg, 91% yield).

**Physical State:** orange film

**TLC:** *R<sub>f</sub>* = 0.2 dragging (4:8:1 pentane/EtOAc/MeOH) Staining of azide is done by PPh<sub>3</sub>/ninhydrin stain.<sup>11</sup>

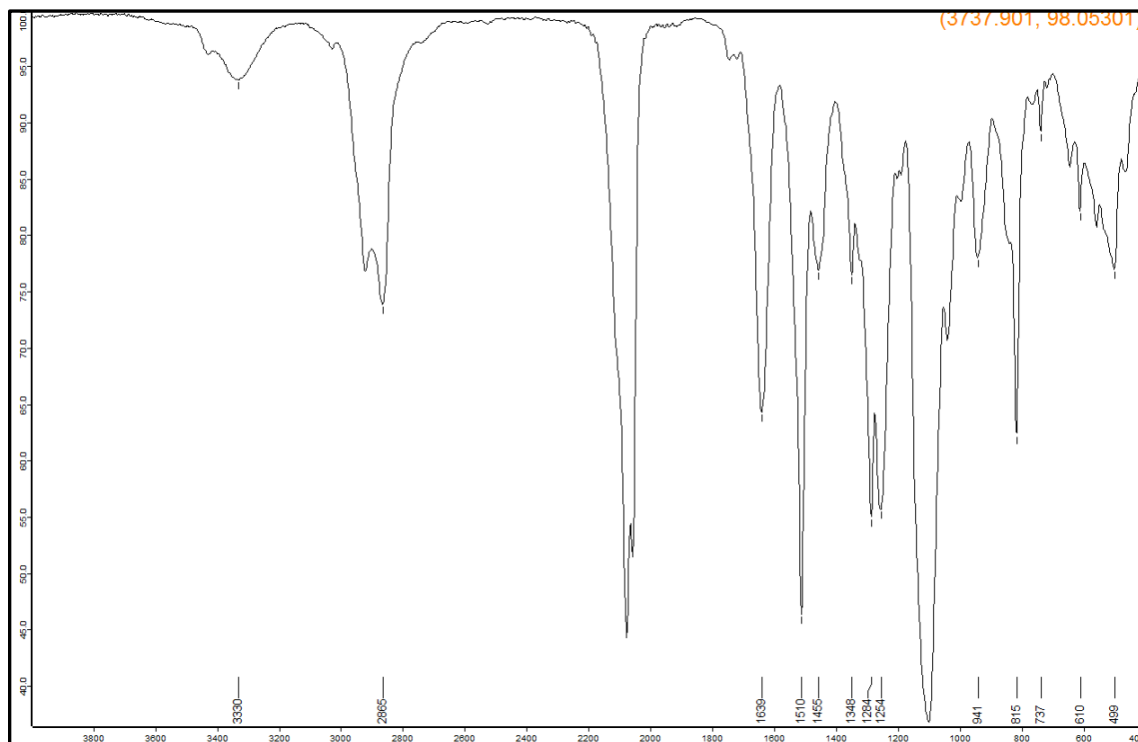
**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>, δ):** 7.28–7.22 (m, 4H), 5.95 (t, *J* = 5.5 Hz, 1H), 3.69–3.54 (m, 20H), 3.38 (t, *J* = 5.1 Hz, 2H), 2.38 (s, 3H)

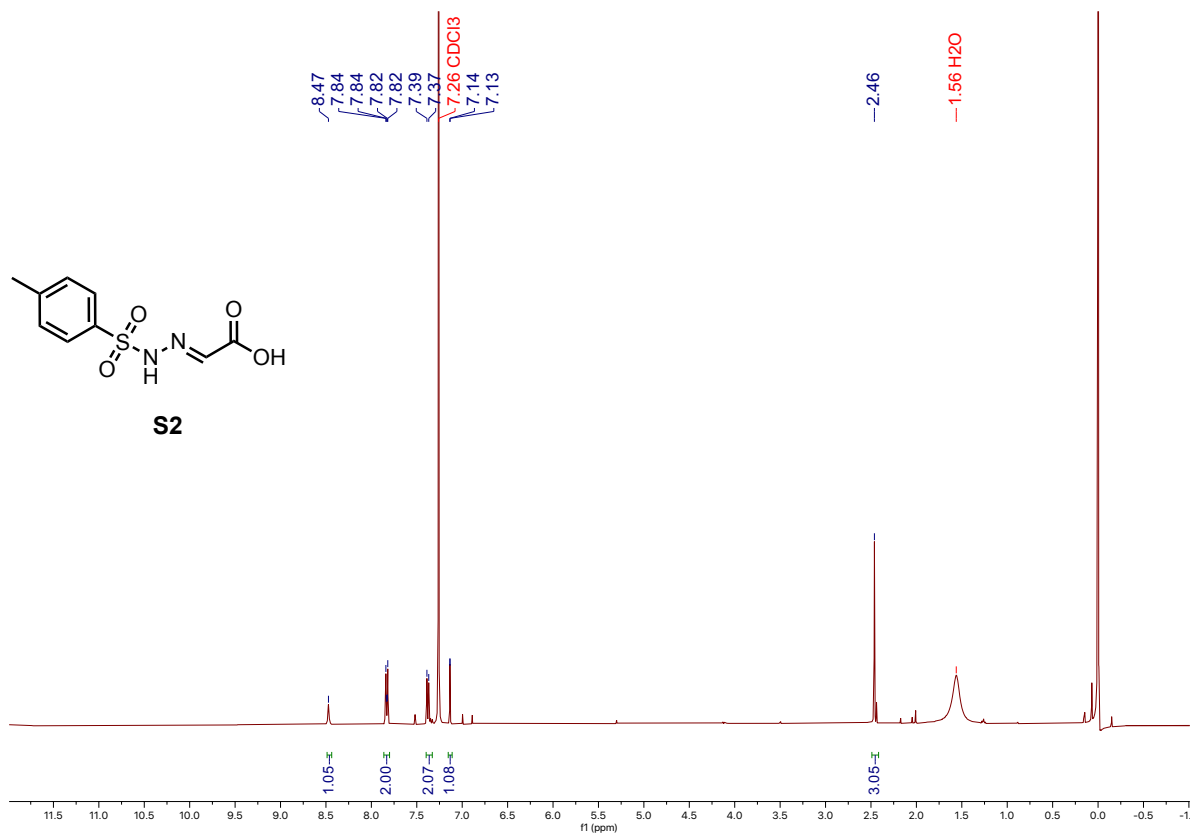
**<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>, δ):** 165.1, 137.6, 130.4, 127.5, 127.5, 123.3, 70.8, 70.8, 70.7, 70.7, 70.7, 70.6, 70.6, 70.3, 70.1, 70.1, 70.1, 50.8, 50.8, 39.9, 29.8, 21.2

*Note: The diazo carbon (C=N=N) signal is not observed as mentioned in General Information (page S6).<sup>10</sup>*

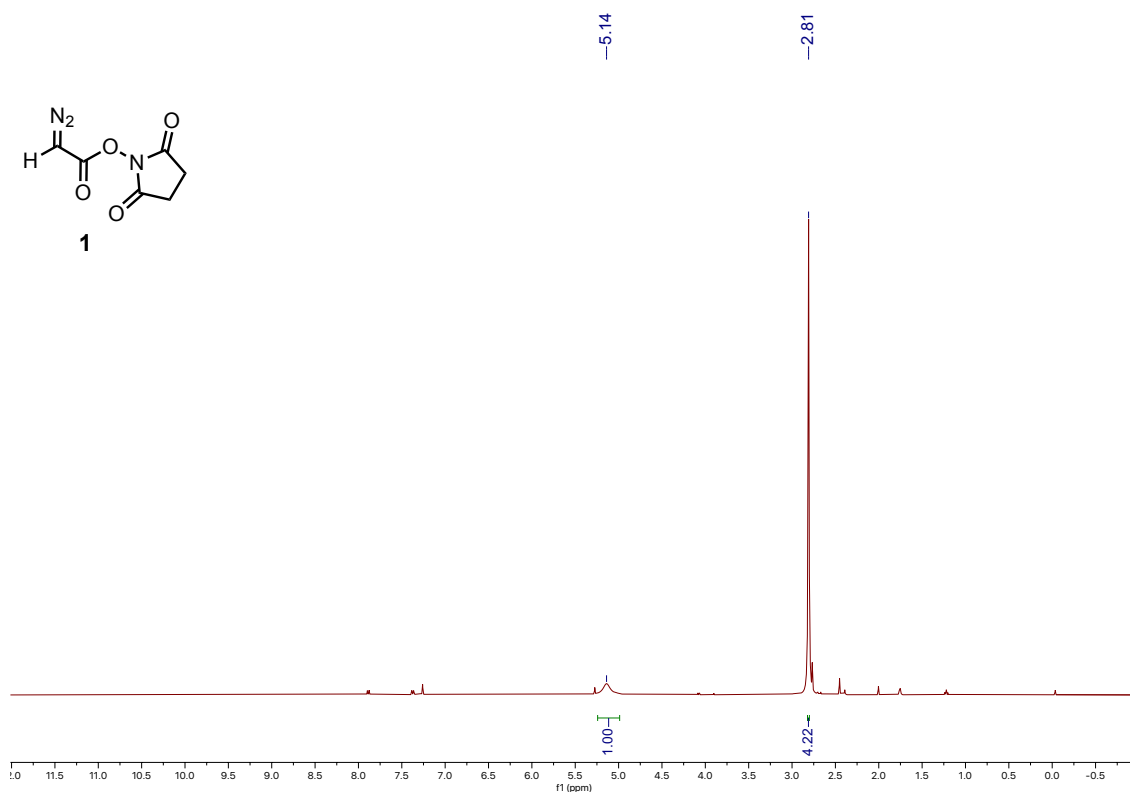
**HRMS (ESI-TOF):** calc'd for C<sub>19</sub>H<sub>29</sub> N<sub>6</sub>O<sub>5</sub> [M + H]<sup>+</sup>, 421.2194; found, 421.2195

**IR (neat):** 2865, 2854, 2075 (diazo), 2056, 1639, 1510, 1455, 1348, 815, 610, 499 cm<sup>-1</sup>

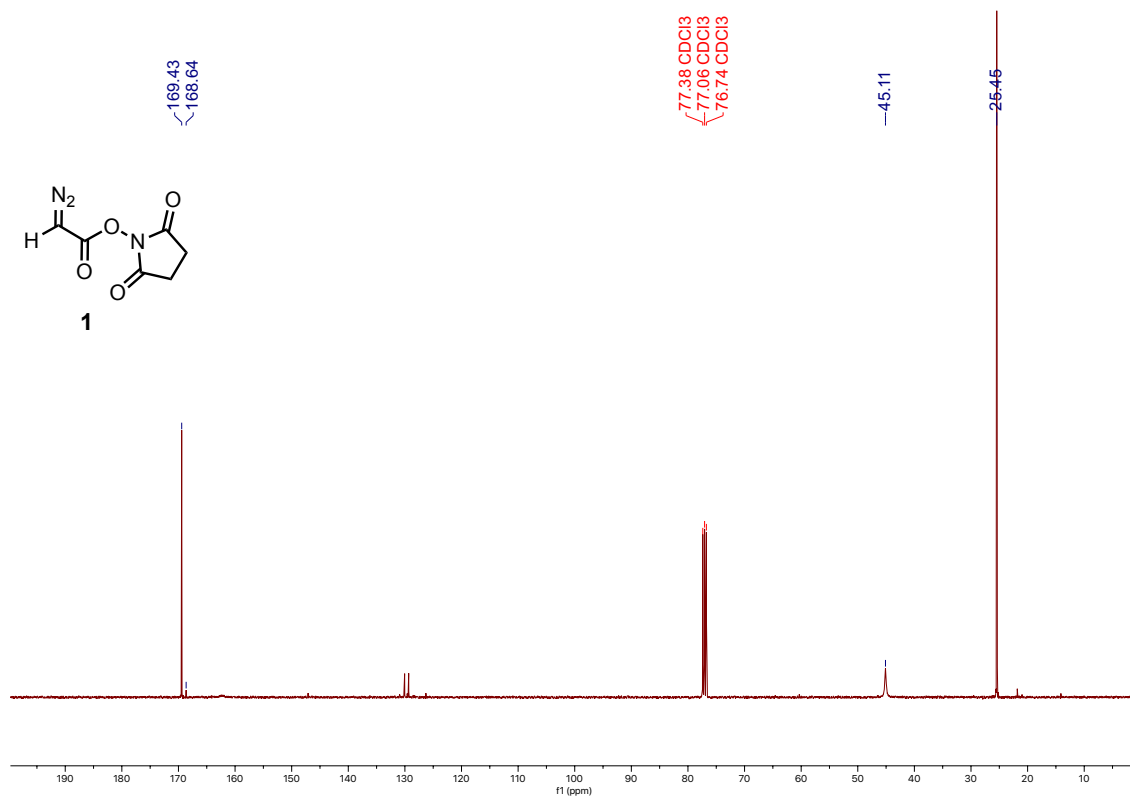


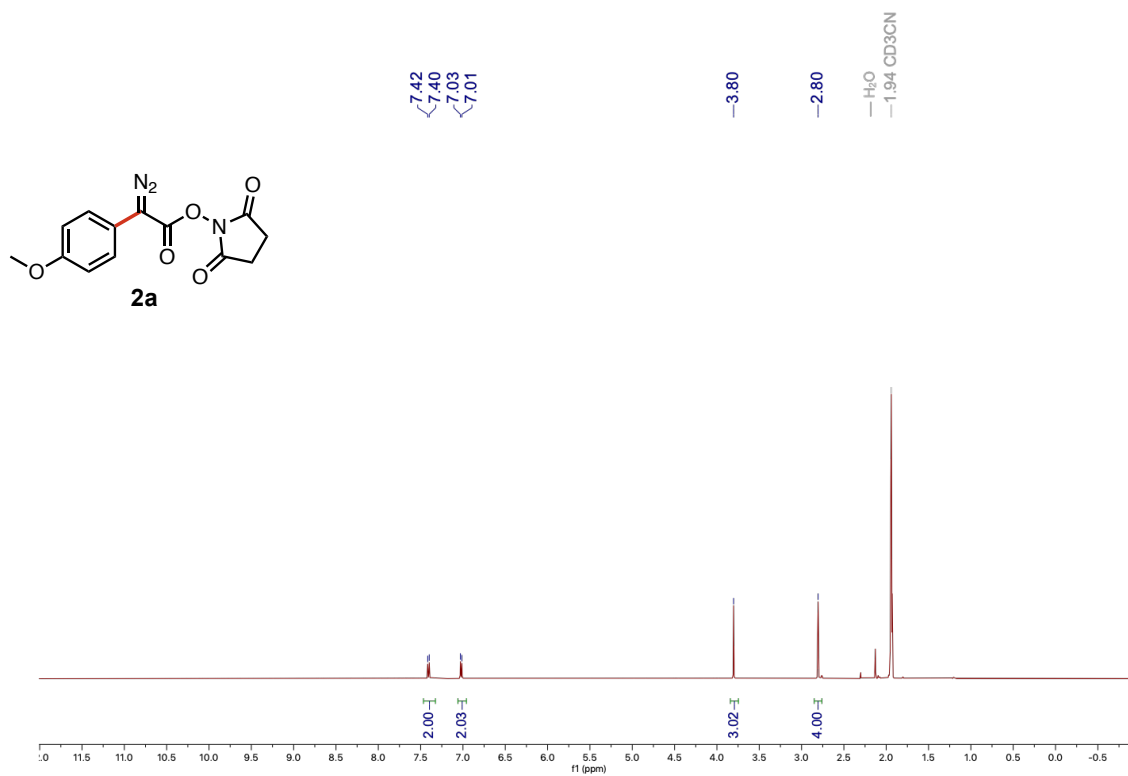
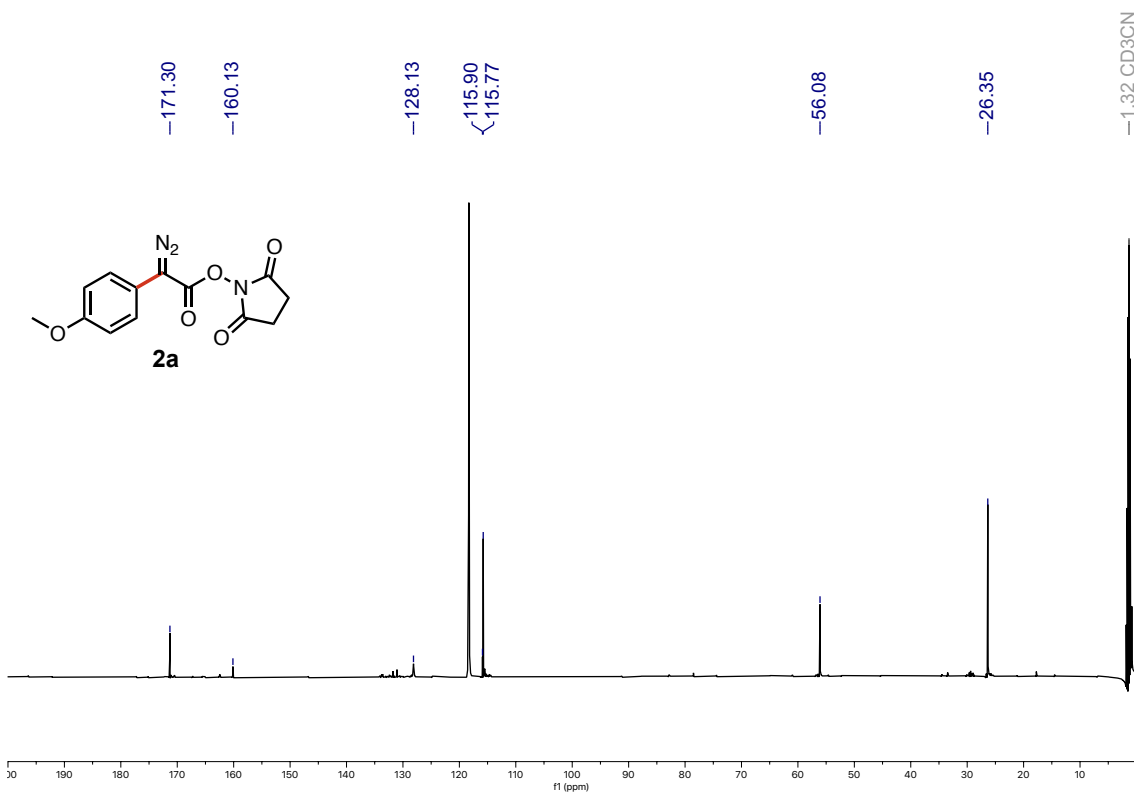
XV.  $^1\text{H}$ ,  $^{13}\text{C}$ , and  $^{19}\text{F}$  NMR Spectra $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$  containing 0.03% v/v TMS) of **S2**

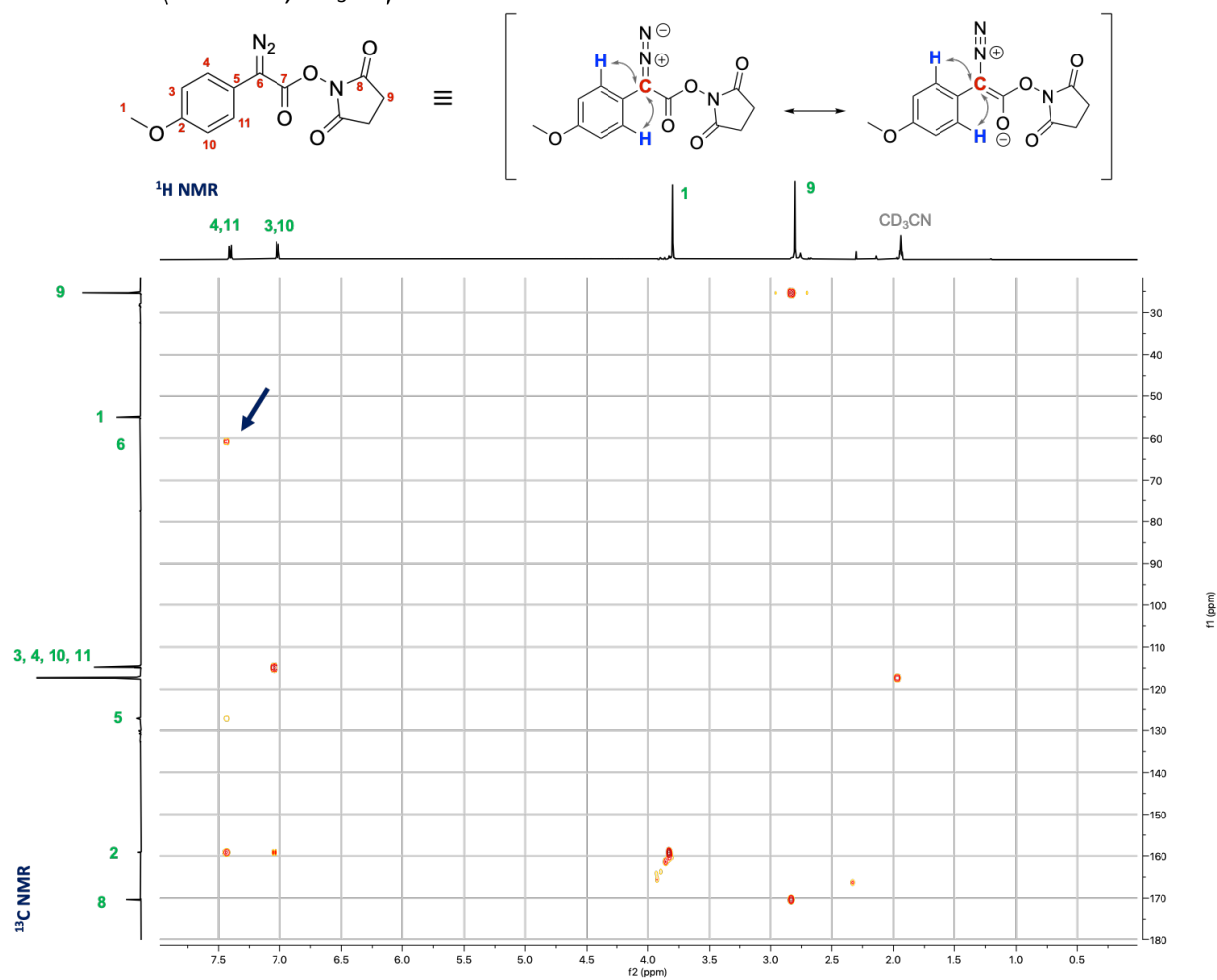
$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$  containing 0.03% v/v TMS) of **1**



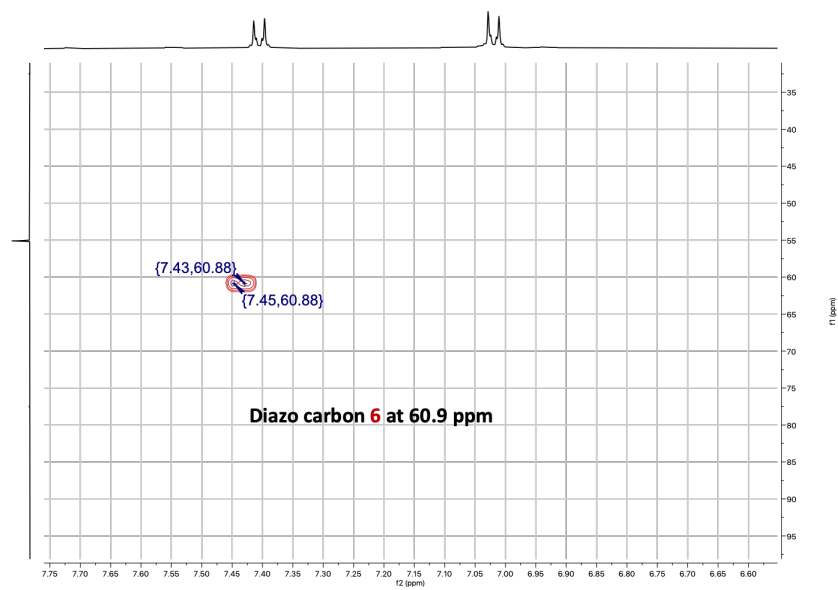
$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$  containing 0.03% v/v TMS) of **1**



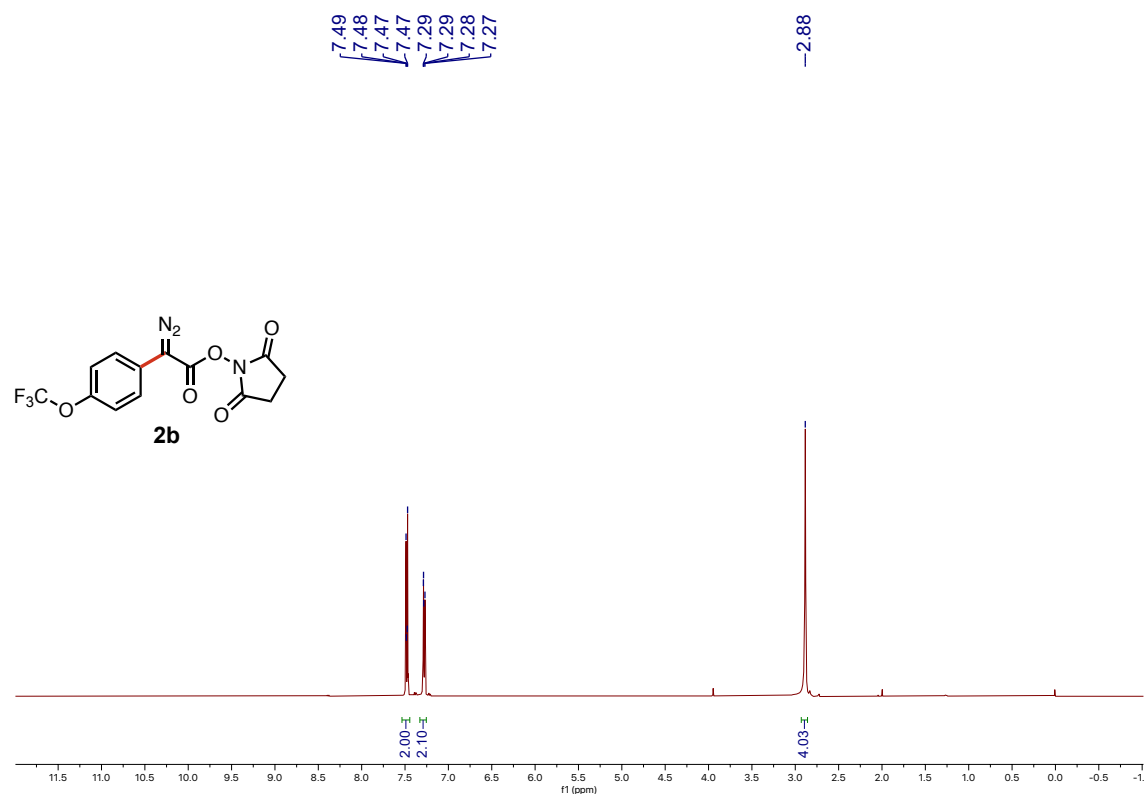
$^1\text{H}$  NMR (500 MHz,  $\text{CD}_3\text{CN}$ ) of **2a** $^{13}\text{C}$  NMR (126 MHz,  $\text{CD}_3\text{CN}$ ) of **2a**

HMBC NMR (500 MHz, CD<sub>3</sub>CN) of **2a**

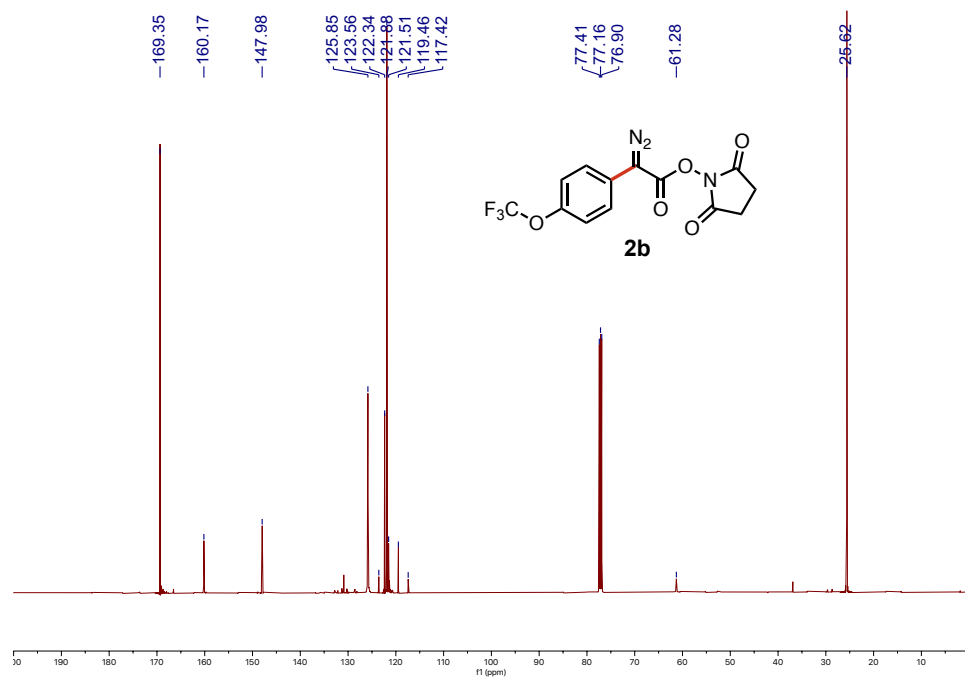
Zoom in:



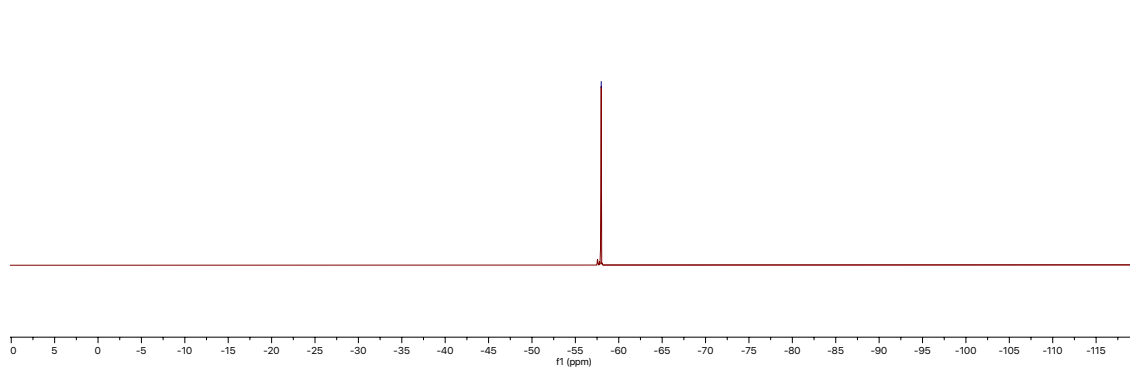
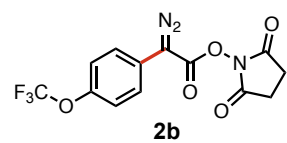
$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$  containing 0.03% v/v TMS) of **2b**

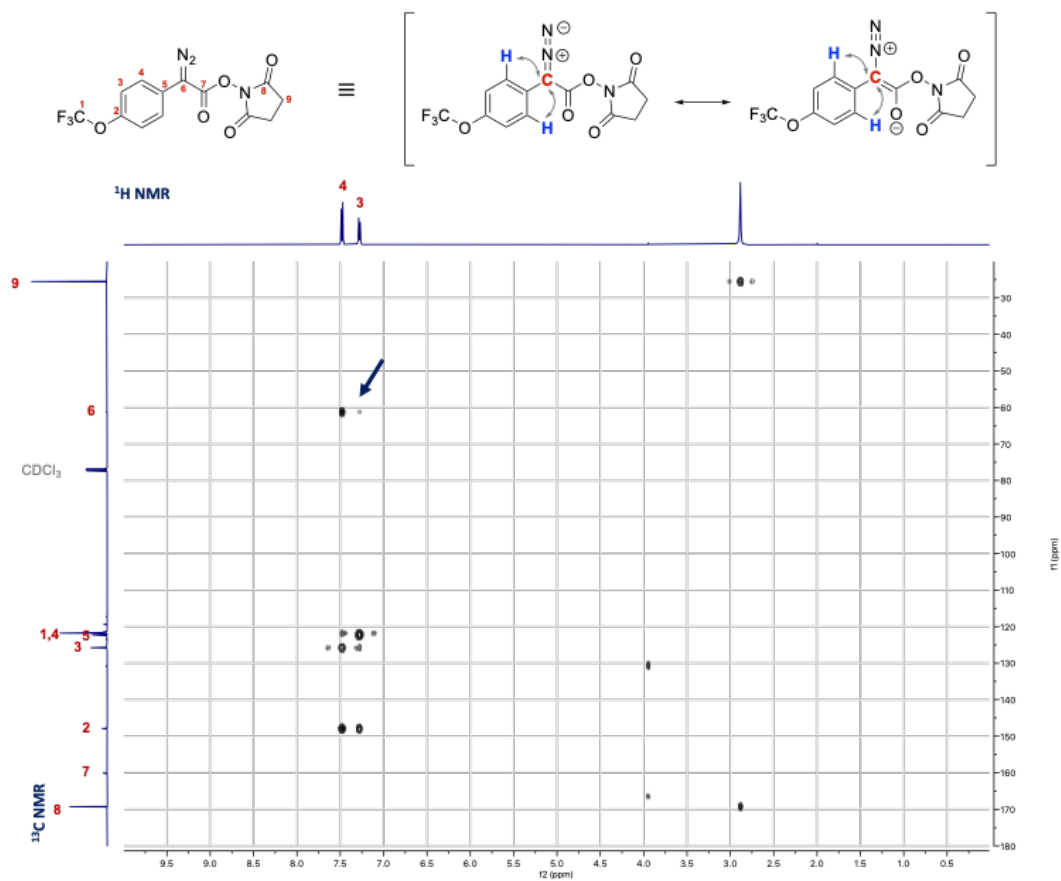


$^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$  containing 0.03% v/v TMS) of **2b** (taken at relaxation time D1 = 1.5 sec)

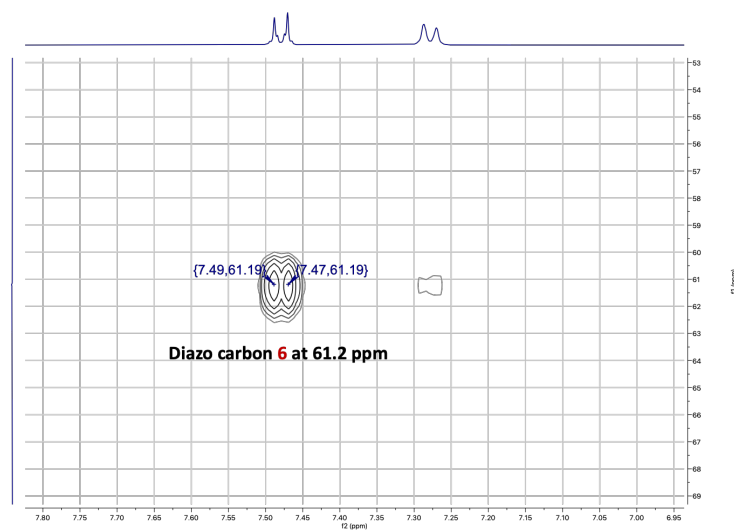


$^{19}\text{F}$  NMR (471 MHz,  $\text{CDCl}_3$  containing 0.03% v/v TMS) of **2b**



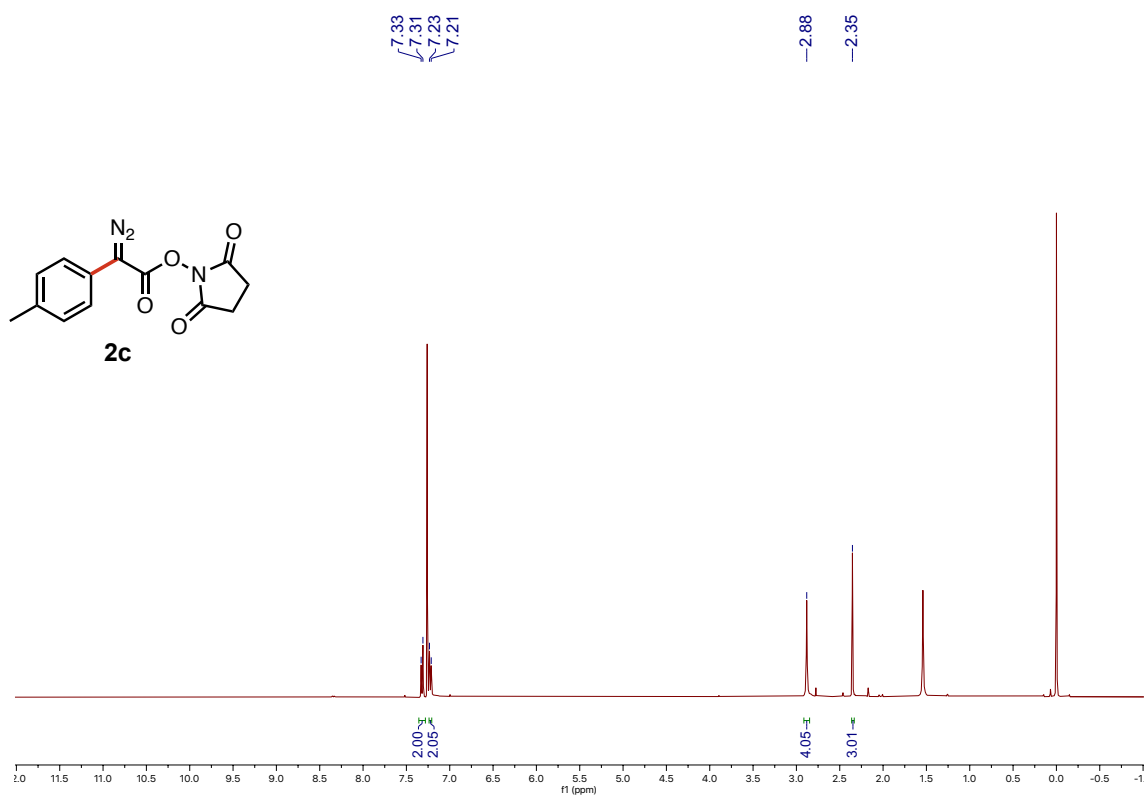
HMBC NMR (500 MHz, CDCl<sub>3</sub> containing 0.03% v/v TMS) of **2b**

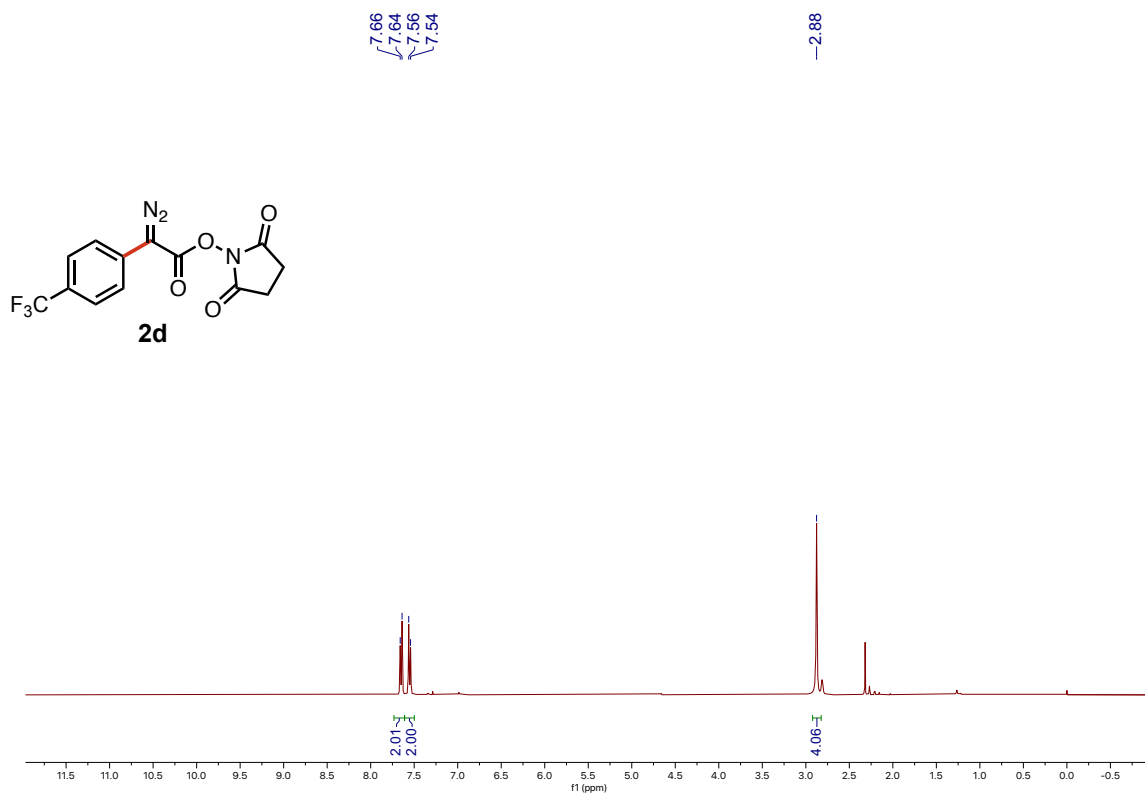
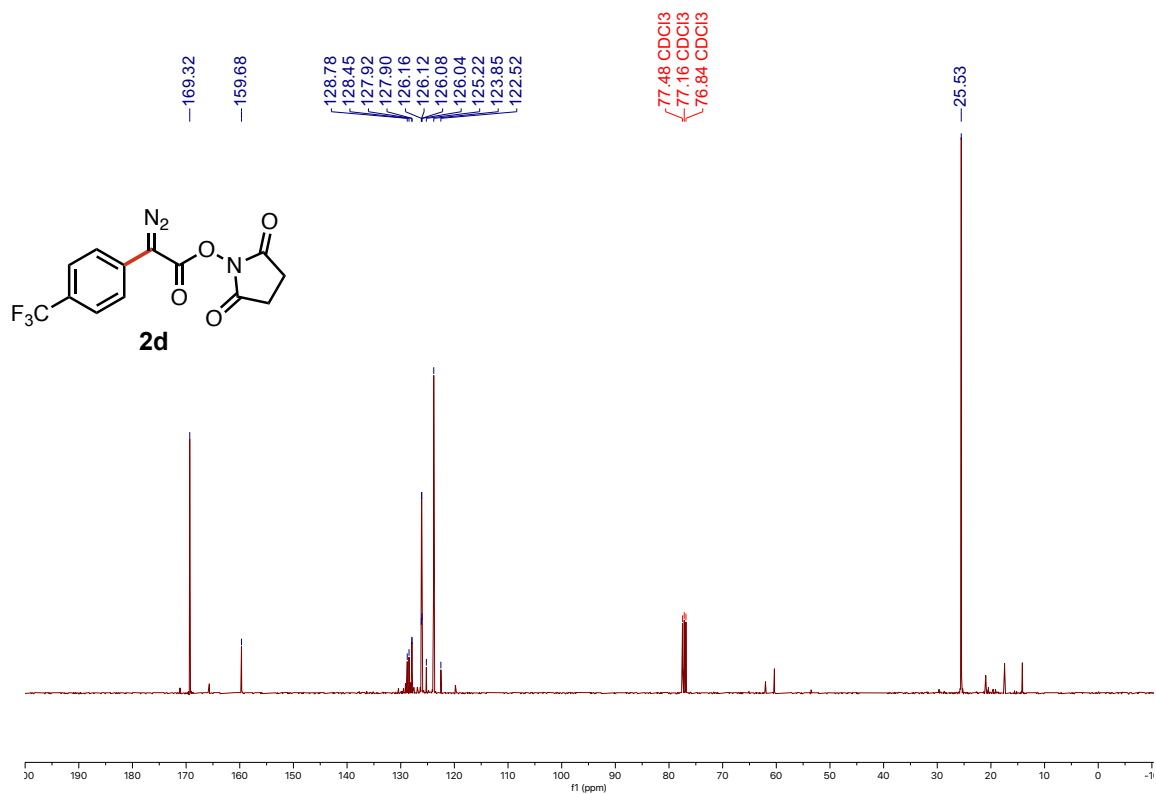
Zoom in:



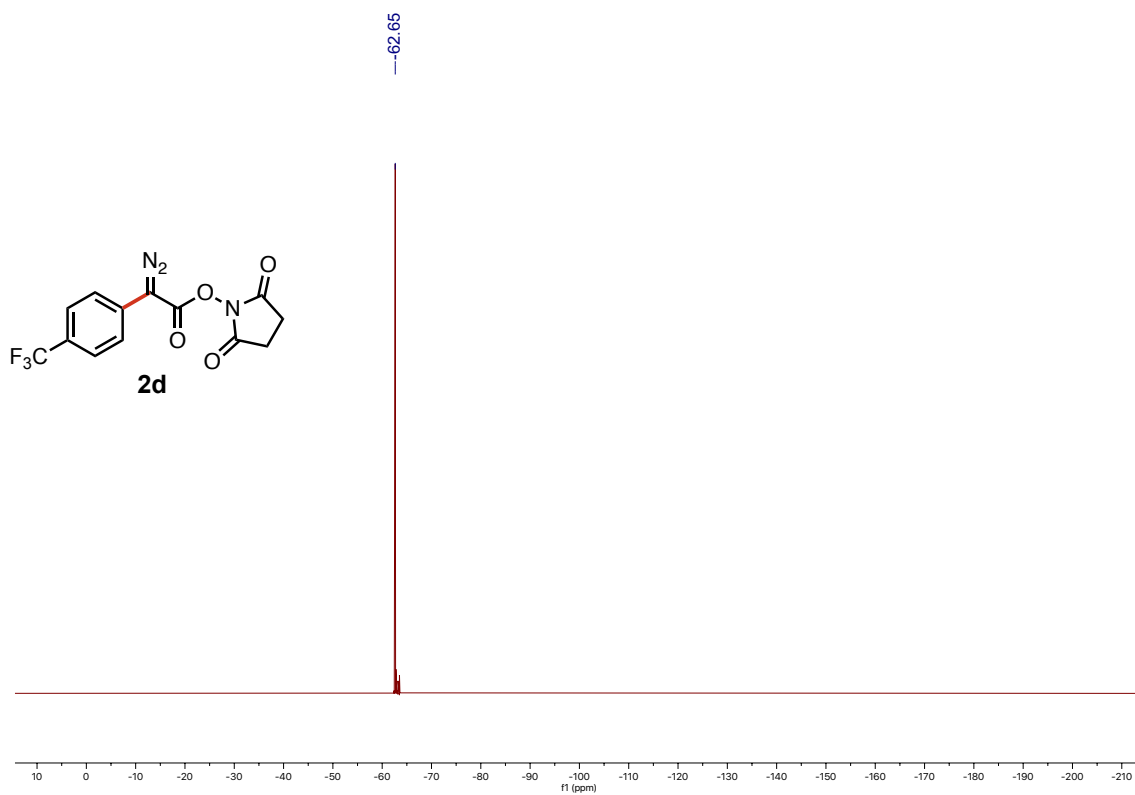


$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$  containing 0.03% v/v TMS) of **2c**

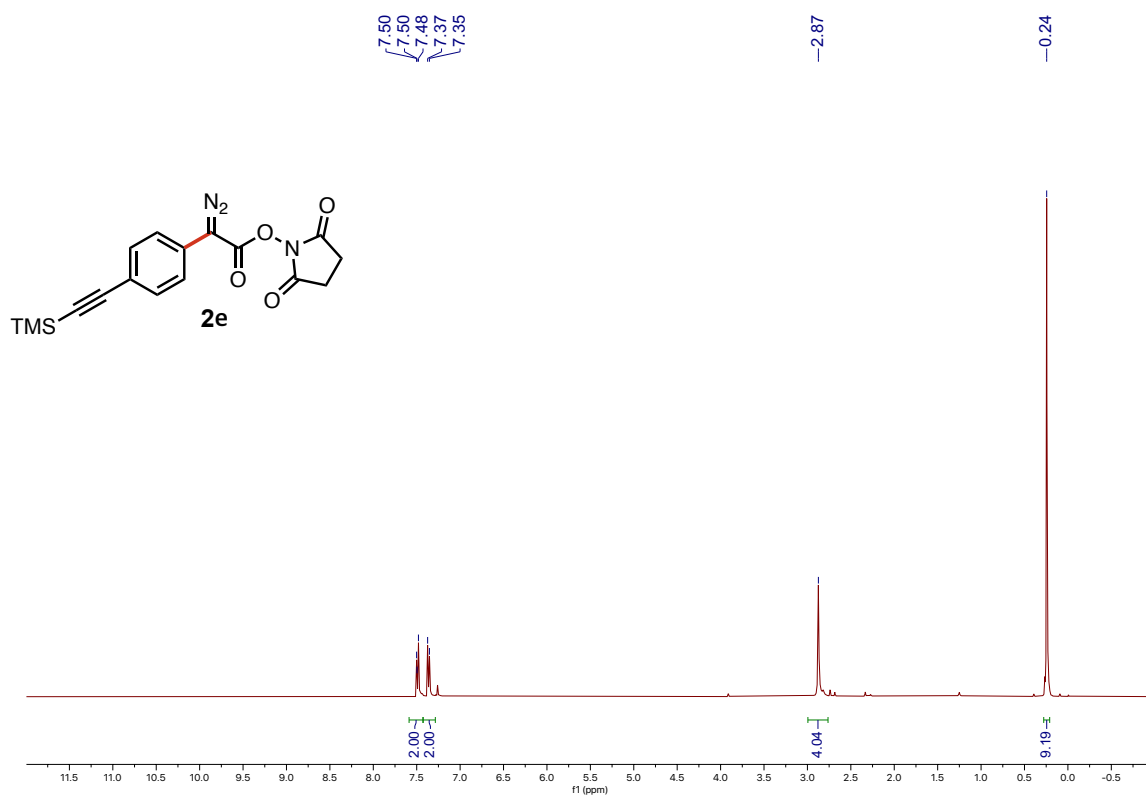


$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$  containing 0.03% v/v TMS) of **2d** $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$  containing 0.03% v/v TMS) of **2d**

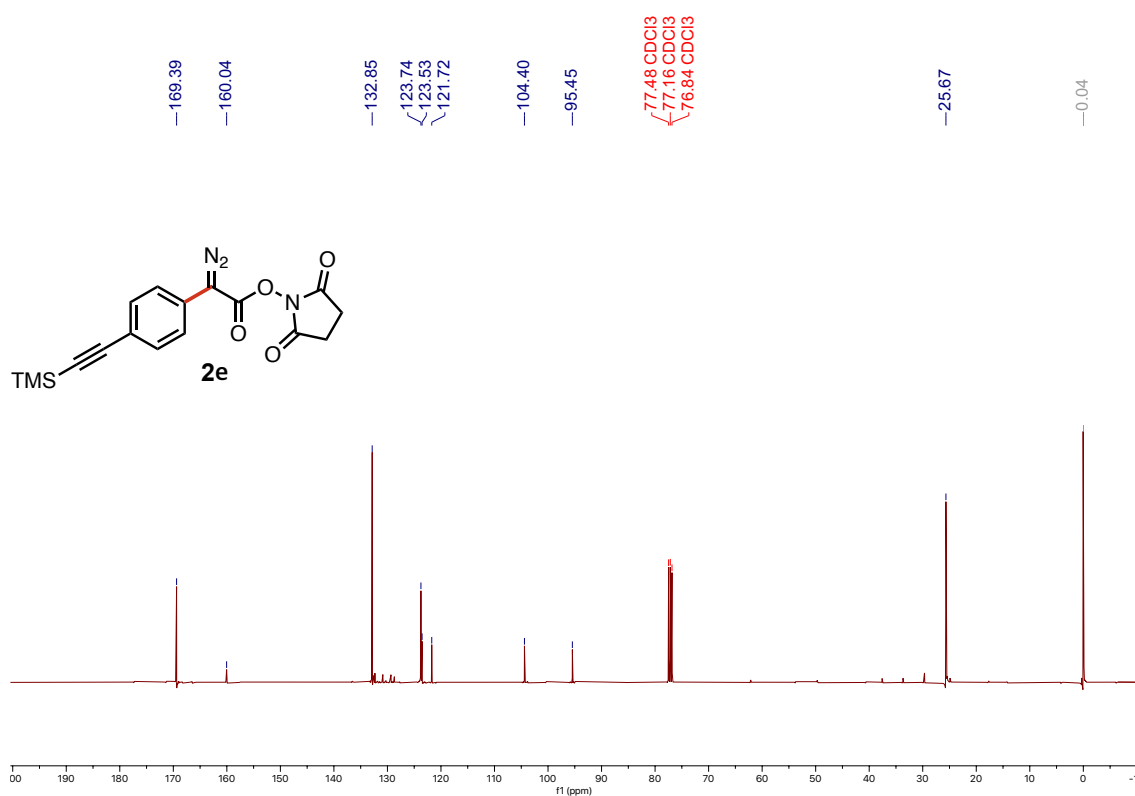
$^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$  containing 0.03% v/v TMS) of **2d**

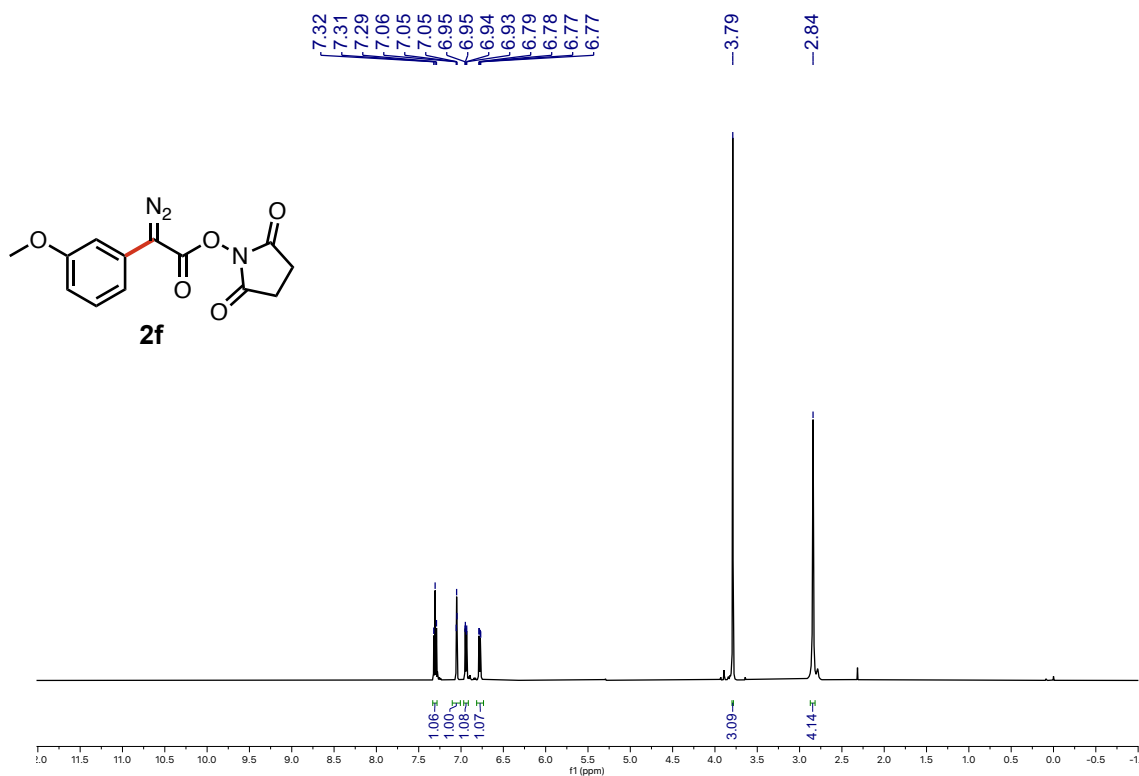
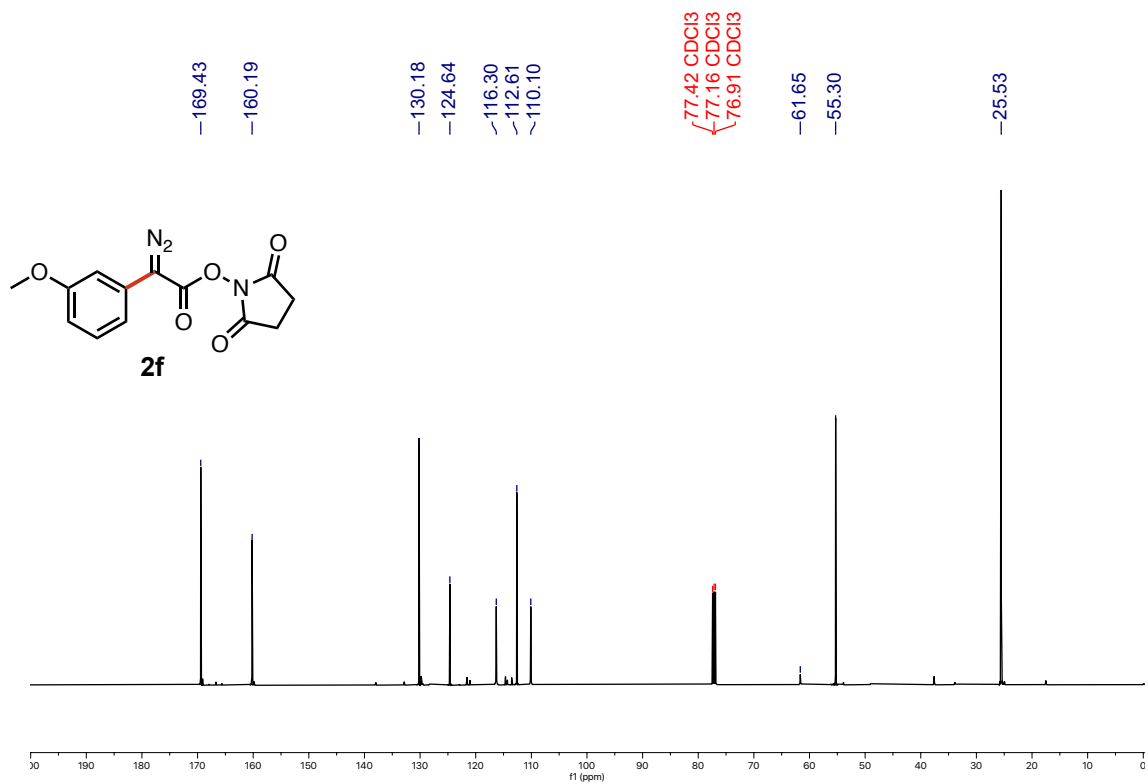


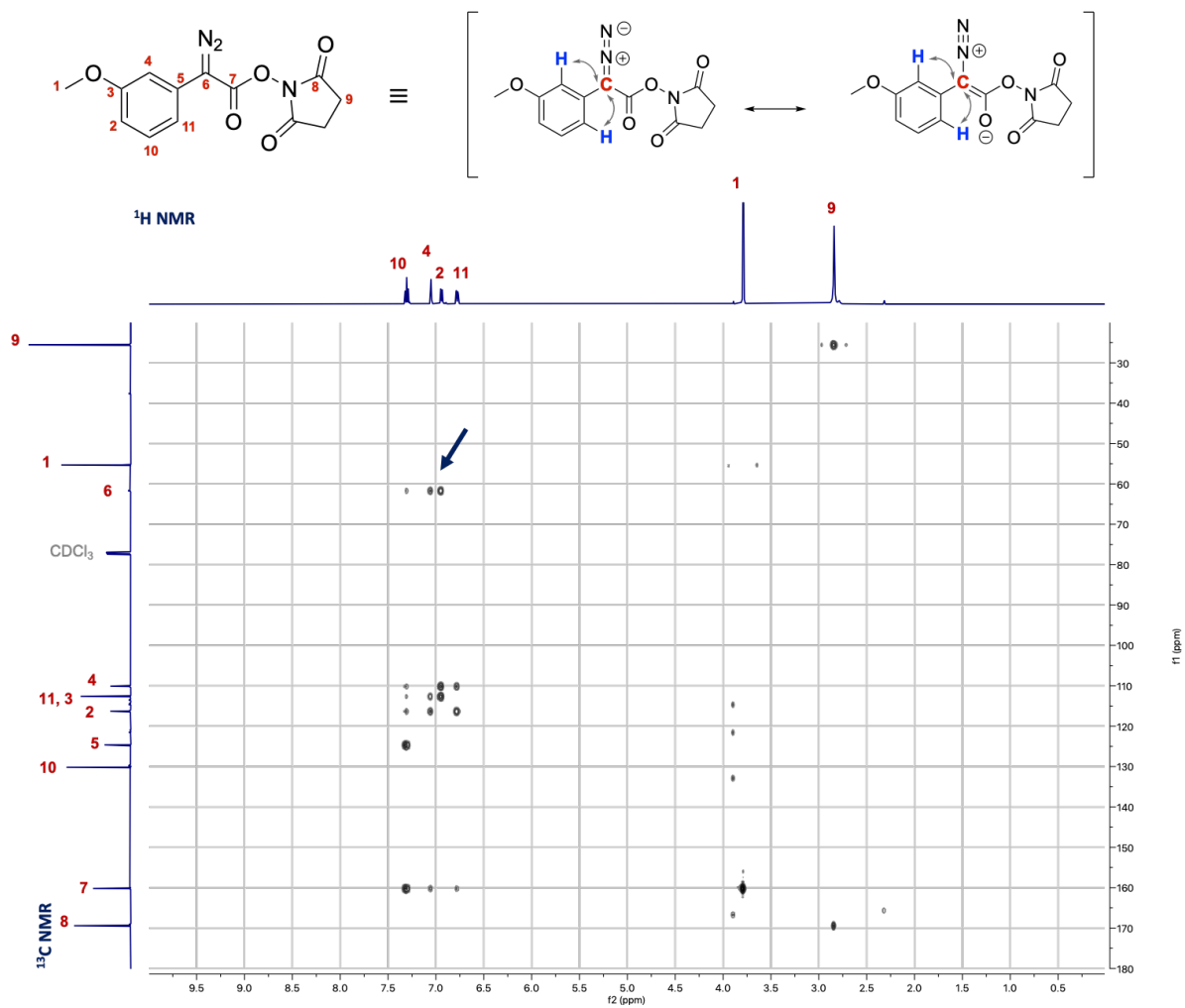
$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$  containing 0.03% v/v TMS) of **2e**



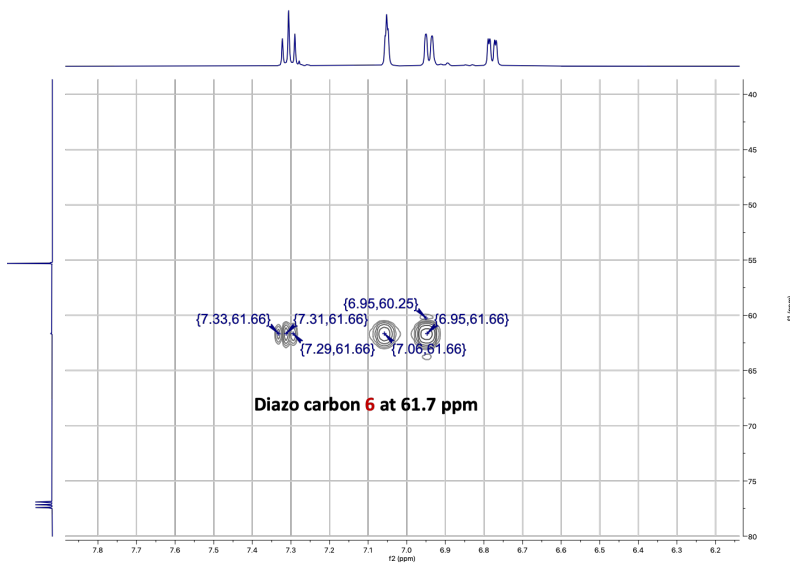
$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$  containing 0.03% v/v TMS) of **2e**

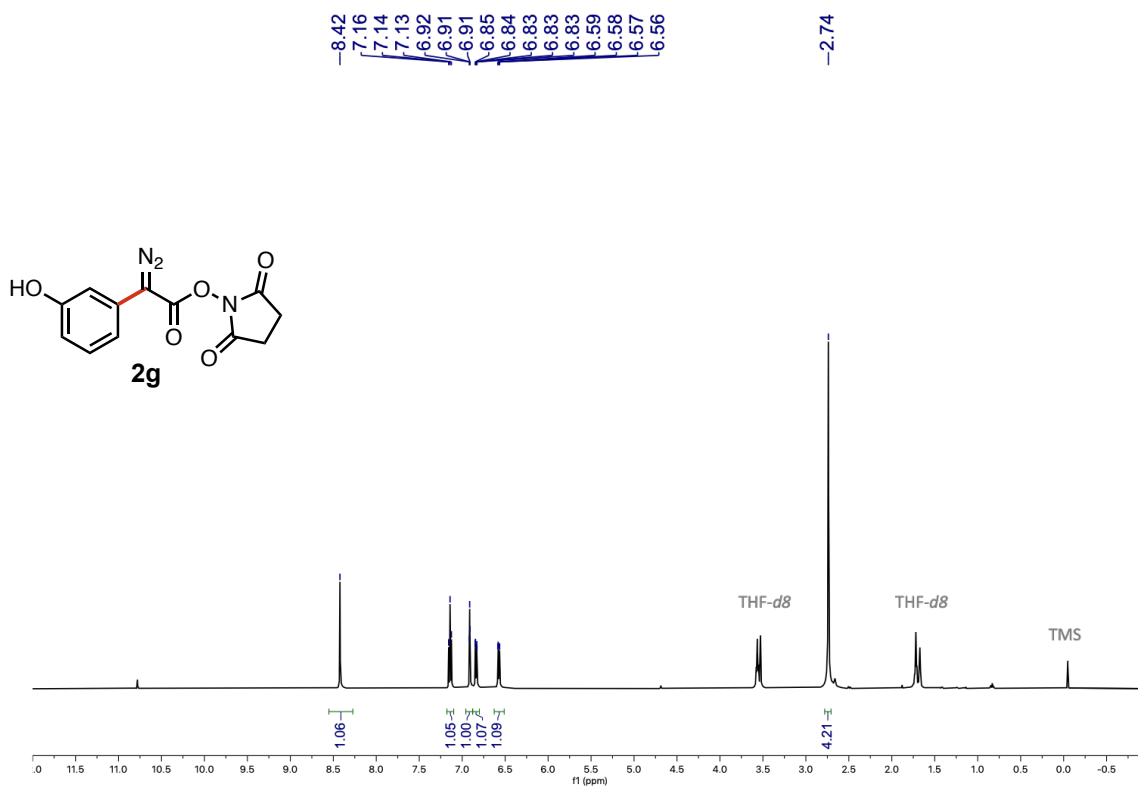
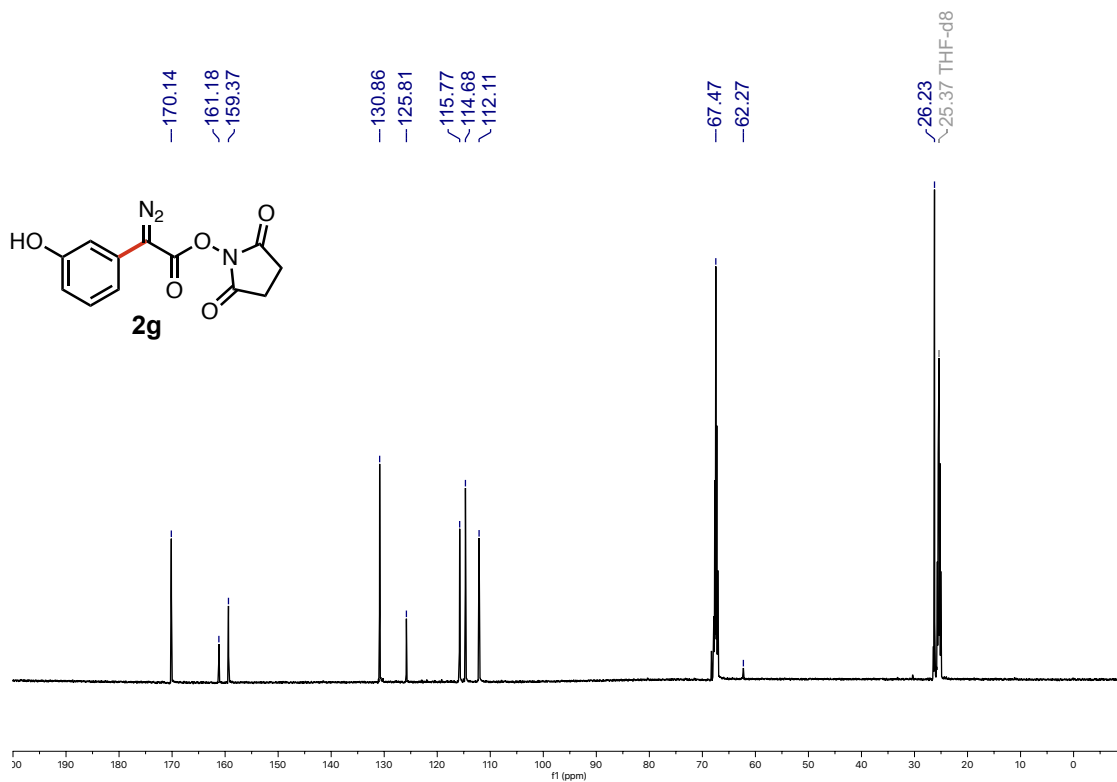


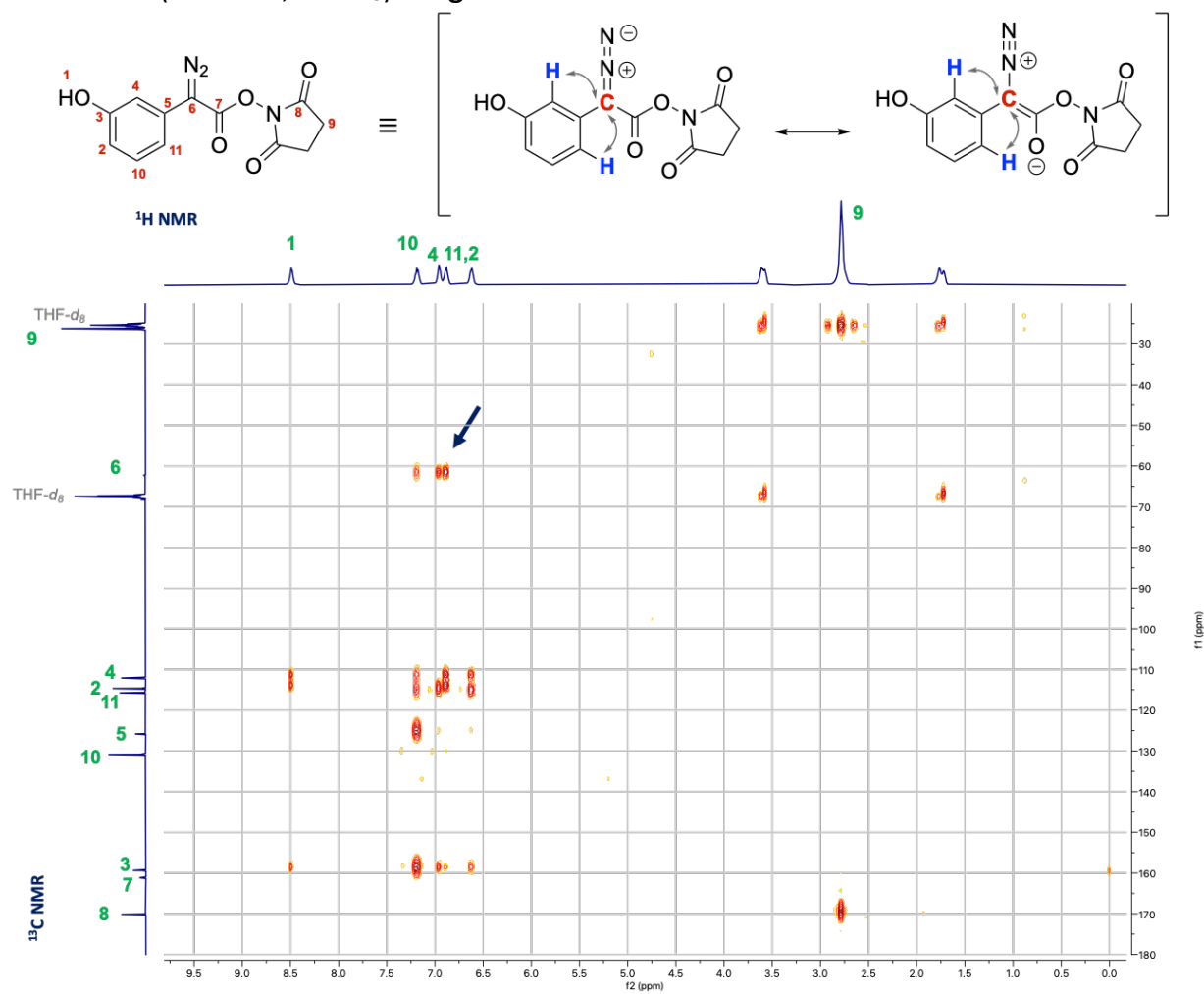
$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$  containing 0.03% v/v TMS) of **2f** $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$  containing 0.03% v/v TMS) of **2f**

HMBC NMR (500 MHz, CDCl<sub>3</sub> containing 0.03% v/v TMS) of **2f**

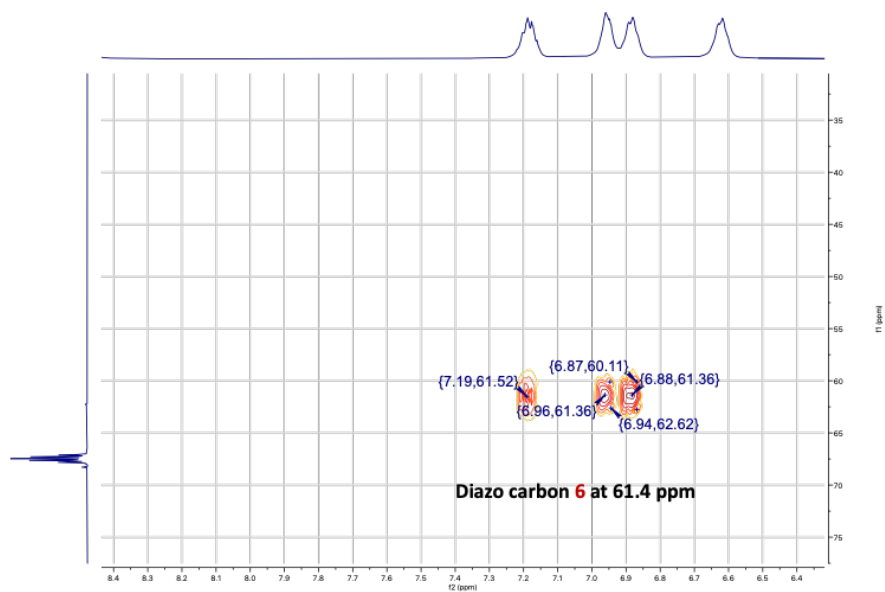
Zoom in:



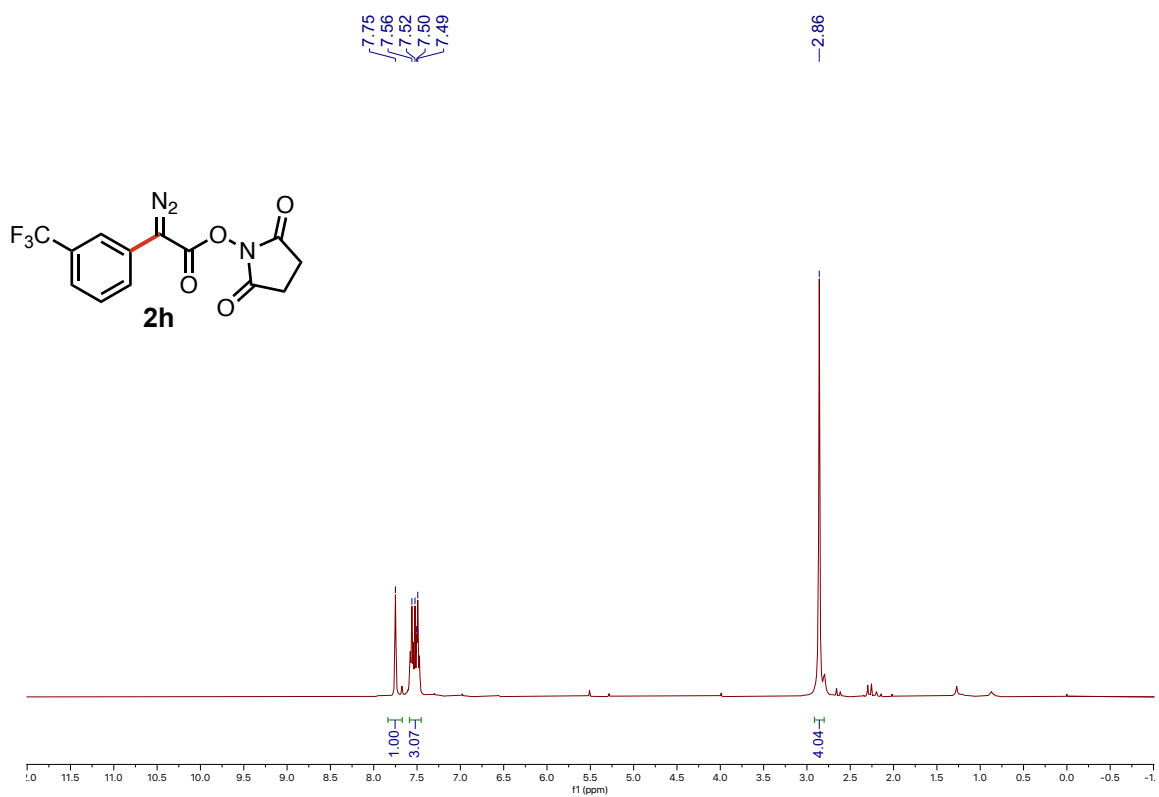
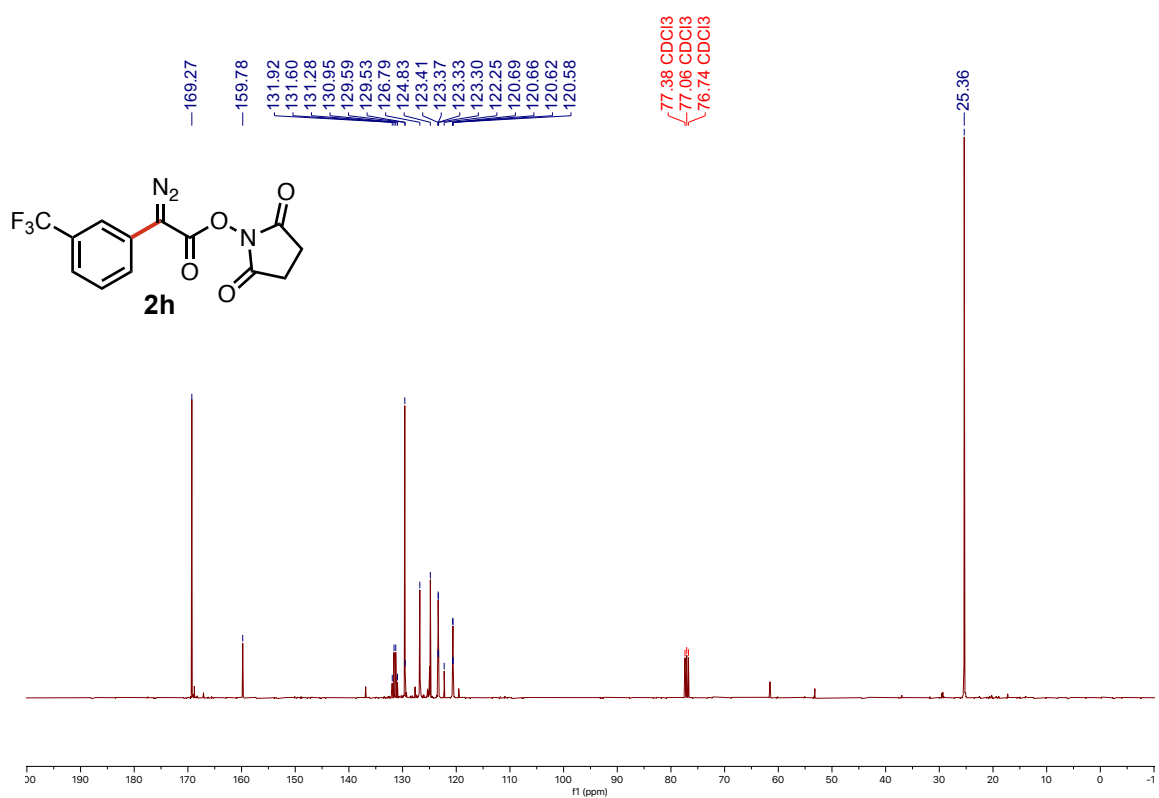
$^1\text{H}$  NMR (500 MHz, THF containing 0.03% v/v TMS) of **2g** $^{13}\text{C}$  NMR (101 MHz, CDCl<sub>3</sub> containing 0.03% v/v TMS) of **2g**

HMBC NMR (500 MHz, THF- $d_8$ ) of **2g**

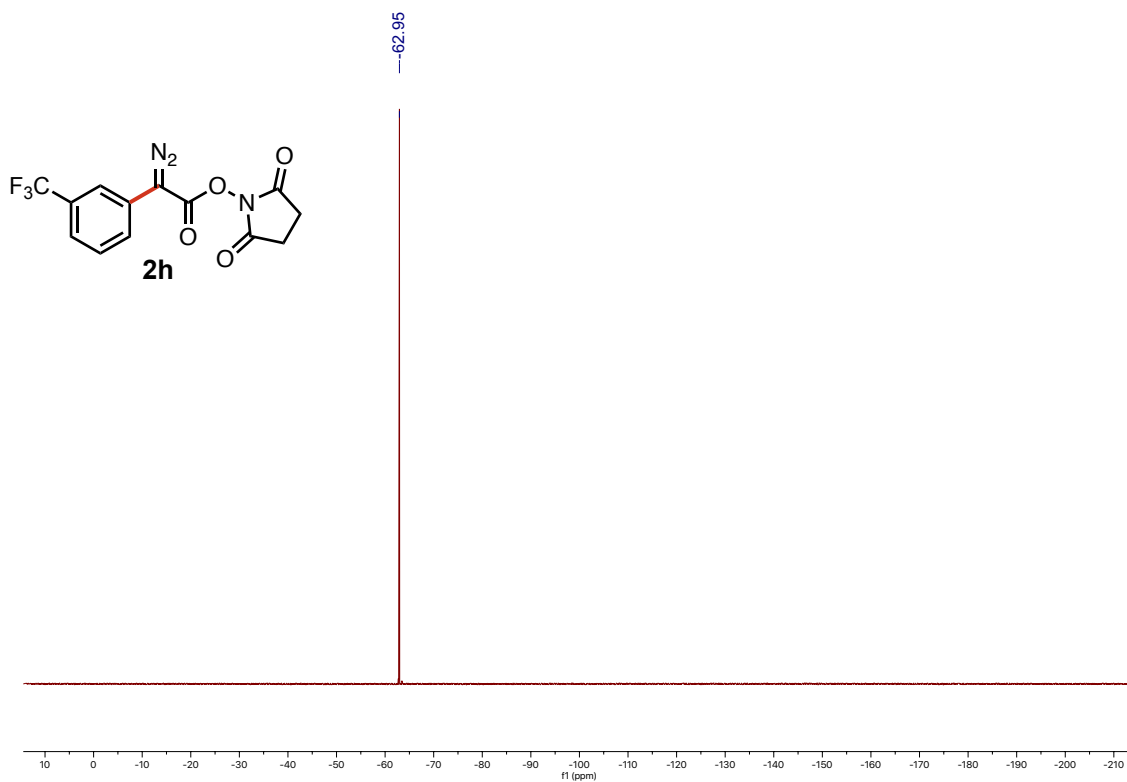
Zoom in:



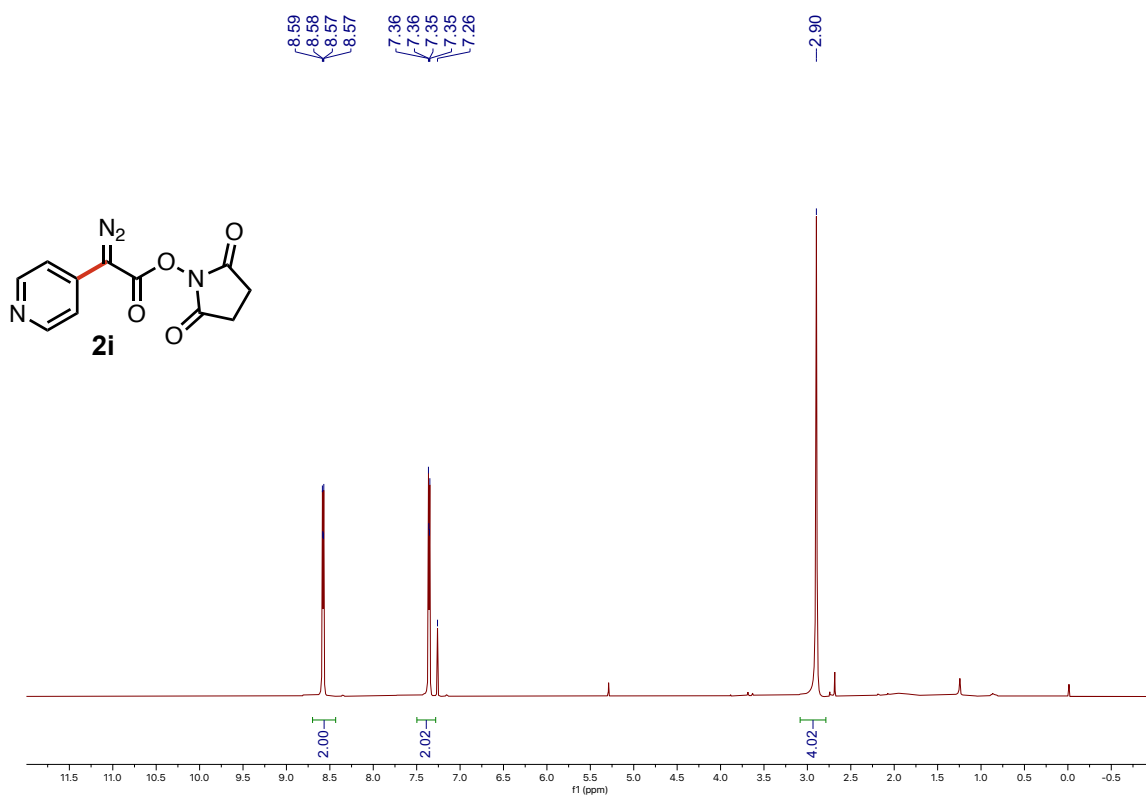


$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$  containing 0.03% v/v TMS) of **2h** $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$  containing 0.03% v/v TMS) of **2h**

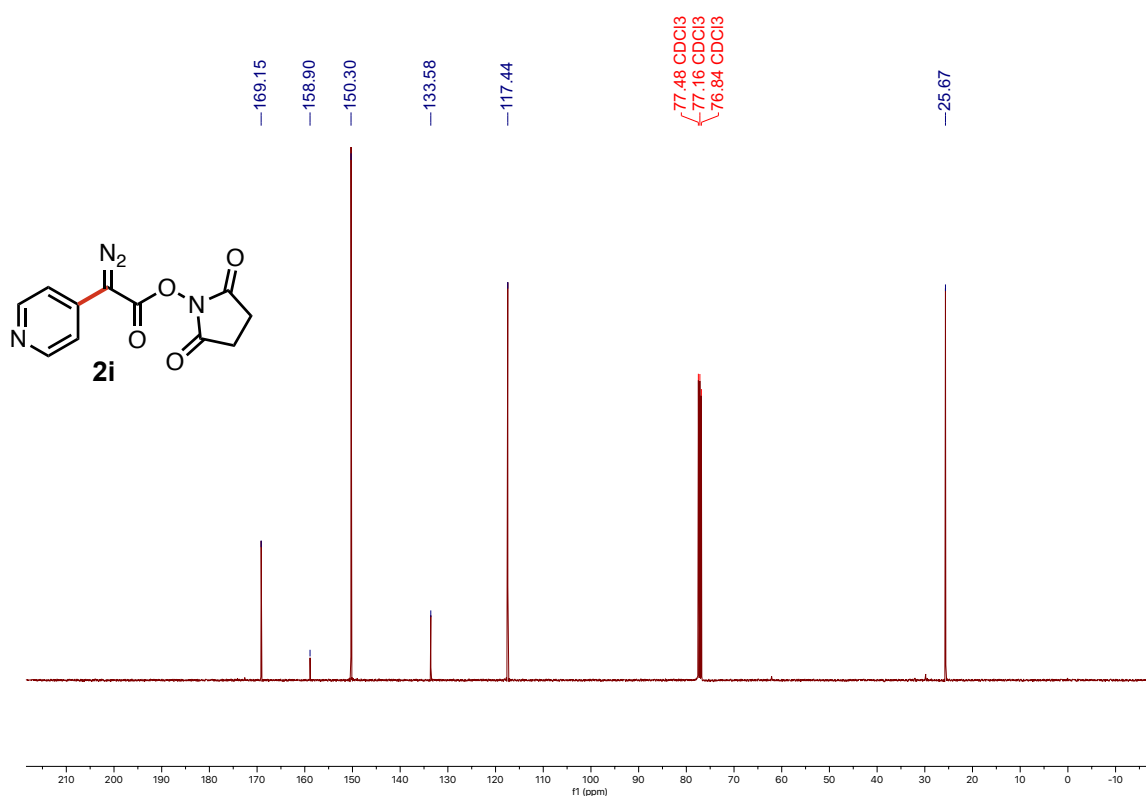
$^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$  containing 0.03% v/v TMS) of **2h**

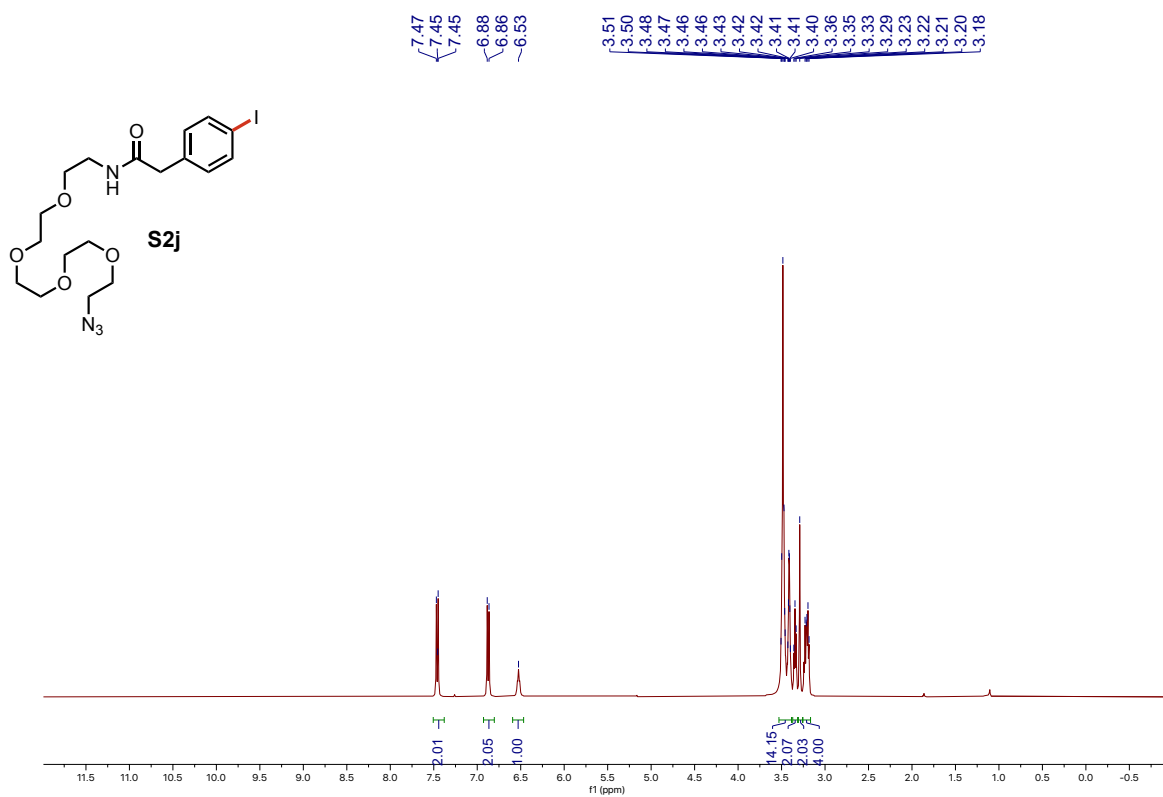
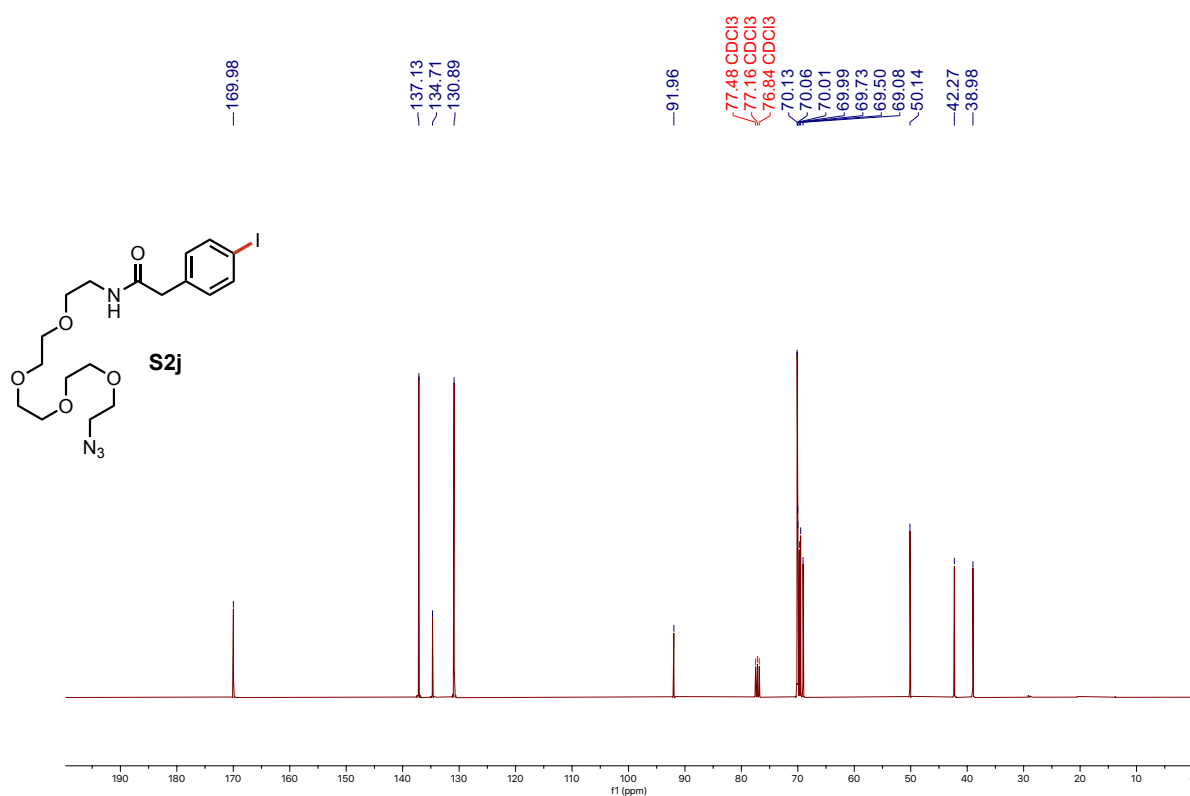


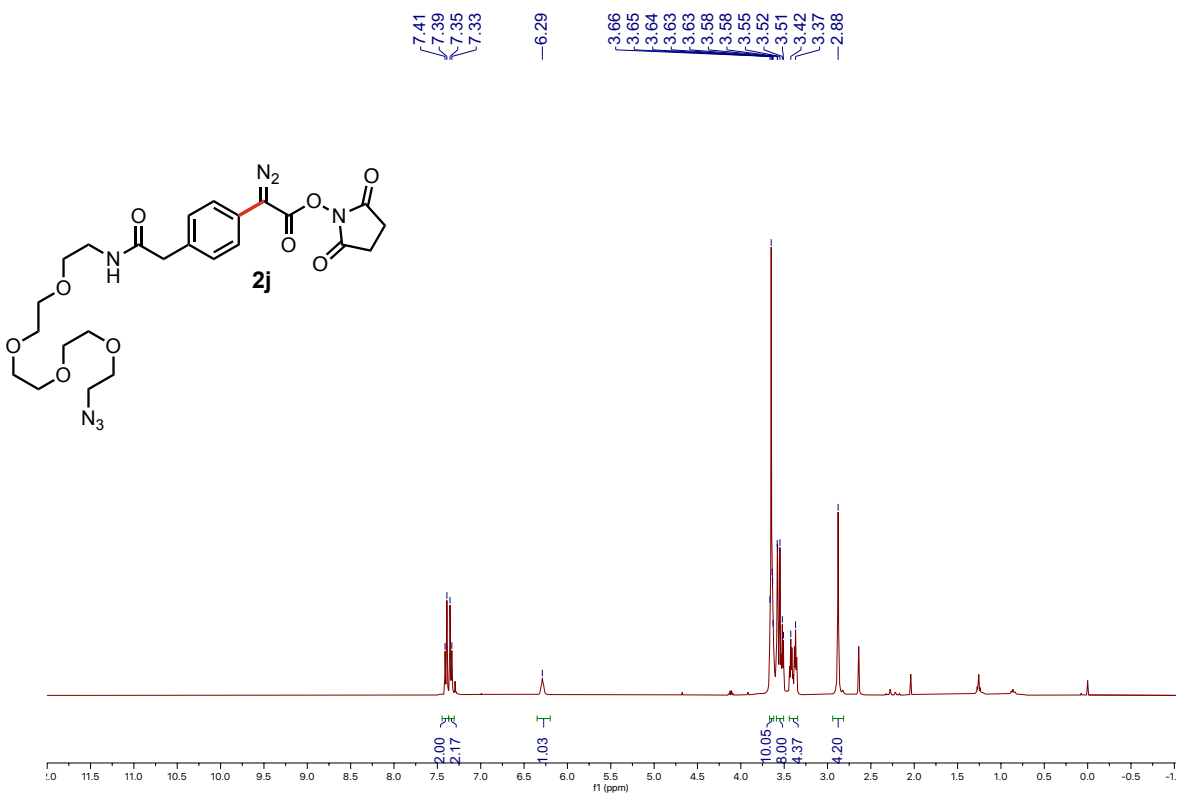
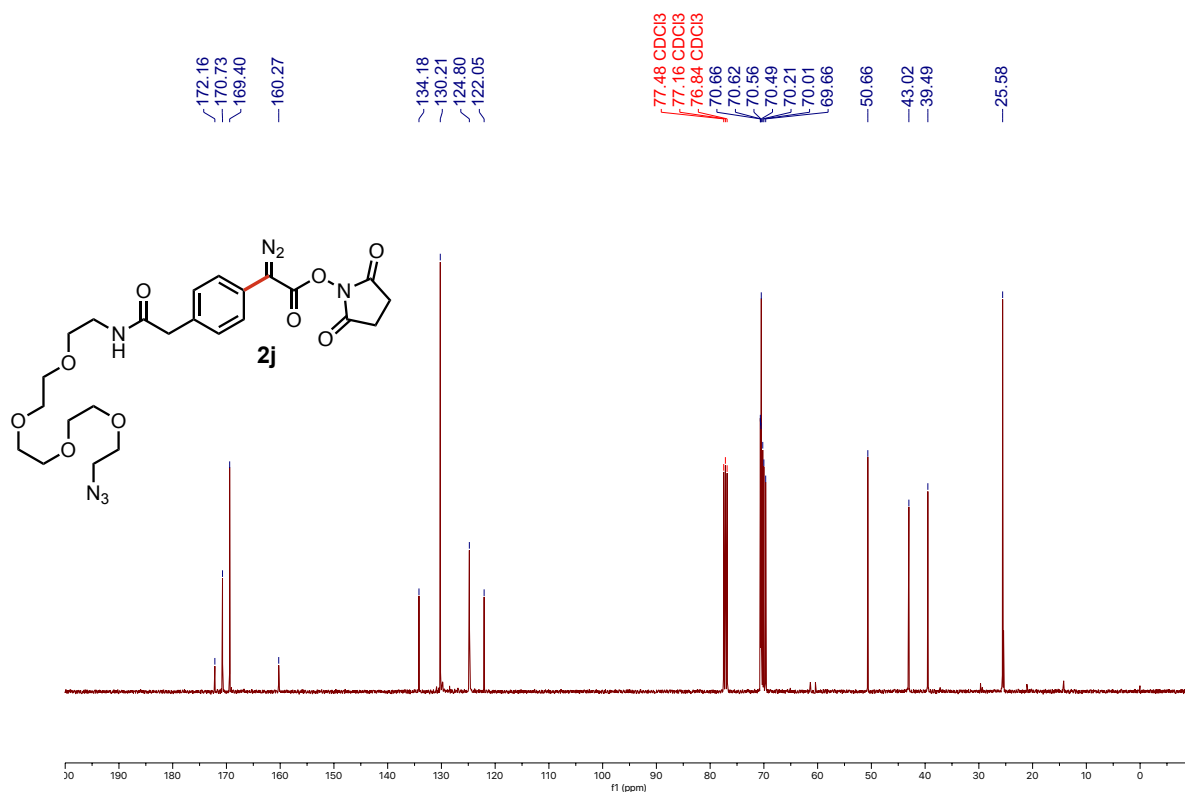
$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$  containing 0.03% v/v TMS) of **2i**



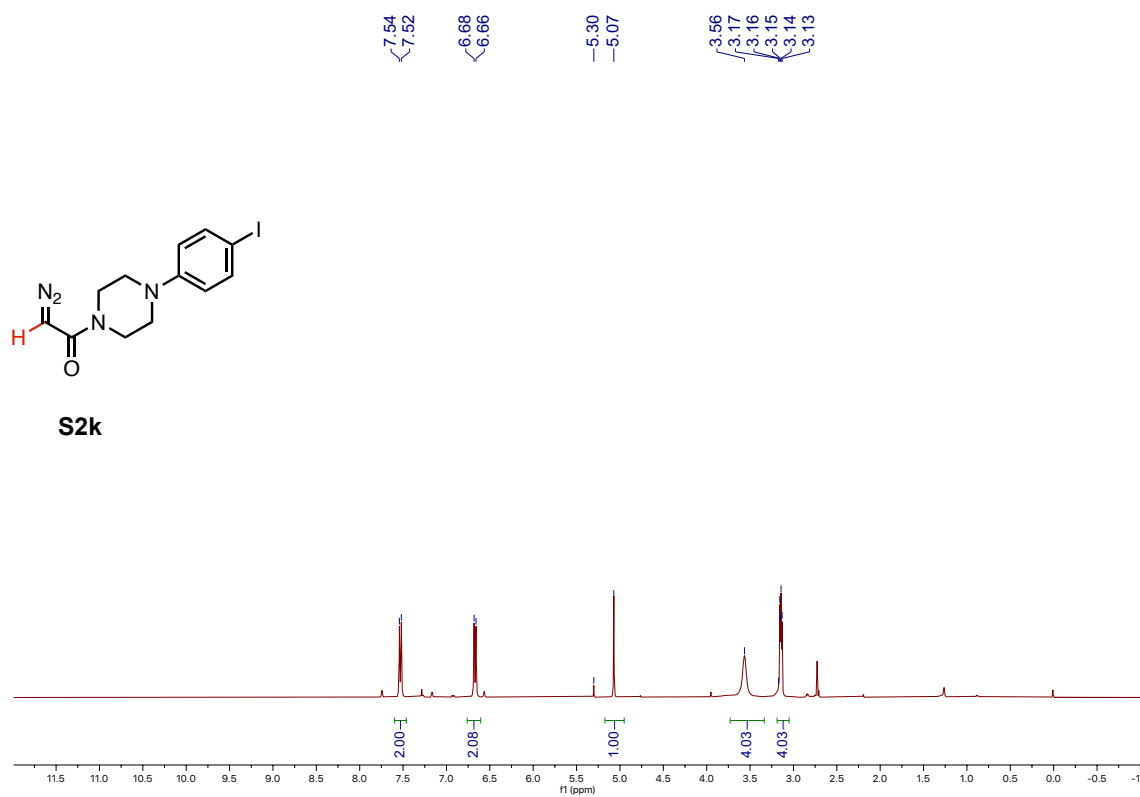
$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$  containing 0.03% v/v TMS) of **2i**



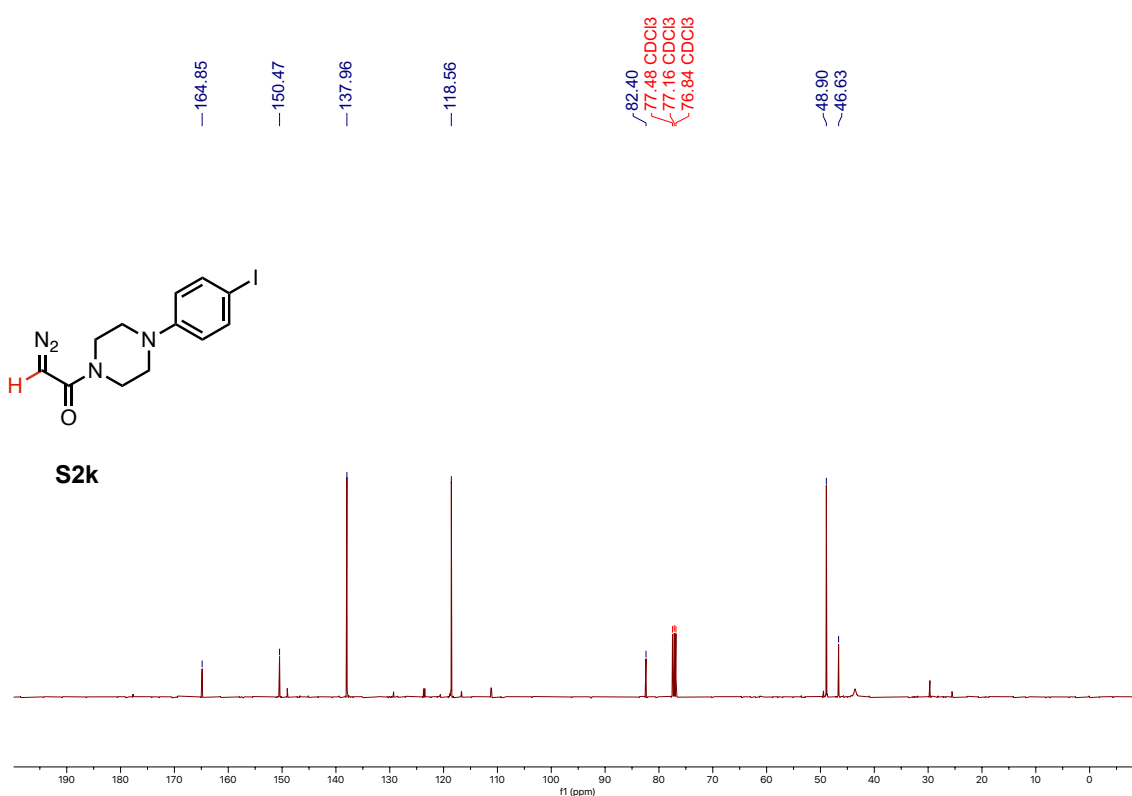
$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$  containing 0.03% v/v TMS) of **S2j** $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$  containing 0.03% v/v TMS) of **S2j**

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub> containing 0.03% v/v TMS) of **2j**<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub> containing 0.03% v/v TMS) of **2j**

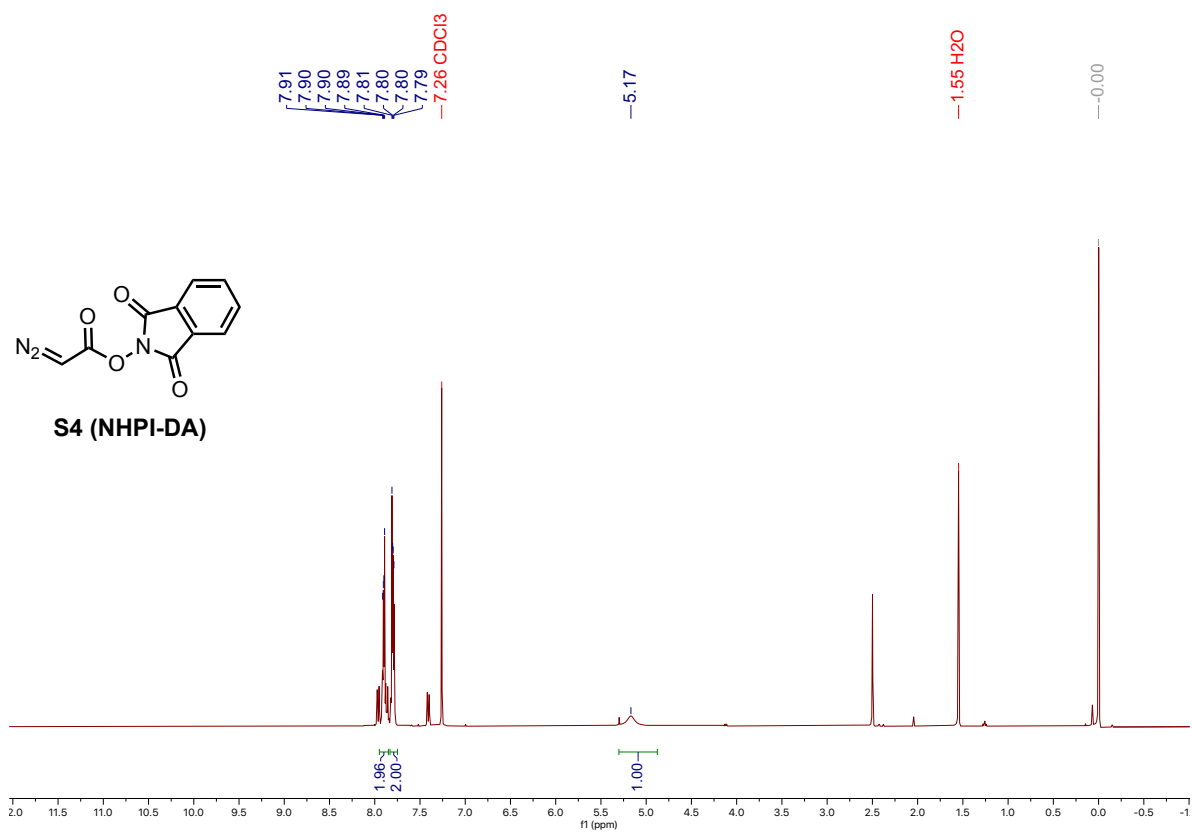
$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$  containing 0.03% v/v TMS) of **S2k**

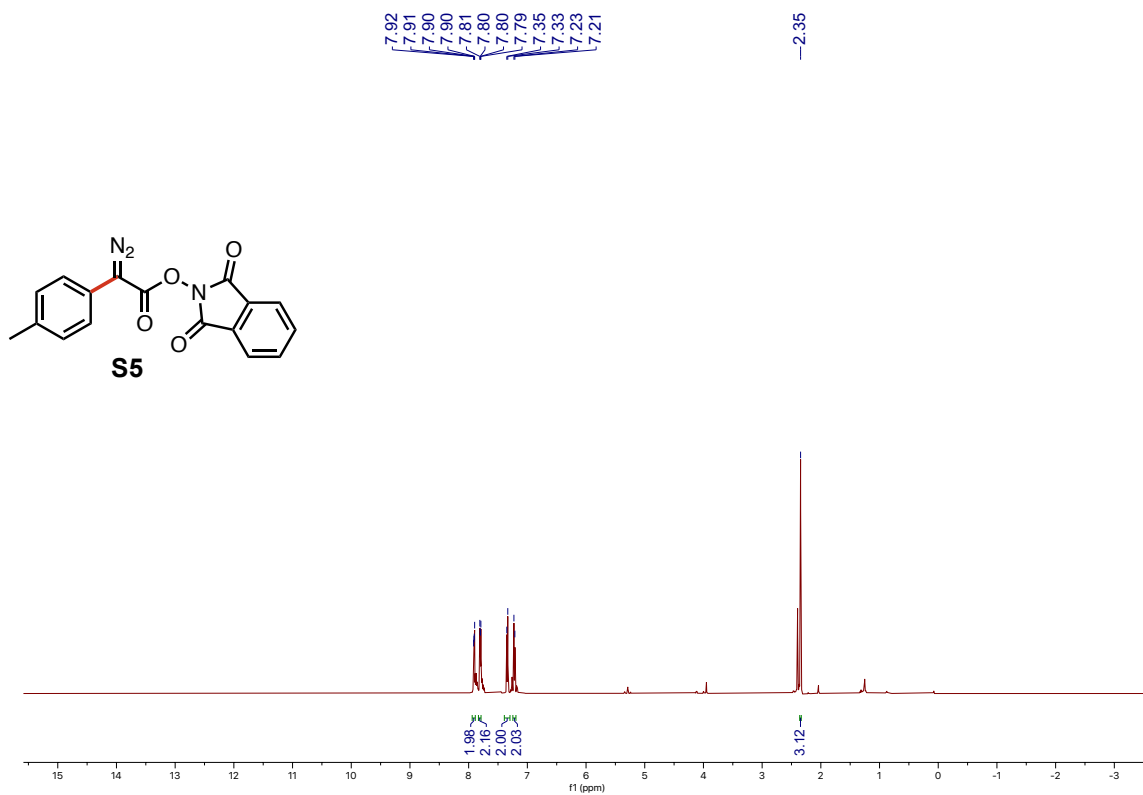
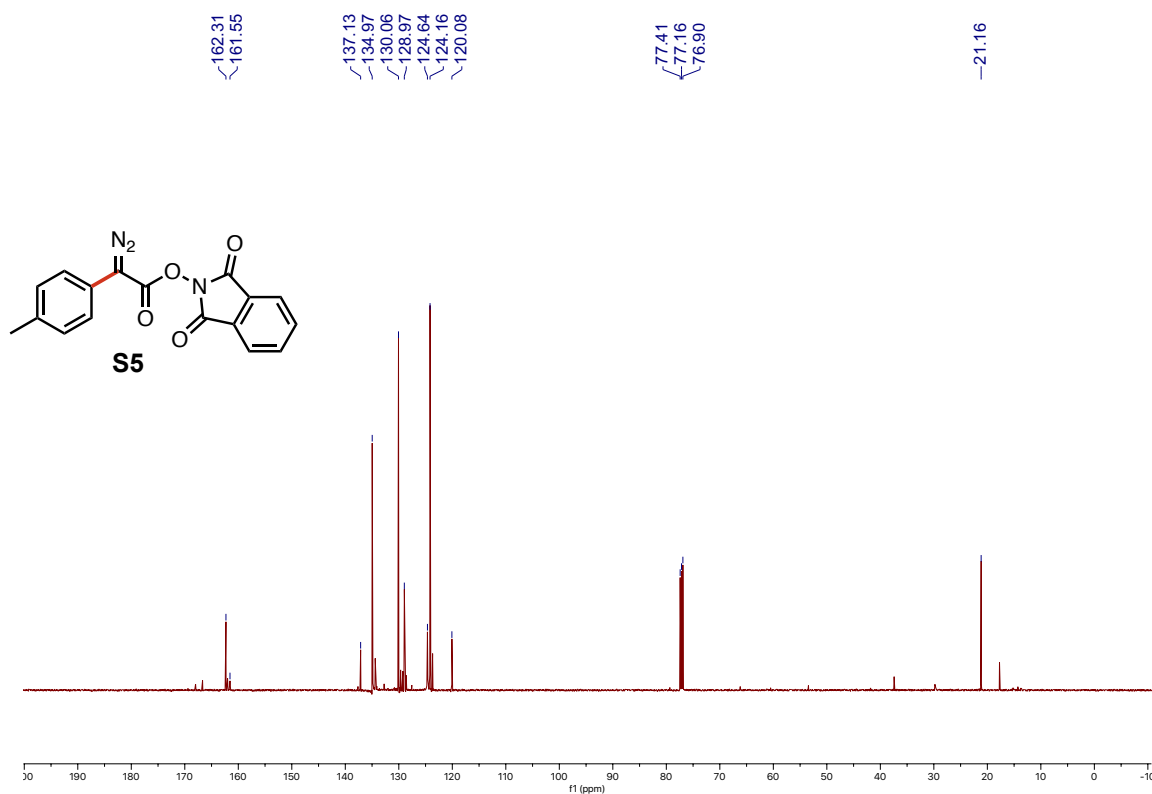


$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$  containing 0.03% v/v TMS) of **S2k**

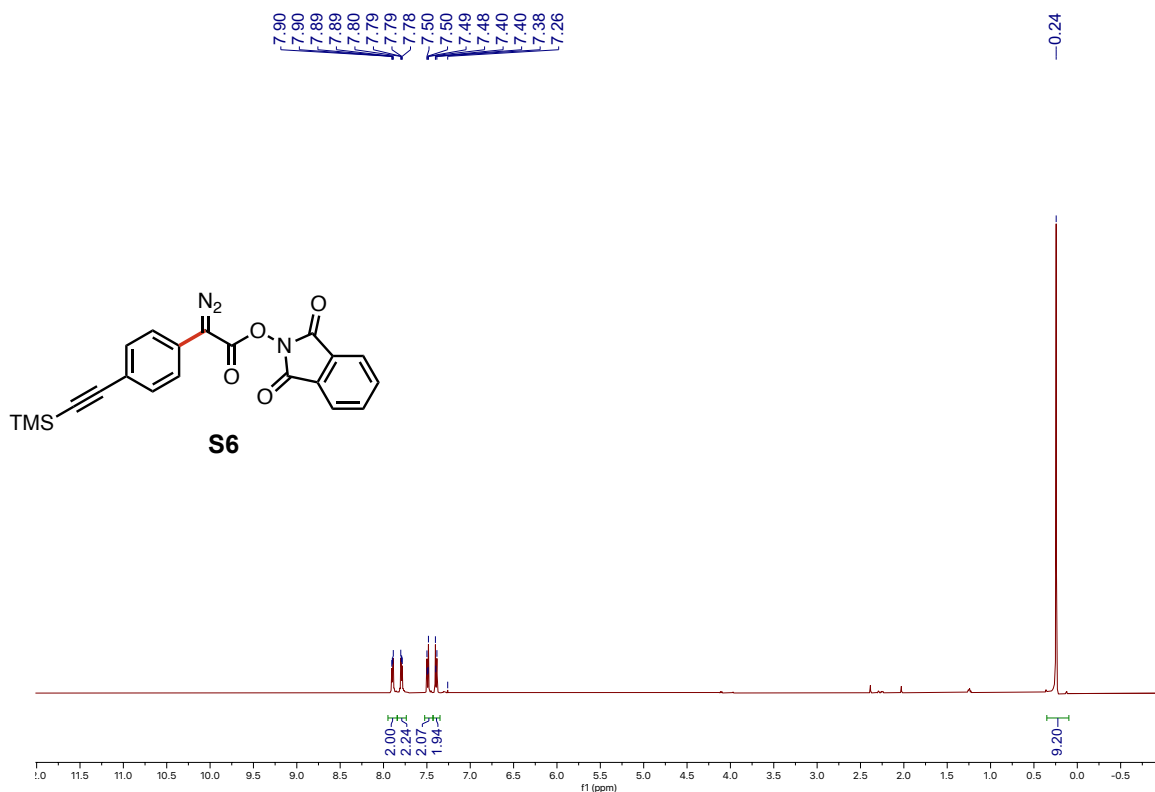
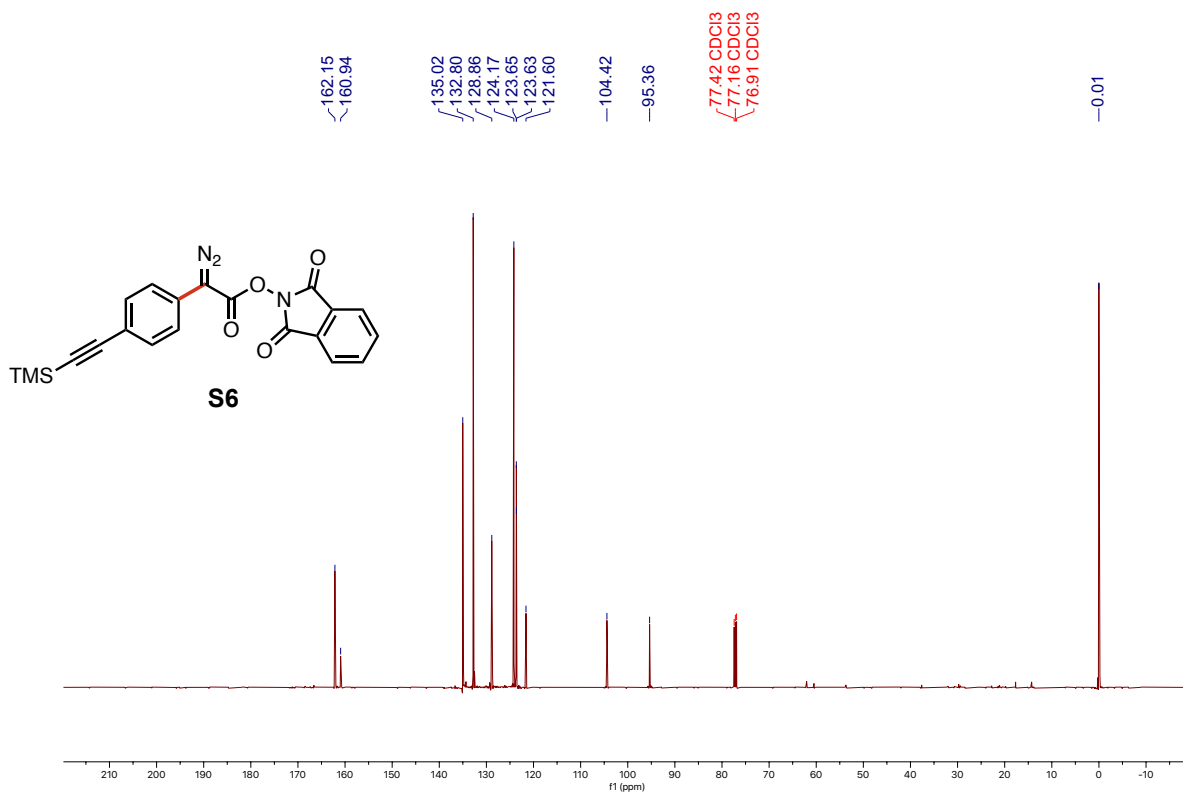


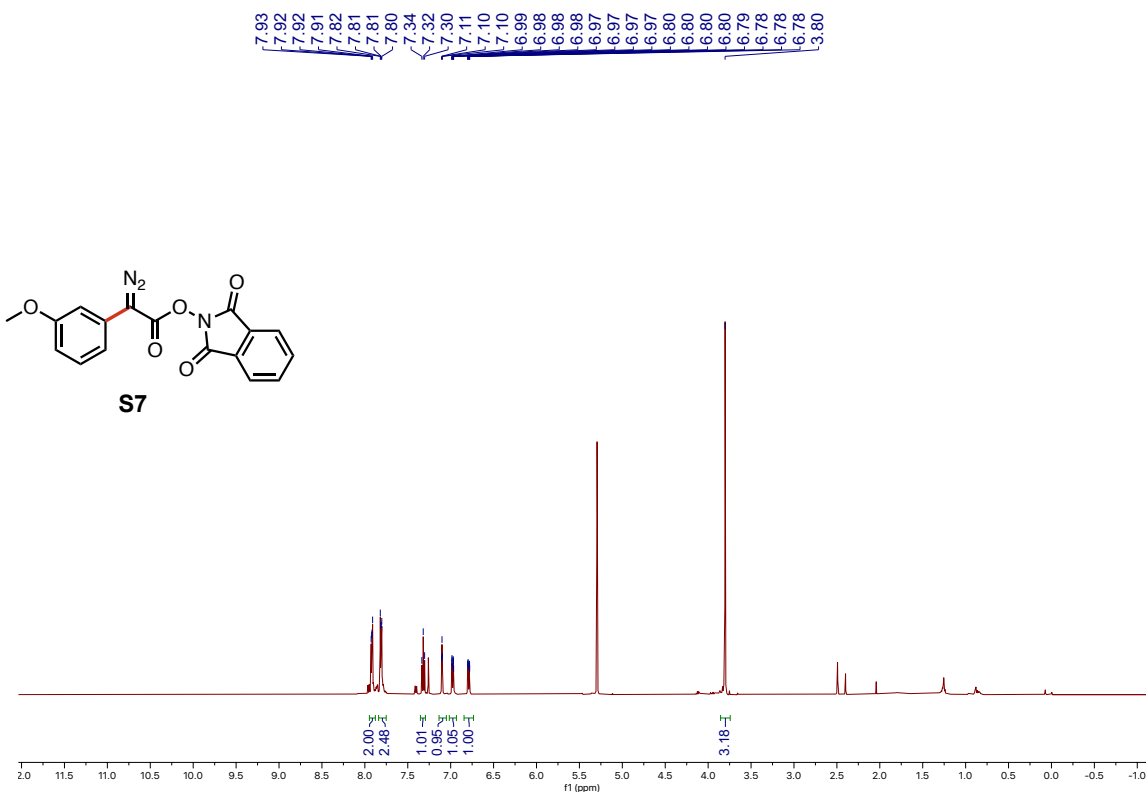
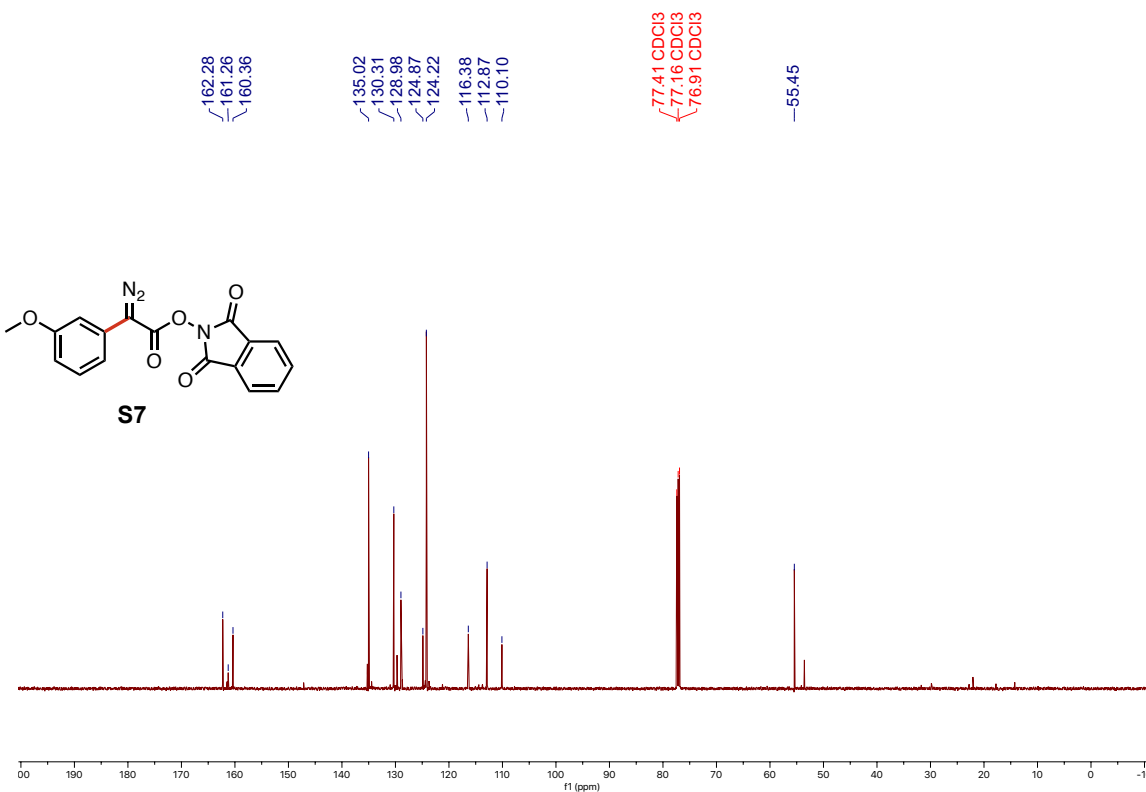
$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$  containing 0.03% v/v TMS) of NHPI-DA (**S4**)

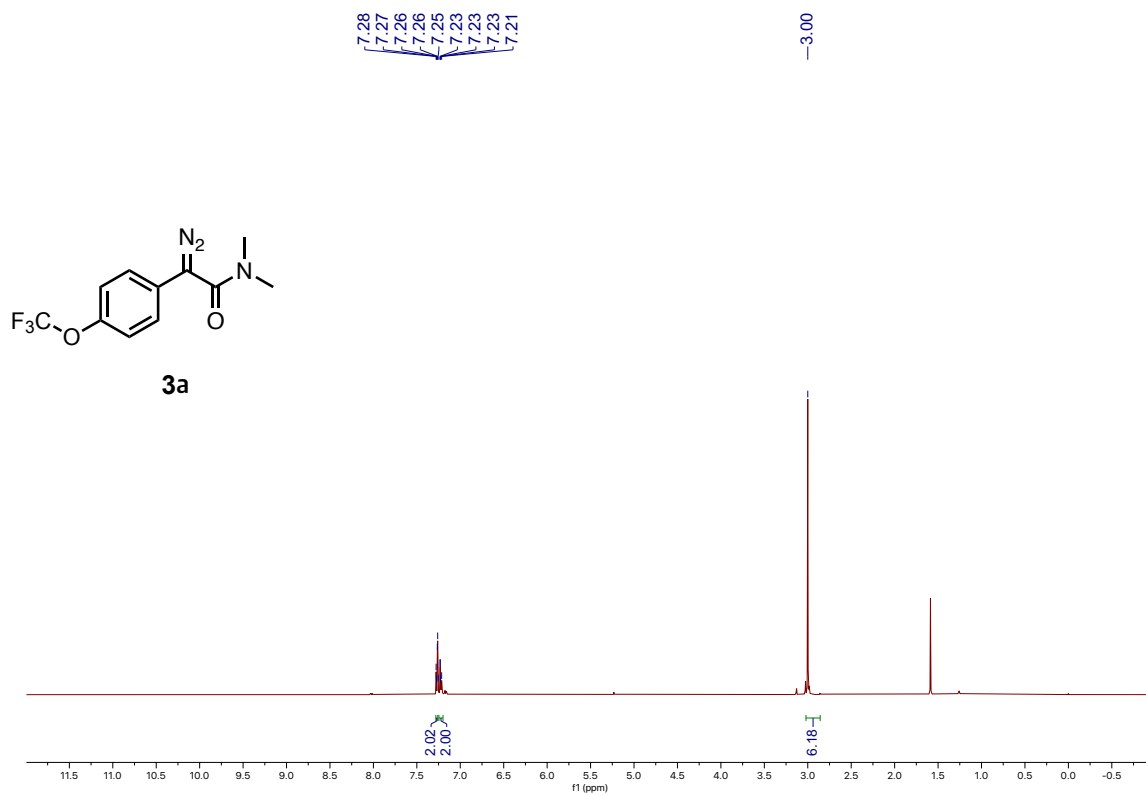
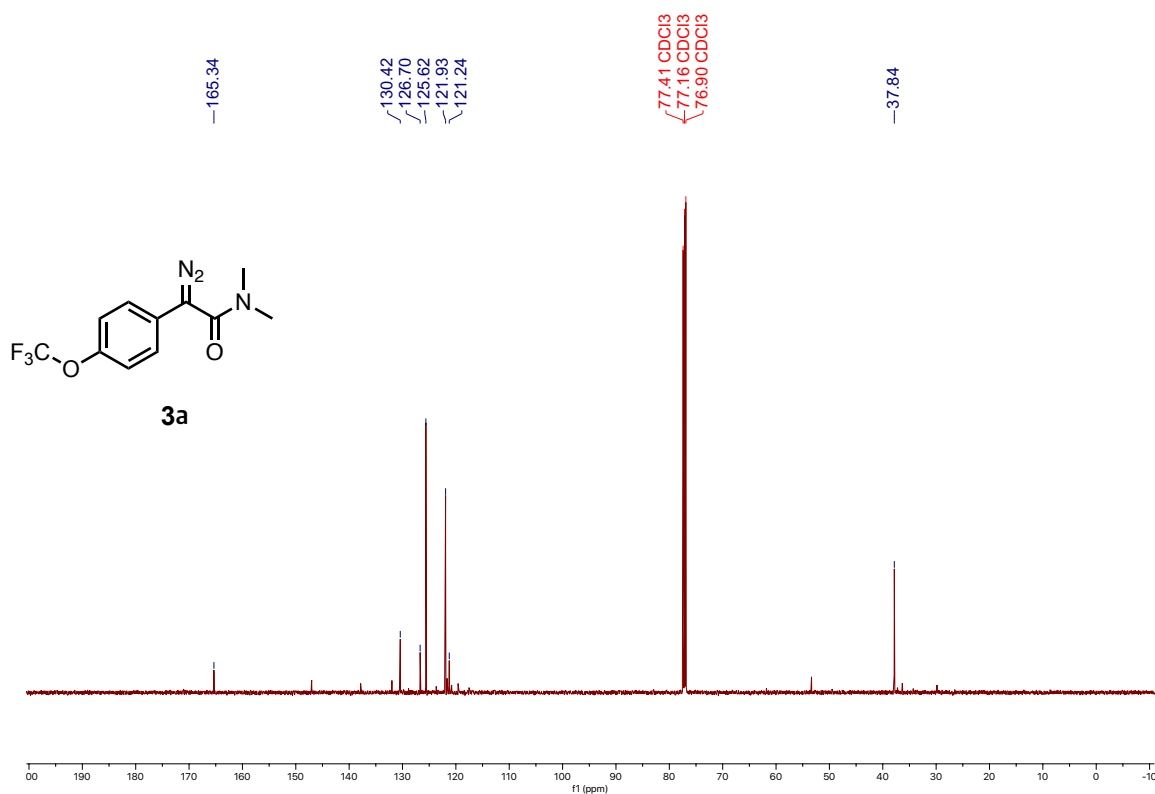


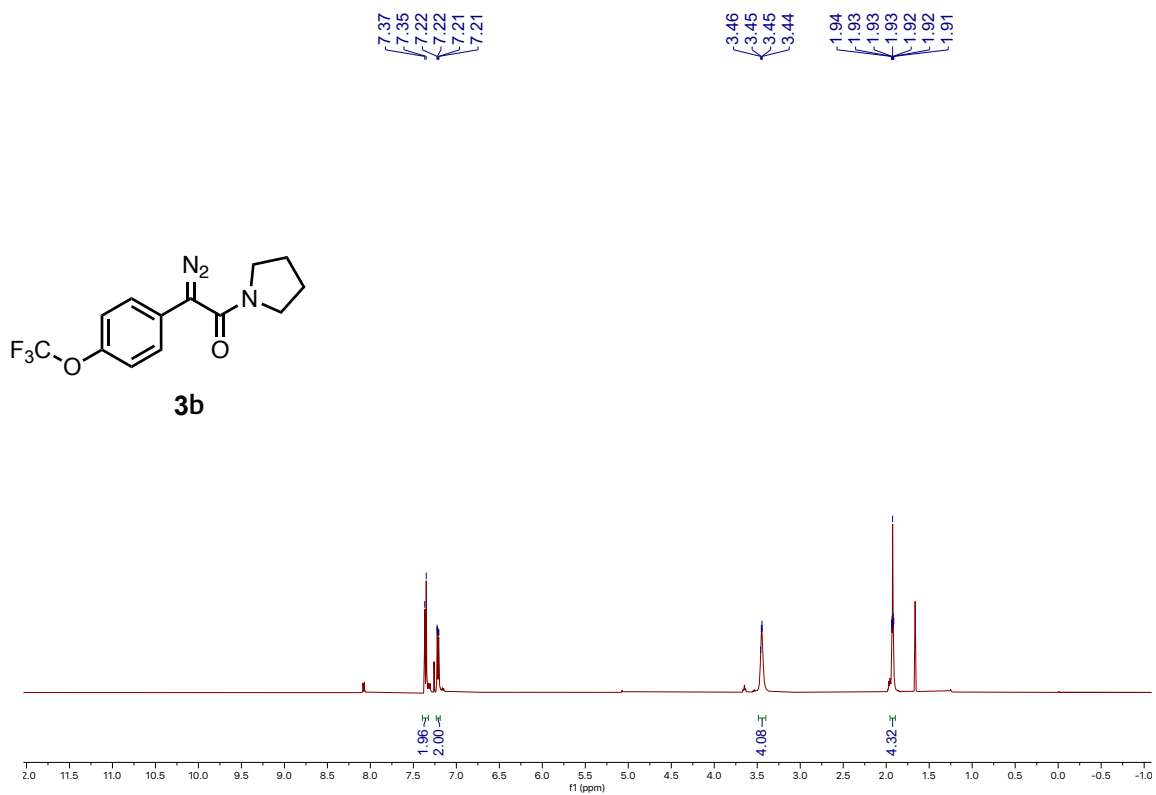
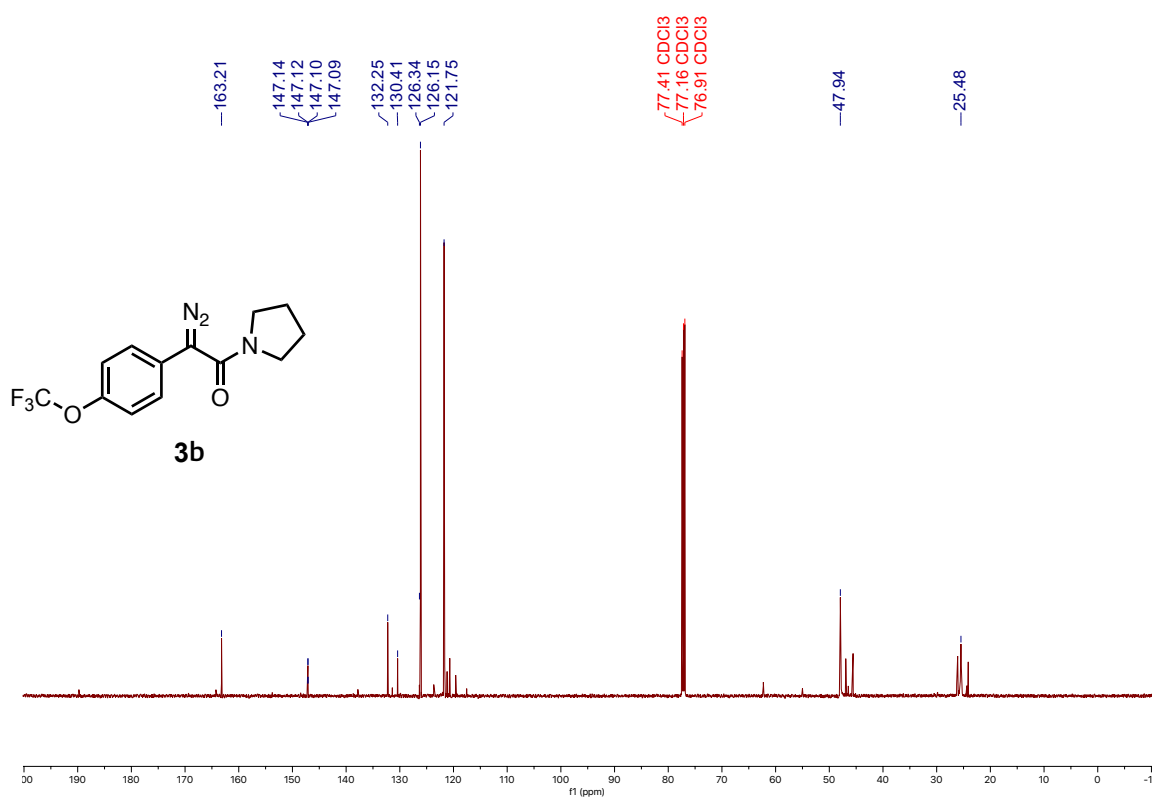
$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$  containing 0.03% v/v TMS) of **S5** $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$  containing 0.03% v/v TMS) of **S5**



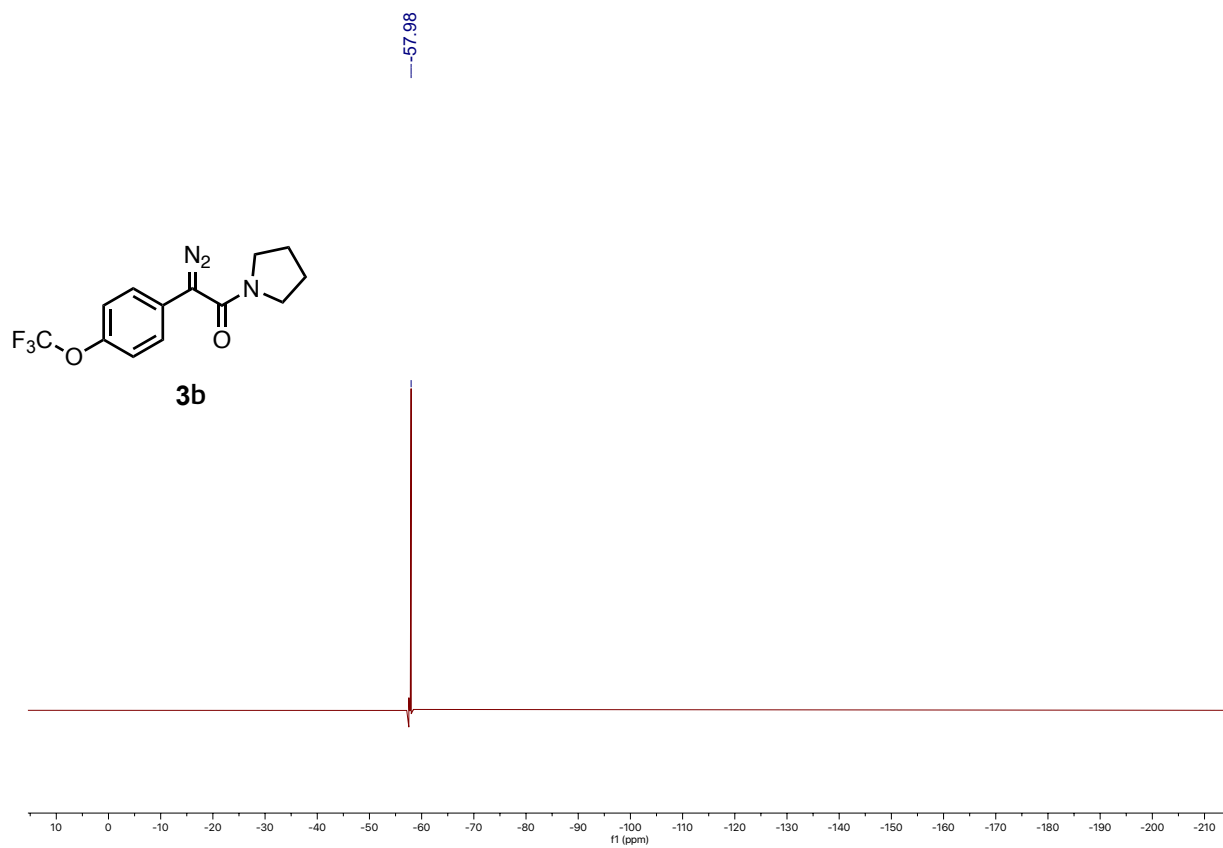
$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$  containing 0.03% v/v TMS) of **S6** $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$  containing 0.03% v/v TMS) of **S6**

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub> containing 0.03% v/v TMS) of **S7**<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub> containing 0.03% v/v TMS) of **S7**

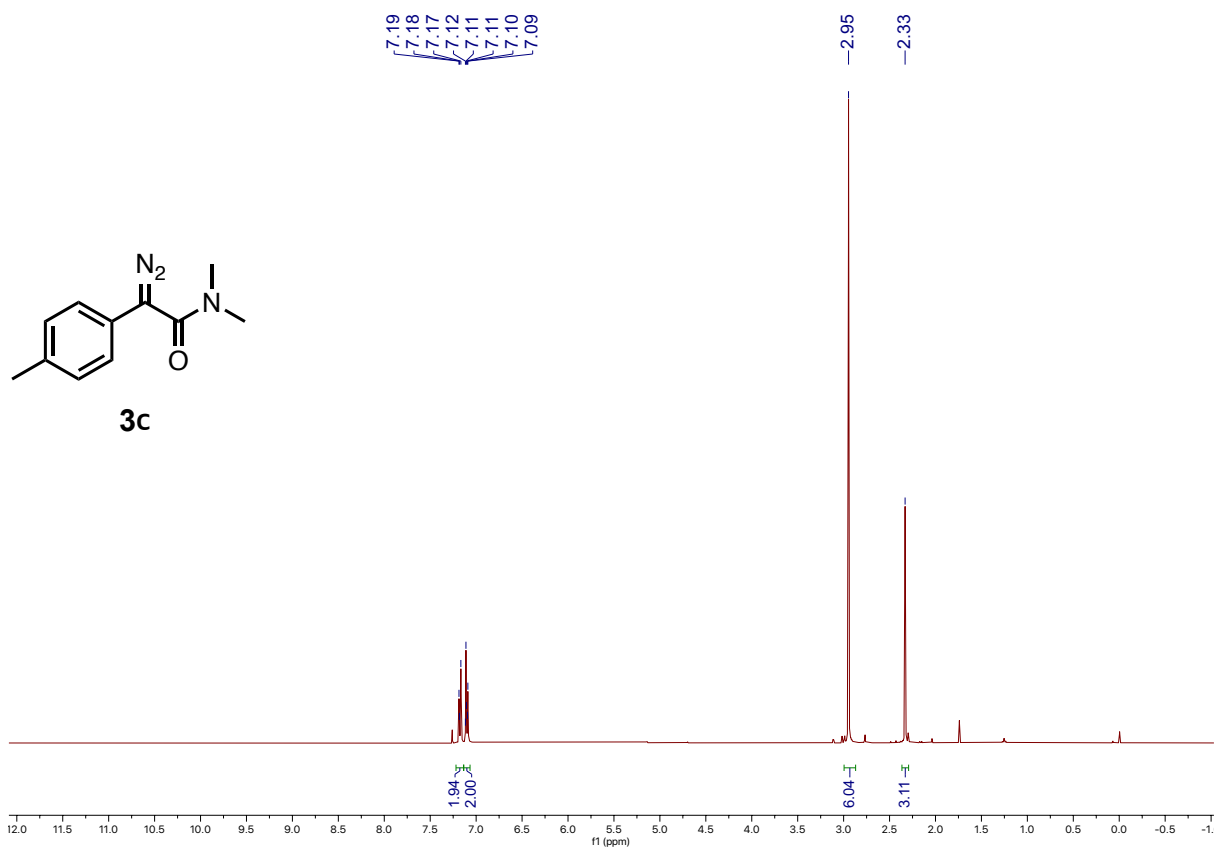
$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$  containing 0.03% v/v TMS) of **3a** $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$  containing 0.03% v/v TMS) of **3a**

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$  containing 0.03% v/v TMS) of **3b** $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$  containing 0.03% v/v TMS) of **3b**

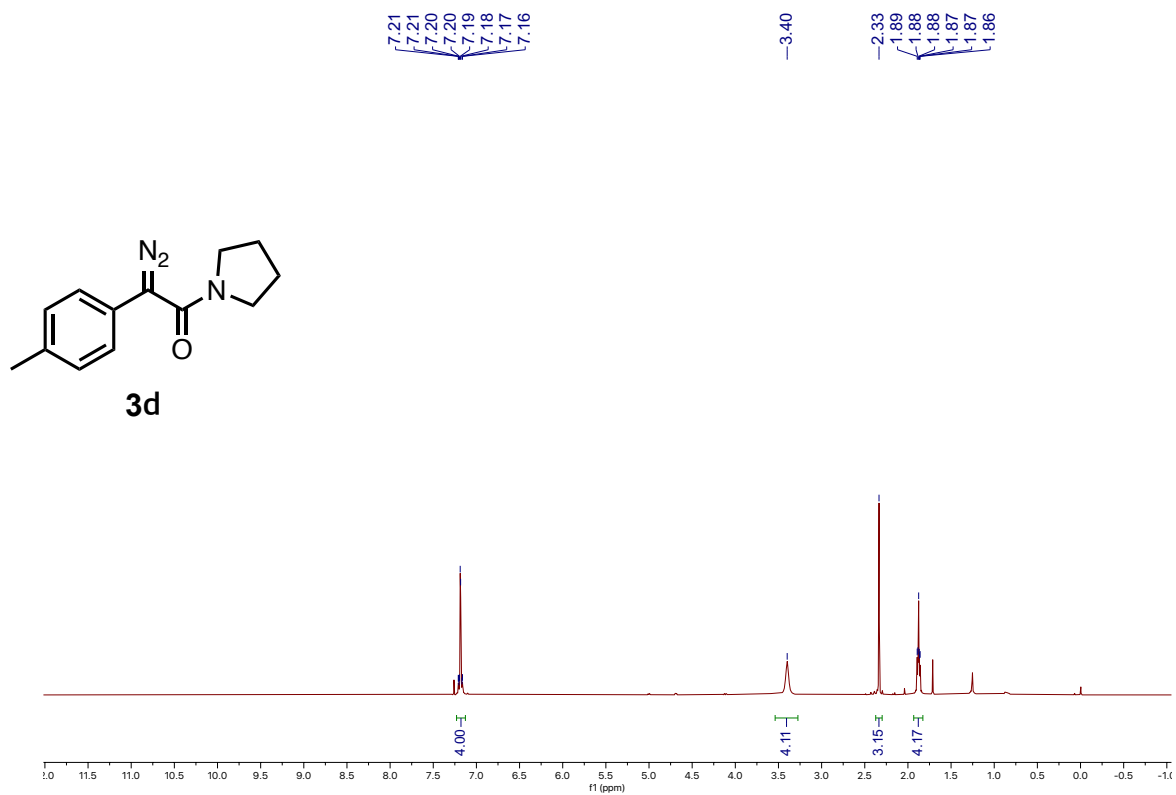
$^{19}\text{F}$  NMR (471 MHz,  $\text{CDCl}_3$  containing 0.03% v/v TMS) of **3b**



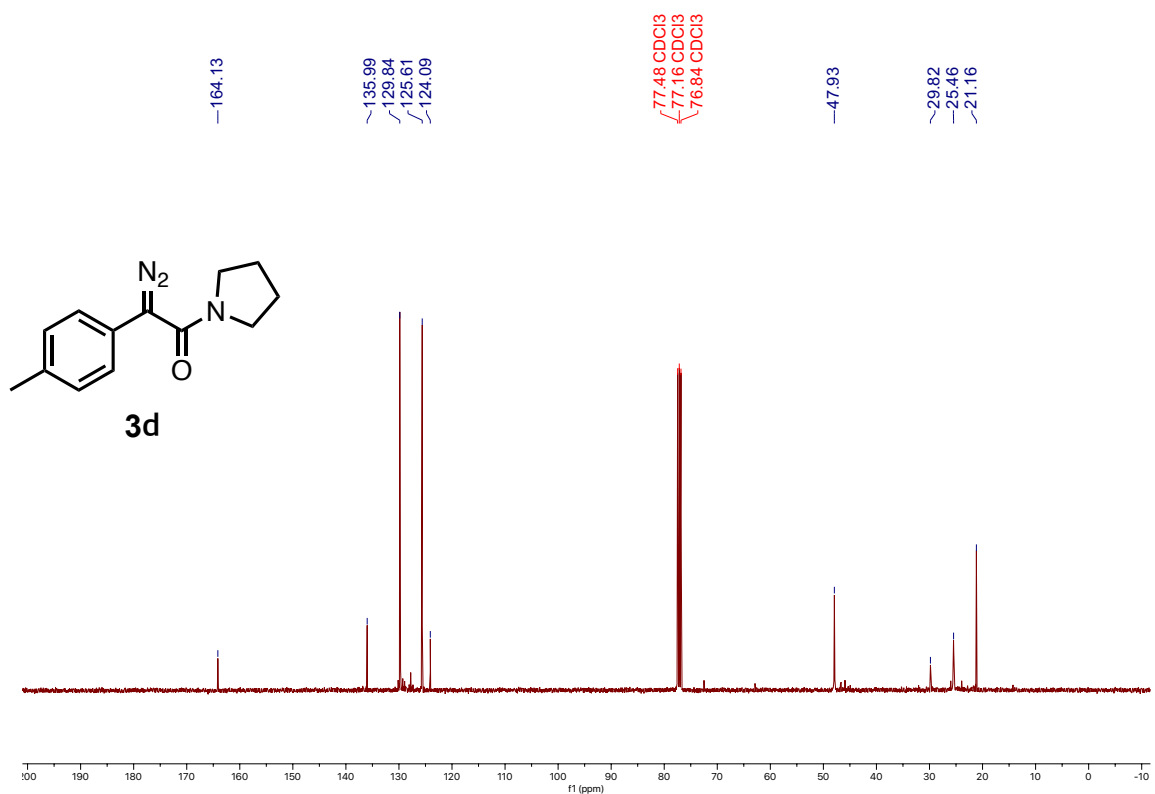
$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$  containing 0.03% v/v TMS) of **3c**



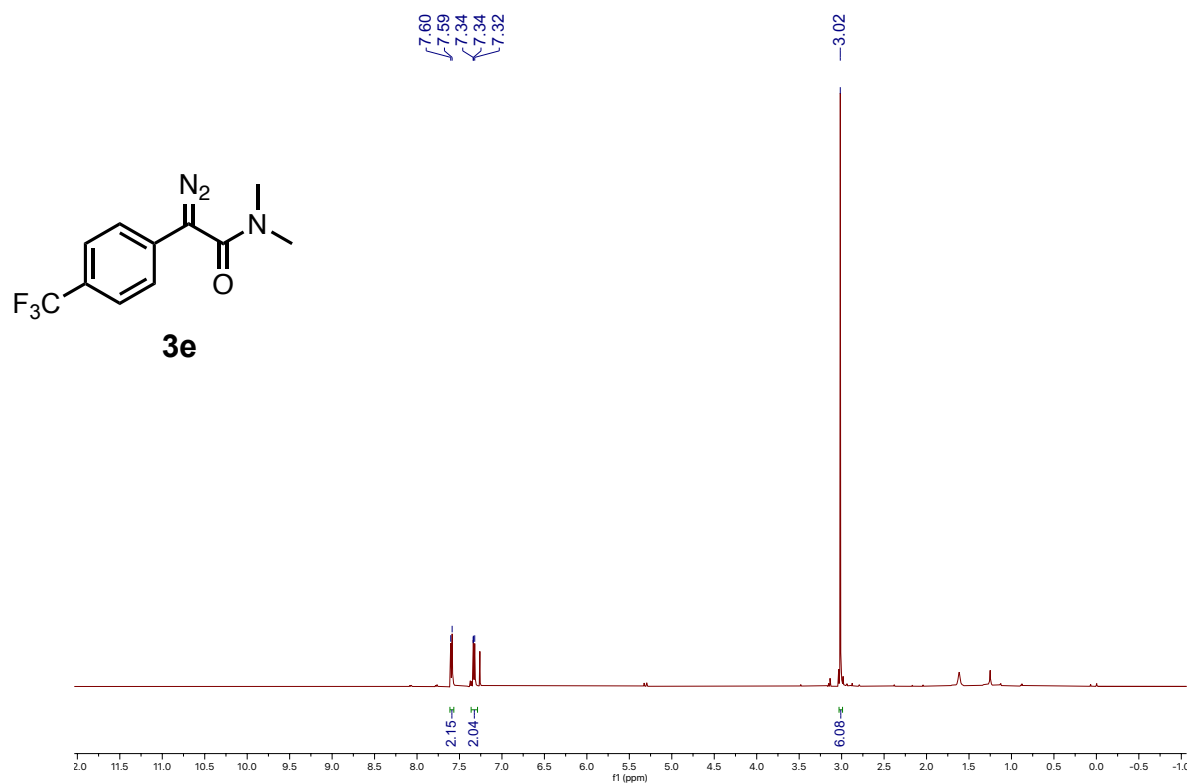
$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$  containing 0.03% v/v TMS) of **3d**



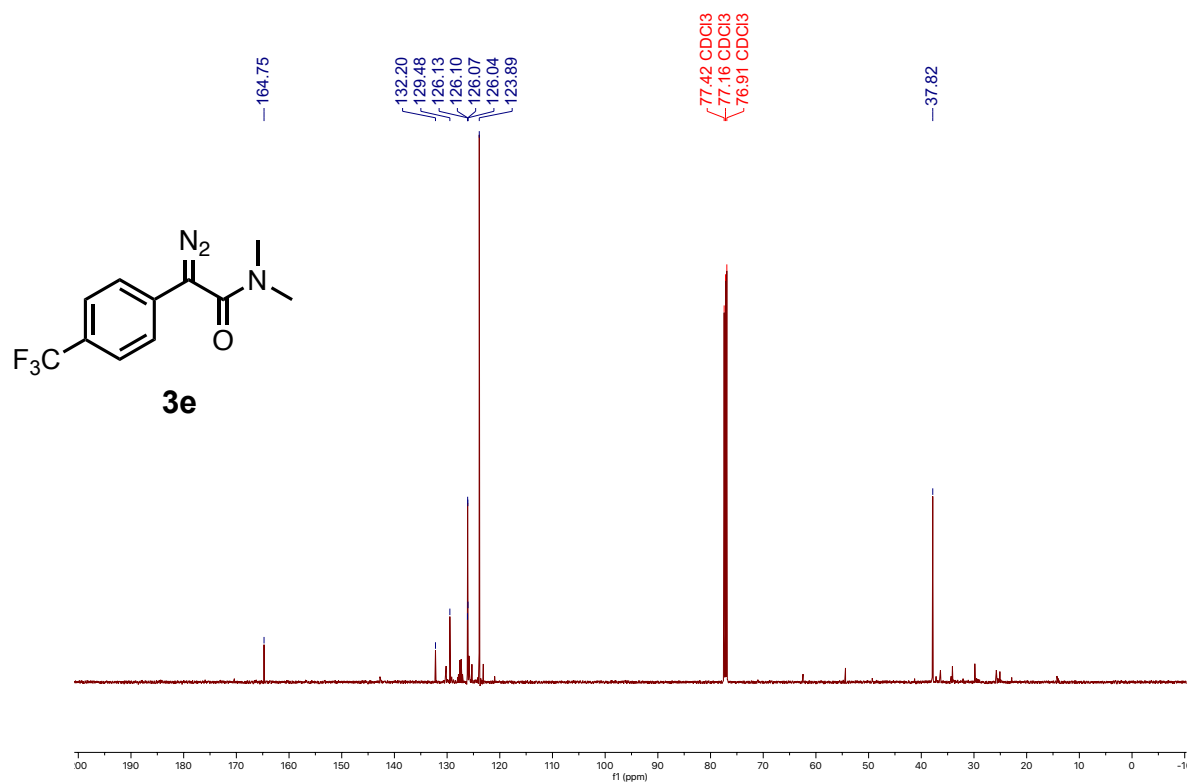
$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$  containing 0.03% v/v TMS) of **3d**



$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$  containing 0.03% v/v TMS) of **3e**

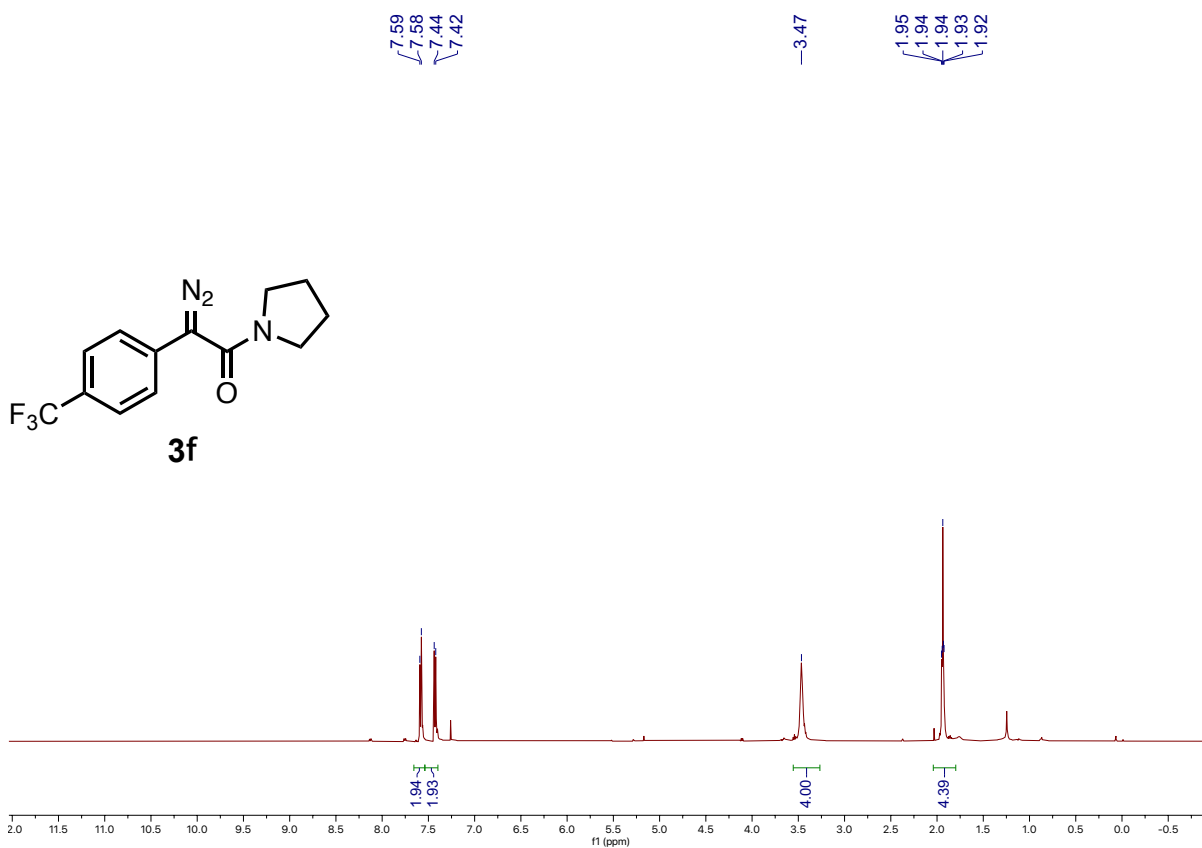


$^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$  containing 0.03% v/v TMS) of **3e**

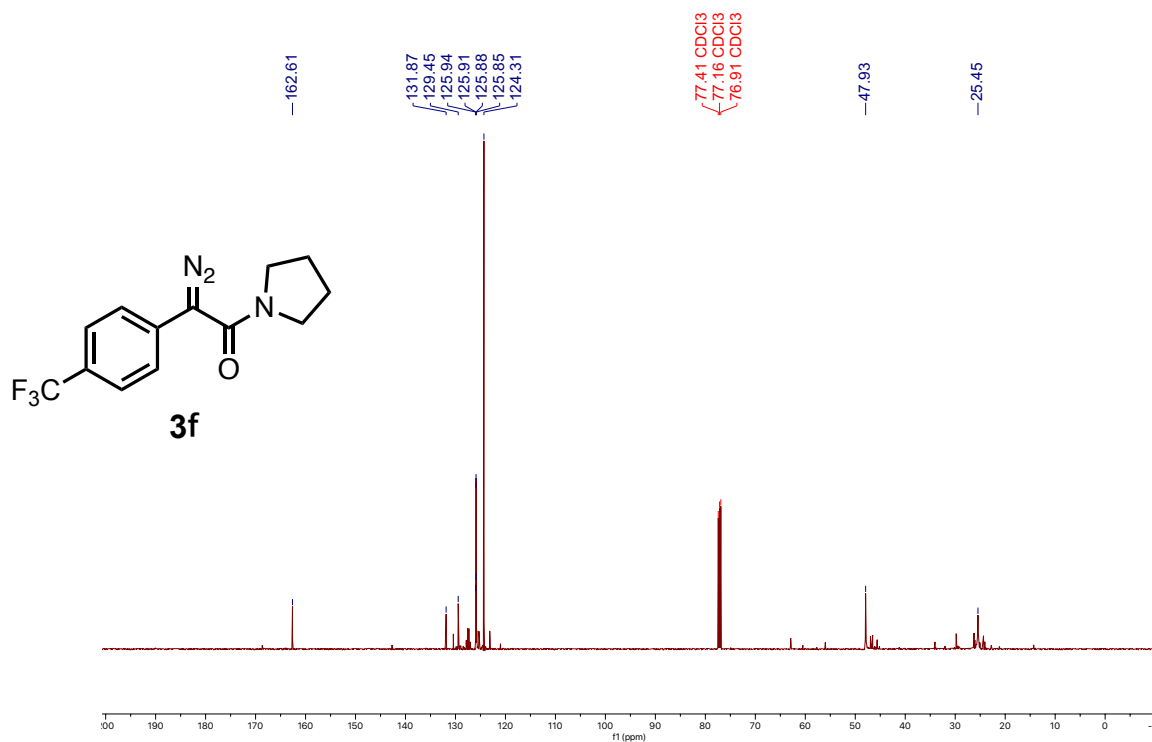




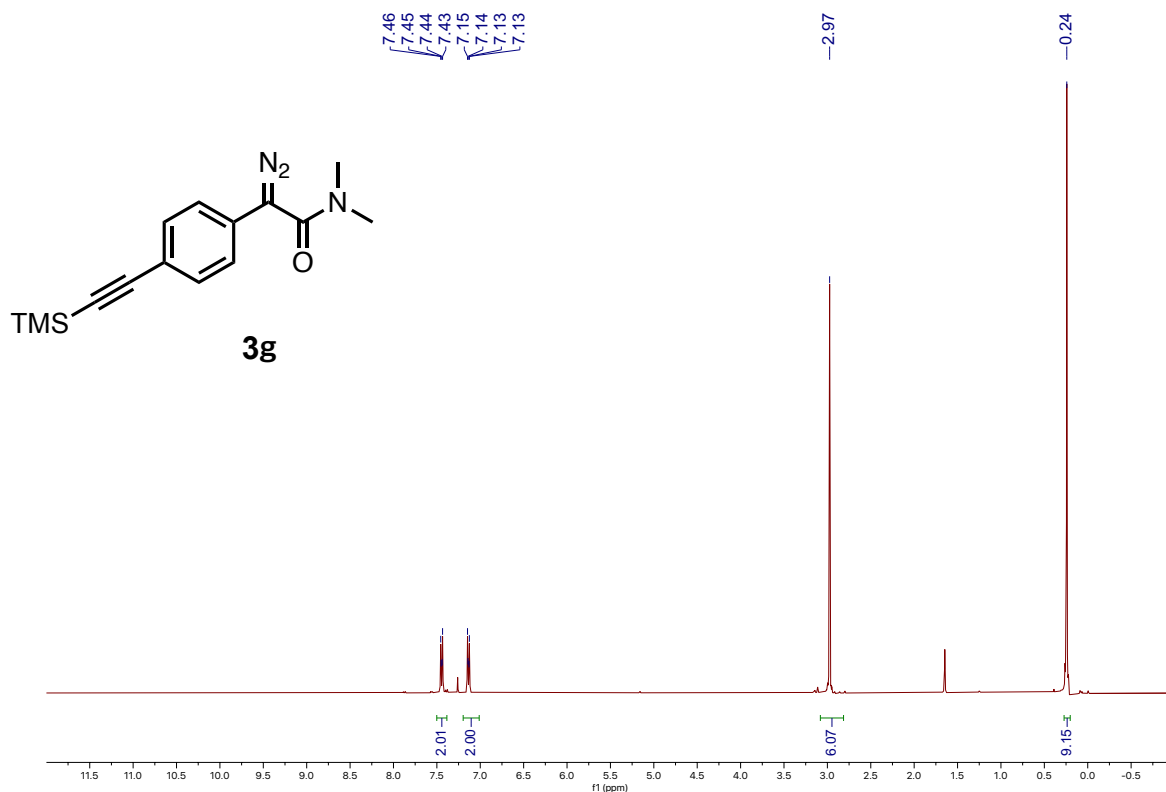
$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$  containing 0.03% v/v TMS) of **3f**



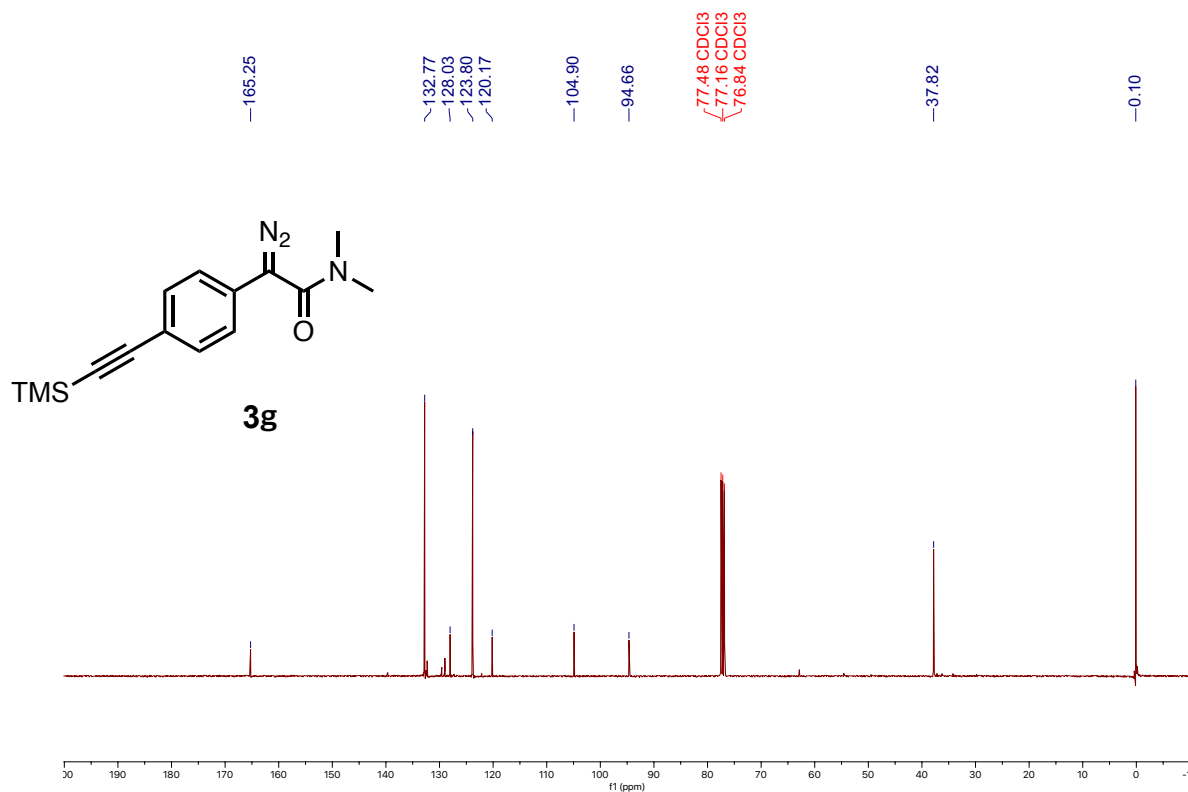
$^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$  containing 0.03% v/v TMS) of **3f**



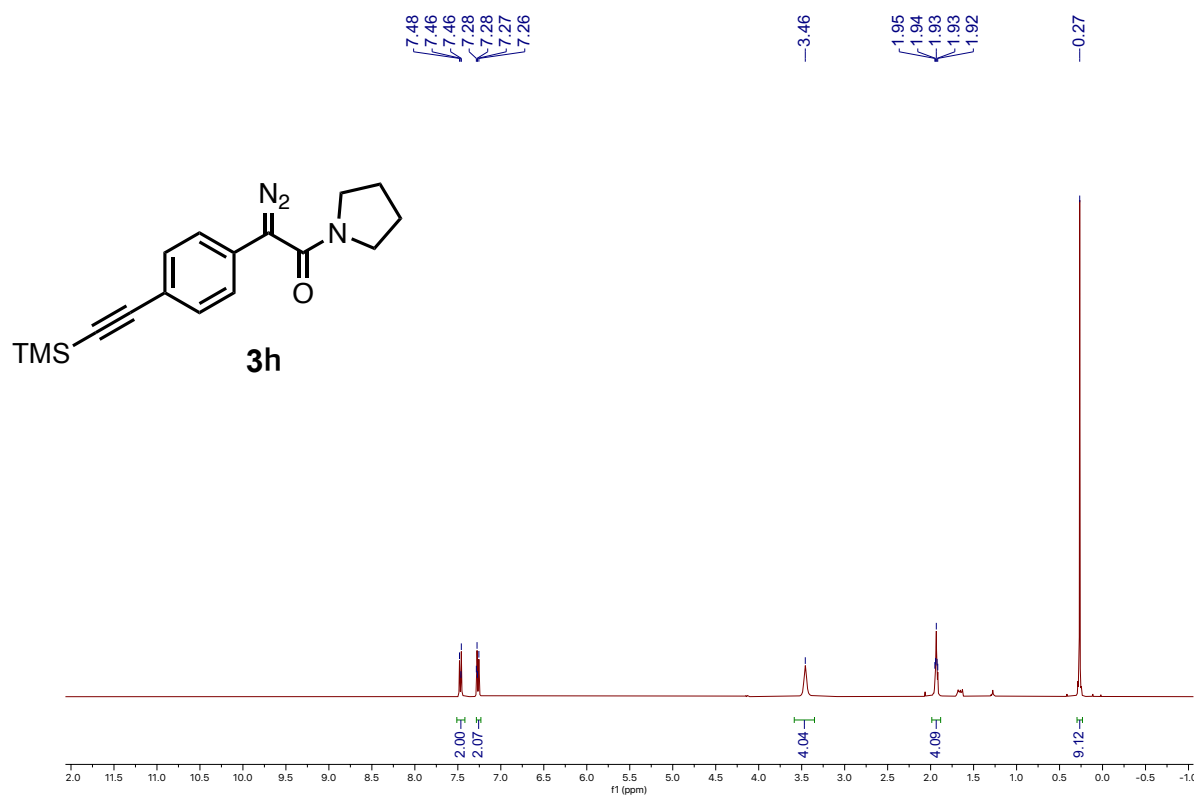
$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$  containing 0.03% v/v TMS) of **3g**



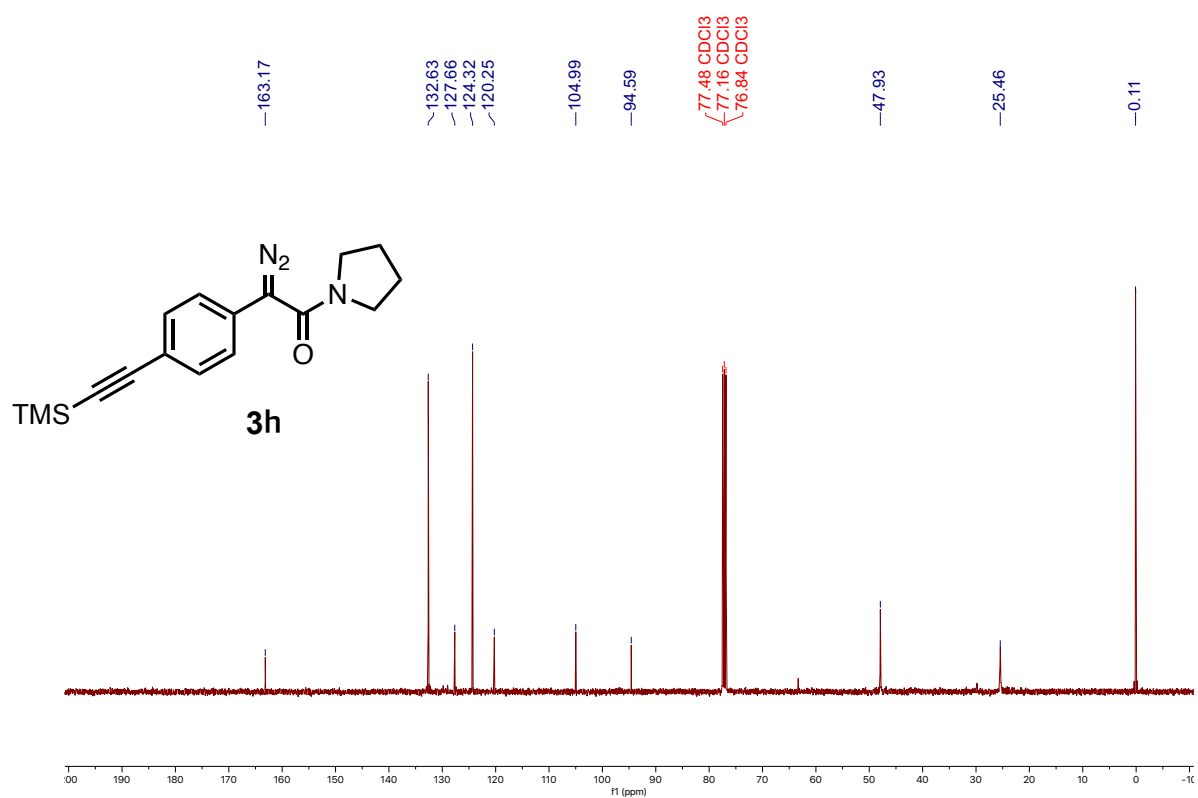
$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$  containing 0.03% v/v TMS) of **3g**

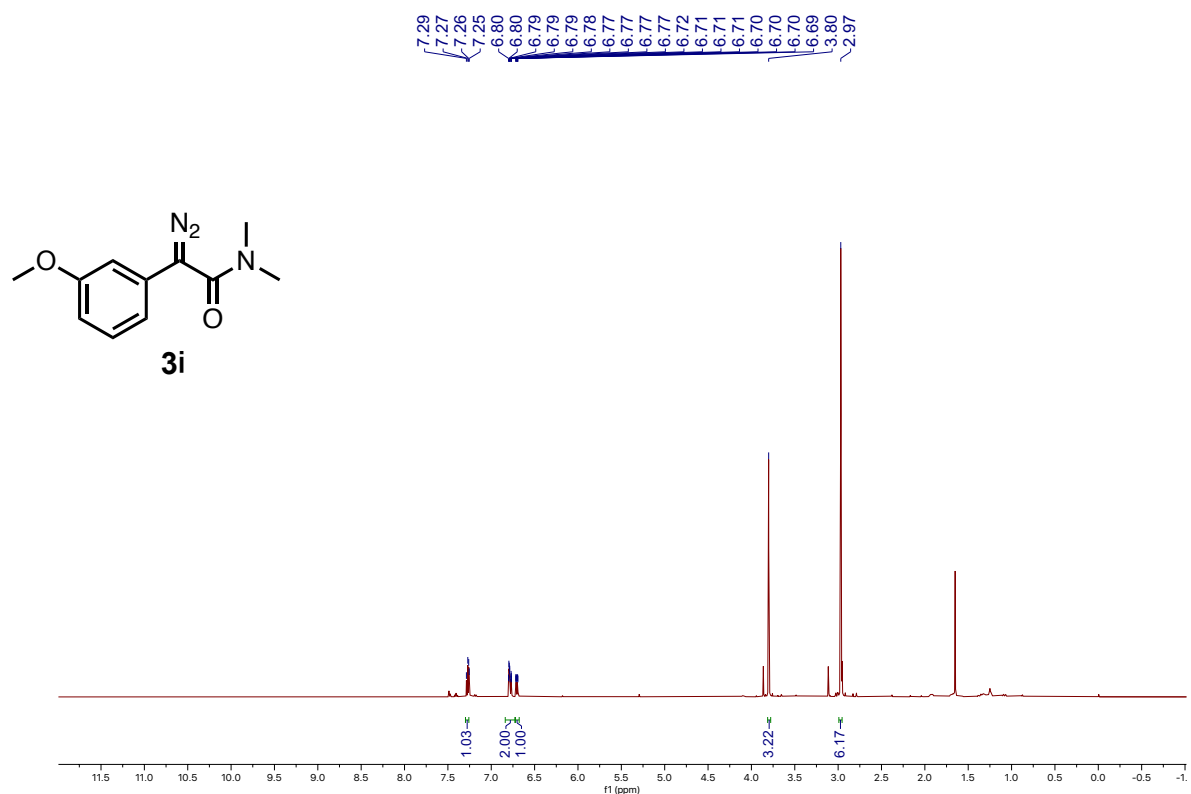
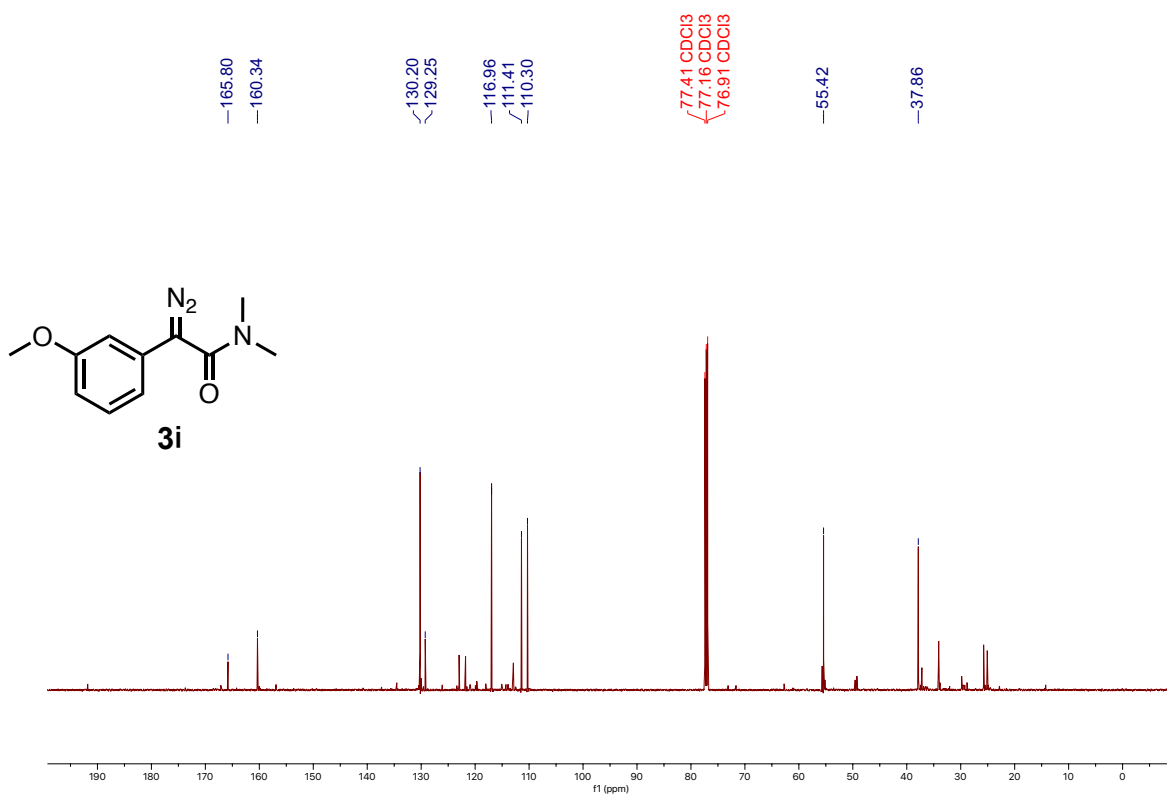


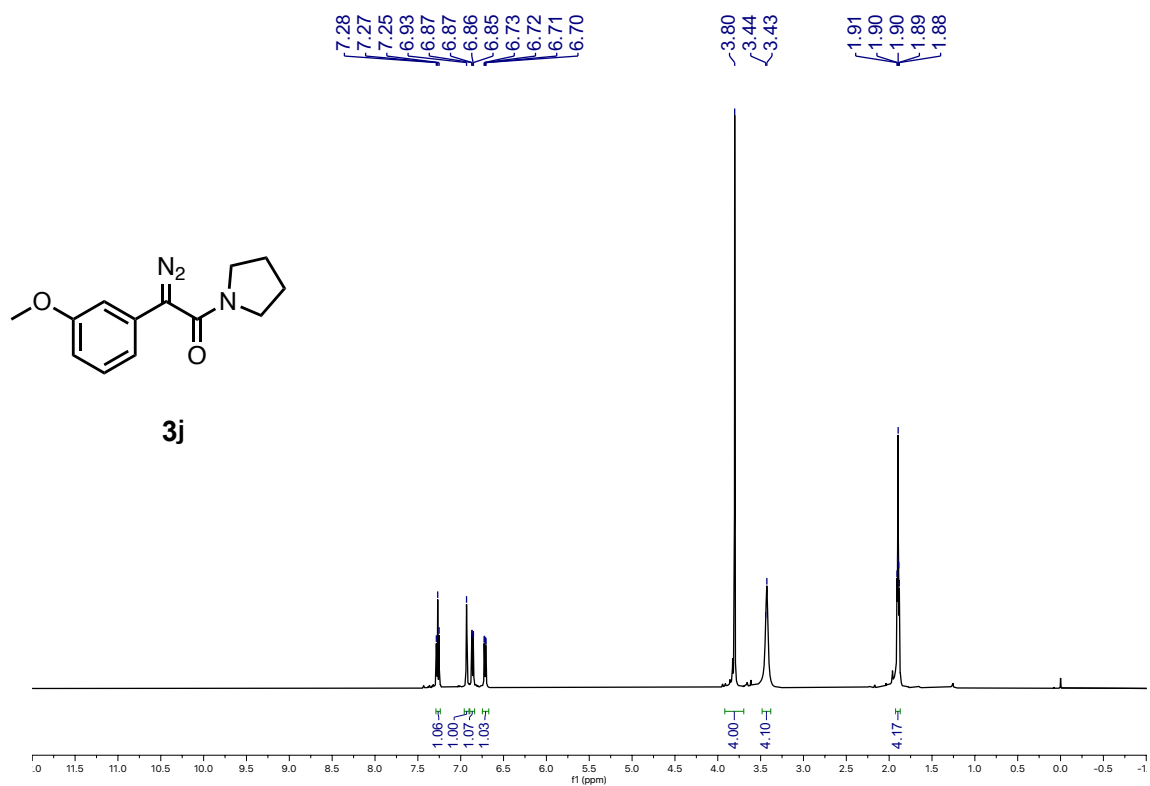
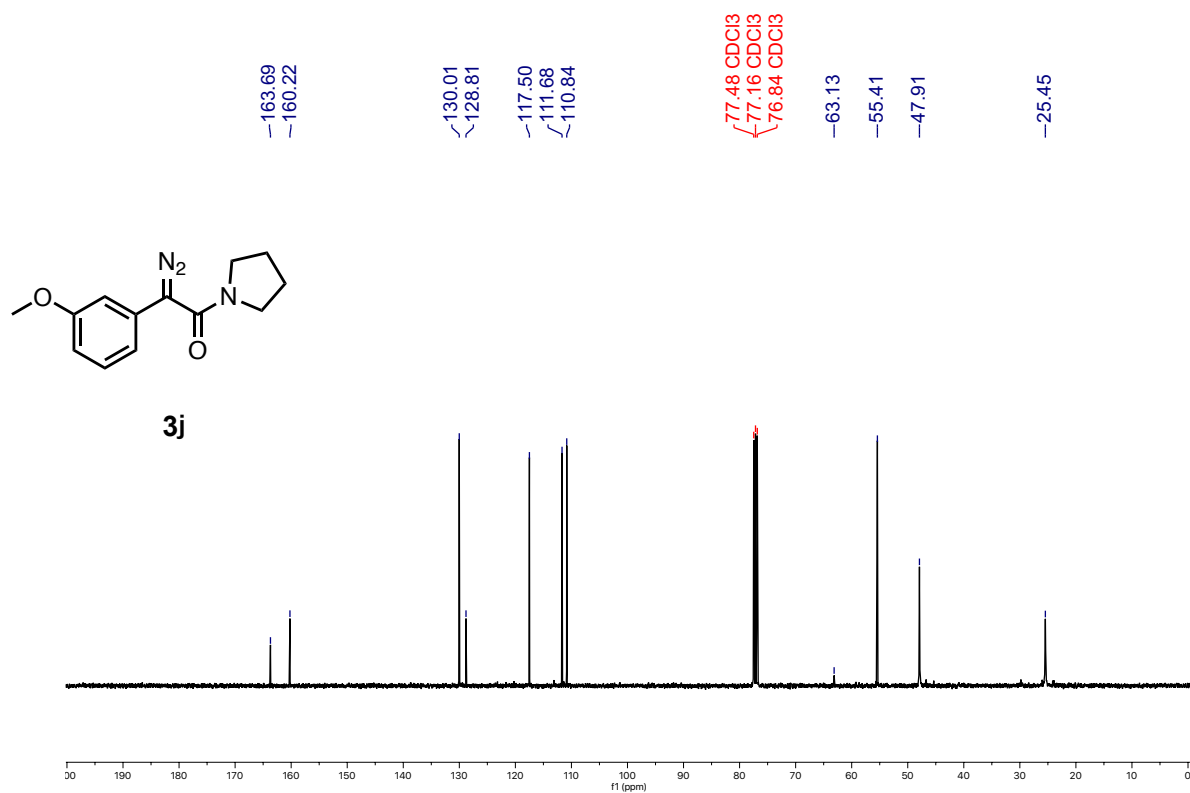
$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$  containing 0.03% v/v TMS) of **3h**

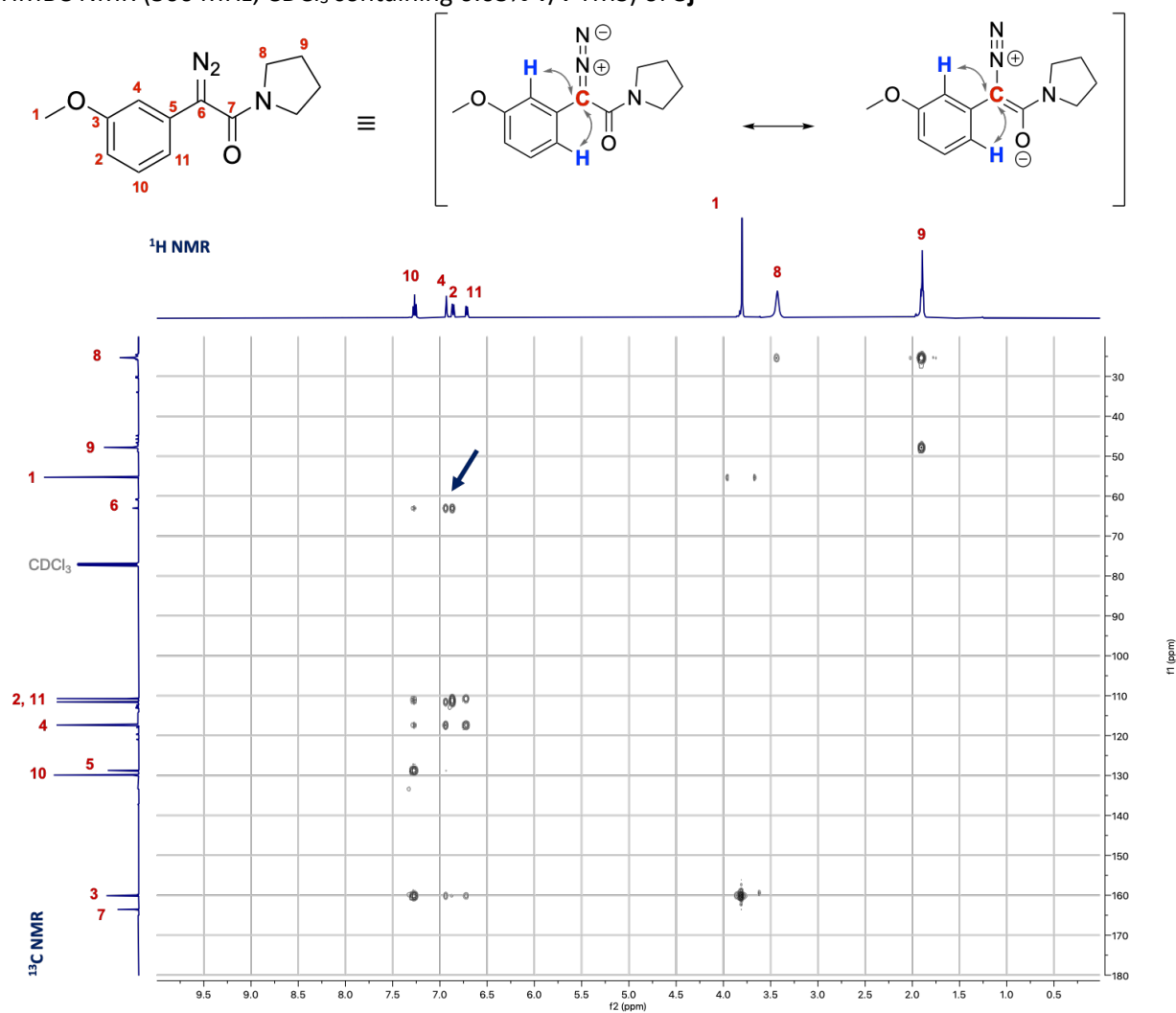


$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$  containing 0.03% v/v TMS) of **3h**

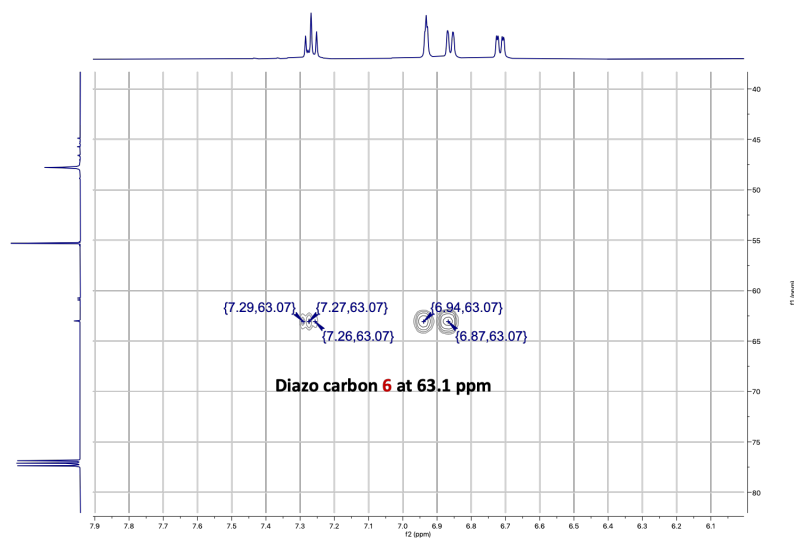


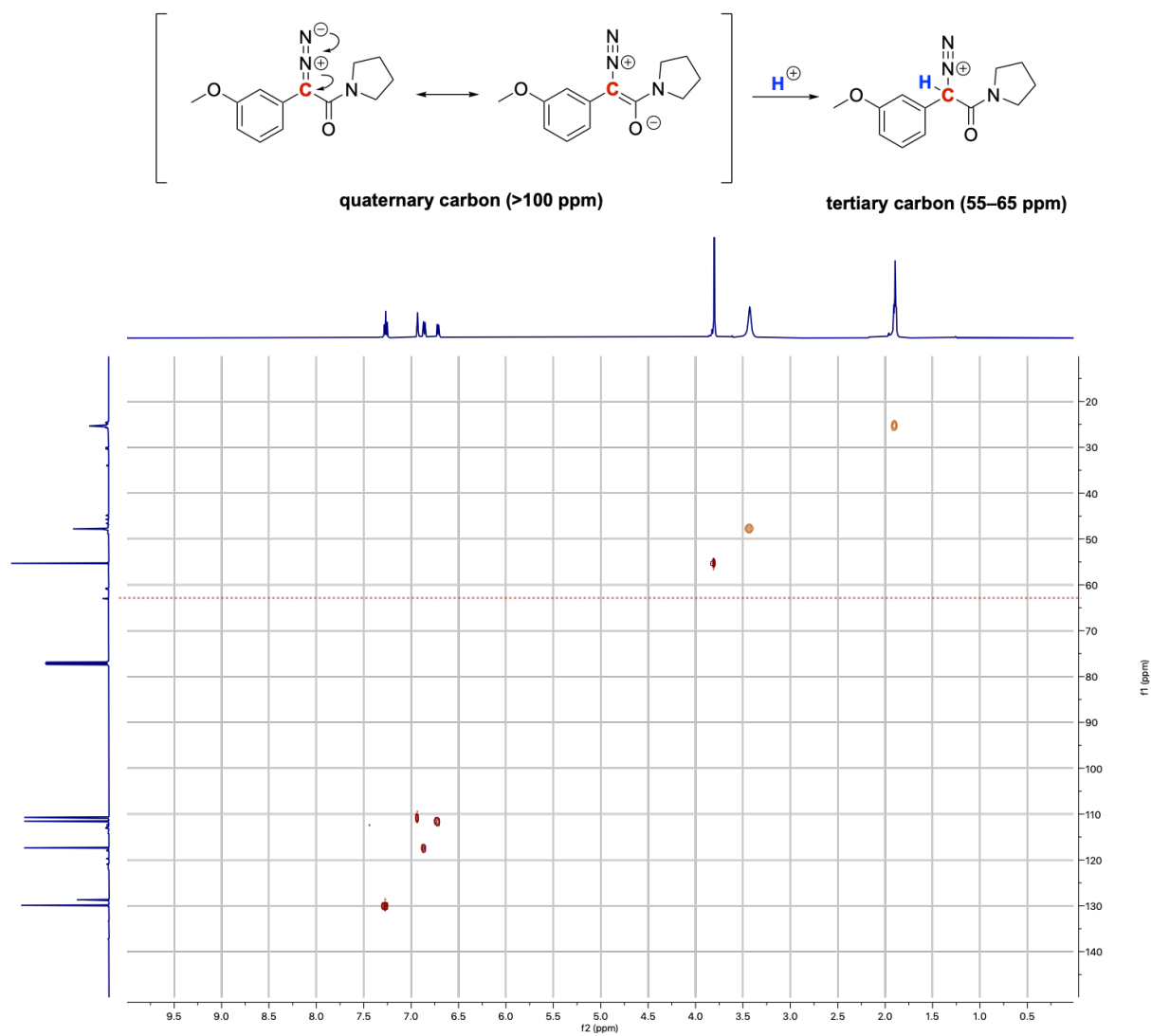
$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$  containing 0.03% v/v TMS) of **3i** $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$  containing 0.03% v/v TMS) of **3i**

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$  containing 0.03% v/v TMS) of **3j** $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$  containing 0.03% v/v TMS) of **3j**

HMBC NMR (500 MHz, CDCl<sub>3</sub> containing 0.03% v/v TMS) of **3j**

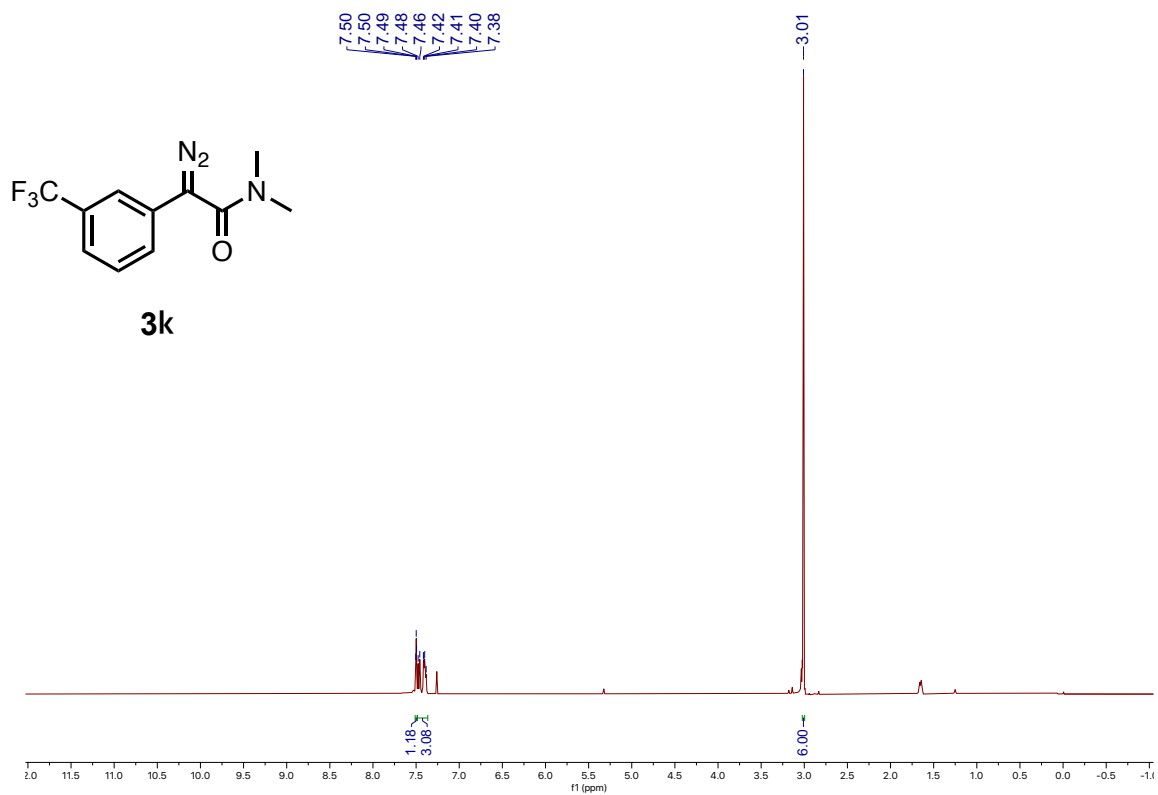
Zoom in:

HSQC NMR (500 MHz, CDCl<sub>3</sub> containing 0.03% v/v TMS) of **3j**

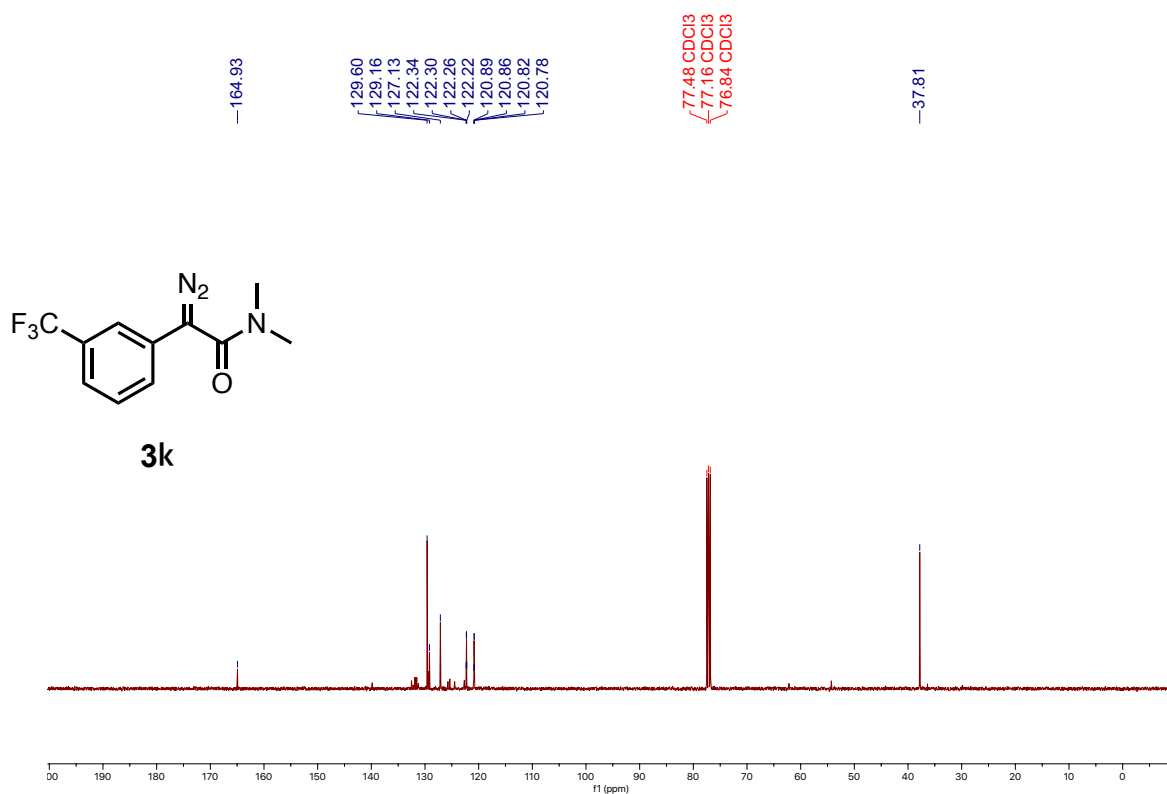


This study was done to confirm the  $^{13}C$  signal peak at 63 ppm is not due to a tertiary carbon from protonated **3j**. No proton signal was observed at corresponding 63 ppm  $^{13}C$  signal.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$  containing 0.03% v/v TMS) of **3k**

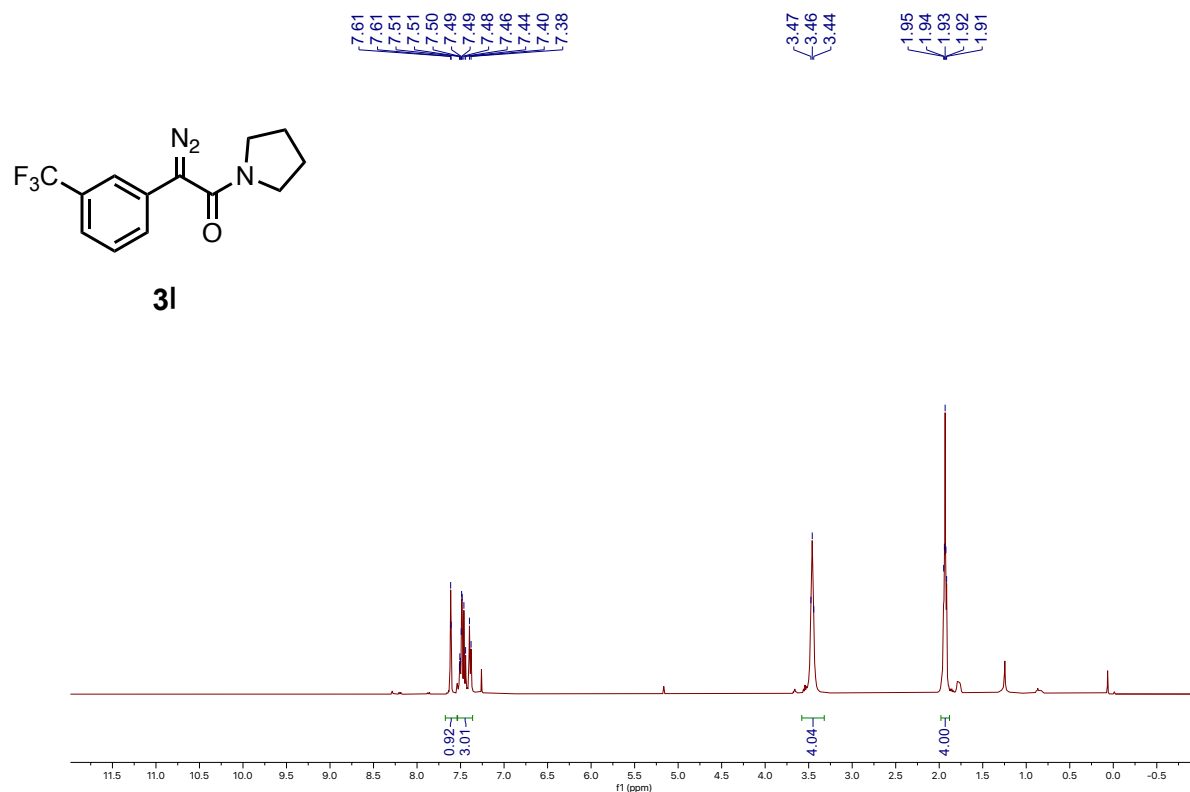


$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$  containing 0.03% v/v TMS) of **3k**

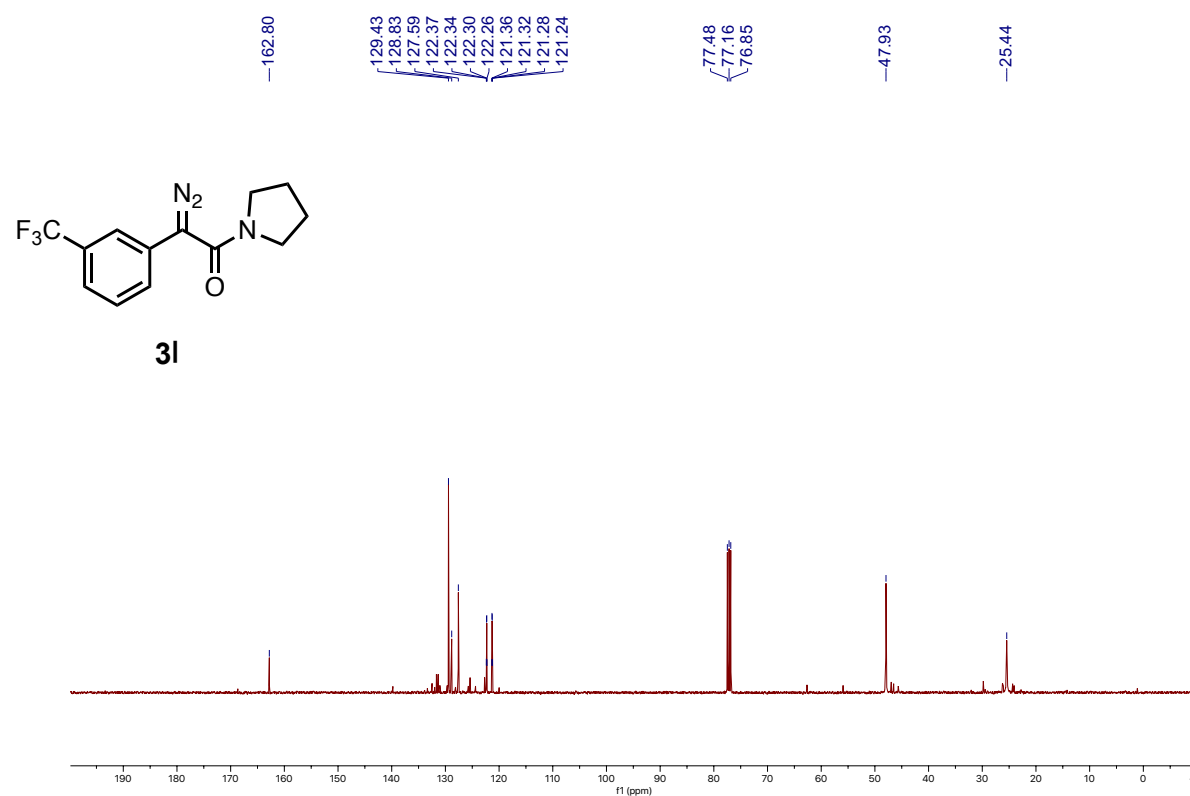




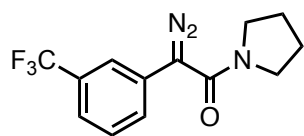
$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$  containing 0.03% v/v TMS) of **31**



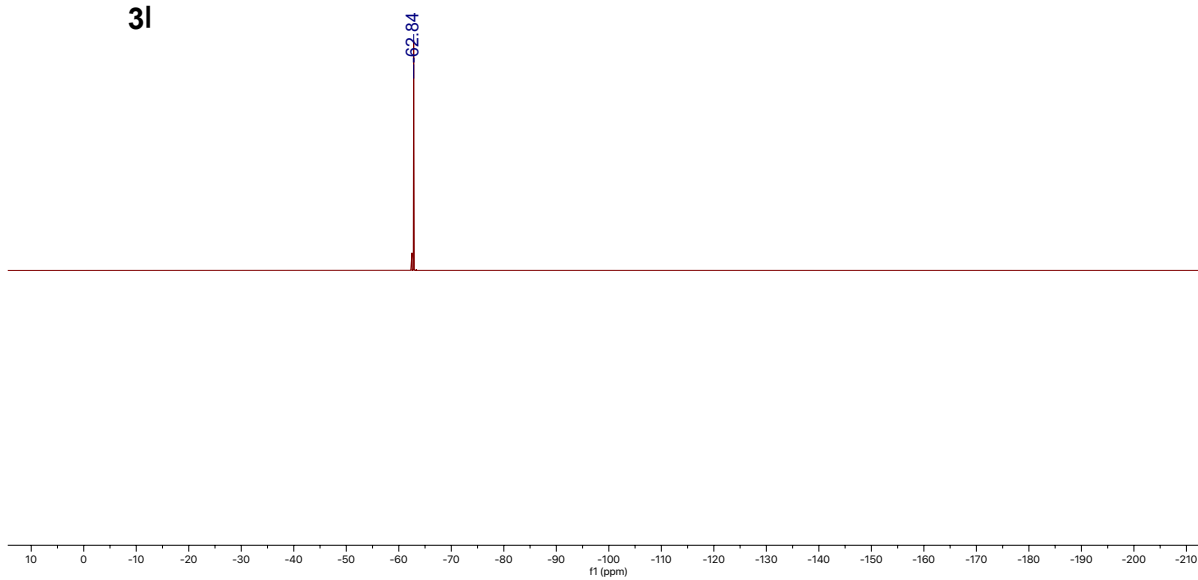
$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$  containing 0.03% v/v TMS) of **31**

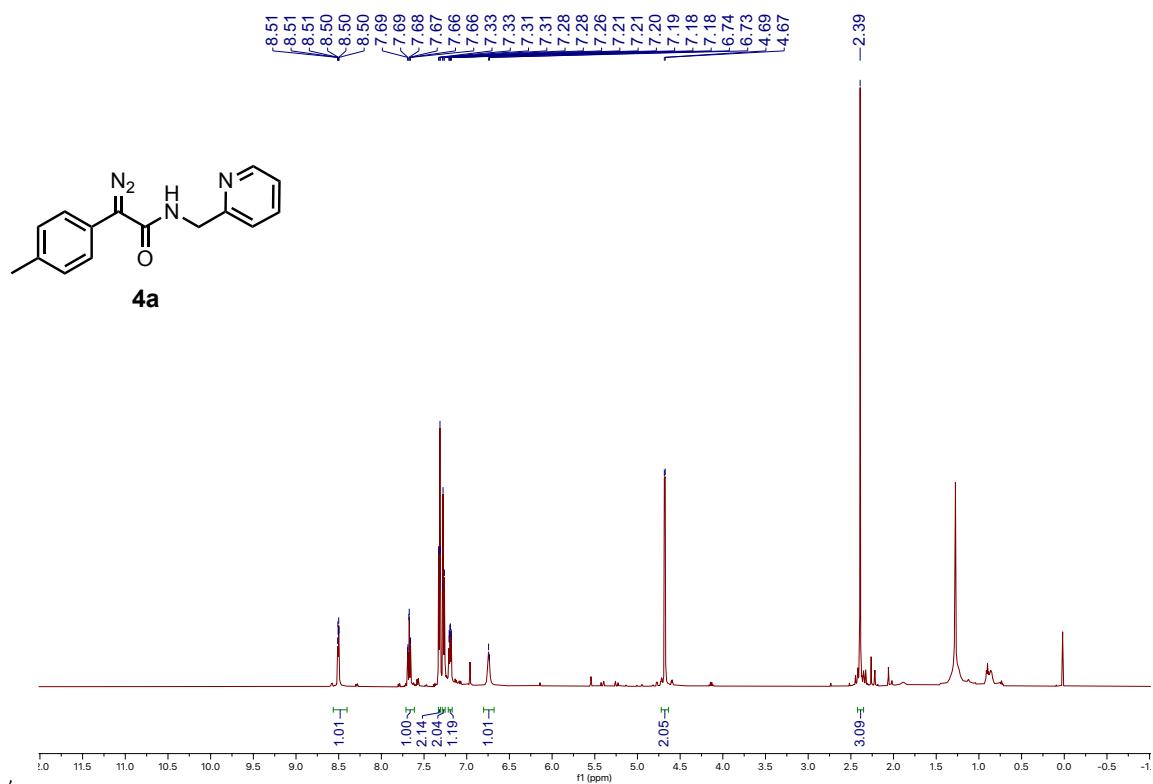
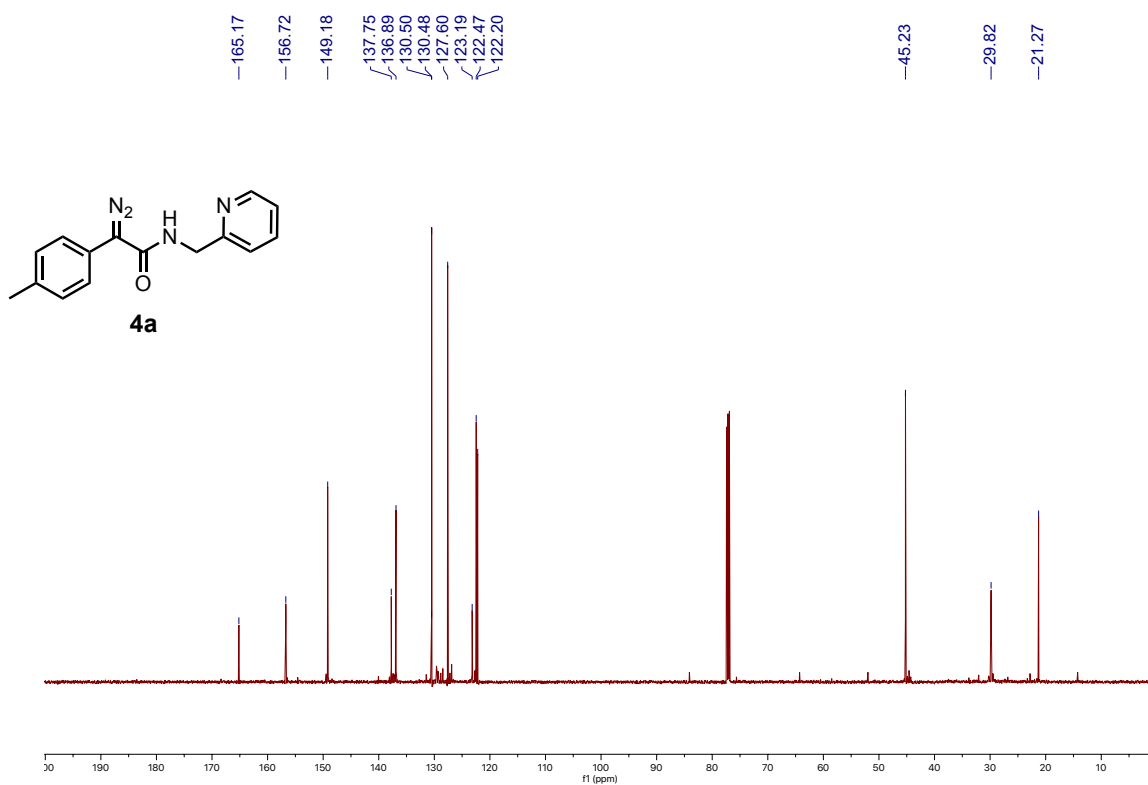


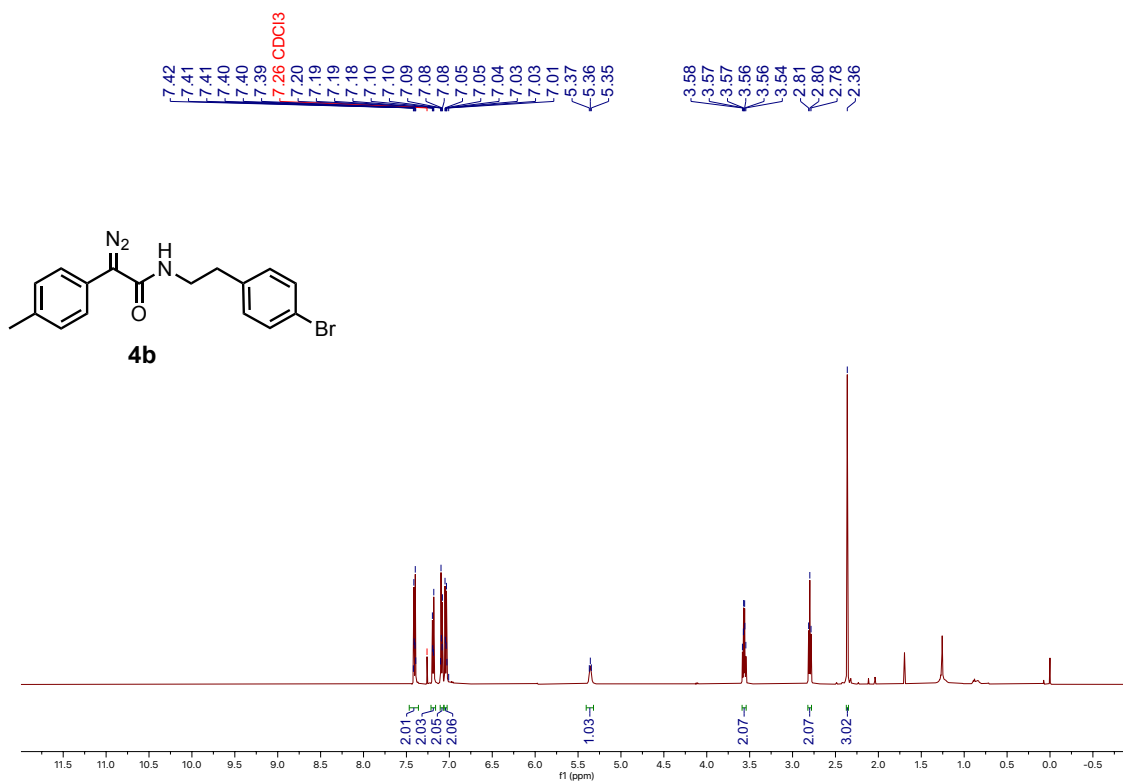
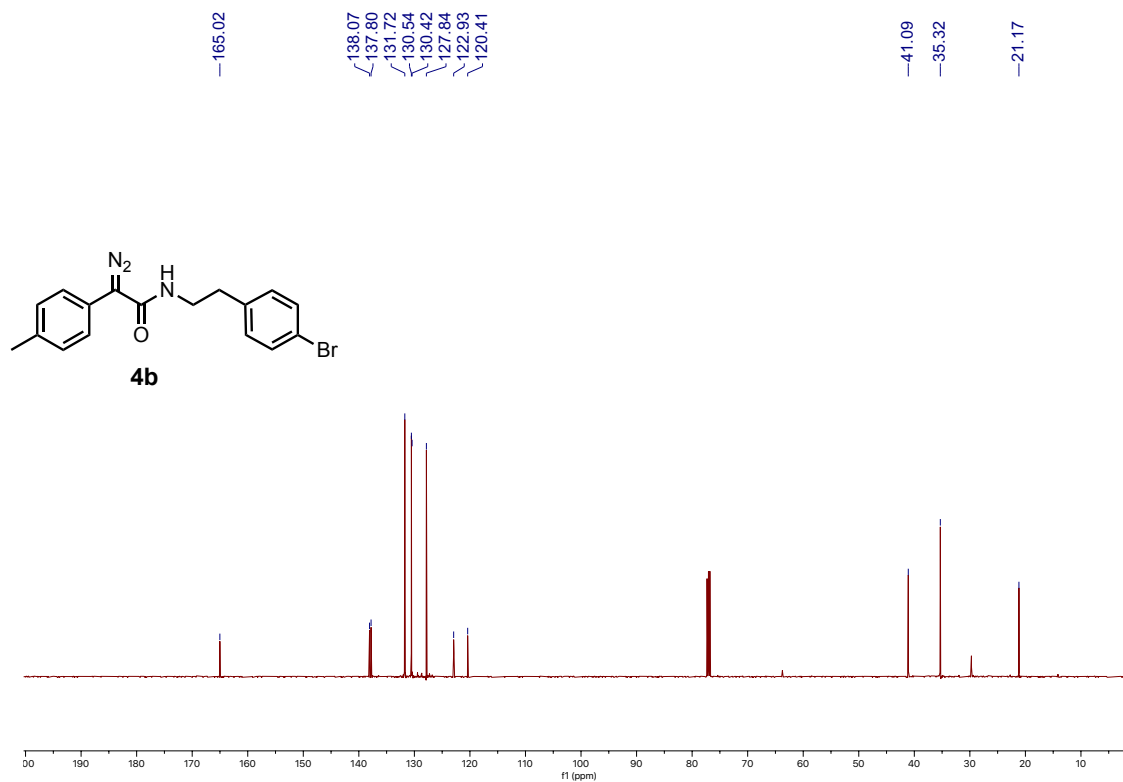
$^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$  containing 0.03% v/v TMS) of **3I**

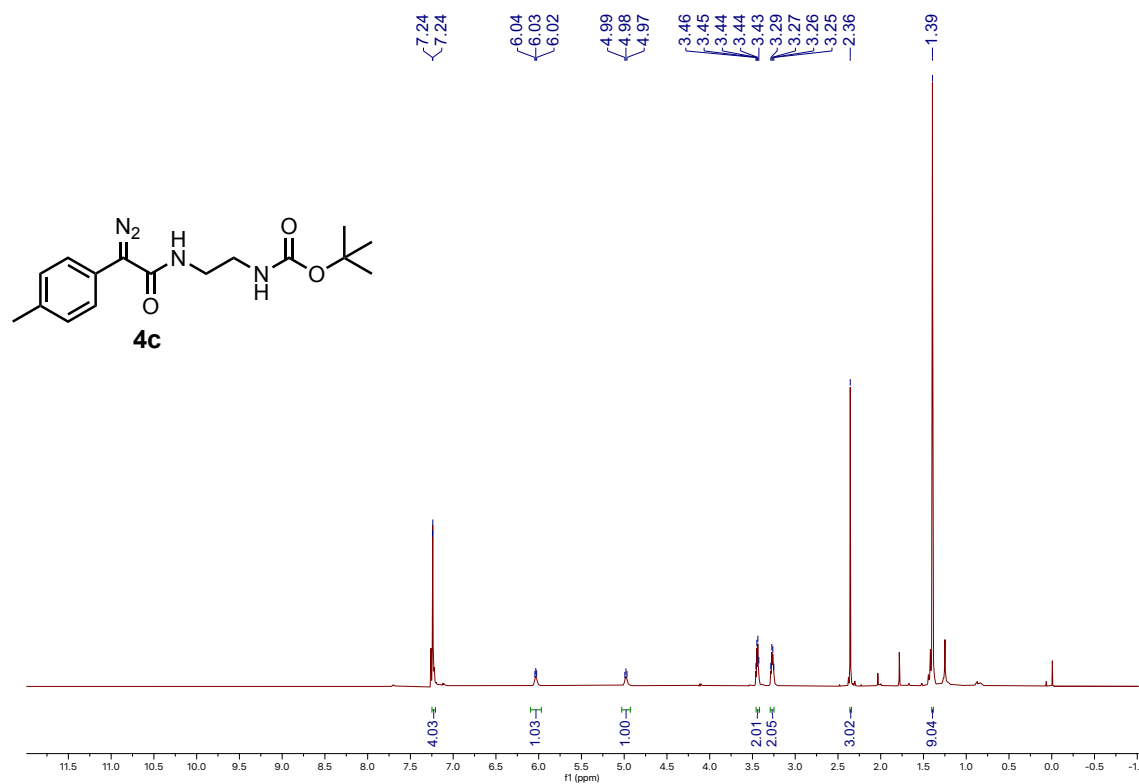
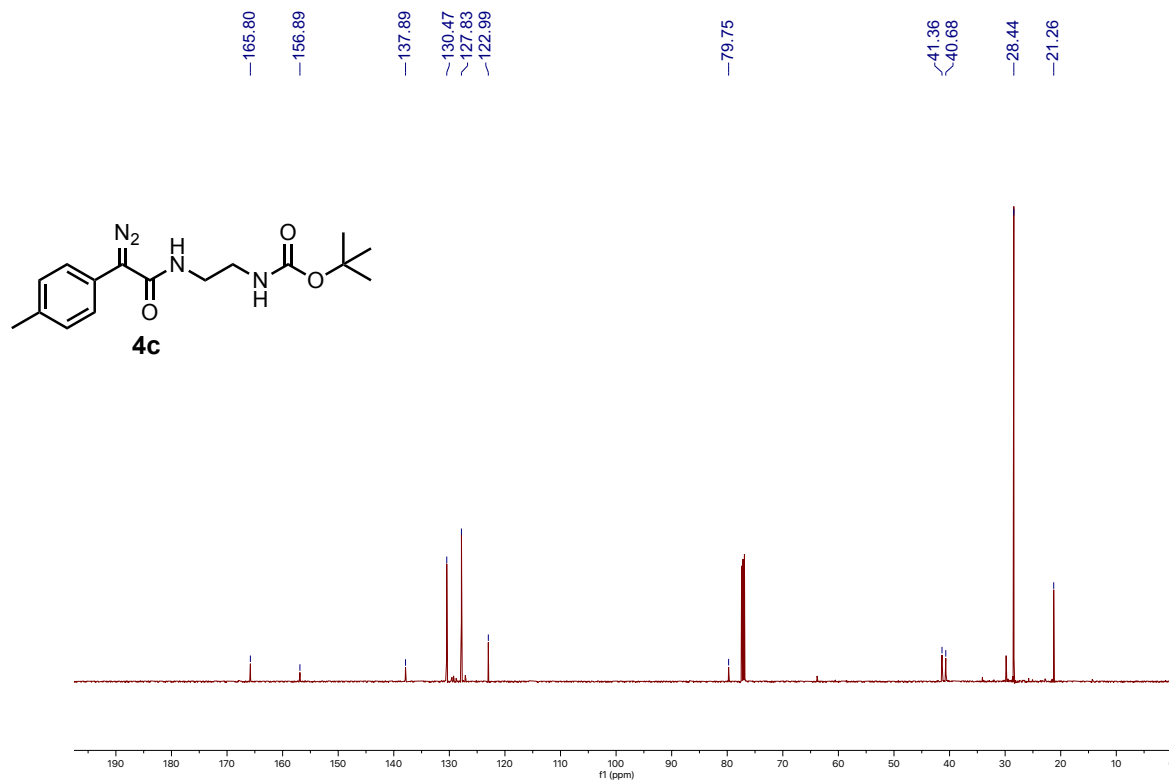


**3I**

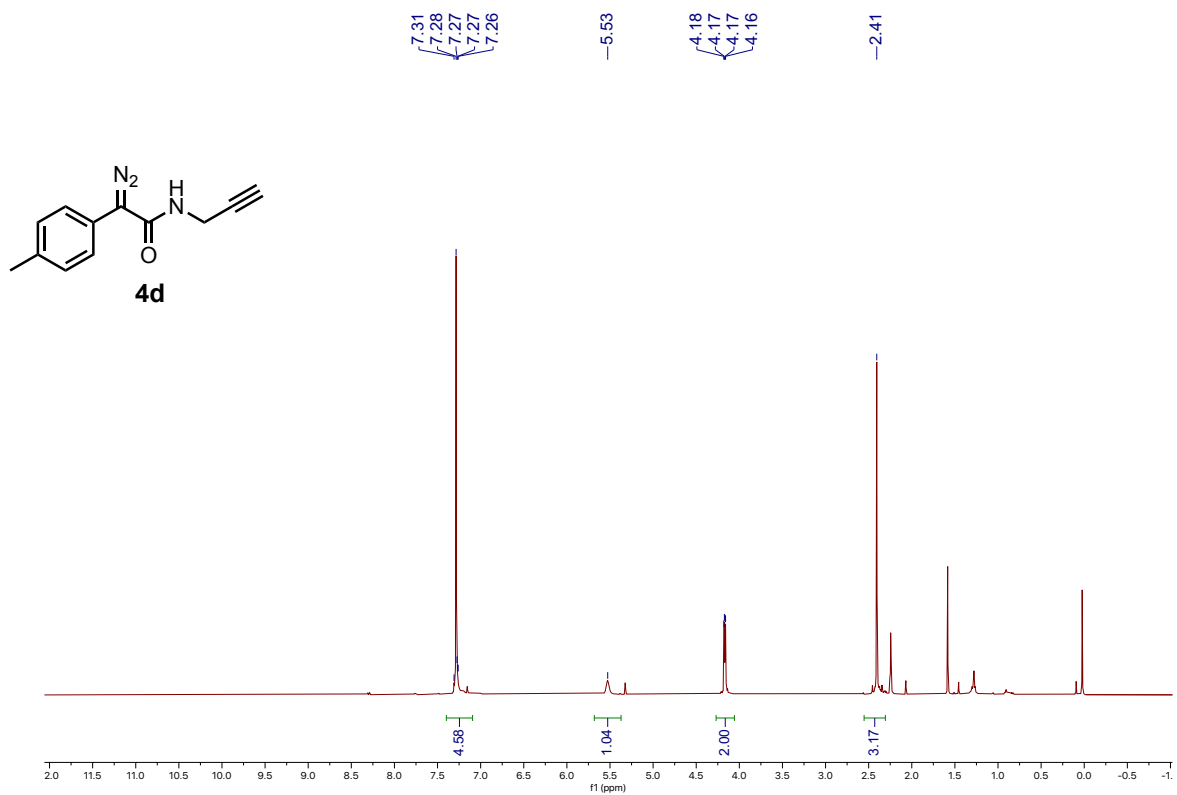


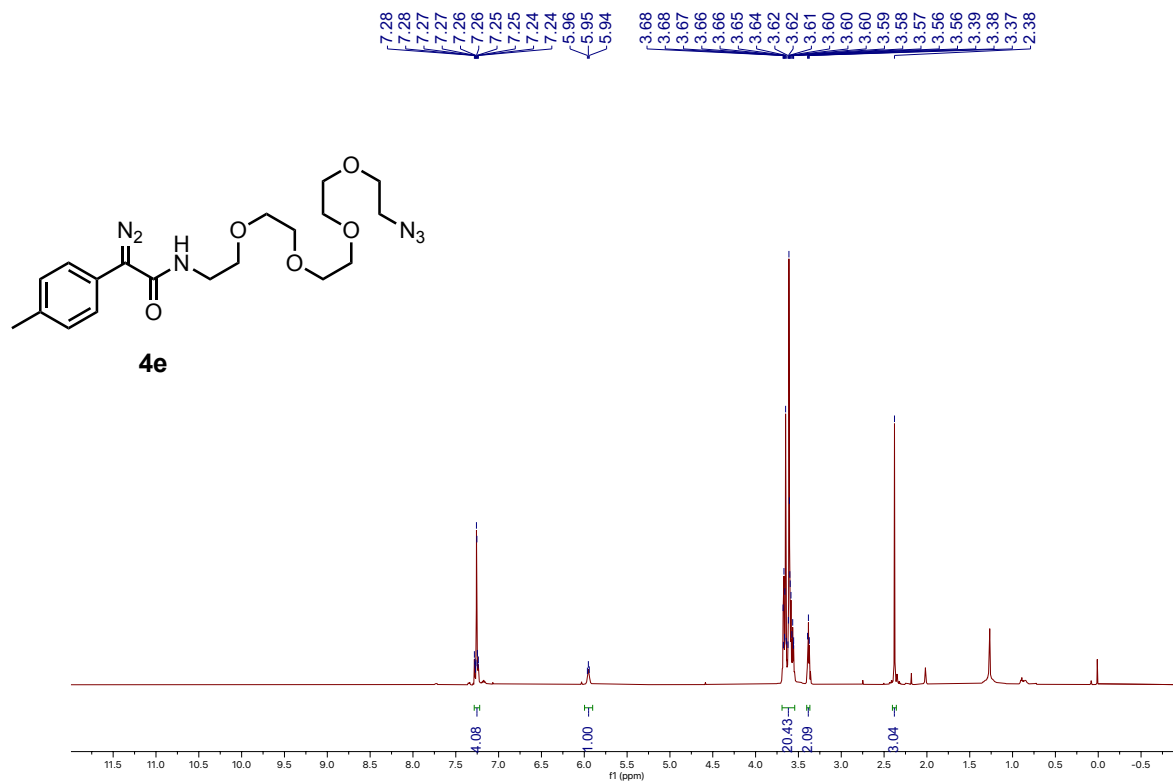
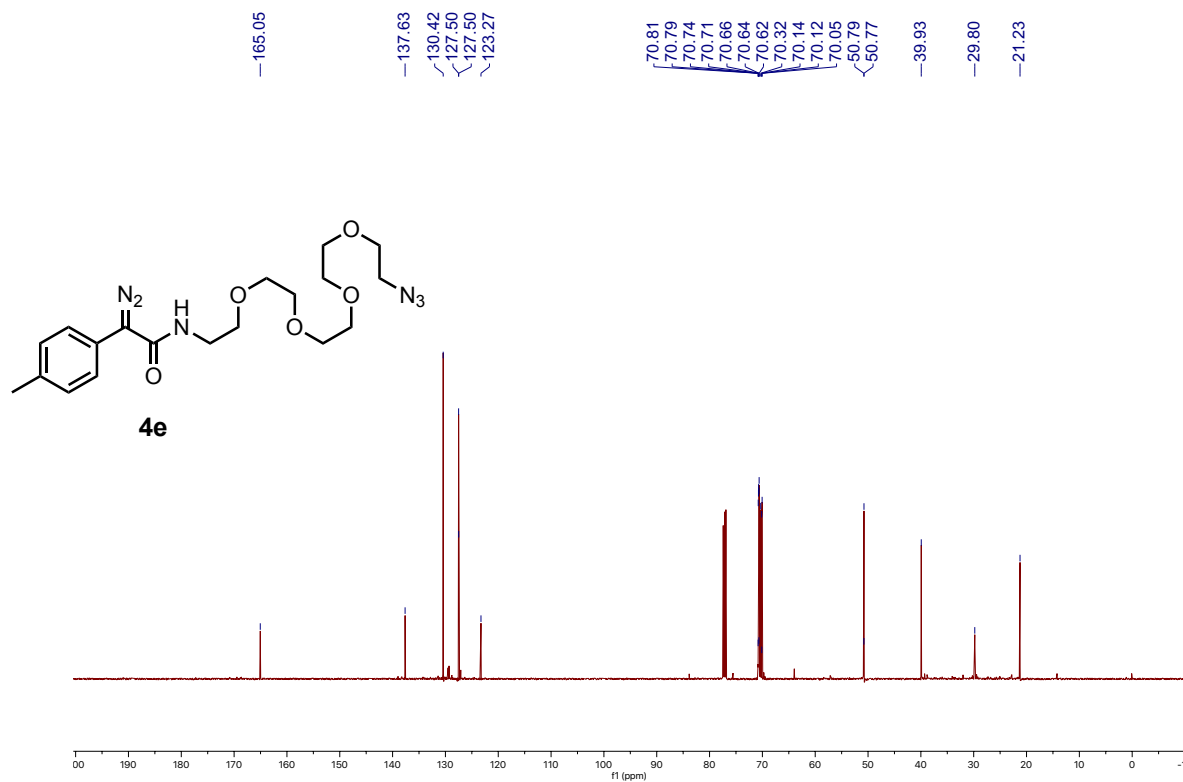
$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$  containing 0.03% v/v TMS) of **4a** $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$  containing 0.03% v/v TMS) of **4a**

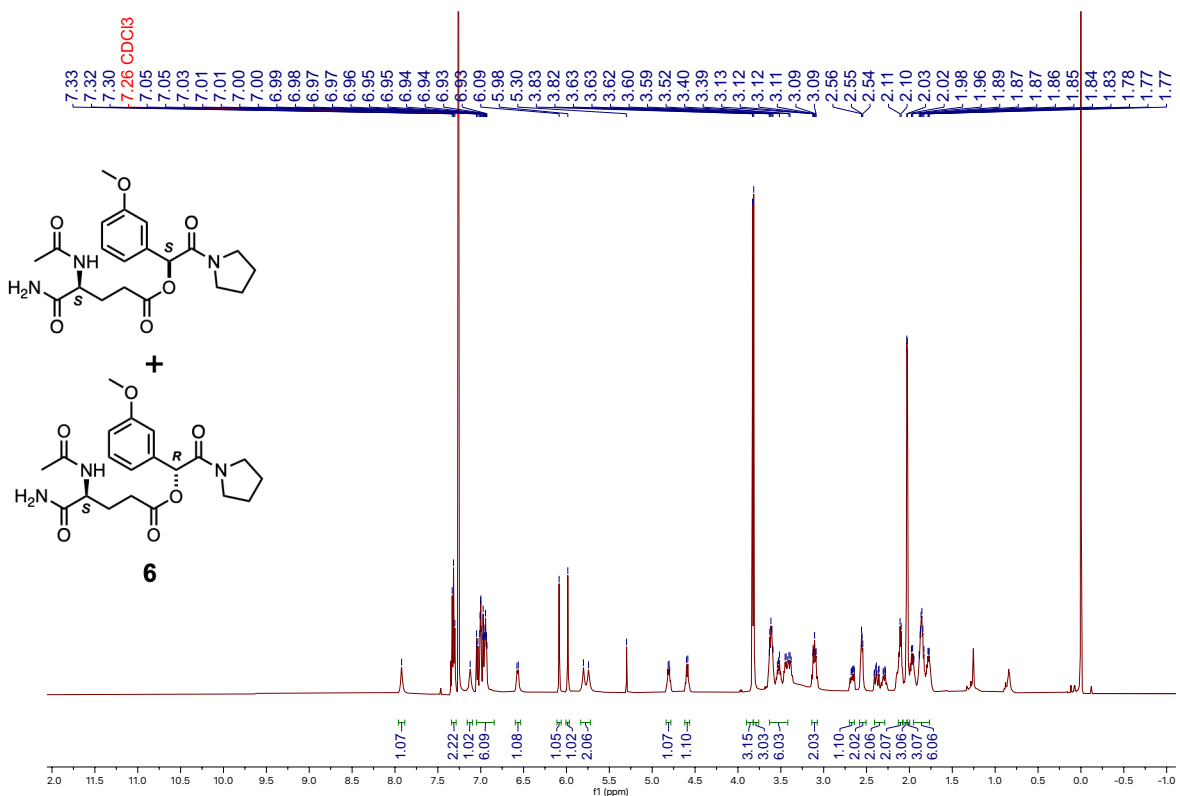
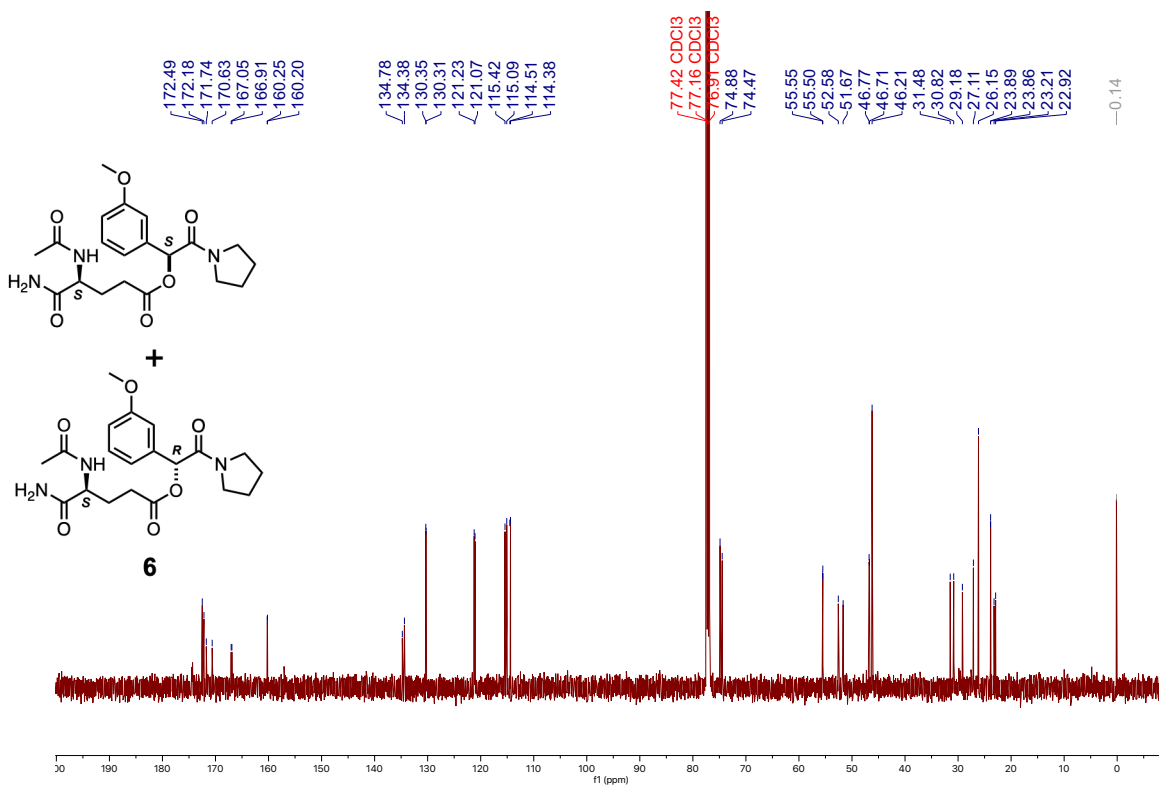
$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$  containing 0.03% v/v TMS) of **4b** $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$  containing 0.03% v/v TMS) of **4b**

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$  containing 0.03% v/v TMS) of **4c** $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$  containing 0.03% v/v TMS) of **4c**

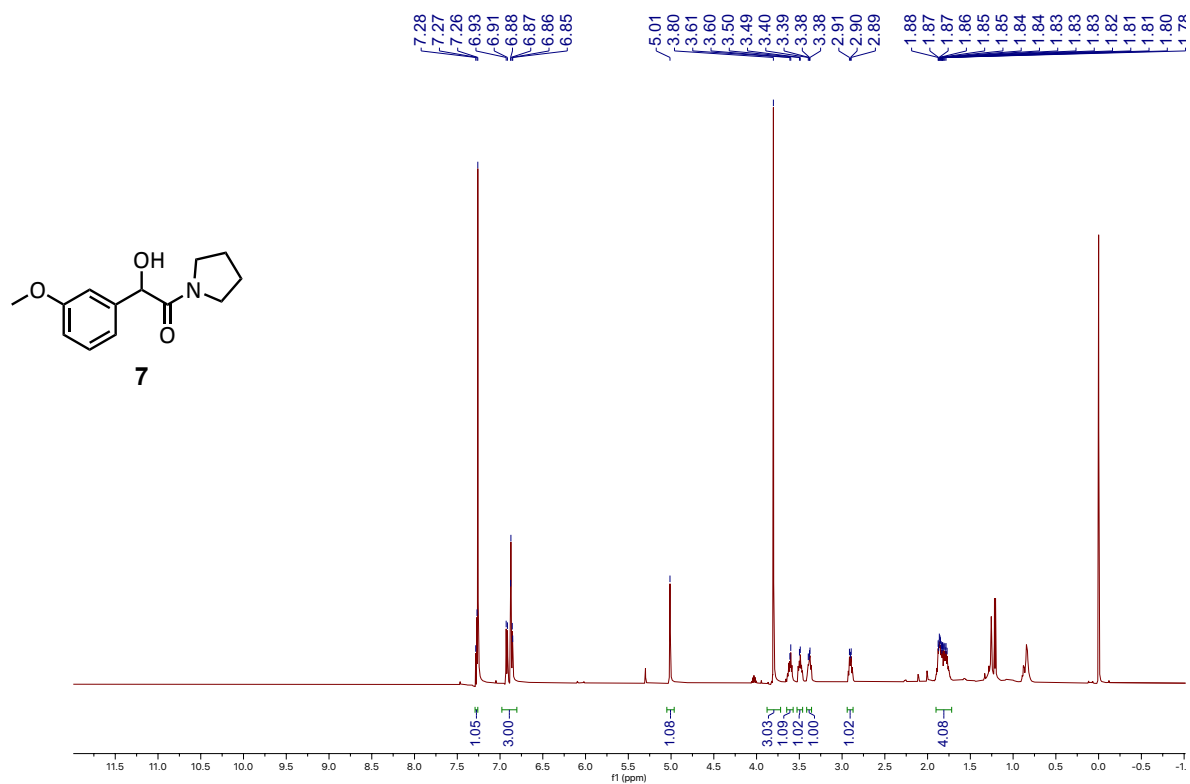
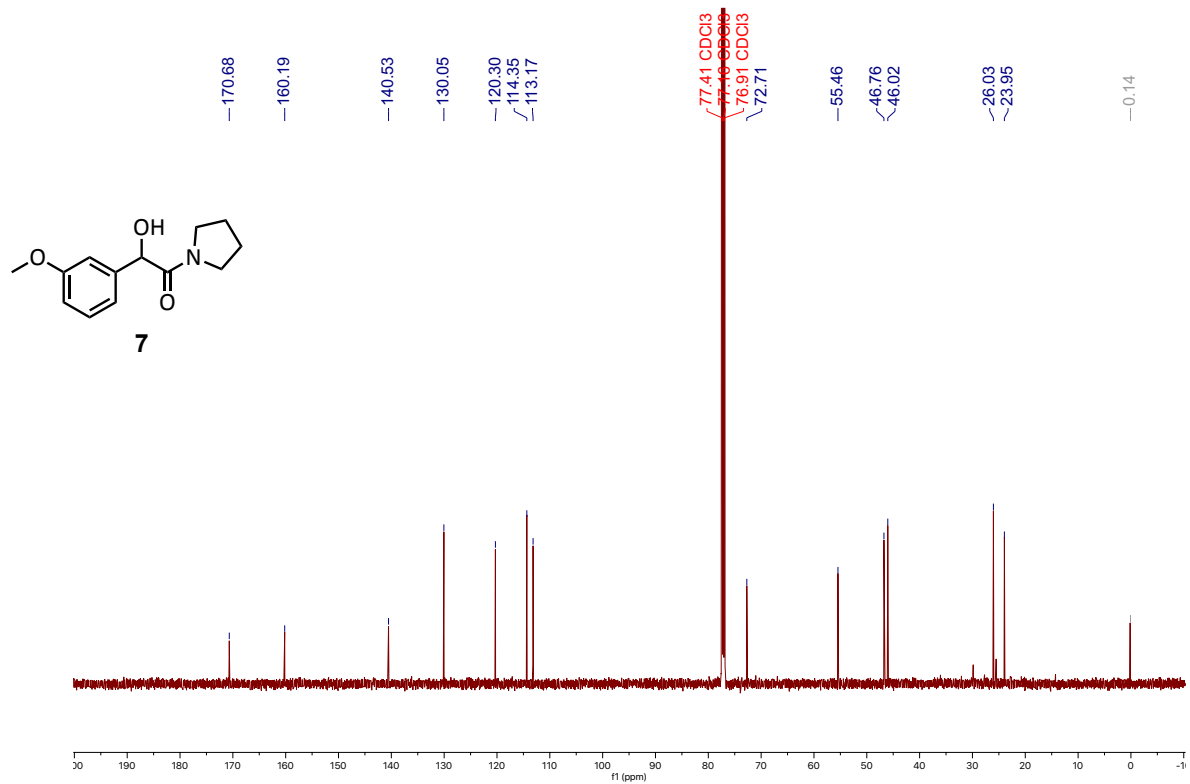
$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$  containing 0.03% v/v TMS) of **4d**



$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$  containing 0.03% v/v TMS) of **4e** $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$  containing 0.03% v/v TMS) of **4e**

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$  containing 0.03% v/v TMS) of **6** $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$  containing 0.03% v/v TMS) of **6**



$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$  containing 0.03% v/v TMS) of **7** $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$  containing 0.03% v/v TMS) of **7**

**XVI. References**

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