Supplementary Information (SI) for Green Chemistry.
This journal is © The Royal Society of Chemistry 2025

Supporting Information

Continuous flow synthesis of cyclobutenes via lithium ynolates

Aki Kohyama,[a]* Motoki Namioka,[a] Hiroshi Naka,[ab] Yosuke Ashikari,[c] Aichiro Nagaki,[c] Hiroshi Takikawa,[a] Yousuke Yamaoka[a]* and Kiyosei Takasu [a]*

[a]*Graduate School of Pharmaceutical Sciences, Kyoto University, Kyoto 606-8501, Japan*
[b] *Deuterium Science Research Unit, Center for the Promotion of Interdisciplinary Education and Research, Kyoto University, Kyoto 606-8501, Japan*
[c] *Faculty of Science Hokkaido University, Kita-10 Nishi-8 Kita-ku, Sapporo, Hokkaido 060-0810, Japan*
koyama.aki.6a@kyoto-u.ac.jp; yyamaoka@hyo-med.ac.jp ; takasu.kiyosei.6r@kyoto-u.ac.jp

Table of Contents

1. General Considerations

1.1. Solvents and reagents

Dehydrated THF and Et_2O were purchased from Kanto Chemical Co. Dehydrated hexane was distilled from CaH_2. Reagents were obtained from commercial suppliers. Methyl acrylate, acetic anhydride, TIPSOTf, and TBSOTf were distilled prior to use. 5,6-Dihydro-2H-pyran-2-one, furan-2(5H)-one, massoia lactone (Aldrich, W374400) were obtained from commercial suppliers and used without purification. α, α, α-Tribromo methylketones **1a**, **1b**, **1c**, **1d** and **S1** were prepared by following our previous report. [1]

1.2. Experimental procedures

All reactions in batch were carried out under argon atmosphere with dehydrated solvents under anhydrous conditions. Each solution on flow synthesis was freshly prepared in flame dried glassware under argon atmosphere with dehydrated solvents with under anhydrous conditions prior to use. All of flasks were flame-dried prior to use. Analytical TLC was performed on pre-coated silica gel plate (Wako Silica gel 70 F254) with visualization by UV-light (254 nm) irradiation and/or indicated stains. Flash column chromatography was performed on silica gel 60N (particle size 63-212 μm) or silica gel 60N (particle size 40-100 μm).

1.3. Analytical instrumentation

^{1}H-NMR and ^{13}C-NMR spectra were recorded on a JEOL JNM-LA 500 spectrometers (^{1}H; 500 MHz, ^{13}C; 126 MHz) or a JEOL JNM ECZ 600R (^{1}H; 600 MHz, ^{13}C; 151 MHz). ^{1}H and ^{13}C NMR spectra were referenced using the residual solvent signal (^{1}H NMR; TMS at 0.00 ppm, ^{13}C NMR; $CDCl_3$ at 77.16 ppm). NMR data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, m = multiplet), coupling constants (Hz), and integration. High-resolution mass spectra were obtained with SHIMADZU LCMS-IT-TOF or Thermo Exactive plus (ESI) spectrometer. Attenuated total reflectance Fourier transform infrared (ATR-IR) spectra were recorded on a Shimadzu IRAffinity-1 with an ATR attachment (MIRacle 10).

Raman spectra were obtained with a ReactRaman 785 analyzer and iC Raman software version 7 (Mettler Toledo).

1.4. General information on continuous flow synthesis

A flow microreactor system was composed of stainless steel pre-cooling units (**P1**, **P2**, etc.), stainless steel microtube reactors (**R1**, **R2**, etc.), T-shaped micromixers (**M1**, **M2**, etc.), PTFE tube, gastight syringes, and syringe pumps (Figure S1).

The pre-cooling units and the microtube reactors are made of stainless steel (SUS316) microtube with inner diameter of 1000 μm (Cat. No. 6010-32910, *GL Sciences*).

The Stainless steel (SUS316L) T-shaped micromixers with inner diameter of 250 or 500 μm (Cat. No. SS116T0250S or SS116T0500S) were manufactured by *Sanko Seiki Co., Inc*, and were purchased from a vender.

The PTFE tube with inner diameter of 0.96 mm was manufactured by *Chukoh Chemical Industries, Ltd.*

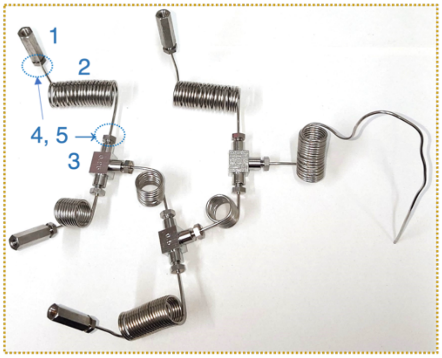
The syringe pumps (Model 11 Elite 70-4500, *Harvard Apparatus*) equipped with gastight syringes (Cat. No. 50-MR-LL-GT, *SGE*) were used to introduce each solution into the flow micromixers via PTFE tubes and SUS connectors.

-Residence time

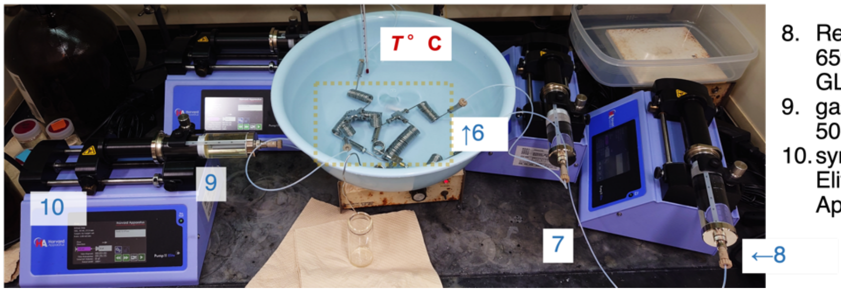
Residence time was calculated as shown below.

$$\text{Residence time (s)} = 60\,\pi\, r^2 L / 1000\nu_{total}$$

r: radius (mm)
L: length (mm)
ν_{total} = total flow rate (mL/min)



1. SUS connector (Union, 1/16 OUW, Cat. No. 6010-43120, GL Sciences)
2. stainless steel (SUS316) microtube with inner diameter of 1000 μm (Cat. No. 6010-32910, GL Sciences)
3. T-shaped micromixers (Cat. No. SS116T0250S and SS116T0500S, Sanko Seiki Co., Inc.)
4. SUS connector (Fitting, 1/16 OW, Cat. No. 6010-43020, GL Sciences)
5. One Ring Ferrule (1/16 FS, cat. No. 6010-41200, GL Sciences)
6. PEEK Tough Fitting (Cat. No. 6010-48600, GL Sciences)
7. PTFE tube (Cat. No. AWG19, Chukoh Chemical Industries, Ltd.)

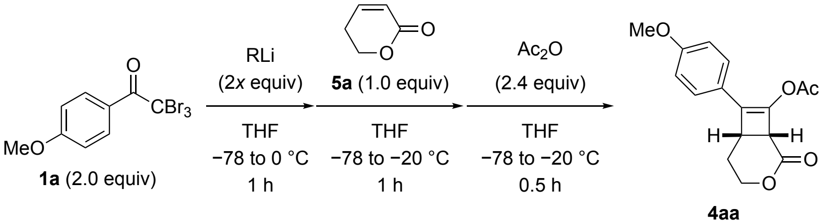


8. Replacement Connector (P-659, Cat. No. 6010-72020, GL Sciences)
9. gastight syringes (Cat. No. 50-MR-LL-GT, SGE)
10. syringe pumps (Model 11 Elite 70-4500, Harvard Apparatus)

Figure S1. General information on continuous flow systems

2. Experimental procedure in batch

2.1 Procedure for table 1, entries 2−4



*Note about the reaction scale: 0.48−0.50 mmol of **5a** were used.*

RLi*^{1} (8.0 equiv or 4.0 equiv) was added dropwise to a solution of **1a** (2.0 quiv) in THF (0.04−0.08 M based on **5a**) at −78 °C. After being stirred for 10 min at −78 °C, the reaction mixture was warmed up to 0 °C. After being stirred for 1 h at 0 °C, the reaction mixture was recooled to −78 °C and **5a** (1.0 equiv) was added to the reaction mixture, and then reaction mixture was warmed up to −20 °C. After being stirred for 1 h at −20 °C, the reaction mixture was recooled to −78 °C. After Ac_2O (2−2.4 equiv) was added to the reaction mixture, the reaction mixture was warmed up to −20 °C. After being stirred at −20 °C for 30 min, the reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with AcOEt (×3). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/AcOEt = 4/1) to afford cyclobutene **4aa**.

*1 ^{t}BuLi: 1.6 M in *n*-pentane, 8.0 equiv
^{s}BuLi: 1.2 M in cyclohexane, 4.0 equiv
^{n}BuLi: 1.6 M in *n*-hexane, 4.0 equiv

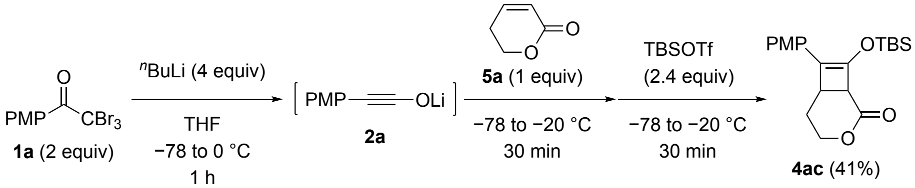
Procedure for entry 1 in table 1 is shown in our previous report. [1]

2.2 Procedures for table 2, table 3: Yields of 4 in parenthesis.

Yields of **4aa**, **4ab**, **4ba**, and **4bb** in batch were shown in our previous report. [1]

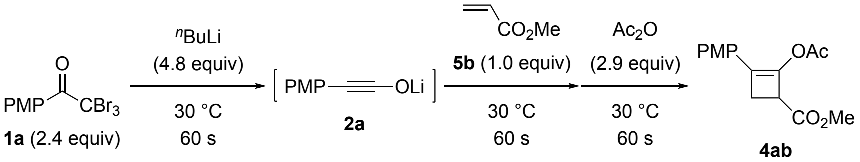
Yields of **4ac** was calculated by the following procedure. *n*-BuLi and THF were used instead of *t*-BuLi and Et_2O

which were used in our previous report, because the original protocol did not afford **4ac**.



A solution of ^{n}BuLi (1.5 mL, 2.4 mmol, 4.0 equiv, 1.6 M in hexane) was added to a solution of **1a** (465 mg, 1.00 mmol, 2.0 quiv) in THF (6 mL) at −78 °C and then the reaction mixture was warmed up to 0 °C. After being stirred for 1 h at 0 °C, the reaction mixture was cooled to −78 °C. After **5a** (51 μL, 0.60 mmol, 1.0 equiv) was added to the reaction mixture at −78 °C, the reaction mixture was warmed up to −20 °C and stirred for 30 min at −20 °C. After the reaction mixture was cooled to −78 °C, TBSOTf (330 μL, 1.44 mmol, 2.4 equiv) was added to the mixture at −78 °C. After being warmed up to −20 °C, the reaction mixture was stirred for 30 min at −20 °C. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with AcOEt (×3). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (Hexane : AcOEt = 9 : 1 to 3 : 1) to afford **4ac** (89 mg, 0.25 mmol, 41%yield) as a colorless oil.

2.3 Procedures for table 3, entry 2



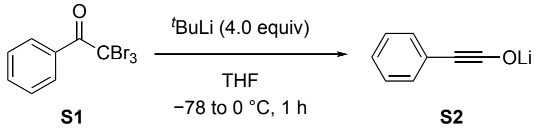
A solution of ^{n}BuLi (2.5 mL, 4.0 mmol, 4.0 equiv, 1.6 M in hexane) was added to a solution of **1a** (774 mg, 2.00 mmol, 2.0 quiv) in THF (10 mL) at 30 °C. After the reaction mixture was stirred for 60 s at 30 °C, **5b** (90 μL, 1.0 mmol, 1.0 equiv) was added to the mixture. After the reaction mixture was stirred for 60 s at 30 °C, Ac_2O (230 μL, 2.43 mmol, 2.4 equiv) was added to the mixture. After being stirred for 60 s at 30 °C, reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with AcOEt (×3). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Yield of **4ab** was determined by ^{1}H NMR (internal standard: Ph_3CH).

3. Experimental procedure in flow

3.1 Screening of reaction temperature and residence time of [2+2] reaction in flow

Before setting a continuous flow system, we screened reaction temperature and residence time of [2+2] reaction in flow by using ynolate **S2** freshly prepared in batch (see 3.7.1, 3.7.2).

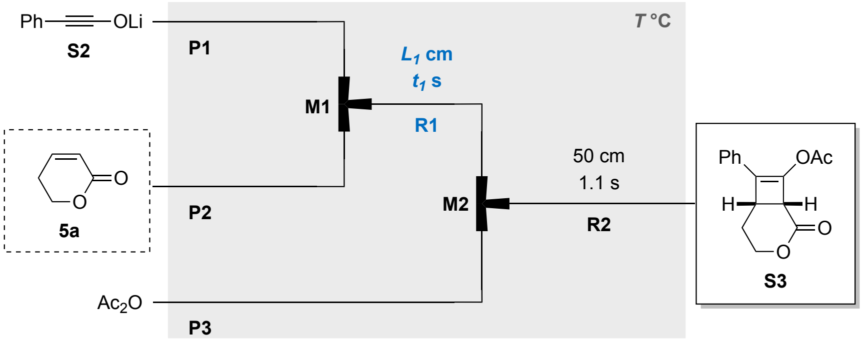
3.1.1 Preparation of ynolate S2



^{t}BuLi (1.6 M in pentane, 11.0 mL, 17.6 mmol, 4.0 equiv) was added dropwise to a solution of 2,2,2-tribromo-1-phenylethan-1-one (S**1**, 1.57 g, 4.40 mmol, 1.0 quiv) in THF (44 mL) at −78 °C. After being stirred for 10 min, the reaction mixture was warmed up to 0 °C and stirred for another 1 h to afford S**2** (0.080 M, purple solution). The resulting lithium ynolate **S2** was immediately used for an experiment shown in table S1.

3.1.2 Continuous flow synthesis of S3

Table S1



		t_1 (s)			
		3.9	7.9	11.8	15.7
T (°C)	40	54%	76%	60%	51%
	30	40%	65%	86%	61%
	20	37%	48%	70%	50%
	0	23%	29%	60%	48%

A flow microreactor system consisting of two T-shaped micromixers **M1** and **M2,** two microtube reactors **R1** and **R2**, and three pre-cooling units **P1**, **P2**, and **P3** were used in a water bath at T °C. After a steady state was reached, the resulting solution was collected in a sample tube filled with saturated aqueous NH_4Cl (6 mL) for 30 s. The collected mixtures* were extracted with AcOEt (10 mL × 3). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Yield was determined by ^{1}H NMR (internal standard: dibromomethane).

*Two samples (2 × 30 s) were used for each condition.

Stock Solutions and Pump Flow Rates

	equiv	*solutions*	*Flow rate / (mL/min)*
S2	2.4	0.080 M in THF/pentane	9.4
5a	1.0	0.12 M in THF	2.6
Ac_2O	2.9	0.096 M in THF	9.4

Relationship between Length (L_1) and Residence time (t_1)

L_1 / cm	t_1 / s
100	3.9
200	7.9
300	11.8
400	15.7

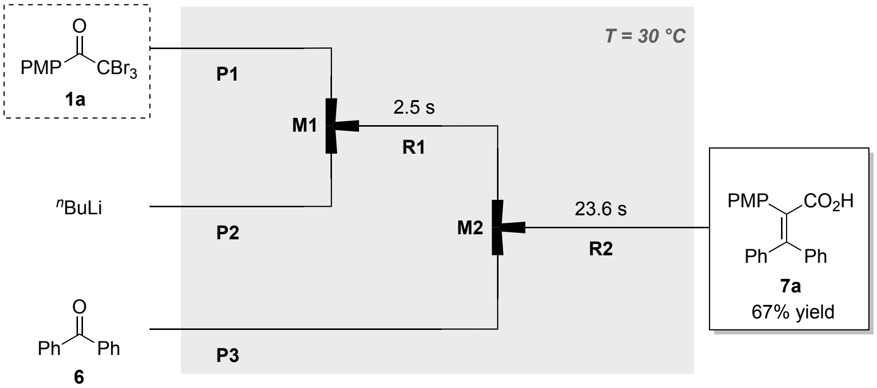
Fixed Lengths

R1	L_1 cm
R2	50 cm (residence time: t_2 = 1.1 s)
P1, P2, P3	100 cm

Fixed inner diameters

M1, M2	500 µm

3.2 Procedure for scheme 4b



A flow microreactor system consisting of two T-shaped micromixers **M1** and **M2**, two stainless steel microtube reactors **R1** and **R2**, and three pre-cooling units **P1**, **P2**, and **P3** were used in a water bath at 30 °C. After a steady state was reached, the resulting solution was collected in a sample tube filled with 10% aqueous NaOH (6 mL) for 30 s. The resulting solution* was acidified with 5% aqueous HCl and extracted with AcOEt (20 mL × 3). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Yield was determined by ^{1}H NMR (internal standard: Ph_3CH).

*Two samples (2 × 30 s) were used for each condition.

Stock Solutions and Pump Flow Rates

	equiv	*solutions*	*Flow rate / (mL/min)*
1a	1.0	0.10 M in THF	7.52
***n*BuLi**	2.0	0.80 M in *n*-hexane	1.88
6	1.0	0.29 M in THF	2.6

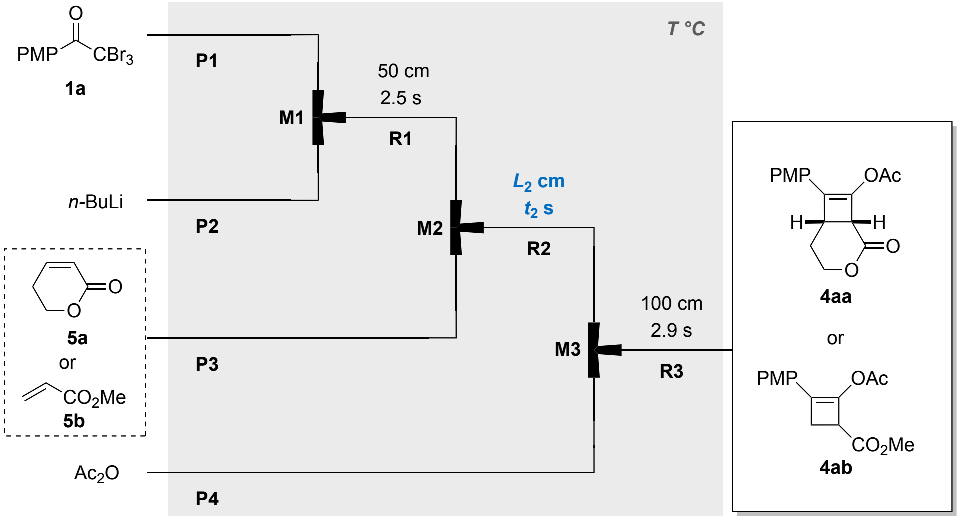
Fixed Lengths

R1	50 cm (residence time: t_1 = 2.5 s)
R2	600 cm (residence time: t_2 = 23.6 s)
P1, P3	100 cm
P2	50 cm

Fixed inner diameters

M1	250 µm
M2	500 µm

3.3 Procedure for table 2



General procedure A (GPA): A flow microreactor system consisting of three T-shaped stainless-steel micromixers **M1**, **M2**, and **M3**, three stainless steel microtube reactors **R1**, **R2**, and **R3**, and four pre-cooling units **P1**, **P2**, **P3**, and **P4** were used in a water bath at *T* °C. After a steady state was reached, the resulting solution was collected in a sample tube filled with saturated aqueous NH_4Cl (6 mL) for 30 s. The collected mixture* was extracted with AcOEt (10 mL × 3). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Yield was determined by ^{1}H NMR (internal standard: Ph_3CH).
*Two samples (2 × 30 s) were used for each condition.

Stock Solutions and Pump Flow Rates

	equiv	*solutions*	*Flow rate / (mL/min)*
1a	2.4	0.10 M in THF	7.52
***n*BuLi**	4.8	0.80 M in *n*-hexane	1.88
5a *or* **5b**	1.0	0.12 M in THF	2.6
Ac_2O	2.9	0.23 M in THF	4.0

Relationship between Length (L_2) and Residence time (t_2)

L_2/ cm	t_2 / s
150	5.9
300	11.8
450	17.7
600	23.6

Fixed Lengths

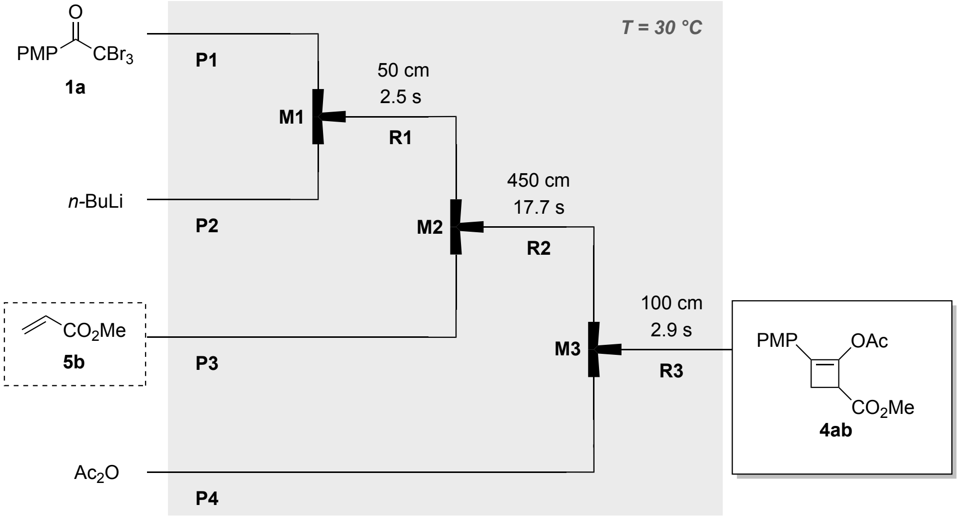
R1	50 cm (residence time: t_1 = 2.5 s)
R3	100 cm (residence time: t_3 = 2.9 s)
P1, P3, P4	100 cm
P2	50 cm

Fixed inner diameters

M1	250 µm
M2, M3	500 µm

3.4 Effect of Equivalent of Ynolates

Table S2



entry	**1a** (equiv) **:** **5b** (equiv)	Yield of **4ab (%)**
1	1.0 : 1.0	54
2	1.5 : 1.0	53
3	2.4 : 1.0	63

Note: Entry 3 is the best condition in Table 2b. Yield was calculated based on **5b**.

Following **GPA** combined with the flow system as shown above, **4ab** was obtained. **Fixed Lengths** and **Fixed inner diameters** are same as shown in section 3.3 on page S6.

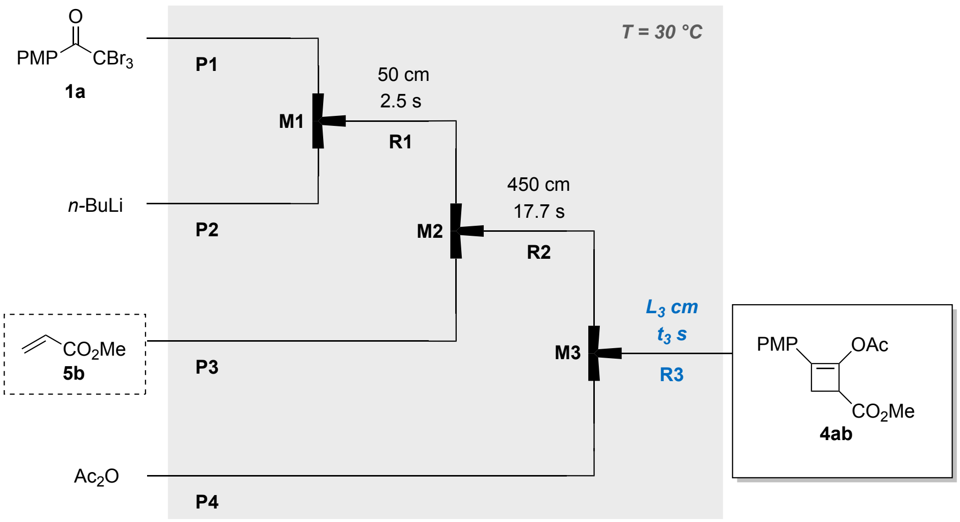
Stock Solutions and Pump Flow Rates

	equiv	*solutions*	*Flow rate / (mL/min)*
1a	x	0.10 M in THF	7.52
***n*BuLi**	2x	0.80 M in *n*-hexane	1.88
5b	1.0	c_3 M in THF	2.6
Ac_2O	1.2x	0.23 M in THF	4.0

Entry 1 (x = 1.0, $c_3 = 0.29$), entry 2 (x = 1.5, $c_3 = 0.19$), entry 3 (x = 2.4, $c_3 = 0.12$)

3.5 Effect of Residence time (t_3) for Acetylation

Table S3



Entry	t_3 (s)	Yield of **4ab** (%)
1	2.9	63
2	5.9	61
3	8.8	62

Following **GPA** combined with the flow system as shown above, **4ab** was obtained. **Stock Solutions and Pump Flow Rates** and **Fixed inner diameters** are same as shown in section 3.3 on page S6.

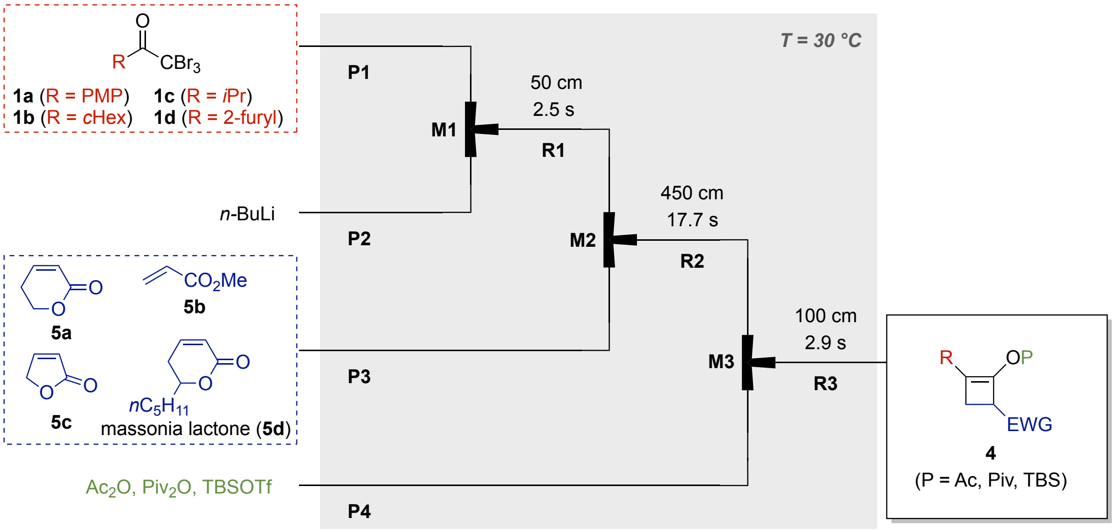
Relationship between Length (L_3) and Residence time (t_3)

L_3/ cm	t_3 / s
100	2.9
200	5.9
300	8.8

Fixed Lengths

R1	50 cm (residence time: t_1 = 2.5 s)
R2	450 cm (residence time: t_2 = 17.7 s)
P1, P3, P4	100 cm
P2	50 cm

3.6 Procedure for figure 4



Following **GPA** combined with the flow system as shown above, **4ba**, **4bb**, **4ca**, **4bb**, **4db**, **4ac**, **4ad**, **4bd**, **4ae**, **4be**, and **4af** were obtained.

Stock Solutions and Pump Flow Rates

	equiv	*solutions*	*Flow rate / (mL/min)*
1a, 1b, 1c, 1d	2.4	0.10 M in THF	7.52
***n*BuLi**	4.8	0.80 M in *n*-hexane	1.88
5a, 5b, 5c, 5d	1.0	0.12 M in THF	2.6
Ac_2O *or* TBSOTf *or* Piv_2O	2.9	0.23 M in THF	4.0

Fixed Lengths

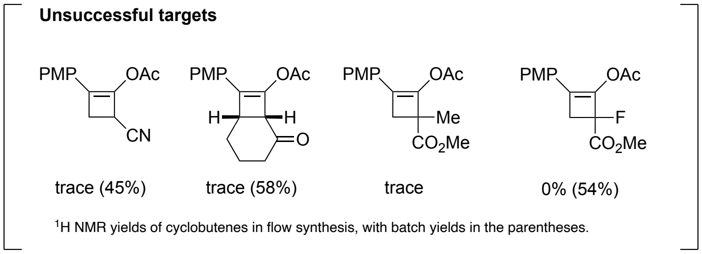
R1	50 cm (residence time: t_1 = 2.5 s)
R2	450 cm (residence time: t_2 = 17.7 s)
R3	100 cm (residence time: t_3 = 2.9 s)
P1, P3, P4	100 cm
P2	50 cm

Fixed inner diameters

M1	250 µm
M2, M3	500 µm

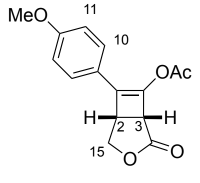
For the flow synthesis of **4ba**, **4ac**, **4ae**, and **4be**, few parameters were changed as follows;
4ba: T = 0 °C, R3 = 50 cm, t_3 = 1.5 s.
4ac: T = 20 °C.
4ae and **4be:** ***5a*** *(0.83 equiv; 0.10 M in THF; 2.6 mL/min)*

note
.



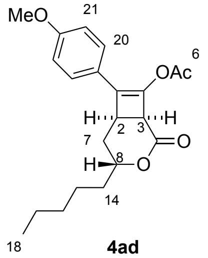
3.6.1 Characterization data of cyclobutenes

Spectroscopic data of **4aa, 4ab, 4ba, 4ca, 4bb** and **4db** were consistent with those previously reported in the literature. [1]



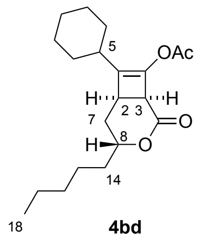
4ac

4ac: R_f 0.20 (hexane:AcOEt = 2:1, UV); ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.30 (dd, *J* = 2.5, 9.0 Hz, 2H, *H10*), 6.91 (dd, *J* = 2.5, 9.0 Hz, 2H, *H11*), 4.43 (dd, *J* = 6.7, 9.9 Hz, 1H, *H15*), 4.39 (dd, *J* = 9.9, 2.1 Hz, 1H, *H15*), 4.23 (d, *J* = 3.9 Hz, 1H, *H3*), 3.83 (s, 3H, -O*Me*), 3.72 (ddd, *J* = 2.1, 3.9, 6.7 Hz, 1H, *H2*), 2.27 (s, 3H, *Ac*).; ^{13}C -NMR (125 MHz, CDCl$_3$): 173.0, 167.1, 159.9, 134.7, 128.3, 127.8, 123.0, 114.5, 67.6, 55.5, 48.4, 35.9, 20.8.; IR (neat): 1767, 1604, 1512, 1253 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{14}NaO_5$ ([M+Na]$^+$) *m/z* 297.0734, found *m/z* 297.0730.



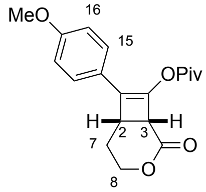
4ad

4ad: R_f 0.20 (hexane:AcOEt = 4:1, UV); ^{1}H NMR (600 MHz, CDCl$_3$): δ 7.31 (d, *J* = 8.9 Hz, 2H, *H20*), 6.91 (d, *J* = 8.9 Hz, 2H, *H21*), 4.66 – 4.45 (m, 1H, *H8*), 4.05 (d, *J* = 4.6 Hz, 1H, *H3*), 3.83 (s, 3H, O-*Me*), 3.45 (ddd, *J* = 1.6, 4.6, 5.0 Hz, 1H, *H2*), 2.25 (s, 3H, *H6*), 2.19 (ddd, *J* = 1.8, 1.8 14.5 Hz, 1H, *H7$_{eq}$*), 1.84 (ddd, *J* = 5.0, 11.5, 14.5 Hz, 1H, *H7$_{ax}$*), 1.71 – 1.62 (m, 1H), 1.54 – 1.43 (m, 2H), 1.37 – 1.15 (m, 5H), 0.84 (t, *J* = 7.1 Hz, 3H, *H18*).; ^{13}C NMR (150 MHz, CDCl$_3$): 170.3, 168.0, 159.8, 130.9, 128.7, 128.4, 123.2, 114.4, 74.7, 55.5, 47.3, 35.2, 32.9, 31.8, 30.8, 24.9, 22.6, 20.7, 14.1; IR (neat): 1761, 1719, 1689, 1607, 1508, 1251 cm^{-1}; HRMS (ESI) calcd for $C_{21}H_{26}NaO_5$ ([M+Na]$^+$) *m/z* 381.1673, found *m/z* 381.1677.



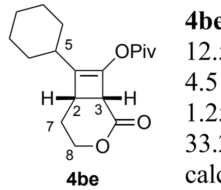
4bd

4bd: R_f 0.30 (hexane:AcOEt = 4:1, UV); ^{1}H NMR (600 MHz, CDCl$_3$): δ 4.66 – 4.53 (m, 1H, *H8*), 3.77 (dd, *J* = 1.9, 4.2 Hz, 1H, *H3*), 3.03 (dd, *J* = 4.2, 4.3 Hz, 1H, *H2*), 2.14 (s, 3H, *Ac*), 2.18 – 2.08 (m, 1H, *H5*), 2.00 (ddd, *J* = 1.8, 1.9, 14.5 Hz, 1H, *H7$_{eq}$*), 1.83 – 1.13 (m, 19H), 0.89 (t, *J* = 7.1 Hz, 3H, *H18*).; ^{13}C NMR (151 MHz, CDCl$_3$): 170.9, 168.5, 137.2, 131.7, 74.7, 46.8, 36.2, 35.2, 33.1, 31.8, 31.2, 30.6, 30.1, 26.04, 25.96, 25.8, 24.9, 22.7, 20.6, 14.2.; IR (neat): 2924, 2854, 1767, 1728, 1249 cm^{-1}; HRMS (ESI) calcd for $C_{20}H_{30}NaO_4$ ([M+Na]$^+$) *m/z* 357.2037, found *m/z* 357.2039.



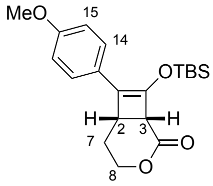
4ae

4ae: R_f 0.20 (hexane:AcOEt = 2:1, UV); ^{1}H NMR (600 MHz, CDCl$_3$): δ 7.28 (d, *J* = 8.9 Hz, 2H, *H15*), 6.89 (d, *J* = 9.0 Hz, 2H, *H16*), 4.59 – 4.49 (m, 1H, *H8$_{ax}$*), 4.21 (dddd, *J* = 1.2, 3.4, 3.4, 11.4 Hz, 1H, *H8$_{eq}$*), 4.02 (d, *J* = 4.1 Hz, 1H, *H3*), 3.47 (ddd, *J* = 3.8, 3.8, 4.1 Hz, 1H, *H2*), 2.18 – 2.11 (m, 2H, *H7*), 1.37 – 1.28 (s, 9H, *Piv*).; ^{13}C NMR (150 MHz, CDCl$_3$): 175.8, 169.8, 159.8, 131.3, 128.2, 128.1, 123.3, 114.4, 64.2, 55.5, 47.6, 39.1, 33.1, 27.1, 25.6.; IR (neat): 1732, 1688, 1607, 1510, 1252 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{22}NaO_5$ ([M+Na]$^+$) *m/z* 353.1360, found *m/z* 353.1365.



4be

4be: R_f 0.40 (hexane:AcOEt = 2:1, UV); ^{1}H NMR (600 MHz, CDCl$_3$): δ 4.59 (ddd, *J* = 2.3, 11.2, 12.5 Hz, 1H, *H8$_{ax}$*), 4.28 – 4.22 (m, 1H, *H8*), 3.77 (dd, *J* = 2.3, 4.3 Hz, 1H, *H3*), 3.06 (dd, *J* = 4.3, 4.5 Hz, 1H, *H2*), 2.14 – 1.99 (m, 2H), 1.98 – 1.92 (m, 1H), 1.82 – 1.58 (m, 5H), 1.39 – 1.16 (m, 4H), 1.25 (s, 9H, *Piv*).; ^{13}C NMR (150 MHz, CDCl$_3$): 176.4, 170.4, 136.4, 132.2, 64.3, 47.2, 38.9, 36.1, 33.2, 30.4, 30.1, 27.0, 26.1, 25.9, 25.8, 25.7.; IR (neat): 2926, 1732, 1701, 1263 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{26}NaO_4$ ([M+Na]$^+$) *m/z* 329.1724, found *m/z* 329.1729.



4af

4af: R_f 0.29 (hexane:AcOEt = 4:1, UV); ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.26 (3H, s, Si-*CH*$_3$), 0.30 (3H, s, Si-*CH*$_3$), 0.98 (9H, s, *tBu*), 2.06 (1H, dddd, *J* = 14.6, 12.4, 4.3, 4.3 Hz, *H7*$_{ax}$), 2.13 (1H, ddd, *J* = 14.6, 4.2, 2.2, 2.2 Hz, *H7*$_{eq}$), 3.28–3.33 (1H, m, *H2*), 3.80 (1H, d, *J* = 4.4 Hz, *H3*), 3.81 (3H, s, O-*Me*), 4.15–4.22 (1H, m, *H8*), 4.46 (1H, ddd, *J* = 12.4, 11.1, 2.2 Hz, *H8*), 6.88 (1H, d, *J* = 8.8 Hz, *H15*), 7.35 (2H, d, *J* = 8.8 Hz, *H14*); ^{13}C NMR (150 MHz, $CDCl_3$): δ -3.9, -3.8, 18.1, 25.7, 31.2, 49.8, 55.4, 64.5, 114.2, 118.6, 125.3, 127.2, 136.2, 158.4, 170.6; IR (neat): 2929, 1728, 1674, 1606, 1510, 1247 cm^{-1}; HRMS (ESI) calcd for $C_{20}H_{28}NaO_4Si$ ($[M+Na]^+$) *m/z* 383.1650, found *m/z* 383.1644.

3.7 Scale-up in flow (procedure for figure 5)

The reaction condition in flow is same as that shown in "**3.4 Procedure for figure 4 in flow**".
After a steady state was reached, the resulting solution was collected in a sample tube filled with saturated aqueous NH_4Cl (6 mL) for 30 s (×20). The collected mixture was extracted with AcOEt (100 mL × 3). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/AcOEt = 4/1) to afford **4aa** (605 mg, 2.09 mmol, 67%yield).

3.8 Calculation for Space-Time Yield (STY) (Table 3, figure 5) [2]

STY = product mol/(reactor volume × operation time).

Reference:

	Product mol / mg	Reactor volume / mL	Operation time / h	STY / $gL^{-1}h^{-1}$
Table 3, entry 1	49	20[*1]	2.5	0.98
Table 3, entry 2	35	50[*2]	0.050	14
Table 3, entry 3	54	4.7[*3]	0.016	7.2×10^2
Figure 5	607	4.7[*3]	0.16	8.1×10^2

[*1] We used a 2-neck flask (20 mL) for the reaction mixture (6.3 mL).
[*2] We used a 2-neck flask (50 mL) for the reaction mixture (10 mL).
[*3] reactor volume = $\pi r^2L = 3.14 \times 0.050^2 \times (50+450+100) = 4.7\ cm^3 = 4.7\ mL$
r: radius (mm)
L: length (mm)

4. In-line Raman Analysis

4.1 General information

Raman spectra were obtained with a ReactRaman 785 analyzer and iC Raman software version 7 (Mettler Toledo). Each spectrum was composed of coadded scans with an exposure time of 3 s and 3 accumulations in the range of 3200−100 cm^{-1}. The system was configured with a 785 nm wavelength, 400 mW laser diode and a fiber Ball Probe. The fiber Ball Probe was attached to a flow cell for ReactIR (1/16 inch, 3/8 inch, Cat. No. SSIR11638, *altFlow*) and a flow reactor shown in figure S2.

Peak area was calculated with iC Raman software version 7 (Mettler Toledo). We selected "area", "two point baseline", and "2177−2248 cm^{-1}" for the calculation. Details are shown in an excel file as a supporting information.

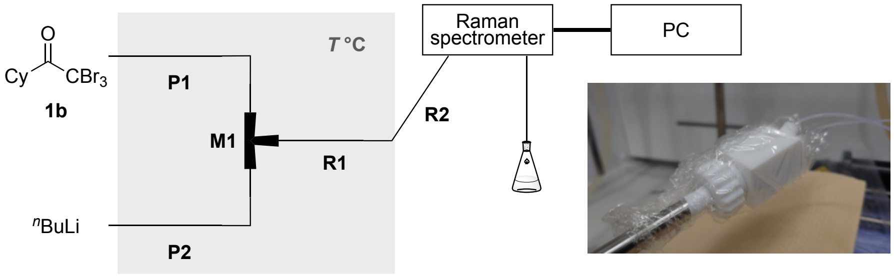


Figure S2. Flow system for In-line Raman analysis

Procedure for figure 3a

A flow microreactor system consisting of a T-shaped stainless steel micromixer **M1**, a stainless steel microtube reactor **R1**, and two pre-cooling units **P1** and **P2** were used in a water bath at *T* °C. After THF and hexane were introduced into a micromixer by the syringe pumps, **1b** and *n*-BuLi were introduced into a micromixer by the syringe pumps. The resulting solution was passed through a PTFE microtube reactor **R2**, and Raman spectra of the resulting solution were measured in a PTFE cell shaded with aluminum foil (see figure S2). Observed Raman spectra was shown in section 4.4. (figure S4—S6)

Stock Solutions and Pump Flow Rates

	equiv	*solutions*	*Flow rate / (mL/min)*
1b	2.4	0.10 M in THF	7.52
***n*BuLi**	4.8	0.80 M in *n*-hexane	1.88
THF*	—	**T**HF	7.52
Hexane*	—	*n*-hexane	1.88

*THF and Hexane were used for control experiment shown in Figure S4.

Fixed Lengths

R1	50 cm (residence time: t_1 = 2.5 s) or 450 cm (residence time: t_1 = 22.5 s)
R2*	50 cm (residence time: t_1 = 2.5 s)
P1	100 cm
P2	50 cm

Fixed inner diameters

M1	250 μm

4.2 Selected Spectroscopic Data for Ketenes and Alkynyl Ethers

IR stretching frequencies from triple bond (**S5~S7**, **S8**), and double bond (**S9**) are shown below.

$^t\mathrm{Bu}{-}{\equiv}{-}\mathrm{OTBS}$

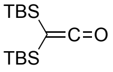
S5
2270 cm^{-1}
JACS. **1986**, *108*, 7125.

$\mathrm{TBS}{-}{\equiv}{-}\mathrm{O}^t\mathrm{Bu}$

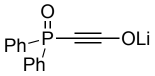
S6
2180 cm^{-1}
JOC. **1990**, *55*, 395.

$\mathrm{TBS}{-}{\equiv}{-}\mathrm{OTBS}$

S7
2182 cm^{-1}
JCS. Perkin Trans. 1, **1996**, 14, 1705.



S9
2074 cm^{-1}
JCS. Perkin Trans. 1, **1996**, 14, 1705.

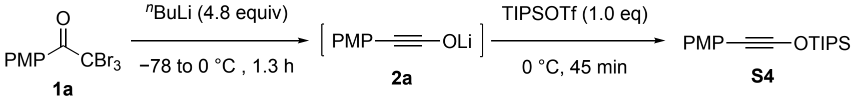

$\mathrm{Ph_2P(O){-}{\equiv}{-}OLi}$

S8*
2129 cm^{-1} (neat)
Chem Commun. **2024**,
doi: 10.1039/d4cc03167a

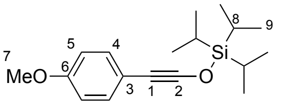
*The authors did not conclude **S8** as ynolates, but the character of ynolates was indicated by analyzing IR stretching frequencies.
We identified that the observed Raman band and IR stretching frequencies are from triple bond of **2b** and **S4** respectively.

*c*Hex—≡—OLi **2b** 2214 cm^{-1} *Our data*	PMP—≡—OTIPS **S4** 2264 cm^{-1} *Our data*

4.3 Preparation of silyl ynolate S4 (NM_359)



To a solution of **1a** (1.54 g, 4.00 mmol) in THF (20 mL) was added dropwise *n*-BuLi (5.0 mL, 8.0 mmol, 1.6 M in *n*-hexane) at −78 °C. After being stirred for 15 min, the reaction mixture was warmed up to 0 °C. After the reaction mixture was stirred for 1.25 h 0 °C, TIPSOTf (1.08 mL, 4.01 mmol) was added dropwise to the mixture at 0 °C. After being stirred for 35 min at 0 °C, the reaction mixture was quenched with saturated aqueous $\mathrm{NaHCO_3}$ and diluted with hexane (30 mL). The resulting solution was separated, and the organic layers were washed with brine, dried over $\mathrm{Na_2SO_4}$, and concentrated under reduced pressure. The residue was filtered through a pad of silica gel and the resulting solution was concentrated under reduced pressure. The residue was purified by GPC to afford silyl ynolate **S4** (0.10 g, 0.33 mmol, 8%) as a colorless oily solid.



S4

S4: IR (neat) 2945, 2868, 2264, 1606, 1514 cm–1; ^{1}H NMR (600 MHz, $\mathrm{CDCl_3}$) 7.23 (2H, d, J = 8.9 Hz, *H4*), 6.77 (2H, d, J = 8.9 Hz, *H5*), 3.77 (3H, s, *-OCH₃*), 1.33 (3H, sept, J = 7.3 Hz, *H8*), 1.17 (18H, d, J = 7.3 Hz, *H9*); ^{13}C[2] NMR (150 MHz, CDCl3) δ 158.1 (*C6*), 132.7 (*C4*), 117.4 (*C5*), 113.9 (*C3*), 95.5 (*C2*), 55.4 (*C7*), 33.0 (*C1*), 17.5 (*C9*), 12.0 (*C8*).; HRMS (ESI) calcd for $\mathrm{C_{18}H_{31}O_3Si}$ ($[\mathrm{M+H_3O}]^+$): 323.2037, found 323.2039.

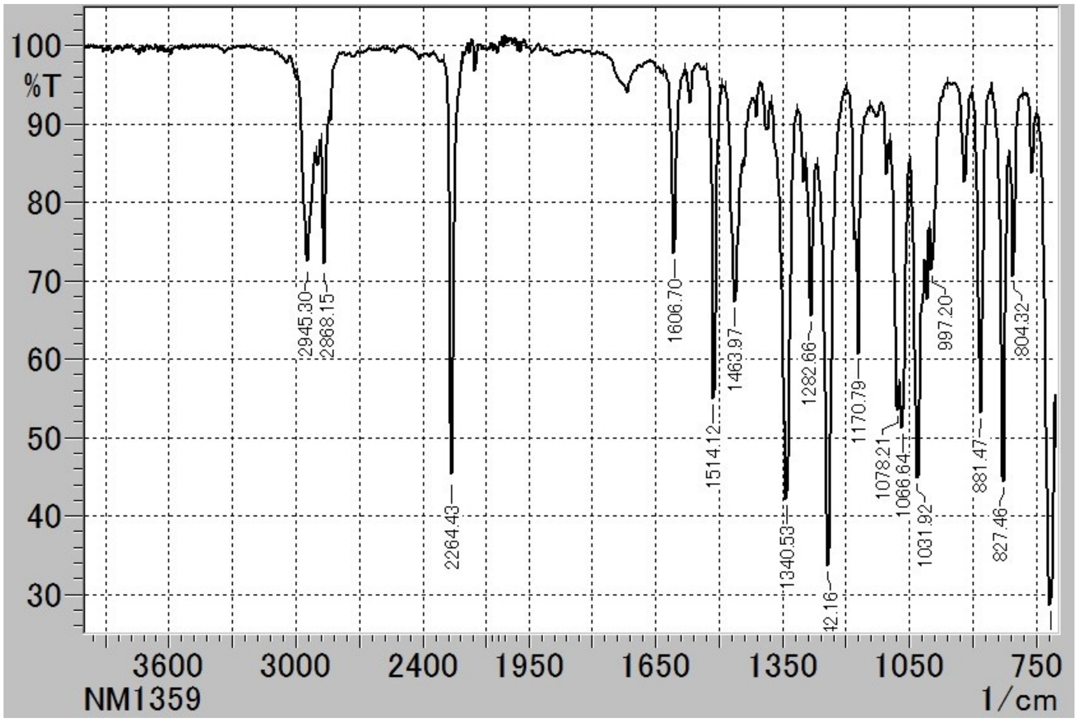


Figure S3. IR spectra of **S4**

4.4 Raman Spectra

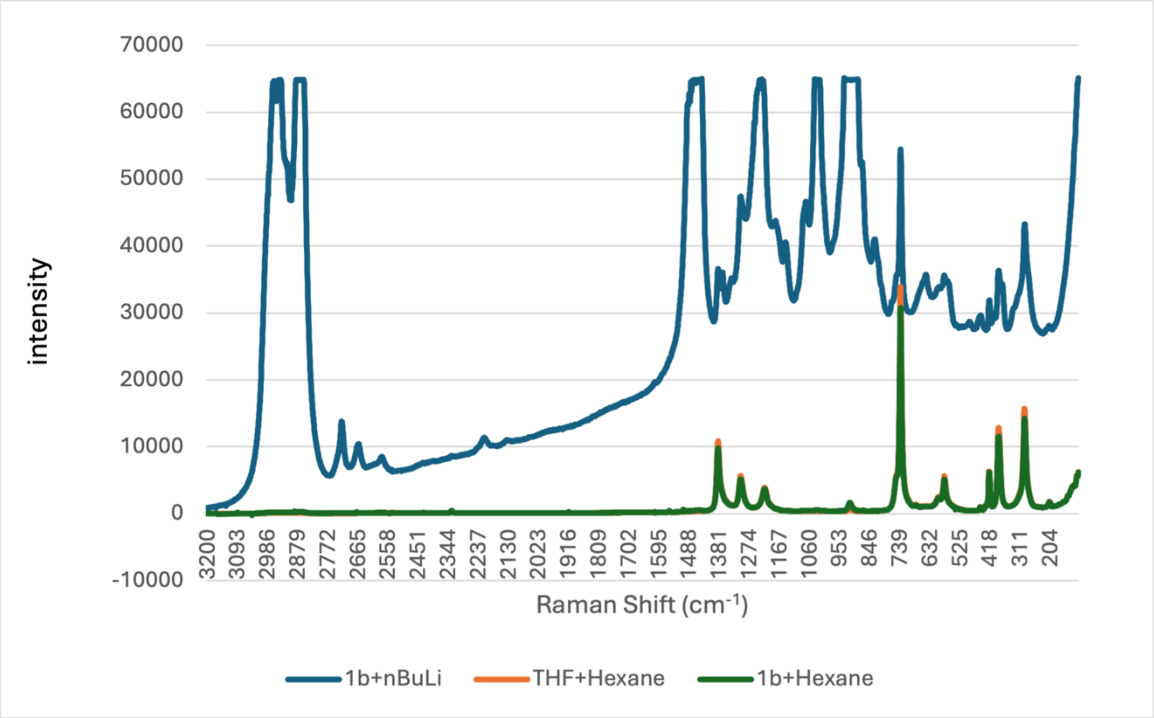


Figure S4. Raman Spectra of solutions (**1b** + *n*-BuLi, THF + Hexane, **1b** + Henxane) in flow cell. Flow parameters are as follows. T = 30 °C. t_1 = 2.5 s.

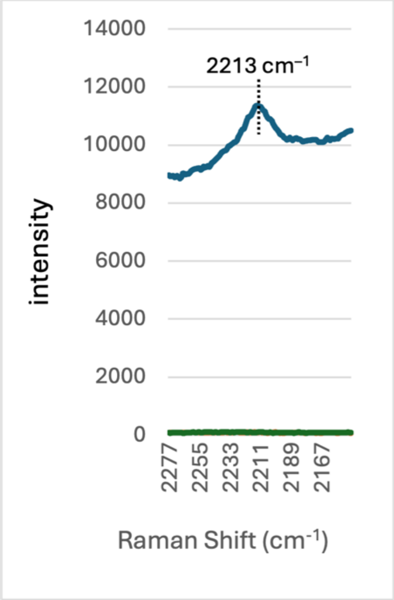
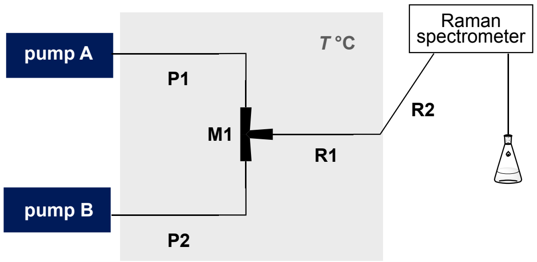


Figure S5. Zoomed Figure S4

Table S4.



Entry	combinations	Pump A	Pump B
1	THF + Hexane	THF	*n*-Hexane
2	**1b** + Hexane	1b	*n*-Hexane
3	**1b** + *n*-BuLi	1b	n-BuLi

Entry 1, 2: control experiments

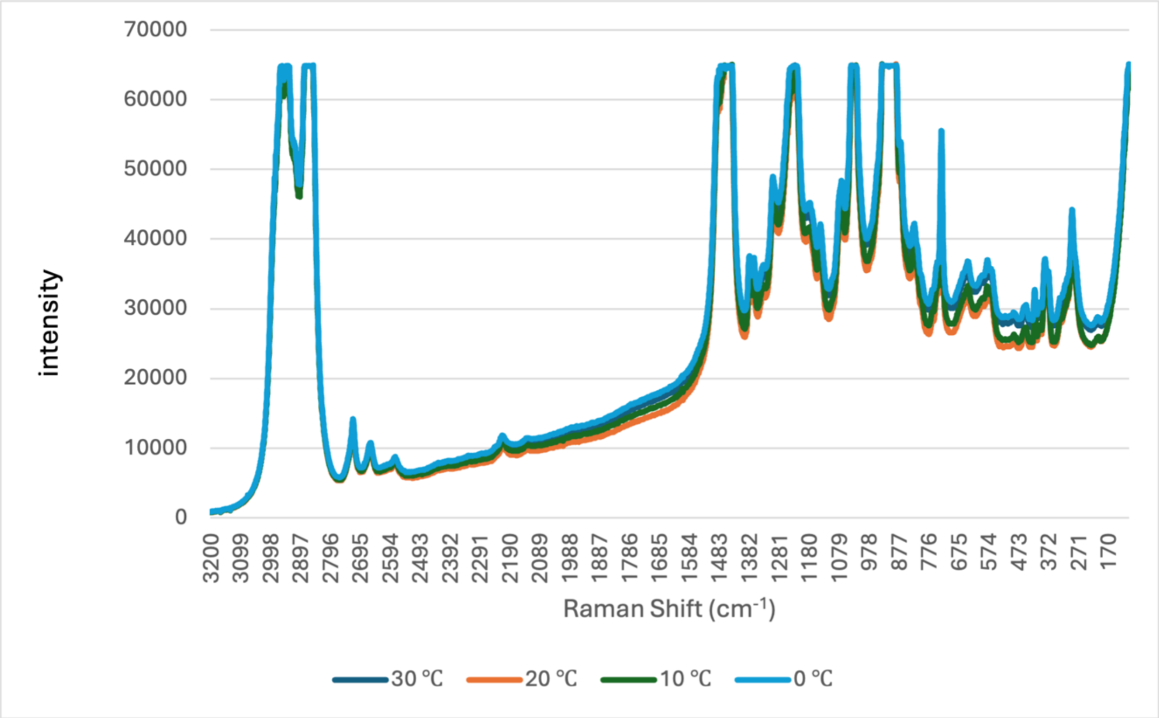


Figure S6. Raman Spectra of a solution (**1b** + *n*-BuLi) in flow cell. Flow parameters are as follows. T = 0, 10, 20, 30 °C. t_1 = 2.5 s.

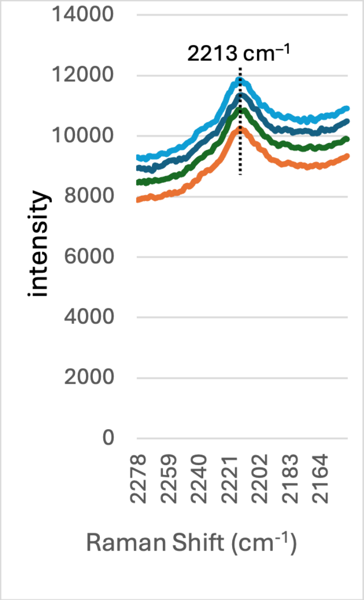


Figure S7. Zoomed Figure S6.

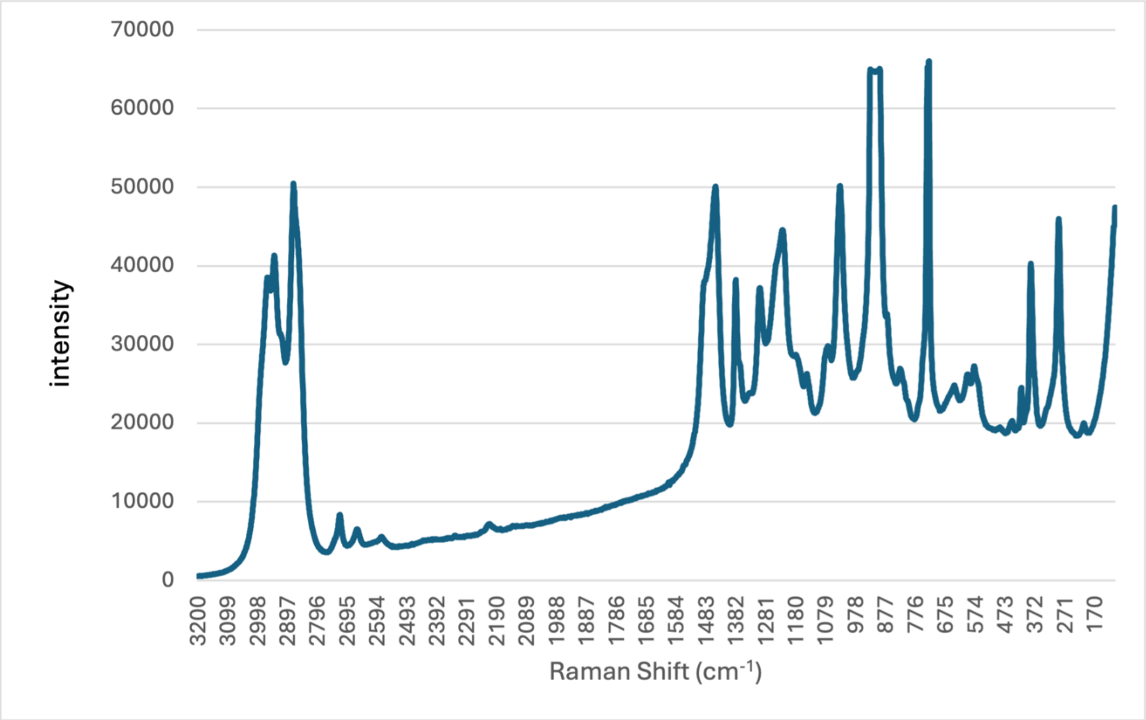


Figure S8. Raman Spectra of a solution (**1b** + *n*-BuLi) in flow cell. Flow parameters are as follows. T = 30 ℃. t_1 = 22.5 s.

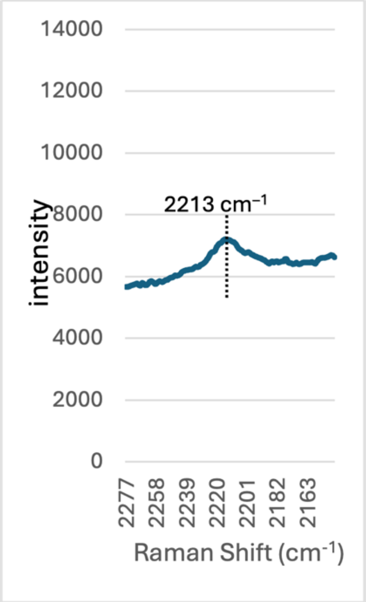


Figure S9. Zoomed Figure S8

5. X-ray Crystallographic Data

Data collection and Structure solution details: Single crystal X-ray data for compound **4ad** was collected on a Rigaku XtaLaB P200 diffractometer Cu-Kα radiation. Data collection, cell refinement, data reduction and analysis were carried out with the CrysAlisPro (Rigaku Oxford Diffraction). The structure was solved by intrinsic phasing methods with the SHELXT program and refines using SHELXL[3] with anisotropic displacement parameters for non-H atoms. CCDC 2412389 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/data_request/cif.

X-ray crystallographic data for compound **4ad** (CCDC 2412389).
Single crystals of **4ad** were obtained by slow evaporation of a solution containing **4ad** in the mixture of hexane and ethyl acetate at room temperature. A suitable crystal was selected and the crystal data and structure refinement results for compound **4ad** are listed in the Table S5.

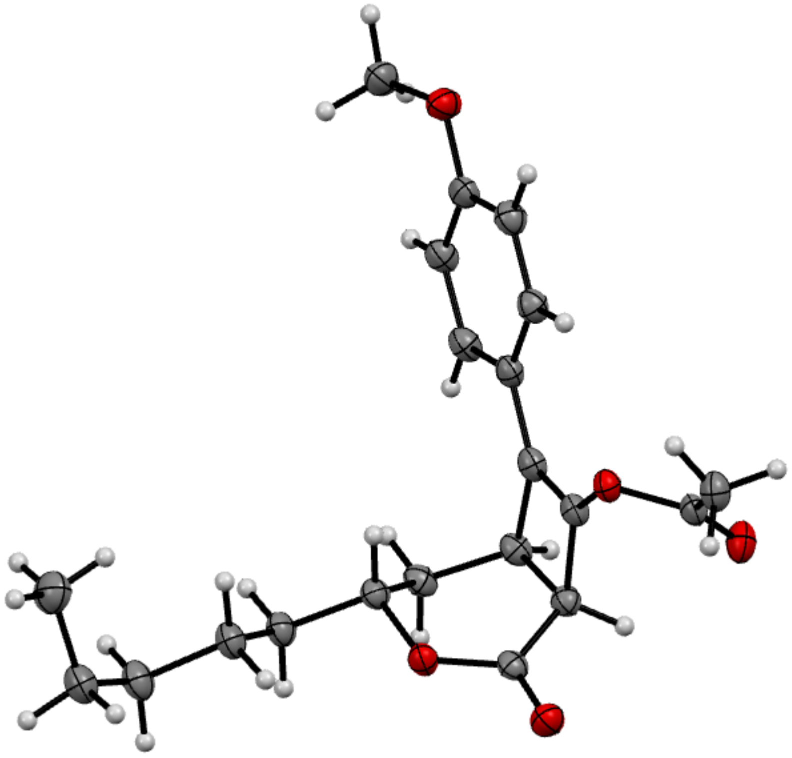


Figure S10. ORTEP view of the compound **4ad** with thermal ellipsoids drawn at the 50% probability level

Table S5 Crystal data and structure refinement for 4ad.

Identification code	241213ak2_auto
Empirical formula	$C_{21}H_{26}O_5$
Formula weight	358.42
Temperature/K	93.00
Crystal system	orthorhombic
Space group	$P2_12_12_1$
a/Å	5.52413(13)
b/Å	15.2460(4)

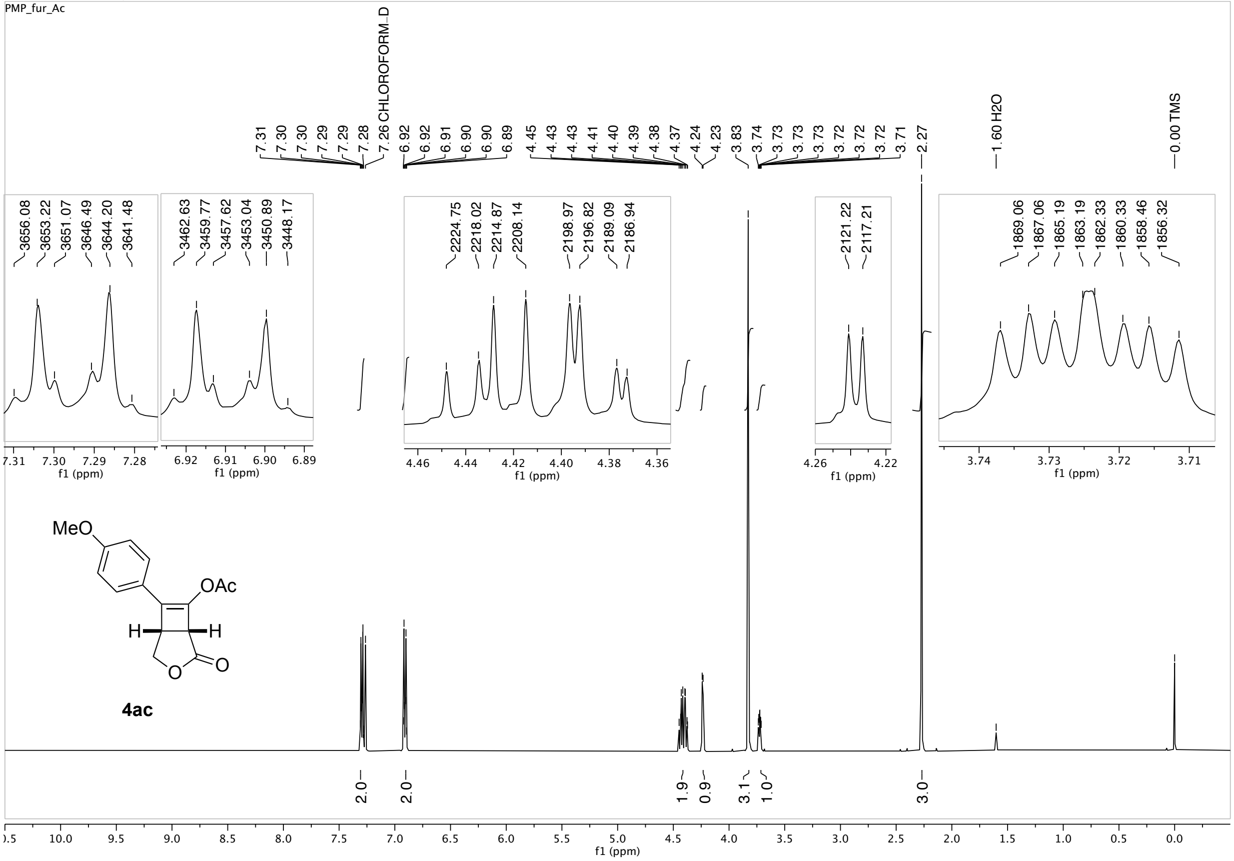
c/Å	22.0591(6)
α/°	90
β/°	90
γ/°	90
Volume/$Å^3$	1857.83(8)
Z	4
ρ_{calc}g/cm^3	1.281
μ/mm^{-1}	0.737
F(000)	768.0
Crystal size/mm^3	0.2 × 0.05 × 0.03
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	7.048 to 144.636
Index ranges	$-4 \leq h \leq 6$, $-18 \leq k \leq 17$, $-27 \leq l \leq 26$
Reflections collected	16572
Independent reflections	3606 [R_{int} = 0.0615, R_{sigma} = 0.0379]
Data/restraints/parameters	3606/0/238
Goodness-of-fit on F^2	1.092
Final R indexes [I>=2σ (I)]	R_1 = 0.0361, wR_2 = 0.0975
Final R indexes [all data]	R_1 = 0.0379, wR_2 = 0.0983
Largest diff. peak/hole / e $Å^{-3}$	0.22/-0.19
Flack parameter	-0.04(12)

6. References

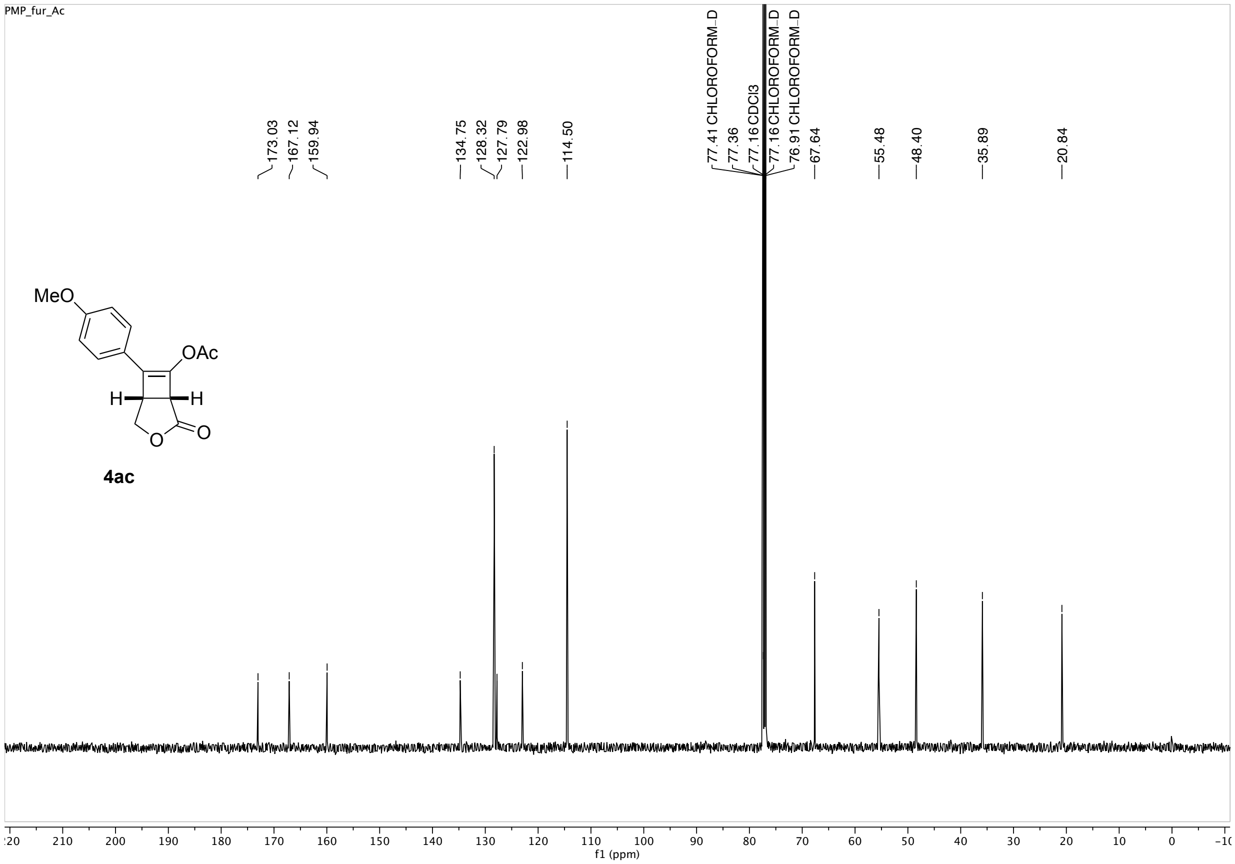
[1] Yamaoka, Y., *et al*., *Org Lett*, **2024**, 26, 1896-1901.
[2] Hone, C. A. and Kappe, C. O. *Chem. Methods*, 2021, **1**, 454-467.
[3] Sheldrick, G. M. A. *Acta Crystallogr., Sect. A: Found. Crystallogr.* **2008**, *64*, 112–122.

2. NMR spectra

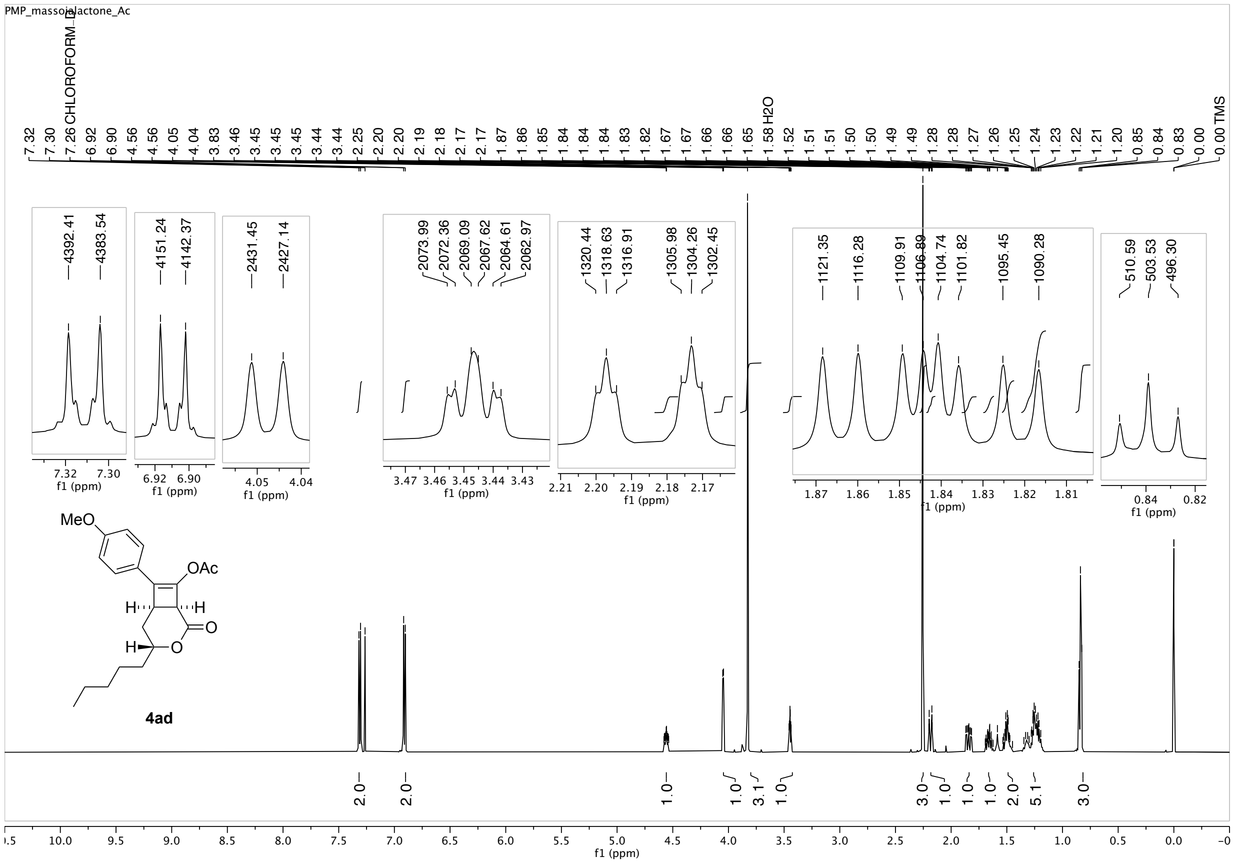
^{1}H-NMR, 500 MHz, CDCl$_3$



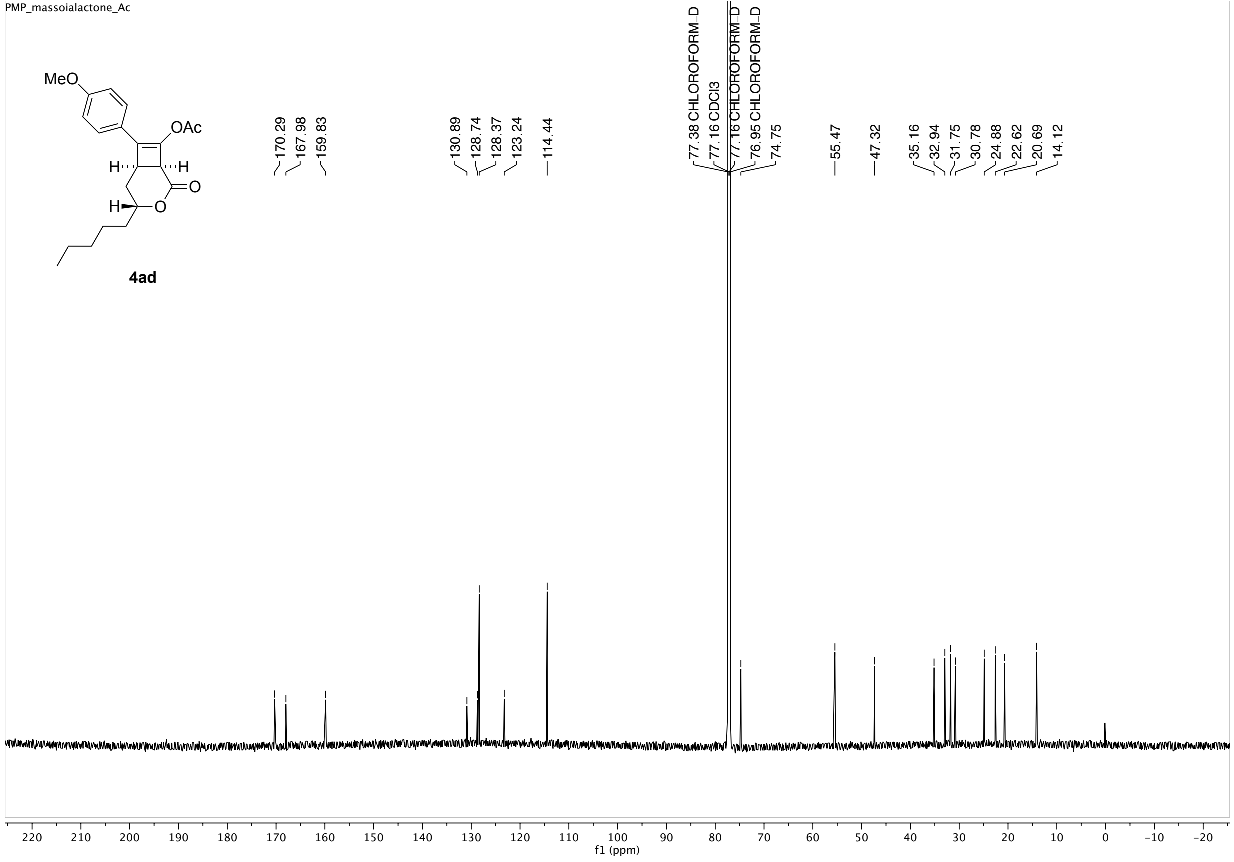
^{13}C{^{1}H}-NMR, 126 MHz, CDCl$_3$



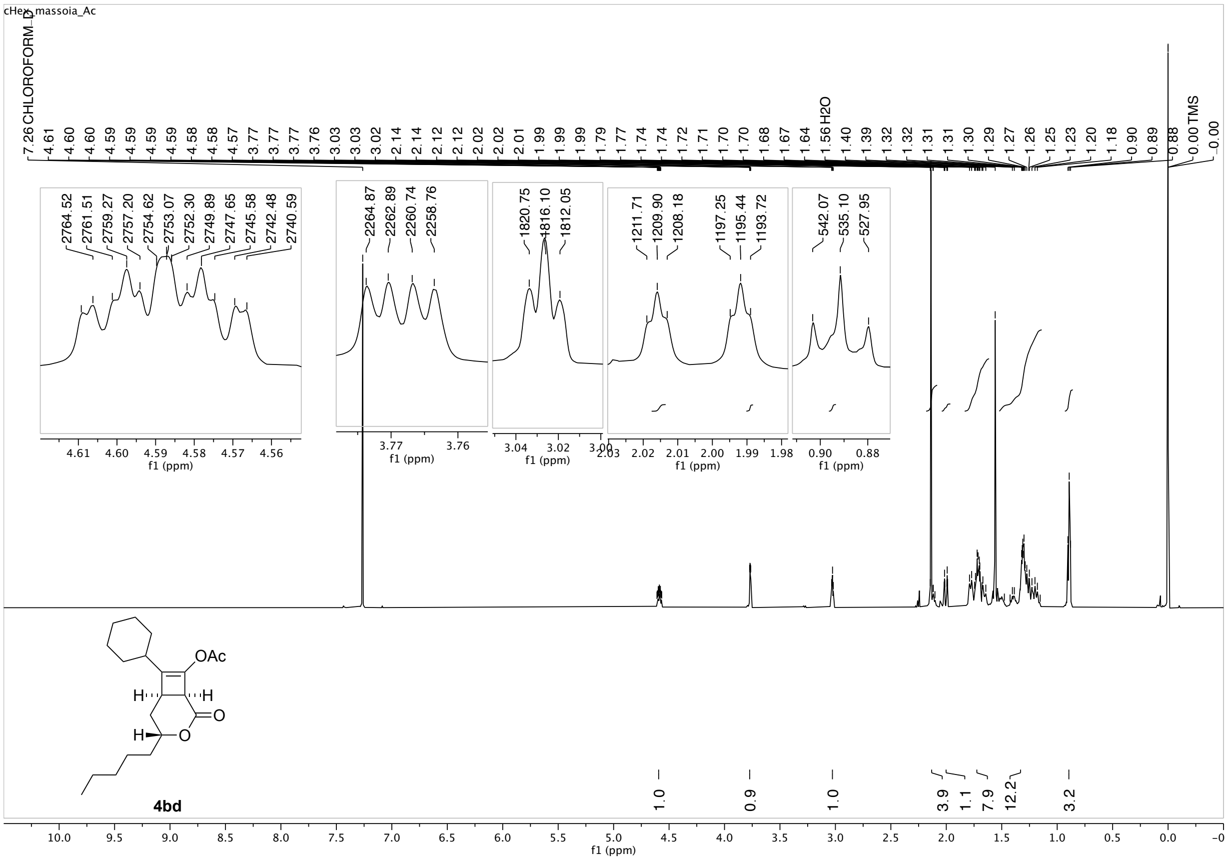
^{1}H-NMR, 600 MHz, CDCl$_3$



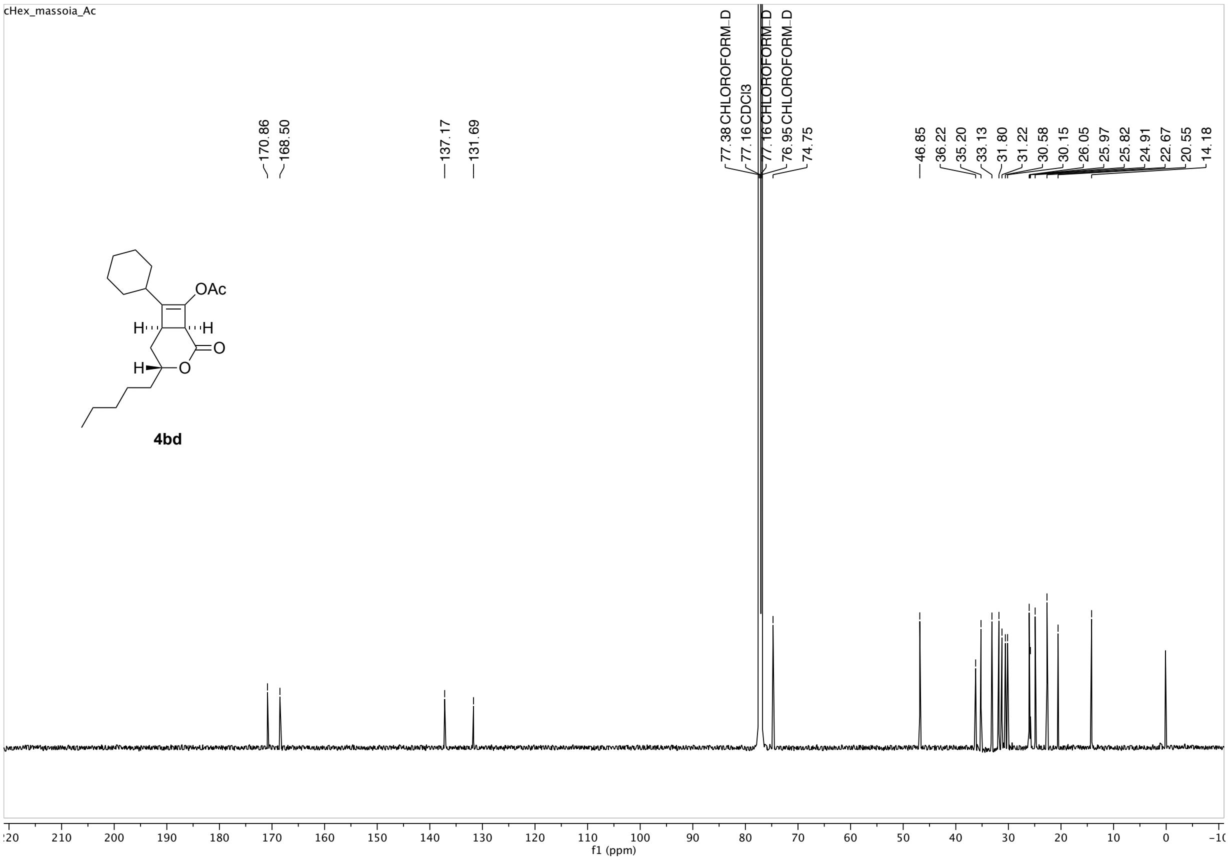
^{13}C{^{1}H}-NMR, 150 MHz, CDCl$_3$



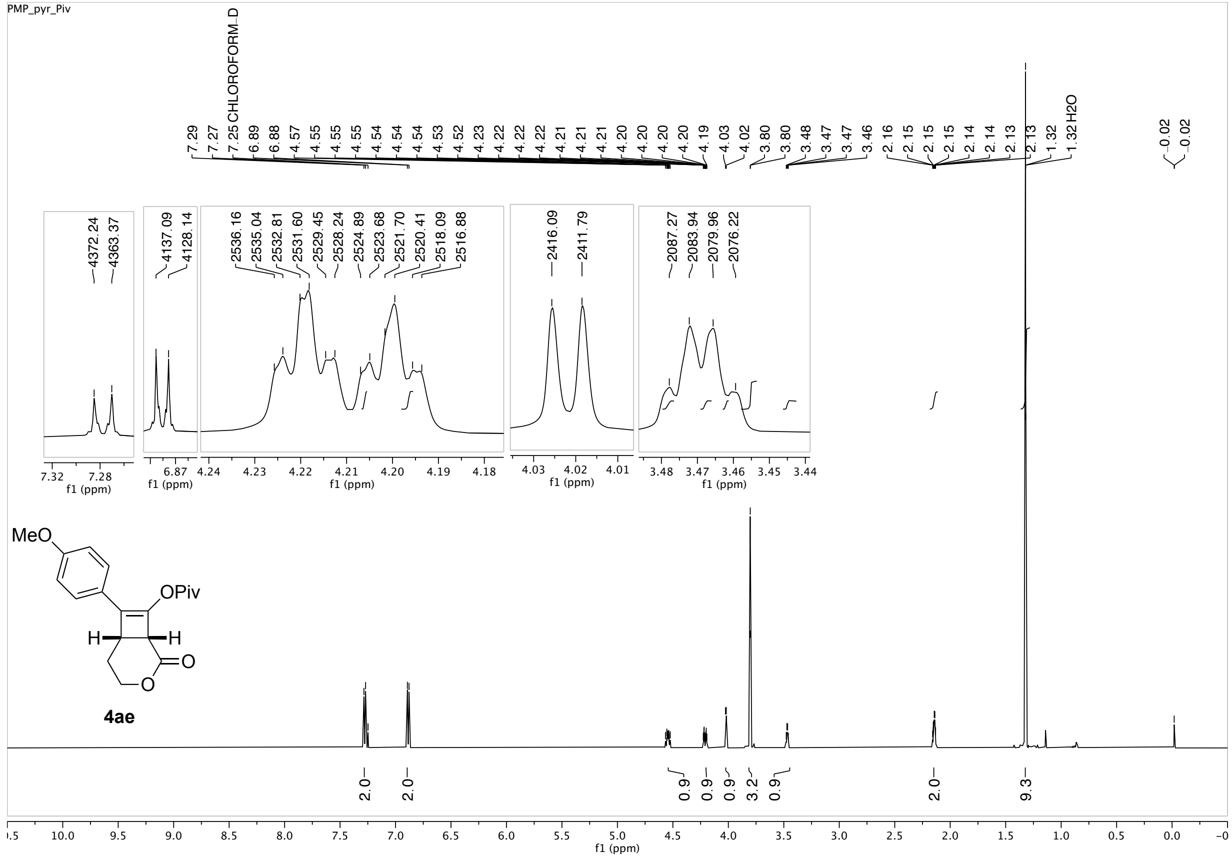
^{1}H-NMR, 600 MHz, CDCl$_3$



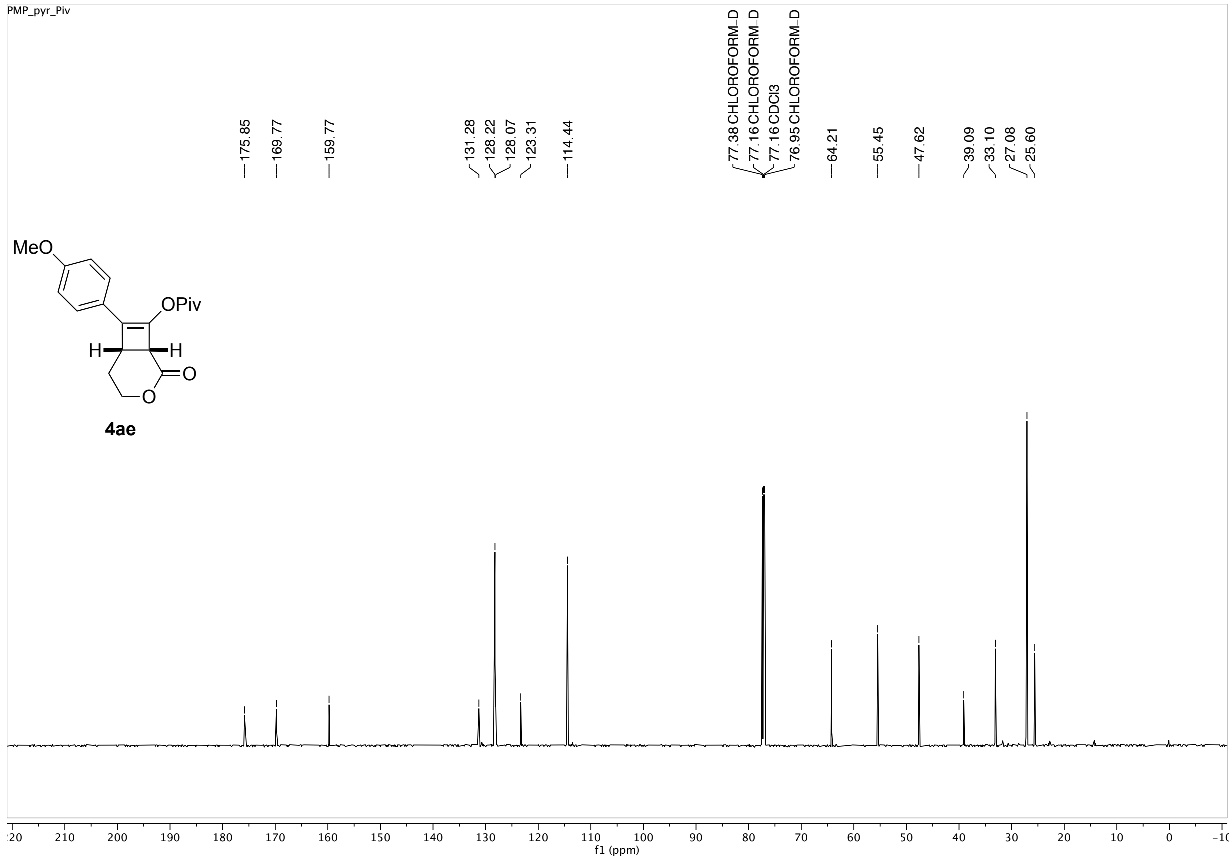
^{13}C{^{1}H}-NMR, 150 MHz, CDCl$_3$



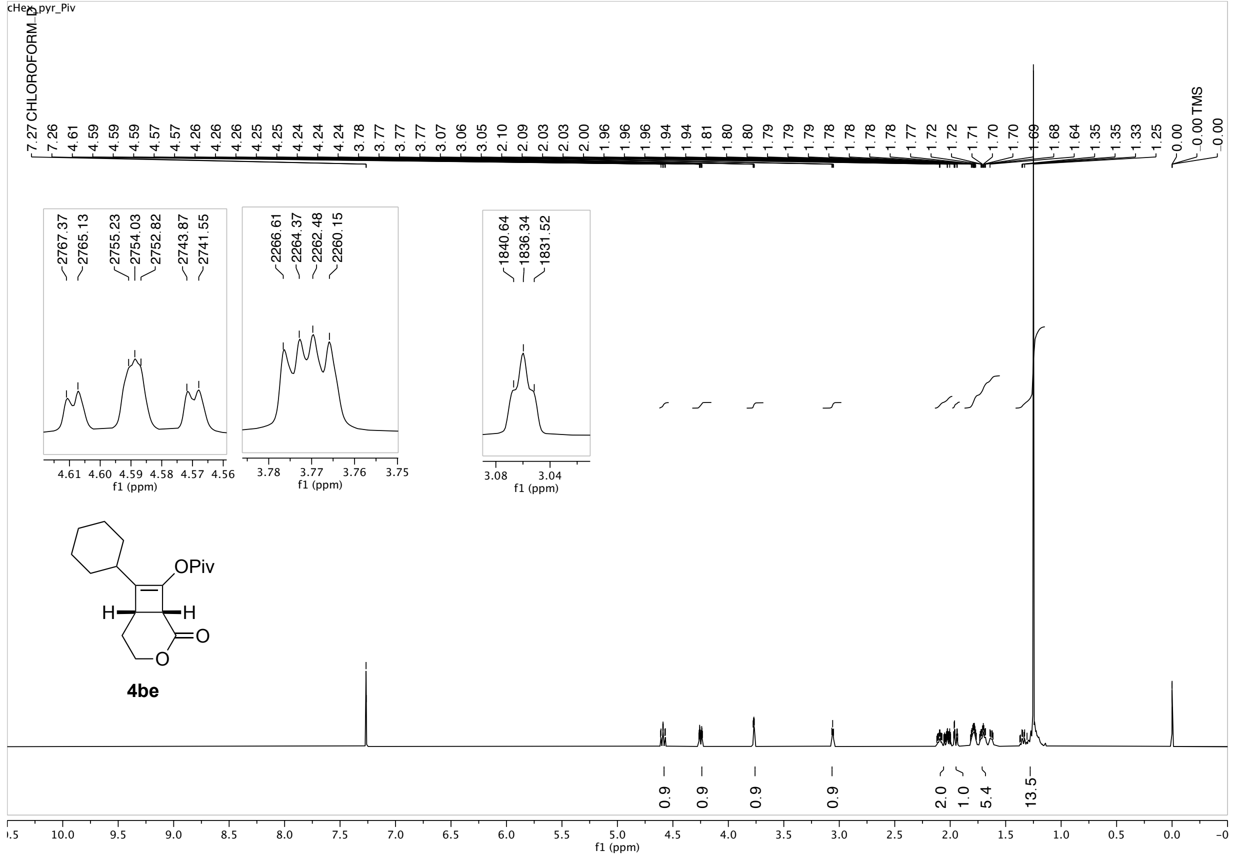
^{1}H-NMR, 600 MHz, CDCl$_3$



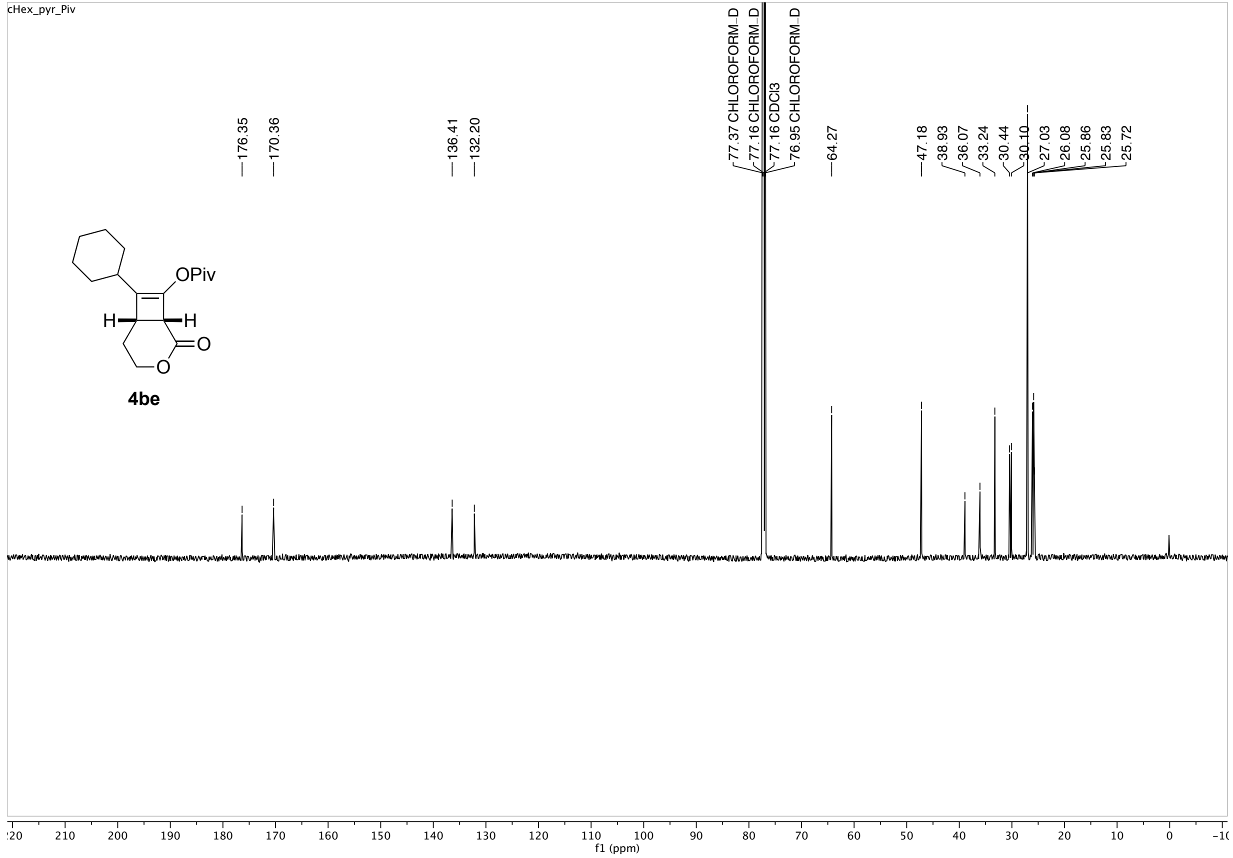
^{13}C{^{1}H}-NMR, 150 MHz, CDCl$_3$



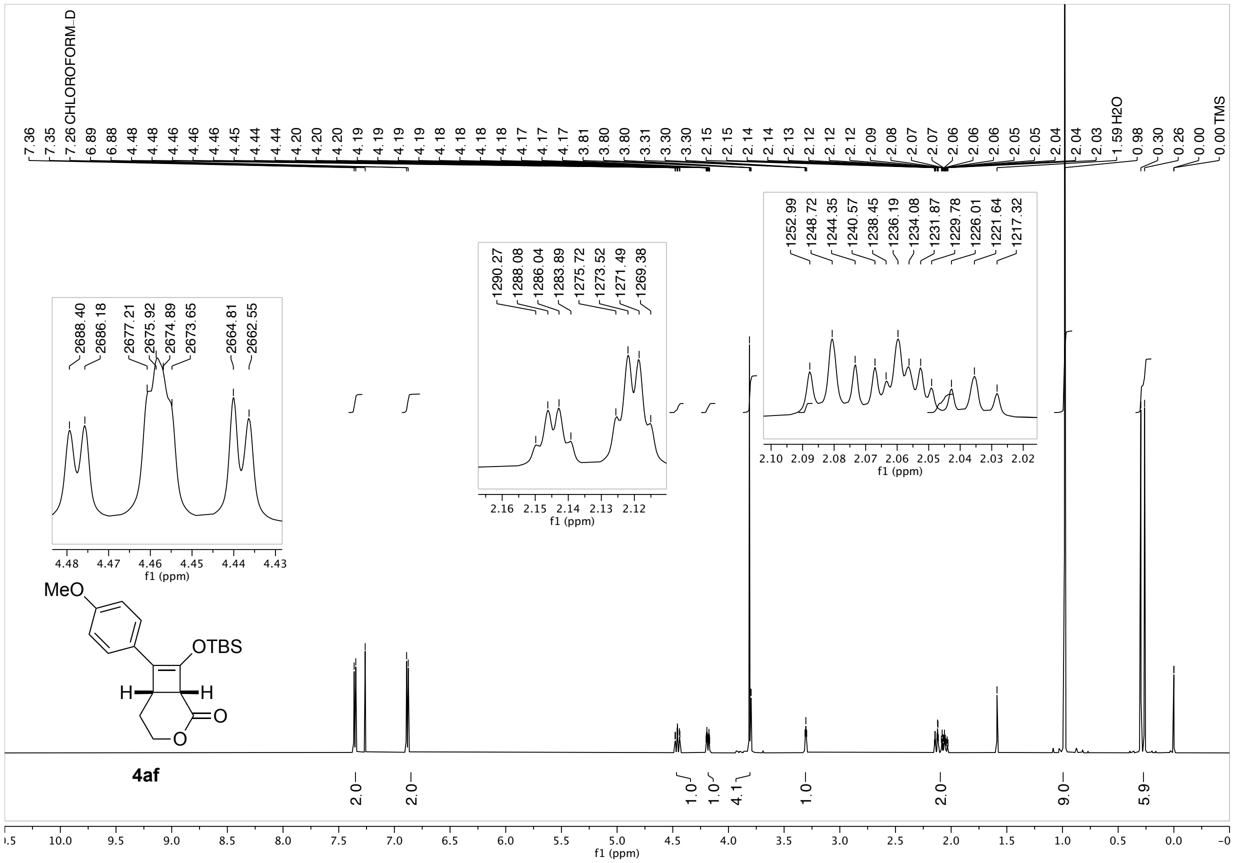
^{1}H-NMR, 600 MHz, CDCl$_3$



^{13}C{^{1}H}-NMR, 150 MHz, CDCl$_3$

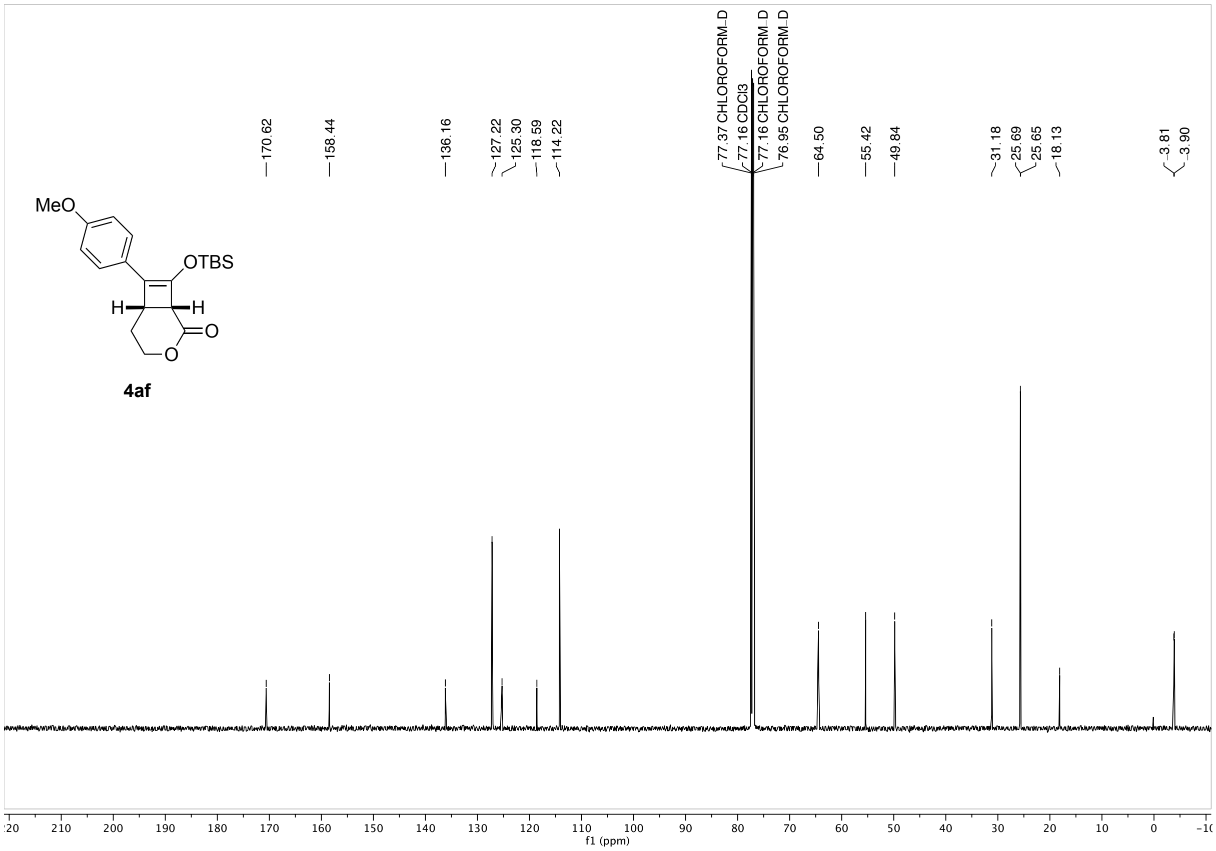


^{1}H-NMR, 600 MHz, $CDCl_3$



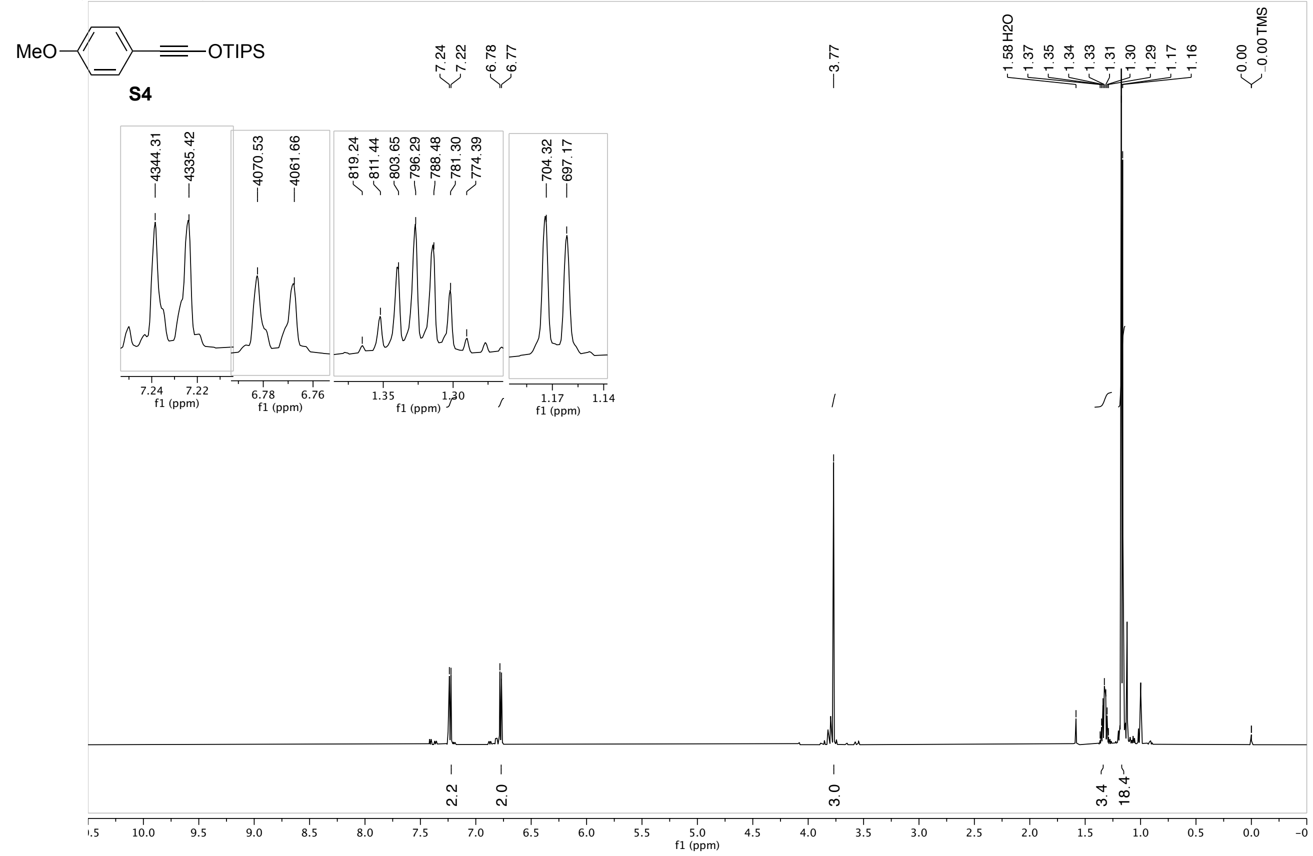
4af

^{13}C{^{1}H}-NMR, 150 MHz, $CDCl_3$

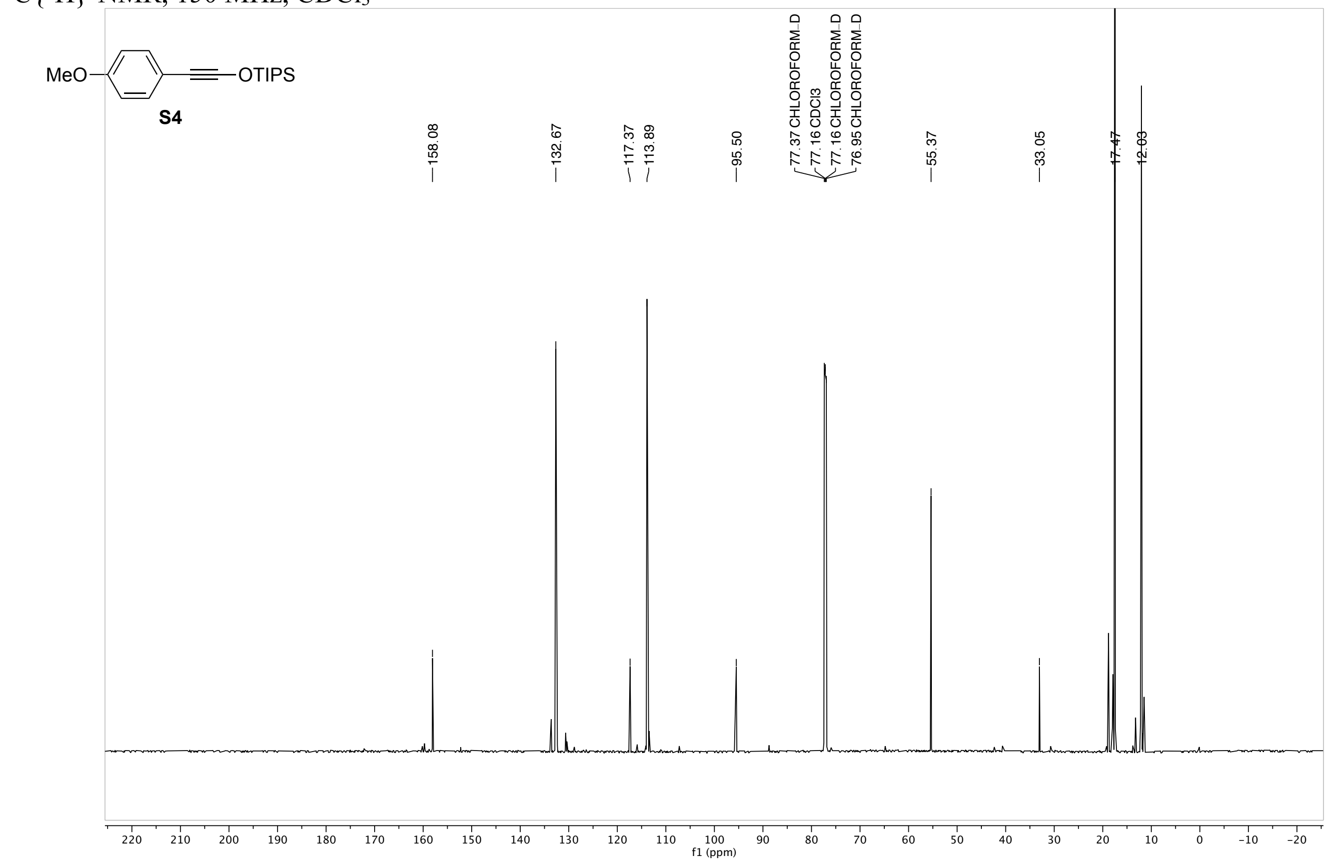


4af

^{1}H-NMR, 600 MHz, CDCl$_3$



^{13}C{^{1}H}-NMR, 150 MHz, CDCl$_3$



DEPT135-$^{13}C\{^{1}H\}$-NMR, 150 MHz, $CDCl_3$