

Supporting Information

**Ground State Electron Transfer as an Initiation Mechanism for Biocatalytic C–C Bond Forming Reactions**

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## 1. General information

### General.

Unless otherwise noted, all chemicals and reagents for chemical reactions were obtained from commercial suppliers and used as received (Sigma-Aldrich, Oakwood Chemical, Combi-Blocks, TCI, and VWR). GDH-105 was purchased as cell-free lysates from Codexis and were used as received. Silica gel chromatography purifications were carried out using AMD Silica Gel 60.  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were recorded on a Bruker UltraShield Plus (500 and 126 MHz, respectively) instrument, and are internally referenced to residual proton signals in  $\text{CDCl}_3$  (7.26 ppm).  $^{19}\text{F}$  NMR spectra were recorded on a Bruker 300 (282 MHz) or 400 (367 MHz) instrument.  $^1\text{H}$  NMR data are reported as follows: chemical shift ( $\delta$  ppm), multiplicity (s = singlet, brs = broad singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublet, dt = doublet of triplet, ddd = doublet of doublet of doublet), coupling constant (Hz), and integration. Data for  $^{13}\text{C}$  NMR are reported in terms of chemical shift relative to  $\text{CDCl}_3$  (77.16 ppm). High resolution mass spectra (HRMS) were obtained on an Agilent 6220 LC/MS with an electrospray ionization time-of-flight (ESI-TOF) detector, or on an Agilent 7200 GC QTOF/MS with electron ionization mode, or on a Thermo Fisher Scientific Exactive series DART Mass Spectrometer. Optical rotations were measured on a Jasco P-1010 polarimeter with a 5 cm cell ( $c$  given in g/100 mL). IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer and peaks are reported in terms of frequency of absorption ( $\text{cm}^{-1}$ ).

### Chromatography.

Analytical high performance liquid chromatography (HPLC) and Electron Spray Ionization (ESI) mass spectrometry were carried out using an Agilent 1260 Infinity LCMS System. Yields and conversions were determined on a Poroshell C18 column (4.6 x 50 mm, 2.7  $\mu\text{m}$ ) against an internal standard 1,3,5-tribromobenzene (TBB) at 210 nm. Chiral HPLC was conducted using an Agilent 1260 Infinity Chiral HPLC system with isopropanol and hexanes as the mobile phases. Chiral OJ-H, OD-H, IC-H, and AS-H columns were used to separate enantiomers (4.6 x 250 mm, 5  $\mu\text{m}$ ).

### Cloning.

pET22b (+) was used as a cloning and expression vector for all enzymes described in this study. Genes for all 'ene'-reductases were purchased as gBlocks from IDT and cloned using the Gibson cloning method.<sup>1</sup> All C-terminal 6xHis tagged constructs were cloned directly between the NdeI and XhoI restriction sites. N-terminal 6xHis tagged constructs were created by the introduction of an N-terminal 6xHis sequence directly after the NdeI site and replacement of the C-terminal 6xHis tag with an XhoI cut site. Cloned plasmids were transformed into *E. coli*. DH5- $\alpha$  cells for storage, and *E. coli*. BL21 (DE3) or *E. coli*. BL21 (DE3, with pGro7 chaperone plasmid) electrocompetent cells for expression.

### Protein and DNA Sequence.

Nicotinamide-dependent cyclohexanone reductase (**NCR**). GenBank accession number: AAV90509.

NCR protein sequence

MPSLFDPIRFGAFTAKNRIWMAPLTRGRATRDHVPTEIMAEYYAQRASAGLIISEATGISQEGL  
GWPYAPGIWSDAQVEAWLPITQAVHDAGGLIFAQLWHMGRMVPSNVSGMQPVAPSASQAPG  
LGHTYDGKKPYDVARALRLDEIPRLDDYEKAARHALKAGFDGVQIHAANGYLIDEFIRDSTN  
HRHDEYGGAVENRIRLLKDVTERVIATIGKERTAVRLSPNGEIQGTVDSPHEQVFIPAAKMLSD  
LDIAFLGMREGAVDGTFGKTDQPKLSPEIRKVFKPPLVLNQDYTFETAQAALDSGVADAISFG  
RPFIGNPDLPRRFFEKAPLTKDVIETWYTQTPKGYTDYPLLGDHHHHHH.

NCR DNA sequence

ATGCCGTCACTGTTTCGATCCAATCCGCTTTGGGGCTTTCACTGCAAAAAATCGTATCTGGA  
TGGCGCCGTTAACACGGGGTCGGGCAACCCGTGACCATGTCCCAACAGAGATAATGGCTG  
AATACTATGCCCAACGCGCATCCGCGGGCTTGATCATCAGCGAGGCGACCGGGATCAGCC  
AAGAGGGCCTGGGCTGGCCCTATGCACCAGGAATCTGGAGTGATGCGCAGGTCGAGGCAT  
GGTTACCCATAACCCAAGCGGTACACGATGCCGGAGGTTTGATATTTGCACAACCTGTGGC  
ACATGGGGCGTATGGTGCCTTCCAACGTTTCTGGAATGCAACCTGTCGCACCTAGCGCTTC  
ACAAGCGCCCGCTTGGGCCATACTTATGATGGCAAAAAGCCATACGATGTAGCCAGAGC  
ATTGAGACTTGACGAGATCCCACGGCTGCTGGACGACTATGAAAAGGCAGCTCGGCACGC  
ACTGAAAGCTGGGTTTCGATGGAGTTCAGATTCATGCTGCCAACGGATACCTGATTGACGA  
GTTTCATCCGGGATTCAACAAATCATAGACACGACGAATACGGGGGGCGGTTGAGAACA  
GAATACGGTTATTGAAGGATGTCACTGAGCGGGTTATCGCAACCATCGGAAAGGAGCGCA  
CAGCAGTGCGTTTAAGTCCGAATGGAGAGATACAAGGCACAGTAGACTCGCATCCAGAAC  
AGGTATTTATCCCGGCTGCAAAGATGTTATCTGATTTAGATATCGCGTTCCTTGGGATGCG  
CGAGGGTGCTGTAGACGGGACATTTGGCAAAACAGACCAGCCAAACTTTCCGCCGAGAT  
CCGTAAAGTTTTCAAGCACCCCTTGTCTGAATCAAGATTACACTTTTCGAGACTGCCAG  
GCTGCGTTAGATTCGGGTGTAGCCGATGCAATCAGTTTTGGTCGTCCATTCATTGGGAATC  
CCGACTTACCGAGAAGATTCTTTGAAAAGGCACCGTTAACTAAGGACGTAATTGAGACTT  
GGTACACTCAGACTCCCAAAGGTTACACCGACTATCCACTGTTAGGTGATCTCGAGCACC  
ACCATCACCACCACTGA.

The detailed protein and DNA sequence information of other tested 'ene'-reductases in this study, namely old yellow enzyme 1 (OYE1), 12-oxophytodienoate reductase 1 (OPR1), morphinone reductase (MorB), gluconobacter oxydans enoate reductase (GluER), pentaerythritol tetranitrate reductase (PETNr), *Bacillus subtilis* NADPH dehydrogenase (YqjM), and *Yersina bercovieri* alkene reductase (YersER), were described elsewhere.<sup>2,3</sup>

### **NCR Protein Expression and Purification.**

Nicotinamide-dependent cyclohexanone reductase (NCR) was produced in *E. coli* BL21 transformed with plasmid encoding NCR, coexpressed with groES-groEL (pGro7) chaperone. Transformed glycerol stocks were used to initiate a 5 mL overnight culture in Luria-Bertani (LB) media with ampicillin (100 µg/mL) and chloramphenicol (25 µg/mL) at 37 °C and 250 rpm. Expression culture (500 mL in a 2 L baffled shake flask) containing ampicillin (100 µg/mL) and chloramphenicol (25 µg/mL) was inoculated with 5 mL of the overnight culture, and grown until the cells reached an OD<sub>600</sub> of 0.5-0.7 (37 °C, 250 rpm). Flasks were chilled on ice and protein expression was induced with 0.1 mM IPTG and 3.3 mM L-arabinose (18 °C, 24 h, 250 rpm). The cells were harvested by centrifugation (4000 x g, 20 min, 4 °C) and frozen at -20 °C for further purification.

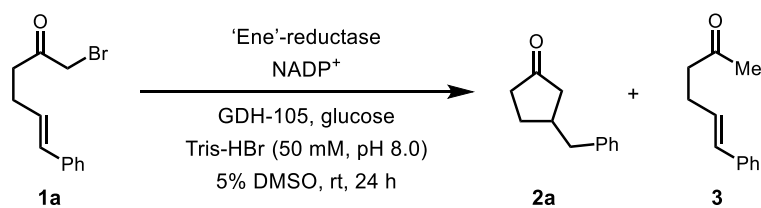
Frozen cells were thawed on ice and resuspended in buffer A (20 mM KPi pH 7, 300 mM NaCl, 25 mM imidazole) to a final concentration of 2 mL/g of wet cells. The resuspended cells were supplemented with lysozyme (1 mg/mL), FMN (1 mg/mL), DNase I (0.1 mg/mL), phenylmethylsulfonyl fluoride (PMSF, 1 mM) and allowed to shake for 30 min at 25 °C. The cells were further disrupted by sonication (2 x 4 min, output control 5, 35% duty cycle, Sonicator QSonica Q500 Ultra Sonicator). Lysates were centrifuged (20,000 x g, 1 h, 4 °C) to pellet insoluble materials. Proteins were purified using a nickel-NTA column (5 mL HisTrap HP, GE Healthcare, Piscataway, NJ) via an AKTASart purifier FPLC system (GE Healthcare). Enzymes were eluted with buffer B (20 mM KPi pH 7, 300 mM NaCl, 250 mM imidazole) over five column volumes. Yellow fractions containing NCR enzymes were pooled, concentrated, and subjected to three buffer exchanges into an imidazole free storage buffer (100 mM KPi pH 8). Concentrated enzymes were aliquoted, flash-frozen in liquid N<sub>2</sub>, and then stored at -20 °C until later use. Protein purity was assessed with SDS-PAGE.

Protein concentrations were determined using the extinction coefficient (12.2 x mM<sup>-1</sup> cm<sup>-1</sup> at 446 nm) for free FMN released after protein denaturation.<sup>4</sup> Extinction coefficient for NCR:  $\epsilon = 10.5 \times \text{mM}^{-1} \text{cm}^{-1}$  at 464 nm.

The detailed protein expression and purification of other tested 'ene'-reductases in this study, including old yellow enzyme 1 (OYE1), 12-oxophytodienoate reductase 1 (OPR1), morphinone reductase (MorB), gluconobacter oxydans enoate reductase (GluER), Pentaerythritol tetranitrate reductase (PETNr), *Bacillus subtilis* NADPH dehydrogenase (YqjM), and *Yersina bercovieri* alkene reductase (YersER), were reported elsewhere.<sup>2,3</sup>

## 2. Detailed experimental procedures

**Supplemental Table 1.** Initial panel of ‘ene’-reductases screened for cyclization reaction.



entry	‘ene’-reductases	yield <sup>a</sup> of <b>2a</b>	er <sup>b</sup>	yield <sup>a</sup> of <b>3</b>
1	MorB	14%	52:48	6%
2	OPR1	31%	80:20	9%
3	NCR	20%	79:21	19%
4	PETNr	66%	66:34	19%
5	YqjM	3%	n.d. <sup>c</sup>	9%
6	ERED-30 <sup>d</sup>	94%	65:35	6%
7	No enzyme	0%	n.d. <sup>c</sup>	trace
8	NCR without regeneration system	0%	n.d. <sup>c</sup>	trace

Reaction conditions: α-bromoketone (1 mg, 0.004 mmol, 1 eq), GDH-105 (0.5 mg), NADP<sup>+</sup> (0.5 mg), glucose (5 mg) and purified ‘ene’-reductases (2 mol% based on α-bromoketone) in 50 mM Tris-HBr buffer pH 8.0, with 5% DMSO (*v/v*) as cosolvent, final total volume is 500 μL. Reaction mixtures were shaken under anaerobic conditions at room temperature for 24 h. <sup>a</sup> Yield determined via LCMS relative to an internal standard (TBB). <sup>b</sup> Enantiomeric ratio (er) determined by HPLC on a chiral stationary phase. <sup>c</sup> n.d., not determined. <sup>d</sup> ERED-30 (1 mol%) was screened from a genetically diverse EREDs library from Prozomix.

### **Site Saturation Mutagenesis of NCR catalysts for radical cyclization**

Site saturation mutagenesis primers were designed using the PCR protocol from Kille *et al.*<sup>5</sup> The PCR products were digested with DpnI, repaired using Gibson Mix<sup>TM</sup>, and used to directly transform *E. coli* BL21 electrocompetent cells (with pGro7 chaperone plasmid) and plated on LB agar plates containing ampicillin (100 µg/mL) and chloramphenicol (25 µg/mL).

### **Screening procedure for $\alpha$ -bromoketone cyclization with NCR mutants.**

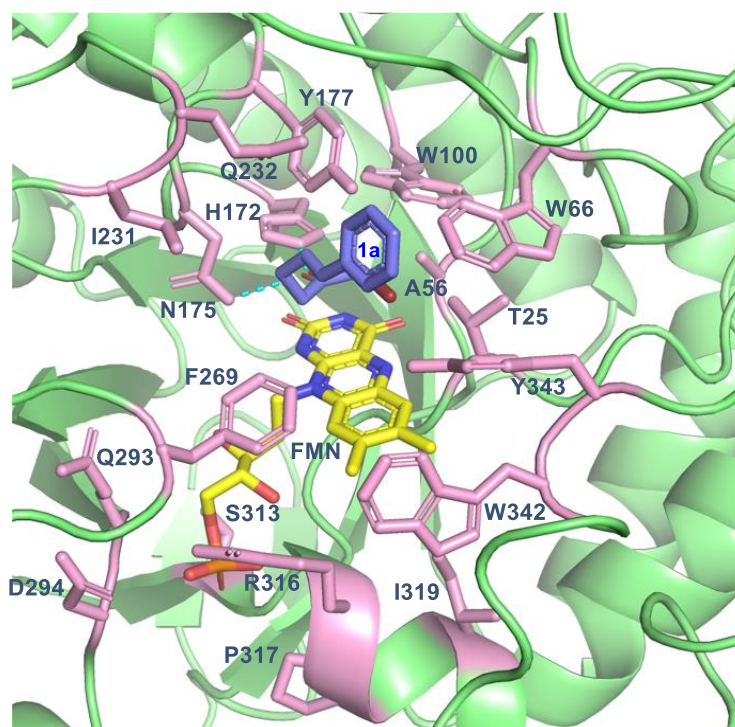
Single colonies were picked with sterile toothpicks and used to inoculate 300 µL of LB media containing ampicillin (100 µg/mL) and chloramphenicol (25 µg/mL) in deep-well 96-well plates, and cultured overnight (37 °C, 250 rpm). A glycerol stock plate of the library was prepared by mixing sterilized glycerol solution (50% v/v, 50 µL/well) with the overnight cell cultures (50 µL/well). The library was sealed and stored at -80 °C. The expression cultures (500 µL of autoinducing Turbo Broth<sup>TM</sup> media containing 100 µg/mL of ampicillin, 25 µg/mL of chloramphenicol and 250 µg/mL of L-arabinose) in 96-well plates were inoculated by adding 50 µL of the overnight cultures, and grown for 24 h (30 °C, 250 rpm). After growth and expression, cells were harvested by centrifugation (4000 x g, 20 min, 4 °C) and frozen at -80 °C overnight. The cell libraries were thawed and resuspended with lysis buffer (100 µL/well) and allowed to shake for 1 h at 25 °C. The crude cell lysates were centrifuged (4000 x g, 20 min, 4 °C) and the supernatants (90 µL/well) were transferred into a new deep-well 96-well plate for screening assay immediately.

In the Coy chamber, the freshly prepared turnover mix (100 µL/well) and substrate (0.4 mg/well in 10 µL DMSO) were added to the supernatants (90 µL/well), and the 96-well plate was sealed with adhesive plate-sealing film and shaken under anaerobic conditions at room temperature for 24 h. Upon completion, the reaction was quenched with acetonitrile (1000 µL/well), and the plate was sealed with a reusable silicone mat, shaken for 30 min, and centrifuged (4500 × g, 15 min). The supernatant (200 µL/well) was filtered through a Millipore 96-well filter plate into a shallow-well plate (1000 x g, 2 min), and the filtrate was retained for LCMS analysis. Promising hits were chosen and subjected to cultivation in shaking flasks for further confirmation. The DNA plasmids of hits were extracted and submitted for sequencing to identify their mutations.

Recipe for Auto Inducing TB Media. For autoinducing cultures, Turbo Broth<sup>TM</sup> media was supplemented with a sterile-filtered solution of 1.25% glucose, 5% lactose, and 15% glycerol (40 mL/L media).

Lysis buffer. 100 mM KPi (pH 8.0) buffer containing lysozyme (1 mg/mL), DNase I (0.1 mg/mL), and PMSF (1 mM).

Turnover mix. 100 mM KPi (pH 8.0) buffer containing GDH-105 (5 mg/mL), FMN (0.5 mg/mL), NADP<sup>+</sup> (1 mg/mL), and glucose (50 mg/mL).

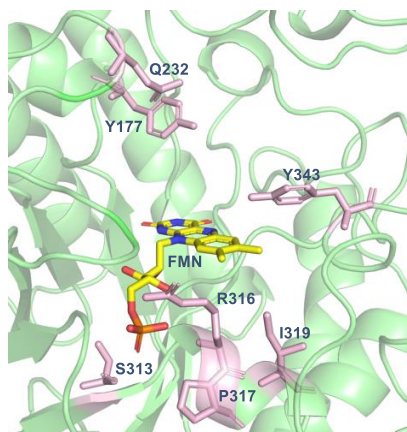


**Supplemental Figure 1.** Docking model of substrate **1a** with wild-type NCR. Residues H172 and N175 are responsible for substrate binding via hydrogen bonds. Pink sticks demonstrate amino acid residues which lining the active site pocket and interact with either the substrate **1a** (purple) or FMN (yellow).



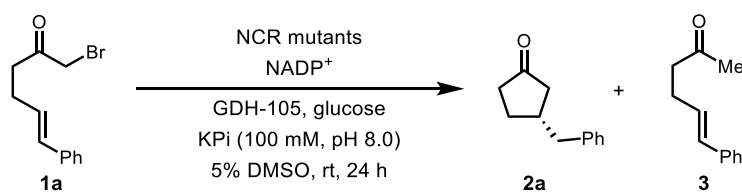
Site saturation mutagenesis **Round 1**

**Supplemental Table 2.** Template and target sites of the 1st round of SSM on NCR for cyclization.



Template	Target sites	Beneficial mutations
NCR wt	Y177, Q232, S313, R316, P317, I319, Y343	Y343W Y343N

**Supplemental Table 3.** Summary of the 1st round of SSM on NCR for cyclization.

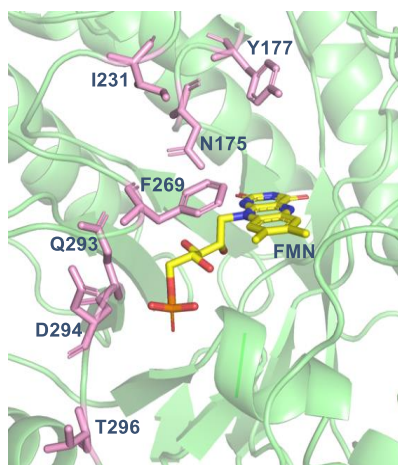


Entry	NCR mutants	Loading	Yield of <b>2a</b> (%)	er	Yield of <b>3</b> (%)
1	NCR wt	1.0 mol%	12	78:22	7
2	Y343W	1.0 mol%	36	86:14	10
3	Y343N	2.0 mol%	70	82:18	7

Standard reaction conditions:  $\alpha$ -bromoketone (1 mg, 0.004 mmol, 1 eq), GDH-105 (0.5 mg), NADP<sup>+</sup> (0.5 mg), glucose (5 mg) and purified NCR mutants (enzyme loading based on  $\alpha$ -bromoketone) in 100 mM KPi buffer pH 8.0, with 5% DMSO (*v/v*) as cosolvent, final total volume is 500  $\mu$ L. Reaction mixtures were shaken under anaerobic conditions at room temperature for 24 h. Yields determined via LCMS relative to an internal standard (TBB). Enantiomeric ratio (er) determined by HPLC on a chiral stationary phase.

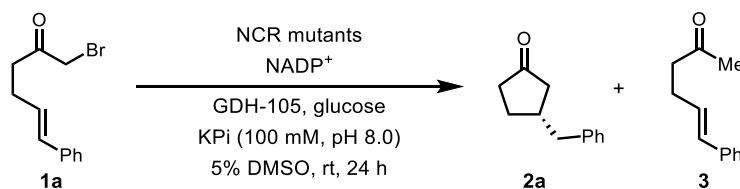
Site saturation mutagenesis **Round 2**

**Supplemental Table 4.** Templates and target sites of the 2nd round of SSM on NCR for cyclization.



Template	Target sites	Beneficial mutations
Y343W	N175, Y177, I231, F269, Q293, D294, T296	Y343W/F269W
Y343N	N175, Y177, I231, F269, Q293, D294, T296	Y343N/F269W

**Supplemental Table 5.** Summary of the 2nd round of SSM on NCR for cyclization.

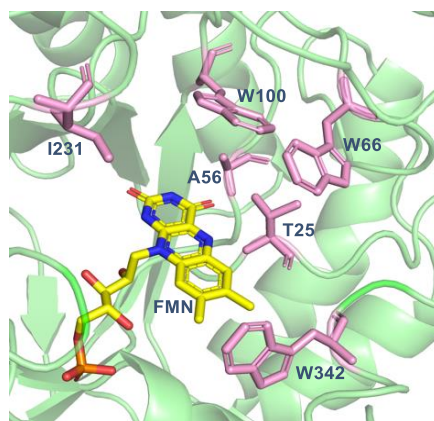


Entry	NCR mutants	Loading	Yield of <b>2a</b> (%)	er	Yield of <b>3</b> (%)
1	Y343W	1.0 mol%	36	86:14	10
2	Y343W/F269W	1.0 mol%	54	89:11	8
3	Y343W/F269W	1.5 mol%	68	89:11	18
4	Y343N	2.0 mol%	70	82:18	7
5	Y343N/F269W	1.0 mol%	85	85:15	10
6	Y343N/F269W	1.5 mol%	88	85:15	11

Reaction condition is described in Supplemental Table 3.

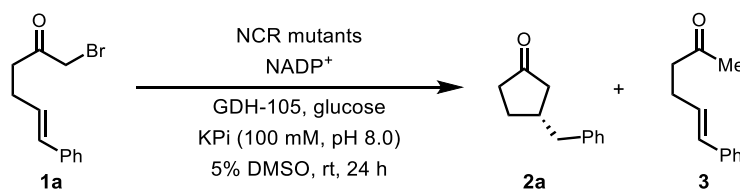
Site saturation mutagenesis **Round 3**

**Supplemental Table 6.** Templates and target sites of the 3rd round of SSM on NCR for cyclization.



Template	Target sites	Beneficial mutations
Y343W/F269W	T25, A56, W66, W100, I231, W342	Y343W/F269W/I231V Y343W/F269W/W342V Y343W/F269W/W342A
Y343N/F269W	T25, A56, W66, W100, I231, W342	Y343N/F269W/I231T Y343N/F269W/I231Q Y343N/F269W/W342V

**Supplemental Table 7.** Summary of the 3rd round of SSM on NCR for cyclization.

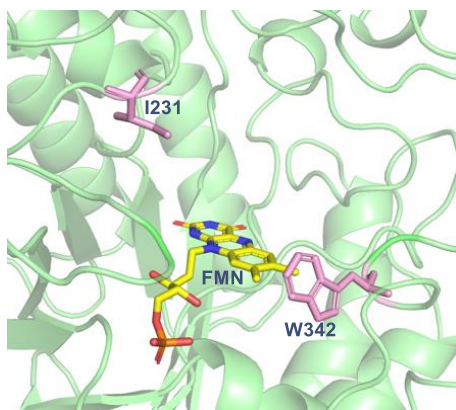


Entry	NCR mutants	Loading	Yield of <b>2a</b> (%)	er	Yield of <b>3</b> (%)
1	Y343W/F269W	1.0 mol%	54	89:11	8
2	Y343W/F269W/231V	1.0 mol%	62	90:10	8
3	Y343W/F269W/342V	1.0 mol%	58	88:12	12
4	Y343W/F269W/342A	1.0 mol%	61	88:12	7
5	Y343N/F269W	1.0 mol%	85	85:15	11
6	Y343N/F269W/231T	1.0 mol%	90	89:11	4
7	Y343N/F269W/231Q	1.0 mol%	87	89:11	3
8	Y343N/F269W/342V	1.0 mol%	84	86:14	9

Reaction condition is described in Supplemental Table 3.

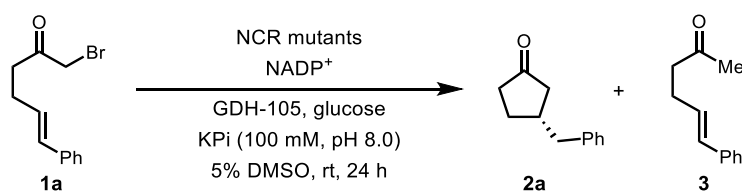
Site saturation mutagenesis **Round 4**

**Supplemental Table 8.** Templates and target sites of the 4th round of SSM on NCR for cyclization.



Template	Target sites	Beneficial mutations
Y343W/F269W/I231V	W342	none
Y343W/F269W/W342A	I231	Y343W/F269W/W342A/I231S (C9) Y343W/F269W/W342A/ I231V
Y343N/F269W/I231T	W342	Y343N/F269W/I231T/W342Q
Y343N/F269W/W342V	I231	none

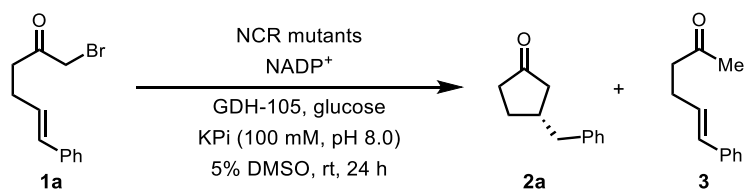
**Supplemental Table 9.** Summary of the 4th round of SSM on NCR for cyclization.



Entry	NCR mutants	Loading	Yield of <b>2a</b> (%)	er	Yield of <b>3</b> (%)
1	Y343W/F269W/342A	1.0 mol%	61	88:12	7
2	Y343W/F269W/W342A/I231V	1.0 mol%	70	95:5	1
3	Y343W/F269W/W342A/I231S (C9)	1.0 mol%	92	95:5	1
4	Y343W/F269W/W342A/I231S	0.75 mol%	73	95:5	1
5	Y343W/F269W/W342A/I231S	0.5 mol%	55	95:5	< 1
6	Y343N/F269W/W342V	1.0 mol%	84	86:14	9
7	Y343N/F269W/I231T/W342Q	1.0 mol%	81	91:9	2

Reaction condition is the same as described in Supplemental Table 3.

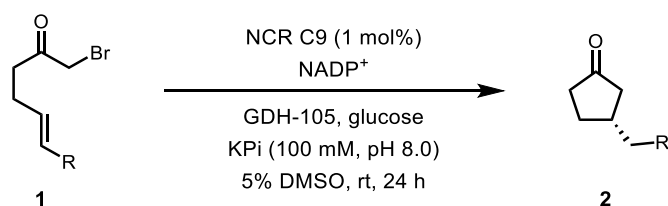
**Supplemental Table 10.** Summary of the site saturation mutagenesis results.



Entry	NCR mutants	Loading	Yield <sup>a</sup> of <b>2a</b>	er <sup>b</sup>	Yield <sup>a</sup> of <b>3</b>
1	WT	1.0 mol%	12%	78:22	7%
2	Y343W	1.0 mol%	36%	86:14	10%
3	Y343W/F269W	1.0 mol%	54%	89:11	8%
4	Y343W/F269W/W342A	1.0 mol%	61%	88:12	7%
5	Y343W/F269W/W342A/I231S (C9)	1.0 mol%	92%	95:5	1%

Reaction conditions: α-bromoketone (1 mg, 0.004 mmol, 1 eq), GDH-105 (0.5 mg), NADP<sup>+</sup> (0.5 mg), glucose (5 mg) and purified NCR mutants (enzyme loading based on α-bromoketone) in 100 mM KPi buffer pH 8.0, with 5% DMSO (v/v) as cosolvent, final total volume is 500 μL. Reaction mixtures were shaken under anaerobic conditions at room temperature for 24 h. <sup>a</sup>Yield determined via LCMS relative to an internal standard (TBB). <sup>b</sup>Enantiomeric ratio (er) determined by HPLC on a chiral stationary phase.

### NCR-C9 catalyzed asymmetric radical cyclization reaction.



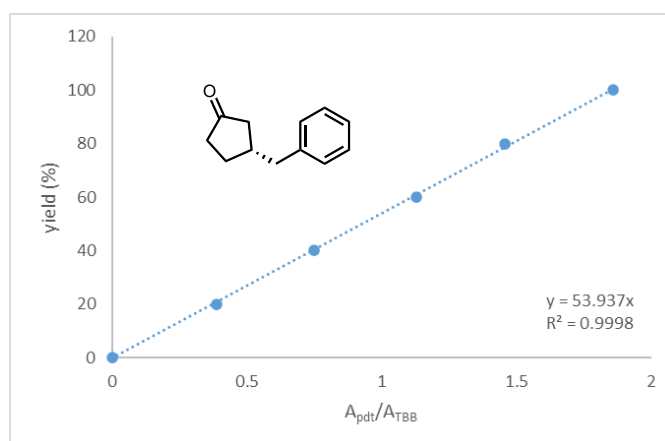
#### General Procedure 1.

In the Coy chamber, a 5 mL vial was charged with GDH-105 (100  $\mu$ L, 5 mg/mL stock solution in 100 mM KPi buffer pH 8.0), glucose (100  $\mu$ L, 50 mg/mL stock solution), NADP<sup>+</sup> (100  $\mu$ L, 5 mg/mL stock solution), NCR mutant C9 (1.0 mol%) and substrate (**1**, 25  $\mu$ L, 160 mM stock in DMSO, 0.004 mmol). Buffer (100 mM KPi buffer pH 8.0) was added to bring the total volume to 500  $\mu$ L with 5% DMSO (*v/v*) as cosolvent. The vial was sealed with a screw cap and shaken under anaerobic conditions at room temperature for 24 h. Upon completion, the reaction was quenched with 1.5 mL of acetonitrile and 50  $\mu$ L of 2 mg/mL 1,3,5-tribromobenzene (TBB) in acetonitrile as the internal standard. The mixture was shaken for 30 min, centrifuged (12000 x g, 5 mins), and the supernatant was filtered and retained for LCMS analysis for yield calculation. After LCMS analysis, the supernatant was concentrated under reduced pressure, extracted with EtOAc, the combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure. The resulting crude residue was dissolved in 10% isopropanol/hexanes (*v/v*) for chiral HPLC analysis.

#### General Procedure 2 for preparative scale reaction.

In the Coy chamber, a 20 mL vial was charged with GDH-105 (2 mL, 5 mg/mL stock solution in 100 mM KPi buffer pH 8.0), glucose (2 mL, 50 mg/mL stock solution), NADP<sup>+</sup> (2 mL, 5 mg/mL stock solution), NCR mutant C9 (1.0 mol%) and substrate (**1**, 500  $\mu$ L, 160 mM stock in DMSO, 0.08 mmol). Buffer (100 mM KPi buffer pH 8.0) was added to bring the total volume to 10 mL with 5% DMSO (*v/v*) as cosolvent. The vial was sealed with a screw cap and shaken under anaerobic conditions at room temperature for 24 h. Upon completion, the reaction was quenched with 30 mL of acetonitrile. The mixture was shaken for 30 min, centrifuged (12000 x g, 5 mins), and the supernatant was filtered, concentrated, and extracted with EtOAc. The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure to provide the crude product, which was purified by flash chromatography (EtOAc/Hexanes, 10%, *v/v*).

(*S*)-3-Benzylcyclopentan-1-one (**2a**)



Prepared according to the general procedure 1 using (*E*)-1-bromo-6-phenylhex-5-en-2-one (**1a**, 0.004 mmol) catalyzed by NCR-C9 mutant (1 mol%).

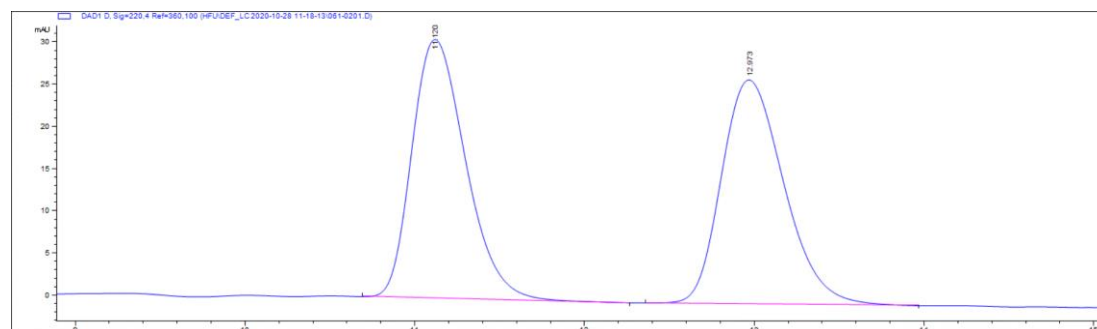
**Yields:** run 1: 93%, run 2: 92%, average yield 92%.

Preparative enzymatic synthesis was conducted according to the general procedure 2 using (*E*)-1-bromo-6-phenylhex-5-en-2-one (0.08 mmol) catalyzed by NCR-C9 mutant (1 mol%).

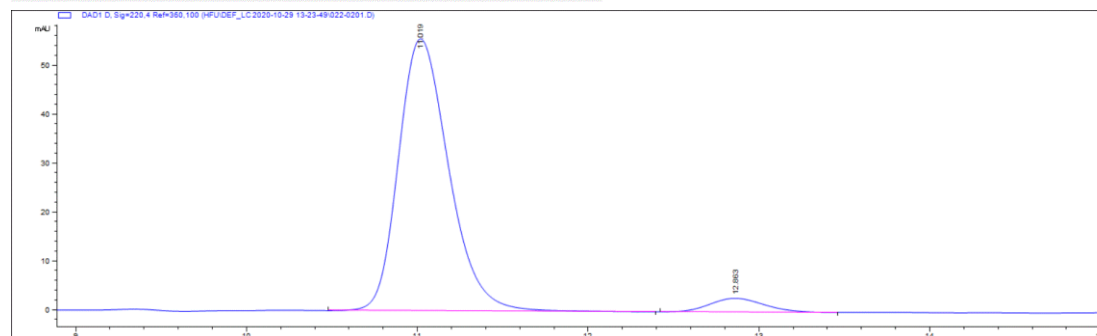
**Isolated yield:** 86% (clear oil, 12.0 mg). Optical rotation:  $[\alpha]_D^{20} = -87.3^\circ$  ( $c = 1.1$ , CHCl<sub>3</sub>).

**Absolute configuration** of the enzymatic product is assigned as *S* by optical rotation based on comparison with the reported data.<sup>6,7</sup>  $[\alpha]_D^{25} = -96^\circ$  ( $c = 1.3$ , CHCl<sub>3</sub>) for the (*S*)-isomer (98:2 er).<sup>6</sup>  $[\alpha]_D^{22} = +83.9^\circ$  ( $c = 1.0$ , CHCl<sub>3</sub>) for the (*R*)-isomer (95:5 er).<sup>7</sup>

**Enantioselectivity:** 95:5 er. Chiral HPLC method: AS-H column, 220 nm, 20% isopropanol/hexanes, flow rate 1.0 mL/min, room temperature,  $t_R$  (major) = 11.02 min,  $t_R$  (minor) = 12.86 min.

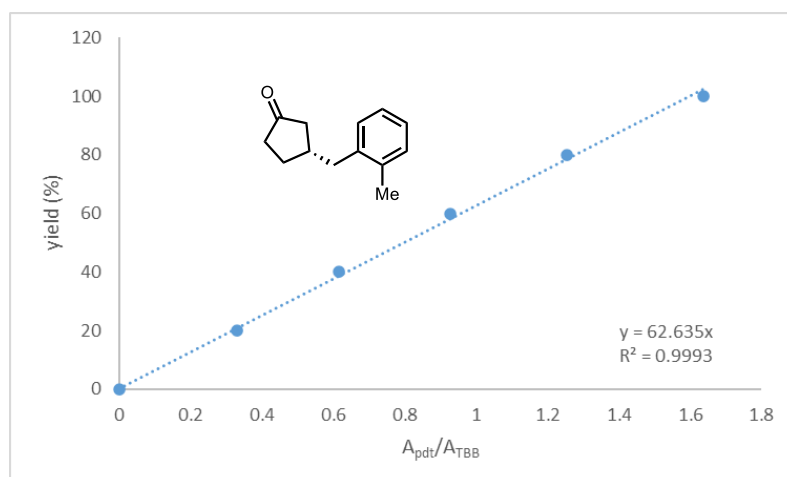


#	Time	Area	Height	Width	Area%	Symmetry
1	11.12	677.1	30.7	0.3452	49.850	0.711
2	12.973	681.2	26.6	0.4031	50.150	0.742



#	Time	Area	Height	Width	Area%	Symmetry
1	11.019	1140.2	55.6	0.3171	94.777	0.736
2	12.863	62.8	2.8	0.3482	5.223	0.833

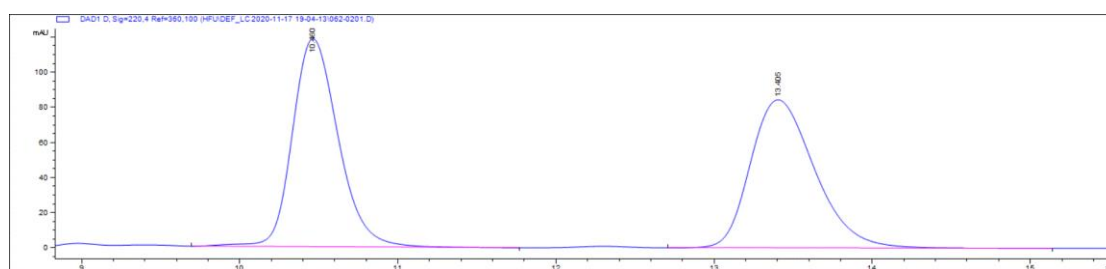
(*S*)-3-(2-Methylbenzyl)cyclopentan-1-one (**2b**)



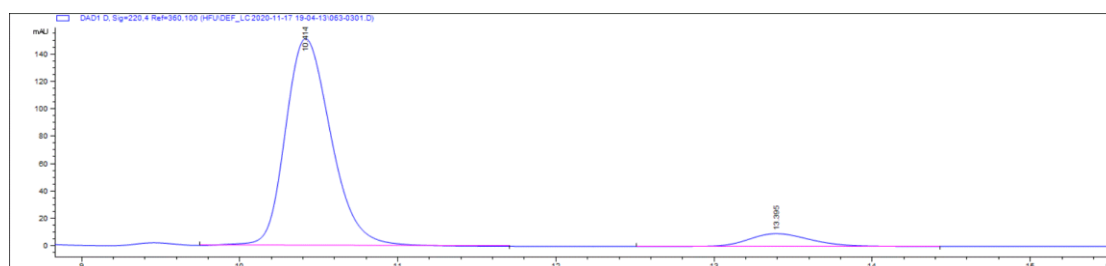
Prepared according to the general procedure 1 using (*E*)-1-bromo-6-(*o*-tolyl)hex-5-en-2-one (**1b**, 0.004 mmol) catalyzed by NCR-C9 mutant (1 mol%).

**Yields:** run 1: 80%, run 2: 82%, average yield 81%.

**Enantioselectivity:** 92:8 er. Chiral HPLC method: AS-H column, 220 nm, 20% isopropanol/hexanes, flow rate 1.0 mL/min, room temperature,  $t_R$  (minor) = 10.41 min,  $t_R$  (major) = 13.39 min.



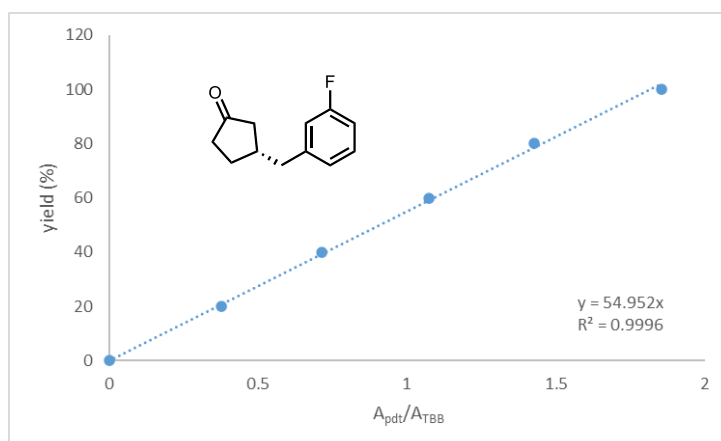
#	Time	Area	Height	Width	Area%	Symmetry
1	10.46	2384.4	118.2	0.3134	50.021	0.775
2	13.405	2382.4	84.1	0.4424	49.979	0.713



#	Time	Area	Height	Width	Area%	Symmetry
1	10.414	3041.6	151.4	0.3123	92.122	0.755
2	13.395	260.1	9.4	0.4284	7.878	0.767



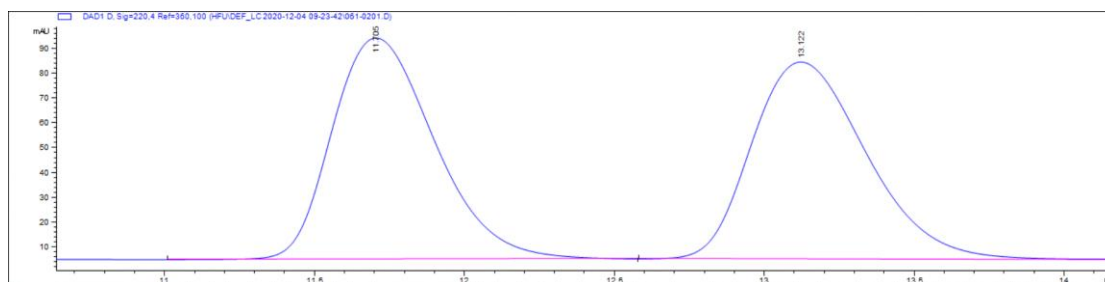
(*S*)-3-(3-Fluorobenzyl)cyclopentan-1-one (**2c**)



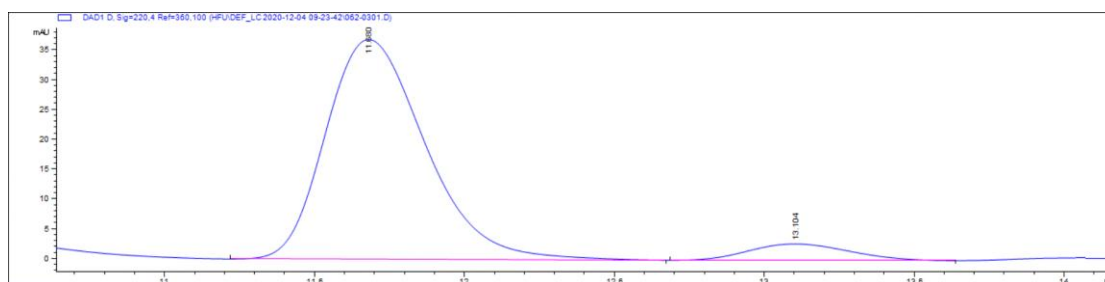
Prepared according to the general procedure 1 using (*E*)-1-bromo-6-(3-fluorophenyl)hex-5-en-2-one (**1c**, 0.004 mmol) catalyzed by NCR-C9 mutant (1 mol%).

**Yields:** run 1: 58%, run 2: 56%, average yield 57%.

**Enantioselectivity:** 93:7 er. Chiral HPLC method: AS-H column, 220 nm, 20% isopropanol/hexanes, flow rate 1.0 mL/min, room temperature,  $t_R$  (major) = 11.68 min,  $t_R$  (minor) = 13.10 min.

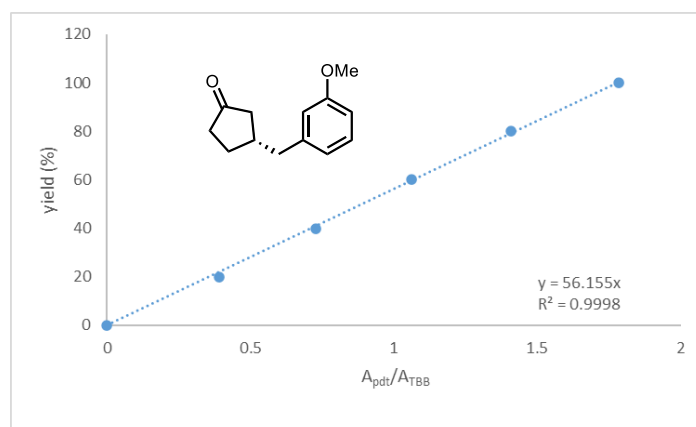


#	Time	Area	Height	Width	Area%	Symmetry
1	11.705	2118.1	89.4	0.3724	49.927	0.717
2	13.122	2124.3	79.6	0.4213	50.073	0.713



#	Time	Area	Height	Width	Area%	Symmetry
1	11.68	852.6	36.9	0.3613	92.983	0.721
2	13.104	64.3	2.8	0.3636	7.017	0.837

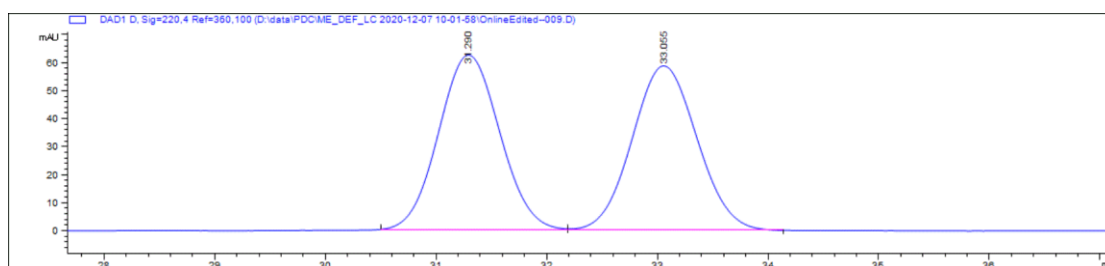
(*S*)-3-(3-Methoxybenzyl)cyclopentan-1-one (**2d**)



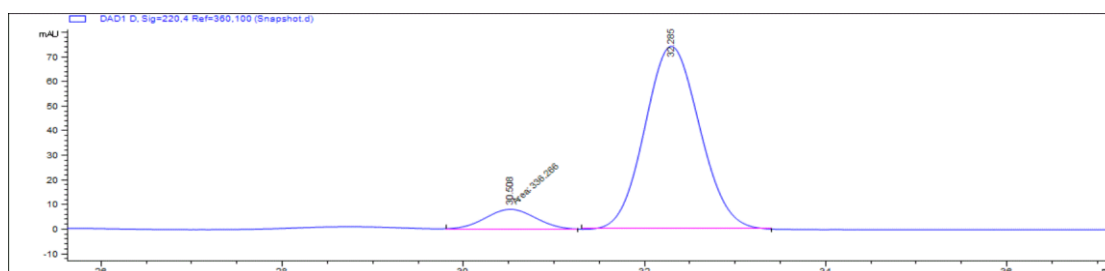
Prepared according to the general procedure 1 using (*E*)-1-bromo-6-(3-methoxyphenyl)hex-5-en-2-one (**1d**, 0.004 mmol) catalyzed by NCR-C9 mutant (1 mol%).

**Yields:** run 1: 69%, run 2: 71%, average yield 70%.

**Enantioselectivity:** 90:10 er. Chiral HPLC method: IC-H column, 220 nm, 5% isopropanol/hexanes, flow rate 1.0 mL/min, room temperature,  $t_R$  (minor) = 30.51 min,  $t_R$  (major) = 32.28 min.

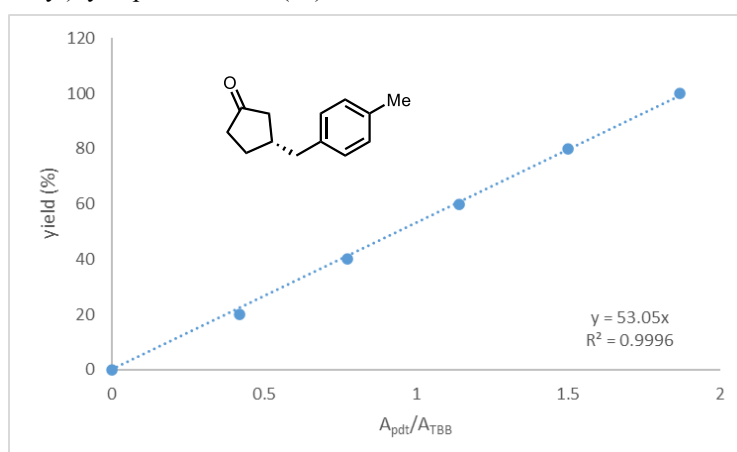


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	31.29	BV	2417.4	62.7	0.6039	50.095	0.924
2	33.055	VB	2408.2	58.9	0.6373	49.905	0.92



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	30.508	MM	336.3	8.4	0.6692	9.635	0.97
2	32.285	VB	3153.7	74.7	0.6603	90.365	0.901

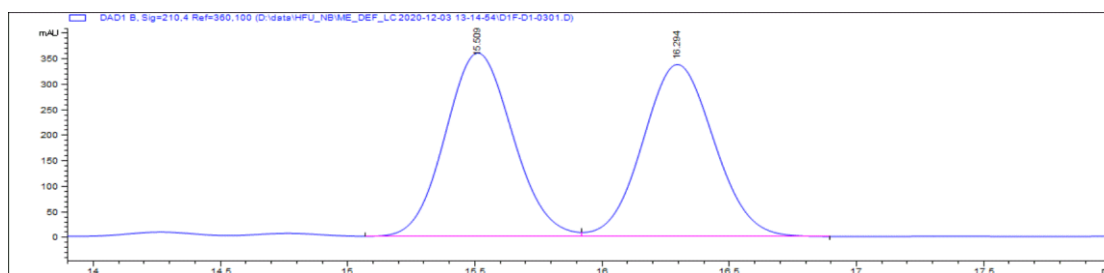
(S)-3-(4-Methylbenzyl)cyclopentan-1-one (**2e**)



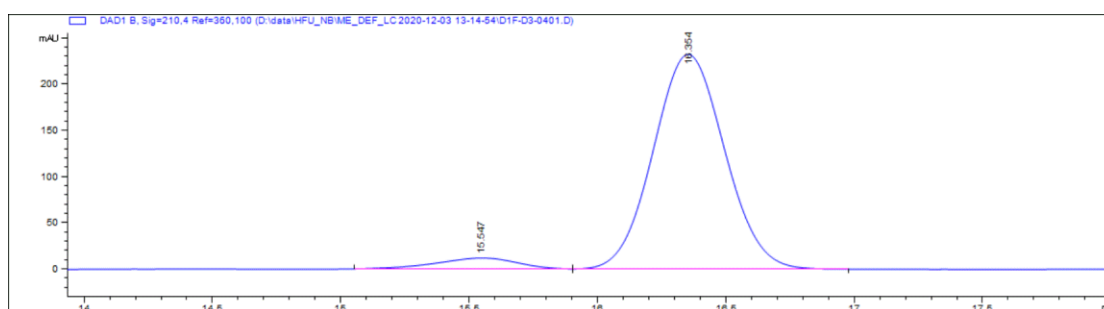
Prepared according to the general procedure 1 using (*E*)-1-bromo-6-(*p*-tolyl)hex-5-en-2-one (**1e**, 0.004 mmol) catalyzed by NCR-C9 mutant (1 mol%).

**Yields:** run 1: 73%, run 2: 74%, average yield 74%.

**Enantioselectivity:** 94:6 er. Chiral HPLC method: IC-H column, 210 nm, 5% isopropanol/hexanes, flow rate 1.0 mL/min, room temperature,  $t_R$  (minor) = 15.55 min,  $t_R$  (major) = 16.35 min.

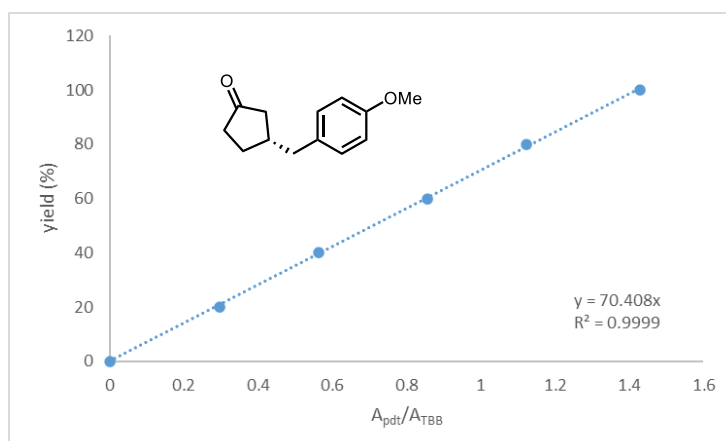


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	15.509	WV	6698	361.7	0.29	50.324	0.901
2	16.294	VB	6611.7	339	0.3055	49.676	0.918



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	15.547	BV	272.9	12.1	0.3455	5.732	1.286
2	16.354	VB	4487.3	231.9	0.3017	94.268	0.927

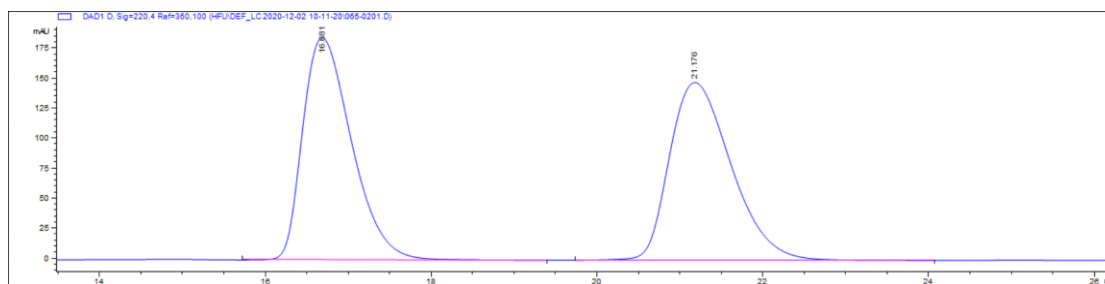
(S)-3-(4-Methoxybenzyl)cyclopentan-1-one (**2f**)



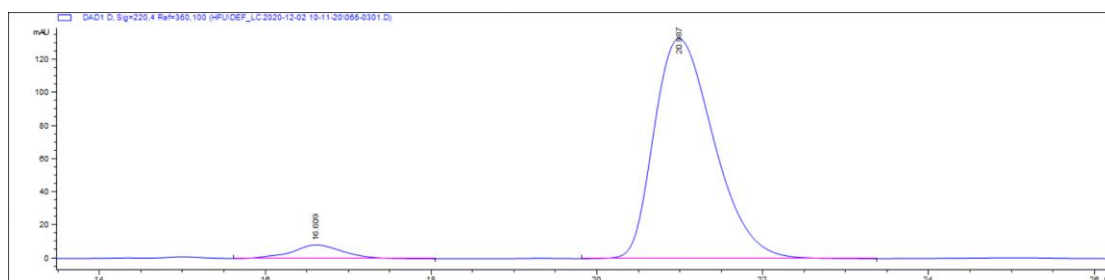
Prepared according to the general procedure 1 using (*E*)-1-bromo-6-(4-methoxyphenyl)hex-5-en-2-one (**1f**, 0.004 mmol) catalyzed by NCR-C9 mutant (1 mol%).

**Yields:** run 1: 86%, run 2: 85%, average yield 86%.

**Enantioselectivity:** 95:5 er. Chiral HPLC method: AS-H column, 220 nm, 20% isopropanol/hexanes, flow rate 1.0 mL/min, room temperature,  $t_R$  (minor) = 16.61 min,  $t_R$  (major) = 20.99 min.

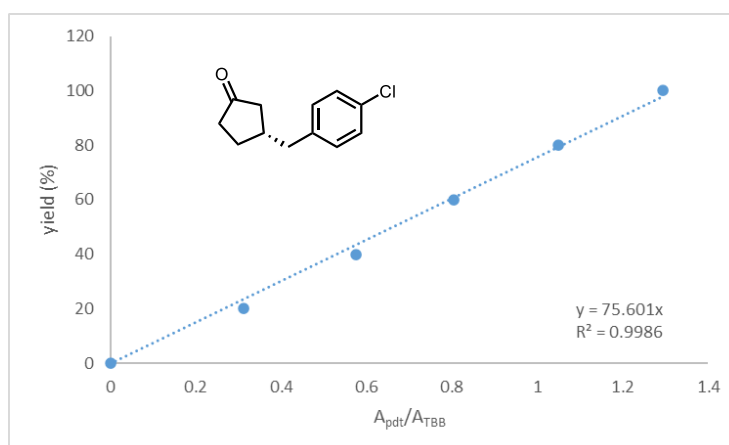


#	Time	Area	Height	Width	Area%	Symmetry
1	16.681	7556.2	184.7	0.6412	49.808	0.622
2	21.176	7614.3	147.6	0.8097	50.192	0.668



#	Time	Area	Height	Width	Area%	Symmetry
1	16.609	354.6	8.3	0.6323	5.071	0.923
2	20.987	6638.8	132.8	0.7874	94.929	0.677

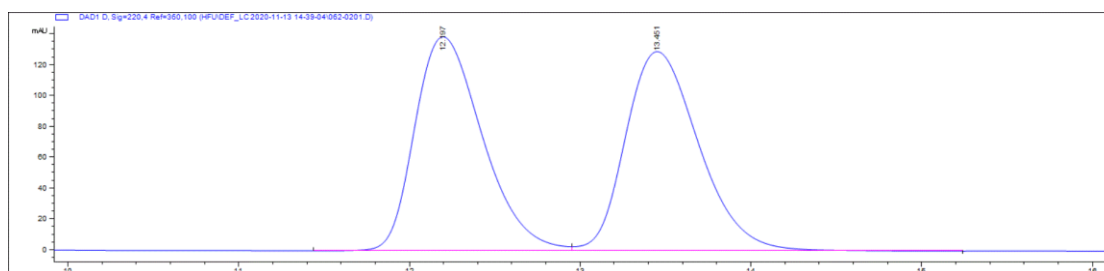
(*S*)-3-(4-Chlorobenzyl)cyclopentan-1-one (**2g**)



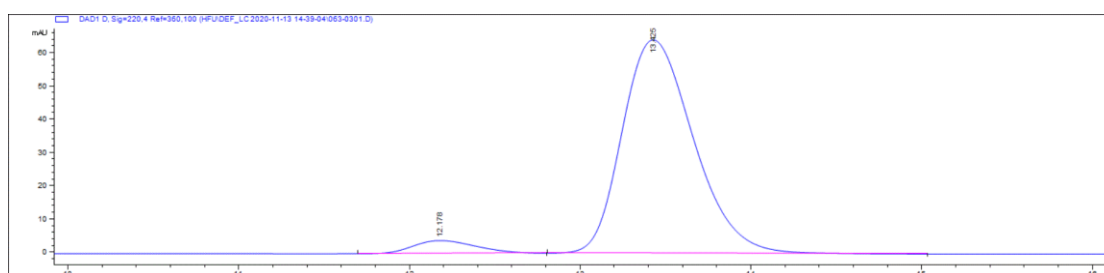
Prepared according to the general procedure 1 using (*E*)-1-bromo-6-(4-chlorophenyl)hex-5-en-2-one (**1g**, 0.004 mmol) catalyzed by NCR-C9 mutant (1 mol%).

**Yields:** run 1: 91%, run 2: 89%, average yield 90%.

**Enantioselectivity:** 95:5 er. Chiral HPLC method: AS-H column, 220 nm, 20% isopropanol/hexanes, flow rate 1.0 mL/min, room temperature,  $t_R$  (minor) = 12.18 min,  $t_R$  (major) = 13.42 min.

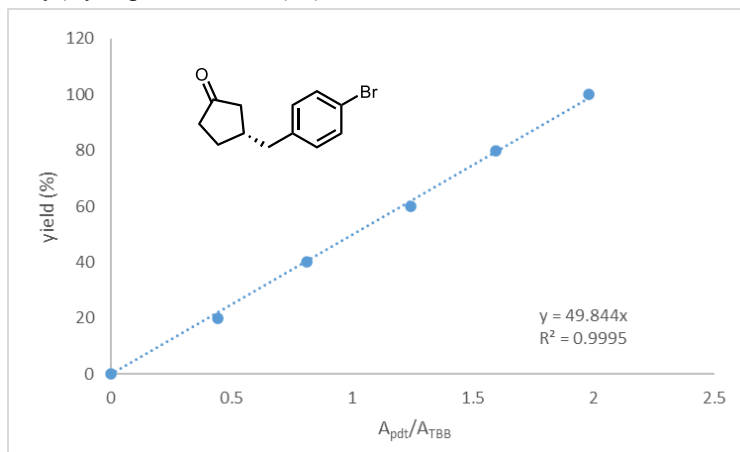


#	Time	Area	Height	Width	Area%	Symmetry
1	12.197	3817.1	138.5	0.4316	49.798	0.679
2	13.451	3848.1	128.9	0.4662	50.202	0.721



#	Time	Area	Height	Width	Area%	Symmetry
1	12.178	99.1	3.9	0.3982	5.043	0.731
2	13.425	1865.6	64.3	0.4547	94.957	0.728

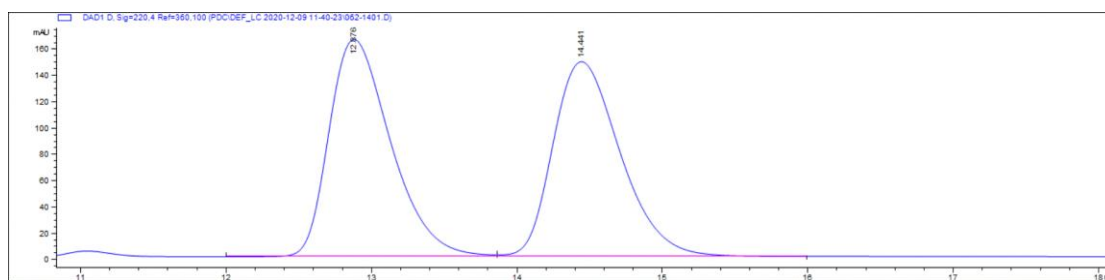
(S)-3-(4-Bromobenzyl)cyclopentan-1-one (**2h**)



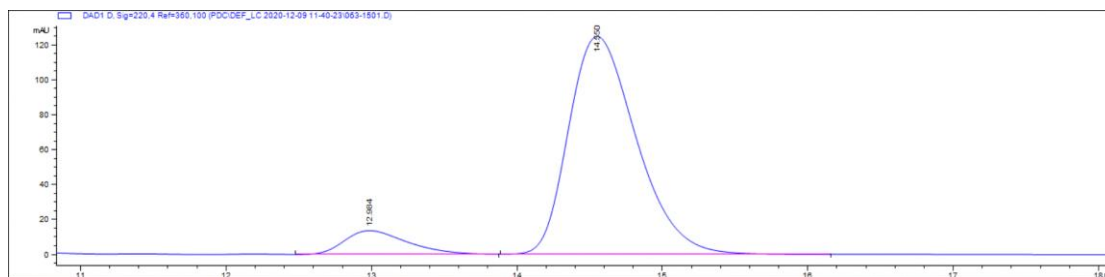
Prepared according to the general procedure 1 using (*E*)-1-bromo-6-(4-bromophenyl)hex-5-en-2-one (**1h**, 0.004 mmol) catalyzed by NCR-C9 mutant (1 mol%).

**Yields:** run 1: 52%, run 2: 60%, average yield 56%.

**Enantioselectivity:** 91:1 er. Chiral HPLC method: AS-H column, 220 nm, 20% isopropanol/hexanes, flow rate 1.0 mL/min, room temperature,  $t_R$  (minor) = 8.32 min,  $t_R$  (major) = 9.34 min.

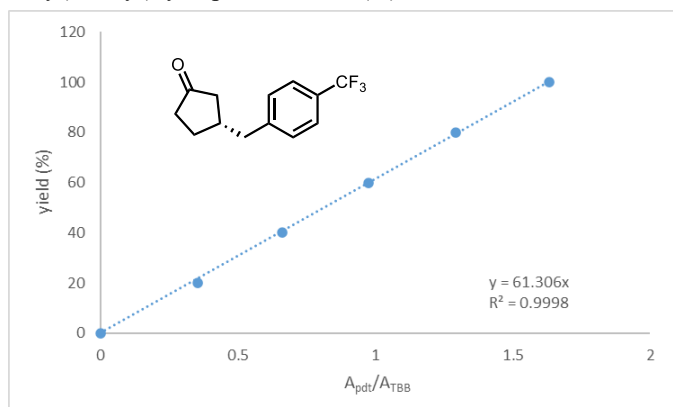


#	Time	Area	Height	Width	Area%	Symmetry
1	12.876	4888	165.5	0.4545	50.570	0.64
2	14.441	4777.9	148.4	0.5016	49.430	0.695



#	Time	Area	Height	Width	Area%	Symmetry
1	12.984	405.5	13.6	0.4586	9.148	0.635
2	14.55	4026.9	124.5	0.5034	90.852	0.691

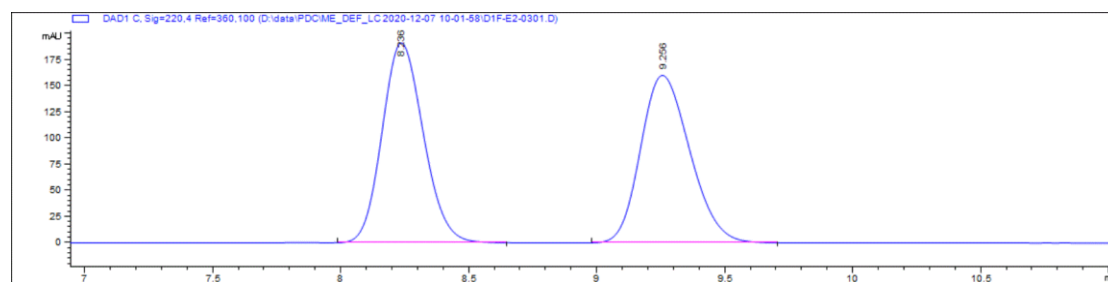
(S)-3-(4-(Trifluoromethyl)benzyl)cyclopentan-1-one (**2i**)



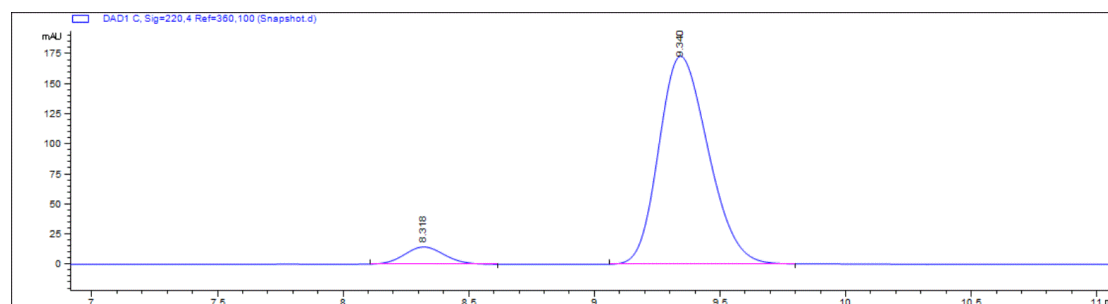
Prepared according to the general procedure 1 using (*E*)-1-bromo-6-(4-(trifluoromethyl)phenyl)hex-5-en-2-one (**1i**, 0.004 mmol) catalyzed by NCR-C9 mutant (1 mol%).

**Yields:** run 1: 75%, run 2: 78%, average yield 77%.

**Enantioselectivity:** 94:6 er. Chiral HPLC method: AS-H column, 220 nm, 20% isopropanol/hexanes, flow rate 1.0 mL/min, room temperature,  $t_R$  (minor) = 8.32 min,  $t_R$  (major) = 9.34 min.

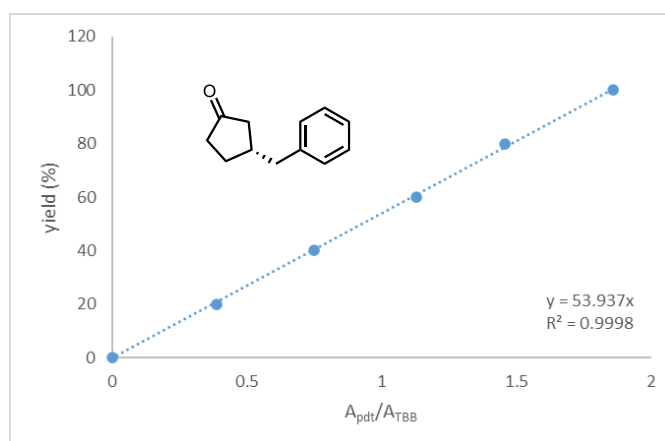


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	8.236	BB	2156.2	192.2	0.1749	49.967	0.835
2	9.256	BB	2159.1	161	0.2104	50.033	0.762



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	8.318	BB	161.8	14.4	0.173	6.437	0.9
2	9.34	BB	2351.8	172.2	0.2133	93.563	0.749

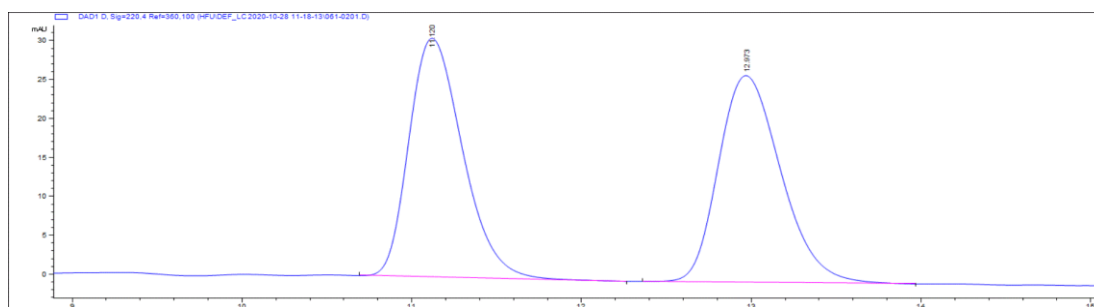
(*S*)-3-Benzylcyclopentan-1-one [**2a**, from (*Z*)-**1a**]



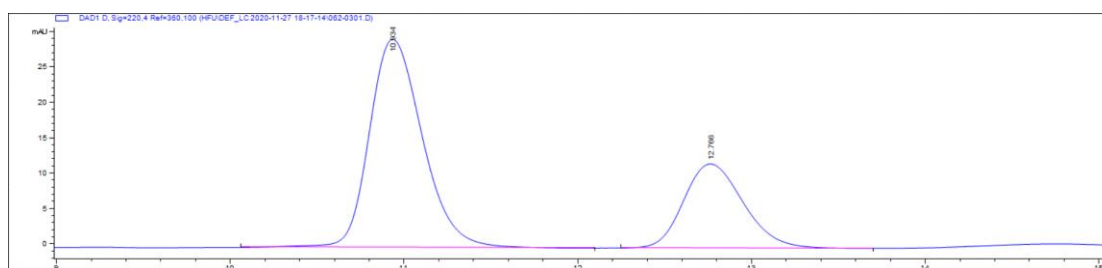
Prepared according to the general procedure 1 using (*Z*)-1-bromo-6-phenylhex-5-en-2-one [(*Z*)-**1a**, 0.004 mmol] catalyzed by NCR-C9 mutant (1 mol%).

**Yields:** run 1: 63%, run 2: 62%, average yield 62%.

**Enantioselectivity:** 69:31 er. Chiral HPLC method: AS-H column, 220 nm, 20% isopropanol/hexanes, flow rate 1.0 mL/min, room temperature,  $t_R$  (major) = 10.93 min,  $t_R$  (minor) = 12.77 min.



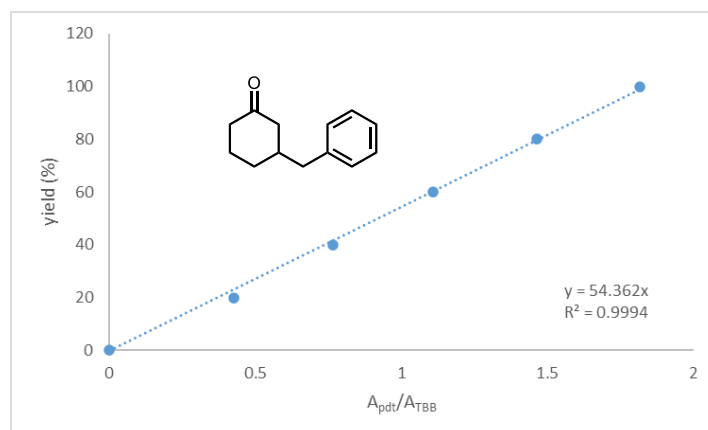
#	Time	Area	Height	Width	Area%	Symmetry
1	11.12	677.1	30.7	0.3452	49.850	0.711
2	12.973	681.2	26.6	0.4031	50.150	0.742



#	Time	Area	Height	Width	Area%	Symmetry
1	10.934	630.1	29.6	0.3326	68.828	0.755
2	12.766	285.4	11.9	0.373	31.172	0.777



3-Benzylcyclohexan-1-one (**2j**, 6-exo-trig product)

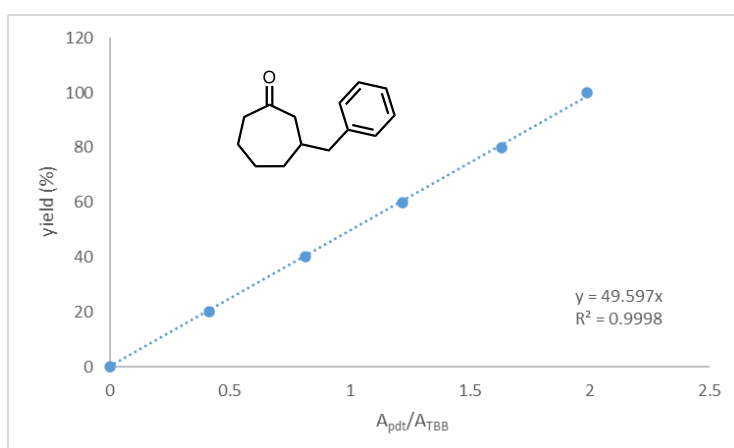


Prepared according to the general procedure 1 using (*E*)-1-bromo-7-phenylhept-6-en-2-one (**1j**, 0.004 mmol) catalyzed by wild-type NCR or NCR-C9 mutant. Product standard was obtained through known methods.<sup>8</sup>

**Yield** with 1 mol% NCR-C9: yield 0%.

**Yield** with 2 mol% NCR WT: yield 9%, er not determined.

### 3-Benzylcycloheptan-1-one (**2k**, 7-exo-trig product)

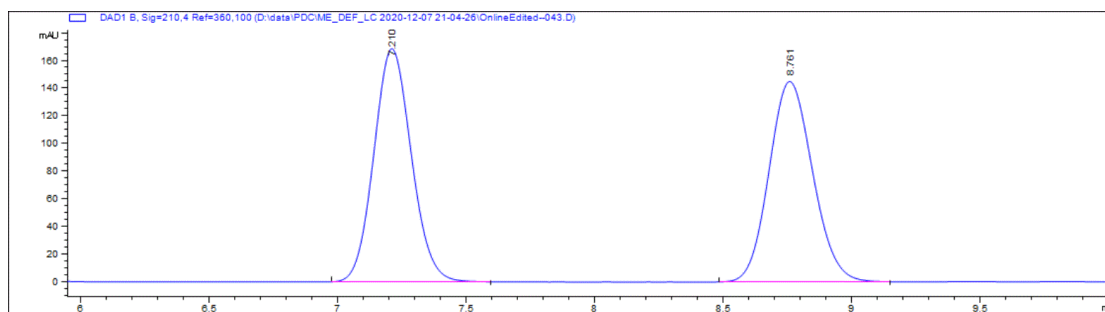


Prepared according to the general procedure 1 using (*E*)-1-bromo-8-phenyloct-7-en-2-one (**1k**, 0.004 mmol) catalyzed by wild-type NCR or NCR-C9 mutant. Product standard was obtained through known methods.<sup>9</sup>

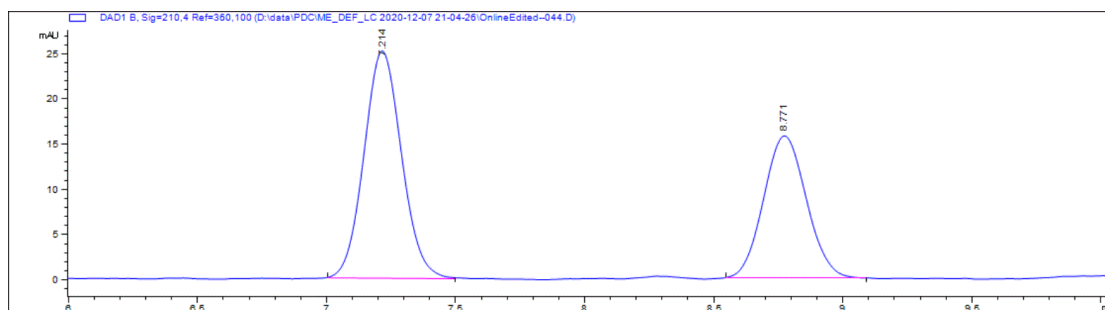
**Yields** with 1 mol% NCR-C9: run 1: 16%, run 2: 15%, average yield 16%.

**Enantioselectivity:** 58:42 er (for NCR-C9 product). Chiral HPLC method: AS-H column, 220 nm, 20% isopropanol/hexanes, flow rate 1.0 mL/min,  $t_R$  (major) = 7.21 min,  $t_R$  (minor) = 8.77 min.

**Yield** with 2 mol% NCR WT: yield 10%, er not determined.

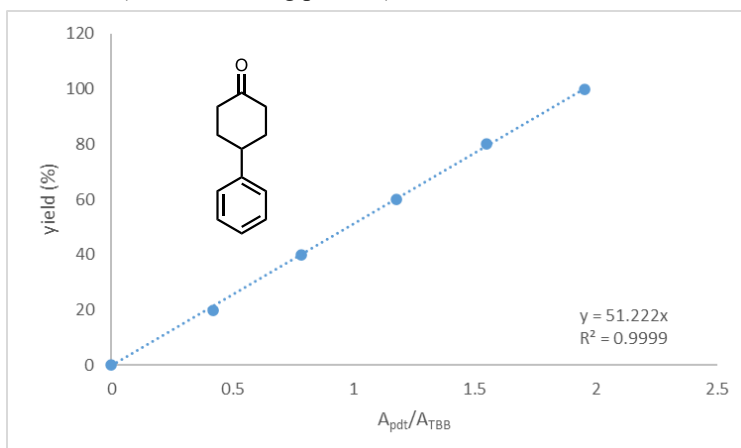


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	7.21	BB	1722.9	169.3	0.1567	50.030	0.888
2	8.761	BB	1720.9	145.5	0.184	49.970	0.858



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	7.214	BB	254.7	25.1	0.1582	58.456	0.905
2	8.771	BB	181	15.7	0.1805	41.544	0.907

#### 4-Phenylcyclohexan-1-one (**2m**, 6-endo-trig product)

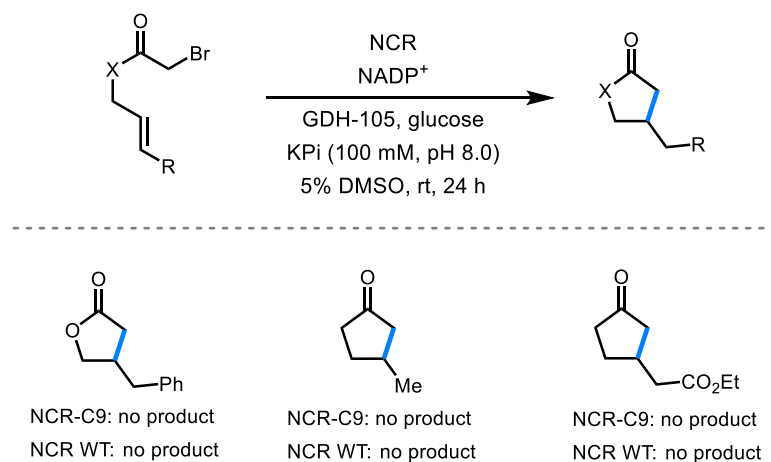


Prepared according to the general procedure 1 using 1-bromo-5-phenylhex-5-en-2-one (**1m**, 0.004 mmol) catalyzed by wild-type NCR or NCR-C9 mutant. Product standard was purchased from Sigma-Aldrich.

**Yields** with 1 mol% NCR-C9: run 1: 27%, run 2: 26%, average yield 26%.

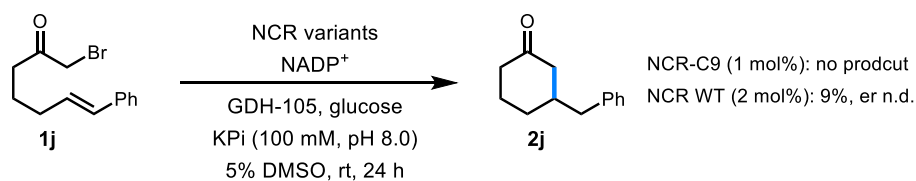
**Yields** with 2 mol% NCR-C9: run 1: 35%, run 2: 34%, average yield 35%.

**Yield** with 2 mol% NCR WT: yield 15%.

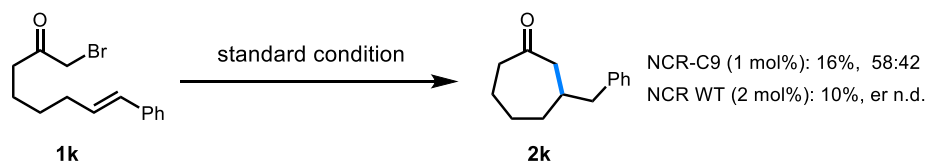


**Supplemental Figure 2.** Substrates not accepted by either NCR-C9 or the wild-type NCR under standard conditions as described in general procedure 1.

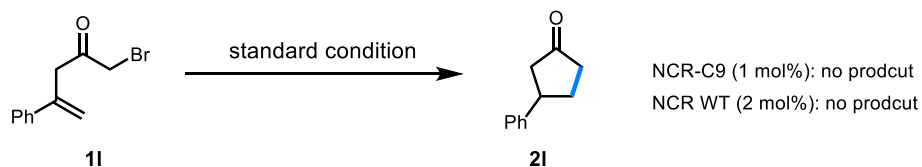
**6-*exo-trig* cyclization**



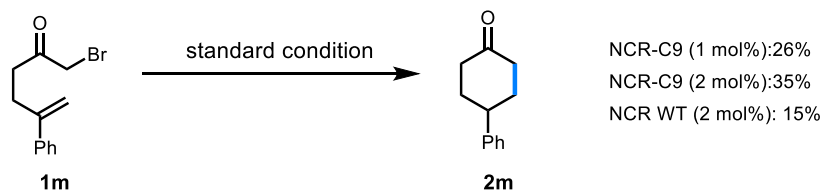
**7-*exo-trig* cyclization**



**5-*endo-trig* cyclization**

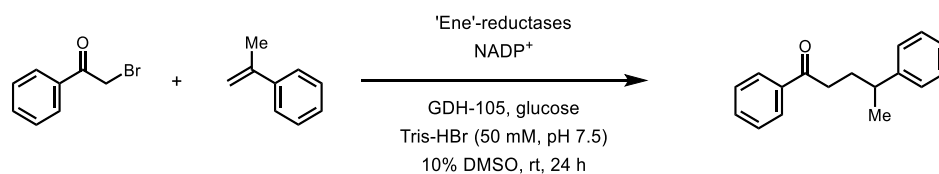


**6-*endo-trig* cyclization**



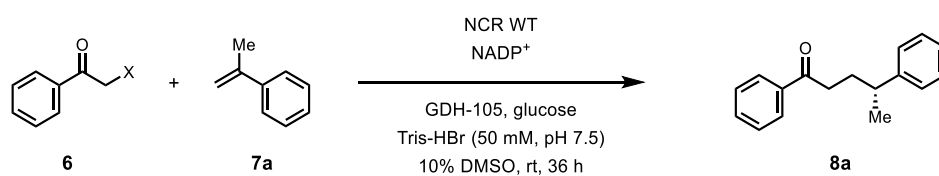
**Supplemental Figure 3.** Different cyclization modes catalyzed by NCR under standard conditions as described in general procedure 1.

**Supplemental Table 11.** Initial panel of 'ene'-reductases screened for intermolecular hydroalkylation.



entry	'ene'-reductases	yield <sup>a</sup>	er <sup>b</sup>
1	GluER-T36A	62%	97:3
2	NCR	99%	97:3
3	OPR1	10%	n.d. <sup>c</sup>
4	OYE1	5%	n.d.
5	YersER	44%	17:83

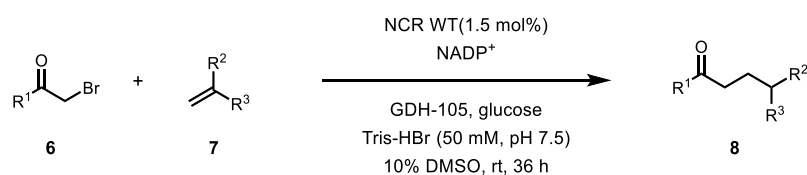
Reaction conditions:  $\alpha$ -bromoacetophenone (0.015 mmol, 3 eq),  $\alpha$ -methylstyrene (0.005 mmol, 1 eq), GDH-105 (0.3 mg), NADP<sup>+</sup> (0.2 mg), glucose (5 mg) and purified 'ene'-reductases (2 mol% based on  $\alpha$ -methylstyrene) in 50 mM Tris-HBr buffer pH 7.5, with 10% DMSO as cosolvent, final total volume is 500  $\mu$ L. Reaction mixtures were shaken under anaerobic conditions at room temperature for 24 h. <sup>a</sup>Yield determined via LCMS relative to an internal standard (TBB). <sup>b</sup> Enantiomeric ratio (er) determined by HPLC on a chiral stationary phase. <sup>c</sup> n.d., not determined.

**Supplemental Table 12.** Reaction optimization and control experiments.

entry	X	conc. of <b>6</b>	light	loading	yield <sup>a</sup>	er <sup>b</sup>
1	Br	10 mM	dark	2 mol%	99%	97:3
2	Cl	10 mM	dark	2 mol%	49%	97:3
3	Br	10 mM	dark	1.5 mol%	90%	96:4
4	Br	10 mM	dark	1.0 mol%	61%	97:3
5	Br	10 mM	blue light	1.0 mol%	64%	97:3
6	Br	10 mM	dark	0.5 mol%	35%	97:3
7	Br	4.2 mM	dark	1.5 mol%	99%	99:1
9	Br	10 mM	dark	No enzyme	0	
10	Br	10 mM	dark	No regeneration system	0	
11	Same condition as in entry 7, but using NCR-C9 as biocatalyst				75%	97:3

Reaction conditions: α-haloacetophenone (0.015 mmol, 3 eq), α-methylstyrene (0.005 mmol, 1 eq), GDH-105 (0.3 mg), NADP<sup>+</sup> (0.2 mg), glucose (5 mg) and purified wild-type NCR in 50 mM Tris-HBr buffer pH 7.5, with 10% DMSO as cosolvent. Reaction mixtures were shaken under anaerobic conditions at room temperature for 36 h. <sup>a</sup> Yield determined via LCMS relative to an internal standard (TBB). <sup>b</sup> Enantiomeric ratio (er) determined by HPLC on a chiral stationary phase.

### Wild-type NCR catalyzed intermolecular hydroalkylation.



#### General Procedure 3.

In the Coy chamber, a 2 mL vial was charged with GDH-105 (100  $\mu$ L, 3 mg/mL stock solution in 50 mM Tris-HBr buffer pH7.5), glucose (100  $\mu$ L, 50 mg/mL stock solution), NADP<sup>+</sup> (100  $\mu$ L, 2 mg/mL stock solution), NCR wild-type protein (1.5 mol% to alkene),  $\alpha$ -bromoketone (25  $\mu$ L, 600 mM DMSO stock solution, 0.015 mmol, 3 eq) and alkene (25  $\mu$ L, 200 mM stock in DMSO, 0.005 mmol, 1 eq). Buffer (50 mM Tris-HBr pH 7.5) and DMSO were added to bring the total volume to 1200  $\mu$ L with 10% DMSO (*v/v*). The vial was sealed with a screw cap and shaken under anaerobic conditions at room temperature for 36 h. Upon completion, the reaction was quenched with 2.4 mL of acetonitrile and 50  $\mu$ L of 2 mg/mL 1,3,5-tribromobenzene (TBB) in acetonitrile as the internal standard. The mixture was shaken for 30 min, centrifuged (12000 x g, 5 mins), and the supernatant was filtered and retained for LCMS analysis for yield calculation. After LCMS analysis, the supernatant was concentrated under reduced pressure, extracted with EtOAc, the combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure. The resulting crude residue was dissolved in 10% isopropanol/hexanes (*v/v*) for chiral HPLC analysis.

#### General Procedure 4.

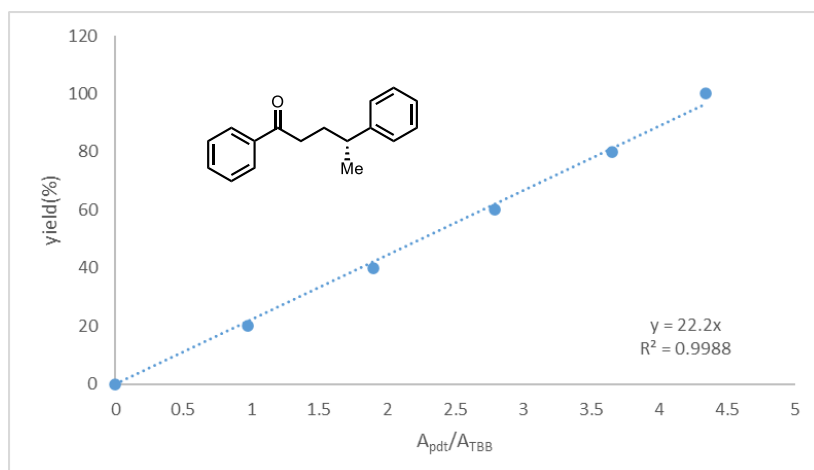
In the Coy chamber, a 2 mL vial was charged with GDH-105 (100  $\mu$ L, 3 mg/mL stock solution in 50 mM Tris-HBr buffer pH7.5), glucose (100  $\mu$ L, 50 mg/mL stock solution), NADP<sup>+</sup> (100  $\mu$ L, 2 mg/mL stock solution), NCR wild-type protein (1.5 mol% to  $\alpha$ -bromoketone),  $\alpha$ -bromoketone (50  $\mu$ L, 100 mM DMSO stock solution, 0.005 mmol, 1 eq) and alkene (0.015 mmol, 3 eq). Buffer (50 mM Tris-HBr pH 7.5) was added to bring the total volume to 500  $\mu$ L with 10% DMSO (*v/v*). The vial was sealed with a screw cap and shaken under anaerobic conditions at room temperature for 36 h. Upon completion, the reaction was quenched with 1.5 mL of acetonitrile and 50  $\mu$ L of 2 mg/mL 1,3,5-tribromobenzene (TBB) in acetonitrile as the internal standard. The mixture was shaken for 30 min, centrifuged (12000 x g, 5 mins), and the supernatant was filtered and retained for LCMS analysis for yield calculation. After LCMS analysis, the supernatant was concentrated under reduced pressure, extracted with EtOAc, the combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure. The resulting crude residue was dissolved in 10% isopropanol/hexanes (*v/v*) for chiral HPLC analysis.

**General Procedure 5 for preparative scale reaction.**

In the Coy chamber, a 30 mL vial was charged with GDH-105 (2 mL, 3 mg/mL stock solution in 50 mM Tris-HBr buffer pH7.5), glucose (2 mL, 50 mg/mL stock solution), NADP<sup>+</sup> (2 mL, 2 mg/mL stock solution), NCR wild-type protein (1.5 mol% to alkene),  $\alpha$ -bromoketone (500  $\mu$ L, 600 mM DMSO stock solution, 0.3 mmol, 3 eq) and alkene (500  $\mu$ L, 200 mM stock in DMSO, 0.1 mmol, 1 eq). Buffer (50 mM Tris-HBr pH 7.5) and DMSO were added to bring the total volume to 24 mL with 10% DMSO (*v/v*). The vial was sealed with a screw cap and shaken under anaerobic conditions at room temperature for 36 h. Upon completion, the reaction was quenched with 50 mL of acetonitrile. The mixture was shaken for 30 min, centrifuged (12000 x g, 5 mins), and the supernatant was filtered, concentrated, and extracted with EtOAc. The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure to provide the crude product, which was purified by preparative TLC (EtOAc/Hexanes, 10%, *v/v*).



(*R*)-1,4-Diphenylpentan-1-one (**8a**)



Prepared according to the general procedure 3 using 2-bromo-1-phenylethan-1-one (0.015 mmol) and prop-1-en-2-ylbenzene (0.005 mmol) catalyzed by wild-type NCR (1.5 mol%).

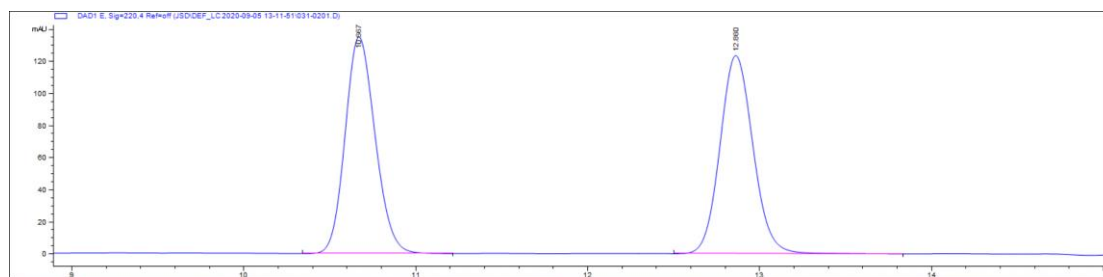
**Yields:** run 1: 99%, run 2: 100%, average yield 99%.

Preparative enzymatic synthesis was conducted according to the general procedure 5 using 2-bromo-1-phenylethan-1-one (0.3 mmol) and prop-1-en-2-ylbenzene (0.1 mmol) catalyzed by wild-type NCR (1.5 mol%).

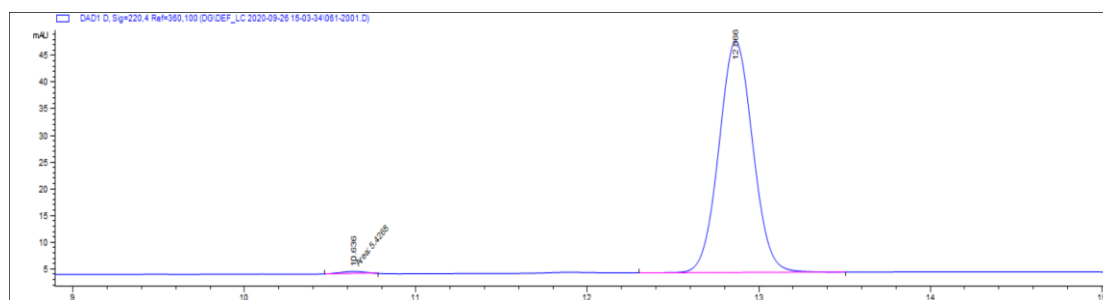
**Isolated yield:** 82% (clear oil, 19.5 mg). Optical rotation:  $[\alpha]_{\text{D}}^{20} = -29.8^\circ$  ( $c = 1.0$ , MeOH).

**Absolute configuration** of the enzymatic product is assigned as *R* by optical rotation base on comparison with the reported data.<sup>10</sup>  $[\alpha]_{\text{D}}^{25} = +26.3^\circ$  ( $c = 1.0$ , MeOH) for the (*S*)-isomer (90:10 er).<sup>10</sup>

**Enantioselectivity:** 99:1 er. Chiral HPLC method: OJ-H column, 220 nm, 5% isopropanol/hexanes, flow rate 1.0 mL/min, room temperature,  $t_{\text{R}}$  (minor) = 10.64 min,  $t_{\text{R}}$  (major) = 12.87 min.

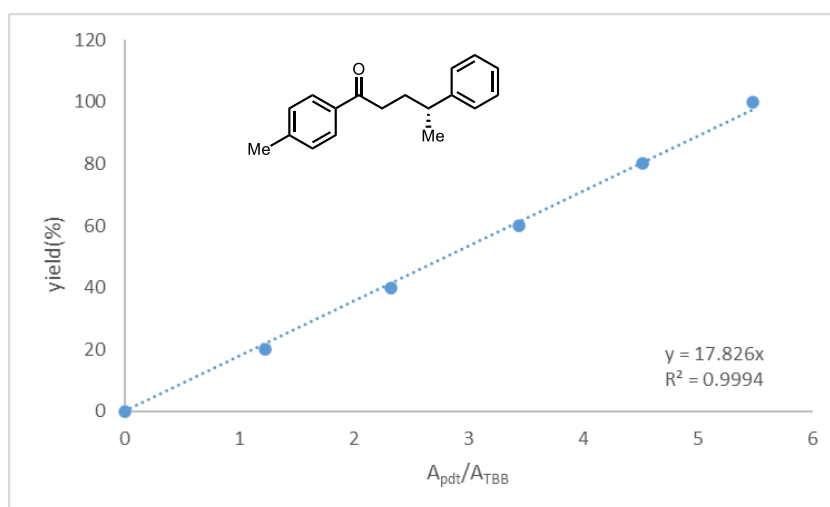


#	Time	Area	Height	Width	Area%	Symmetry
1	10.667	1643.1	135.5	0.1875	49.765	0.817
2	12.866	1658.6	123.9	0.2082	50.235	0.872



#	Time	Area	Height	Width	Area%	Symmetry
1	10.636	5.4	4.8E-1	0.1901	0.906	1.198
2	12.866	593.5	43.2	0.2142	99.094	0.935

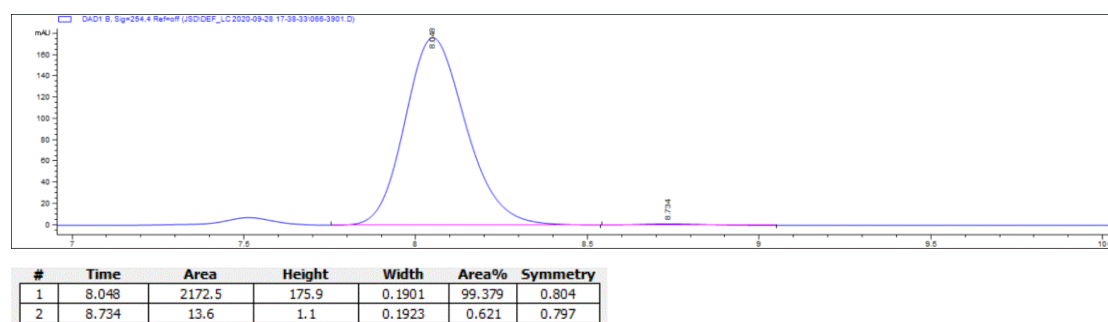
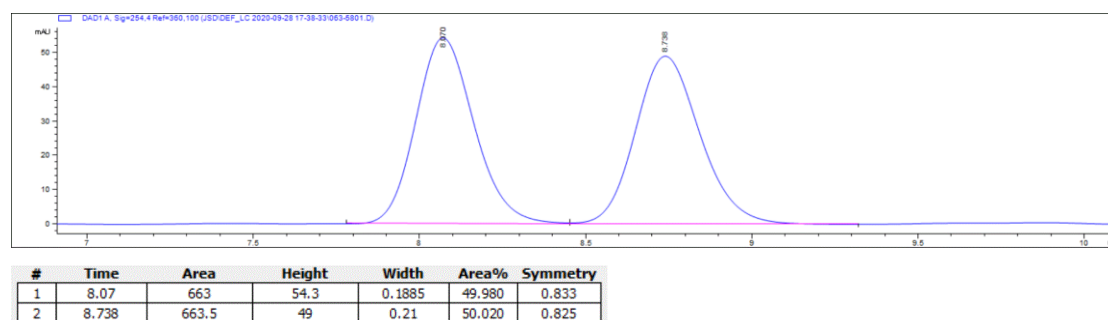
(*R*)-4-Phenyl-1-(*p*-tolyl)pentan-1-one (**8b**)



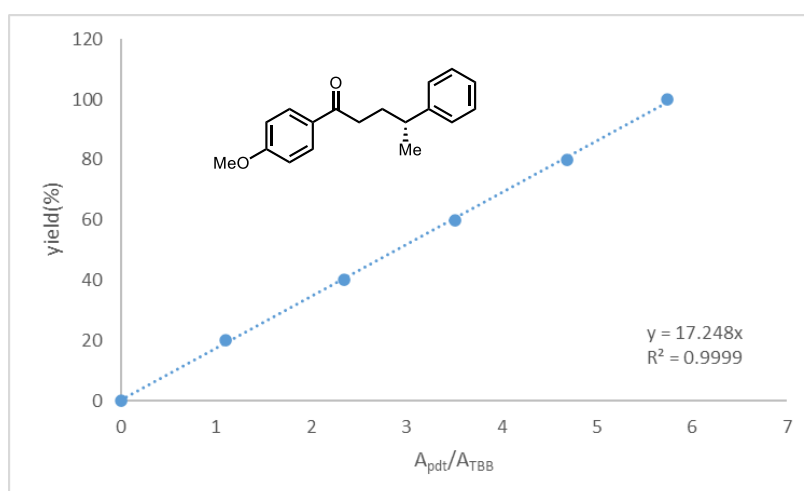
Prepared according to the general procedure 3 using 2-bromo-1-(*p*-tolyl)ethan-1-one (0.015 mmol) and prop-1-en-2-ylbenzene (0.005 mmol) catalyzed by wild-type NCR (1.5 mol%).

**Yields:** run 1: 97%, run 2: 92%, average yield 95%.

**Enantioselectivity:** 99:1 er. Chiral HPLC method: OD-H column, 254 nm, 1% isopropanol/hexanes, flow rate 1.0 mL/min, room temperature,  $t_R$  (major) = 8.05 min,  $t_R$  (minor) = 8.73 min.



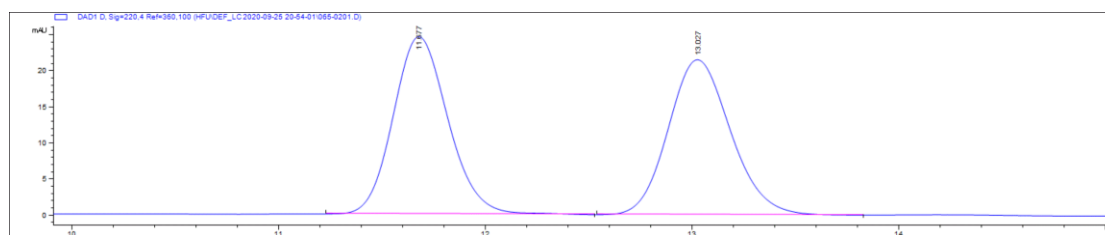
(*R*)-1-(4-Methoxyphenyl)-4-phenylpentan-1-one (**8c**)



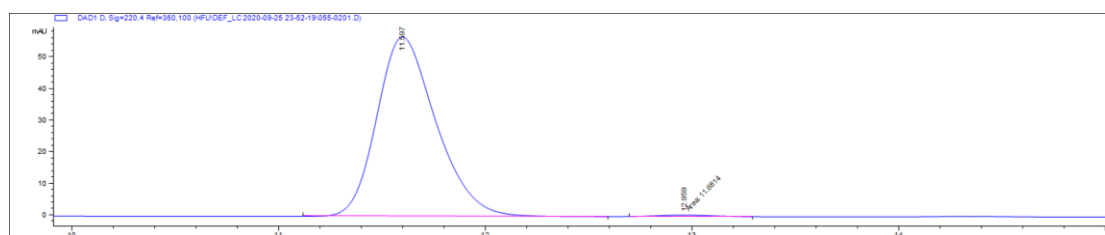
Prepared according to the general procedure 3 using 2-bromo-1-(4-methoxyphenyl)ethan-1-one (0.015 mmol) and prop-1-en-2-ylbenzene (0.005 mmol) catalyzed by wild-type NCR (1.5 mol%).

**Yields:** run 1: 80%, run 2: 81%, average yield 81%.

**Enantioselectivity:** 99:1 er. Chiral HPLC method: OD-H column, 220 nm, 2% isopropanol/hexanes, flow rate 1.0 mL/min, room temperature,  $t_R$  (major) = 11.60 min,  $t_R$  (minor) = 12.96 min.

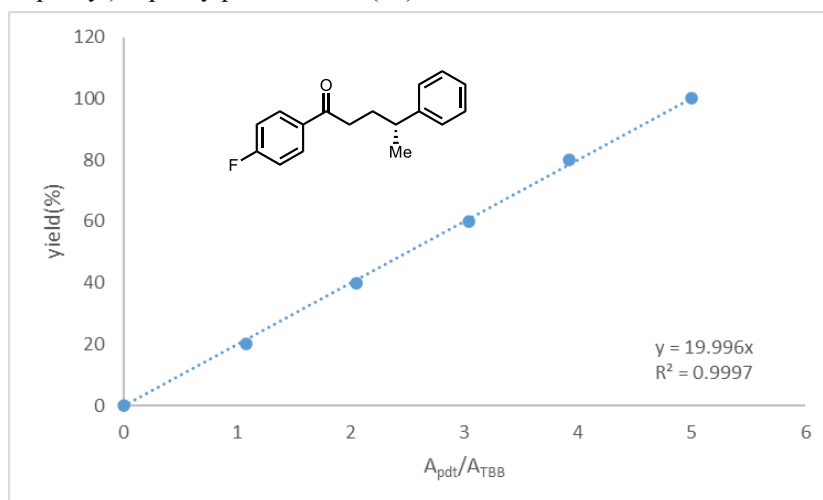


#	Time	Area	Height	Width	Area%	Symmetry
1	11.677	458.4	24.8	0.286	50.192	0.839
2	13.027	454.9	21.6	0.3253	49.808	0.846



#	Time	Area	Height	Width	Area%	Symmetry
1	11.597	1132.6	56.9	0.3022	98.979	0.731
2	12.959	11.7	5.6E-1	0.3499	1.021	0.822

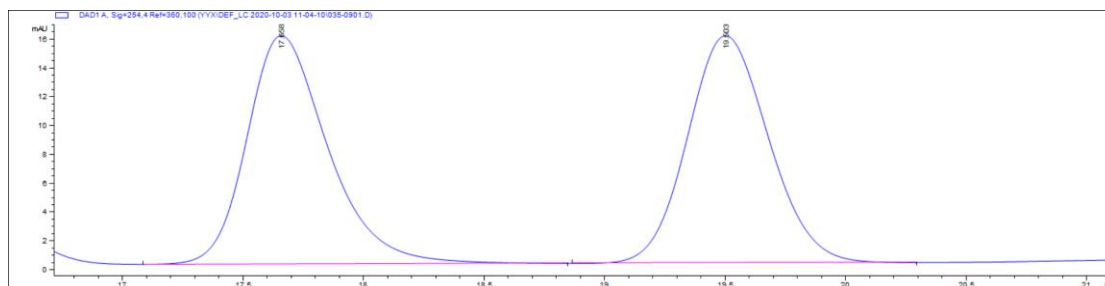
(*R*)-1-(4-Fluorophenyl)-4-phenylpentan-1-one (**8d**)



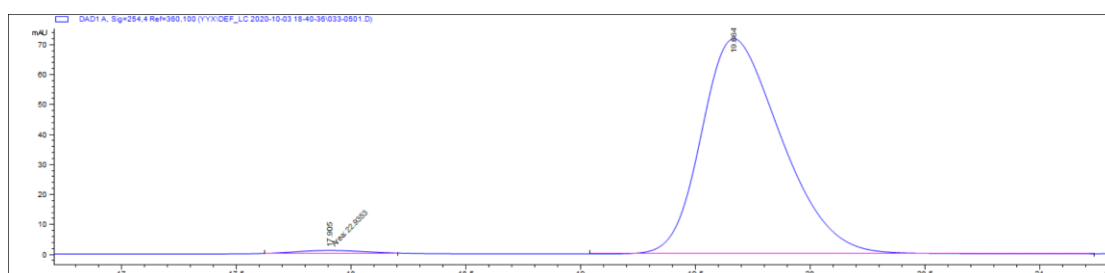
Prepared according to the general procedure 3 using 2-bromo-1-(4-fluorophenyl)ethan-1-one (0.015 mmol) and prop-1-en-2-ylbenzene (0.005 mmol) catalyzed by wild-type NCR (1.5 mol%).

**Yields:** run 1: 90%, run 2: 88%, average yield 89%.

**Enantioselectivity:** 99:1 er. Chiral HPLC method: OJ-H column, 254 nm, 5% isopropanol/hexanes, flow rate 1.0 mL/min, room temperature,  $t_R$  (minor) = 17.90 min,  $t_R$  (major) = 19.66 min.

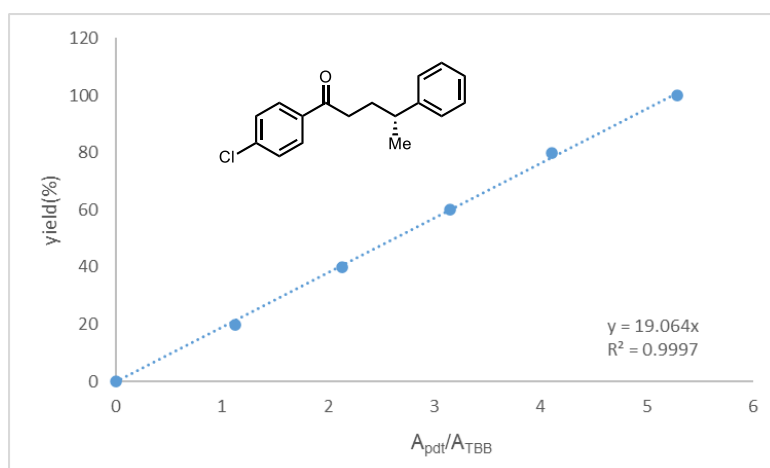


#	Time	Area	Height	Width	Area%	Symmetry
1	17.658	370.2	15.8	0.3572	50.092	0.7
2	19.503	368.8	15.7	0.3634	49.908	0.86



#	Time	Area	Height	Width	Area%	Symmetry
1	17.905	22.9	1.1	0.3521	1.306	0.987
2	19.664	1732.8	71.5	0.3726	98.694	0.649

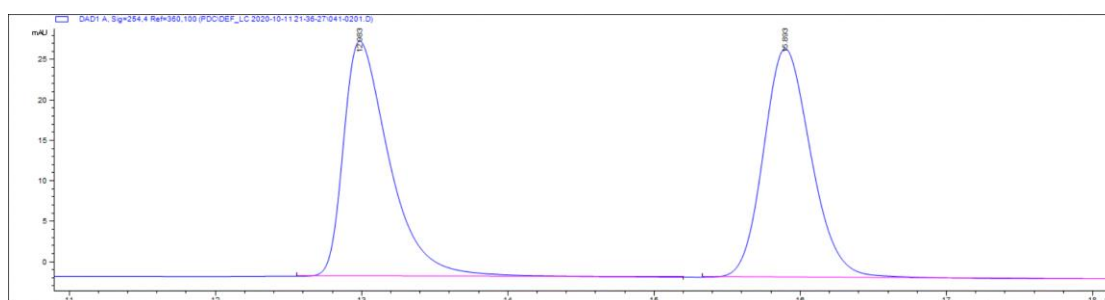
(*R*)-1-(4-Chlorophenyl)-4-phenylpentan-1-one (**8e**)



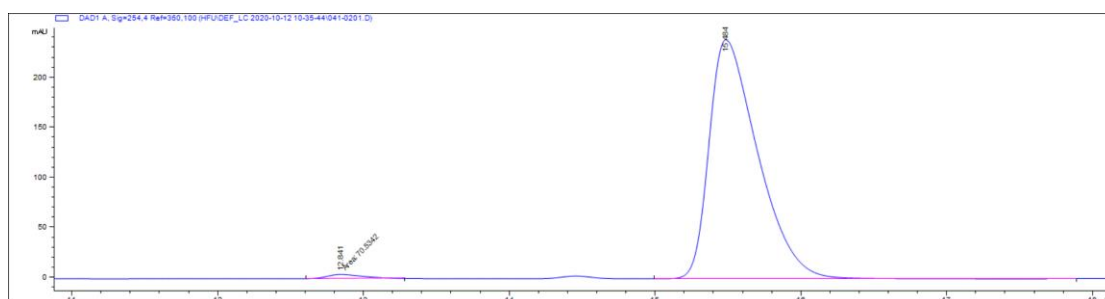
Prepared according to the general procedure 3 using 2-bromo-1-(4-chlorophenyl)ethan-1-one (0.015 mmol) and prop-1-en-2-ylbenzene (0.005 mmol) catalyzed by wild-type NCR (1.5 mol%).

**Yields:** run 1: 70%, run 2: 77%, average yield 73%.

**Enantioselectivity:** 99:1 er. Chiral HPLC method: OJ-H column, 254 nm, 5% isopropanol/hexanes, flow rate 1.0 mL/min, room temperature,  $t_R$  (major) = 12.84 min,  $t_R$  (minor) = 15.48 min.

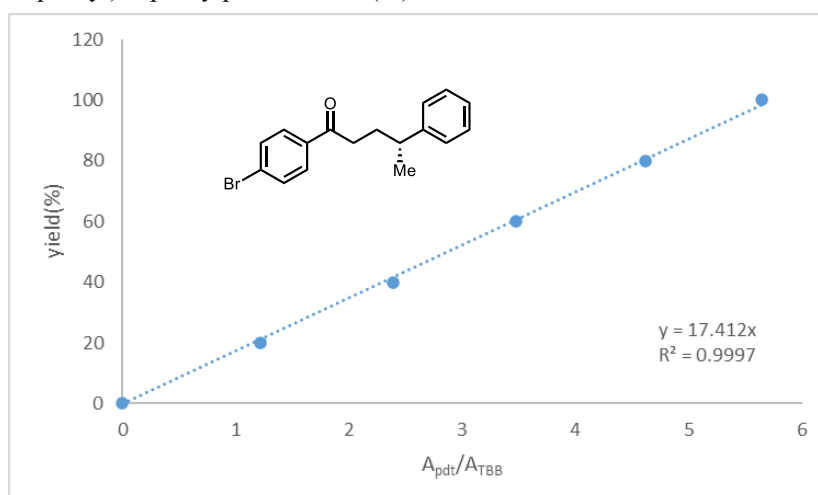


#	Time	Area	Height	Width	Area%	Symmetry
1	12.983	638.4	29.1	0.3296	49.750	0.502
2	15.893	644.9	28.4	0.3491	50.250	0.792



#	Time	Area	Height	Width	Area%	Symmetry
1	12.841	70.5	4.1	0.2853	1.255	0.592
2	15.484	5550.2	239.2	0.3507	98.745	0.502

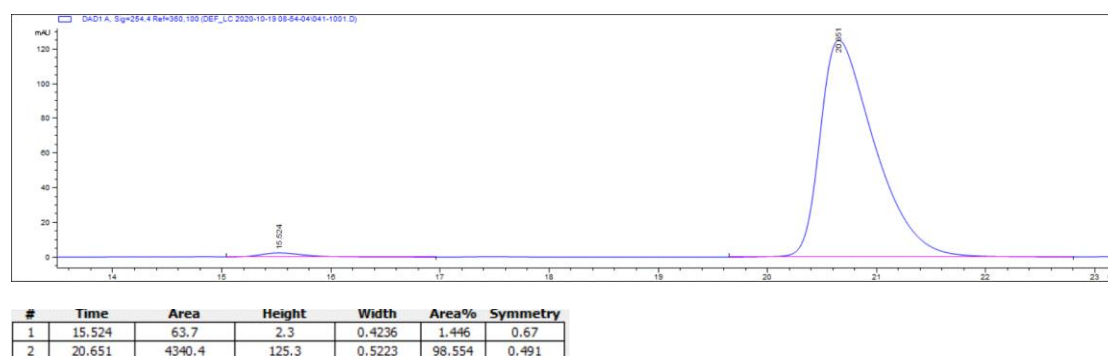
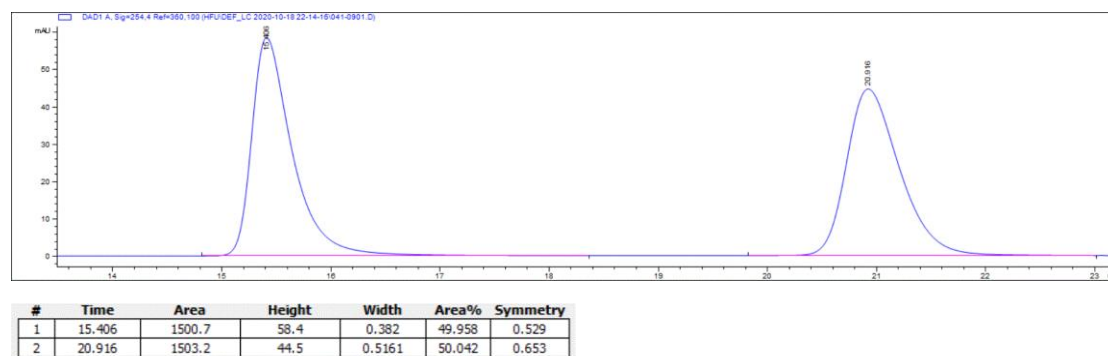
(*R*)-1-(4-Bromophenyl)-4-phenylpentan-1-one (**8f**)



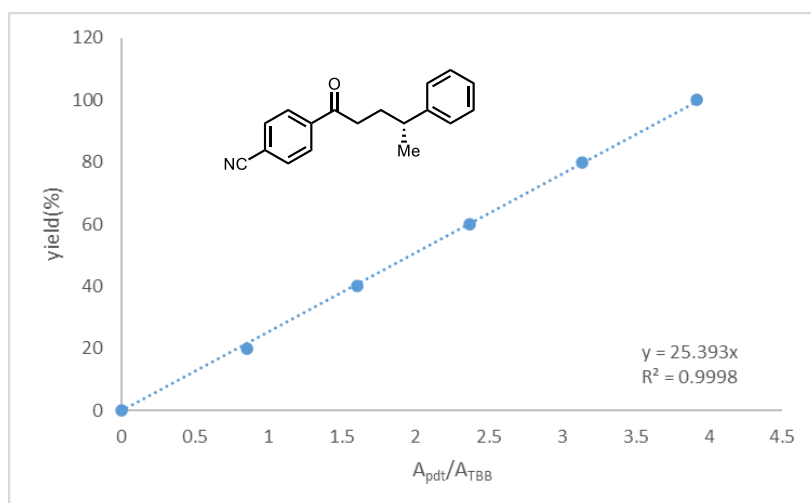
Prepared according to the general procedure 3 using 2-bromo-1-(4-bromophenyl)ethan-1-one (0.015 mmol) and prop-1-en-2-ylbenzene (0.005 mmol) catalyzed by wild-type NCR (1.5 mol%).

**Yields:** run 1: 67%, run 2: 72%, average yield 69%.

**Enantioselectivity:** 99:1 er. Chiral HPLC method: OJ-H column, 254 nm, 5% isopropanol/hexanes, flow rate 1.0 mL/min, room temperature,  $t_R$  (minor) = 15.52 min,  $t_R$  (major) = 20.65 min.



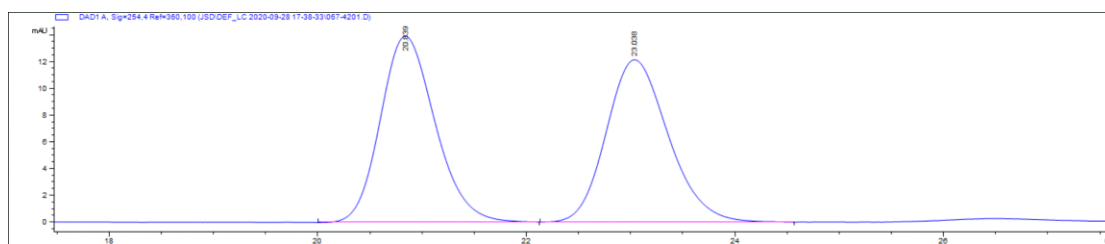
(*R*)-1-(4-Cyanophenyl)-4-phenylpentan-1-one (**8g**)



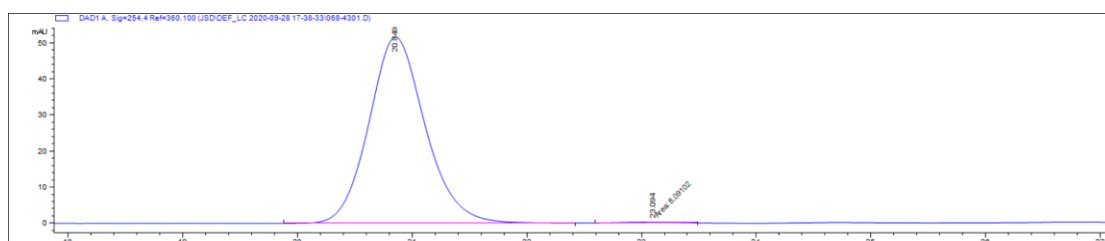
Prepared according to the general procedure 3 using 2-bromo-1-(4-cyanophenyl)ethan-1-one (0.015 mmol) and prop-1-en-2-ylbenzene (0.005 mmol) catalyzed by wild-type NCR (1.5 mol%).

**Yields:** run 1: 73%, run 2: 72%, average yield 73%.

**Enantioselectivity:** 99:1 er. Chiral HPLC method: OD-H column, 254 nm, 2% isopropanol/hexanes, flow rate 1.0 mL/min, room temperature,  $t_R$  (major) = 20.85 min,  $t_R$  (minor) = 23.09 min.

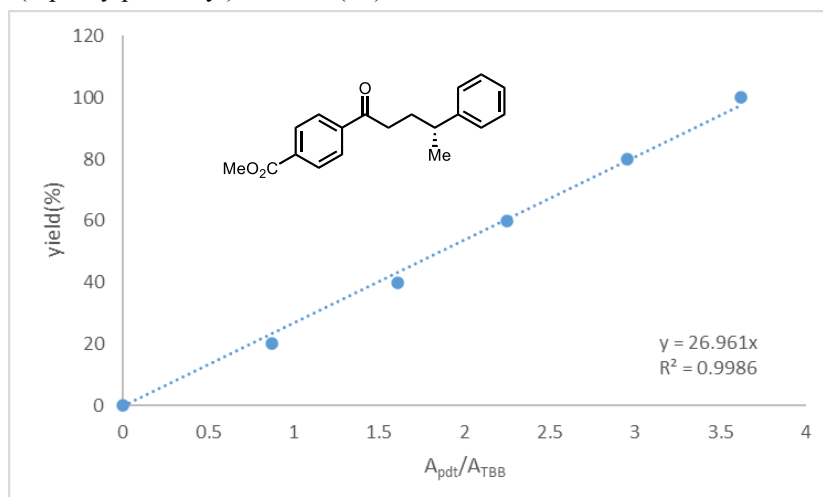


#	Time	Area	Height	Width	Area%	Symmetry
1	20.839	507.4	13.9	0.5652	50.320	0.803
2	23.038	501	12.1	0.6355	49.680	0.798



#	Time	Area	Height	Width	Area%	Symmetry
1	20.849	1764.1	51.6	0.5169	99.543	0.856
2	23.094	8.1	2.6E-1	0.3869	0.457	1.473

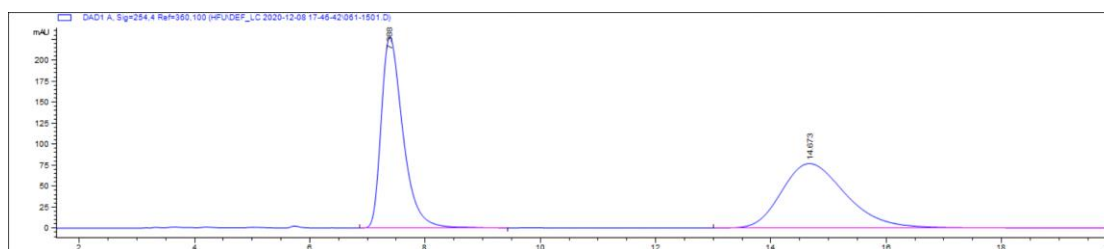
(*R*)-Methyl 4-(4-phenylpentanoyl)benzoate (**8h**)



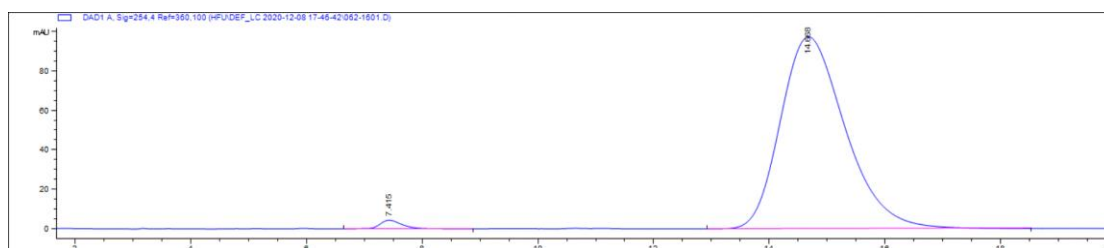
Prepared according to the general procedure 3 using methyl 4-(2-bromoacetyl)benzoate (0.015 mmol) and prop-1-en-2-ylbenzene (0.005 mmol) catalyzed by wild-type NCR (1.5 mol%).

**Yields:** run 1: 98%, run 2: 99%, average yield 98%

**Enantioselectivity:** 98:2 er. Chiral HPLC method: AS-H column, 254 nm, 20% isopropanol/hexanes, flow rate 1.0 mL/min, room temperature,  $t_R$  (minor) = 7.41 min,  $t_R$  (major) = 14.67 min.



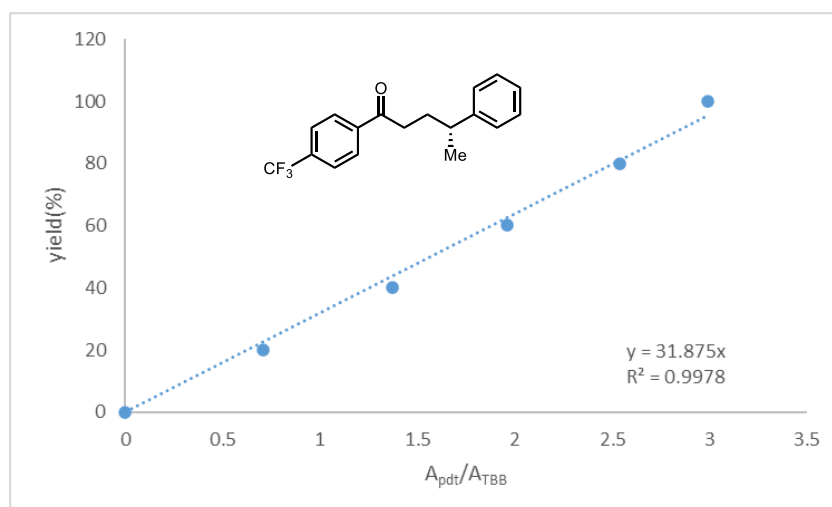
#	Time	Area	Height	Width	Area%	Symmetry
1	7.388	5935.6	226.8	0.3993	50.021	0.61
2	14.673	5930.7	76.5	1.2028	49.979	0.723



#	Time	Area	Height	Width	Area%	Symmetry
1	7.415	119.9	4.4	0.4089	1.567	0.683
2	14.668	7528.3	96.8	1.1989	98.433	0.722



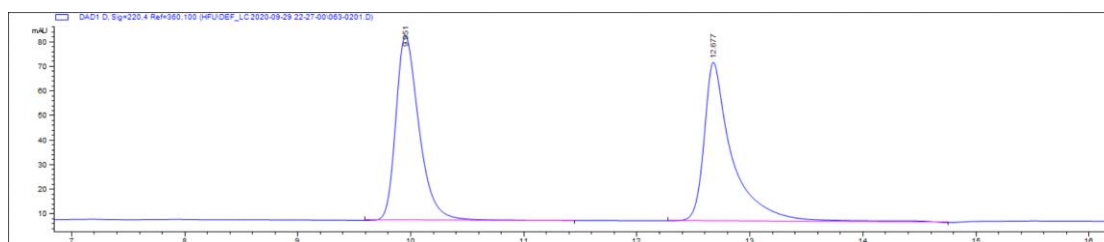
(*R*)-4-Phenyl-1-(4-(trifluoromethyl)phenyl)pentan-1-one (**8i**)



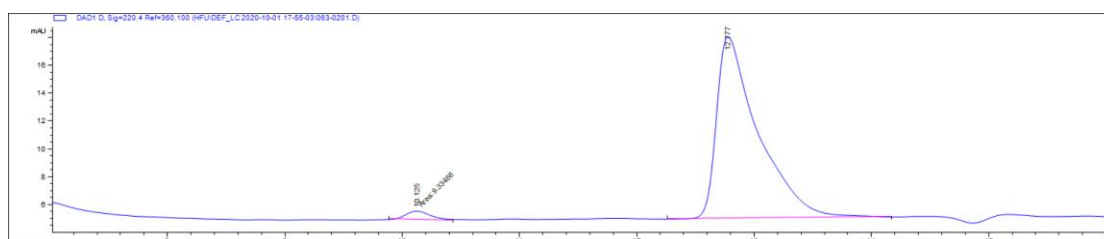
Prepared according to the general procedure 3 using 2-bromo-1-(4-(trifluoromethyl)phenyl)ethan-1-one (0.015 mmol) and prop-1-en-2-ylbenzene (0.005 mmol) catalyzed by wild-type NCR (1.5 mol%).

**Yields:** run 1: 46%, run 2: 42%, average yield 44%.

**Enantioselectivity:** 97:3 er. Chiral HPLC method: OJ-H column, 220 nm, 5% isopropanol/hexanes, flow rate 1.0 mL/min, room temperature,  $t_R$  (minor) = 10.13 min,  $t_R$  (major) = 12.78 min.

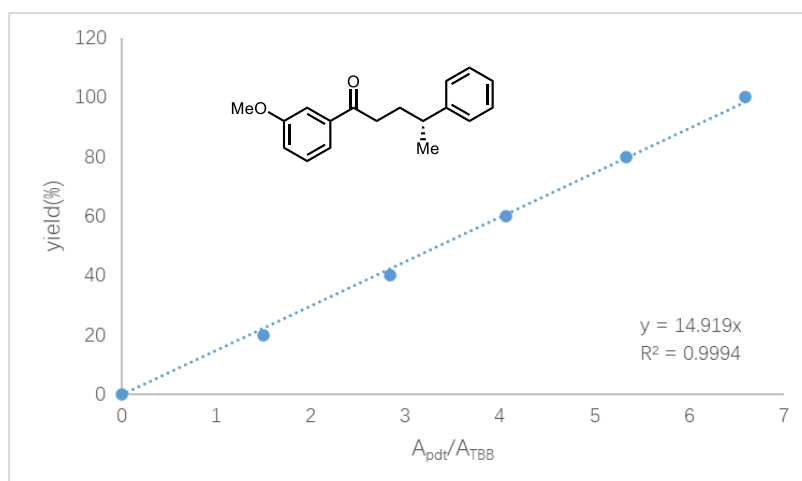


#	Time	Area	Height	Width	Area%	Symmetry
1	9.951	1071.9	74.9	0.2169	48.740	0.65
2	12.677	1127.4	64.4	0.2441	51.260	0.437



#	Time	Area	Height	Width	Area%	Symmetry
1	10.125	9.3	6.3E-1	0.2486	2.811	0.706
2	12.777	322.7	13.1	0.3478	97.189	0.355

(*R*)-1-(3-Methoxyphenyl)-4-phenylpentan-1-one (**8j**)



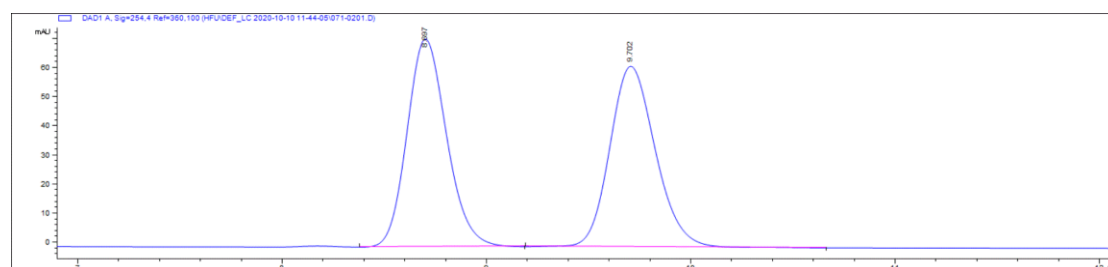
Prepared according to the general procedure 3 using 2-bromo-1-(3-methoxyphenyl)ethan-1-one (0.015 mmol) and prop-1-en-2-ylbenzene (0.005 mmol) catalyzed by wild-type NCR (1.5 mol%).

**Yields:** run 1: 94%, run 2: 97%, average yield 96%.

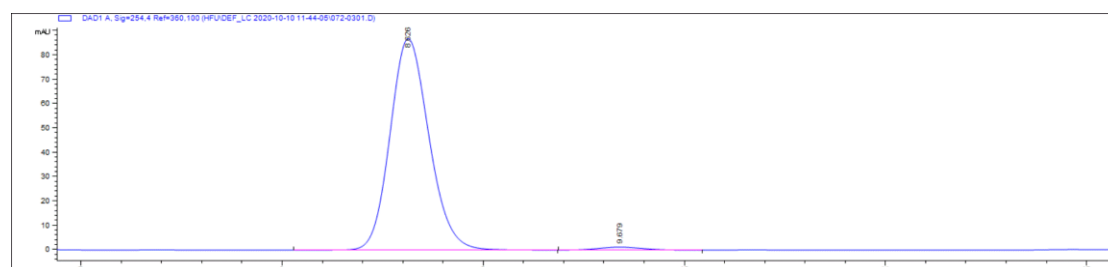
Preparative enzymatic synthesis was conducted according to the general procedure 4 using 2-bromo-1-(3-methoxyphenyl)ethan-1-one (0.3 mmol) and prop-1-en-2-ylbenzene (0.1 mmol) catalyzed by wild-type NCR (1.5 mol%).

**Isolated yield:** 84% (clear oil, 22.5 mg). Optical rotation:  $[\alpha]_{\text{D}}^{20} = -37.0^\circ$  ( $c = 1.0$ , MeOH).

**Enantioselectivity:** 98:2 er. Chiral HPLC method: OD-H column, 254 nm, 2% isopropanol/hexanes, flow rate 1.0 mL/min, room temperature,  $t_{\text{R}}$  (major) = 8.63 min,  $t_{\text{R}}$  (minor) = 9.68 min.

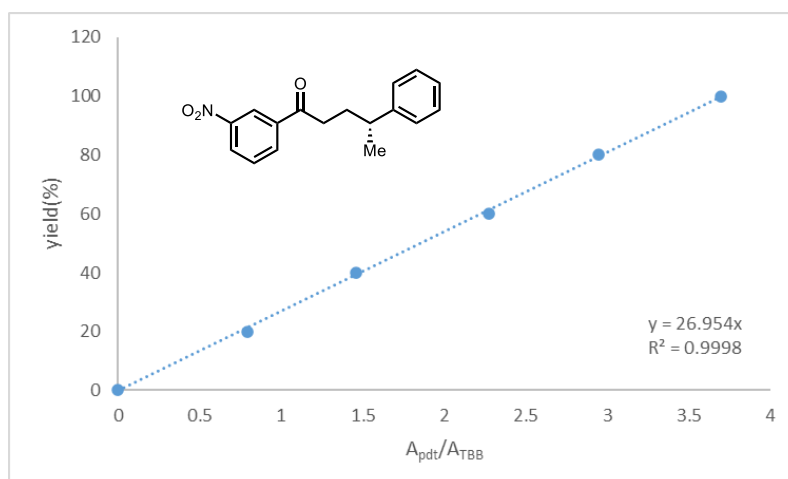


#	Time	Area	Height	Width	Area%	Symmetry
1	8.697	963.3	71.6	0.2069	49.919	0.827
2	9.702	966.5	62.3	0.2391	50.081	0.814



#	Time	Area	Height	Width	Area%	Symmetry
1	8.626	1169.6	86.9	0.209	98.478	0.832
2	9.679	18.1	1.2	0.2337	1.522	0.877

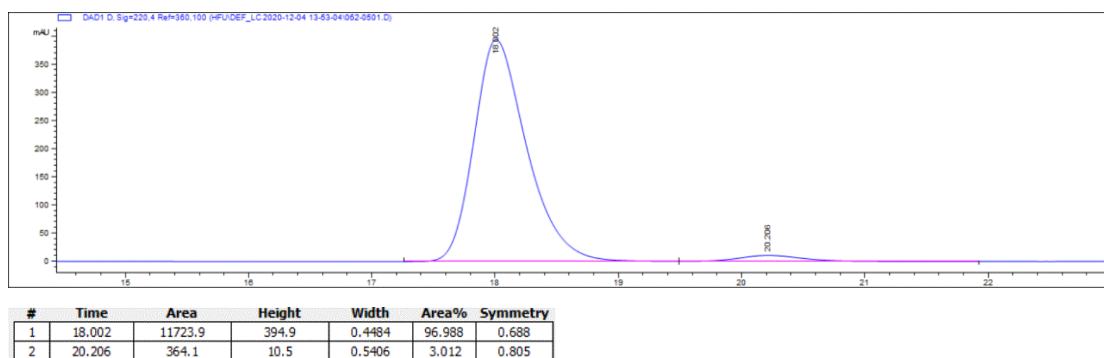
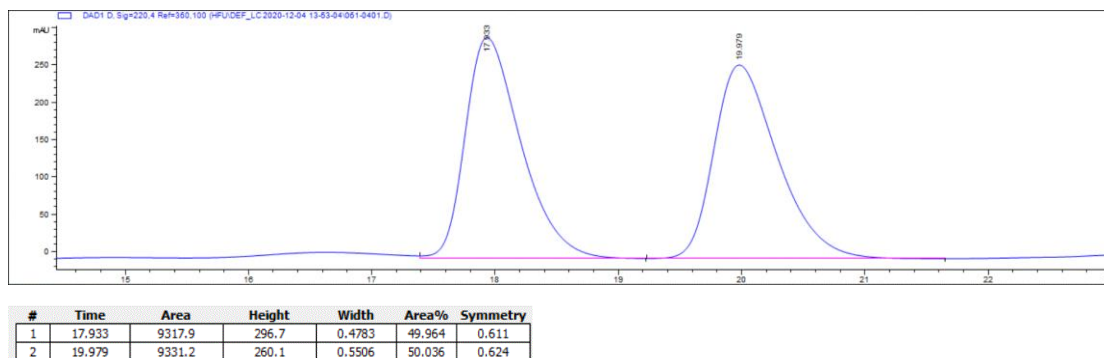
(*R*)-1-(3-Nitrophenyl)-4-phenylpentan-1-one (**8k**)



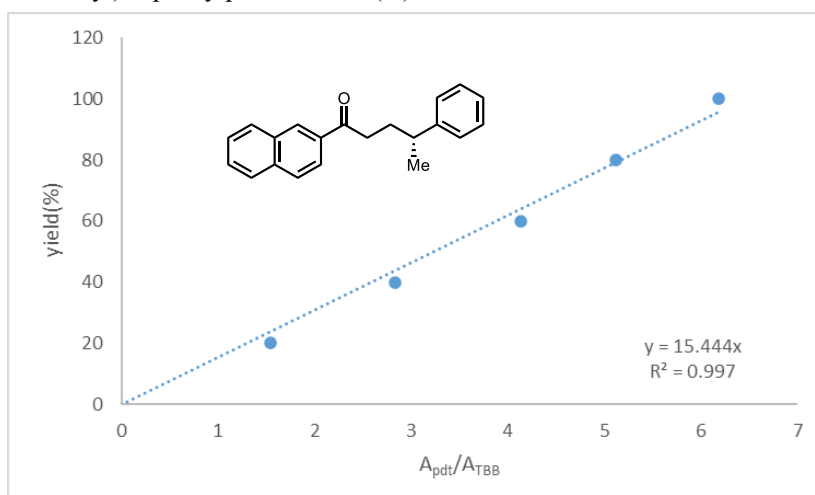
Prepared according to the general procedure 3 using 2-bromo-1-(3-nitrophenyl)ethan-1-one (0.015 mmol) and prop-1-en-2-ylbenzene (0.005 mmol) catalyzed by wild-type NCR (1.5 mol%).

**Yields:** run 1: 68%, run 2: 77%, average yield 72%.

**Enantioselectivity:** 97:3 er. Chiral HPLC method: OD-H column, 220 nm, 2% isopropanol/hexanes, flow rate 1.0 mL/min, room temperature,  $t_R$  (major) = 18.00 min,  $t_R$  (minor) = 20.21 min.



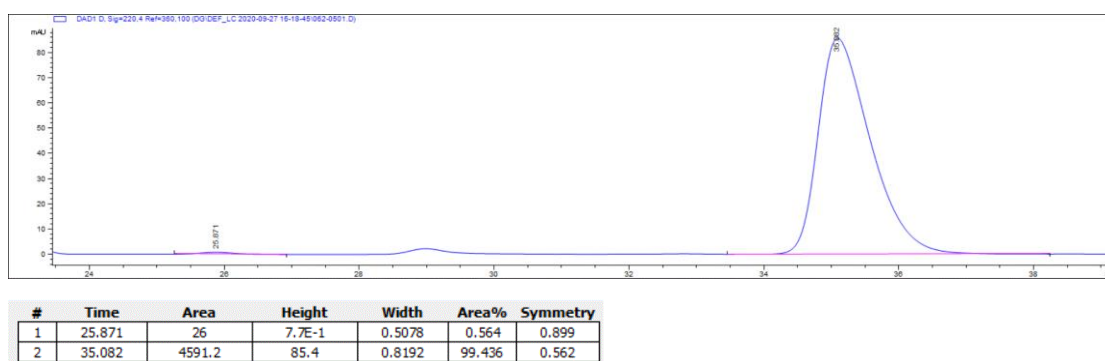
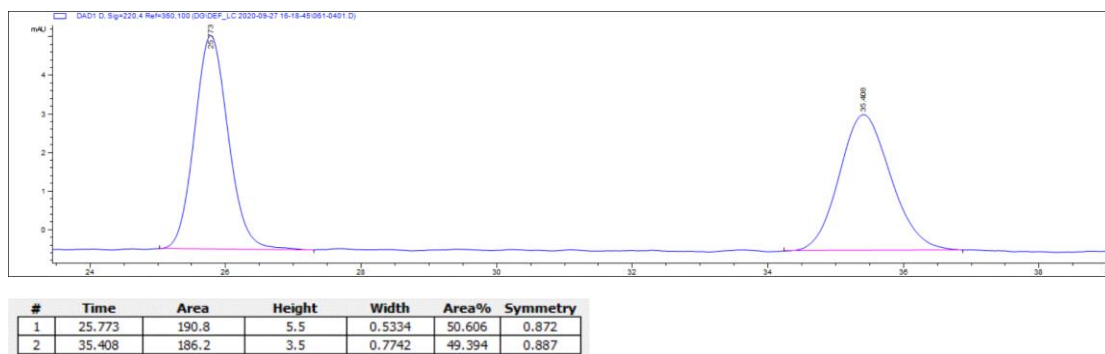
(*R*)-1-(Naphthalen-2-yl)-4-phenylpentan-1-one (**81**)



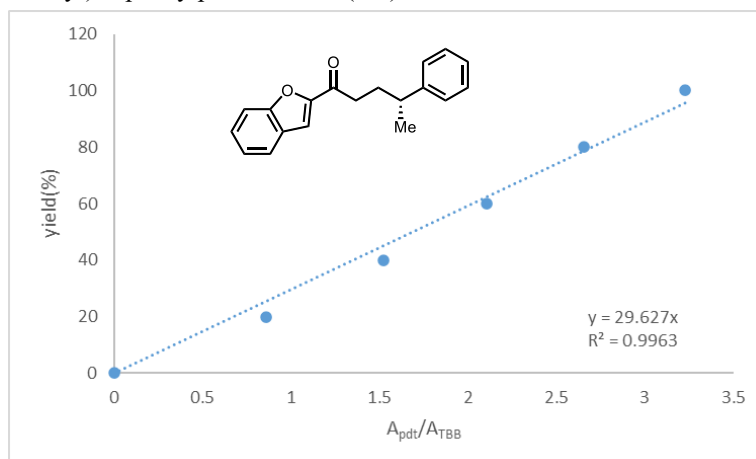
Prepared according to the general procedure 3 using 2-bromo-1-(naphthalen-2-yl)ethan-1-one (0.015 mmol) and prop-1-en-2-ylbenzene (0.005 mmol) catalyzed by wild-type NCR (1.5 mol%).

**Yields:** run 1: 84%, run 2: 81%, average yield 83%.

**Enantioselectivity:** 99:1 er. Chiral HPLC method: OJ-H column, 220 nm, 5% isopropanol/hexanes, flow rate 1.0 mL/min, room temperature,  $t_R$  (minor) = 25.87 min,  $t_R$  (major) = 35.08 min.



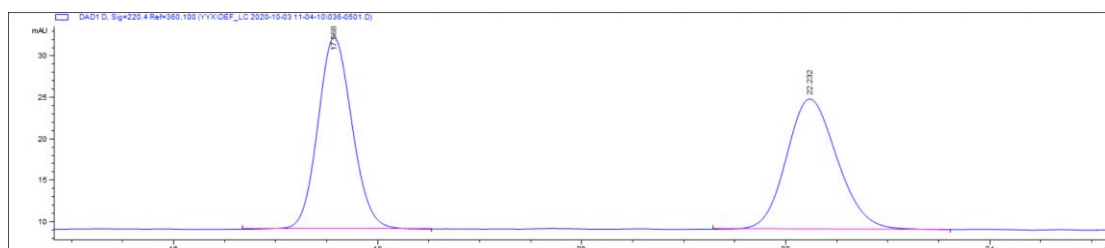
(*R*)-1-(Benzofuran-2-yl)-4-phenylpentan-1-one (**8m**)



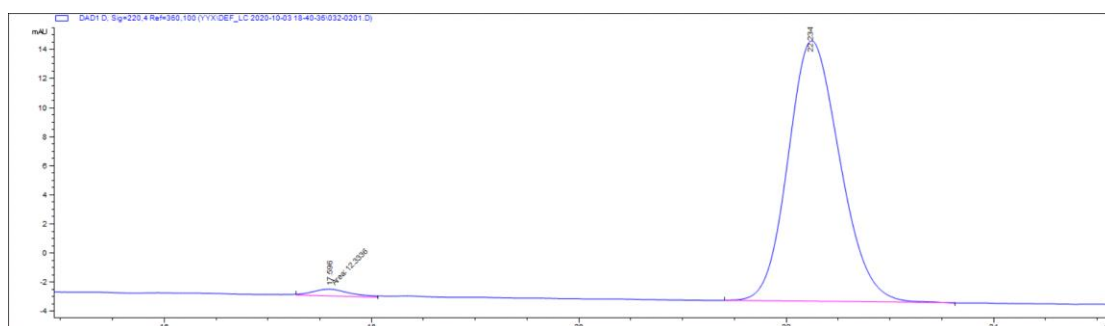
Prepared according to the general procedure 3 using 1-(benzofuran-2-yl)-2-bromoethan-1-one (0.015 mmol) and prop-1-en-2-ylbenzene (0.005 mmol) catalyzed by wild-type NCR (1.5 mol%).

**Yields:** run 1: 89%, run 2: 81%, average yield 85%.

**Enantioselectivity:** 98:2 er. Chiral HPLC method: OJ-H column, 220 nm, 10% isopropanol/hexanes, flow rate 1.0 mL/min, room temperature,  $t_R$  (minor) = 17.60 min,  $t_R$  (major) = 22.23 min.

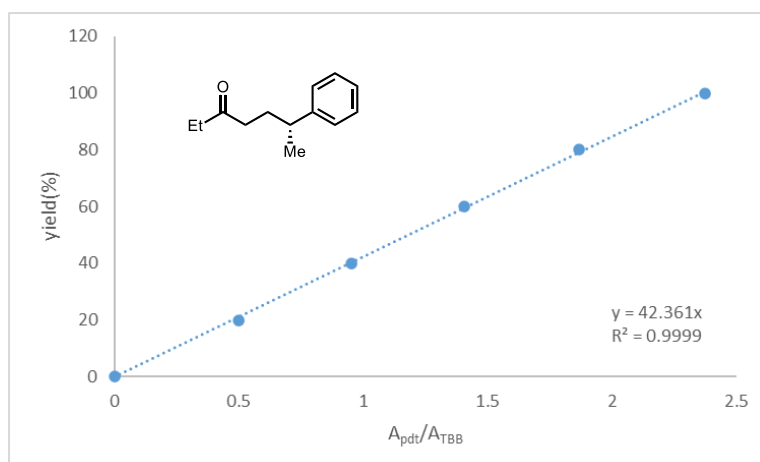


#	Time	Area	Height	Width	Area%	Symmetry
1	17.568	542.7	23.3	0.3622	49.775	0.87
2	22.232	547.6	15.8	0.5364	50.225	0.822



#	Time	Area	Height	Width	Area%	Symmetry
1	17.596	12.3	4.8E-1	0.4248	1.946	0.8
2	22.234	621.6	17.9	0.5351	98.054	0.802

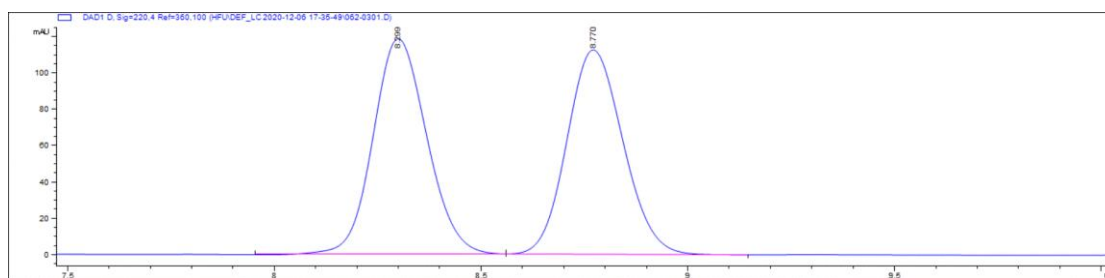
(*R*)-6-Phenylheptan-3-one (**8n**)



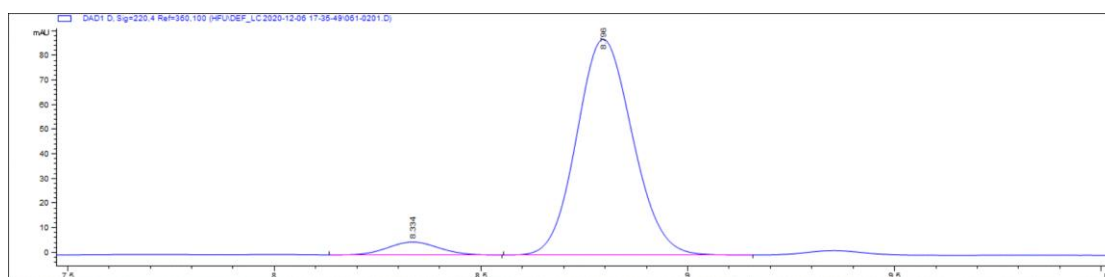
Prepared according to the general procedure 3 using 1-bromobutan-2-one (0.015 mmol) and prop-1-en-2-ylbenzene (0.005 mmol) catalyzed by wild-type NCR (1.5 mol%).

**Yields:** run 1: 62%, run 2: 63%, average yield 63%.

**Enantioselectivity:** 95:5 er. Chiral HPLC method: OJ-H column, 220 nm, 5% isopropanol/hexanes, flow rate 1.0 mL/min, room temperature,  $t_R$  (minor) = 8.33 min,  $t_R$  (major) = 8.80 min.

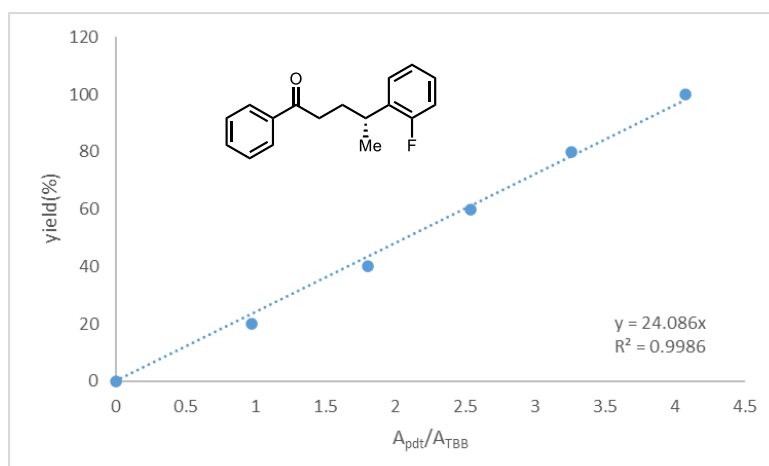


#	Time	Area	Height	Width	Area%	Symmetry
1	8.299	1080.6	119.1	0.1399	50.299	0.857
2	8.77	1067.8	112.9	0.1484	49.701	0.849



#	Time	Area	Height	Width	Area%	Symmetry
1	8.334	45.6	5.3	0.1352	5.249	0.924
2	8.796	823.6	87.7	0.1476	94.751	0.867

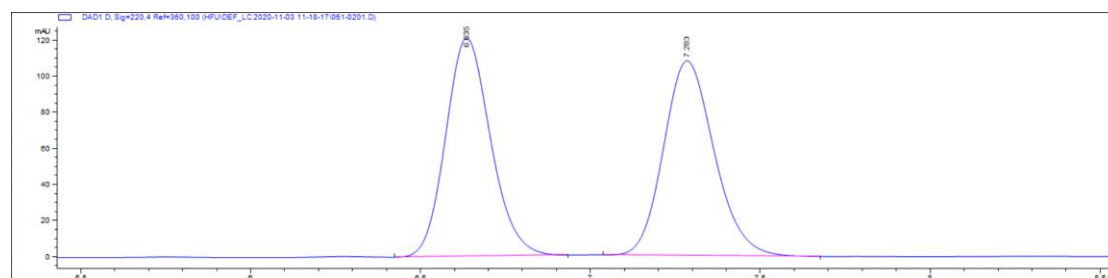
(*R*)-4-(2-Fluorophenyl)-1-phenylpentan-1-one (**8o**)



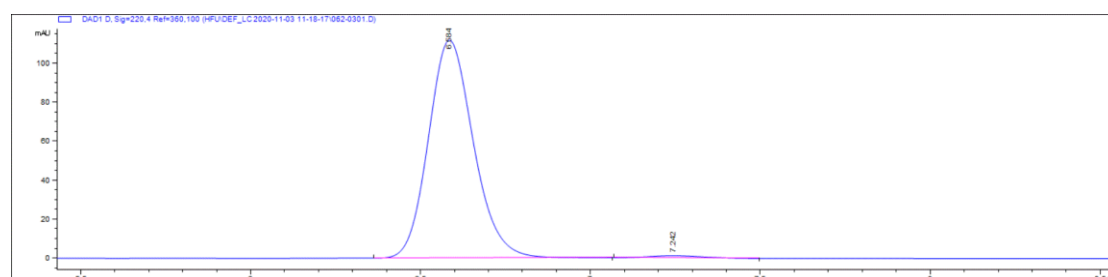
Prepared according to the general procedure 3 using 2-bromo-1-phenylethan-1-one (0.015 mmol) and 1-fluoro-2-(prop-1-en-2-yl)benzene (0.005 mmol) catalyzed by wild-type NCR (1.5 mol%).

**Yields:** run 1: 56%, run 2: 60%, average yield 58%.

**Enantioselectivity:** 99:1 er. Chiral HPLC method: OD-H column, 220 nm, 2% isopropanol/hexanes, flow rate 1.0 mL/min, room temperature,  $t_R$  (major) = 6.58 min,  $t_R$  (minor) = 7.24 min.

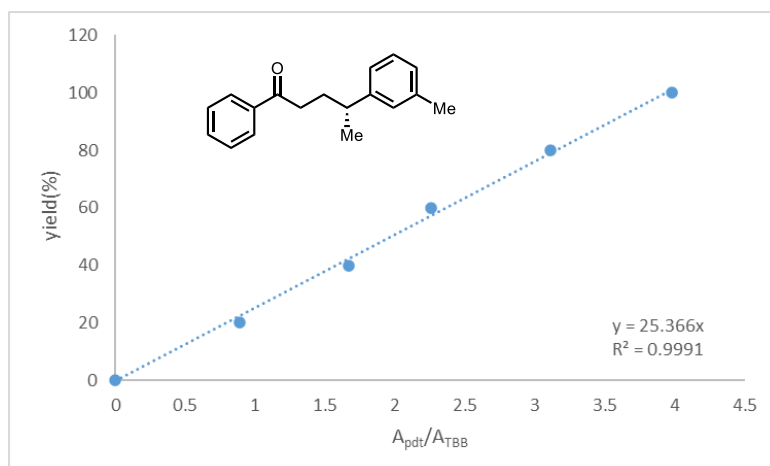


#	Time	Area	Height	Width	Area%	Symmetry
1	6.635	1109.5	121	0.143	49.856	0.84
2	7.283	1115.9	107.9	0.1607	50.144	0.825



#	Time	Area	Height	Width	Area%	Symmetry
1	6.584	1028.6	111.9	0.1412	98.817	0.83
2	7.242	12.3	1.2	0.159	1.183	0.762

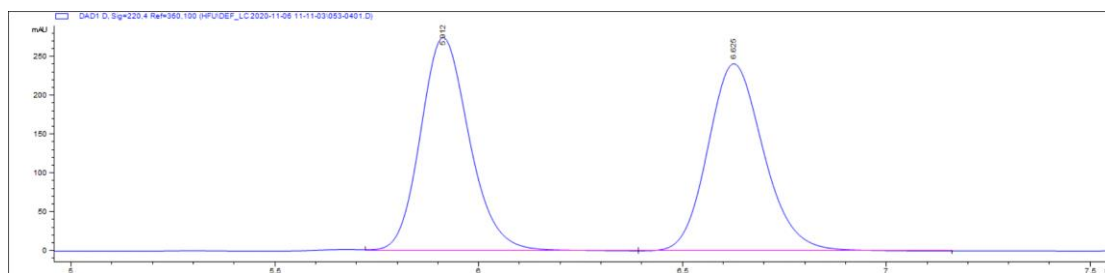
(R)-1-Phenyl-4-(m-tolyl)pentan-1-one (**8p**)



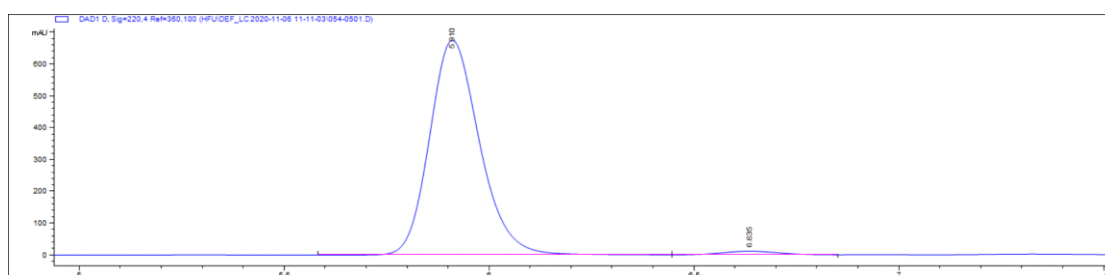
Prepared according to the general procedure 3 using 2-bromo-1-phenylethan-1-one (0.015 mmol) and 1-methyl-3-(prop-1-en-2-yl)benzene (0.005 mmol) catalyzed by wild-type NCR (1.5 mol%).

**Yields:** run 1: 90%, run 2: 86%, average yield 88%.

**Enantioselectivity:** 98:2 er. Chiral HPLC method: OD-H column, 220 nm, 2% isopropanol/hexanes, flow rate 1.0 mL/min, room temperature,  $t_R$  (major) = 5.91 min,  $t_R$  (minor) = 6.64 min.



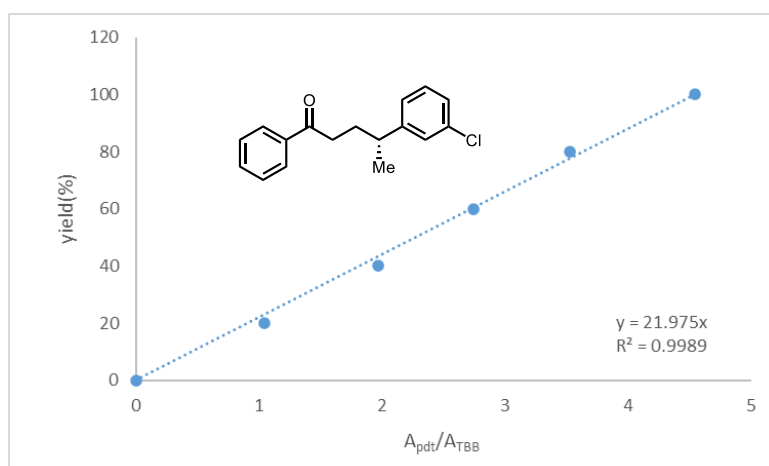
#	Time	Area	Height	Width	Area%	Symmetry
1	5.912	2309.3	276.3	0.1295	50.132	0.82
2	6.625	2297.2	242	0.1468	49.868	0.827



#	Time	Area	Height	Width	Area%	Symmetry
1	5.91	5727.9	676.9	0.1287	98.095	0.791
2	6.635	111.2	11.6	0.1483	1.905	0.908



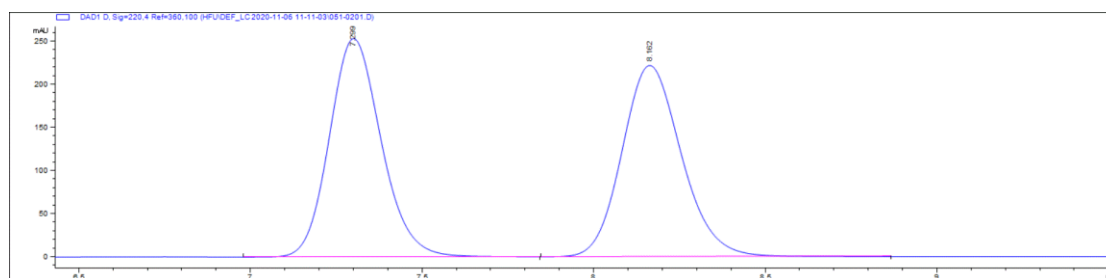
(*R*)-4-(3-Chlorophenyl)-1-phenylpentan-1-one (**8q**)



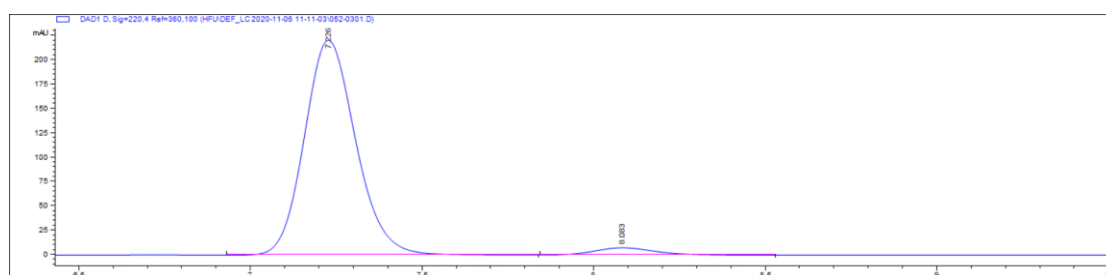
Prepared according to the general procedure 3 using 2-bromo-1-phenylethan-1-one (0.005 mmol) and 1-chloro-3-(prop-1-en-2-yl)benzene (0.015 mmol) catalyzed by wild-type NCR (1.5 mol%).

**Yields:** run 1: 66%, run 2: 67%, average yield 66% (general procedure 2).

**Enantioselectivity:** 96:4 er. Chiral HPLC method: OD-H column, 220 nm, 2% isopropanol/hexanes, flow rate 1.0 mL/min, room temperature,  $t_R$  (major) = 7.23 min,  $t_R$  (minor) = 8.08 min.

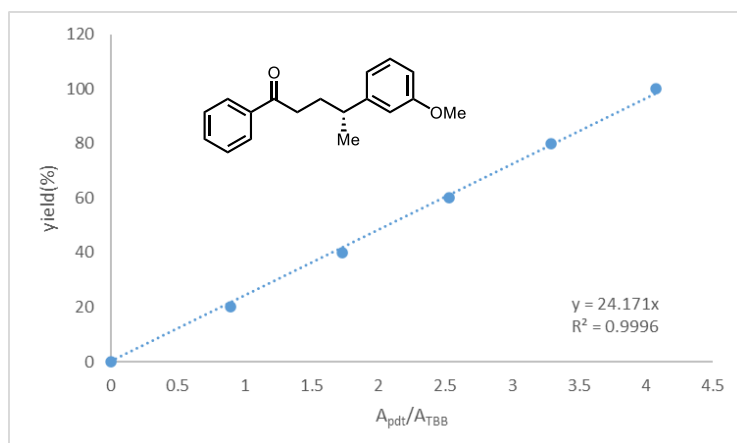


#	Time	Area	Height	Width	Area%	Symmetry
1	7.299	2664.2	254.3	0.1602	49.879	0.836
2	8.162	2677.2	222.6	0.1843	50.121	0.831



#	Time	Area	Height	Width	Area%	Symmetry
1	7.226	2296.7	221.1	0.1612	96.273	0.835
2	8.083	88.9	7.4	0.1843	3.727	0.819

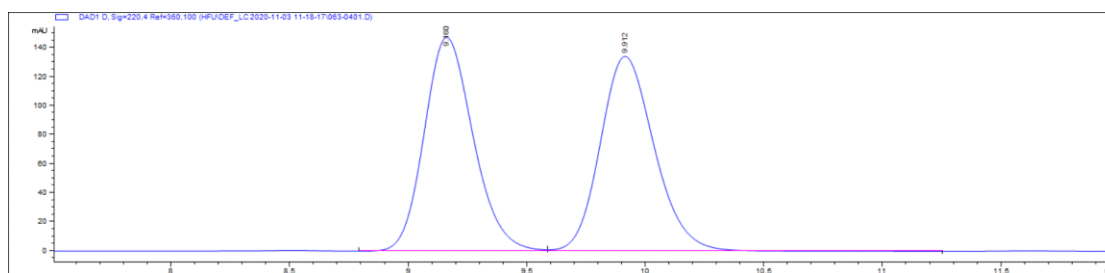
(*R*)-4-(3-Methoxyphenyl)-1-phenylpentan-1-one (**8r**)



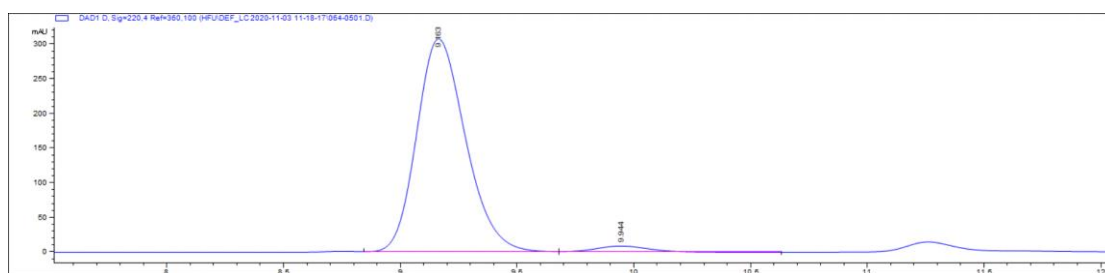
Prepared according to the general procedure 3 using 2-bromo-1-phenylethan-1-one (0.015 mmol) and 1-methoxy-3-(prop-1-en-2-yl)benzene (0.005 mmol) catalyzed by wild-type NCR (1.5 mol%).

**Yields:** run 1: 76%, run 2: 77%, average yield 77%.

**Enantioselectivity:** 97:3 er. Chiral HPLC method: OD-H column, 220 nm, 2% isopropanol/hexanes, flow rate 1.0 mL/min, room temperature,  $t_R$  (major) = 9.16 min,  $t_R$  (minor) = 9.94 min.

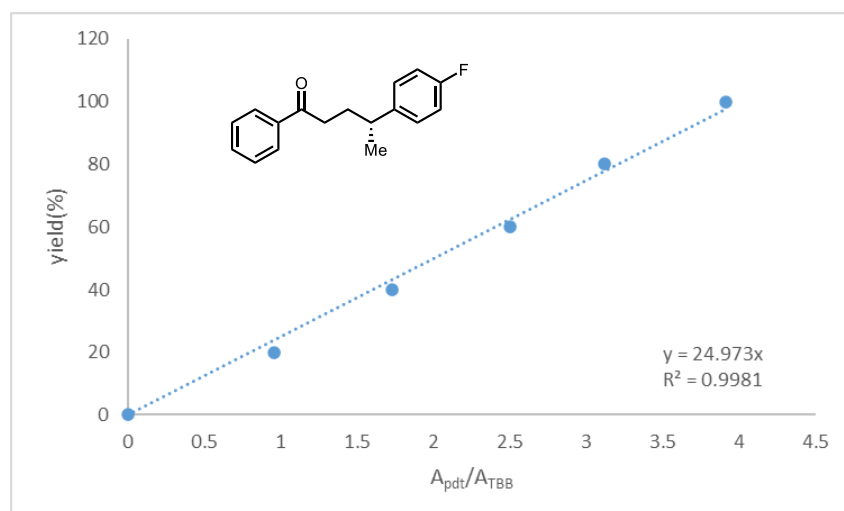


#	Time	Area	Height	Width	Area%	Symmetry
1	9.16	2116.6	147.3	0.2217	49.853	0.812
2	9.912	2129.1	134.1	0.2452	50.147	0.802



#	Time	Area	Height	Width	Area%	Symmetry
1	9.163	4502	308.6	0.2262	96.855	0.772
2	9.944	146.2	8.9	0.2516	3.145	0.879

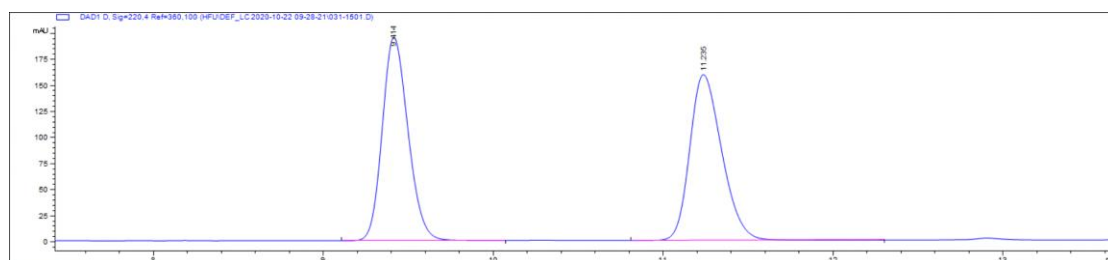
(*R*)-4-(4-Fluorophenyl)-1-phenylpentan-1-one (**8s**)



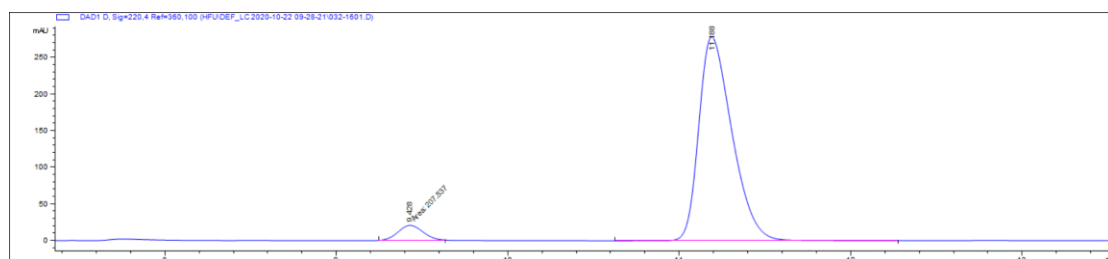
Prepared according to the general procedure 3 using 2-bromo-1-phenylethan-1-one (0.015 mmol) and 1-fluoro-4-(prop-1-en-2-yl)benzene (0.005 mmol) catalyzed by wild-type NCR (1.5 mol%).

**Yields:** run 1: 92%, run 2: 99%, average yield 96%.

**Enantioselectivity:** 95:5 er. Chiral HPLC method: OJ-H column, 220 nm, 5% isopropanol/hexanes, flow rate 1.0 mL/min, room temperature,  $t_R$  (minor) = 9.43 min,  $t_R$  (major) = 11.19 min.

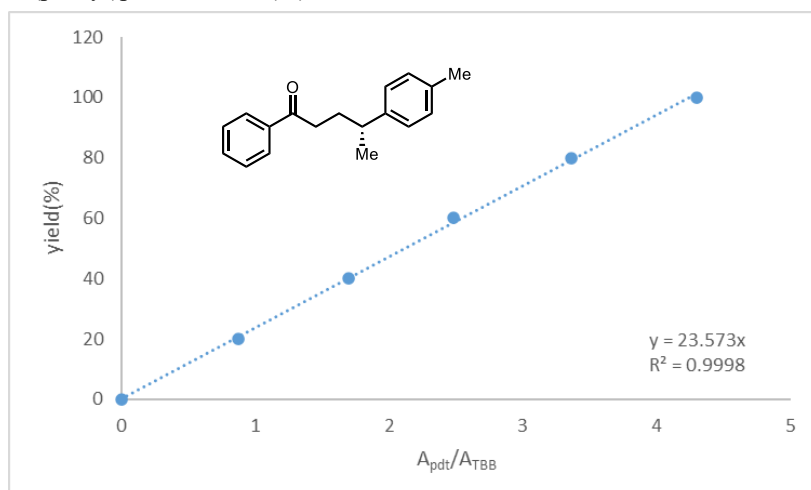


#	Time	Area	Height	Width	Area%	Symmetry
1	9.414	2053.7	195.3	0.1627	49.639	0.784
2	11.235	2083.5	159	0.2008	50.361	0.704



#	Time	Area	Height	Width	Area%	Symmetry
1	9.428	207.5	20.5	0.169	5.267	0.904
2	11.188	3732.6	278.3	0.2064	94.733	0.603

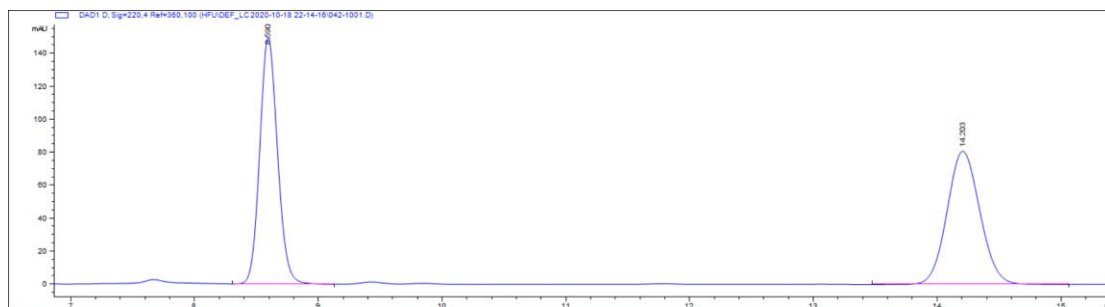
(*R*)-1-Phenyl-4-(*p*-tolyl)pentan-1-one (**8t**)



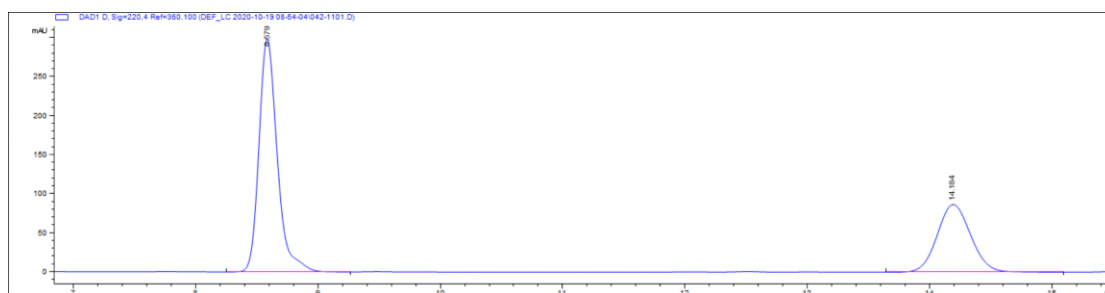
Prepared according to the general procedure 4 using 2-bromo-1-phenylethan-1-one (0.005 mmol) and 1-methyl-4-(prop-1-en-2-yl)benzene (0.015 mmol) catalyzed by wild-type NCR (1.5 mol%).

**Yields:** run 1: 64%, run 2: 53%, average yield 59%.

**Enantioselectivity:** 65:35 er. Chiral HPLC method: OJ-H column, 220 nm, 5% isopropanol/hexanes, flow rate 1.0 mL/min, room temperature,  $t_R$  (major) = 8.58 min,  $t_R$  (minor) = 14.18 min.

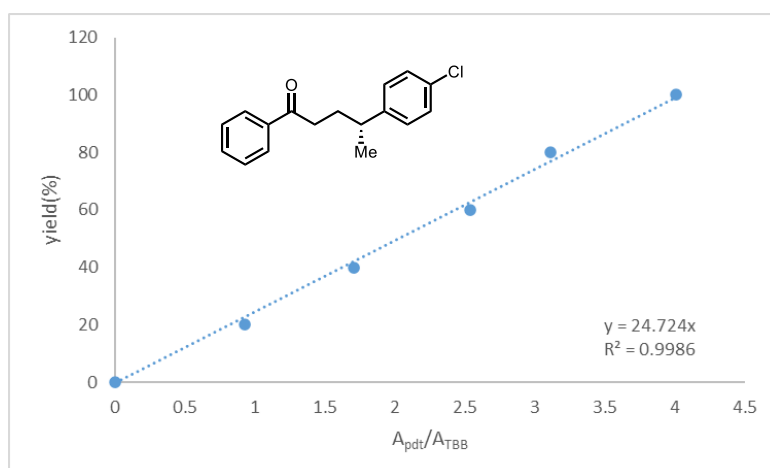


#	Time	Area	Height	Width	Area%	Symmetry
1	8.59	1493.9	149.8	0.1543	50.057	0.859
2	14.203	1490.5	80.9	0.287	49.943	0.893



#	Time	Area	Height	Width	Area%	Symmetry
1	8.579	3105.4	299.2	0.1591	65.319	0.755
2	14.184	1648.8	86.9	0.2954	34.681	0.879

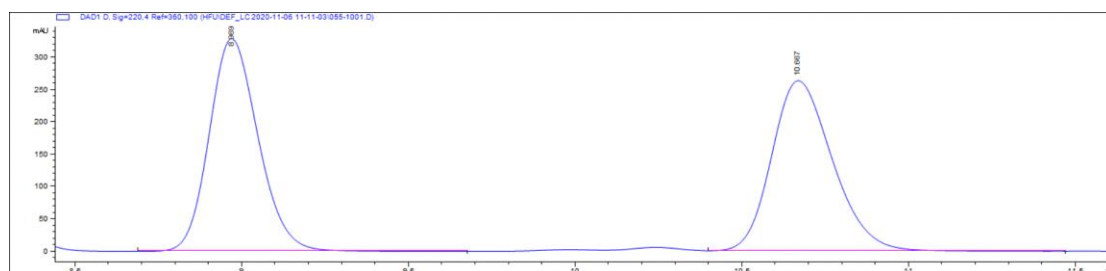
(R)-4-(4-Chlorophenyl)-1-phenylpentan-1-one (**8u**)



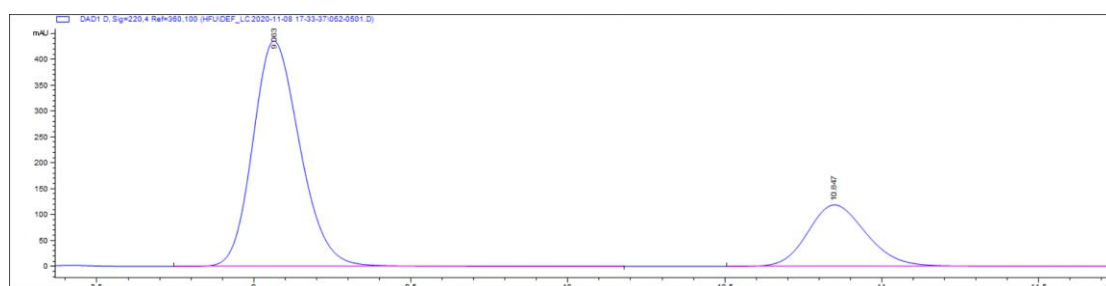
Prepared according to the general procedure 4 using 2-bromo-1-phenylethan-1-one (0.005 mmol) and 1-chloro-4-(prop-1-en-2-yl)benzene (0.015 mmol) catalyzed by wild-type NCR (1.5 mol%).

**Yields:** run 1: 70%, run 2: 68%, average yield 69%.

**Enantioselectivity:** 75:25 er. Chiral HPLC method: OJ-H column, 220 nm, 5% isopropanol/hexanes, flow rate 1.0 mL/min, room temperature,  $t_R$  (major) = 9.06 min,  $t_R$  (minor) = 10.85 min.

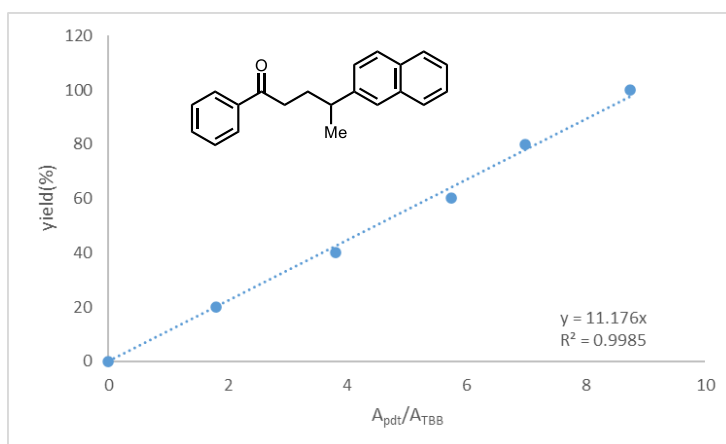


#	Time	Area	Height	Width	Area%	Symmetry
1	8.969	3365.4	331	0.1566	50.009	0.805
2	10.667	3364.1	265.2	0.196	49.991	0.747



#	Time	Area	Height	Width	Area%	Symmetry
1	9.063	4549.3	437.4	0.1613	74.646	0.779
2	10.847	1545.2	119.1	0.1994	25.354	0.801

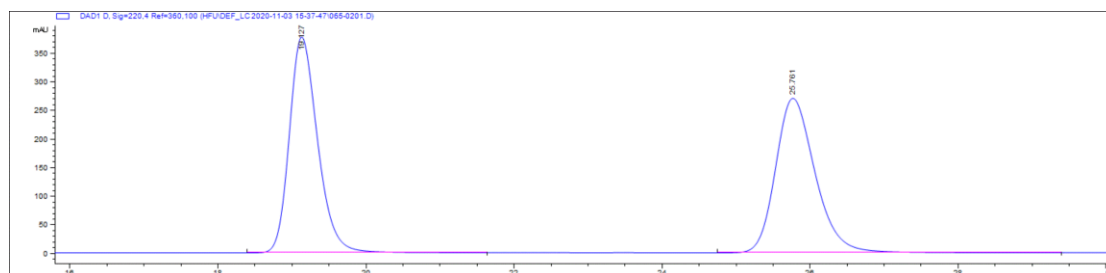
4-(Naphthalen-2-yl)-1-phenylpentan-1-one (**8v**)



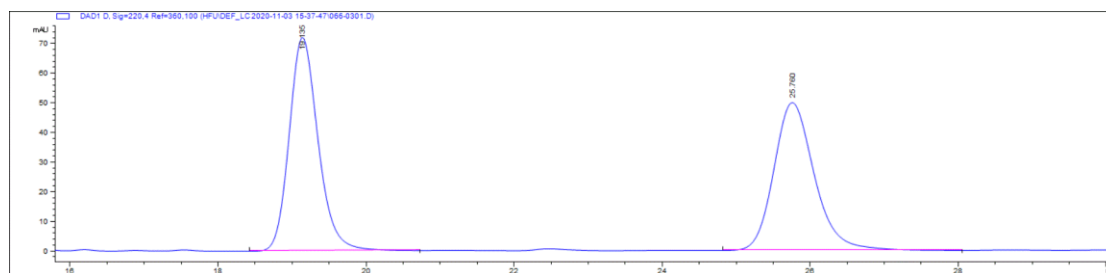
Prepared according to the general procedure 4 using 2-bromo-1-phenylethan-1-one (0.005 mmol) and 2-(prop-1-en-2-yl)naphthalene (0.015 mmol) catalyzed by wild-type NCR (1.5 mol%).

**Yields:** run 1: 30%, run 2: 31%, average yield 31%.

**Enantioselectivity:** 51:49 er. Chiral HPLC method: OJ-H column, 220 nm, 5% isopropanol/hexanes, flow rate 1.0 mL/min, room temperature,  $t_R$  (major) = 19.14 min,  $t_R$  (minor) = 25.76 min.

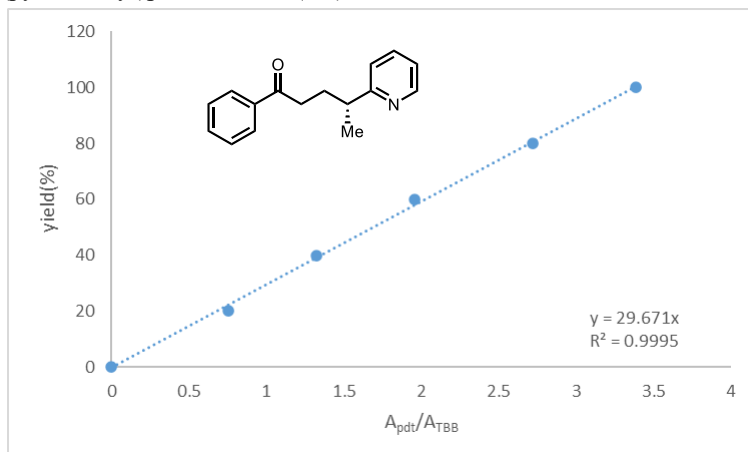


#	Time	Area	Height	Width	Area%	Symmetry
1	19.127	10038.3	378	0.4078	49.943	0.731
2	25.761	10061.2	270.6	0.5697	50.057	0.736



#	Time	Area	Height	Width	Area%	Symmetry
1	19.135	1967.8	72.4	0.4172	50.753	0.799
2	25.76	1909.4	50.1	0.5846	49.247	0.785

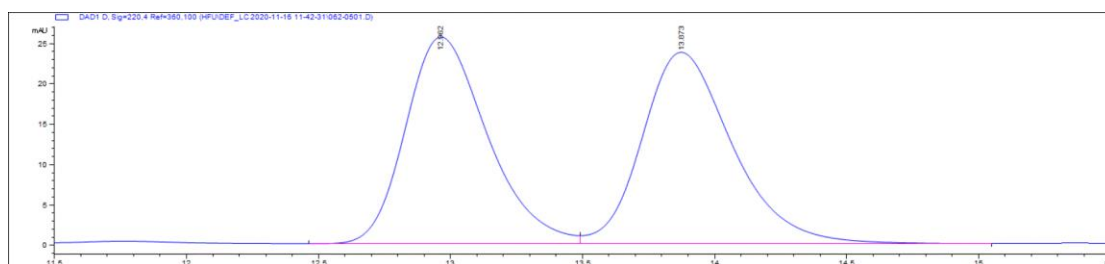
(*R*)-1-Phenyl-4-(pyridin-2-yl)pentan-1-one (**8w**)



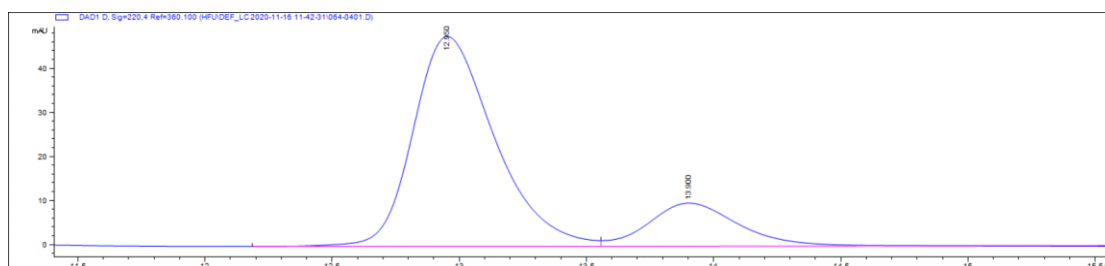
Prepared according to the general procedure 3 using 2-bromo-1-phenylethan-1-one (0.015 mmol) and 2-(prop-1-en-2-yl)pyridine (0.005 mmol) catalyzed by wild-type NCR (1.5 mol%).

**Yields:** run 1: 59%, run 2: 62%, average yield 61%.

**Enantioselectivity:** 81:19 er. Chiral HPLC method: OD-H column, 220 nm, 2% isopropanol/hexanes, flow rate 1.0 mL/min, room temperature,  $t_R$  (major) = 12.95 min,  $t_R$  (minor) = 13.90 min.

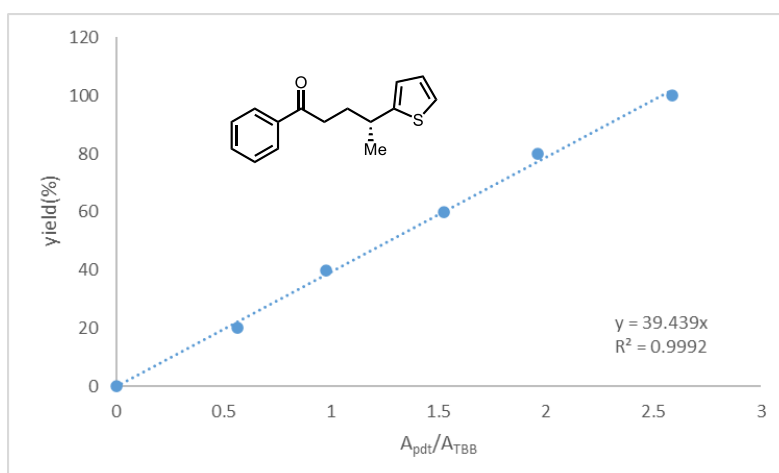


#	Time	Area	Height	Width	Area%	Symmetry
1	12.962	554.2	25.6	0.3303	49.485	0.726
2	13.873	565.7	23.7	0.3642	50.515	0.723



#	Time	Area	Height	Width	Area%	Symmetry
1	12.95	1056.6	47.5	0.3378	81.233	0.692
2	13.9	244.1	9.8	0.3793	18.767	0.748

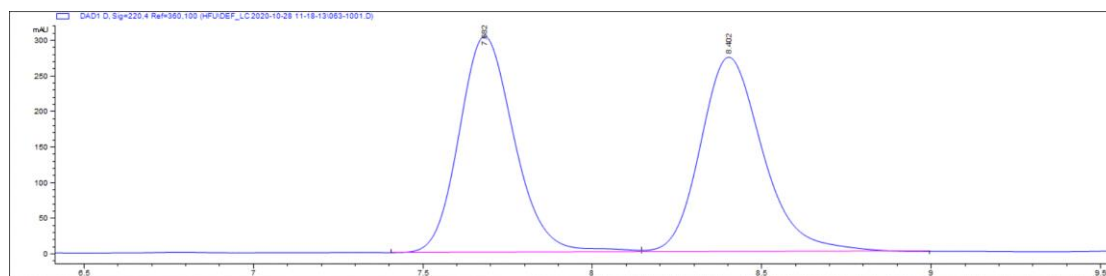
(*R*)-1-Phenyl-4-(thiophen-2-yl)pentan-1-one (**8x**)



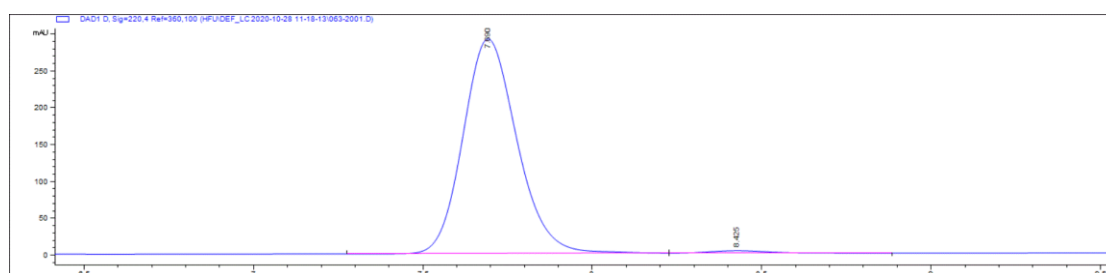
Prepared according to the general procedure 3 using 2-bromo-1-phenylethan-1-one (0.015 mmol) and 2-(prop-1-en-2-yl)thiophene (0.005 mmol) catalyzed by wild-type NCR (1.5 mol%).

**Yields:** run 1: 71%, run 2: 79%, average yield 74%.

**Enantioselectivity:** 99:1 er. Chiral HPLC method: OD-H column, 220 nm, 2% isopropanol/hexanes, flow rate 1.0 mL/min, room temperature,  $t_R$  (major) = 7.69 min,  $t_R$  (minor) = 8.42 min.



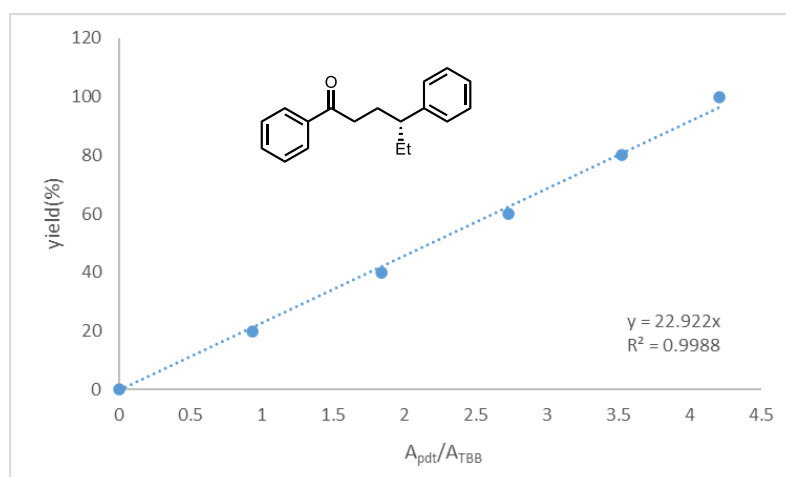
#	Time	Area	Height	Width	Area%	Symmetry
1	7.682	3431.5	302.9	0.1742	49.529	0.811
2	8.402	3496.7	272.8	0.1976	50.471	0.78



#	Time	Area	Height	Width	Area%	Symmetry
1	7.69	3217.2	290.9	0.171	98.578	0.815
2	8.425	46.4	3.5	0.2002	1.422	0.833



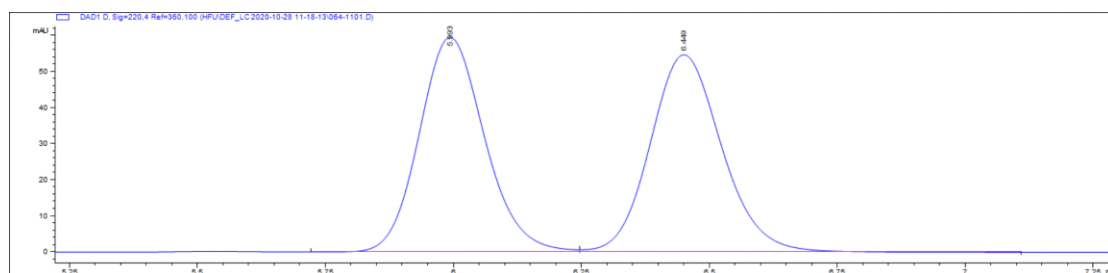
(*R*)-1,4-Diphenylhexan-1-one (**8y**)



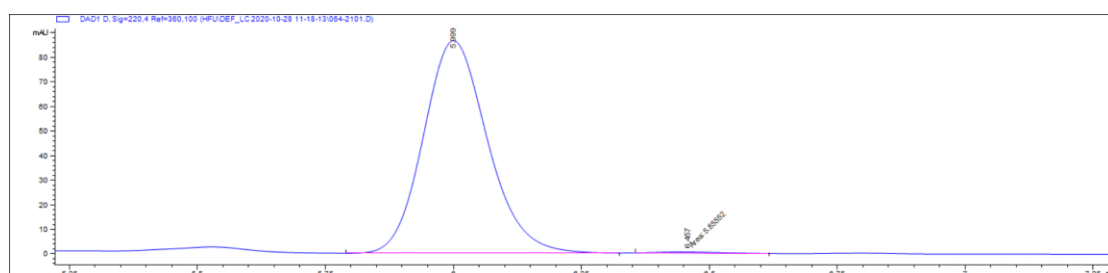
Prepared according to the general procedure 4 using 2-bromo-1-phenylethan-1-one (0.005 mmol) and but-1-en-2-ylbenzene (0.015 mmol) catalyzed by wild-type NCR (1.5 mol%).

**Yields:** run 1: 51%, run 2: 54%, average yield 53%.

**Enantioselectivity:** 99:1 er. Chiral HPLC method: OD-H column, 220 nm, 2% isopropanol/hexanes, flow rate 1.0 mL/min, room temperature,  $t_R$  (major) = 6.00 min,  $t_R$  (minor) = 6.46 min.

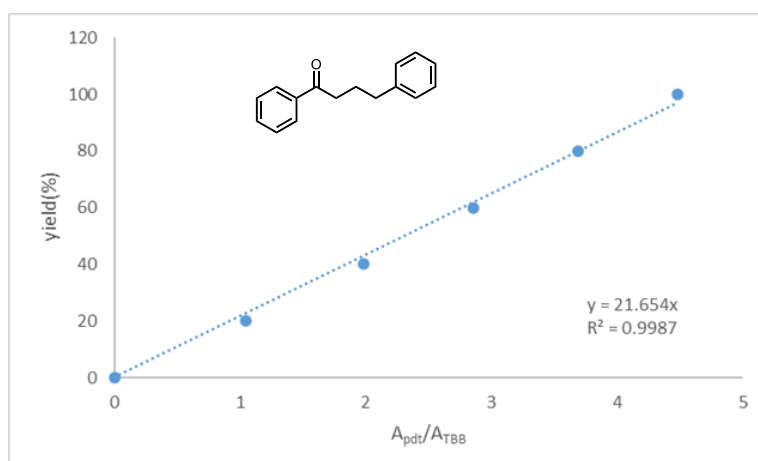


#	Time	Area	Height	Width	Area%	Symmetry
1	5.993	527.9	59.5	0.1355	49.829	0.85
2	6.449	531.5	54.7	0.1513	50.171	0.851



#	Time	Area	Height	Width	Area%	Symmetry
1	5.999	755.9	87	0.1334	99.231	0.836
2	6.457	5.9	5.9E-1	0.1647	0.769	0.528

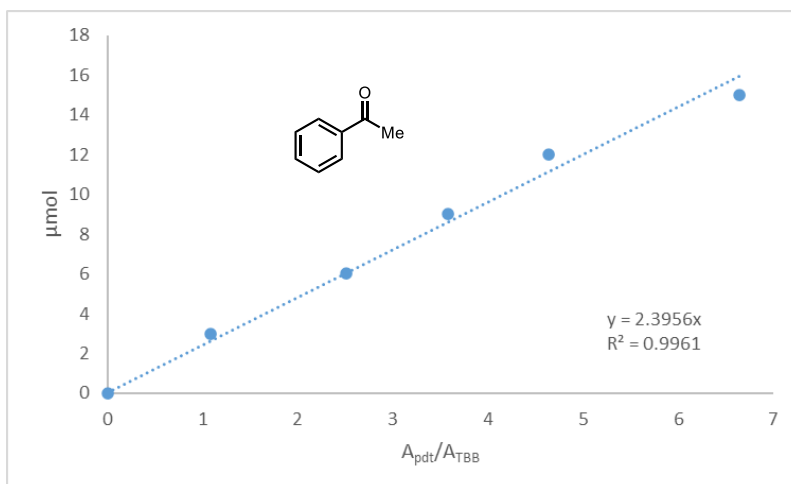
### 1,4-Diphenylbutan-1-one (**8z**)



Prepared according to the general procedure 3 using 2-bromo-1-phenylethan-1-one (0.015 mmol) and styrene (0.005 mmol) catalyzed by wild-type NCR (1.5 mol%). Product standard was purchased from Oakwood Chemical.

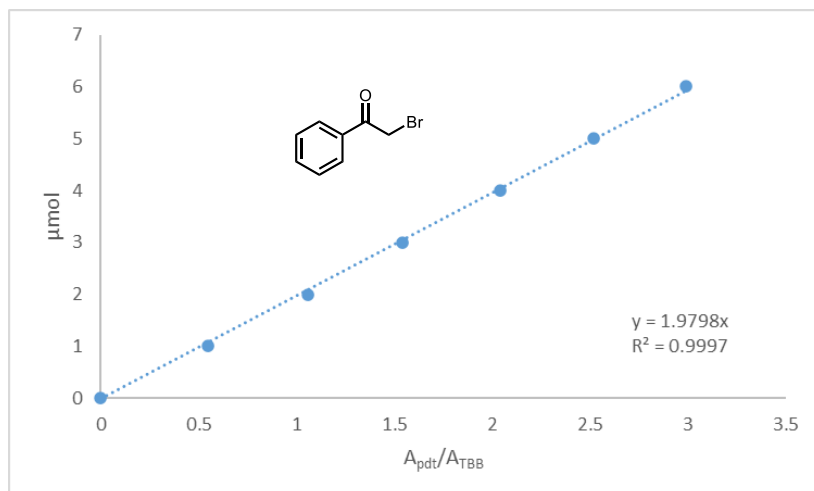
**Yields:** run 1: 35%, run 2: 39%, average yield 37%.

## Acetophenone

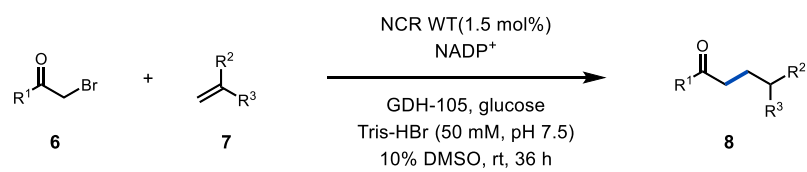


Standard Curve was prepared based on UV absorbance at 210 nm using 1,3,5-tribromobenzene (TBB) as internal standard. Product standard was purchased from Sigma-Aldrich.

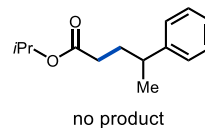
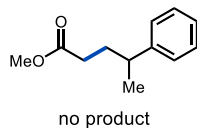
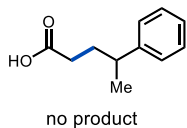
## $\alpha$ -Bromoacetophenone



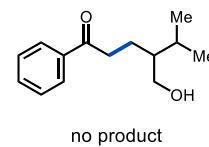
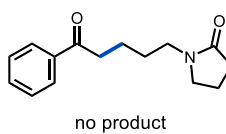
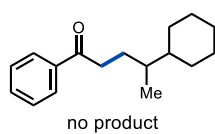
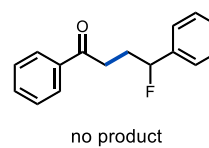
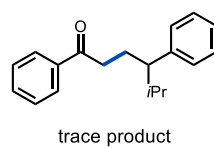
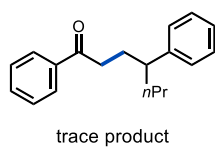
Standard Curve was prepared based on UV absorbance at 210 nm using 1,3,5-tribromobenzene (TBB) as internal standard. Product standard was purchased from Sigma-Aldrich.



***α-Bromo Carbonyls:***



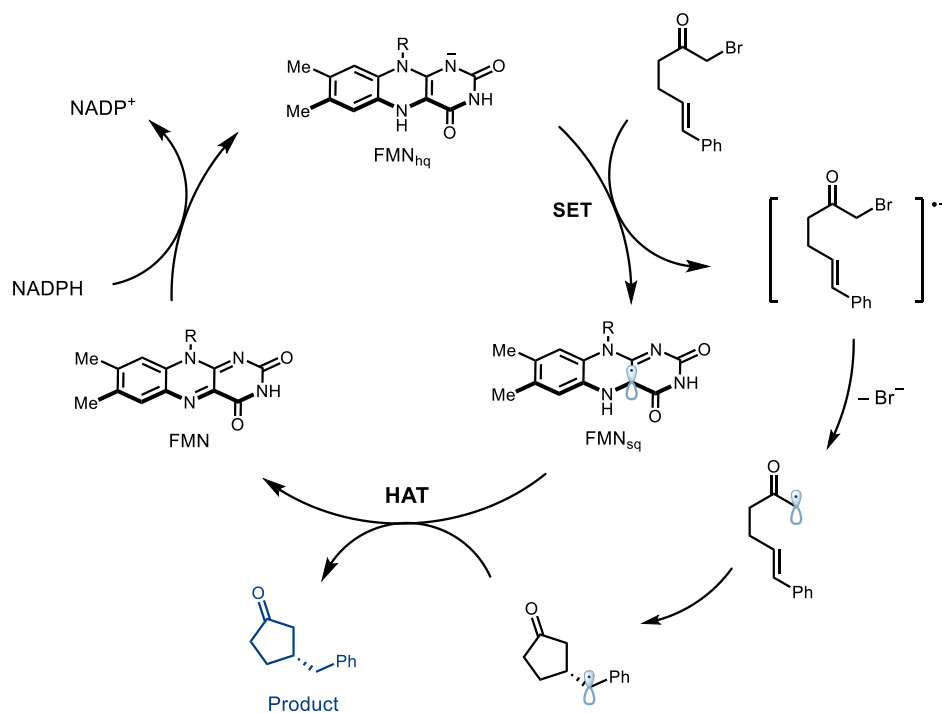
***Substituted Alkenes:***



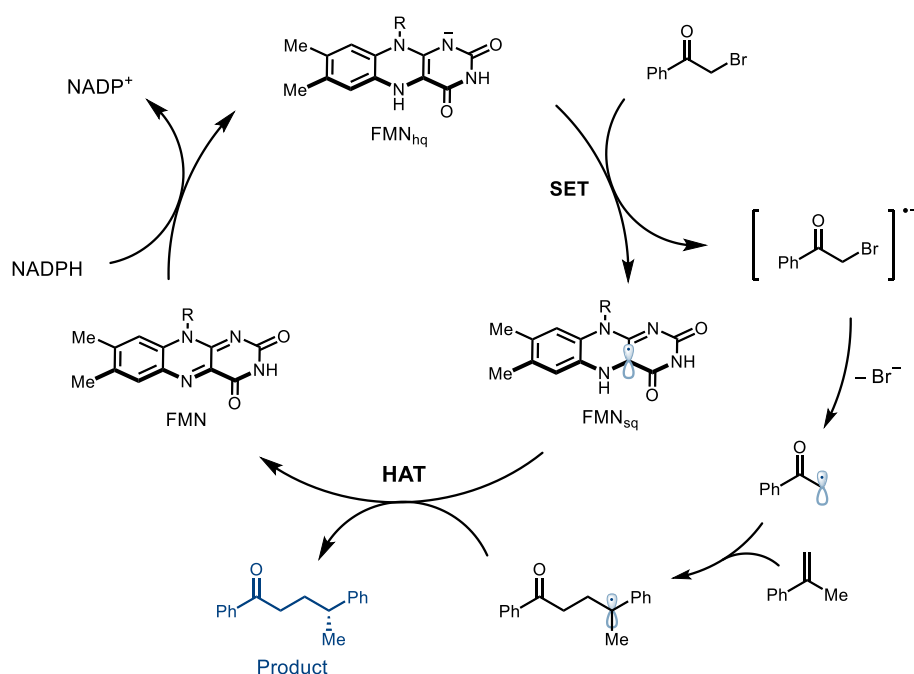
**Supplemental Figure 4.** Substrates not accepted by the wild-type NCR under standard conditions as described in general procedure 3.

## Proposed mechanisms.

### A. Proposed mechanism for the cyclization catalyzed by NCR-C9



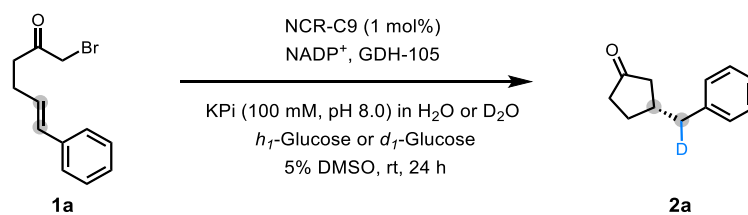
### B. Proposed mechanism for the intermolecular hydroalkylation catalyzed wild-type NCR



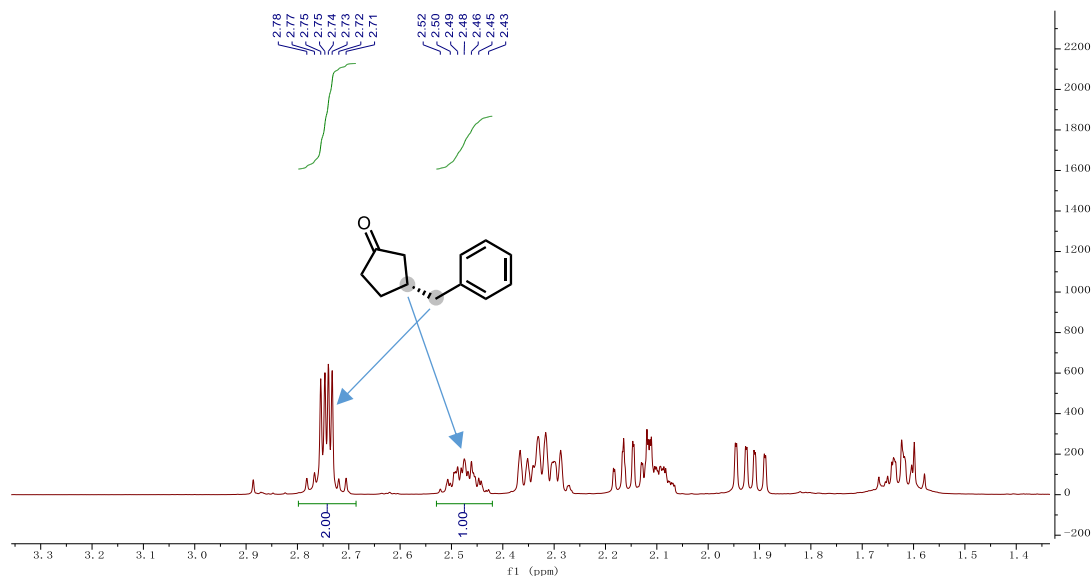
**Supplemental Figure 5.** A. Proposed mechanism for the cyclization catalyzed by NCR-C9. B. Proposed mechanism for the intermolecular hydroalkylation catalyzed wild-type NCR.

## Deuterium labeling experiments

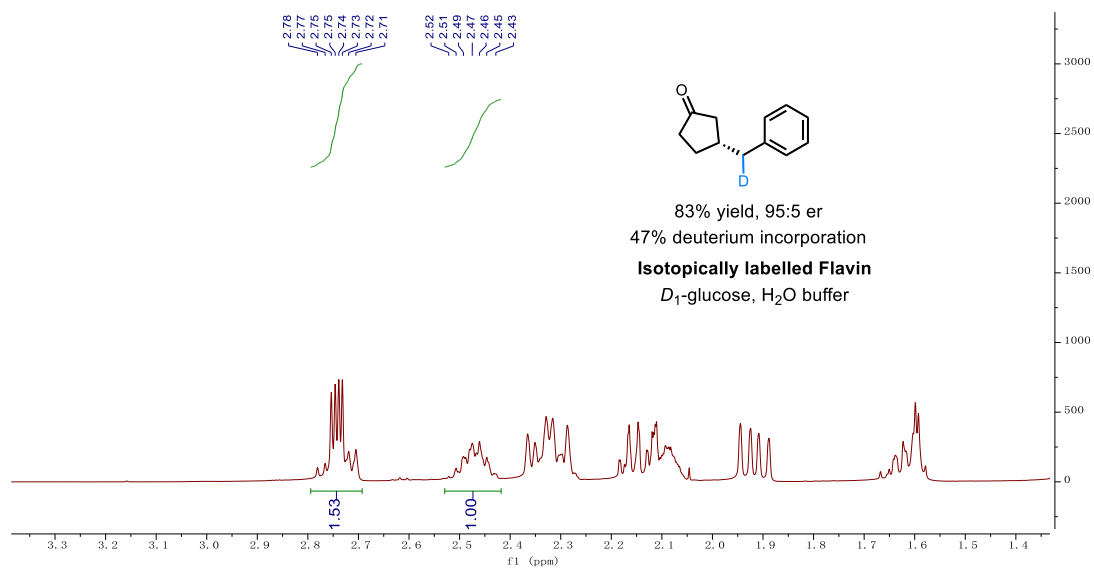
### Deuterium labeling experiment of the NCR-C9 catalyzed cyclization.



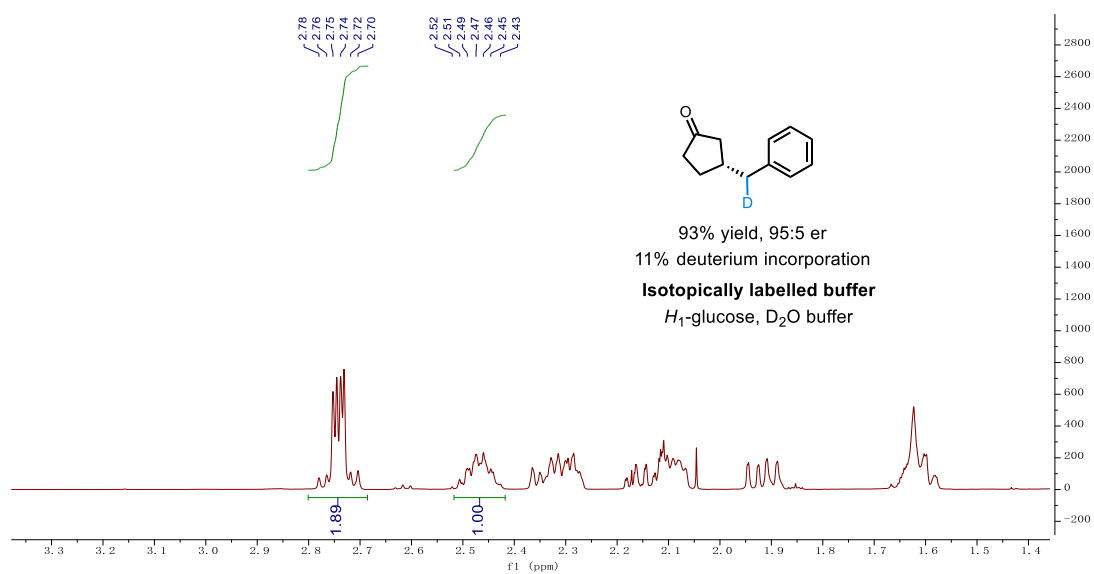
In the Coy chamber, a 20 mL vial was charged with GDH-105 (5 mg), either *d*<sub>1</sub>-glucose or *h*<sub>1</sub>-glucose (50 mg), NADP<sup>+</sup> (5 mg), NCR mutant C9 (1.0 mol%) and substrate (**1a**, 250 μL, 160 mM stock in DMSO, 0.04 mmol). Buffer (100 mM KPi buffer pH 8.0, in either H<sub>2</sub>O or D<sub>2</sub>O) was added to bring the total volume to 5 mL with 5% DMSO (*v/v*) as cosolvent. The vial was sealed with a screw cap and shaken under anaerobic conditions at room temperature for 24 h. Upon completion, the reaction was quenched with 15 mL of acetonitrile. The mixture was shaken for 30 min, centrifuged (12000 x g, 5 mins), and the supernatant was filtered for LCMS analysis for yield calculation, followed by concentrated, and extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure to provide the crude product, which was purified by preparative TLC (EtOAc/Hexanes, 10%, *v/v*). The purified product **2a** were dissolved in CDCl<sub>3</sub> for <sup>1</sup>H NMR analysis. The benzylic proton peaks were integrated from 2.78 – 2.71 ppm. The aliphatic proton attached to the tertiary carbon (2.52 – 2.43 ppm) was used as a reference.



Supplemental Figure 6. <sup>1</sup>H NMR of the aliphatic region of product **2a** standard.

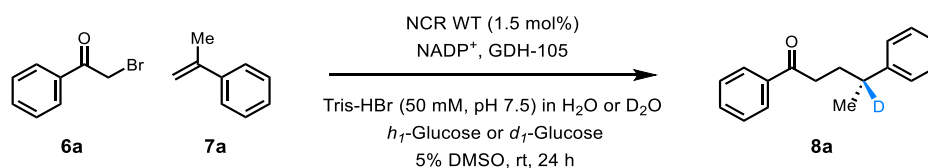


**Supplemental Figure 7.** <sup>1</sup>H NMR of the aliphatic region of product **2a** obtained from *d*<sub>1</sub>-glucose in H<sub>2</sub>O buffer. 47% deuterium incorporation was observed at the benzylic position.

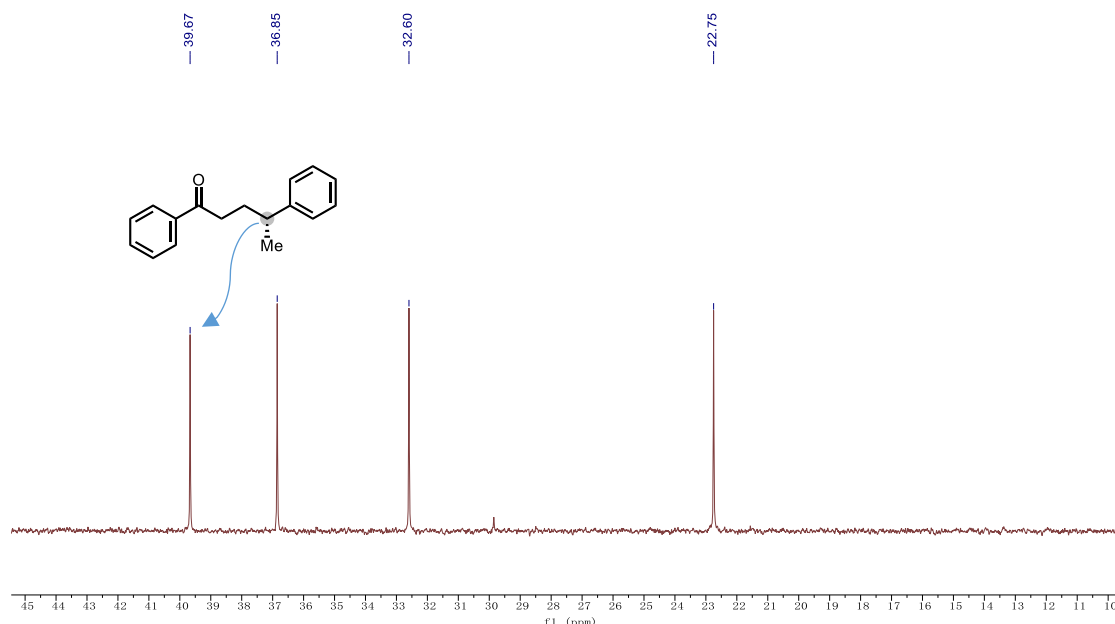


**Supplemental Figure 8.** <sup>1</sup>H NMR of the aliphatic region of product **2a** obtained from *h*<sub>1</sub>-glucose in D<sub>2</sub>O buffer. 11% deuterium incorporation was observed at the benzylic position.

### Deuterium labeling experiment of the wild-type NCR catalyzed intermolecular hydroalkylation.

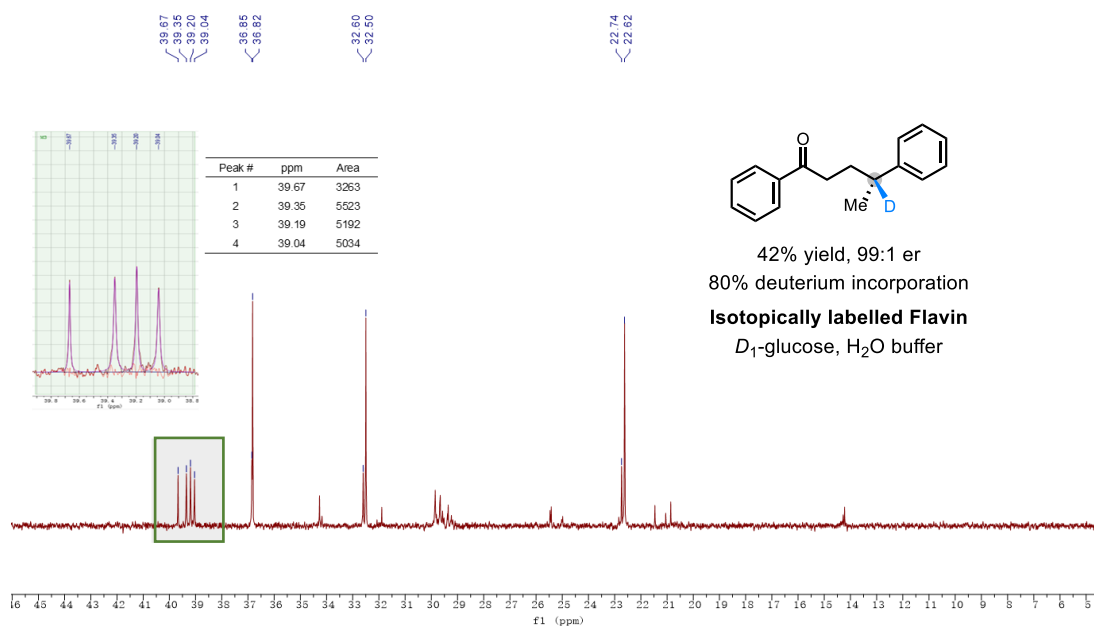


In the Coy chamber, a 30 mL vial was charged with GDH-105 (3 mg), either *d*<sub>1</sub>-glucose or *h*<sub>1</sub>-glucose (50 mg), NADP<sup>+</sup> (2 mg), NCR wild-type protein (1.5 mol% to alkene),  $\alpha$ -bromoketone (**6a**, 250  $\mu$ L, 600 mM stock in DMSO, 0.15 mmol, 3 eq) and alkene (**7a**, 250  $\mu$ L, 200 mM stock in DMSO, 0.05 mmol, 1 eq). Buffer (50 mM Tris-HBr pH 7.5 in either H<sub>2</sub>O or D<sub>2</sub>O) and DMSO were added to bring the total volume to 12 mL with 10% DMSO (*v/v*). The vial was sealed with a screw cap and shaken under anaerobic conditions at room temperature for 36 h. Upon completion, the reaction was quenched with 25 mL of acetonitrile. The mixture was shaken for 30 min, centrifuged (12000  $\times$  g, 5 mins), and the supernatant was filtered for LCMS analysis for yield calculation, followed by concentrated, and extracted with EtOAc (3  $\times$  10 mL). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure to provide the crude product, which was purified by preparative TLC (EtOAc/Hexanes, 10%, *v/v*). The purified product **8a** were dissolved in CDCl<sub>3</sub> for NMR analysis. As the benzylic proton peaks in the <sup>1</sup>H NMR are overlapping with other aliphatic peaks, quantitative <sup>13</sup>C NMR was used to determine the deuterium incorporation at the benzylic position.

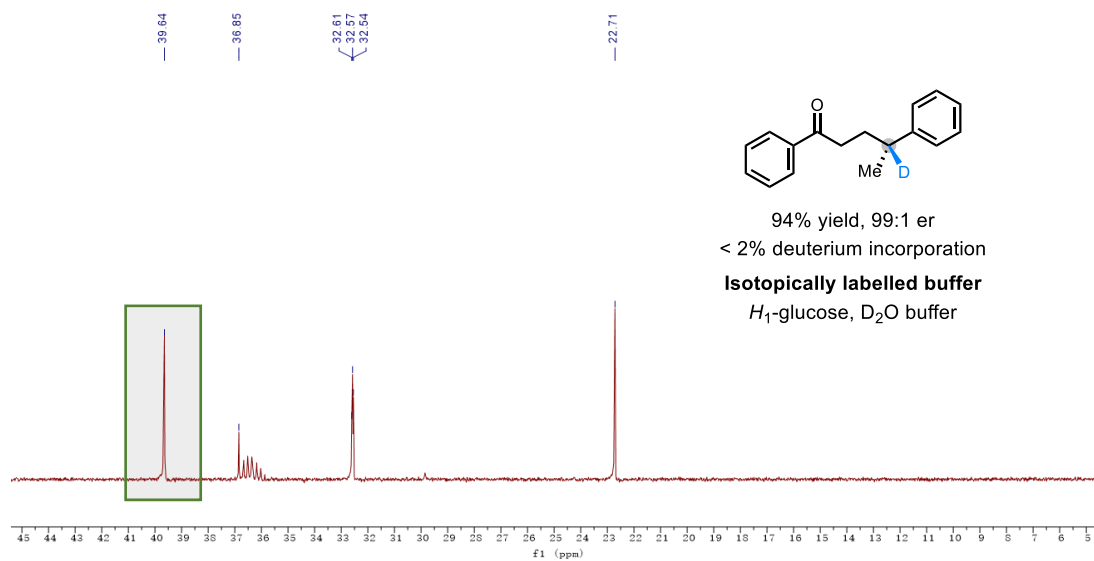


Supplemental Figure 9. <sup>13</sup>C NMR of the aliphatic region of product **8a** standard.



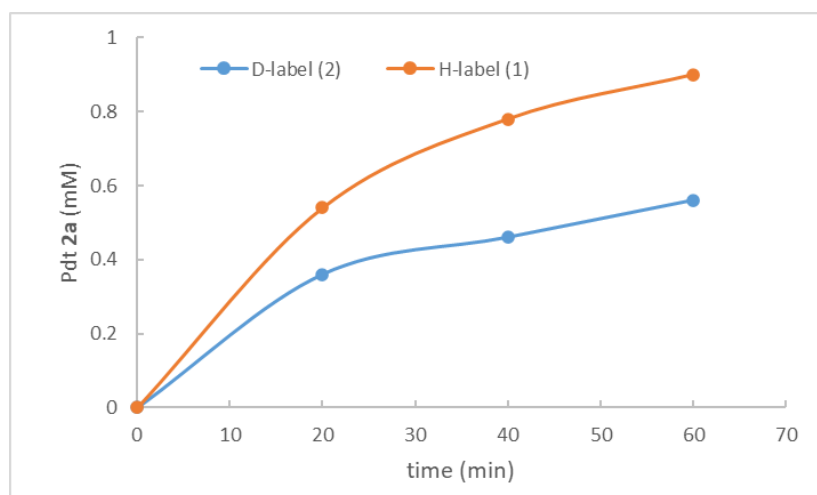
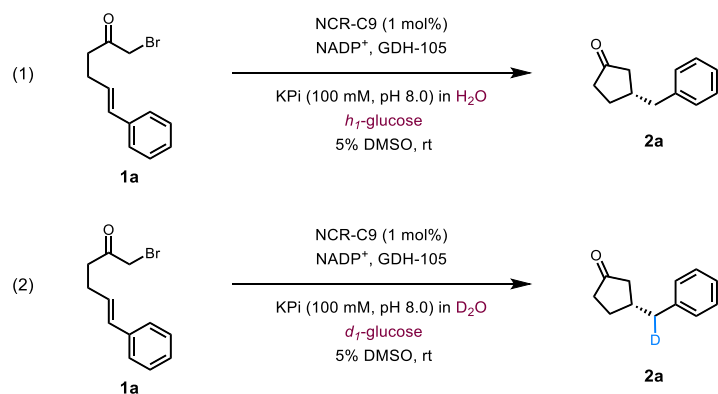


**Supplemental Figure 10.** Quantitative <sup>13</sup>C NMR of the aliphatic region of product **8a** obtained from *d*<sub>1</sub>-glucose in H<sub>2</sub>O buffer. 80% deuterium incorporation was observed at the benzylic position.



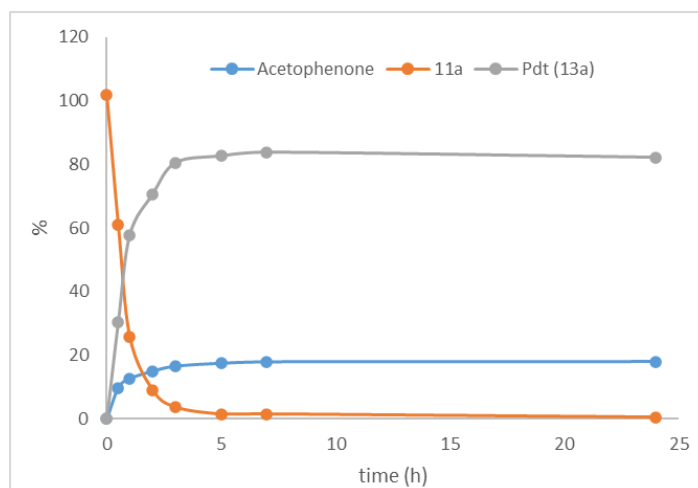
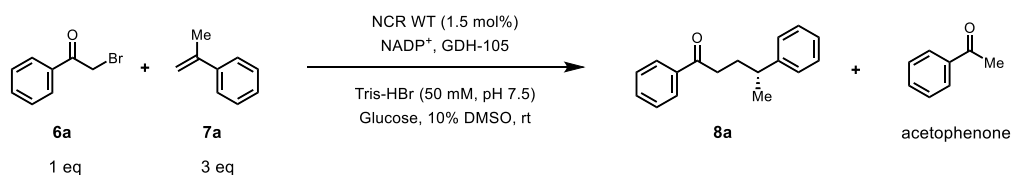
**Supplemental Figure 11.** Quantitative <sup>13</sup>C NMR of the aliphatic region of product **8a** obtained from *h*<sub>1</sub>-glucose in D<sub>2</sub>O buffer. No deuterium incorporation was observed at the benzylic position.

### Isotopic effect experiments for NCR-C9 catalyzed cyclization

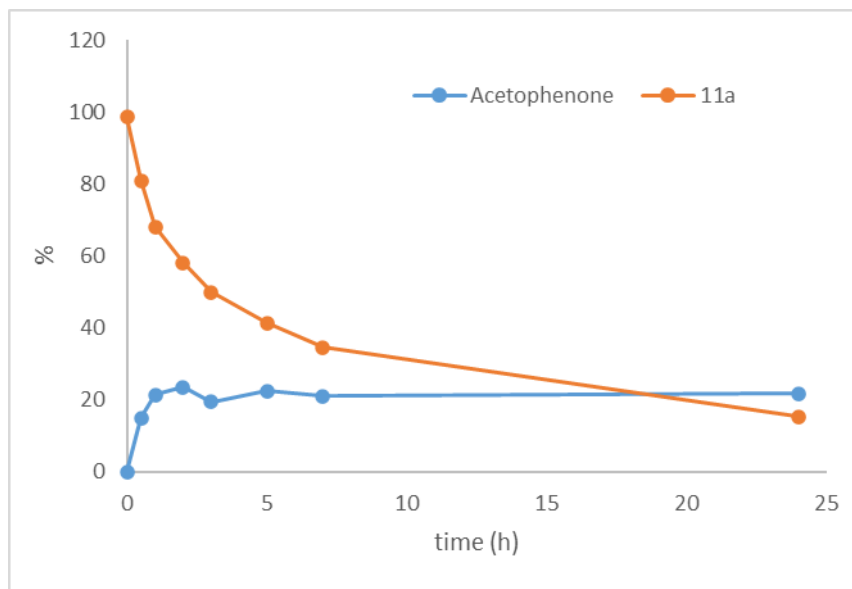
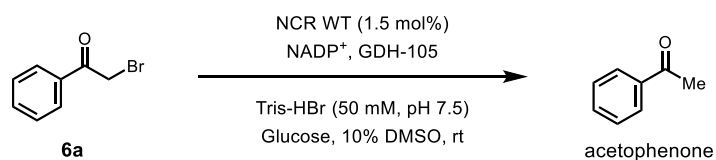


**Supplemental Figure 12.** Isotopic effect experiments for NCR-C9 catalyzed cyclization. Reaction conditions: the reaction mixture (500  $\mu$ L) consisted of substrate  $\alpha$ -bromoketone (**1a**, 0.004 mmol), GDH-105 (0.5 mg), either  $h_1$ -glucose or  $d_1$ -glucose (5.0 mg), NADP<sup>+</sup> (0.5 mg), purified NCR-C9 protein (1.0 mol%) in buffer (100 mM KPi buffer pH 8.0, in either H<sub>2</sub>O or D<sub>2</sub>O) with 5% DMSO as cosolvent at room temperature. The cyclization product **2a** was determined *via* HPLC-MS at t = 0, 20, 40, 60 min.

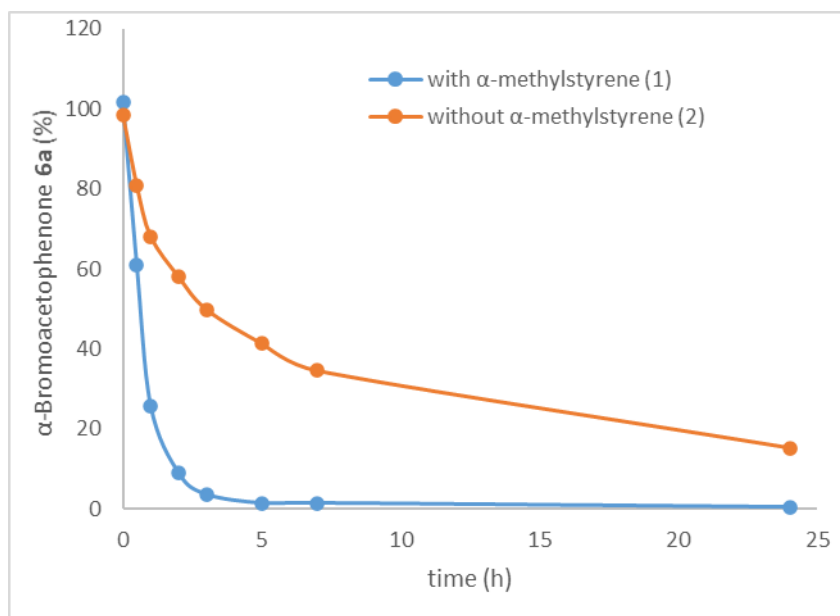
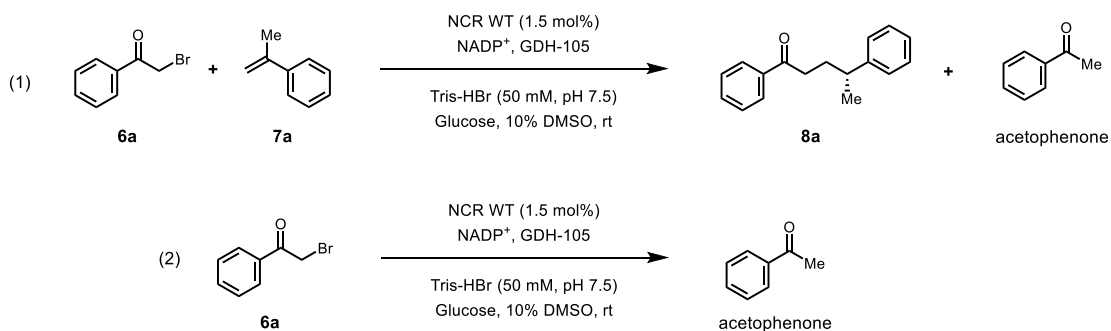
### Reaction progress curves



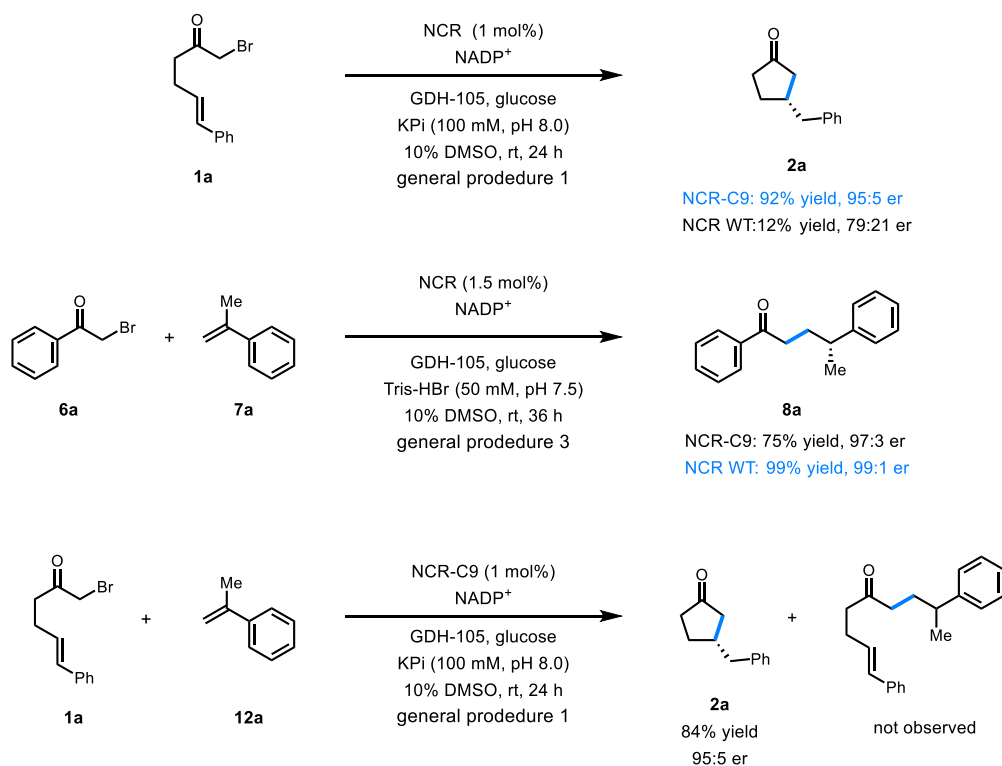
**Supplemental Figure 13.** Reaction progress for intermolecular hydroalkylation catalyzed by wild-type NCR. Reaction conditions: the reaction mixture (500  $\mu\text{L}$ ) consisted of  $\alpha$ -bromoacetophenone (**6a**, 0.005 mmol, 1 eq), GDH-105 (0.3 mg), glucose (5.0 mg),  $\text{NADP}^+$  (0.2 mg), purified wild-type NCR protein (1.5 mol%), and  $\alpha$ -methylstyrene (**7a**, 0.015 mmol, 3 eq) in buffer (50 mM Tris-HBr buffer pH 7.5) with 10% DMSO as cosolvent at room temperature. The  $\alpha$ -bromoacetophenone **6a**, hydroalkylation product **8a**, and acetophenone were determined *via* HPLC at  $t = 0, 0.5, 1, 2, 3, 5, 7,$  and 24 h.



**Supplemental Figure 14.** Reaction progress for direct reduction catalyzed by wild-type NCR. Reaction conditions: the reaction mixture (500  $\mu$ L) consisted of  $\alpha$ -bromoacetophenone (**6a**, 0.005 mmol, 1 eq), GDH-105 (0.3 mg), glucose (5.0 mg), NADP<sup>+</sup> (0.2 mg), and purified wild-type NCR protein (1.5 mol%) in buffer (50 mM Tris-HBr buffer pH 7.5) with 10% DMSO as cosolvent at room temperature. The  $\alpha$ -bromoacetophenone **6a** and acetophenone were determined *via* HPLC at t = 0, 0.5, 1, 2, 3, 5, 7, and 24 h.

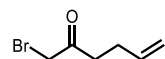
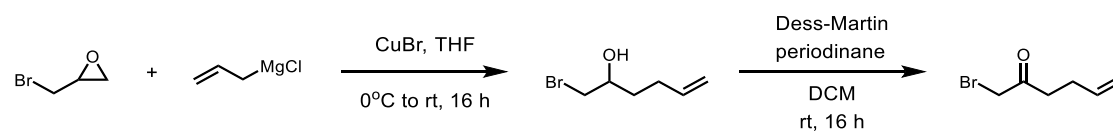


**Supplemental Figure 15.**  $\alpha$ -Methylstyrene affect the depletion of  $\alpha$ -bromoacetophenone in NCR-catalyzed reaction. Conditions: the reaction mixture (500  $\mu$ L) consisted of  $\alpha$ -bromoacetophenone (**6a**, 0.005 mmol, 1 eq), GDH-105 (0.3 mg), glucose (5.0 mg), NADP<sup>+</sup> (0.2 mg), purified wild-type NCR protein (1.5 mol%), with  $\alpha$ -methylstyrene (*equation 1*) or without  $\alpha$ -methylstyrene (*equation 2*) (**7a**, 0.015 mmol, 3 eq), in buffer (50 mM Tris-HBr buffer pH 7.5) with 10% DMSO as cosolvent at room temperature. The remaining  $\alpha$ -bromoacetophenone **6a** was determined *via* HPLC at t = 0, 0.5, 1, 2, 3, 5, 7, and 24 h.



**Supplemental Figure 16.** Specification of the evolved NCR-C9 for cyclization and wild-type NCR for intermolecular hydroalkylation.

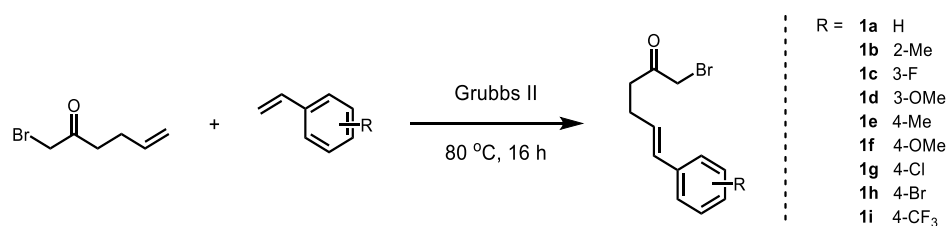
## Synthesis of substrates for cyclization



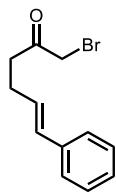
### 1-Bromo-5-hexen-2-one

Adapted from the method by Alam *et al.*<sup>11</sup> To a stirred suspension of  $\text{CuBr}$  (52 mg, 0.36 mmol, 0.1 eq) in dry THF (40 mL) was added 18 mL of allyl magnesium chloride solution (2 M in THF, 36 mmol, 1 eq) dropwise under nitrogen atmosphere at  $0^\circ\text{C}$  and the mixture was stirred at  $0^\circ\text{C}$  for 30 min. Epibromohydrin (3 mL, 36 mmol, 1 eq) was then added dropwise to the reaction mixture, which was warmed up to room temperature and further stirred over 16 h. The reaction was quenched with saturated  $\text{NH}_4\text{Cl}$  aqueous solution and extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated *in vacuo* to give a colorless oil. The residual oil was dissolved in dry DCM (50 mL), Dess-Martin periodinane (16.8 g, 39.6 mmol, 1.1 eq) was added and the reaction mixture was stirred at room temperature overnight. The reaction was quenched with saturated  $\text{Na}_2\text{S}_2\text{O}_3$  aqueous solution and extracted with DCM. The organic layers were combined, washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated *in vacuo* to give a brown oil as a crude product, which was purified by flash chromatography (EtOAc/Hexanes, 10%, v/v) to afford the desired product as a colorless oil (3.5 g, 55% yield over 2 steps).

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  5.81 (ddt,  $J = 16.8, 10.2, 6.5$  Hz, 1H), 5.11 – 4.95 (m, 2H), 3.89 (s, 2H), 2.77 (t,  $J = 7.3$  Hz, 2H), 2.42 – 2.29 (m, 2H). The NMR spectra is in agreement with published data.<sup>12</sup>



**General metathesis procedure.** Adapted from the method by Ahn *et al.*<sup>13</sup> A 25 mL three-necked flask was fitted with a reflux condenser, flame-dried, and charged with a magnetic stir bar and Grubbs II catalyst (19 mg, 0.022 mmol, 0.02 eq). In a separate vial, 1-bromo-5-hexen-2-one starting material (200 mg, 1.12 mmol, 1 eq) and styrene (22.4 mmol, 20 eq) were mixed and added to the flask containing the Grubbs II catalyst. The mixture was heated to  $80^\circ\text{C}$  for 16 h. The solid residue was dissolved in DCM, and triphenylphosphine oxide (0.61 g, 2.2 mmol, 100 eq with respect to catalyst) was added and stirred for 24 h. The mixture was concentrated *in vacuo* and purified by flash chromatography (EtOAc/Hexanes, 10%, v/v).



**(E)-1-Bromo-6-phenylhex-5-en-2-one (1a)**

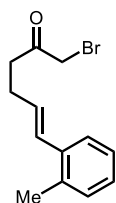
White solid. Yield: 23%.

$^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.34 – 7.28 (m, 4H), 7.23 – 7.19 (m, 1H), 6.43 (d,  $J = 15.8$  Hz, 1H), 6.19 (dt,  $J = 15.8, 6.9$  Hz, 1H), 3.90 (s, 2H), 2.85 (t,  $J = 7.3$  Hz, 2H), 2.54 (qd,  $J = 7.2, 1.6$  Hz, 2H).

$^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )  $\delta$  201.5, 137.3, 131.4, 128.7, 128.2, 127.4, 126.2, 39.6, 34.4, 27.3.

HRMS (ESI):  $m/z$  calcd for  $\text{C}_{12}\text{H}_{14}\text{BrO}$   $[\text{M}+\text{H}]^+$ : 253.0223, found: 253.0221.

IR: 2947.2, 1726.6, 1389.3, 1245.6, 1076.3, 966.3, 747.2 ( $\text{cm}^{-1}$ ).



**(E)-1-Bromo-6-(o-tolyl)hex-5-en-2-one (1b)**

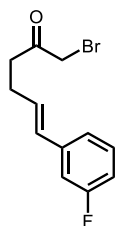
Clear oil. Yield: 27%.

$^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.40 – 7.38 (m, 1H), 7.18 – 7.12 (m, 3H), 6.64 (d,  $J = 15.6$  Hz, 1H), 6.05 (dt,  $J = 15.7, 6.9$  Hz, 1H), 3.91 (s, 2H), 2.86 (t,  $J = 7.2$  Hz, 2H), 2.56 (qd,  $J = 7.2, 1.6$  Hz, 2H), 2.33 (s, 3H).

$^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )  $\delta$  201.4, 136.5, 135.2, 130.3, 129.5, 129.3, 127.3, 126.2, 125.6, 39.7, 34.4, 27.6, 19.9.

HRMS (GCMS-EI):  $m/z$  calcd for  $\text{C}_{13}\text{H}_{15}\text{BrO}$   $[\text{M}]^+$ : 266.0313, found: 266.0308.

IR: 3014.7, 1714.7, 1483.9, 1395.8, 1275.8, 1260.9, 964.6, 744.3 ( $\text{cm}^{-1}$ ).



**(E)-1-Bromo-6-(3-fluorophenyl)hex-5-en-2-one (1c)**

White solid. Yield: 19%.

$^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.27 – 7.22 (m, 1H), 7.08 (d,  $J = 7.7$  Hz, 1H), 7.03 (dt,  $J = 10.3, 2.1$  Hz, 1H), 6.90 (td,  $J = 8.4, 2.4$  Hz, 1H), 6.40 (d,  $J = 15.8$  Hz, 1H), 6.20 (dt,  $J = 15.8, 6.9$  Hz, 1H), 3.90 (s, 2H), 2.85 (t,  $J = 7.2$  Hz, 2H), 2.54 (qd,  $J = 7.1, 1.5$  Hz, 2H).

$^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )  $\delta$  201.2, 163.1 (d,  $J = 245.1$  Hz), 139.6 (d,  $J = 7.7$  Hz), 130.3 (d,  $J = 2.6$  Hz), 129.97 (d,  $J = 8.4$  Hz), 129.54, 122.0 (d,  $J = 2.8$  Hz), 114.0 (d,  $J = 21.4$  Hz), 112.50 (d,  $J = 21.8$

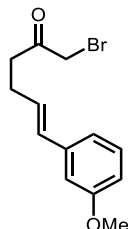


Hz), 39.2, 34.2, 27.0.

$^{19}\text{F}$  NMR (282 MHz,  $\text{CDCl}_3$ )  $\delta$  -113.7.

HRMS (DART-MS):  $m/z$  calcd for  $\text{C}_{12}\text{H}_{13}\text{BrFO}$   $[\text{M}+\text{H}]^+$ : 271.0128, found 271.0130.

IR: 2921.7, 1721.1, 1581.8, 1387.5, 1275.5, 1076.0, 962.1, 754.6, 681.5 ( $\text{cm}^{-1}$ ).



(*E*)-1-Bromo-6-(3-methoxyphenyl)hex-5-en-2-one (**1d**)

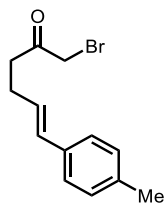
Light yellow oil. Yield: 26%.

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.21 (t,  $J = 7.9$  Hz, 1H), 6.93 (d,  $J = 7.7$  Hz, 1H), 6.87 (t,  $J = 2.1$  Hz, 1H), 6.77 (ddd,  $J = 8.2, 2.6, 0.9$  Hz, 1H), 6.40 (d,  $J = 15.8$  Hz, 1H), 6.18 (dt,  $J = 15.8, 6.9$  Hz, 1H), 3.90 (s, 2H), 3.81 (s, 3H), 2.85 (t,  $J = 7.2$  Hz, 2H), 2.53 (qd,  $J = 7.1, 1.4$  Hz, 2H).

$^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  201.4, 159.9, 138.8, 131.3, 129.7, 128.5, 118.9, 113.0, 111.5, 55.4, 39.5, 34.4, 27.3.

HRMS (ESI):  $m/z$  calcd for  $\text{C}_{13}\text{H}_{16}\text{BrO}_2$   $[\text{M}+\text{H}]^+$ : 283.0328, found: 283.0334.

IR: 2942.8, 1714.4, 1578.0, 1488.8, 1431.3, 1261.1, 1154.6, 1041.3, 965.2, 764.9, 688.5 ( $\text{cm}^{-1}$ ).



(*E*)-1-Bromo-6-(*p*-tolyl)hex-5-en-2-one (**1e**)

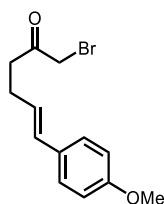
White solid. Yield: 26%.

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.22 (d,  $J = 8.1$  Hz, 2H), 7.10 (d,  $J = 7.9$  Hz, 2H), 6.40 (d,  $J = 15.8$  Hz, 1H), 6.13 (dt,  $J = 15.8, 6.9$  Hz, 1H), 3.90 (s, 2H), 2.84 (t,  $J = 7.3$  Hz, 2H), 2.52 (qd,  $J = 7.1, 1.5$  Hz, 2H), 2.32 (s, 3H).

$^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  201.5, 137.2, 134.6, 131.2, 129.4, 127.1, 126.1, 39.7, 34.4, 27.3, 21.3.

HRMS (ESI):  $m/z$  calcd for  $\text{C}_{13}\text{H}_{16}\text{BrO}$   $[\text{M}+\text{H}]^+$ : 267.0393, found: 267.0379.

IR: 2923.5, 1732.0, 1511.3, 1388.9, 1275.7, 1082.9, 967.1, 754.5 ( $\text{cm}^{-1}$ ).



(*E*)-1-Bromo-6-(4-methoxyphenyl)hex-5-en-2-one (**1f**)

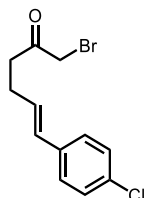
Light yellow oil. Yield: 32%.

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.28 – 7.25 (m, 2H), 6.87 – 6.79 (m, 2H), 6.37 (d,  $J = 15.8$  Hz, 1H), 6.04 (dt,  $J = 15.8, 6.9$  Hz, 1H), 3.90 (s, 2H), 3.80 (s, 3H), 2.83 (t,  $J = 7.3$  Hz, 2H), 2.51 (qd,  $J = 7.2, 1.5$  Hz, 2H).

$^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  201.5, 159.1, 130.8, 130.1, 127.3, 125.9, 114.1, 55.4, 39.7, 34.4, 27.3.

HRMS (ESI):  $m/z$  calcd for  $\text{C}_{13}\text{H}_{16}\text{BrO}_2$   $[\text{M}+\text{H}]^+$ : 283.0328, found: 283.0336.

IR: 2924.5, 1719.2, 1606.6, 1510.7, 1393.4, 1275.8, 1252.3, 1176.9, 959.3, 754.1 ( $\text{cm}^{-1}$ ).



(*E*)-1-bromo-6-(4-chlorophenyl)hex-5-en-2-one (**1g**)

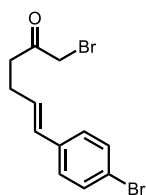
White solid. Yield: 32%.

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.25 (s, 4H), 6.38 (d,  $J = 15.9$  Hz, 1H), 6.16 (dt,  $J = 15.8, 6.9$  Hz, 1H), 3.90 (s, 2H), 2.85 (t,  $J = 7.2$  Hz, 2H), 2.53 (qd,  $J = 7.1, 1.5$  Hz, 2H).

$^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  201.4, 135.8, 132.9, 130.2, 128.9, 128.8, 127.4, 39.4, 34.3, 27.2.

HRMS (ESI):  $m/z$  calcd for  $\text{C}_{12}\text{H}_{13}\text{BrClO}$   $[\text{M}+\text{H}]^+$ : 286.9833, found: 286.9829.

IR: 2992.2, 1719.5, 1488.2, 1387.9, 1275.8, 1088.9, 1010.4, 968.6, 855.6, 750.2 ( $\text{cm}^{-1}$ ).



(*E*)-1-bromo-6-(4-bromophenyl)hex-5-en-2-one (**1h**)

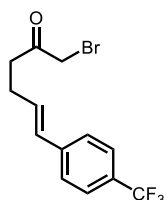
White solid. Yield: 29%.

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.41 (d,  $J = 8.5$  Hz, 2H), 7.19 (d,  $J = 8.4$  Hz, 2H), 6.37 (d,  $J = 15.8$  Hz, 1H), 6.18 (dt,  $J = 15.8, 6.9$  Hz, 1H), 3.90 (s, 2H), 2.85 (t,  $J = 7.2$  Hz, 2H), 2.52 (qd,  $J = 7.1, 1.4$  Hz, 2H).

$^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  201.3, 136.3, 131.7, 130.3, 129.1, 127.7, 121.0, 39.4, 34.3, 27.2.

HRMS (DART-MS):  $m/z$  calcd for  $\text{C}_{12}\text{H}_{13}\text{Br}_2\text{O}$   $[\text{M}+\text{H}]^+$ : 330.9328, found 330.9330.

IR: 2940.7, 1722.6, 1485.7, 1385.7, 1244.7, 1073.1, 1006.3, 968.2, 849.2, 793.9, 692.7 ( $\text{cm}^{-1}$ ).



(*E*)-1-bromo-6-(4-(trifluoromethyl)phenyl)hex-5-en-2-one (**1i**)

White solid. Yield: 37%.

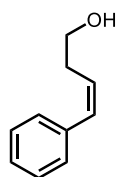
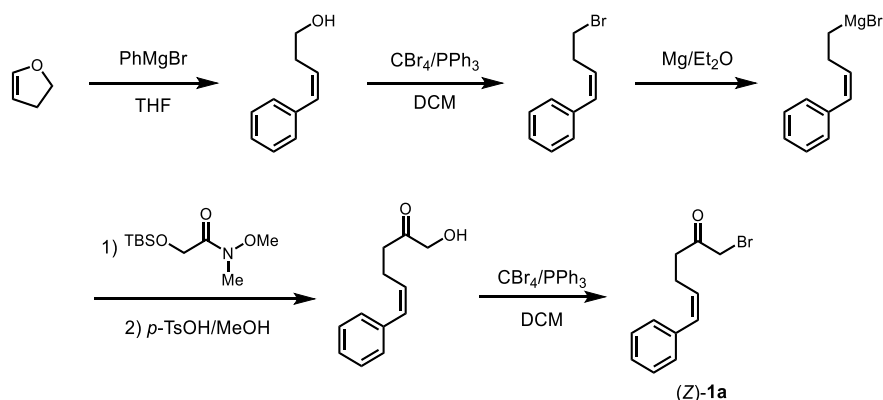
$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.54 (d,  $J = 8.1$  Hz, 2H), 7.41 (d,  $J = 8.1$  Hz, 2H), 6.46 (d,  $J = 15.9$  Hz, 1H), 6.30 (dt,  $J = 15.8, 6.8$  Hz, 1H), 3.90 (s, 2H), 2.87 (t,  $J = 7.2$  Hz, 2H), 2.57 (qd,  $J = 7.1, 1.5$  Hz, 2H).

$^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  201.2, 140.8 (d,  $J = 1.5$  Hz), 131.0, 130.2, 129.2 (q,  $J = 32.3$  Hz), 126.3, 125.6 (q,  $J = 3.8$  Hz), 124.4 (q,  $J = 272.2$  Hz), 39.2, 34.2, 27.2.

$^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ )  $\delta$  -62.5.

HRMS (GCMS-EI):  $m/z$  calcd for  $\text{C}_{13}\text{H}_{12}\text{BrF}_3\text{O}$   $[\text{M}]^+$ : 321.0096, found: 321.0092.

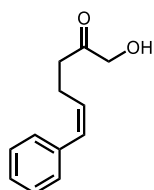
IR: 2942.8, 1714.3, 1578.0, 1488.8, 1431.3, 1261.4, 1154.6, 1041.2, 965.1, 744.3, 688.4 ( $\text{cm}^{-1}$ ).



#### (Z)-4-Phenylbut-3-en-1-ol

Adapted from the method by Yuxiang *et al.*<sup>14</sup> To a solution of phenylmagnesium bromide (3 M in  $\text{Et}_2\text{O}$ , 7 mL, 21 mmol) was slowly added  $\text{NiCl}_2(\text{PPh}_3)_3$  dry powder (0.6 g, 0.92 mmol) under nitrogen atmosphere at 0 °C. Then 2,3-dihydrofuran (1.6 mL, 21.3 mmol) was added dropwise and the reaction mixture was stirred at room temperature for 18 h. The mixture was poured to a saturated  $\text{NH}_4\text{Cl}$  aqueous solution, and then extracted with  $\text{Et}_2\text{O}$ , washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated to give a crude residue, which was purified by flash chromatography ( $\text{EtOAc}/\text{Hexanes}$ , 20%,  $v/v$ ) to afford the desired product as a colorless oil (1.33 g, 43% yield).

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.37 – 7.29 (m, 4H), 7.26 – 7.22 (m, 1H), 6.59 (d,  $J = 11.7$  Hz, 1H), 5.70 (dt,  $J = 11.7, 7.3$  Hz, 1H), 3.76 (t,  $J = 6.6$  Hz, 2H), 2.62 (qd,  $J = 6.6, 1.8$  Hz, 2H), 1.42 (brs, 1H). The NMR spectra is in agreement with published data.<sup>14</sup>



#### (Z)-1-Hydroxy-6-phenylhex-5-en-2-one

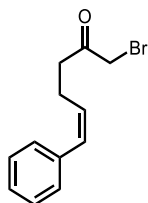
To a stirred solution of (Z)-4-phenylbut-3-en-1-ol (590 mg, 4 mmol) in dry DCM (10 mL) was added

PPh<sub>3</sub> (1.15 g, 4.4 mmol) and CBr<sub>4</sub> (1.46 g, 4.4 mmol) under nitrogen atmosphere at 0 °C, and then the reaction mixture was stirred at room temperature for 2 h. The mixture was poured to a saturated NaHCO<sub>3</sub> aqueous solution, and then extracted with DCM, washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated to give a crude oil, which was purified by flash chromatography (EtOAc/Hexanes, 20%, v/v) to afford the bromination product (*Z*)-(4-bromobut-1-en-1-yl)benzene (750 mg, yield 85%).

To a flame dry flask was added with Mg (120 mg, 4.9 mmol), dry Et<sub>2</sub>O (2 mL), and dibromoethane (two drops) under nitrogen atmosphere at 0 °C. The bromination product (*Z*)-(4-bromobut-1-en-1-yl)benzene (860 mg, 4.1 mmol) was dissolved in dry Et<sub>2</sub>O (2 mL), then added dropwise to the reaction mixture, and the mixture was stirred at 0 °C for 30 min. A solution of the appropriate Weinreb amide (840 mg, 3.6 mmol) in dry Et<sub>2</sub>O (10 mL) was dropwise added to the freshly prepared Grignard reagent, then the reaction mixture was stirred at room temperature for 4 h. The mixture was quenched with saturated NH<sub>4</sub>Cl aqueous solution, and then extracted with Et<sub>2</sub>O, washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and, concentrated to give a crude product. The resulting product was immediately dissolved in dry MeOH (24 mL) and then *p*-toluenesulfonic acid (35 mg, 0.2 mmol) was added, the mixture was stirred at room temperature for 16 h. The solvent was removed under reduced pressure to provide a crude oil, which was further purified by flash chromatography (EtOAc/Hexanes, 25%, v/v) to afford the desired  $\alpha$ -hydroxyketone as a clear oil (100 mg, yield 13% over 3 steps).

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.36 – 7.33 (m, 2H), 7.26 – 7.23 (m, 3H), 6.49 (d, *J* = 11.5 Hz, 1H), 5.58 (dt, *J* = 11.5, 7.2 Hz, 1H), 4.23 (d, *J* = 4.6 Hz, 2H), 3.07 (t, *J* = 4.7 Hz, 1H), 2.68 (qd, *J* = 7.3, 1.8 Hz, 2H), 2.54 (t, *J* = 7.4 Hz, 2H).

<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)  $\delta$  209.0, 137.1, 130.7, 129.9, 128.8, 128.4, 127.1, 68.3, 38.5, 22.8.



(*Z*)-1-Bromo-6-phenylhex-5-en-2-one [(*Z*)-**1a**]

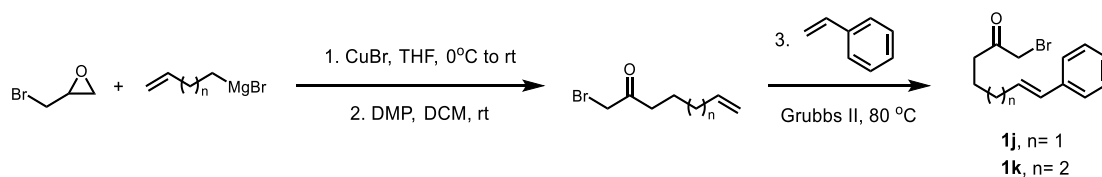
To a stirred solution of (*Z*)-1-hydroxy-6-phenylhex-5-en-2-one (95 mg, 0.5 mmol) in dry DCM (3 mL) was added PPh<sub>3</sub> (145 mg, 0.55 mmol) and CBr<sub>4</sub> (180 mg, 0.55 mmol) under nitrogen atmosphere at 0 °C, and then the reaction mixture was stirred at room temperature for 2 h. The mixture was poured to a saturated NaHCO<sub>3</sub> aqueous solution, and then extracted with DCM, washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated to give the crude product, which was purified by flash chromatography (EtOAc/Hexanes, 10%, v/v) to afford the desired product (clear oil, 83 mg, yield 66%).

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.35 – 7.31 (m, 2H), 7.26 – 7.21 (m, 3H), 6.47 (d, *J* = 11.6 Hz, 1H), 5.59 (dt, *J* = 11.6, 7.2 Hz, 1H), 3.85 (s, 2H), 2.79 (t, *J* = 7.3 Hz, 2H), 2.64 (qd, *J* = 7.3, 1.8 Hz, 2H).

<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)  $\delta$  201.5, 137.2, 130.6, 130.0, 128.8, 128.4, 127.0, 39.9, 34.2, 23.1.

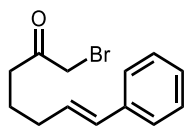
HRMS (GCMS-EI): *m/z* calcd for C<sub>12</sub>H<sub>13</sub>BrO [M]<sup>+</sup>: 253.0223, found: 253.0220.

IR: 3012.6, 1713.7, 1493.2, 1397.2, 1275.7, 1260.8, 1073.6, 916.8, 764.9, 697.9 (cm<sup>-1</sup>).



**Step 1 and step 2.** Adapted from the method by Alam *et al.*<sup>11</sup> To a stirred suspension of CuBr (26 mg, 0.18 mmol, 0.1 eq) in dry THF (20 mL) was added freshly prepared Grignard reagent solution (in THF, 18 mmol, 1 eq) dropwise under nitrogen atmosphere at 0 °C and the mixture was stirred at 0 °C for 30 min. Epibromohydrin (1.5 mL, 18 mmol, 1 eq) was then added dropwise to the reaction mixture, which was warmed up to room temperature and further stirred over 16 h. The reaction was quenched with saturated NH<sub>4</sub>Cl aqueous solution and extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo* to give a colorless oil. The residual oil was dissolved in dry DCM (30 mL), Dess-Martin periodinane (8.4 g, 19.8 mmol, 1.1 eq) was added and the reaction mixture was stirred at room temperature overnight. The reaction was quenched with saturated Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> aqueous solution and extracted with DCM. The organic layers were combined, washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo* to give a brown oil as a crude product, which was purified by flash chromatography (EtOAc/Hexanes, 10%, v/v) to afford the desired product as a colorless oil.

**Step 3.** A 25 mL three-necked flask was fitted with a reflux condenser, flame-dried, and charged with a magnetic stir bar and Grubbs II catalyst (19 mg, 0.022 mmol, 0.02 eq). In a separate vial, bromoketone starting material (1.12 mmol, 1 eq) and styrene (22.4 mmol, 20 eq) were mixed and added to the flask containing the Grubbs II catalyst. The mixture was heated to 80 °C for 16 h. The solid residue was dissolved in DCM, and triphenylphosphine oxide (0.61 g, 2.2 mmol, 100 eq with respect to catalyst) was added and stirred for 24 h. The mixture was concentrated *in vacuo* and purified by flash chromatography (EtOAc/Hexanes, 10%, v/v).



(*E*)-1-Bromo-7-phenylhept-6-en-2-one (**1j**)

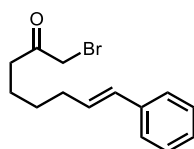
Brown oil. 18% yield over three steps.

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.35 – 7.28 (m, 4H), 7.23 – 7.19 (m, 1H), 6.40 (d, *J* = 15.8 Hz, 1H), 6.16 (dt, *J* = 15.8, 7.0 Hz, 1H), 3.88 (s, 2H), 2.71 (t, *J* = 7.2 Hz, 2H), 2.25 (qd, *J* = 7.1, 1.5 Hz, 2H), 1.83 (p, *J* = 7.3 Hz, 2H).

<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 202.1, 137.6, 131.1, 129.6, 128.7, 127.2, 126.1, 39.1, 34.4, 32.3, 23.4.

HRMS (GCMS-EI): *m/z* calcd for C<sub>13</sub>H<sub>15</sub>BrO [M]<sup>+</sup>: 266.0303, found: 266.0306.

IR: 2937.9, 1729.4, 1382.7, 1260.8, 1071.7, 969.1, 750.1, 692.6 (cm<sup>-1</sup>).



(*E*)-1-Bromo-8-phenyloct-7-en-2-one (**1k**)

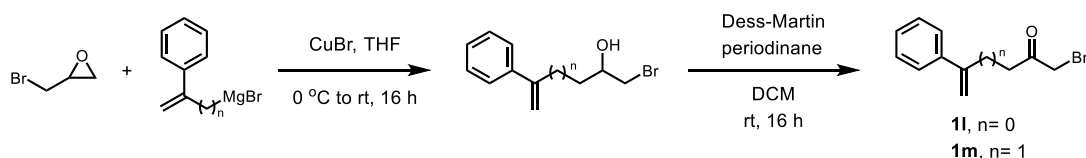
Light yellow oil. 26% yield over three steps.

$^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.35 – 7.28 (m, 4H), 7.21 – 7.18 (m, 1H), 6.39 (d,  $J = 15.8$  Hz, 1H), 6.20 (dt,  $J = 15.8, 6.9$  Hz, 1H), 3.88 (s, 2H), 2.69 (t,  $J = 7.3$  Hz, 2H), 2.24 (qd,  $J = 7.2, 1.5$  Hz, 2H), 1.72 – 1.66 (m, 2H), 1.53 – 1.47 (m, 2H).

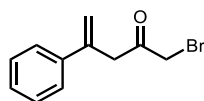
$^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )  $\delta$  202.2, 137.8, 130.4, 130.3, 128.6, 127.1, 126.1, 39.8, 34.4, 32.8, 28.8, 23.5.

HRMS (GCMS-EI):  $m/z$  calcd for  $\text{C}_{14}\text{H}_{17}\text{BrO}$   $[\text{M}]^+$ : 280.0468, found: 280.0463.

IR: 2932.6, 1713.6, 1448.5, 1275.8, 1260.7, 964.4, 748.5, 692.4 ( $\text{cm}^{-1}$ ).



Adapted from the method by Alam *et al.*<sup>11</sup> To a stirred suspension of CuBr (26 mg, 0.18 mmol, 0.1 eq) in dry THF (20 mL) was added freshly prepared Grignard reagent (in THF, 18 mmol, 1 eq) dropwise under nitrogen atmosphere at 0 °C and the mixture was stirred at 0 °C for 30 min. Epibromohydrin (1.5 mL, 18 mmol, 1 eq) was then added dropwise to the reaction mixture, which was warmed up to room temperature and further stirred over 16 h. The reaction was quenched with saturated  $\text{NH}_4\text{Cl}$  aqueous solution and extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated *in vacuo* to give a colorless oil. The residual oil was dissolved in dry DCM (30 mL), Dess-Martin periodinane (8.4 g, 19.8 mmol, 1.1 eq) was added and the reaction mixture was stirred at room temperature overnight. The reaction was quenched with saturated  $\text{Na}_2\text{S}_2\text{O}_3$  aqueous solution and extracted with DCM. The organic layers were combined, washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated *in vacuo* to give a brown oil as a crude product, which was purified by flash chromatography (EtOAc/Hexanes, 10%, *v/v*) to afford the desired product as a colorless oil.



1-Bromo-4-phenylpent-4-en-2-one (**1l**)

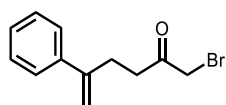
Purple oil. 35% yield over two steps.

$^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.41 – 7.39 (m, 2H), 7.36 – 7.28 (m, 3H), 5.65 (s, 1H), 5.27 (d,  $J = 1.3$  Hz, 1H), 3.91 (s, 2H), 3.85 (s, 2H).

$^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )  $\delta$  199.9, 140.6, 139.3, 128.8, 128.4, 125.9, 117.7, 47.1, 33.6.

HRMS (GCMS-EI):  $m/z$  calcd for  $C_{11}H_{11}BrO$   $[M]^+$ : 237.9984, found: 237.9988.

IR: 3026.9, 1721.1, 1626.5, 1390.6, 1275.7, 1047.7, 906.3, 755.4, 701.6 ( $cm^{-1}$ ).



1-Bromo-5-phenylhex-5-en-2-one (**1m**)

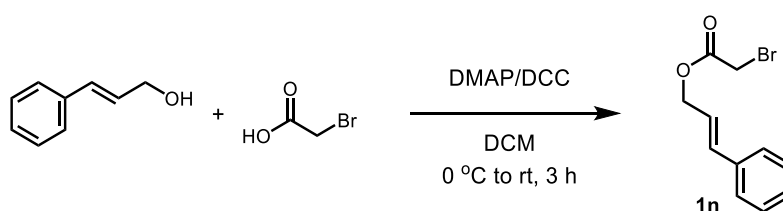
Clear oil. 40% yield over two steps.

$^1H$  NMR (500 MHz,  $CDCl_3$ )  $\delta$  7.40 – 7.38 (m, 2H), 7.36 – 7.33 (m, 2H), 7.31 – 7.27 (m, 1H), 5.31 (s, 1H), 5.10 (d,  $J = 1.3$  Hz, 1H), 3.84 (s, 2H), 2.89 – 2.77 (m, 4H).

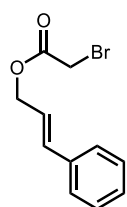
$^{13}C$  NMR (126 MHz,  $CDCl_3$ )  $\delta$  201.5, 146.7, 140.4, 128.6, 127.9, 126.2, 113.4, 38.8, 34.4, 29.6.

HRMS (GCMS-EI):  $m/z$  calcd for  $C_{12}H_{13}BrO$   $[M]^+$ : 252.0152, found: 252.0150.

IR: 2985.2, 1715.6, 1494.3, 1276.0, 1260.8, 1069.5, 898.6, 750.2, 702.2 ( $cm^{-1}$ ).



To a stirred solution of bromo acetic acid (97 mg, 0.7 mmol) in dry DCM (5 mL) was added 4-dimethylaminopyridine (DMAP, 37 mg, 0.3mmol), (*E*)-3-phenylprop-2-en-1-ol (67 mg, 0.5 mmol) and *N,N'*-dicyclohexylcarbodiimide (DCC, 144 mg, 0.7 mmol) under nitrogen atmosphere at 0 °C. The reaction mixture was warmed up to room temperature and further stirred for 3 h. Celite was added to the reaction mixture, and the reaction mixture was filtered after stirring for 30 min. The filtrate was collected and concentrated *in vacuo* to give the crude product, which was purified by flash chromatography (EtOAc/Hexanes, 10%, *v/v*) to afford the desired product as a colorless oil (59 mg, 46% yield).



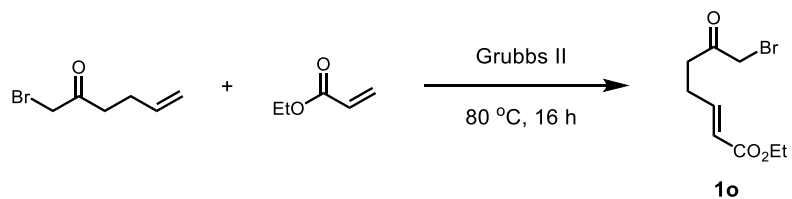
Cinnamyl 2-bromoacetate (**1n**)

$^1H$  NMR (500 MHz,  $CDCl_3$ )  $\delta$  7.43 – 7.38 (m, 2H), 7.36 – 7.31 (m, 2H), 7.30 – 7.26 (m, 1H), 6.70 (d,  $J = 15.9$  Hz, 1H), 6.29 (dt,  $J = 15.9, 6.6$  Hz, 1H), 4.83 (dd,  $J = 6.6, 1.4$  Hz, 2H), 3.88 (s, 2H).

$^{13}C$  NMR (126 MHz,  $CDCl_3$ )  $\delta$  167.2, 136.0, 135.4, 128.8, 128.5, 126.8, 122.1, 66.9, 26.0.

HRMS (GCMS-EI):  $m/z$  calcd for  $C_{11}H_{11}BrO_2$   $[M]^+$ : 253.9944, found: 253.9942.

IR: 3026.1, 1735.9, 1448.6, 1273.2, 1153.7, 1108.5, 962.6, 747.3, 691.8 ( $cm^{-1}$ ).



Ethyl (*E*)-7-bromo-6-oxohept-2-enoate (**1o**)

Compound (**1o**) was prepared by following the general metathesis procedure.

Brown solid. Yield: 21%.

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 6.91 (dt, *J* = 15.6, 6.8 Hz, 1H), 5.85 (dt, *J* = 15.6, 1.6 Hz, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 3.88 (s, 2H), 2.85 (t, *J* = 7.3 Hz, 2H), 2.52 (qd, *J* = 7.0, 1.6 Hz, 2H), 1.28 (t, *J* = 7.1 Hz, 3H).

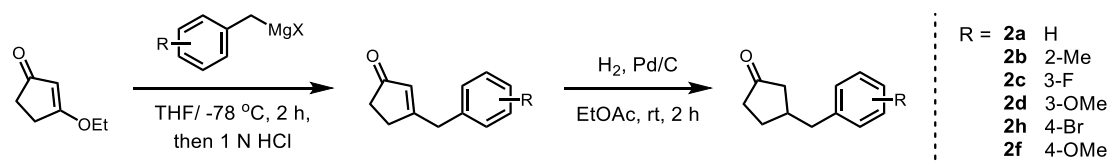
<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 200.6, 166.4, 146.3, 122.7, 60.5, 37.9, 34.0, 26.1, 14.4.

HRMS (GCMS-EI): *m/z* calcd for C<sub>9</sub>H<sub>13</sub>BrO<sub>3</sub> [M]<sup>+</sup>: 249.0121, found: 249.0119.

IR: 2983.0, 1709.5, 1654.8, 1367.9, 1268.1, 1172.4, 1038.74, 973.8, 857.6 (cm<sup>-1</sup>).

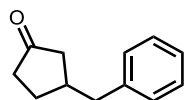


## Synthesis of reference compounds for cyclization reaction



Adapted from the method by Tuttle *et al.*<sup>7</sup> To a stirred freshly prepared Grignard reagent (2.9 mmol, 1.2 eq) in dry THF (10 mL) was added 3-ethoxycyclopent-2-enone (300 mg, 2.4 mmol, 1 eq) dropwise under N<sub>2</sub> atmosphere at -78 °C (dry ice in acetone) and the reaction mixture was stirred at -78 °C for 2 h. The reaction mixture was warmed up to -30 °C for 1 h, and then the reaction was quenched by the addition of a 1 N HCl until the pH 1. The solution was warmed up to room temperature, and the reaction mixture was extracted with Et<sub>2</sub>O. The organic layers were combined, washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated *in vacuo* to give an oil as a crude product, which was purified by flash chromatography (EtOAc/Hexanes, 30%, *v/v*) to afford the 3-(arylmethyl)cyclopent-2-enone as a colorless oil.

The resulting oil (1 mmol) was dissolved in EtOAc (5 mL), followed by the addition of Pd/C (10%, 10 mg), and the reaction was stirred under H<sub>2</sub> atmosphere (balloon) for 2 h at room temperature. After completion of the reaction, the reaction mixture was filtered through Celite and washed with EtOAc (5 mL). The filtrate was concentrated under vacuum to provide the pure product.



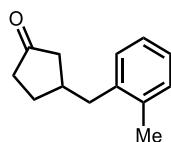
### 3-Benzylcyclopentan-1-one (**2a**)

Clear oil. 21% yield over two steps.

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.32 – 7.29 (m, 2H), 7.24 – 7.20 (m, 1H), 7.18 – 7.16 (m, 2H), 2.78 – 2.71 (m, 2H), 2.52 – 2.43 (m, 1H), 2.37 – 2.27 (m, 2H), 2.18 – 2.07 (m, 2H), 1.92 (ddd, *J* = 18.2, 10.0, 1.5 Hz, 1H), 1.67 – 1.58 (m, 1H).

<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 219.4, 140.2, 128.9, 128.6, 126.4, 45.1, 41.6, 39.0, 38.5, 29.2.

The NMR spectra is in agreement with published data.<sup>15</sup>



### 3-(2-Methylbenzyl)cyclopentan-1-one (**2b**)

Clear oil. 15% yield over two steps.

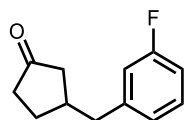
<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.17 – 7.09 (m, 4H), 2.79 – 2.71 (m, 2H), 2.53 – 2.43 (m, 1H), 2.38 – 2.30 (m, 2H), 2.32 (s, 3H), 2.19 – 2.08 (m, 2H), 1.94 (ddd, *J* = 18.2, 9.9, 1.5 Hz, 1H), 1.70 – 1.61 (m, 1H).

<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 219.4, 138.4, 136.0, 130.6, 129.6, 126.5, 126.0, 45.3, 38.7, 38.5, 37.7,

29.4, 19.6.

HRMS (GCMS-EI):  $m/z$  calcd for  $C_{13}H_{16}O$   $[M]^+$ : 188.1196, found: 188.1201.

IR: 2954.0, 1737.8, 1492.7, 1458.3, 1402.5, 1157.5, 743.7 ( $cm^{-1}$ ).



3-(3-Fluorobenzyl)cyclopentan-1-one (**2c**)

Clear oil. 30% yield over two steps.

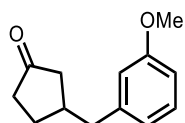
$^1H$  NMR (500 MHz,  $CDCl_3$ )  $\delta$  7.29 – 7.26 (m, 1H), 6.98 – 6.89 (m, 3H), 2.80 – 2.733 (m, 2H), 2.54 – 2.44 (m, 1H), 2.40 – 2.30 (m, 2H), 2.22 – 2.10 (m, 2H), 1.93 (dd,  $J = 17.7, 9.7$  Hz, 1H), 1.68 – 1.59 (m, 1H).

$^{13}C$  NMR (126 MHz,  $CDCl_3$ )  $\delta$  218.8, 163.0 (d,  $J = 245.7$  Hz), 142.7 (d,  $J = 7.1$  Hz), 130.0 (d,  $J = 8.3$  Hz), 124.6 (d,  $J = 2.7$  Hz), 115.7 (d,  $J = 20.8$  Hz), 113.3 (d,  $J = 21.0$  Hz), 44.9, 41.4, 38.8, 38.4, 29.2.

$^{19}F$  NMR (282 MHz,  $CDCl_3$ )  $\delta$  -113.5.

HRMS (GCMS-EI):  $m/z$  calcd for  $C_{12}H_{13}FO$   $[M]^+$ : 192.0954, found: 192.0950.

IR: 2962.3, 1738.2, 1587.1, 1448.4, 1275.6, 1252.7, 1140.8, 935.3, 874.3, 749.7, 693.1 ( $cm^{-1}$ ).



3-(3-Methoxybenzyl)cyclopentan-1-one (**2d**)

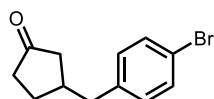
Clear oil. 25% yield over two steps.

$^1H$  NMR (500 MHz,  $CDCl_3$ )  $\delta$  7.22 (t,  $J = 7.8$  Hz, 1H), 6.77 – 6.71 (m, 3H), 3.80 (s, 3H), 2.75 – 2.68 (m, 2H), 2.52 – 2.42 (m, 1H), 2.37 – 2.27 (m, 2H), 2.18 – 2.07 (m, 2H), 1.91 (ddd,  $J = 18.3, 10.1, 1.6$  Hz, 1H), 1.66 – 1.57 (m, 1H).

$^{13}C$  NMR (126 MHz,  $CDCl_3$ )  $\delta$  219.4, 159.8, 141.8, 129.6, 121.3, 114.8, 111.4, 55.3, 45.1, 41.6, 38.9, 38.5, 29.2.

HRMS (GCMS-EI):  $m/z$  calcd for  $C_{13}H_{16}O_2$   $[M]^+$ : 204.1155, found: 204.1150.

IR: 2949.8, 1737.0, 1600.4, 1583.7, 1488.4, 1259.0, 1152.7, 1040.7, 746.9, 697.1 ( $cm^{-1}$ ).



3-(4-Bromobenzyl)cyclopentan-1-one (**2h**)

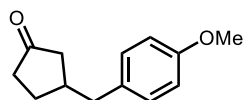
Clear oil. 12% yield over two steps.

$^1H$  NMR (500 MHz,  $CDCl_3$ )  $\delta$  7.41 (d,  $J = 8.3$  Hz, 2H), 7.04 (d,  $J = 8.4$  Hz, 2H), 2.73 – 2.65 (m, 2H), 2.48 – 2.38 (m, 1H), 2.35 – 2.28 (m, 2H), 2.18 – 2.04 (m, 2H), 1.88 (ddd,  $J = 18.2, 10.0, 1.5$  Hz, 1H), 1.64 – 1.55 (m, 1H).

$^{13}C$  NMR (126 MHz,  $CDCl_3$ )  $\delta$  218.9, 139.1, 131.6, 130.6, 120.2, 44.9, 41.0, 38.8, 38.4, 29.1..

HRMS (GCMS-EI):  $m/z$  calcd for  $C_{12}H_{13}BrO$   $[M]^+$ : 252.0156, found: 252.0150.

IR: 2922.6, 1735.0, 1487.2, 1402.4, 1156.6, 1070.3, 1010.8, 826.0, 797.4 ( $cm^{-1}$ ).



### 3-(4-Methoxybenzyl)cyclopentan-1-one (**2f**)

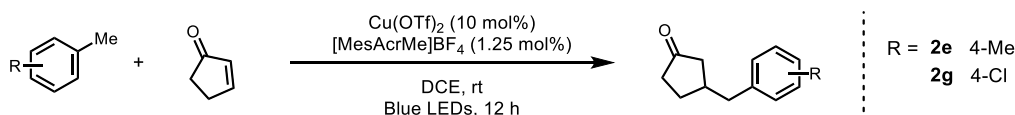
Clear oil. 32% yield over two steps.

$^1H$  NMR (500 MHz,  $CDCl_3$ )  $\delta$  7.08 (d,  $J = 8.5$  Hz, 2H), 6.84 (d,  $J = 8.6$  Hz, 2H), 3.79 (s, 3H), 2.74 – 2.62 (m, 2H), 2.51 – 2.24 (m, 3H), 2.20 – 2.04 (m, 2H), 1.90 (dd,  $J = 17.8, 9.5$  Hz, 1H), 1.67 – 1.53 (m, 1H).

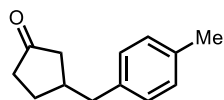
$^{13}C$  NMR (126 MHz,  $CDCl_3$ )  $\delta$  219.5, 158.2, 132.2, 129.8, 113.9, 55.4, 45.0, 40.7, 39.1, 38.5, 29.1.

HRMS (GCMS-EI):  $m/z$  calcd for  $C_{13}H_{16}O_2$   $[M]^+$ : 204.1153, found: 204.1150.

IR: 2917.0, 17335.8, 1611.3, 1510.4, 1243.7, 1157.2, 1032.4, 811.6, 753.8 ( $cm^{-1}$ ).



Adapted from method by Liu *et al.*<sup>16</sup> Starting material *p*-xylene or 1-chloro-4-methylbenzene (5 mmol, 5 eq),  $Cu(OTf)_2$  (72 mg, 0.5 mmol, 10 mol%) and  $[MesAcrMe]BF_4$  (50 mg, 0.0625 mmol, 1.25 mol%) were added to a flame-dried 9-dram vial. Anhydrous DCE (10 mL) was added followed by the cyclopentanone (1 eq) through a septa and the vial was stirred at room temperature overnight and 10 cm from 40 W Tuna Blue LED lights, cooled by two fans. The desired compound was purified by column chromatography (EtOAc/Hexanes, 10%,  $v/v$ ) as a clear colorless oil.



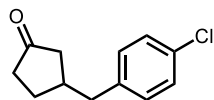
### 3-(4-Methylbenzyl)cyclopentan-1-one (**2e**)

Clear oil. 20% yield.

$^1H$  NMR (500 MHz,  $CDCl_3$ )  $\delta$  7.11 (d,  $J = 7.8$  Hz, 2H), 7.06 (d,  $J = 7.7$  Hz, 2H), 2.74 – 2.66 (m, 2H), 2.50 – 2.40 (m, 1H), 2.36 – 2.28 (m, 2H), 2.33 (s, 3H), 2.18 – 2.06 (m, 2H), 1.91 (dd,  $J = 18.1, 9.9$  Hz, 1H), 1.66 – 1.57 (m, 1H).

$^{13}C$  NMR (126 MHz,  $CDCl_3$ )  $\delta$  219.5, 137.0, 135.8, 129.2, 128.8, 45.1, 41.2, 39.0, 38.5, 29.2, 21.1.

The NMR spectra is in agreement with published data.<sup>16</sup>



3-(4-Chlorobenzyl)cyclopentan-1-one (**2g**)

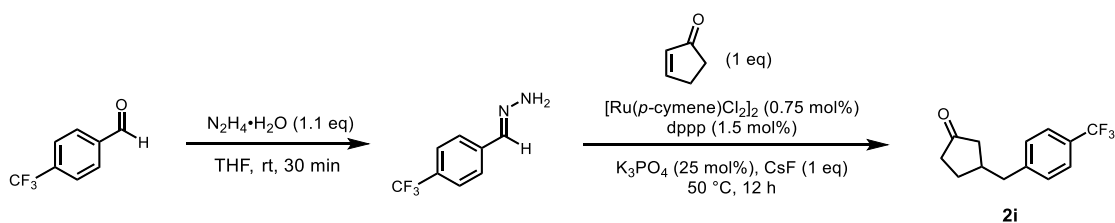
Clear oil. 10% yield.

$^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.27 (d,  $J = 7.9$  Hz, 2H), 7.10 (d,  $J = 8.3$  Hz, 2H), 2.75 – 2.67 (m, 2H), 2.48 – 2.39 (m, 1H), 2.36 – 2.29 (m, 2H), 2.19 – 2.06 (m, 2H), 1.89 (ddd,  $J = 18.2, 10.0, 1.5$  Hz, 1H), 1.63 – 1.57 (m, 1H).

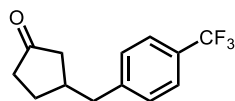
$^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )  $\delta$  219.0, 138.6, 132.1, 130.2, 128.7, 44.9, 40.9, 38.8, 38.4, 29.1.

HRMS (GCMS-EI):  $m/z$  calcd for  $\text{C}_{12}\text{H}_{13}\text{ClO}$   $[\text{M}]^+$ : 208.0657, found: 208.0655.

IR: 2923.4, 1734.7, 1490.4, 1404.9, 1275.8, 1093.0, 1014.7, 801.2, 750.8 ( $\text{cm}^{-1}$ ).



Adapted from method by Dai *et al.*<sup>17</sup> The *p*-trifluoromethyl benzaldehyde (1.64 mL, 12 mmol, 1 eq) was stirred in THF (5 mL) with hydrazine monohydrate (630  $\mu\text{L}$ , 13 mmol, 1.1 eq) for 30 min. In a separate flame-dried flask was added  $[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$  (46 mg, 0.075 mmol, 0.75 mol%), 1,3-bis(diphenylphosphino)propane (dppp, 62 mg, 0.15 mmol, 1.5 mol%),  $\text{K}_3\text{PO}_4$  (530 mg, 2.5 mmol, 25 mol%), and CsF (1.52 g, 10 mmol, 1 eq). The cyclopentenone (1 eq) was added to this flask followed by the hydrazine solution under  $\text{N}_2$ . The reaction was stirred at 50  $^\circ\text{C}$  overnight. The desired compound was purified by column chromatography (EtOAc/Hexanes, 10%, *v/v*).



3-(4-(Trifluoromethyl)benzyl)cyclopentan-1-one (**2i**)

Clear oil (79% yield).

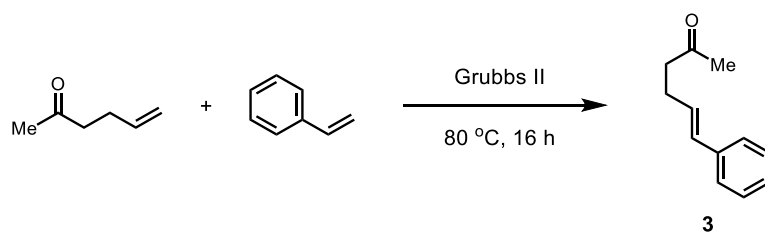
$^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.56 (d,  $J = 8.0$  Hz, 2H), 7.28 (d,  $J = 8.0$  Hz, 2H), 2.85 – 2.76 (m, 2H), 2.53 – 2.43 (m, 1H), 2.37 – 2.28 (m, 2H), 2.20 – 2.07 (m, 2H), 1.91 (ddd,  $J = 18.2, 10.1, 1.5$  Hz, 1H), 1.65 – 1.57 (m, 1H).

$^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )  $\delta$  218.6, 144.3 (d,  $J = 1.2$  Hz), 129.2, 128.8 (q,  $J = 32.4$  Hz), 125.6 (q,  $J = 3.8$  Hz), 124.4 (q,  $J = 271.8$  Hz), 44.9, 41.4, 38.7, 38.4, 29.2.

$^{19}\text{F NMR}$  (376 MHz,  $\text{CDCl}_3$ )  $\delta$  -62.4.

HRMS (GCMS-EI):  $m/z$  calcd for  $\text{C}_{13}\text{H}_{13}\text{F}_3\text{O}$   $[\text{M}]^+$ : 242.0923, found: 242.0919.

IR: 2961.6, 1739.2, 1618.3, 1322.2, 1158.1, 1115.9, 1065.4, 1018.3, 818.5, 754.6 ( $\text{cm}^{-1}$ ).



(*E*)-6-phenylhex-5-en-2-one (**3**)

Compound (**3**) was prepared by following the general metathesis procedure.

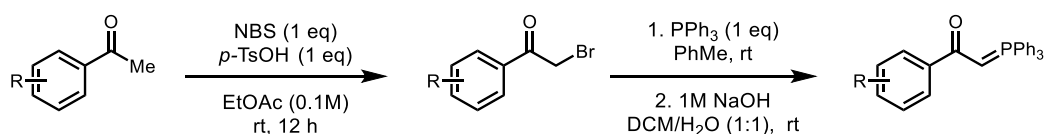
Clear oil. Yield: 31%.

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.34 – 7.27 (m, 4H), 7.22 – 7.18 (m, 1H), 6.41 (d,  $J$  = 15.9 Hz, 1H), 6.20 (dt,  $J$  = 15.8, 6.8 Hz, 1H), 2.62 (t,  $J$  = 7.3 Hz, 2H), 2.49 (qd,  $J$  = 6.6, 1.3 Hz, 2H), 2.17 (s, 3H).

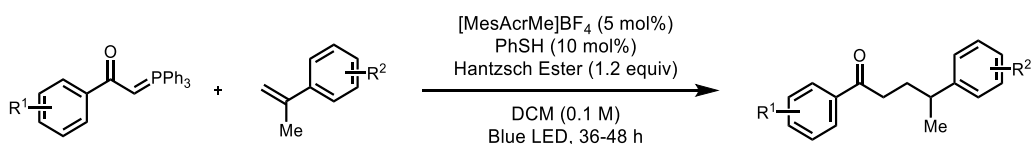
<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)  $\delta$  208.2, 137.5, 130.9, 128.9, 128.6, 127.2, 126.1, 43.3, 30.2, 27.2.

The NMR spectra is in agreement with published data.<sup>18</sup>

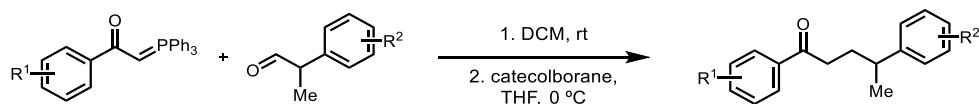
### Synthesis of racemic intermolecular reference products.



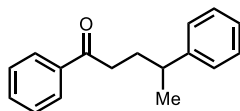
To obtain the Wittig reagent, the corresponding ketone (1 eq), *N*-bromosuccinamide (1 eq) and *p*-toluenesulfonic acid (1 eq) were dissolved in EtOAc and stirred at room temperature overnight. Upon complete conversion of starting material (the starting material and bromoacetone are often difficult to separate), the corresponding bromoacetone was purified *via* column chromatography. To the bromoacetone (1 eq) was added PPh<sub>3</sub> (1 eq) and PhMe. This mixture was allowed to stir at room temperature for 2 h, over which the mixture became thick with white precipitate. The phosphonium bromide salt was isolated by filtration washed with Et<sub>2</sub>O three times. The crude white solid was redissolved in CH<sub>2</sub>Cl<sub>2</sub> in an Erlenmeyer flask and a roughly equal volume of 1 M NaOH aqueous solution was added. This mixture was stirred for 2 h before the organic layer was dried with Na<sub>2</sub>SO<sub>4</sub> and the solvent removed by rotary evaporation to give the desired Wittig reagent.



**General procedure 6** adapted from method by Das *et al.*<sup>19</sup> In a flame-dried 9-dram vial equipped with a magnetic stir bar was added the corresponding Wittig reagent (1.2 mmol, 1 eq), 9-mesityl-10-methylacridinium tetrafluoroborate (24 mg 0.06 mmol, 5 mol%), Hantzsch ester (366 mg 1.44 mmol, 1.2 eq). The vial was sealed with a septa and electrical tape. Following this, dry CH<sub>2</sub>Cl<sub>2</sub> (12 mL) was added to the vial through the septa and the entire vial was freeze-pump-thawed three times. Then, the corresponding styrene (3.6 mmol, 1.44 mmol, 3 eq) was added followed by thiophenol (12  $\mu$ L, 0.12 mmol, 10 mol%). The reaction was allowed to stir, while being cooled using a fan, for 36-48 h, with 10 cm away from 40 W Tuna Blue LED lights. Upon completion of the reaction, the solvent was removed by rotary evaporation and the desired product was obtained by column chromatography and or preparative TLC. All compounds were made using general procedure 6 unless otherwise specified.



**General procedure 7.** In a 9-dram vial equipped with a magnetic stir bar was added the corresponding Wittig reagent (1.2 mmol, 1 eq). The solid was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (5 mL), before adding the corresponding aldehyde (1.2 mmol, 1 eq). This mixture was stirred until completion by TLC and the solvent was removed by rotary evaporation. The desired alkene was obtained by column chromatography and or prep TLC. The alkene was then dissolved in THF (12 mL), cooled to 0 °C and catecholborane was added dropwise at 0 °C. This mixture was allowed to stir overnight. The solvent was removed by rotary evaporation. The desired alkene was obtained by column chromatography and or preparative TLC.



1,4-Diphenylpentan-1-one (**8a**)

White solid (46% yield).

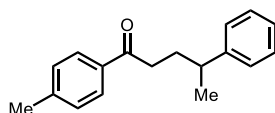
$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.86 – 7.84 (m, 2H), 7.52 (t,  $J = 7.4$  Hz, 1H), 7.41 (t,  $J = 7.8$  Hz, 2H), 7.34 – 7.28 (m, 2H), 7.24 – 7.18 (m, 3H), 2.92 – 2.75 (m, 3H), 2.12 – 2.04 (m, 1H), 2.04 – 1.95 (m, 1H), 1.32 (d,  $J = 6.9$  Hz, 3H).

$^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  200.5, 146.7, 137.1, 133.0, 128.6, 128.1, 127.2, 126.3, 39.7, 36.9, 32.6, 22.7.

HRMS (ESI):  $m/z$  calcd for  $\text{C}_{17}\text{H}_{19}\text{O}$   $[\text{M}+\text{H}]^+$ : 239.1430, found: 239.1429.

IR: 3026, 2961, 1678, 1579, 1493, 1447, 1378, 1273, 1214, 978, 750, 700 ( $\text{cm}^{-1}$ ).

The NMR spectra is in agreement with published data.<sup>19</sup>



4-Phenyl-1-(*p*-tolyl)pentan-1-one (**8b**)

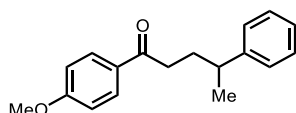
Clear colorless oil (19% yield).

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.75 (d,  $J = 8.2$  Hz, 2H), 7.34 – 7.28 (m, 2H), 7.24 – 7.18 (m, 5H), 2.90 – 2.72 (m, 3H), 2.39 (s, 3H), 2.12 – 2.03 (m, 1H), 2.02 – 1.93 (m, 1H), 1.31 (d,  $J = 7.0$  Hz, 3H).

$^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  200.2, 146.7, 143.8, 134.6, 129.3, 128.6, 128.3, 127.2, 126.3, 39.7, 36.7, 32.7, 22.7, 21.7.

HRMS (ESI):  $m/z$  calcd for  $\text{C}_{18}\text{H}_{21}\text{O}$   $[\text{M}+\text{H}]^+$ : 253.1587, found: 253.1590.

IR: 2923, 1680, 1606, 1493, 1452, 1265, 1180, 735, 700 ( $\text{cm}^{-1}$ ).



1-(4-Methoxyphenyl)-4-phenylpentan-1-one (**8c**)

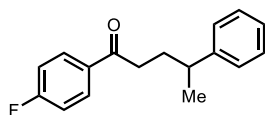
Clear colorless oil (28% yield).

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.88 – 7.79 (m, 2H), 7.34 – 7.27 (m, 2H), 7.24 – 7.17 (m, 3H), 6.92 – 6.84 (m, 2H), 3.85 (s, 3H), 2.86 – 2.70 (m, 3H), 2.12 – 1.92 (m, 2H), 1.31 (d,  $J = 6.9$  Hz, 3H).

$^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  199.1, 163.4, 146.8, 130.4, 130.2, 128.6, 127.2, 126.3, 113.7, 55.6, 39.7, 36.5, 32.8, 22.7.

HRMS (ESI):  $m/z$  calcd for  $\text{C}_{18}\text{H}_{21}\text{O}_2$   $[\text{M}+\text{H}]^+$ : 269.1536, found: 269.1540.

IR: 2960, 1673, 1598, 1576, 1508, 1452, 1309, 1254, 1168, 1028, 838, 762, 700 ( $\text{cm}^{-1}$ ).



1-(4-Fluorophenyl)-4-phenylpentan-1-one (**8d**)

Clear colorless oil (24% yield).

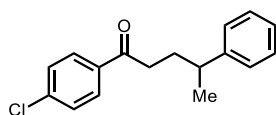
$^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.89 – 7.84 (m, 2H), 7.35 – 7.28 (m, 2H), 7.20 (d,  $J = 8.0$  Hz, 3H), 7.11 – 7.03 (m, 2H), 2.88 – 2.71 (m, 3H), 2.12 – 2.03 (m, 1H), 2.03 – 1.93 (m, 1H), 1.31 (d,  $J = 7.0$  Hz, 3H).

$^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )  $\delta$  198.7, 165.6 (d,  $J = 254.4$  Hz), 146.4, 133.4 (d,  $J = 3.0$  Hz), 130.6 (d,  $J = 9.3$  Hz), 128.5, 127.1, 126.3, 115.6 (d,  $J = 21.9$  Hz), 39.5, 36.6, 32.5, 22.6.

$^{19}\text{F NMR}$  (376 MHz,  $\text{CDCl}_3$ ): –105.7 (s).

HRMS (ESI):  $m/z$  calcd for  $\text{C}_{17}\text{H}_{18}\text{FO}$   $[\text{M}+\text{H}]^+$ : 257.1336, found: 257.1334.

The NMR spectra is in agreement with published data.<sup>19</sup>



1-(4-Chlorophenyl)-4-phenylpentan-1-one (**8e**)

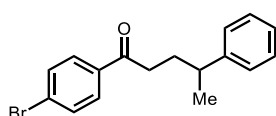
Clear colorless oil (2% yield).

$^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.77 (d,  $J = 8.7$  Hz, 2H), 7.38 (d,  $J = 8.7$  Hz, 2H), 7.31 (t,  $J = 7.6$  Hz, 2H), 7.24 – 7.18 (m, 3H), 2.88 – 2.70 (m, 3H), 2.12 – 2.03 (m, 1H), 2.02 – 1.93 (m, 1H), 1.31 (d,  $J = 6.9$  Hz, 3H).

$^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )  $\delta$  199.2, 146.5, 139.4, 135.4, 129.6, 128.9, 128.7, 127.2, 126.4, 39.6, 36.8, 32.5, 22.7.

HRMS (ESI):  $m/z$  calcd for  $\text{C}_{17}\text{H}_{18}\text{ClO}$   $[\text{M}+\text{H}]^+$ : 273.1041, found: 273.1043.

IR: 2999, 2967, 1687, 1590, 1092, 701 ( $\text{cm}^{-1}$ ).



1-(4-Bromophenyl)-4-phenylpentan-1-one (**8f**)

Clear colorless oil (17% yield).

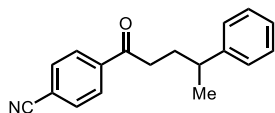
$^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.73 – 7.66 (m, 2H), 7.58 – 7.52 (m, 2H), 7.34 – 7.28 (m, 2H), 7.24 – 7.17 (m, 3H), 2.87 – 2.70 (m, 3H), 2.11 – 2.03 (m, 1H), 2.02 – 1.93 (m, 1H), 1.31 (d,  $J = 6.9$  Hz, 3H).

$^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )  $\delta$  199.4, 146.5, 135.8, 131.9, 129.7, 128.7, 128.2, 127.2, 126.4, 39.6, 36.8, 32.5, 22.7.

HRMS (ESI):  $m/z$  calcd for  $\text{C}_{17}\text{H}_{18}\text{BrO}$   $[\text{M}+\text{H}]^+$ : 317.0536, found: 317.0535.

IR: 2923, 1683, 1584, 1493, 1212, 1007, 982, 788, 758, 700 ( $\text{cm}^{-1}$ ).





1-(4-Cyanophenyl)-4-phenylpentan-1-one (**8g**)

Prepared using general procedure 7.

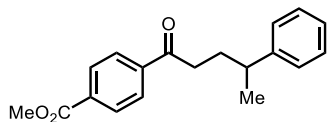
Clear colorless oil (15% yield).

$^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.87 – 7.79 (m, 2H), 7.67 – 7.61 (m, 2H), 7.24 (t,  $J = 7.5$  Hz, 2H), 7.17 – 7.10 (m, 3H), 2.85 – 2.66 (m, 3H), 2.07 – 1.96 (m, 1H), 1.96 – 1.86 (m, 1H), 1.25 (d,  $J = 6.9$  Hz, 3H).

$^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )  $\delta$  199.0, 146.2, 140.0, 132.6, 128.7, 128.5, 127.2, 126.5, 118.1, 116.3, 39.6, 37.1, 32.3, 22.7.

HRMS (ESI):  $m/z$  calcd for  $\text{C}_{18}\text{H}_{18}\text{NO}$   $[\text{M}+\text{H}]^+$ : 264.1383, found: 264.1379.

IR: 2960, 2231, 1689, 1605, 1493, 1452, 1403, 1213, 983, 764, 700 ( $\text{cm}^{-1}$ ).



Methyl 4-(4-phenylpentanoyl)benzoate (**8h**)

Prepared using general procedure 7.

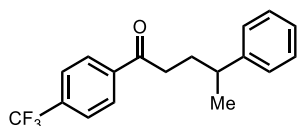
Clear colorless oil (15% yield).

$^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.10 – 8.03 (m, 2H), 7.91 – 7.85 (m, 2H), 7.34 – 7.28 (m, 2H), 7.23 – 7.17 (m, 3H), 3.94 (s, 3H), 2.92 – 2.77 (m, 3H), 2.12 – 2.05 (m, 1H), 2.04 – 1.95 (m, 1H), 1.32 (d,  $J = 6.9$  Hz, 3H).

$^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )  $\delta$  200.0, 166.4, 146.5, 140.3, 133.8, 129.9, 128.7, 128.0, 127.2, 126.4, 52.6, 39.6, 37.2, 32.4, 22.8.

HRMS (DART-MS):  $m/z$  calcd for  $\text{C}_{19}\text{H}_{21}\text{O}_3$   $[\text{M}+\text{H}]^+$ : 297.1485, found 297.1487.

IR: 2958, 2926, 1720, 1573, 1438, 1377, 1211, 1107, 981, 870, 759, 698 ( $\text{cm}^{-1}$ ).



4-Phenyl-1-(4-(trifluoromethyl)phenyl)pentan-1-one (**8i**)

Clear colorless oil (11% yield).

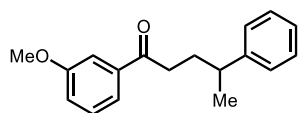
$^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.93 (d,  $J = 8.8$  Hz, 2H), 7.68 (d,  $J = 8.0$  Hz, 2H), 7.35 – 7.29 (m, 2H), 7.25 – 7.19 (m, 3H), 2.96 – 2.74 (m, 3H), 2.15 – 2.06 (m, 1H), 2.05 – 1.96 (m, 1H), 1.33 (d,  $J = 6.9$  Hz, 3H).

$^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )  $\delta$  199.3, 146.3, 139.6 (q,  $J = 1.2$  Hz), 134.2 (q,  $J = 32.6$  Hz), 128.6, 128.3, 127.8, 126.4, 125.6 (q,  $J = 3.7$  Hz), 123.63 (q,  $J = 272.6$  Hz), 39.5, 37.0, 32.3, 22.6.

$^{19}\text{F NMR}$  (376 MHz,  $\text{CDCl}_3$ )  $\delta$  –63.1.

HRMS (ESI):  $m/z$  calcd for  $\text{C}_{18}\text{H}_{18}\text{F}_3\text{O}$   $[\text{M}+\text{H}]^+$ : 307.1304, found: 307.1308.

IR: 2960, 2923, 1689, 1410, 1322, 1167, 1121, 1107, 1065, 1014, 984, 765, 698 ( $\text{cm}^{-1}$ ).



1-(3-Methoxyphenyl)-4-phenylpentan-1-one (**8j**)

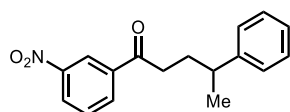
Clear colorless oil (9% yield).

$^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.44 – 7.37 (m, 2H), 7.35 – 7.28 (m, 3H), 7.21 (d,  $J = 6.8$  Hz, 3H), 7.09 – 7.04 (m, 1H), 3.83 (s, 3H), 2.90 – 2.74 (m, 3H), 2.11 – 1.94 (m, 2H), 1.31 (d,  $J = 6.9$  Hz, 3H).

$^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )  $\delta$  200.3, 159.9, 146.7, 138.5, 129.6, 128.7, 127.2, 126.3, 120.8, 119.5, 112.4, 55.6, 39.7, 37.0, 32.7, 22.7.

HRMS (ESI):  $m/z$  calcd for  $\text{C}_{18}\text{H}_{21}\text{O}_2$ : 269.1536  $[\text{M}+\text{H}]^+$ , found: 269.1535.

IR: 2959, 1682, 1582, 1451, 1261, 1042, 766, 700 ( $\text{cm}^{-1}$ ).



1-(3-Nitrophenyl)-4-phenylpentan-1-one (**8k**)

Prepared using general procedure 7.

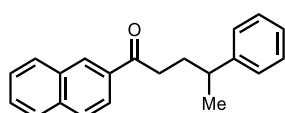
Clear colorless oil (15% yield).

$^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.65 (t,  $J = 2.0$  Hz, 1H), 8.38 (ddd,  $J = 8.2, 2.3, 1.1$  Hz, 1H), 8.16 (dt,  $J = 7.8, 1.4$  Hz, 1H), 7.62 (t,  $J = 8.0$  Hz, 1H), 7.33 – 7.29 (m, 2H), 7.23 – 7.19 (m, 3H), 2.97 – 2.78 (m, 3H), 2.16 – 1.96 (m, 2H), 1.33 (d,  $J = 6.9$  Hz, 3H).

$^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )  $\delta$  198.1, 148.6, 146.2, 138.3, 133.7, 129.9, 128.8, 127.3, 127.2, 126.5, 123.0, 39.6, 37.1, 32.3, 22.8.

HRMS (GCMS-EI):  $m/z$  calcd for  $\text{C}_{17}\text{H}_{17}\text{NO}_3$   $[\text{M}]^+$ : 283.1208, found: 283.1208.

IR: 2961, 2926, 1691, 1529, 1493, 1451, 1275, 1259, 1081, 1019, 909, 762, 694 ( $\text{cm}^{-1}$ ).



1-(Naphthalen-2-yl)-4-phenylpentan-1-one (**8l**)

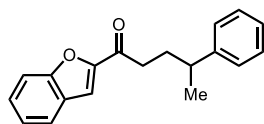
Clear colorless oil (23% yield).

$^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.30 (d,  $J = 1.7$  Hz, 1H), 7.95 (dd,  $J = 8.6, 1.8$  Hz, 1H), 7.90 (d,  $J = 8.6$  Hz, 1H), 7.86 (d,  $J = 8.4$  Hz, 2H), 7.58 (ddd,  $J = 8.2, 6.8, 1.4$  Hz, 1H), 7.53 (ddd,  $J = 8.0, 6.8, 1.3$  Hz, 1H), 7.36 – 7.30 (m, 2H), 7.26 – 7.20 (m, 3H), 3.05 – 2.89 (m, 2H), 2.89 – 2.80 (m, 1H), 2.19 – 2.01 (m, 2H), 1.34 (d,  $J = 7.0$  Hz, 3H).

$^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )  $\delta$  200.5, 146.7, 135.6, 134.4, 132.6, 129.8, 129.7, 128.7, 128.5, 127.9, 127.3, 126.8, 126.4, 124.0, 39.7, 36.9, 32.9, 22.8.

HRMS (ESI):  $m/z$  calcd for  $\text{C}_{21}\text{H}_{21}\text{O}$   $[\text{M}+\text{H}]^+$ : 289.1587, found: 289.1589.

IR: 2947, 1680, 1625, 141, 1372, 1277, 1173, 797, 762, 747, 700 ( $\text{cm}^{-1}$ ).



1-(Benzofuran-2-yl)-4-phenylpentan-1-one (**8m**)

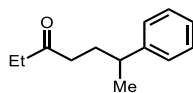
Clear colorless oil (23% yield).

$^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.67 (d,  $J = 7.9$  Hz, 1H), 7.55 (dd,  $J = 8.5, 0.9$  Hz, 1H), 7.46 (ddd,  $J = 8.4, 7.1, 1.3$  Hz, 1H), 7.36 (d,  $J = 1.1$  Hz, 1H), 7.34 – 7.27 (m, 3H), 7.22 (d,  $J = 7.1$  Hz, 3H), 2.93 – 2.75 (m, 3H), 2.16 – 1.99 (m, 2H), 1.33 (d,  $J = 6.9$  Hz, 3H).

$^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )  $\delta$  191.5, 155.7, 152.6, 146.5, 128.7, 128.3, 127.3, 127.1, 126.4, 124.0, 123.4, 112.8, 112.6, 39.7, 37.2, 32.5, 22.7.

HRMS (ESI):  $m/z$  calcd for  $\text{C}_{19}\text{H}_{19}\text{O}_2$   $[\text{M}+\text{H}]^+$ : 279.1380, found: 279.1384.

IR: 3027, 2959, 2920, 1680, 159, 1493, 1380, 1281, 1157, 996, 920, 764, 697 ( $\text{cm}^{-1}$ ).



6-Phenylheptan-3-one (**8n**)

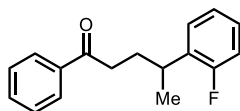
Clear colorless oil (60% yield).

$^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.29 (t,  $J = 7.5$  Hz, 2H), 7.22 – 7.13 (m, 3H), 2.73 – 2.61 (m, 1H), 2.32 (q,  $J = 7.4$  Hz, 2H), 2.34 – 2.18 (m, 2H), 1.96 – 1.78 (m, 2H), 1.26 (d,  $J = 6.9$  Hz, 3H), 0.99 (t,  $J = 7.3$  Hz, 3H).

$^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )  $\delta$  211.8, 146.7, 128.6, 127.2, 126.3, 40.6, 39.6, 36.1, 32.1, 22.6, 8.0.

HRMS (ESI):  $m/z$  calcd for  $\text{C}_{17}\text{H}_{19}\text{O}$   $[\text{M}+\text{H}]^+$ : 191.1430, found: 191.1425.

IR: 3026, 2963, 2926, 1712, 1594, 1453, 1275, 1260, 759, 700 ( $\text{cm}^{-1}$ ).



4-(2-Fluorophenyl)-1-phenylpentan-1-one (**8o**)

Clear colorless oil (85% yield).

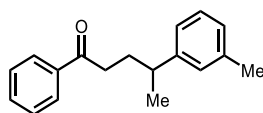
$^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.89 – 7.84 (m, 2H), 7.56 – 7.50 (m, 1H), 7.46 – 7.38 (m, 2H), 7.26 – 7.21 (m, 1H), 7.21 – 7.14 (m, 1H), 7.10 (td,  $J = 7.5, 1.4$  Hz, 1H), 7.01 (ddd,  $J = 10.6, 8.1, 1.4$  Hz, 1H), 3.22 – 3.15 (m, 1H), 2.94 (ddd,  $J = 17.2, 9.6, 6.1$  Hz, 1H), 2.81 (ddd,  $J = 17.0, 9.5, 5.4$  Hz, 1H), 2.14 – 1.99 (m, 2H), 1.33 (d,  $J = 7.0$  Hz, 3H).

$^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )  $\delta$  200.2, 161.0 (d,  $J = 244.4$  Hz), 137.1, 133.2, 133.1, 128.7, 128.1, 128.1, 127.6 (d,  $J = 8.3$  Hz), 124.4 (d,  $J = 3.5$  Hz), 115.5 (d,  $J = 23.0$  Hz), 36.8, 32.3, 31.4, 21.4.

$^{19}\text{F NMR}$  (376 MHz,  $\text{CDCl}_3$ )  $\delta$  -118.6 (s).

IR: 2965, 1684, 1580, 1490, 1449, 1227, 1002, 753, 690 ( $\text{cm}^{-1}$ ).

HRMS (ESI):  $m/z$  calcd for  $\text{C}_{17}\text{H}_{18}\text{FO}$   $[\text{M}+\text{H}]^+$ : 257.1336, found: 257.1336.



1-Phenyl-4-(*m*-tolyl)pentan-1-one (**8p**)

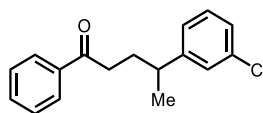
Clear colorless oil (39% yield).

$^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.89 – 7.82 (m, 2H), 7.56 – 7.50 (m, 1H), 7.45 – 7.38 (m, 2H), 7.24 – 7.16 (m, 1H), 7.05 – 6.97 (m, 3H), 2.91 – 2.72 (m, 3H), 2.33 (s, 3H), 2.11 – 1.94 (m, 2H), 1.30 (d,  $J = 6.9$  Hz, 3H).

$^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )  $\delta$  200.6, 146.6, 138.2, 137.1, 133.0, 128.6, 128.5, 128.2, 128.0, 127.1, 124.2, 39.6, 36.9, 32.6, 22.8, 21.6.

IR: 2959, 1682, 1598, 1448, 1362, 1205, 1179, 1002, 974, 784, 744, 794, 690 ( $\text{cm}^{-1}$ ).

HRMS (ESI):  $m/z$  calcd for  $\text{C}_{18}\text{H}_{21}\text{O}$   $[\text{M}+\text{H}]^+$ : 253.1587, found: 253.1590.



4-(3-Chlorophenyl)-1-phenylpentan-1-one (**8q**)

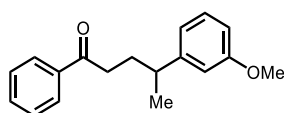
Clear colorless oil (9% yield).

$^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.89 – 7.83 (m, 2H), 7.56 – 7.50 (m, 1H), 7.46 – 7.40 (m, 2H), 7.25 – 7.16 (m, 3H), 7.09 (dt,  $J = 7.6, 1.5$  Hz, 1H), 2.91 – 2.75 (m, 3H), 2.11 – 2.04 (m, 1H), 2.01 – 1.94 (m, 1H), 1.30 (d,  $J = 6.9$  Hz, 3H).

$^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )  $\delta$  200.2, 148.9, 137.0, 134.4, 133.1, 129.9, 128.7, 128.1, 127.4, 126.6, 125.5, 39.5, 36.6, 32.4, 22.6.

IR: 2961, 1682, 1596, 1572, 1448, 1275, 1214, 1080, 1001, 974, 784, 742, 690 ( $\text{cm}^{-1}$ ).

HRMS (ESI):  $m/z$  calcd for  $\text{C}_{17}\text{H}_{18}\text{OCl}$   $[\text{M}+\text{H}]^+$ : 273.1041, found: 273.1044.



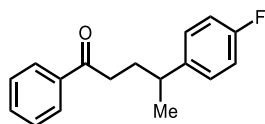
4-(3-Methoxyphenyl)-1-phenylpentan-1-one (**8r**)

Clear colorless oil (3% yield).

$^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.90 – 7.82 (m, 2H), 7.58 – 7.48 (m, 1H), 7.44 – 7.37 (m, 2H), 7.25 – 7.19 (m, 1H), 6.80 (dt,  $J = 7.7, 1.4$  Hz, 1H), 6.78 – 6.72 (m, 2H), 3.79 (s, 3H), 2.92 – 2.73 (m, 3H), 2.12 – 2.03 (m, 1H), 2.03 – 1.93 (m, 1H), 1.31 (d,  $J = 6.9$  Hz, 3H).

$^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )  $\delta$  200.5, 159.9, 148.4, 137.1, 133.0, 129.6, 128.6, 128.1, 119.7, 113.1, 111.4, 55.3, 39.7, 36.8, 32.5, 22.7.

HRMS (ESI):  $m/z$  calcd for  $\text{C}_{18}\text{H}_{21}\text{O}_2$   $[\text{M}+\text{H}]^+$ : 269.1536, found: 269.1536.



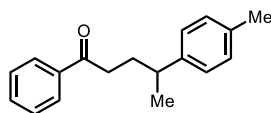
4-(4-Fluorophenyl)-1-phenylpentan-1-one (**8s**)

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.89 – 7.80 (m, 2H), 7.57 – 7.50 (m, 1H), 7.46 – 7.38 (m, 2H), 7.19 – 7.11 (m, 2H), 6.99 (t,  $J = 8.5$  Hz, 2H), 2.91 – 2.74 (m, 3H), 2.12 – 2.02 (m, 1H), 2.00 – 1.90 (m, 1H), 1.29 (d,  $J = 6.9$  Hz, 3H).

$^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  200.3, 161.5 (d,  $J = 243.6$  Hz), 142.3 (d,  $J = 3.2$  Hz) 137.1, 133.1, 128.7, 128.5 (d,  $J = 7.8$  Hz), 128.1, 115.37 (d,  $J = 21.0$  Hz), 38.9, 36.7, 32.7, 22.8.

$^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ )  $\delta$  -117.3.

The NMR spectra is in agreement with published data.<sup>10</sup>



1-Phenyl-4-(p-tolyl)pentan-1-one (**8t**)

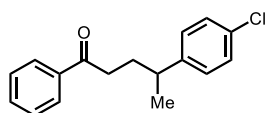
Clear colorless oil (12% yield).

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.89 – 7.82 (m, 2H), 7.55 – 7.49 (m, 1H), 7.44 – 7.38 (m, 2H), 7.14 – 7.07 (m, 4H), 2.91 – 2.72 (m, 3H), 2.33 (s, 3H), 2.10 – 2.02 (m, 1H), 2.01 – 1.93 (m, 1H), 1.29 (d,  $J = 6.9$  Hz, 3H).

$^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  200.6, 143.6, 137.1, 135.8, 133.0, 129.3, 128.6, 128.2, 127.1, 39.3, 36.9, 32.6, 22.9, 21.1.

HRMS (ESI):  $m/z$  calcd for  $\text{C}_{18}\text{H}_{21}\text{O}$   $[\text{M}+\text{H}]^+$ : 253.1587, found: 253.1589.

IR: 2958, 1682, 1597, 1580, 1514, 1448, 1362, 1213, 1179, 1002, 817, 744, 700 ( $\text{cm}^{-1}$ ).



4-(4-Chlorophenyl)-1-phenylpentan-1-one (**8u**)

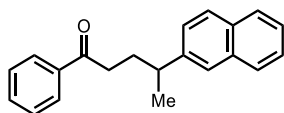
Clear colorless oil (9% yield).

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.87 – 7.83 (m, 2H), 7.54 (t,  $J = 7.4$  Hz, 1H), 7.42 (t,  $J = 7.7$  Hz, 2H), 7.29 – 7.26 (m, 2H), 7.17 – 7.11 (m, 2H), 2.90 – 2.74 (m, 3H), 2.11 – 2.02 (m, 1H), 2.00 – 1.91 (m, 1H), 1.29 (d,  $J = 6.9$  Hz, 3H).

$^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  200.2, 145.2, 137.0, 133.1, 131.9, 128.8, 128.7, 128.6, 128.1, 39.1, 36.6, 32.4, 22.7.

HRMS (ESI):  $m/z$  calcd for  $\text{C}_{17}\text{H}_{18}\text{ClO}$   $[\text{M}+\text{H}]^+$ : 273.1041, found: 273.1041.

The NMR spectra is in agreement with published data.<sup>10</sup>



4-(Naphthalen-2-yl)-1-phenylpentan-1-one (**8v**)

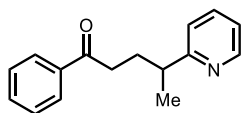
Clear colorless oil (89% yield).

$^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.85 – 7.77 (m, 5H), 7.65 – 7.61 (m, 1H), 7.52 – 7.48 (m, 1H), 7.48 – 7.42 (m, 2H), 7.41 – 7.36 (m, 3H), 3.02 – 2.94 (m, 1H), 2.94 – 2.78 (m, 2H), 2.22 – 2.07 (m, 2H), 1.40 (d,  $J = 6.9$  Hz, 3H).

$^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )  $\delta$  200.5, 144.1, 137.1, 133.7, 133.0, 132.5, 128.6, 128.4, 128.1, 127.7, 127.7, 126.1, 125.7, 125.6, 125.4, 39.8, 36.9, 32.4, 22.8.

HRMS (ESI):  $m/z$  calcd for  $\text{C}_{21}\text{H}_{21}\text{O}$   $[\text{M}+\text{H}]^+$ : 289.1587, found: 289.1593.

IR: 2959, 1682, 1598, 1582, 1258, 1208, 1042, 781, 745, 691 ( $\text{cm}^{-1}$ ).



1-Phenyl-4-(pyridin-2-yl)pentan-1-one (**8w**)

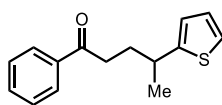
Clear colorless oil (14% yield).

$^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.56 (ddd,  $J = 4.8, 1.9, 0.9$  Hz, 1H), 7.92 – 7.83 (m, 2H), 7.61 (td,  $J = 7.6, 1.9$  Hz, 1H), 7.56 – 7.50 (m, 1H), 7.45 – 7.38 (m, 2H), 7.17 (dt,  $J = 7.7, 1.1$  Hz, 1H), 7.12 (ddd,  $J = 7.5, 4.9, 1.1$  Hz, 1H), 3.04 – 2.96 (m, 1H), 2.95 – 2.81 (m, 2H), 2.23 – 2.14 (m, 1H), 2.13 – 2.05 (m, 1H), 1.35 (d,  $J = 6.9$  Hz, 3H).

$^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )  $\delta$  200.4, 165.7, 149.4, 137.1, 136.6, 133.0, 128.6, 128.2, 121.9, 121.5, 41.6, 36.8, 31.5, 21.3.

HRMS (ESI):  $m/z$  calcd for  $\text{C}_{16}\text{H}_{18}\text{NO}$   $[\text{M}+\text{H}]^+$ : 240.1383, found: 240.1384.

IR: 2925, 1684, 1591, 1747, 1449, 1433, 744, 690 ( $\text{cm}^{-1}$ ).



1-Phenyl-4-(thiophen-2-yl)pentan-1-one (**8x**)

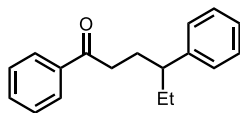
Clear colorless oil (19% yield).

$^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.91 – 7.87 (m, 2H), 7.57 – 7.51 (m, 1H), 7.43 (t,  $J = 7.8$  Hz, 2H), 7.15 (dd,  $J = 5.1, 1.2$  Hz, 1H), 6.93 (dd,  $J = 5.1, 3.4$  Hz, 1H), 6.82 (d,  $J = 3.5$  Hz, 1H), 3.22 – 3.12 (m, 1H), 2.93 (t,  $J = 7.5$  Hz, 2H), 2.17 – 2.09 (m, 1H), 2.05 – 1.96 (m, 1H), 1.39 (d,  $J = 6.9$  Hz, 3H).

$^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )  $\delta$  200.2, 150.9, 137.1, 133.1, 128.7, 128.2, 126.7, 123.3, 122.9, 36.5, 35.1, 33.6, 23.7.

HRMS (ESI):  $m/z$  calcd for  $\text{C}_{15}\text{H}_{17}\text{OS}$   $[\text{M}+\text{H}]^+$ : 245.0995, found: 245.0993.

IR: 2961, 1681, 1597, 1448, 1208, 1002, 743, 690 ( $\text{cm}^{-1}$ ).



1,4-Diphenylhexan-1-one (**8y**)

Clear colorless oil (11% yield).

$^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.85 – 7.79 (m, 2H), 7.54 – 7.48 (m, 1H), 7.40 (t,  $J = 7.8$  Hz, 2H), 7.30 (t,  $J = 7.5$  Hz, 2H), 7.23 – 7.18 (m, 1H), 7.18 – 7.14 (m, 2H), 2.86 – 2.71 (m, 2H), 2.51 (tt,  $J = 9.9, 5.0$  Hz, 1H), 2.22 – 2.12 (m, 1H), 1.99 – 1.90 (m, 1H), 1.79 – 1.69 (m, 1H), 1.68 – 1.59 (m, 1H), 0.81 (t,  $J = 7.4$  Hz, 3H).

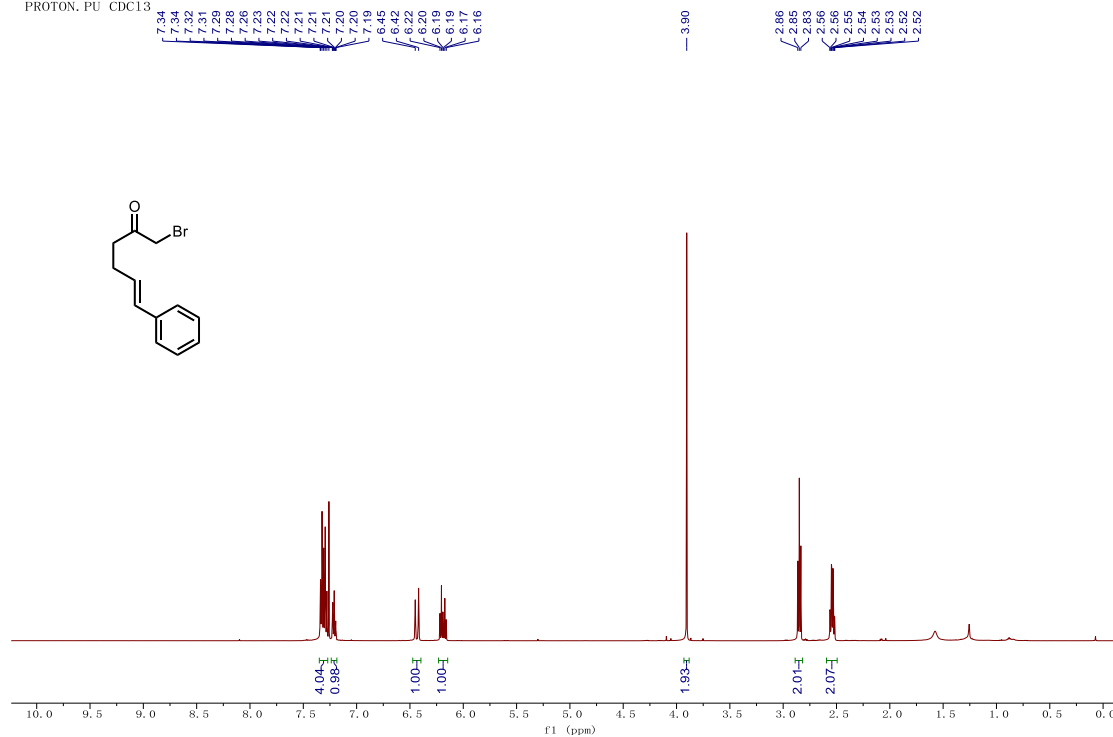
$^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )  $\delta$  200.6, 144.9, 137.1, 133.0, 128.6, 128.6, 128.1, 127.9, 126.3, 47.5, 36.8, 30.8, 30.1, 12.3.

HRMS (ESI):  $m/z$  calcd for  $\text{C}_{18}\text{H}_{21}\text{O}$   $[\text{M}+\text{H}]^+$ : 253.1587, found: 253.1587.

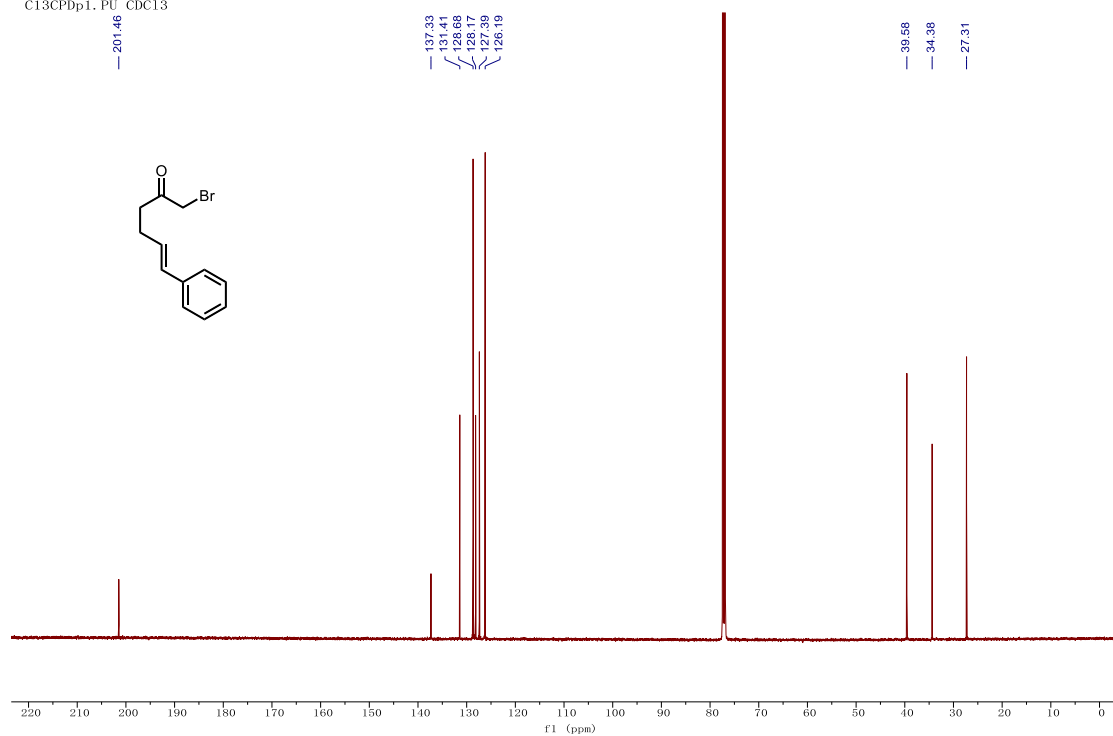
IR: 2929, 2954, 1678, 1596, 1492, 1447, 1371, 1211, 974, 754, 743, 730, 697 ( $\text{cm}^{-1}$ ).

### 3. NMR spectra

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PROTON, PU CDC13

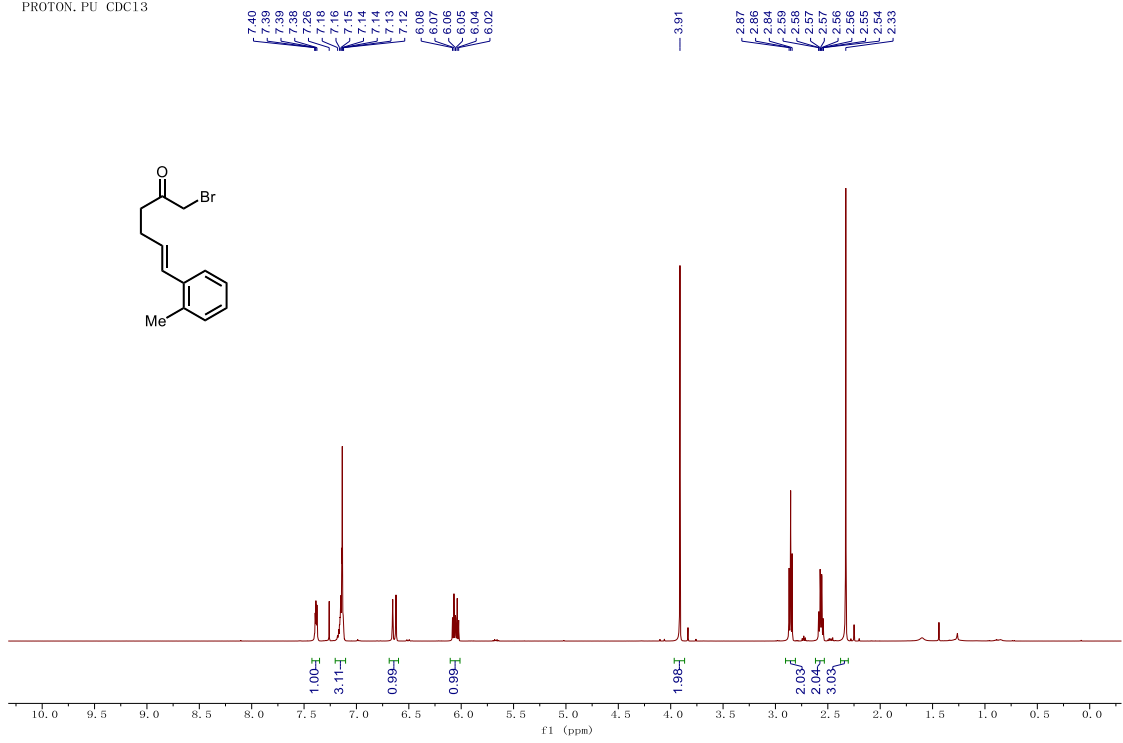


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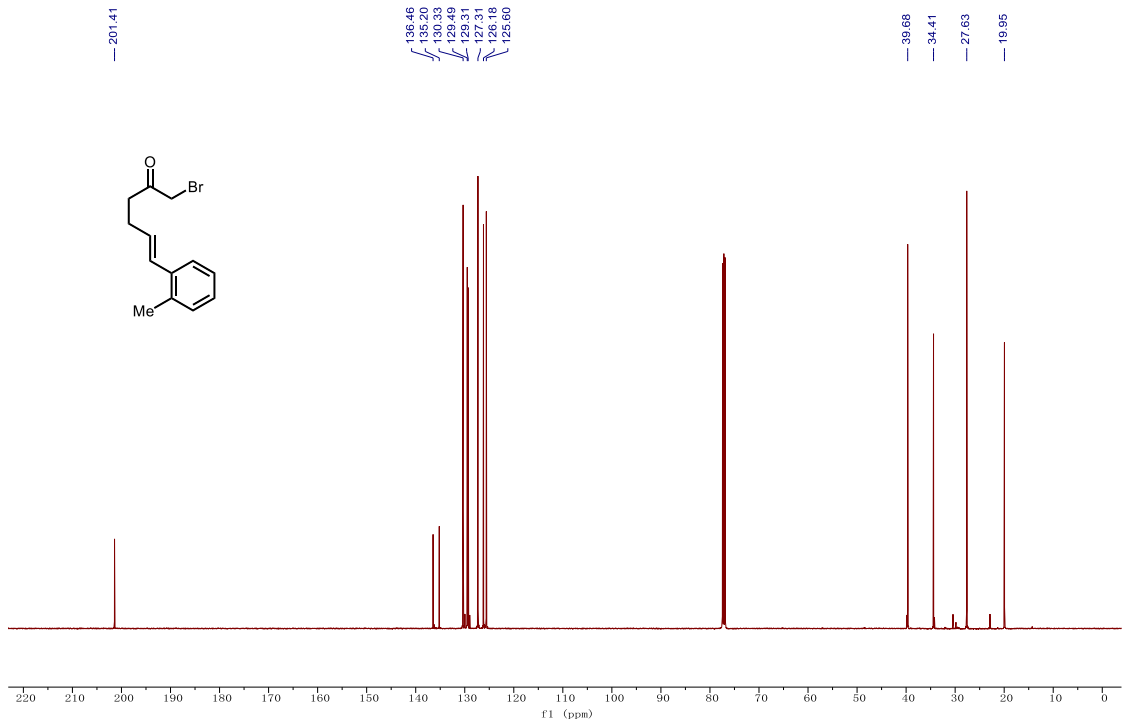




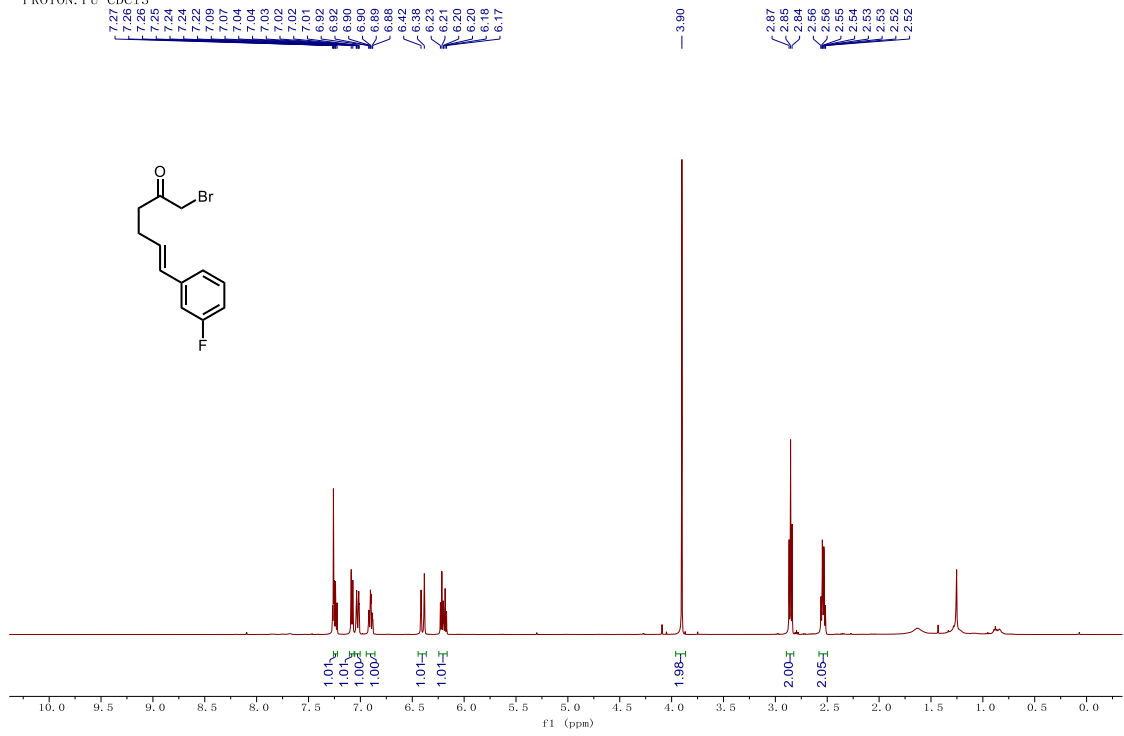
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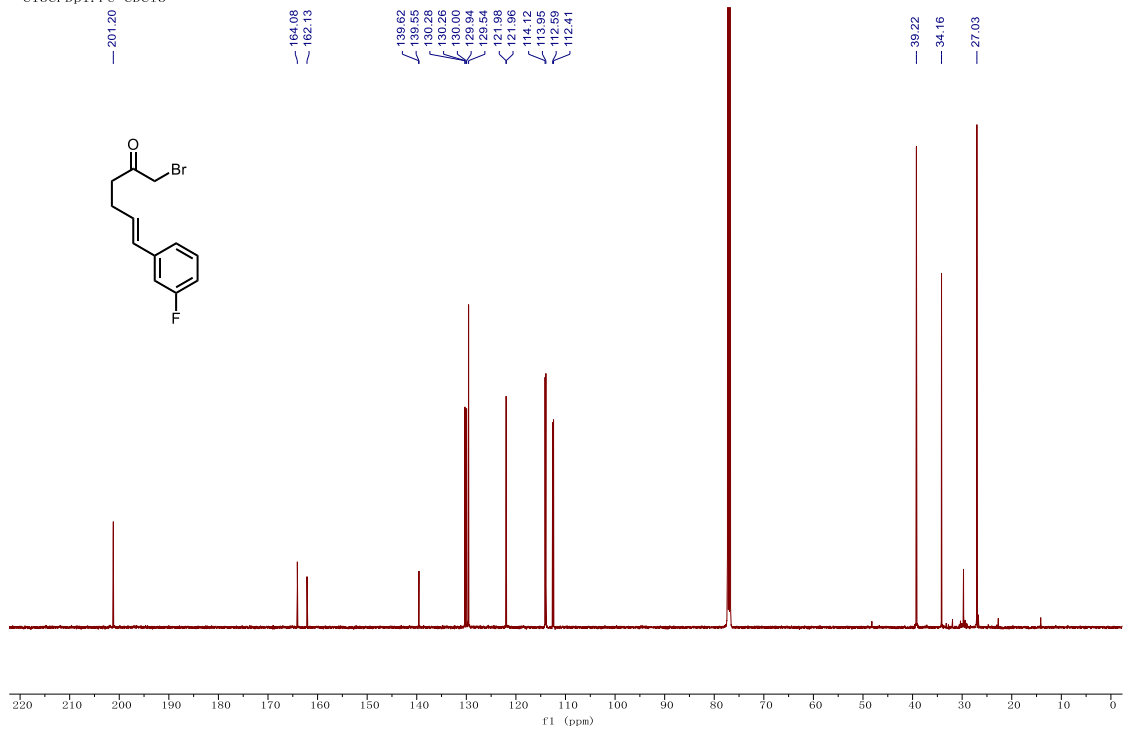
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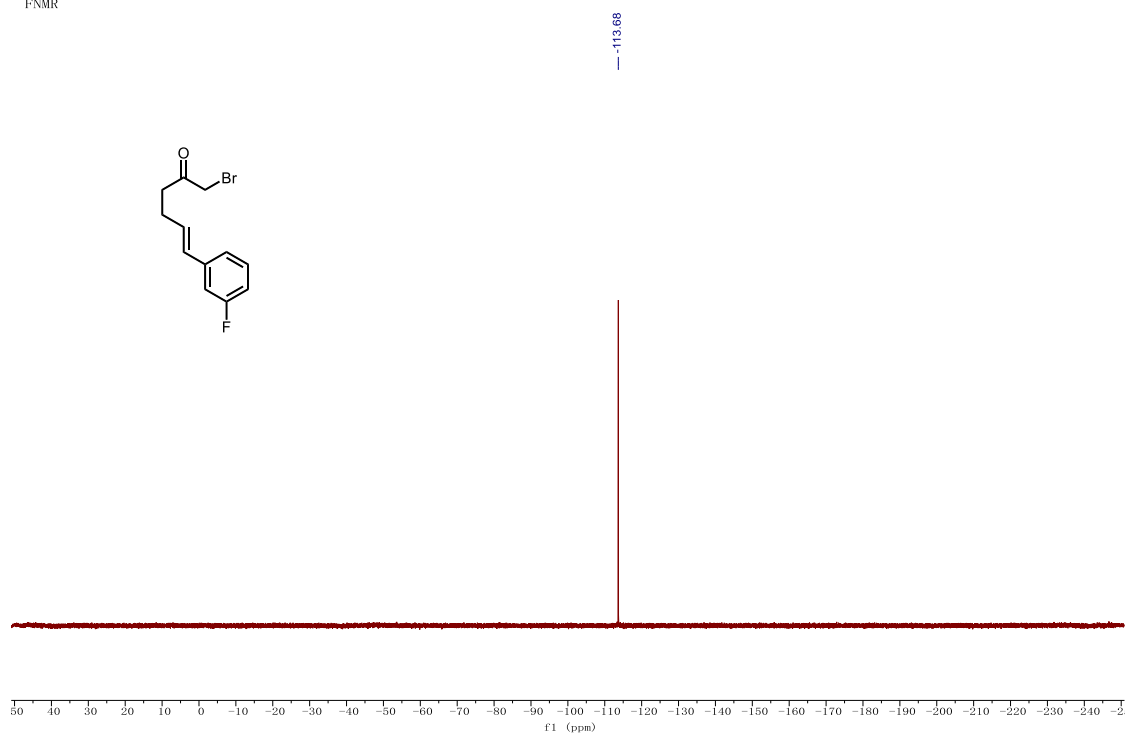
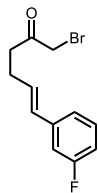
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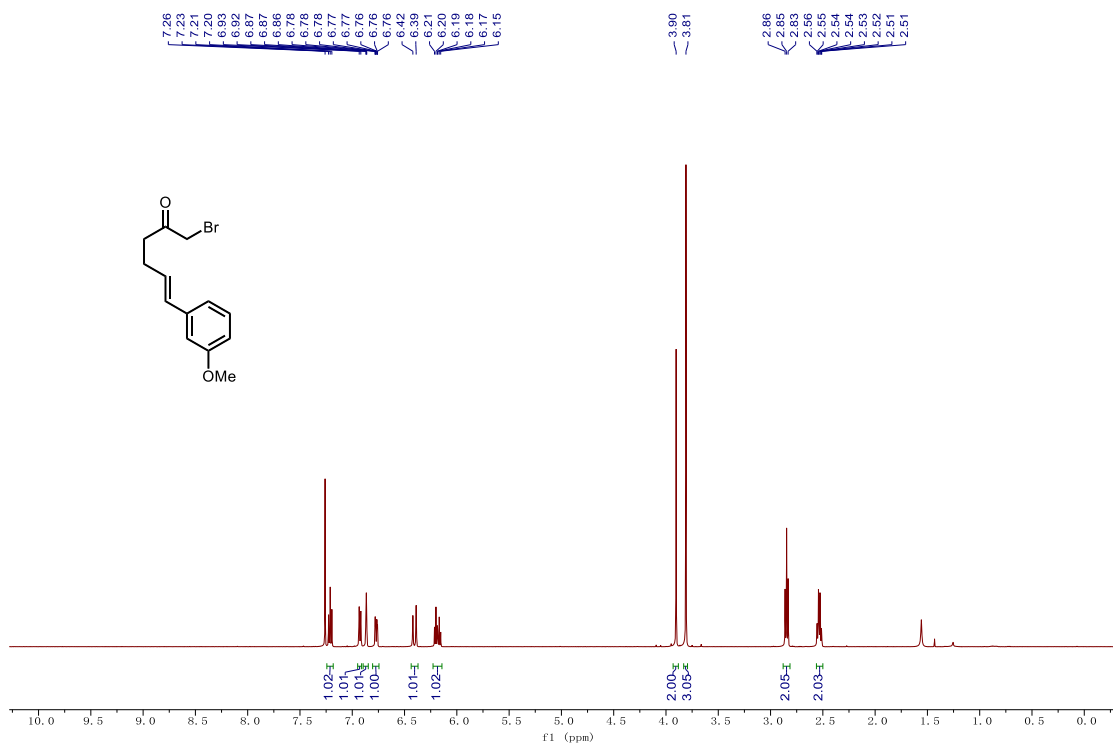
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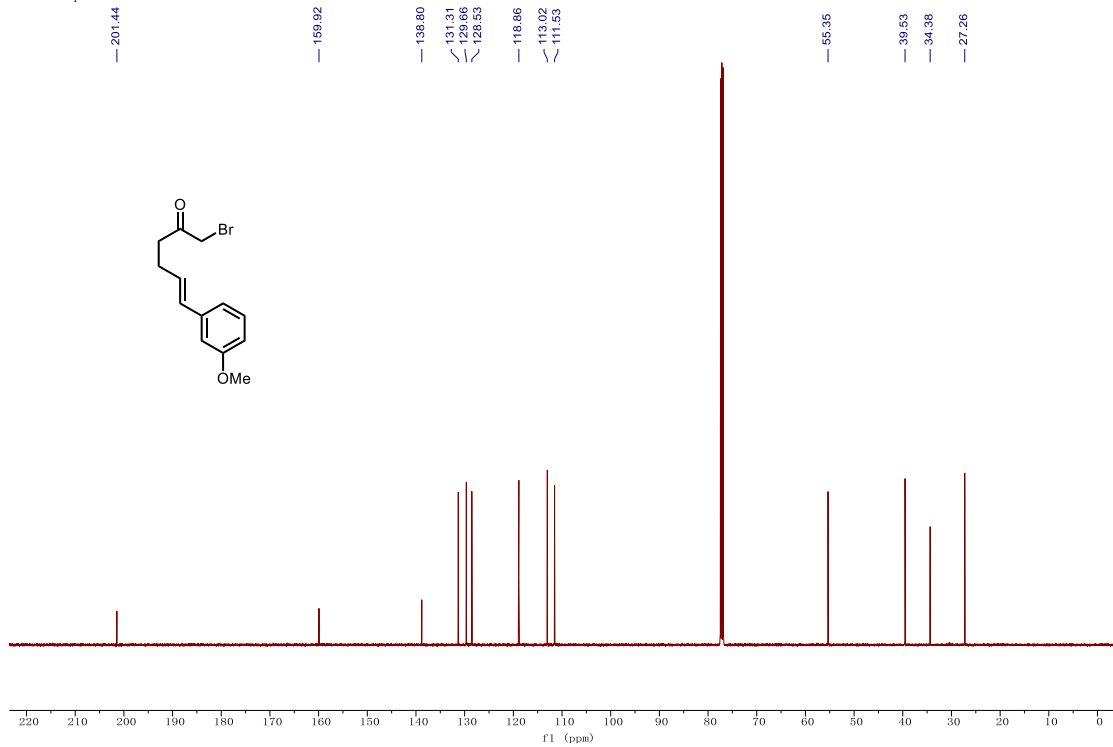
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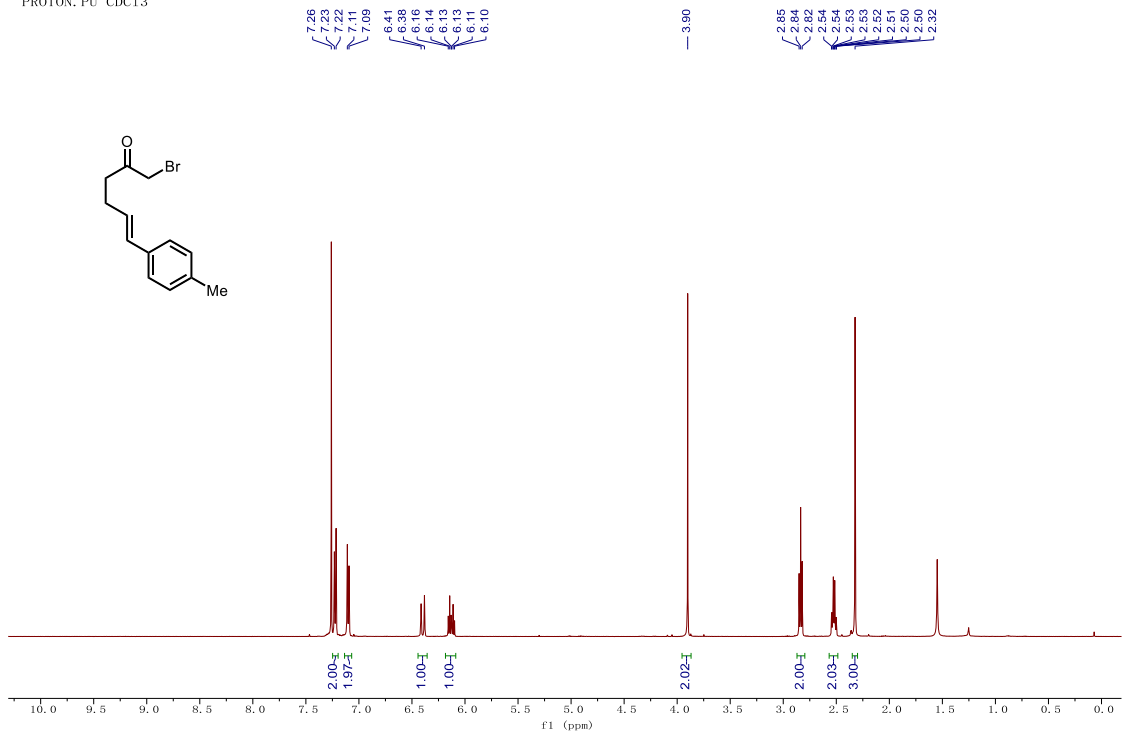
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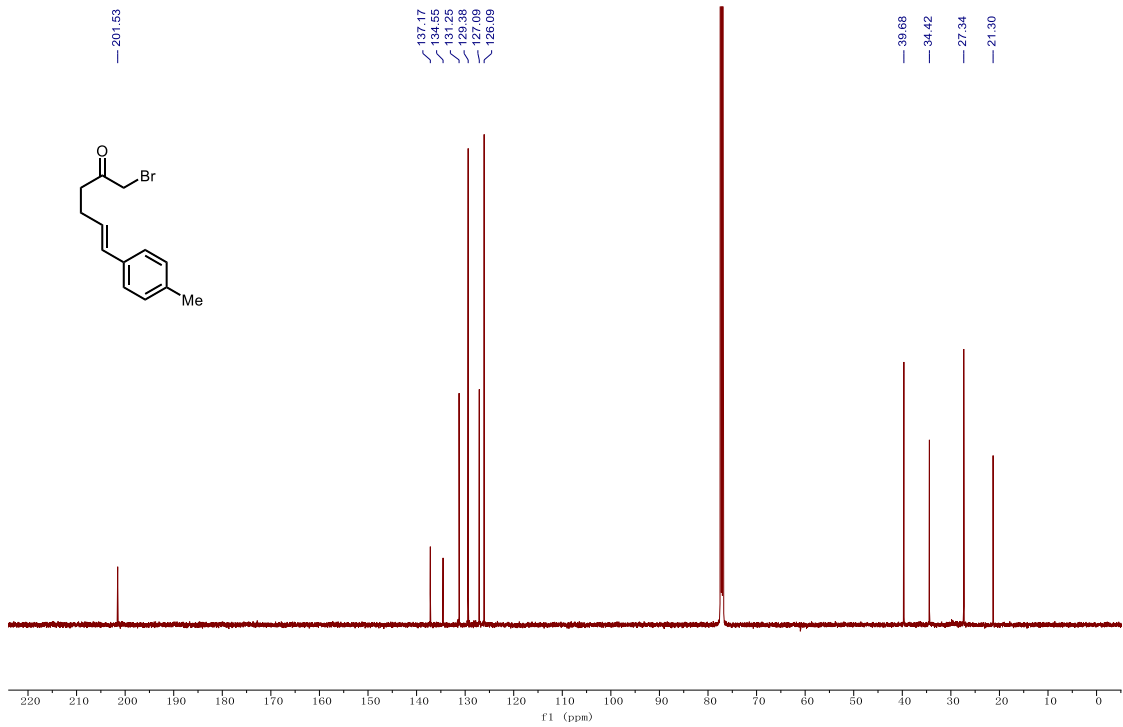
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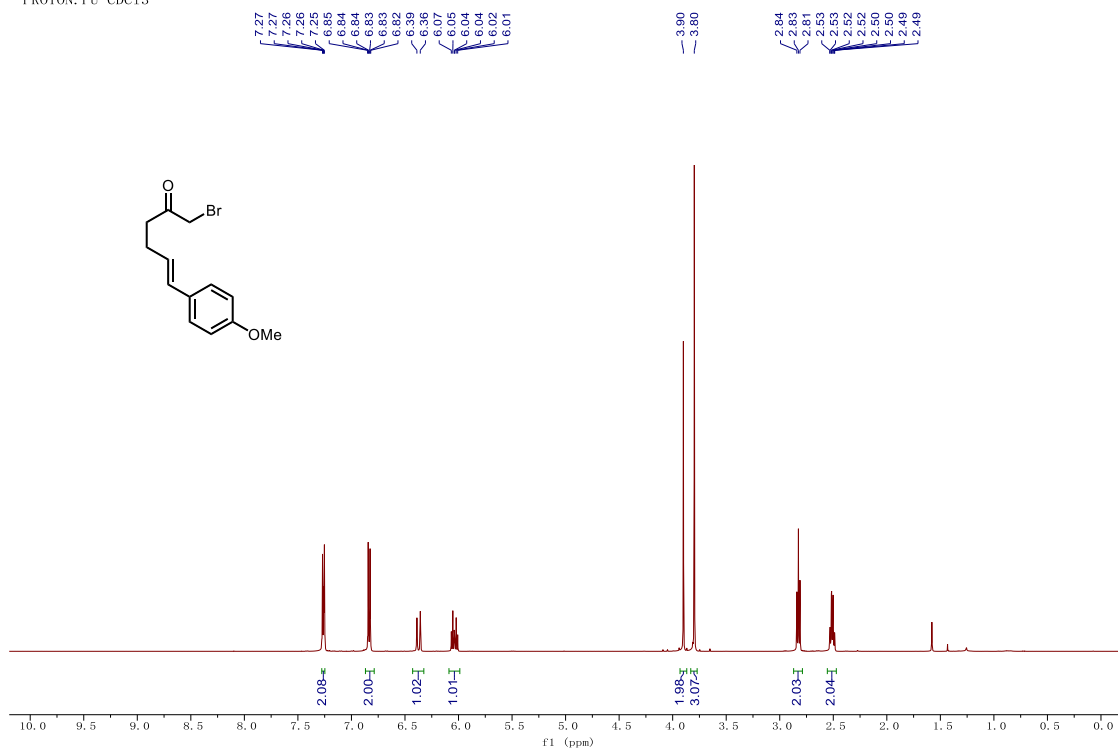
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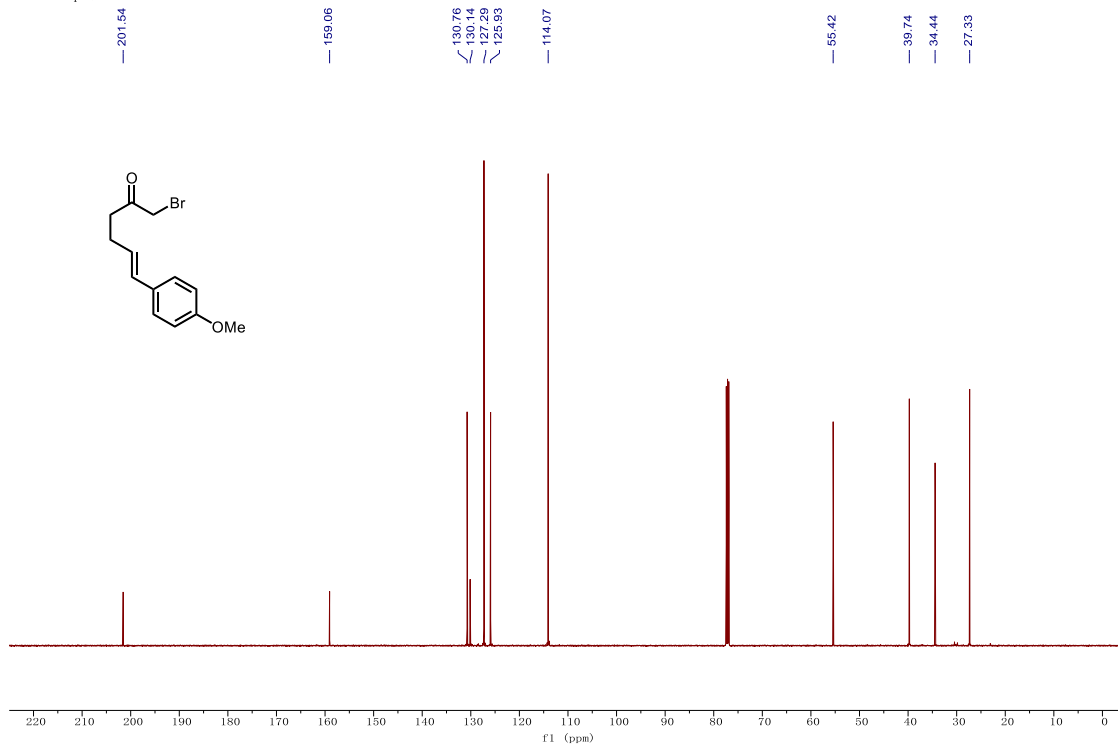
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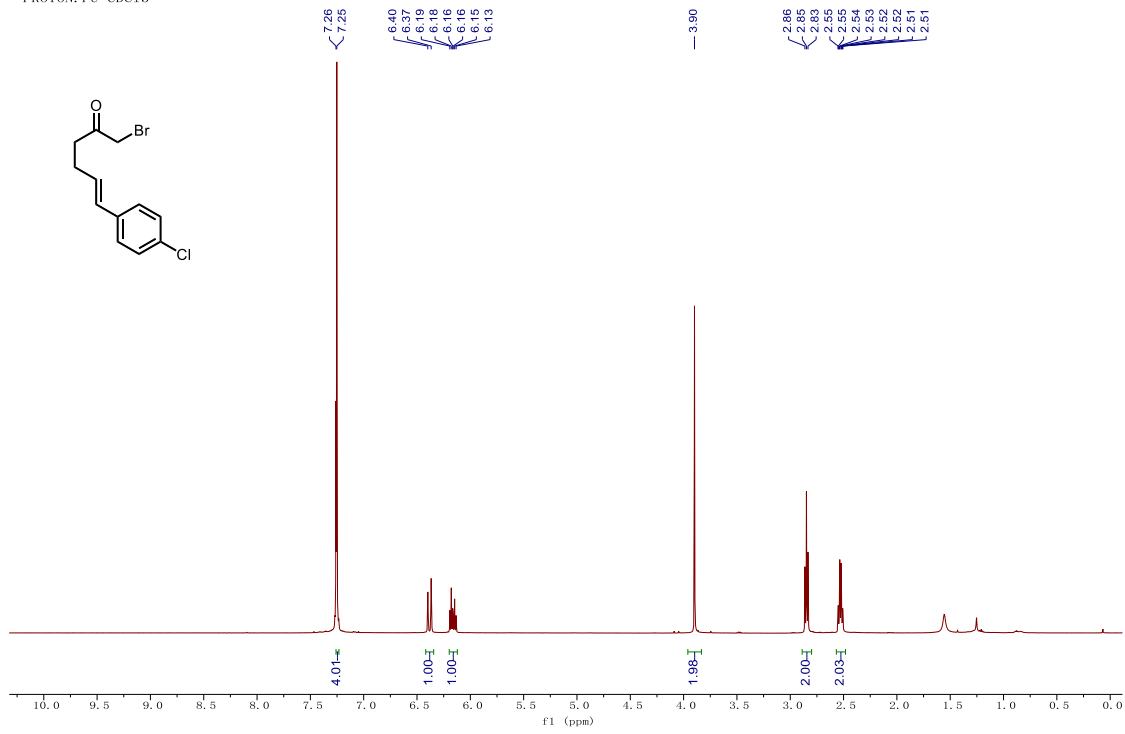
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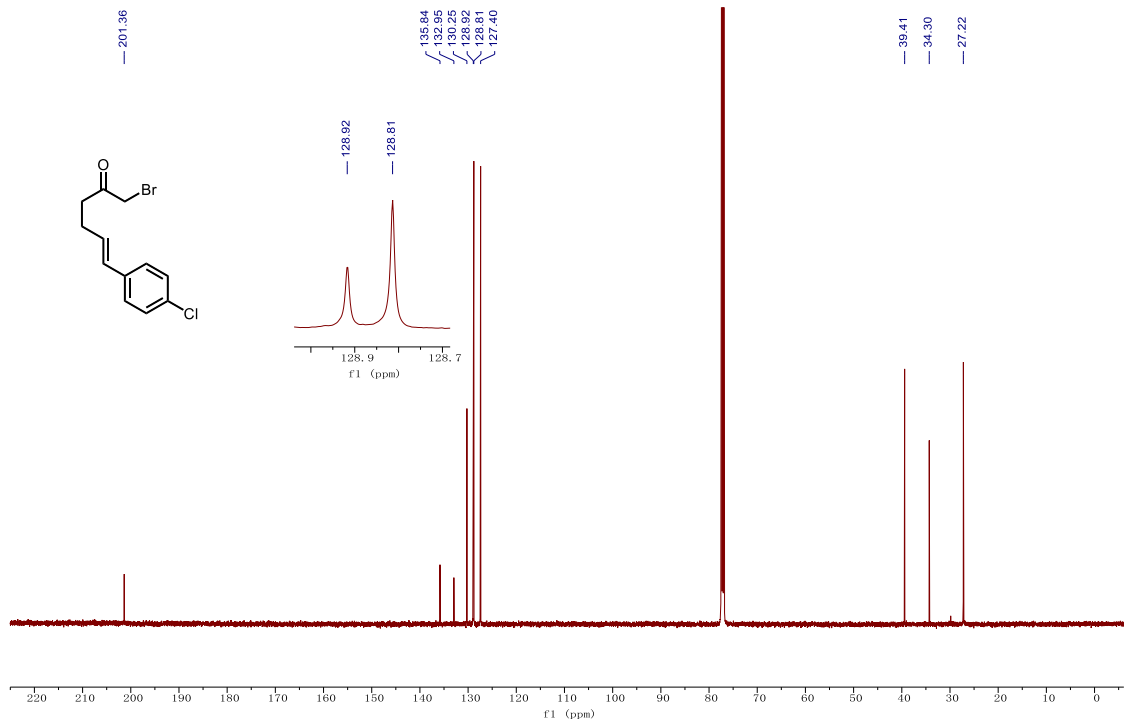
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C13CPDp1, PU CDC13



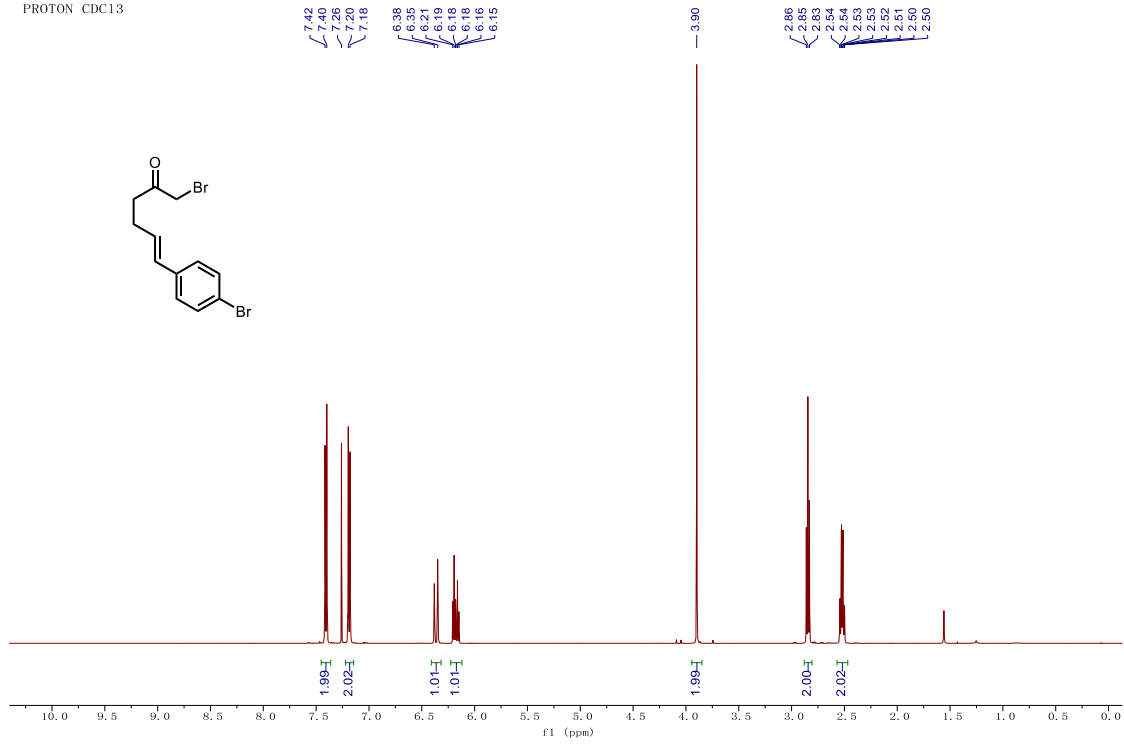
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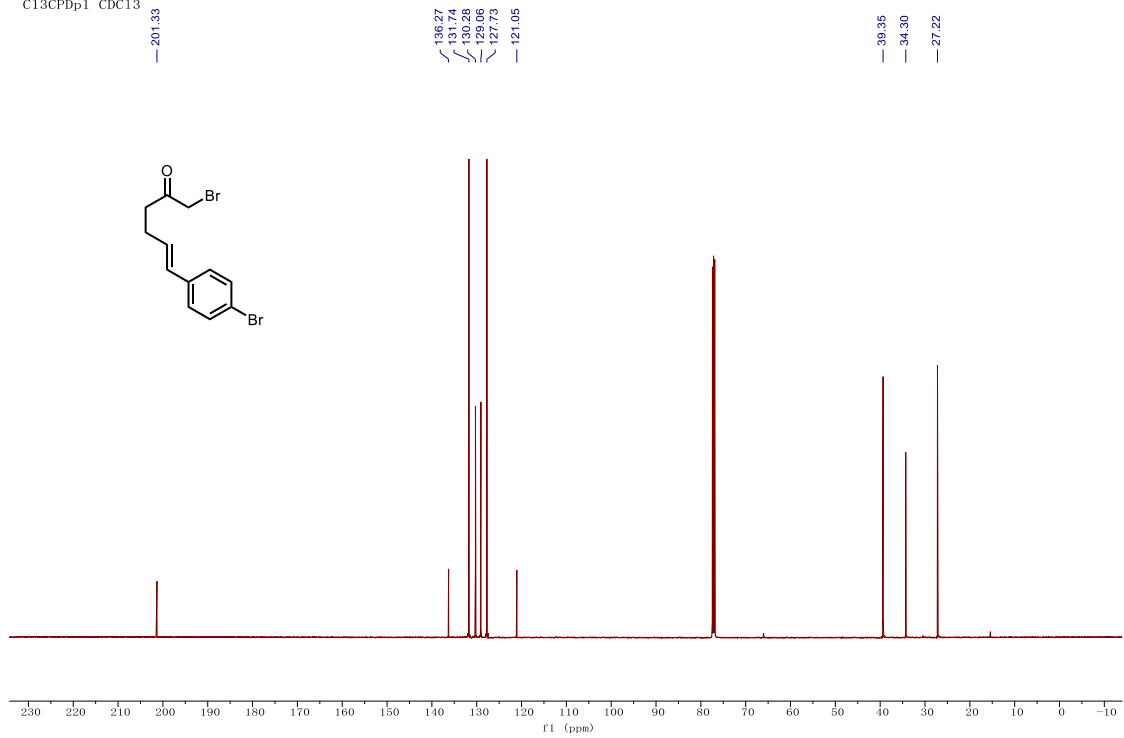
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C13CPDp1, PU CDC13



HFU-sub-07-pBr  
PROTON CDC13

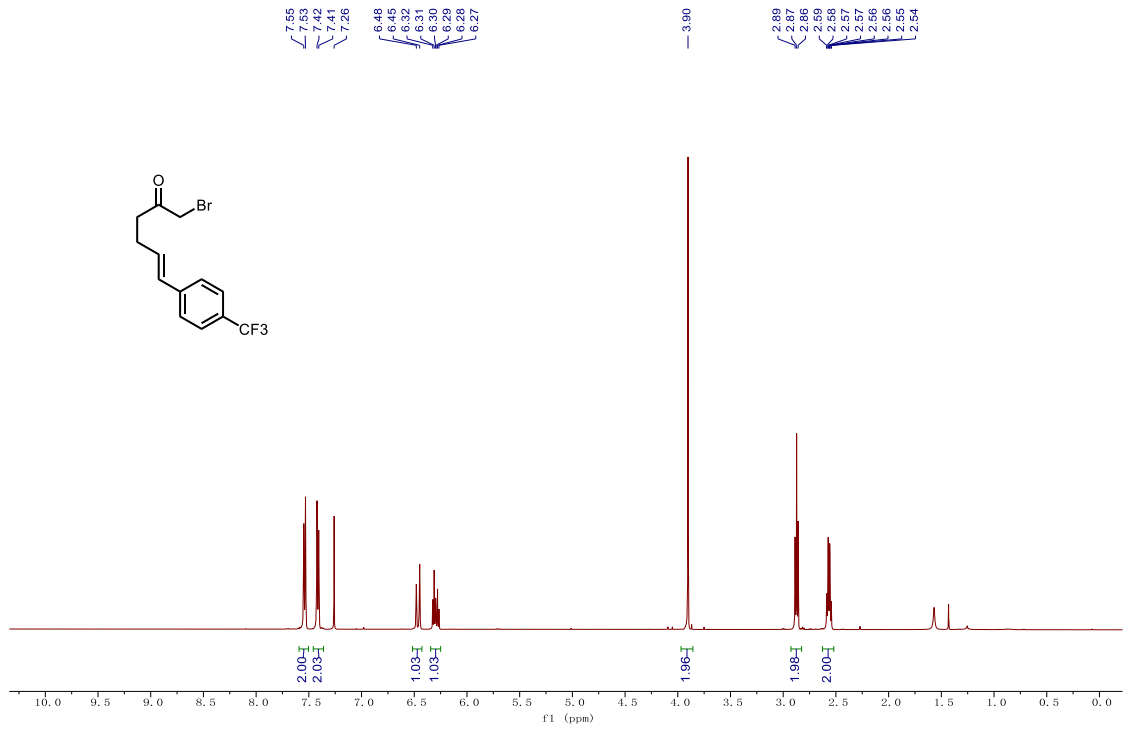


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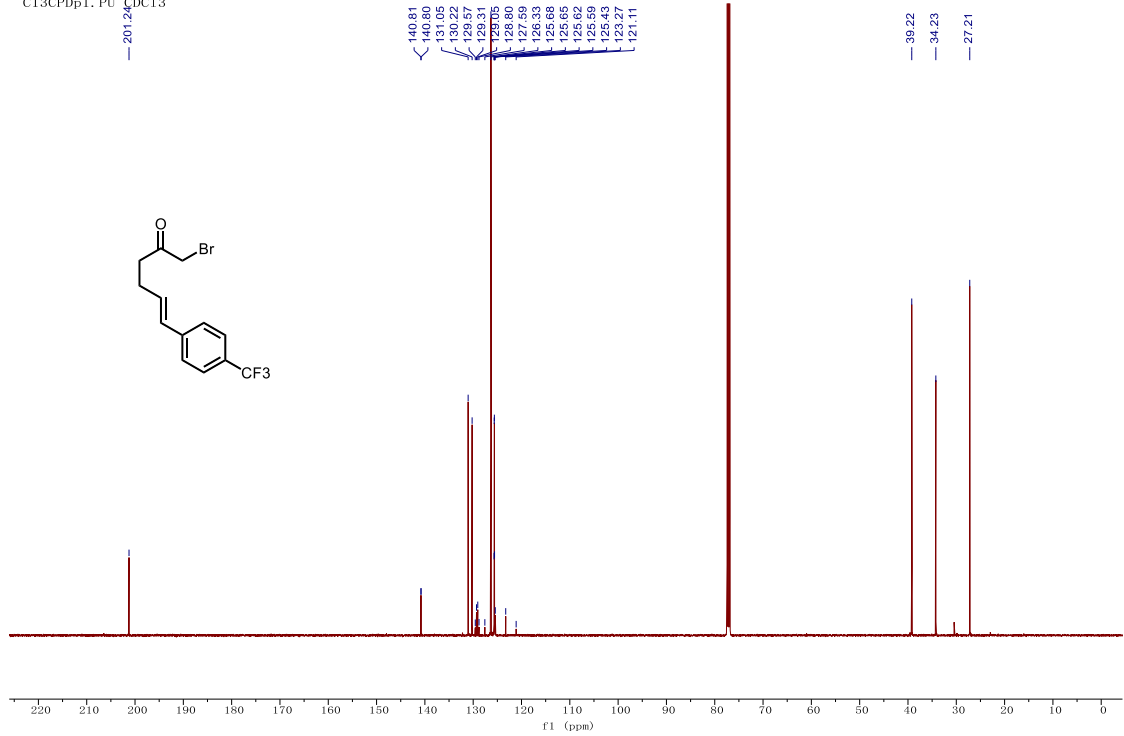




HFU-sub-09-pCF3  
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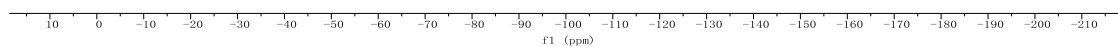
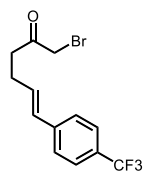


HFU-sub-09-pCF3  
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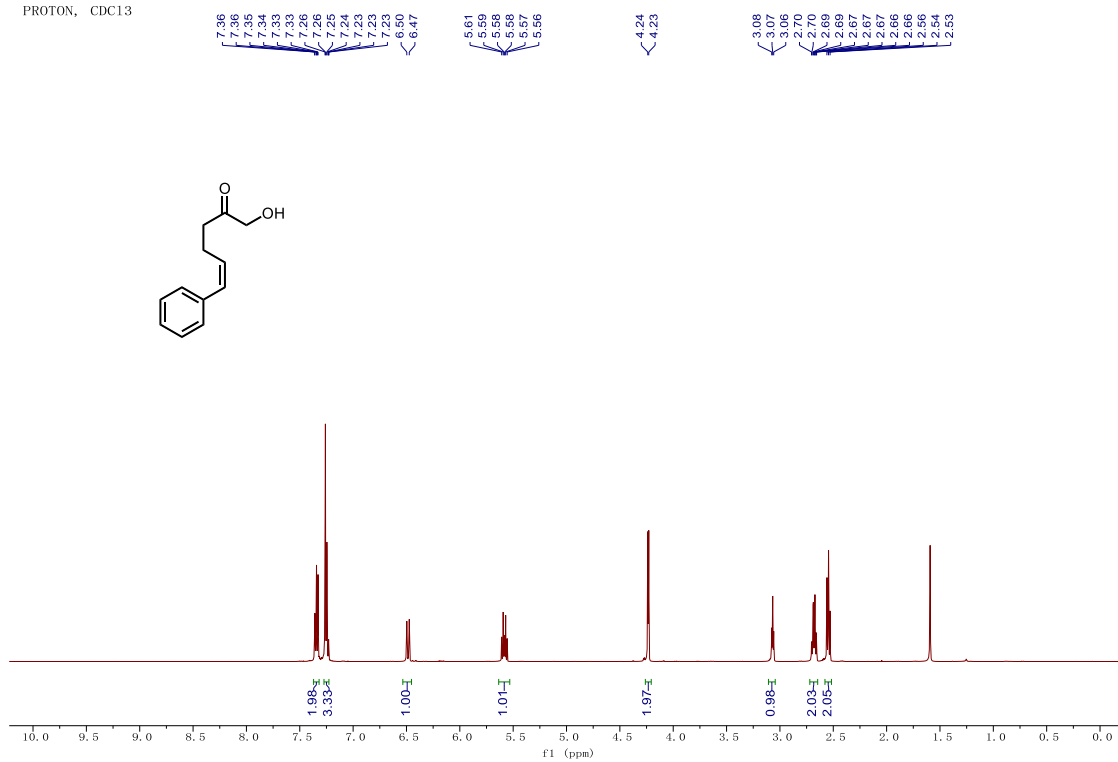
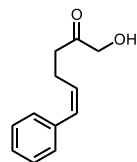


HFU-09  
FNMR

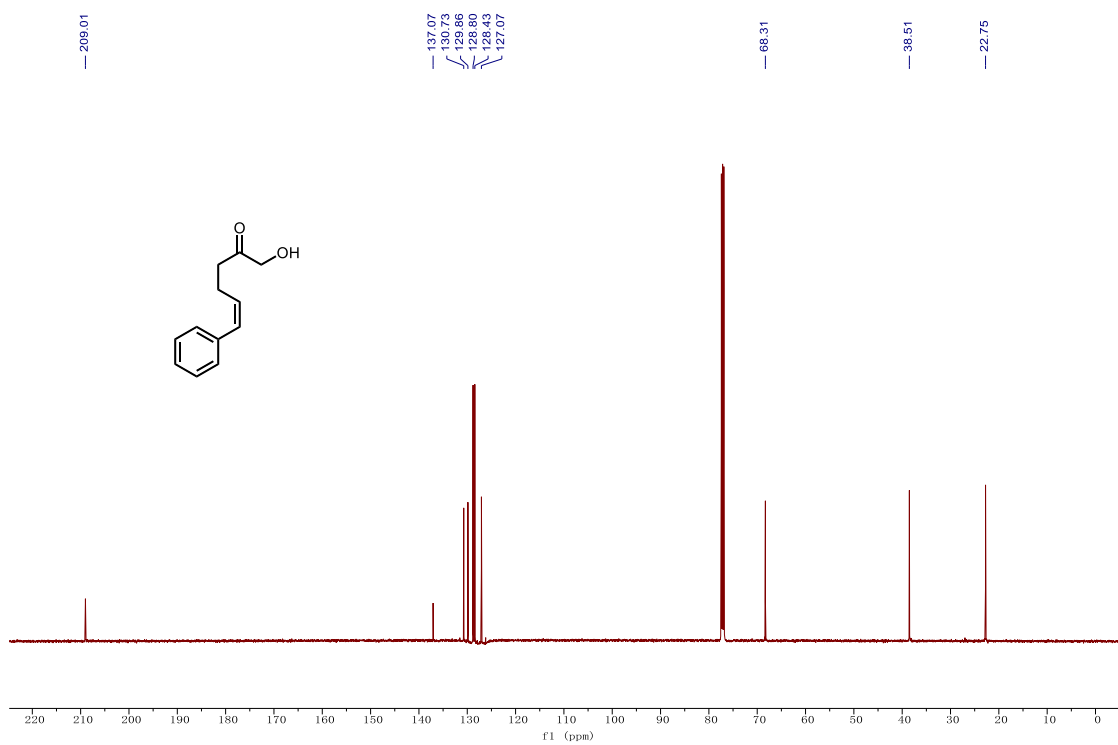
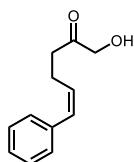
— 62.49



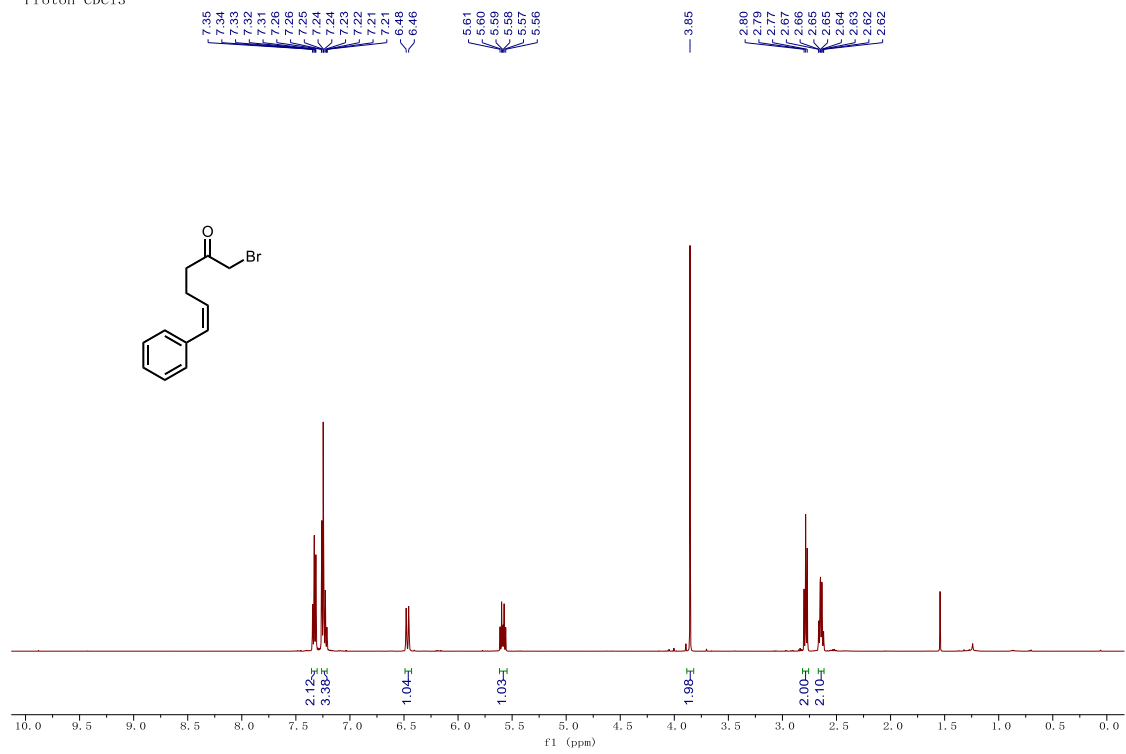
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PROTON, CDCl3



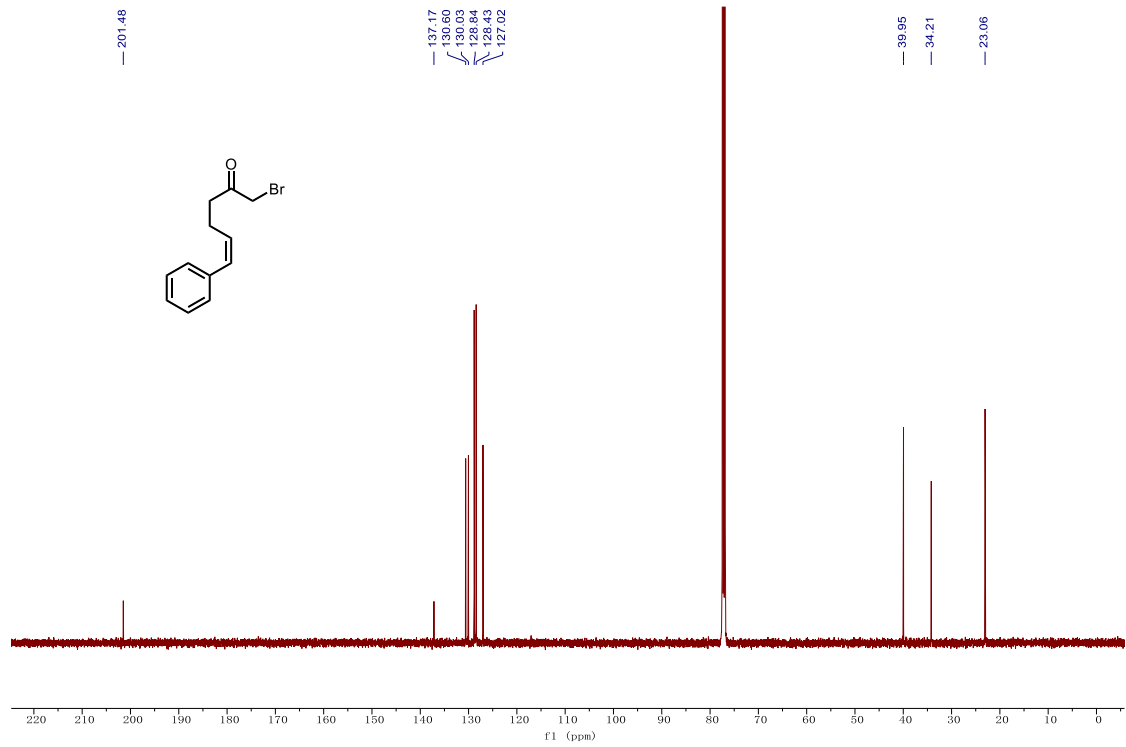
KIM-KF-004  
CNMR, CDCl3



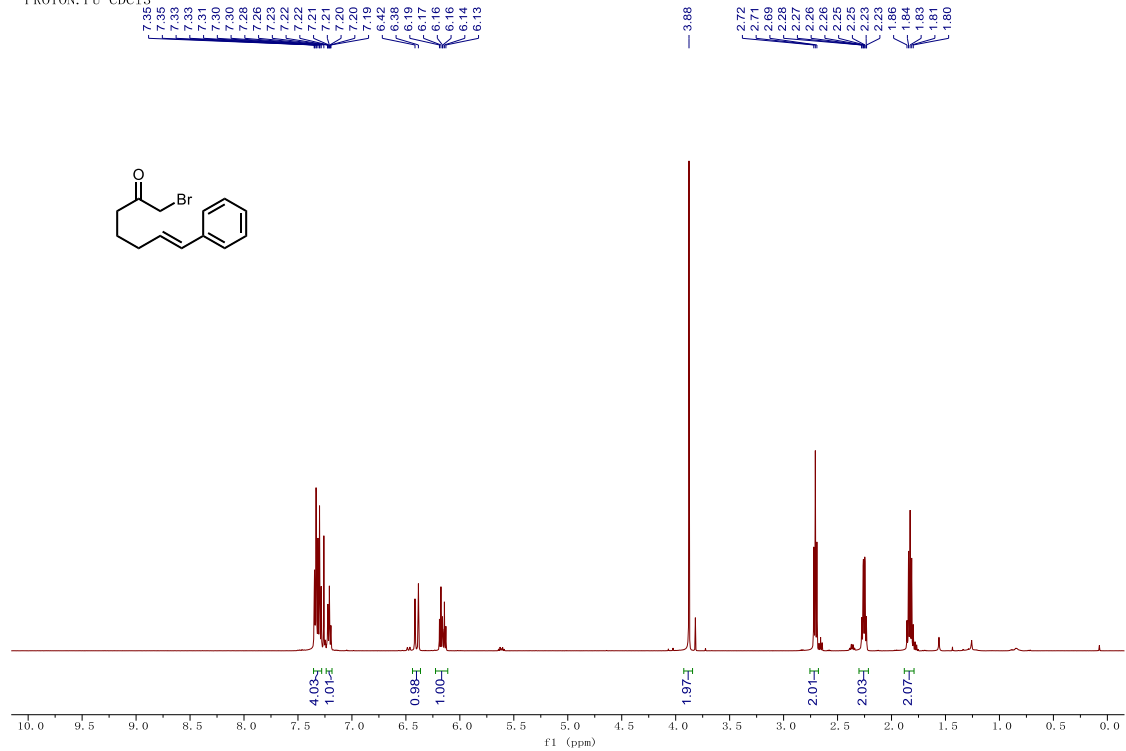
HFU-sub-Z-isomer  
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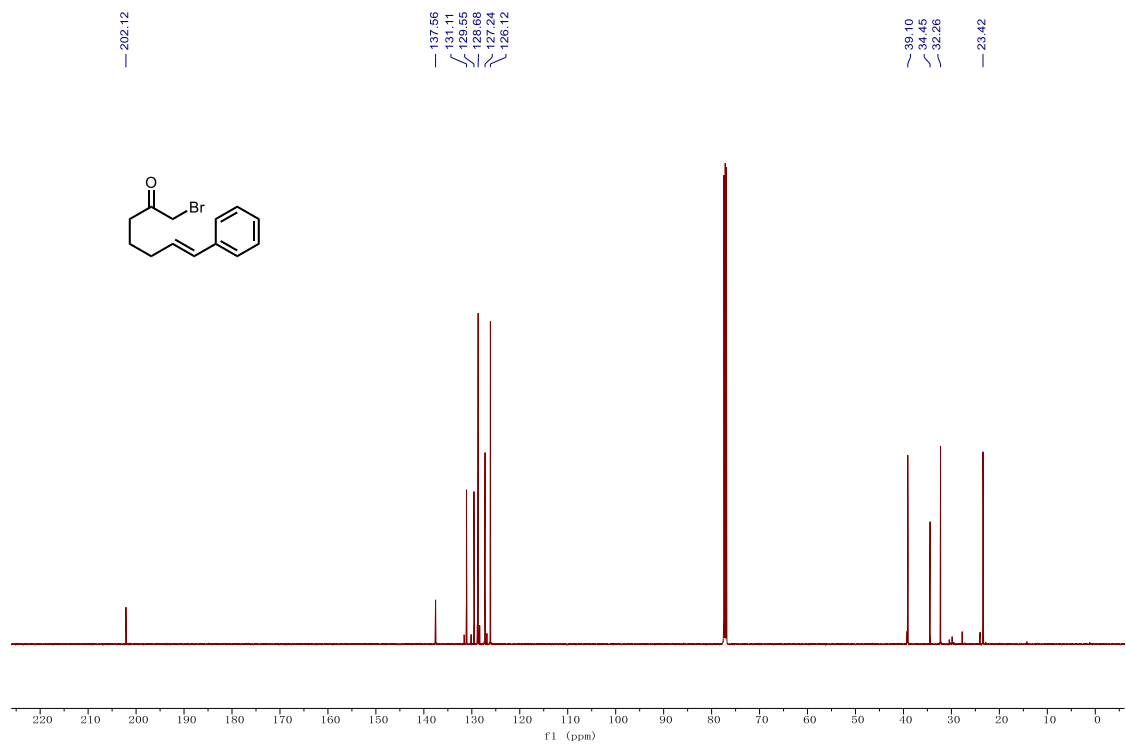
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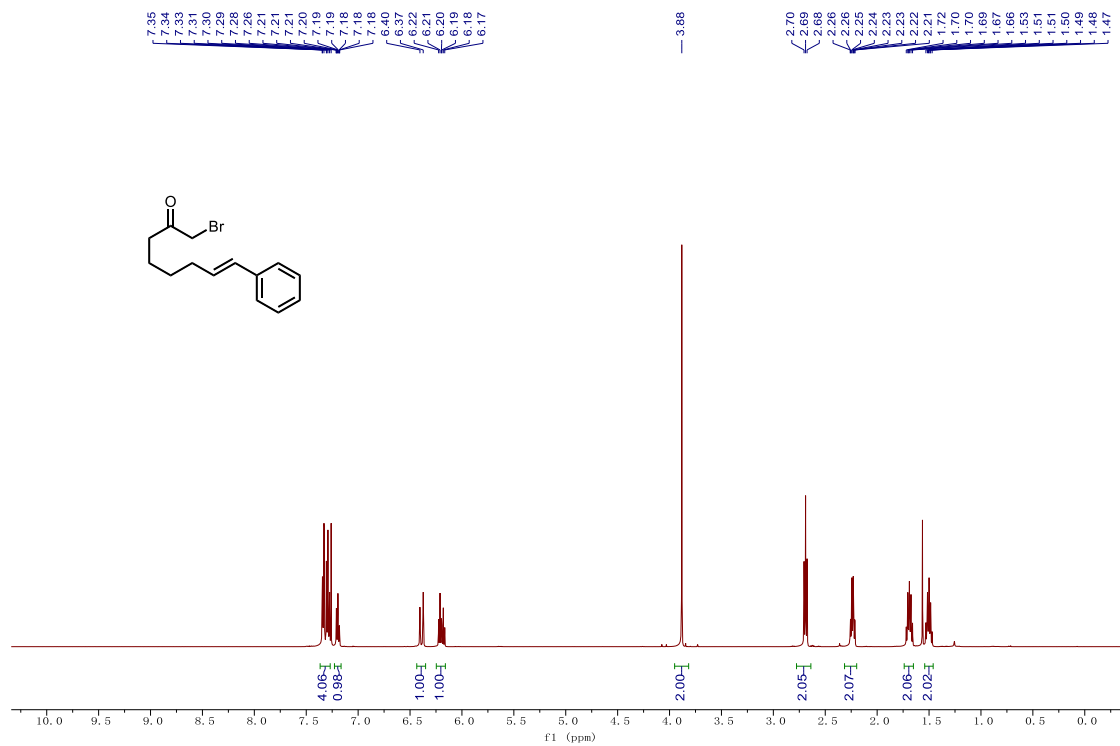
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PROTON, PU CDC13



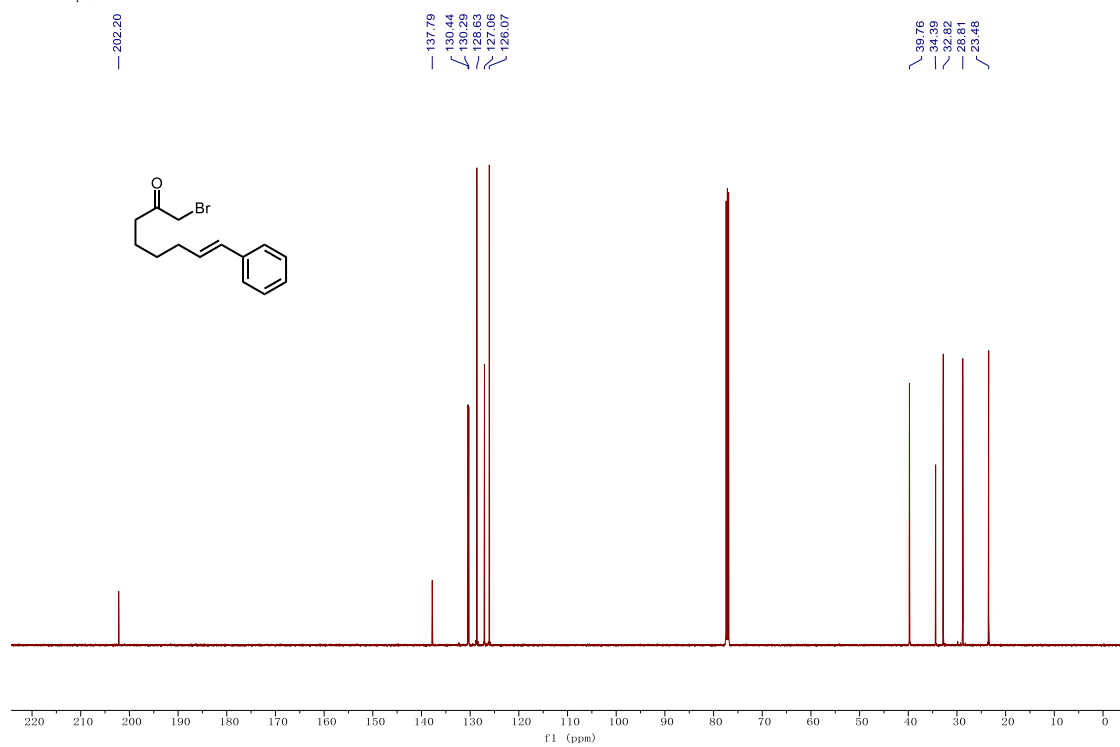
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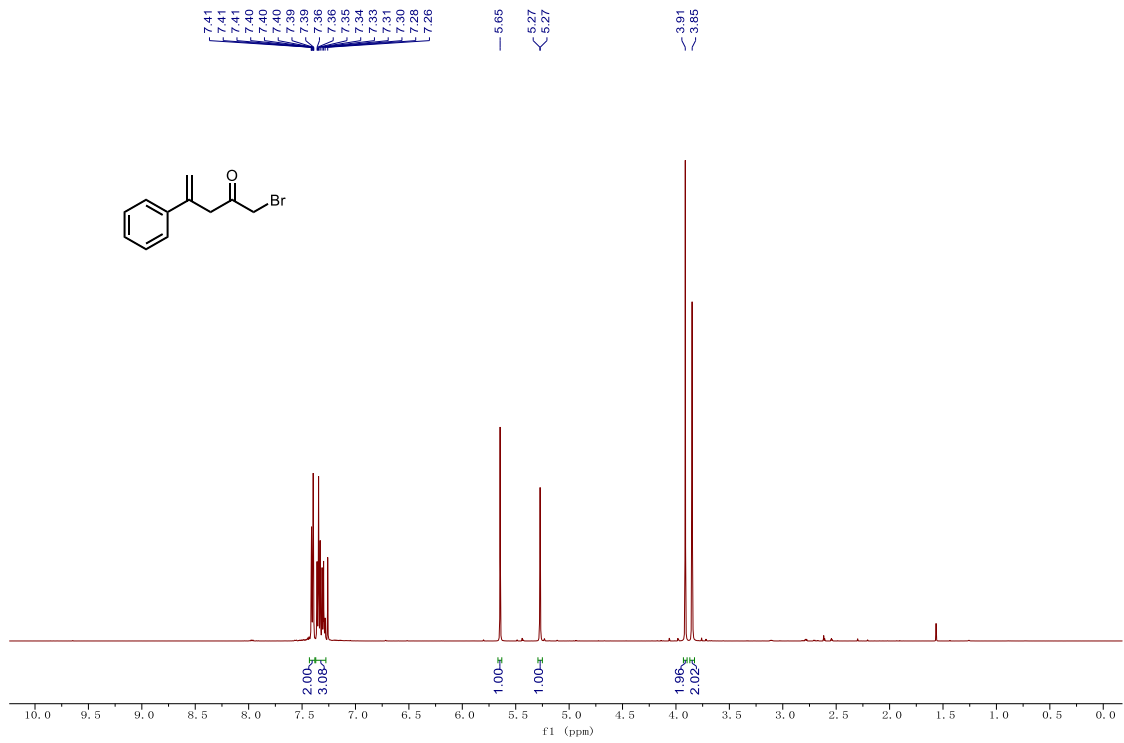
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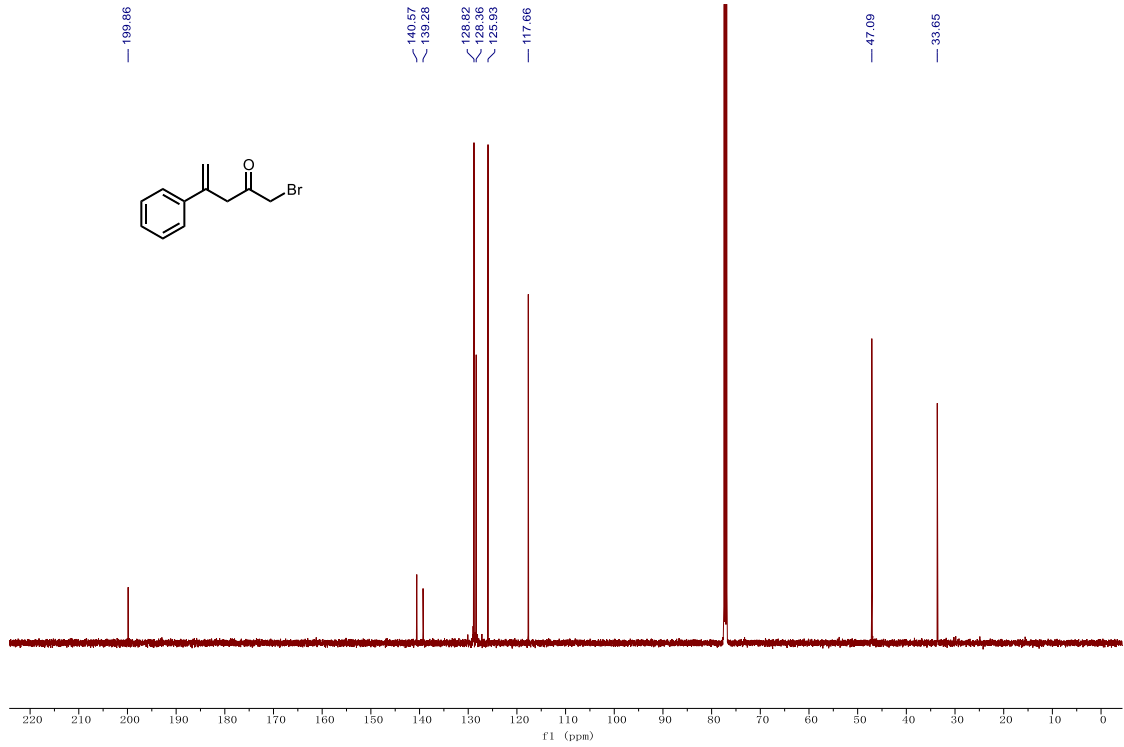
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C13CPDp1, PU CDC13



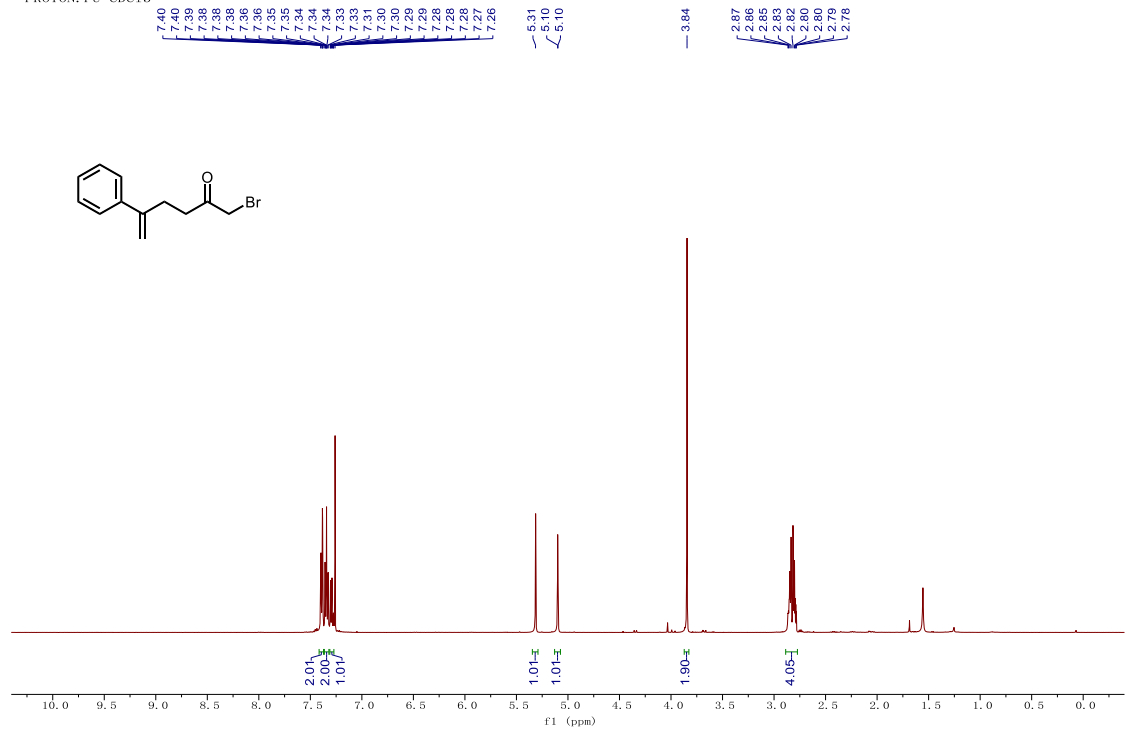
HFU-sub-5-endo  
Proton CDC13



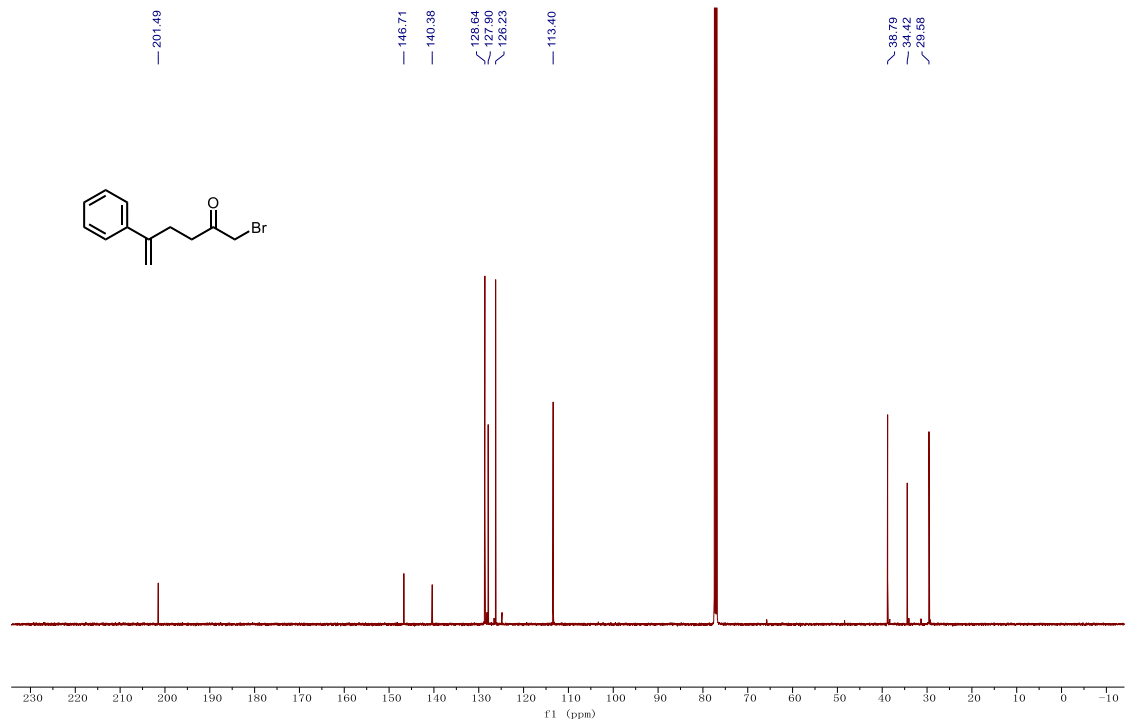
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HFU-sub-6-endo  
PROTON, PU CDC13

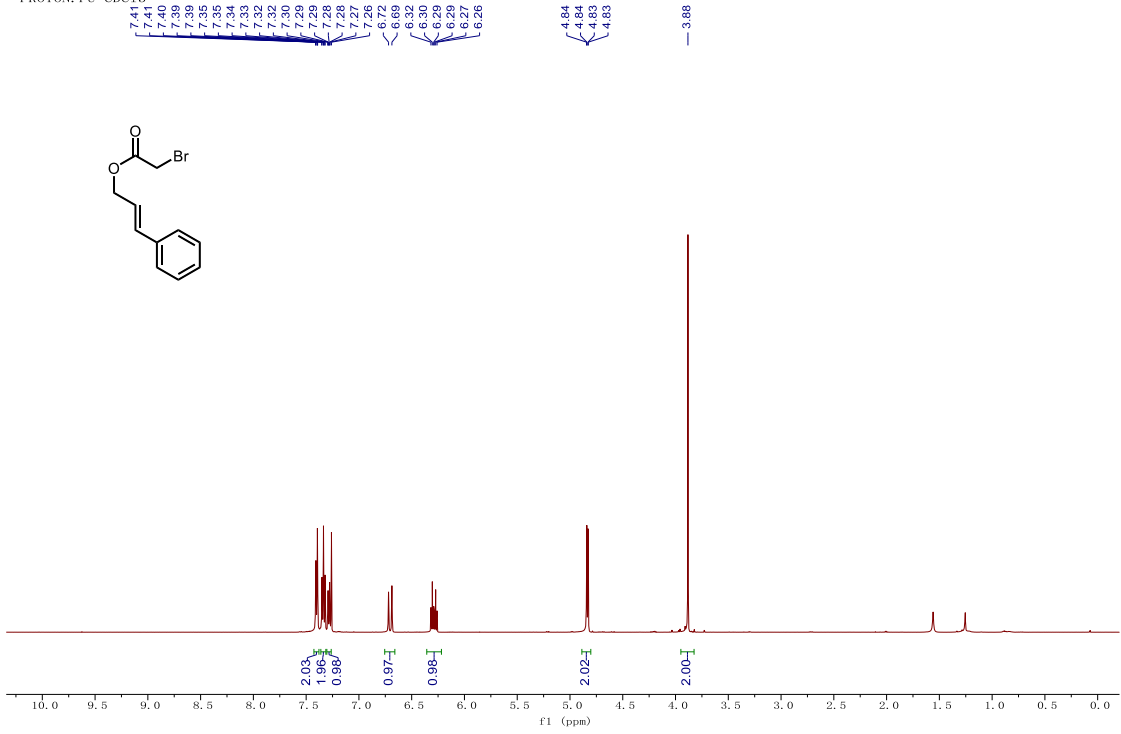


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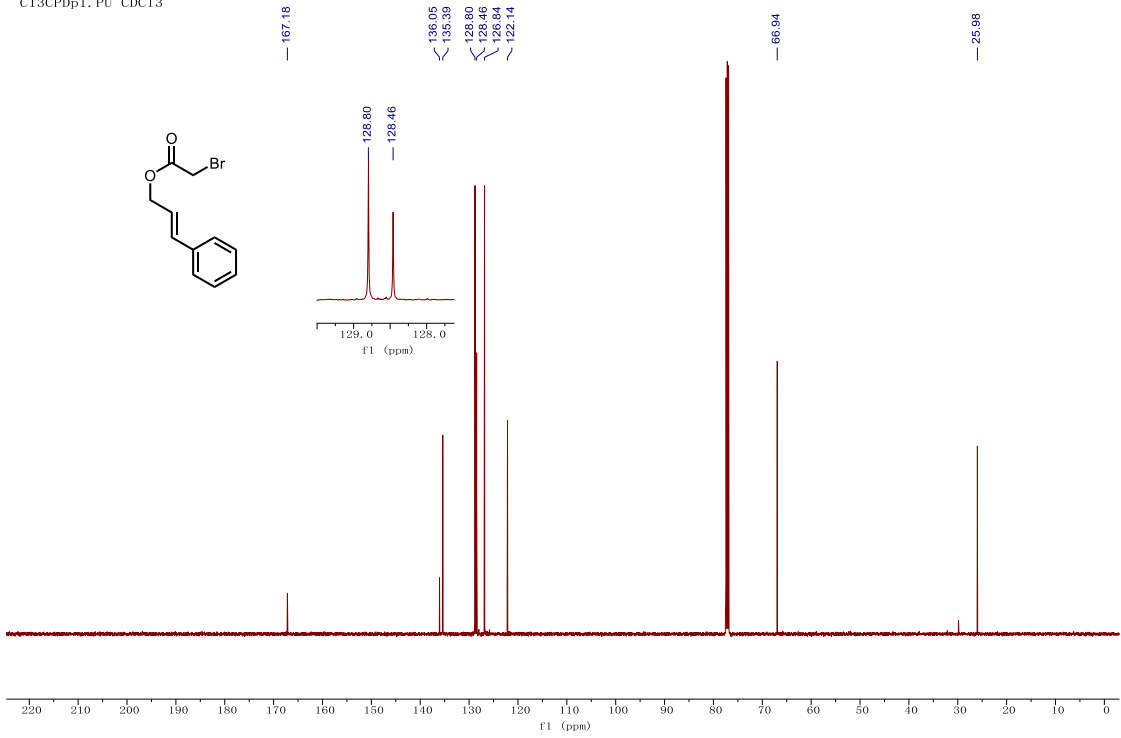




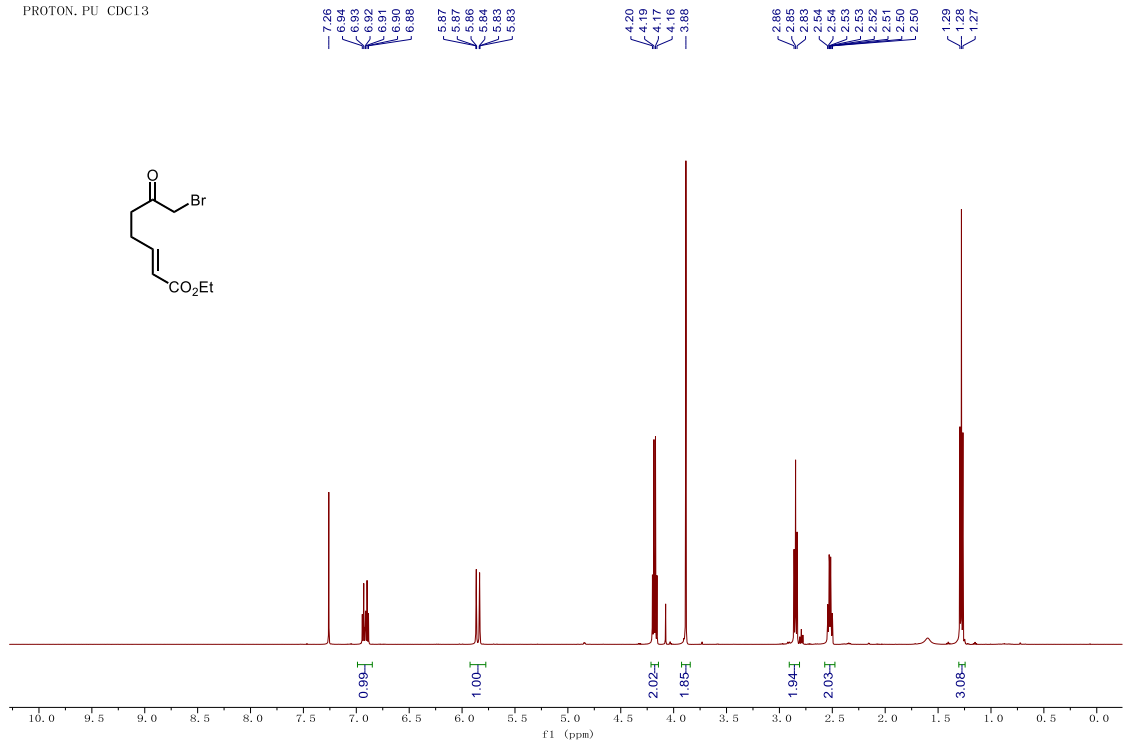
HFU-sub-ester  
PROTON, PU CDC13



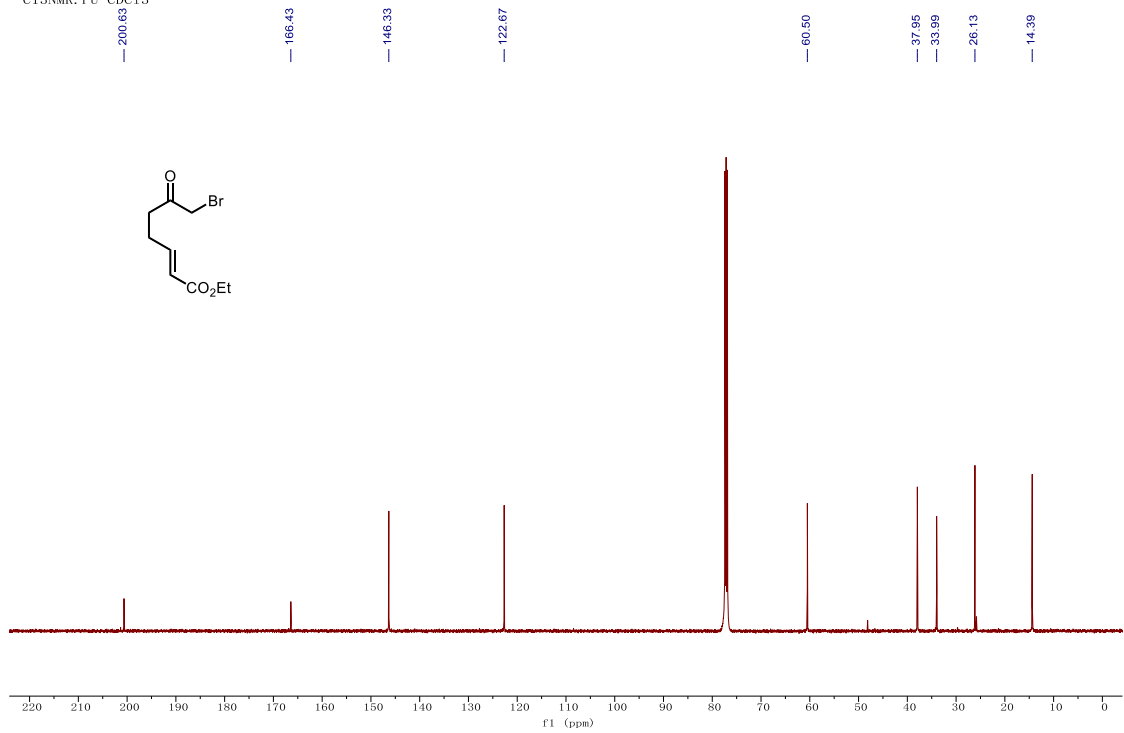
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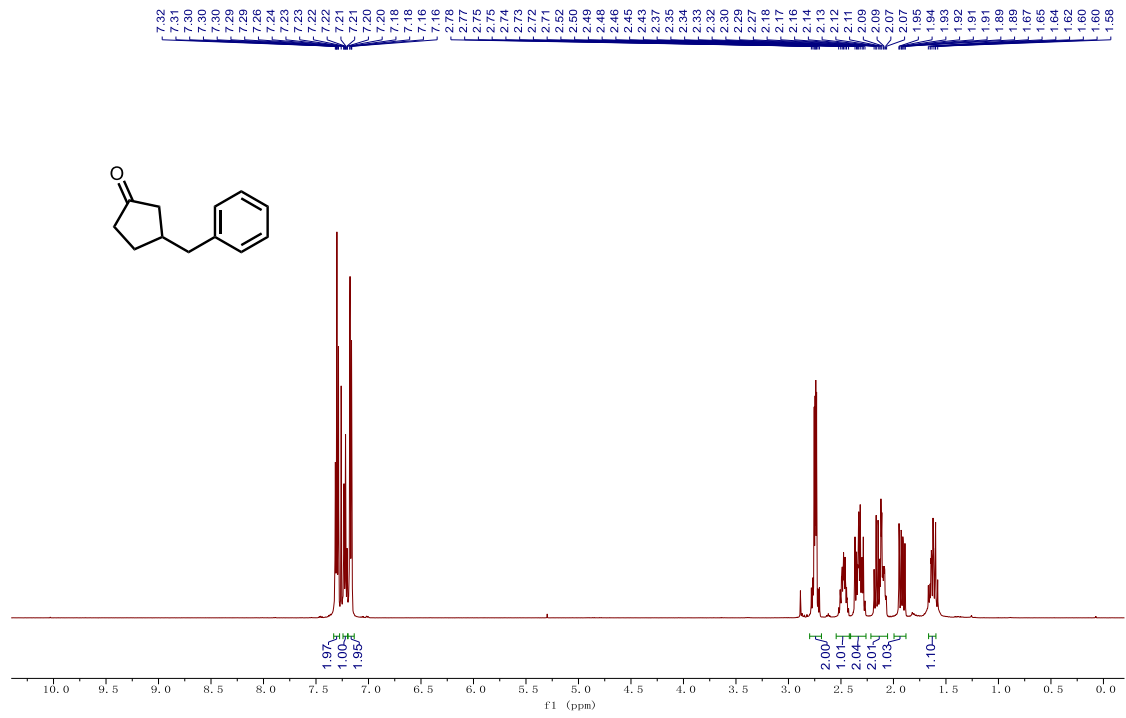
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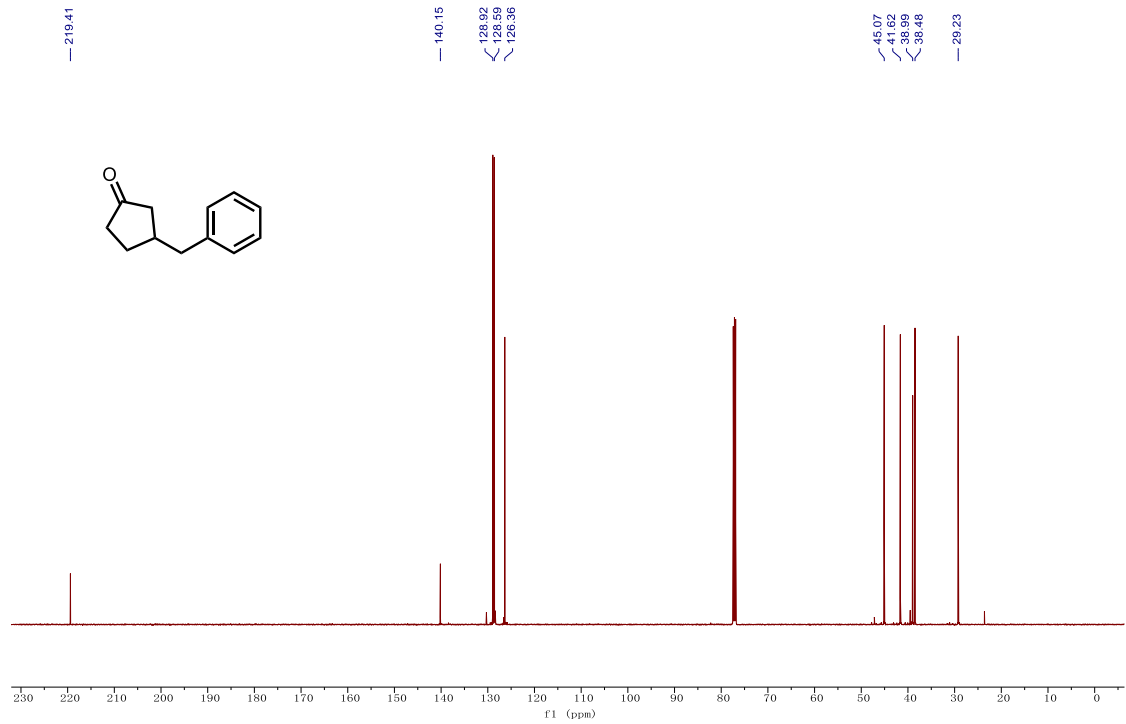
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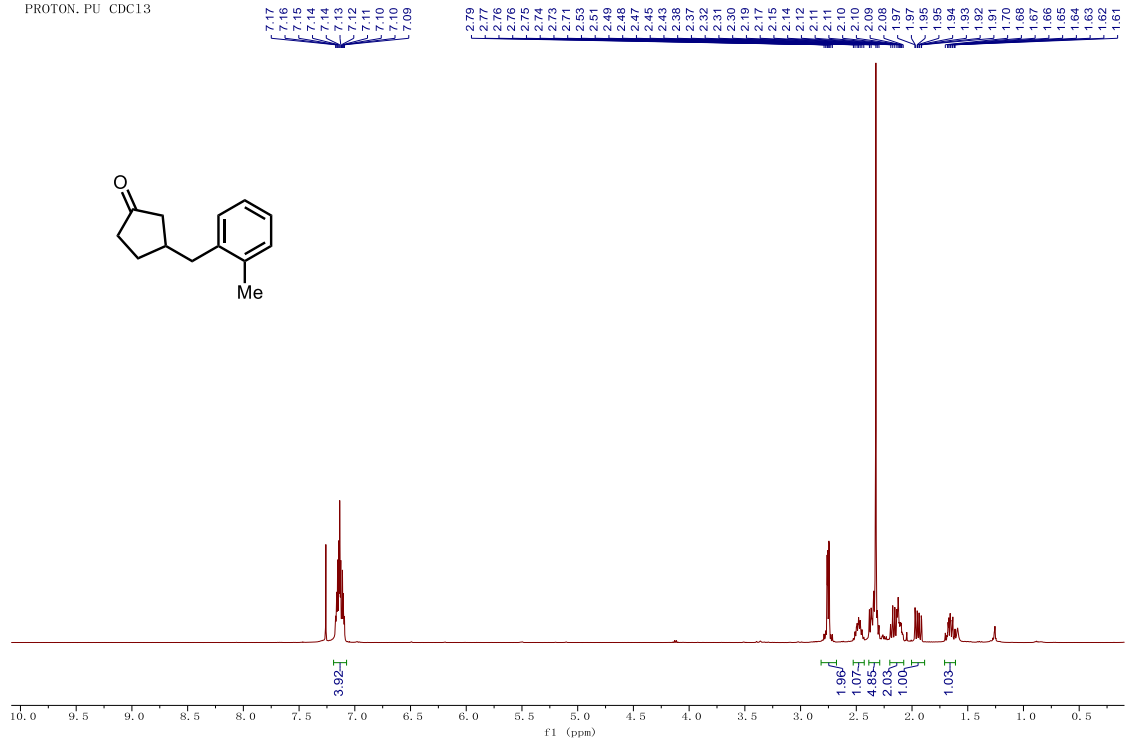
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PROTON. PU CDC13



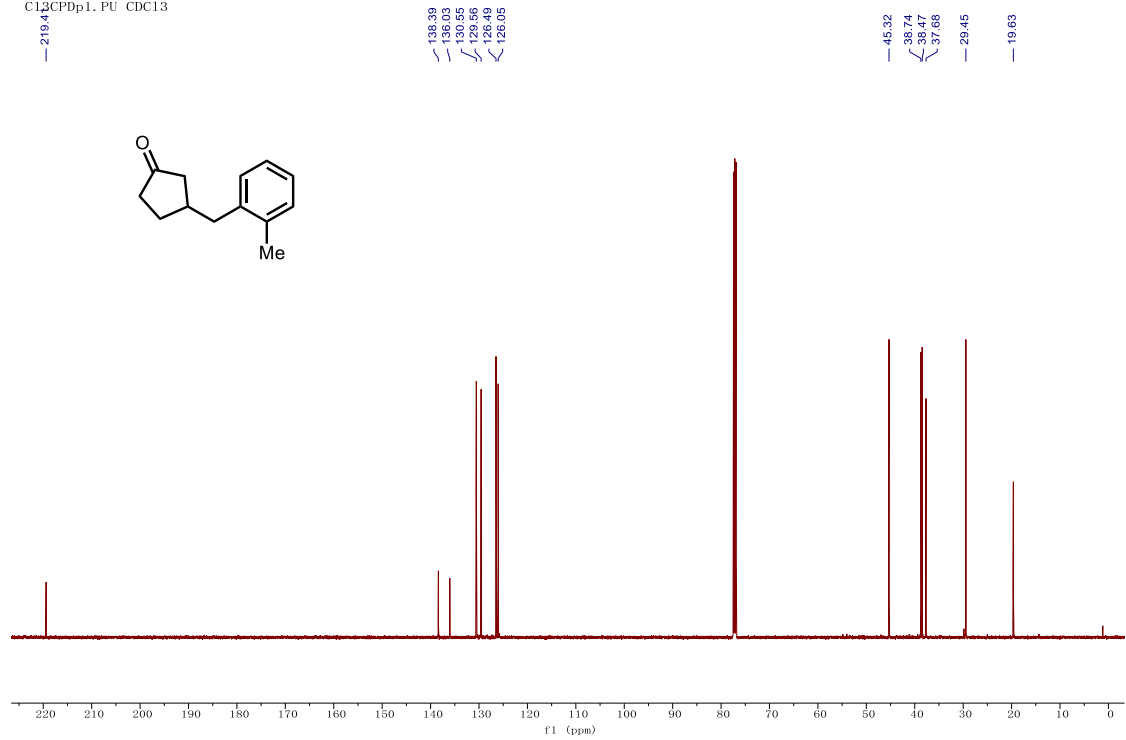
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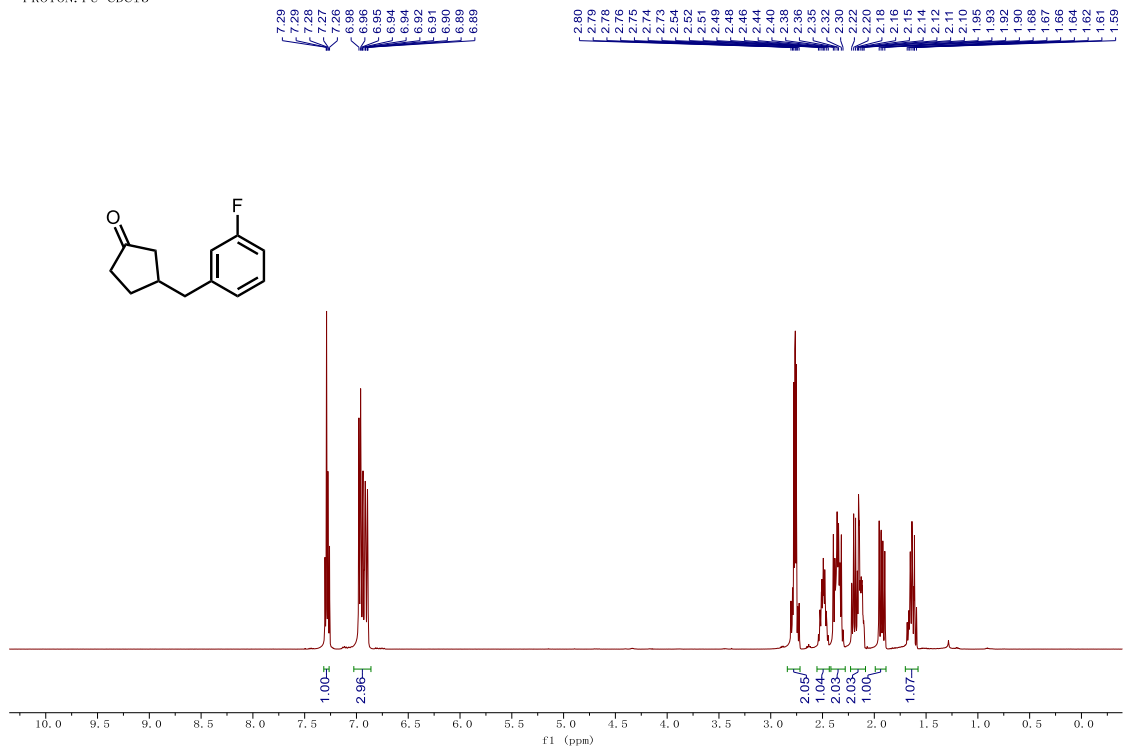
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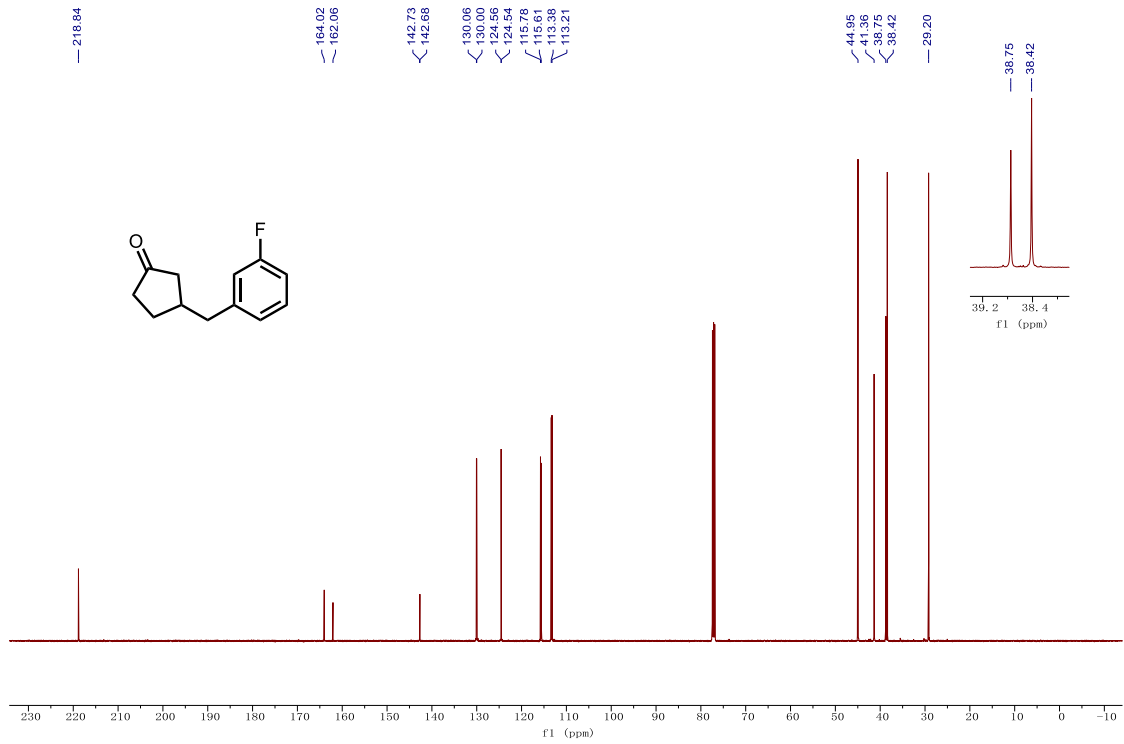
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C13CPDp1. PU CDC13



HFU-pdt-c-mF  
PROTON, PU CDC13

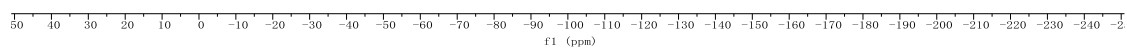
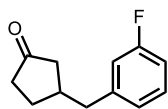


HFU-pdt-c-mF  
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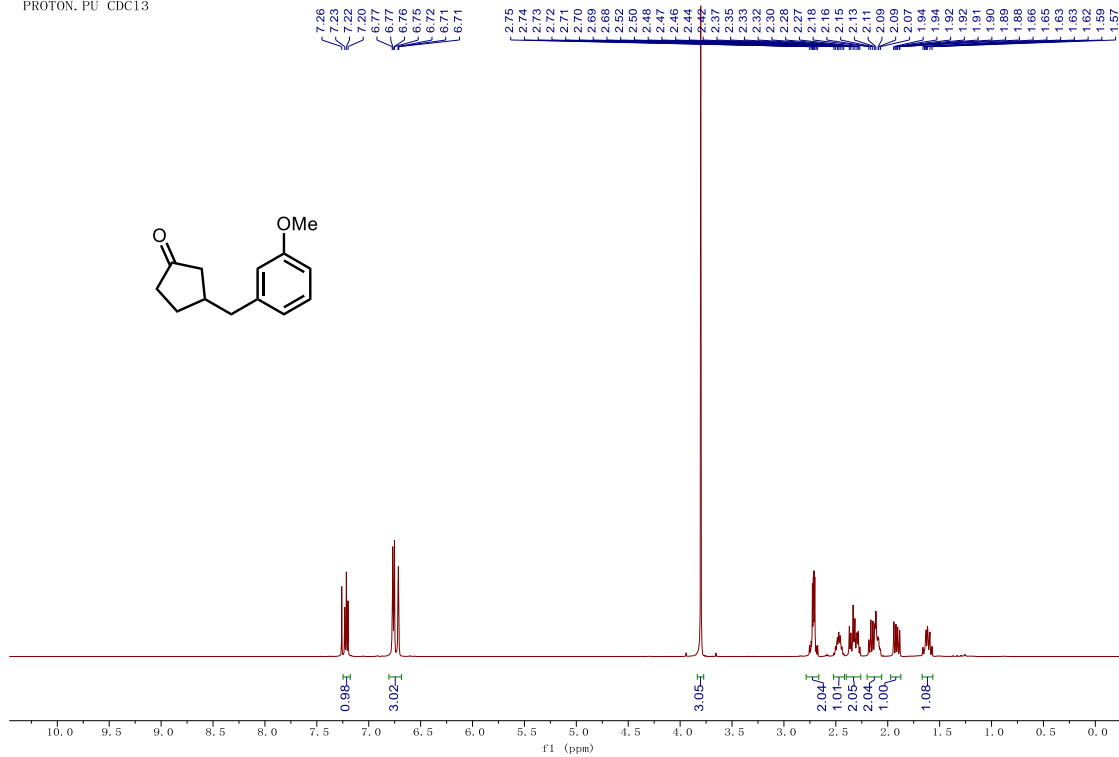


HFU-pdt-mF  
FNMR

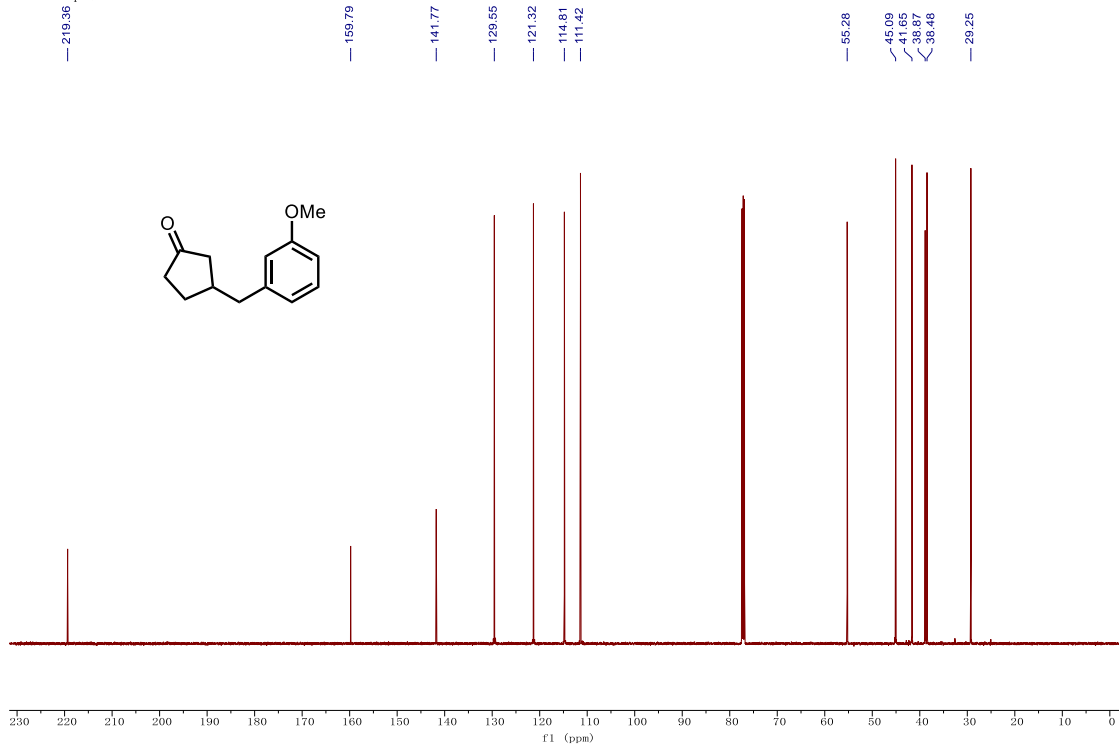
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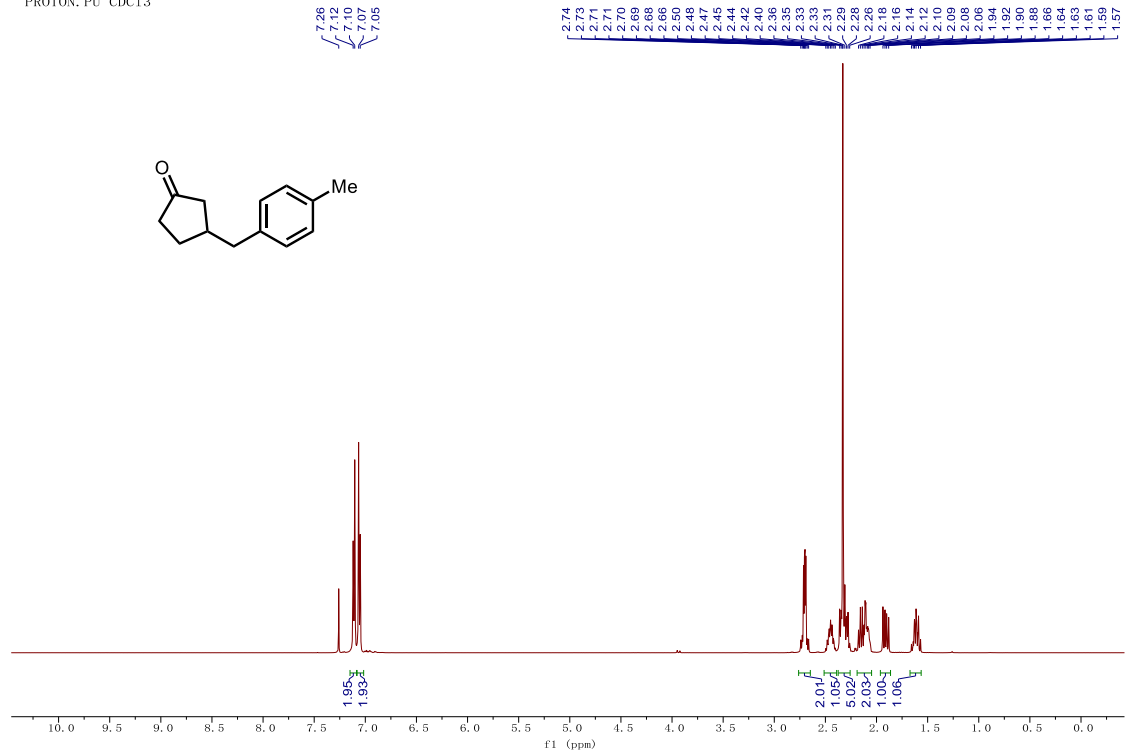
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PROTON. PU CDC13



HFU-pdt-mOMe  
C13CPDp1. PU CDC13



HL-pdt-pMe  
PROTON, PU CDC13

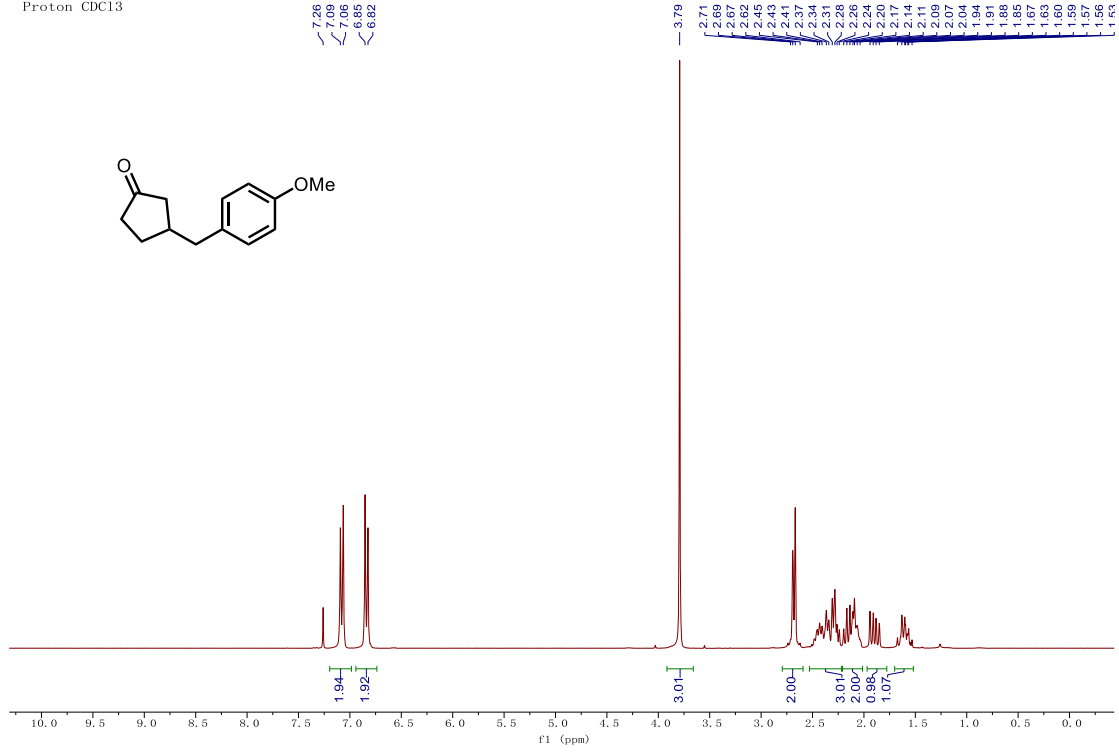


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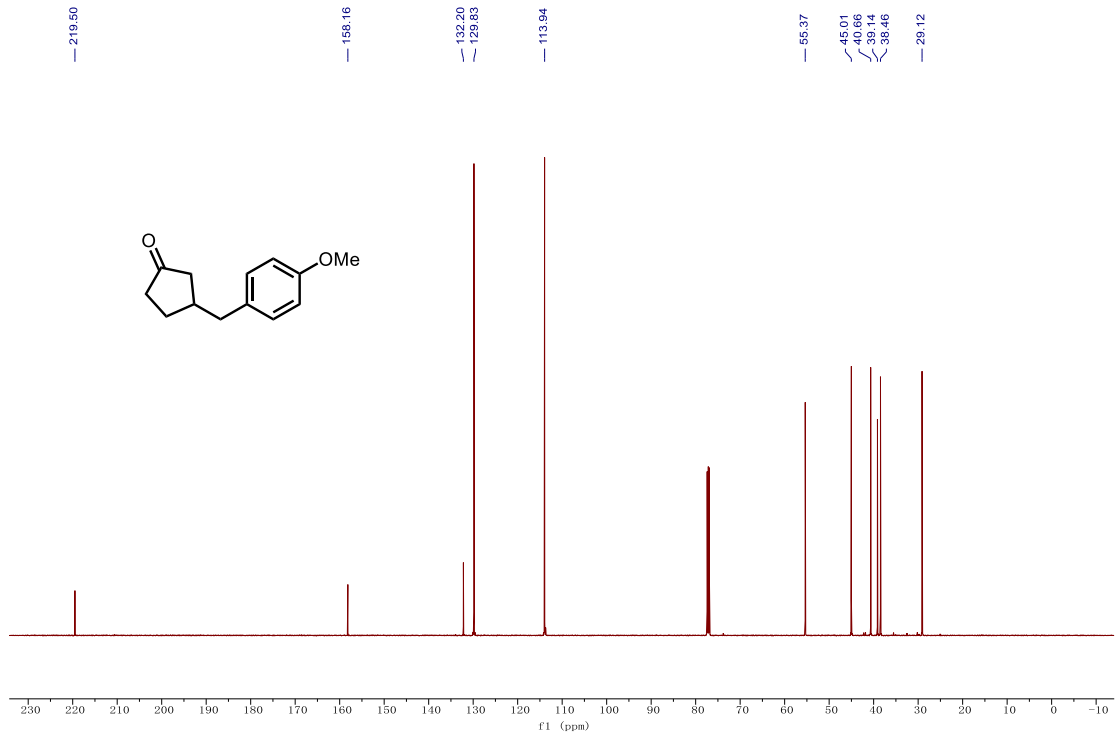




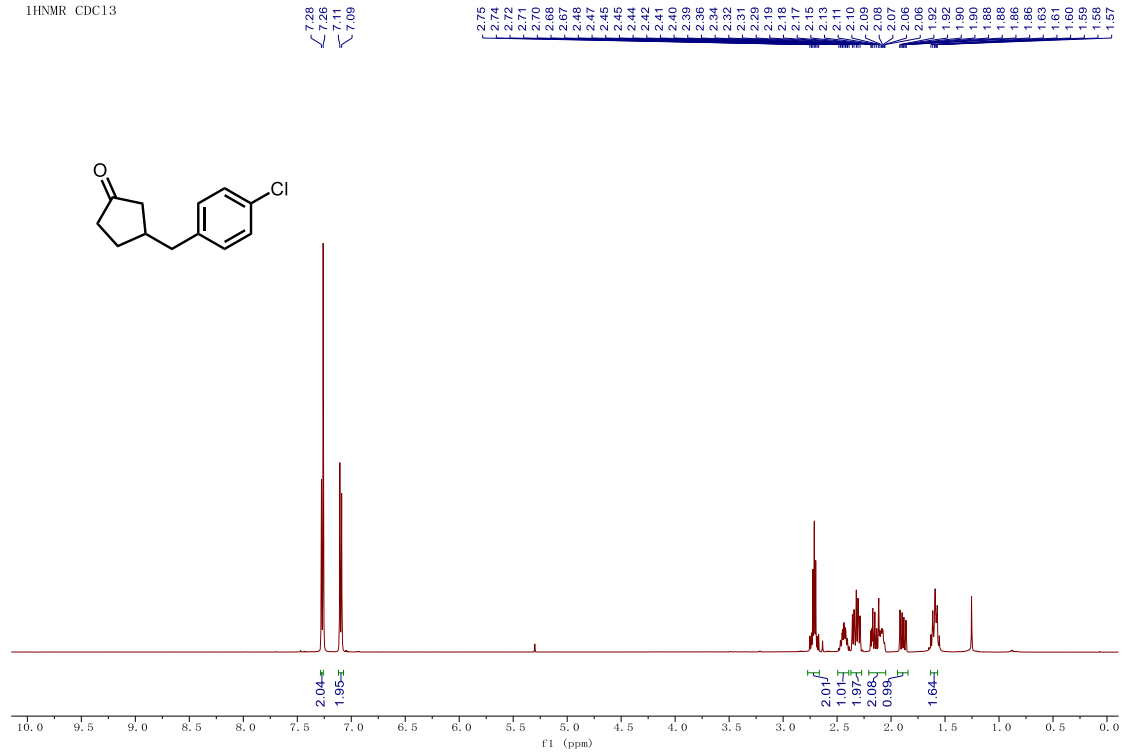
HFU-pdt-c-pOMe  
Proton CDC13



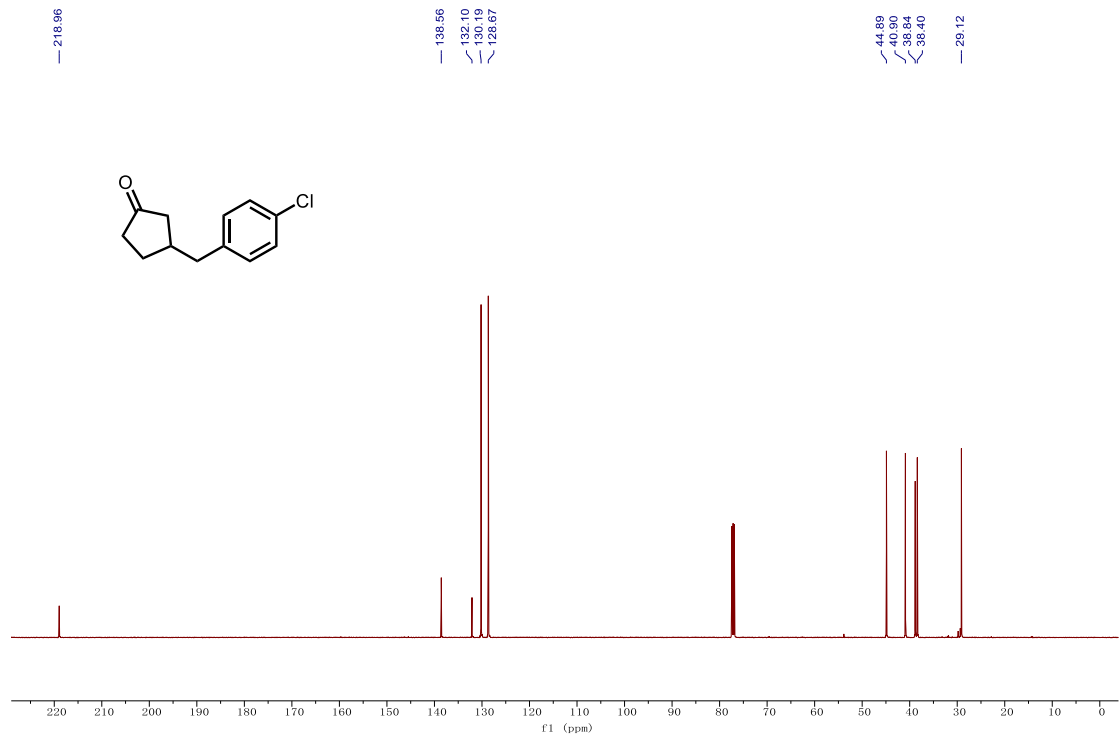
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C13CPDp1. PU CDC13



HL-pdt-pCl  
1H NMR CDCl<sub>3</sub>



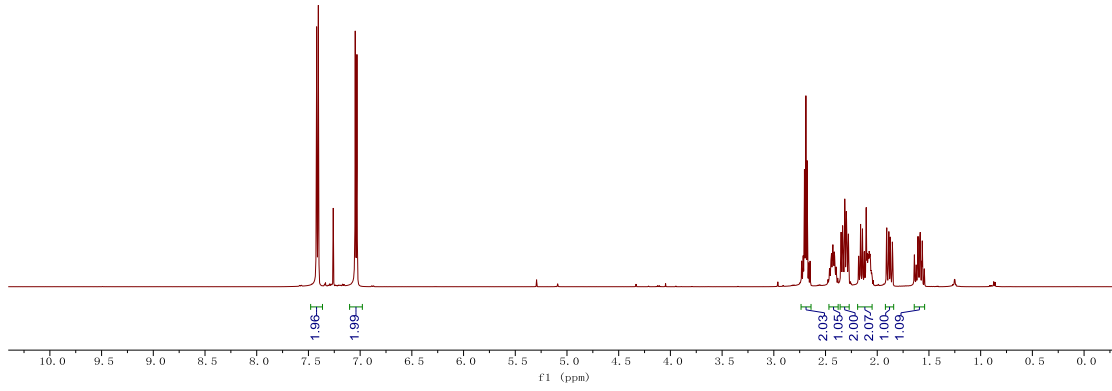
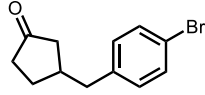
HL-pdt-pCl  
13C NMR CDCl<sub>3</sub>



HFU-pdt-pBr  
PROTON. PU CDC13

7.42  
7.40  
7.26  
7.05  
7.03

2.73  
2.72  
2.70  
2.68  
2.66  
2.65  
2.48  
2.46  
2.45  
2.43  
2.40  
2.38  
2.35  
2.33  
2.31  
2.30  
2.29  
2.18  
2.16  
2.14  
2.13  
2.11  
2.10  
2.08  
2.07  
2.07  
2.04  
1.91  
1.89  
1.87  
1.85  
1.85  
1.84  
1.82  
1.82  
1.58  
1.56  
1.55



HFU-pdt-pBr  
C13CPDp1. PU CDC13

218.89

139.09

131.65

130.61

120.16

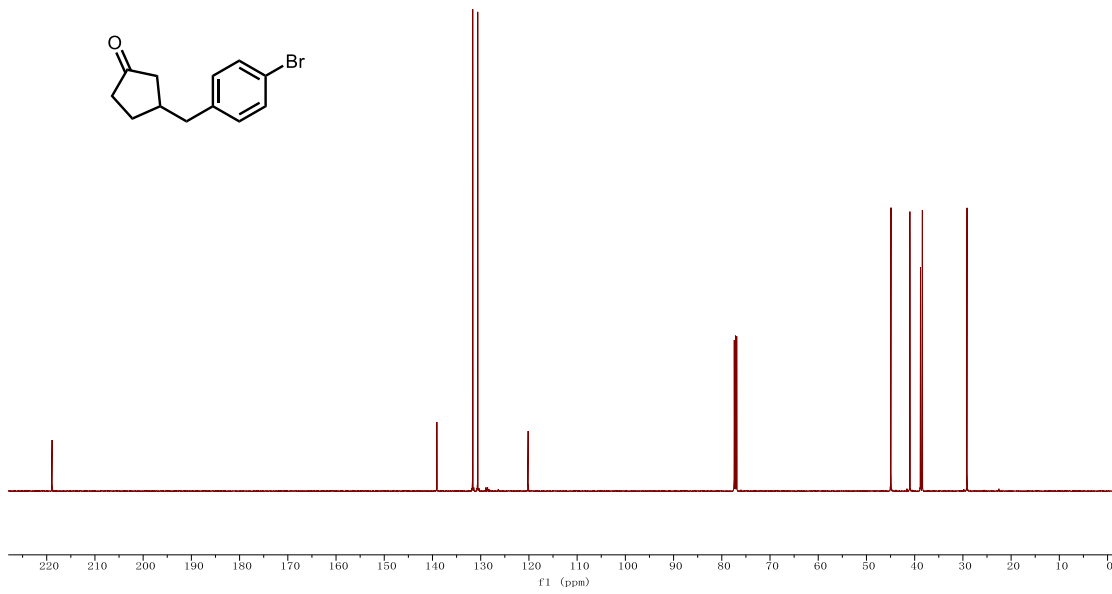
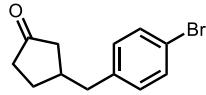
44.91

40.99

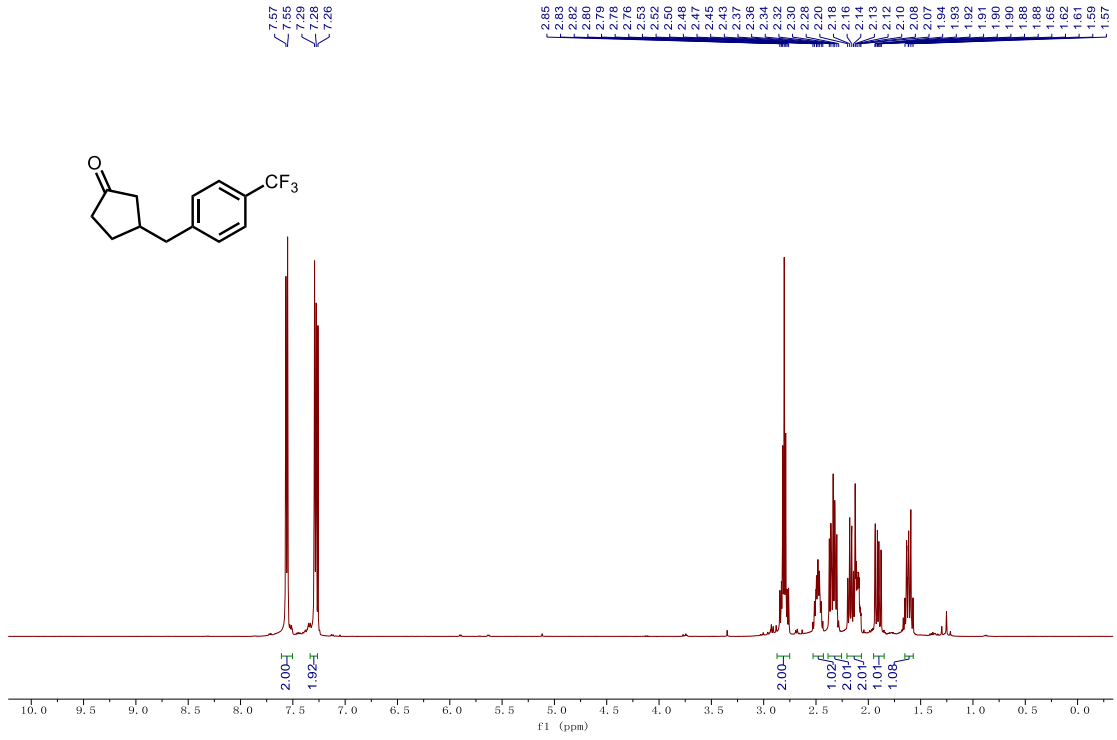
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36.41

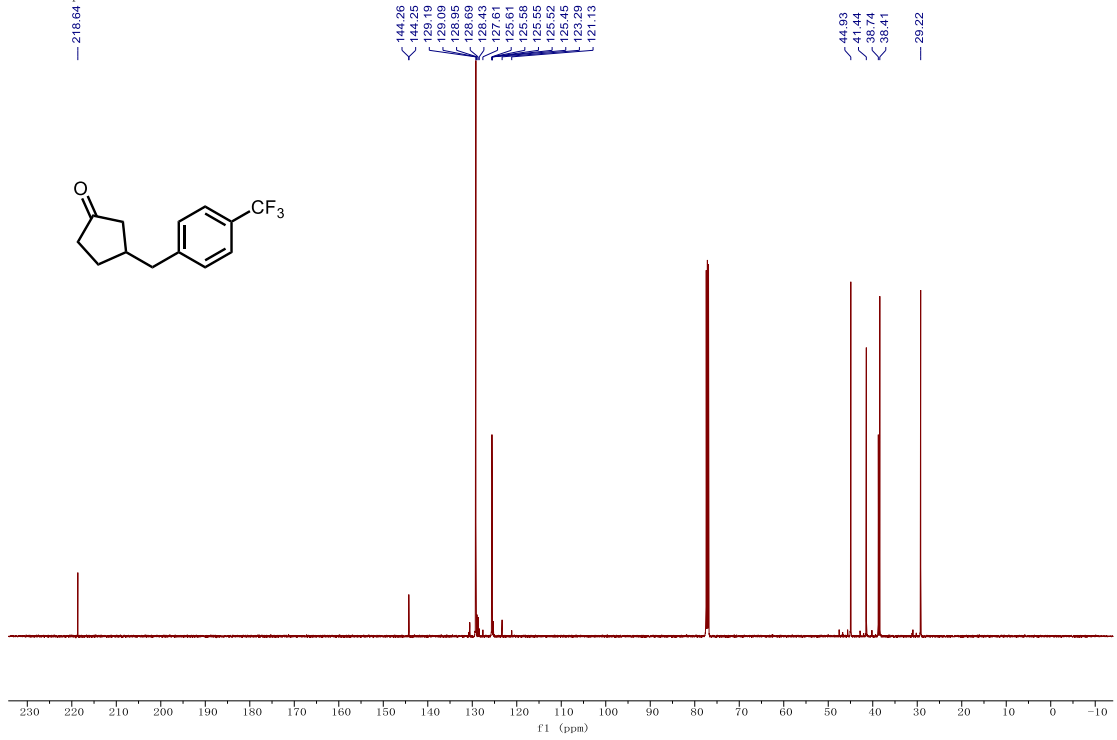
28.14



HL-pdt-pCF3  
PROTON, PU CDC13

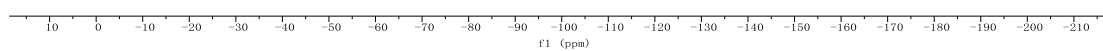
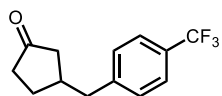


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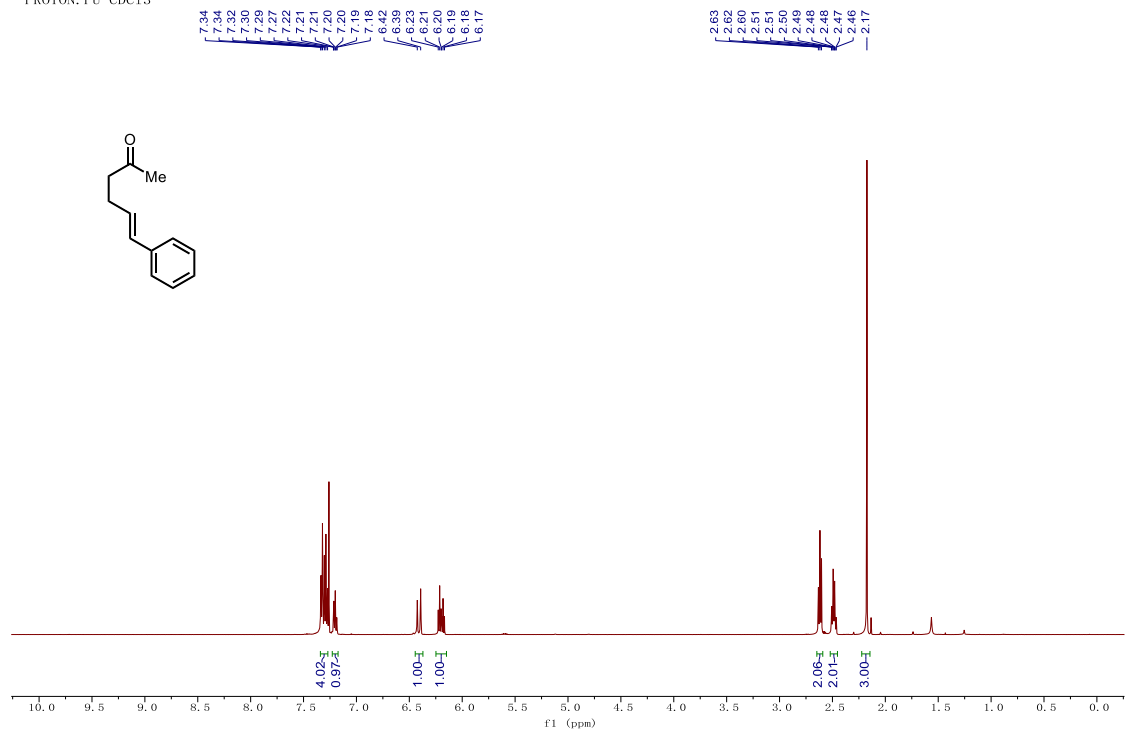


HL-pdt-CF3  
FNMR

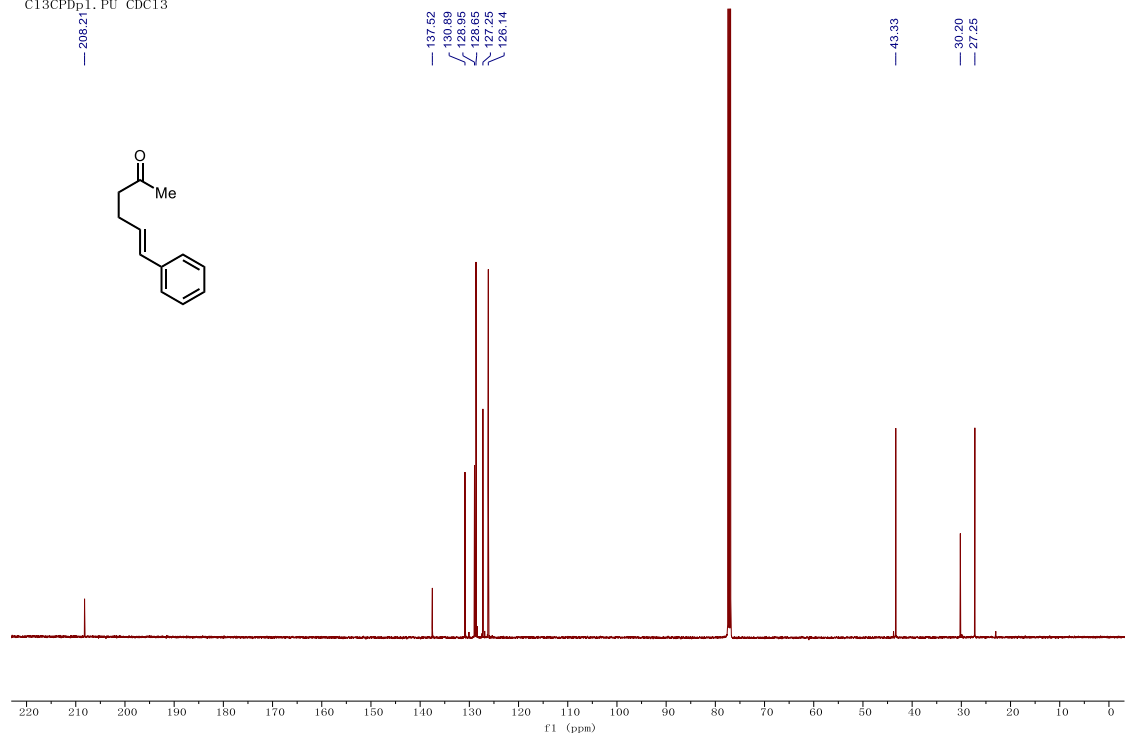
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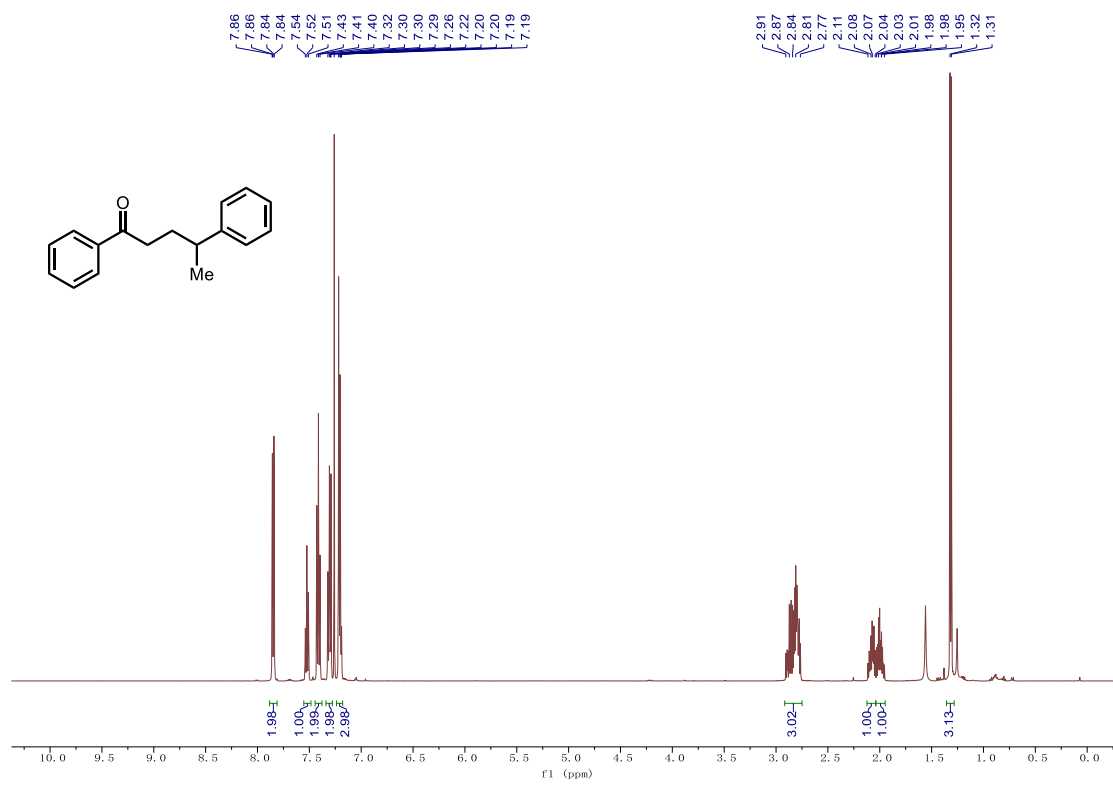


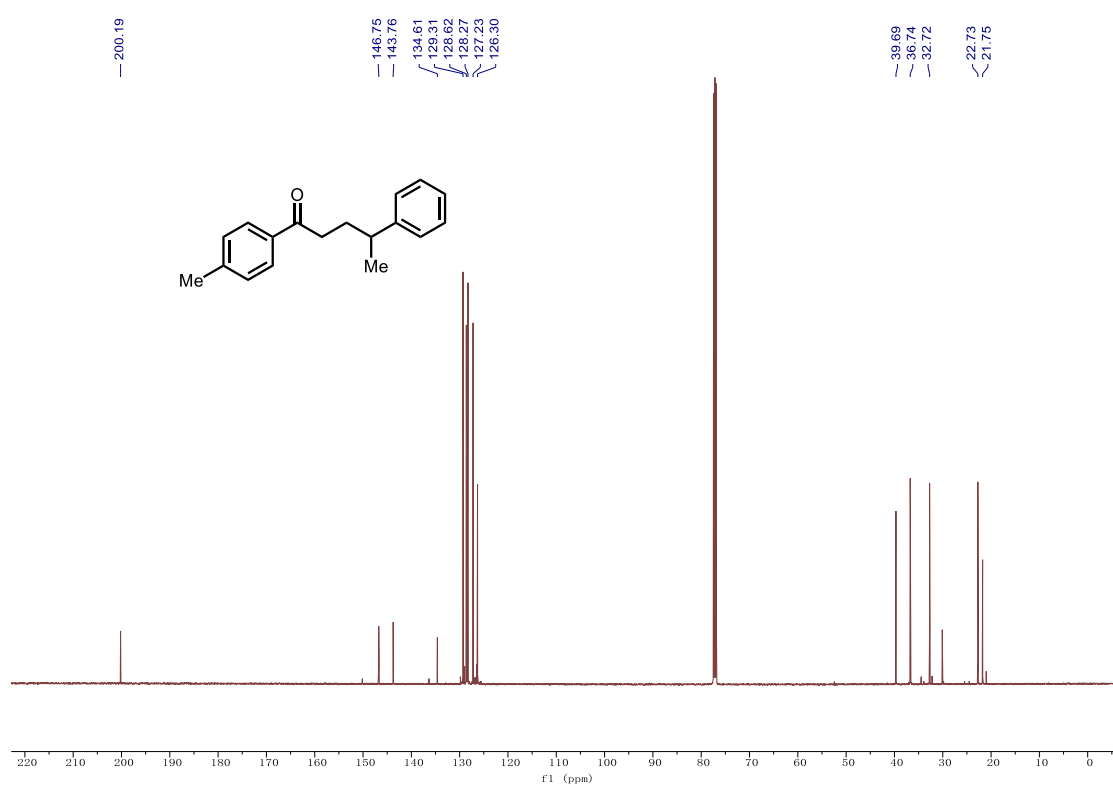
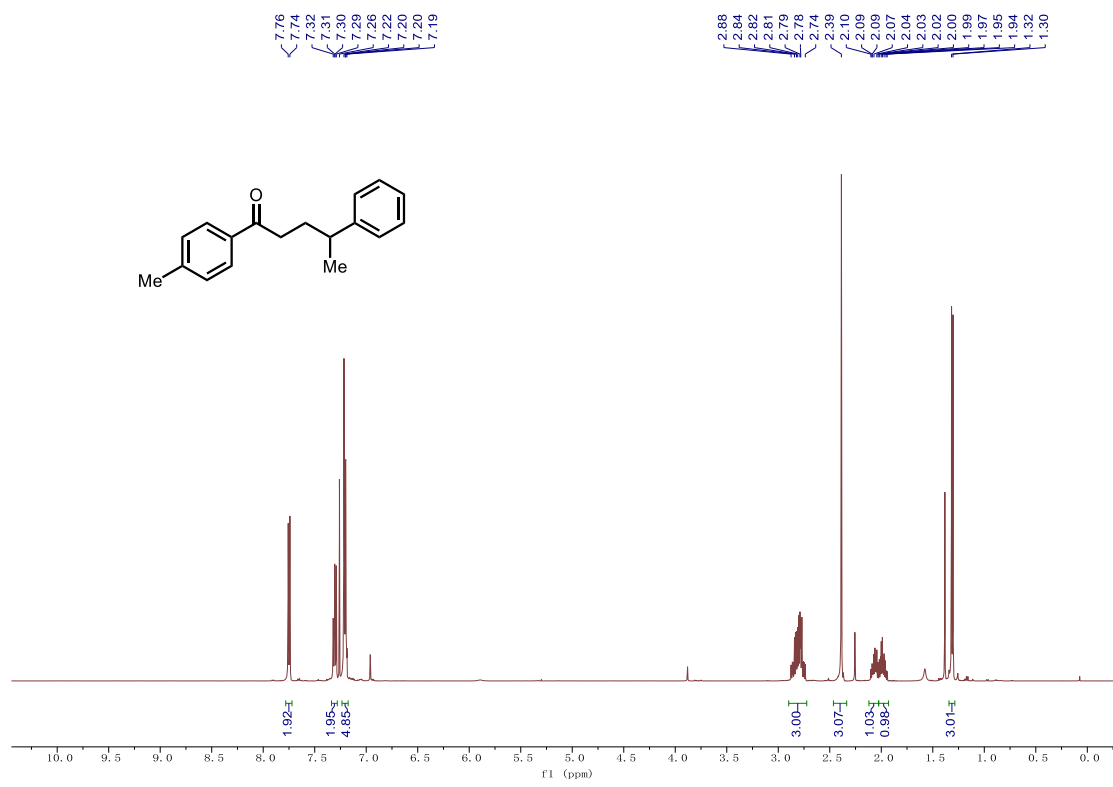
HFU-HAT.  
PROTON. PU CDC13



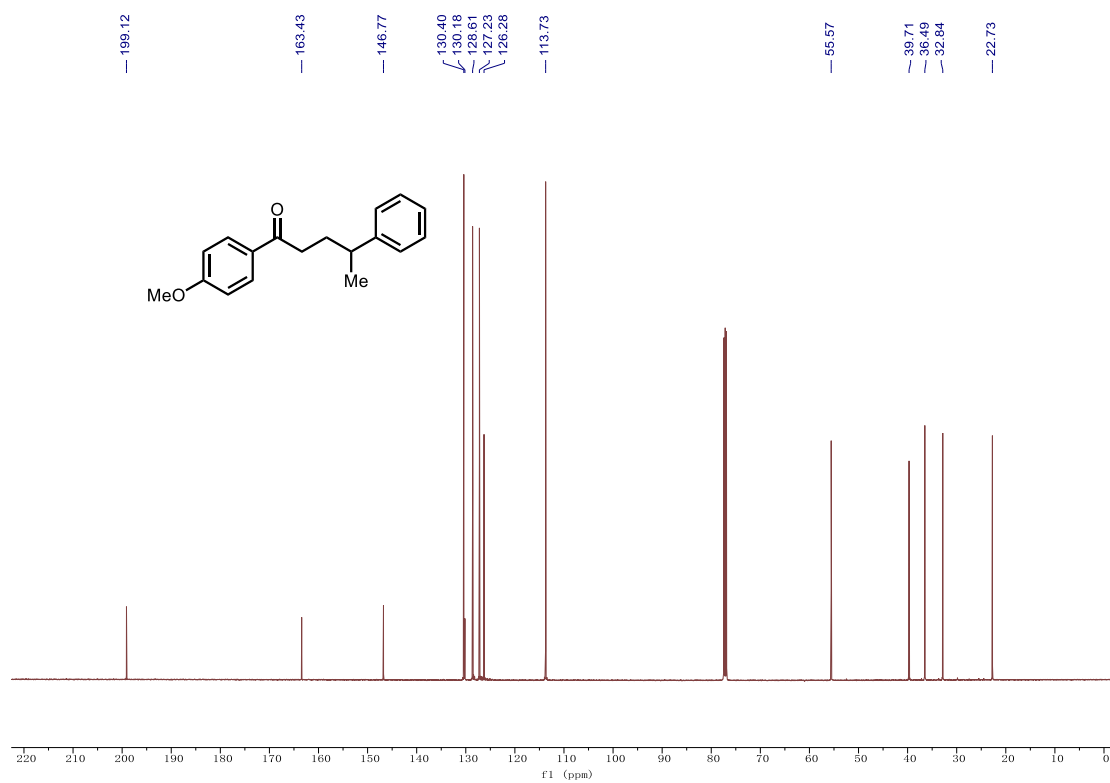
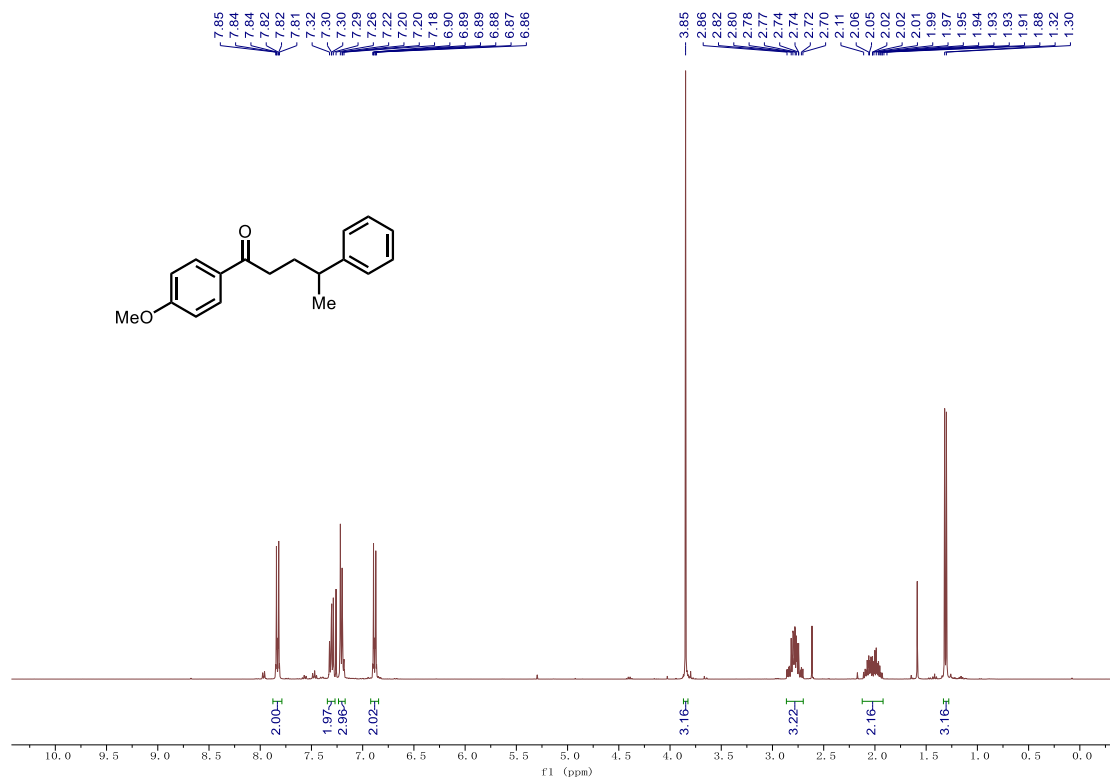
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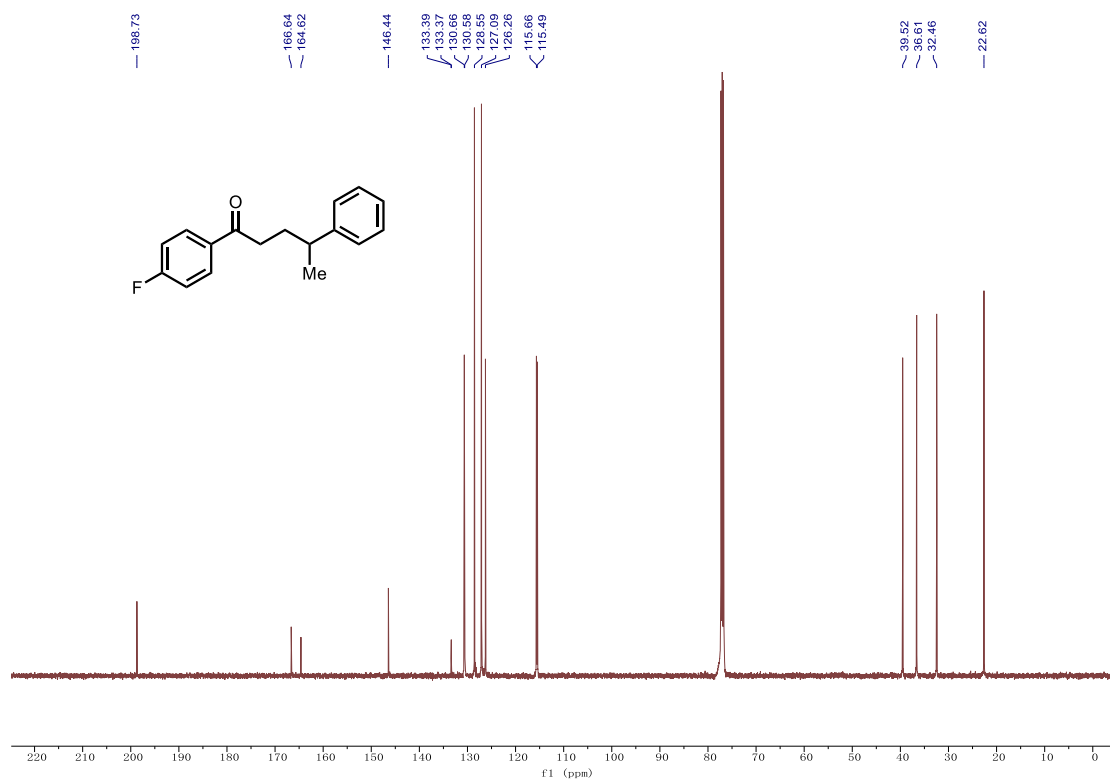
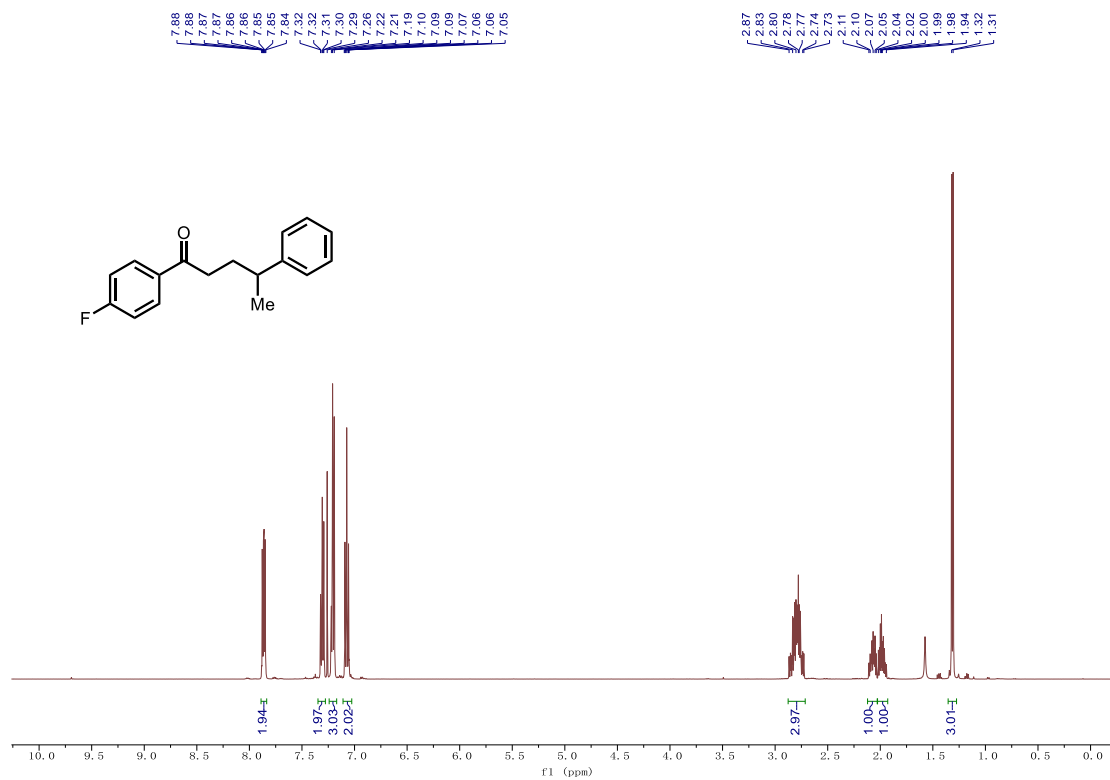


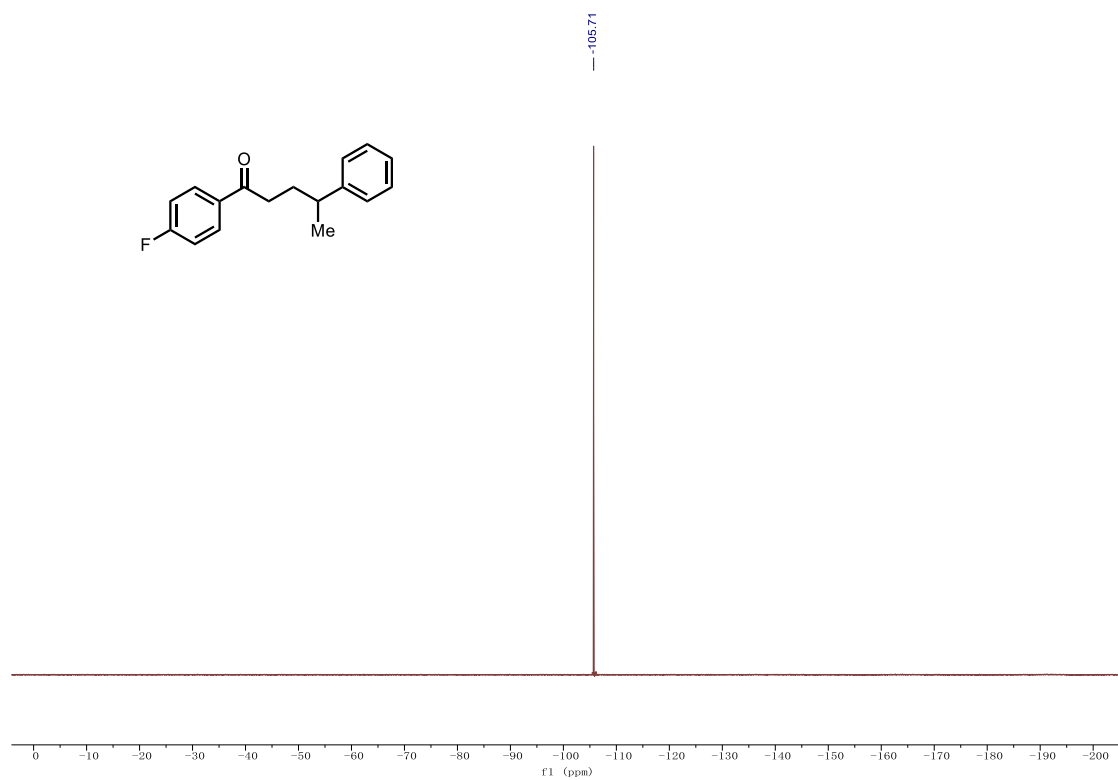


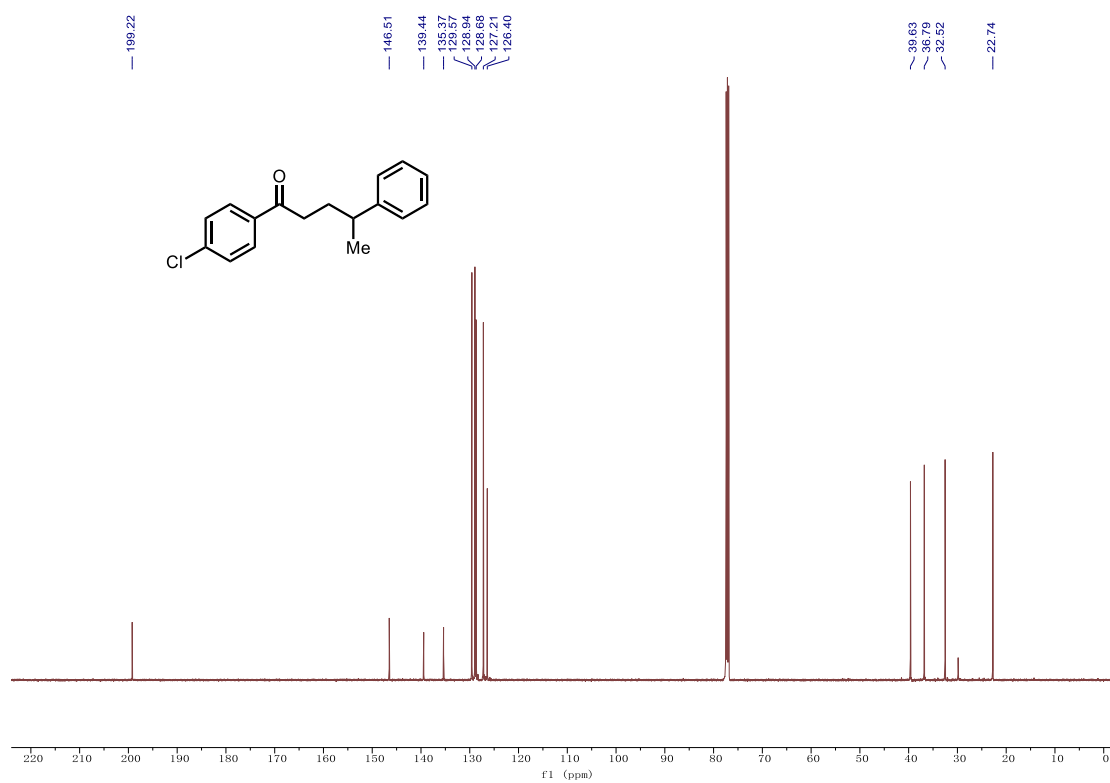
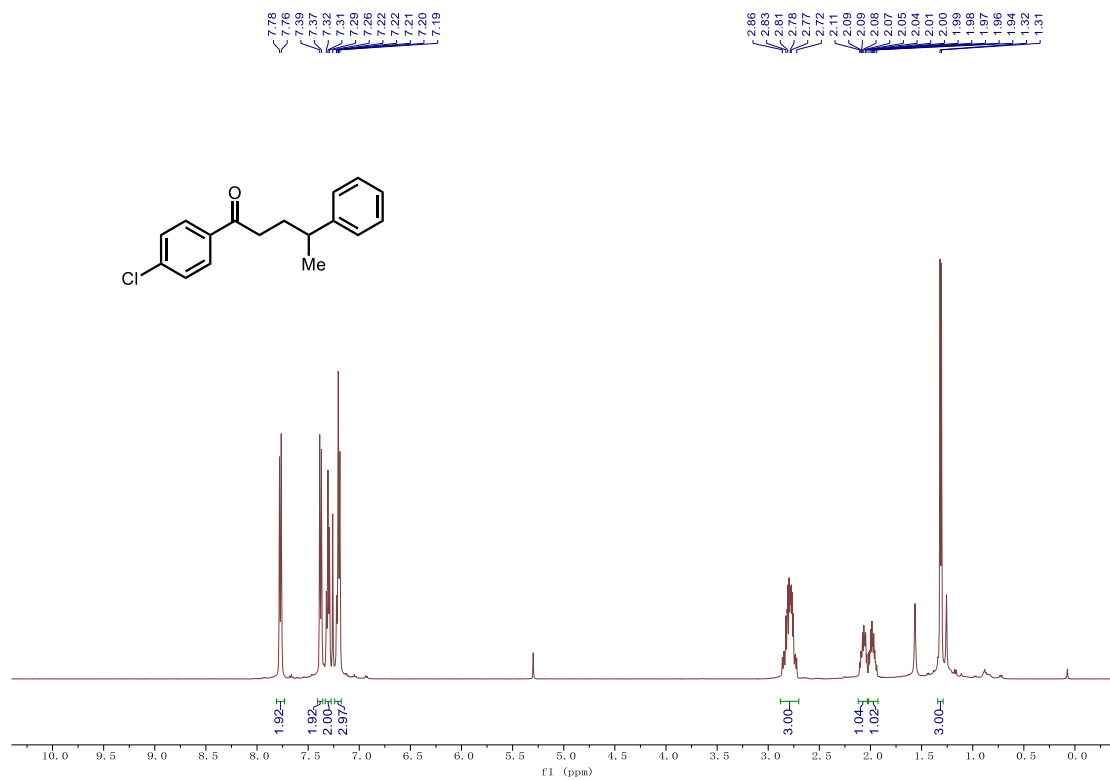


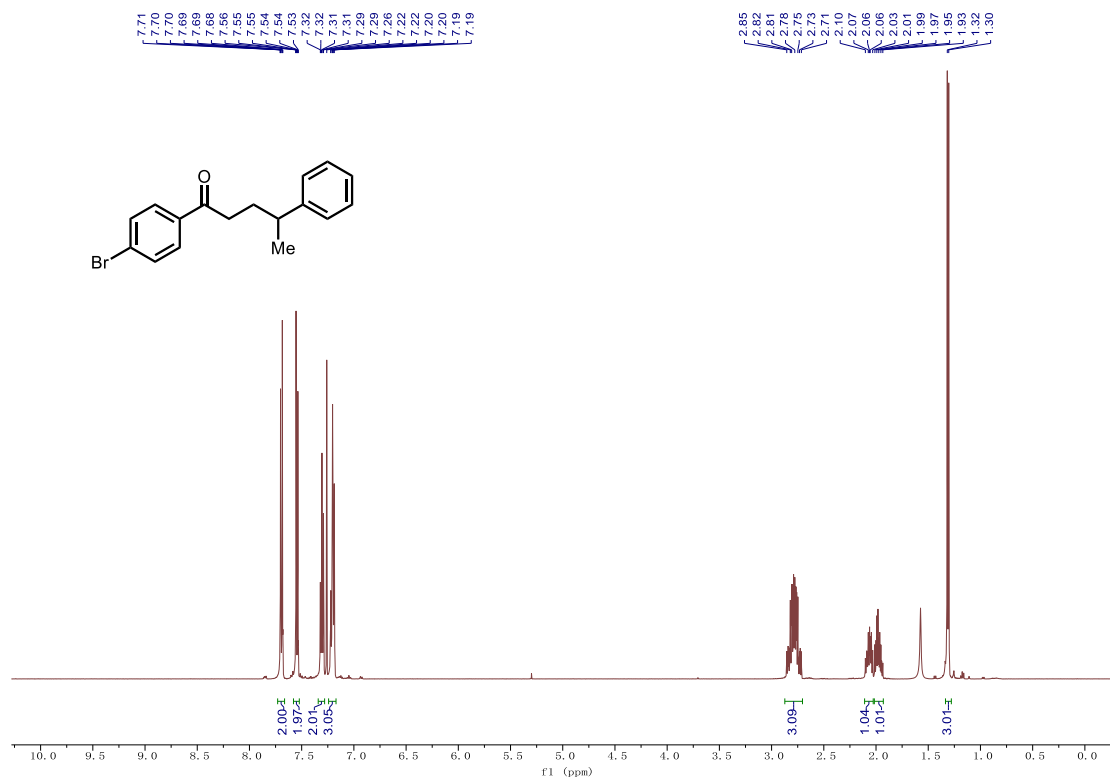


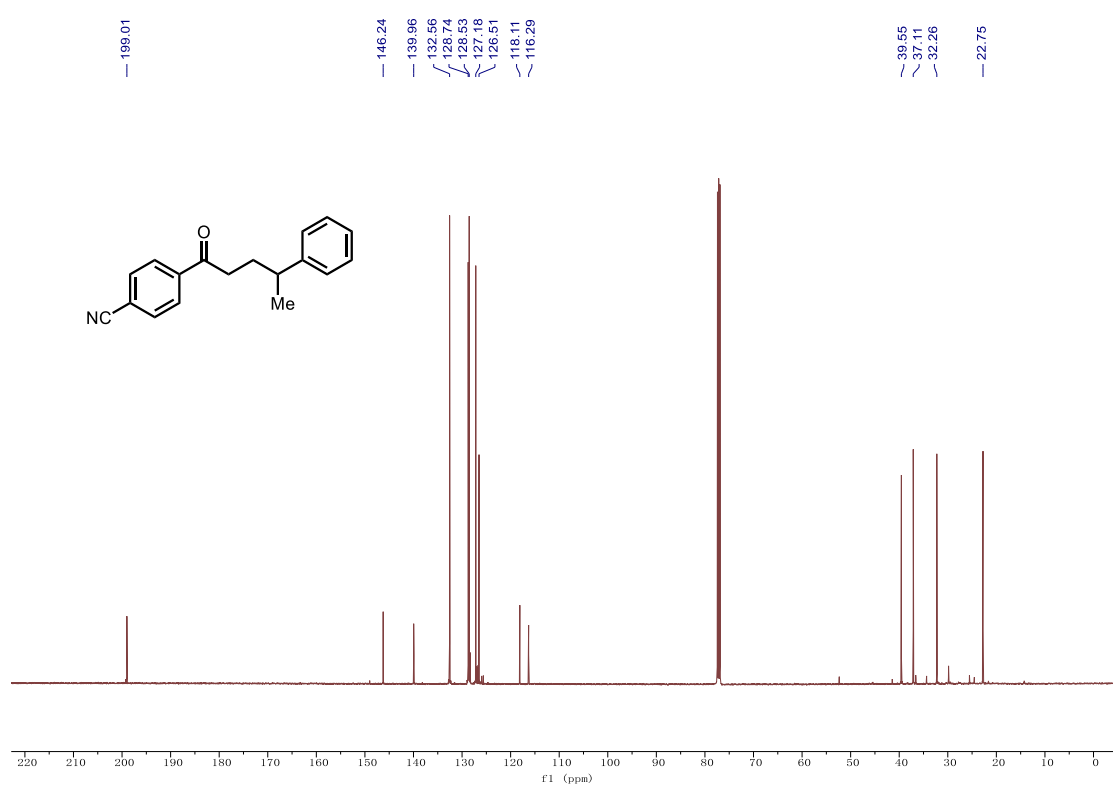
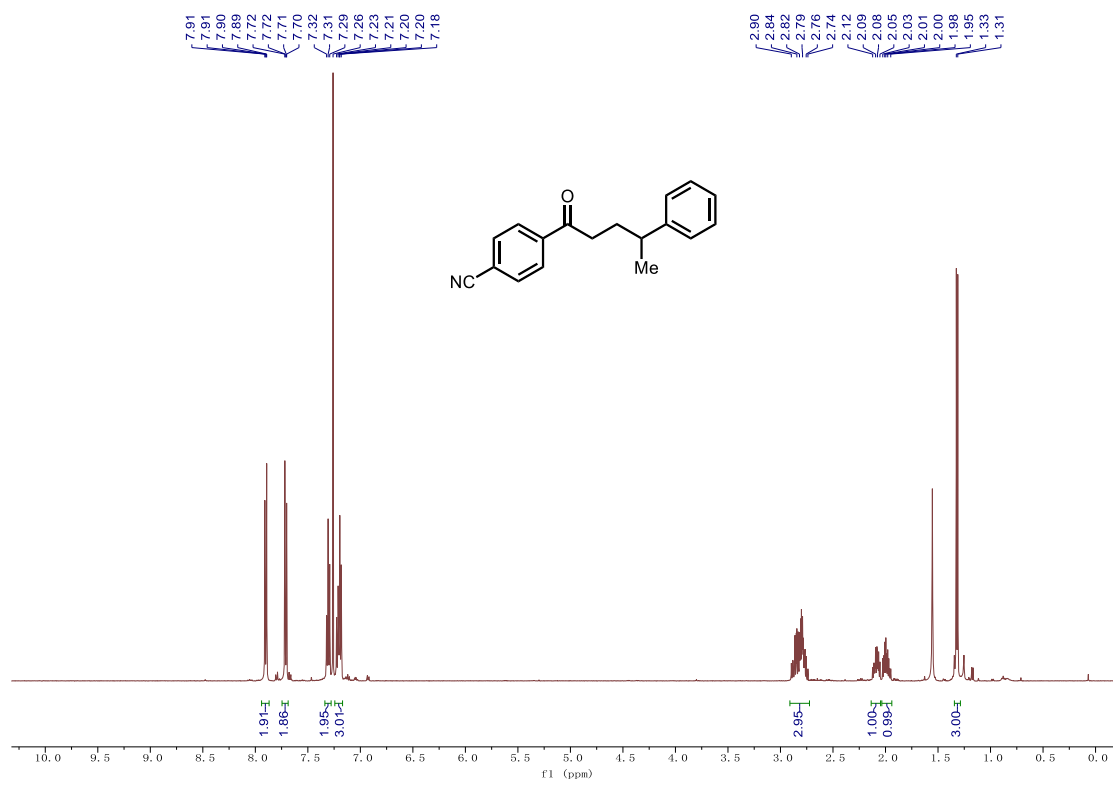


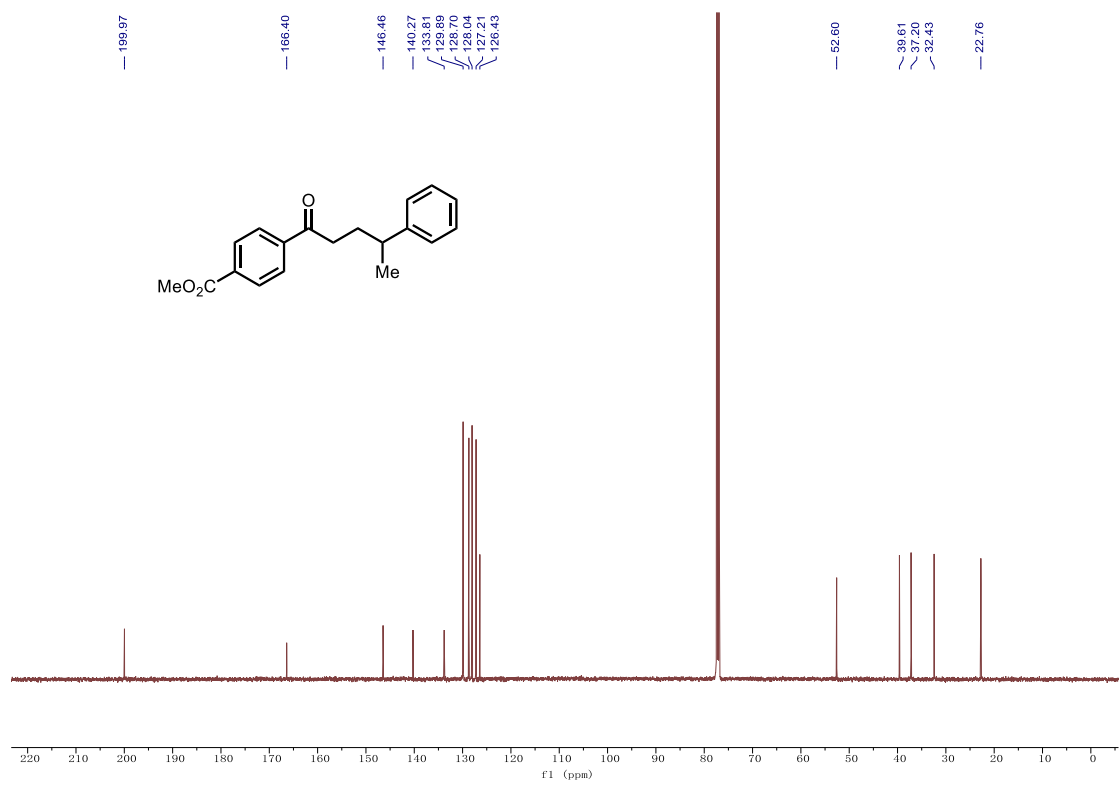
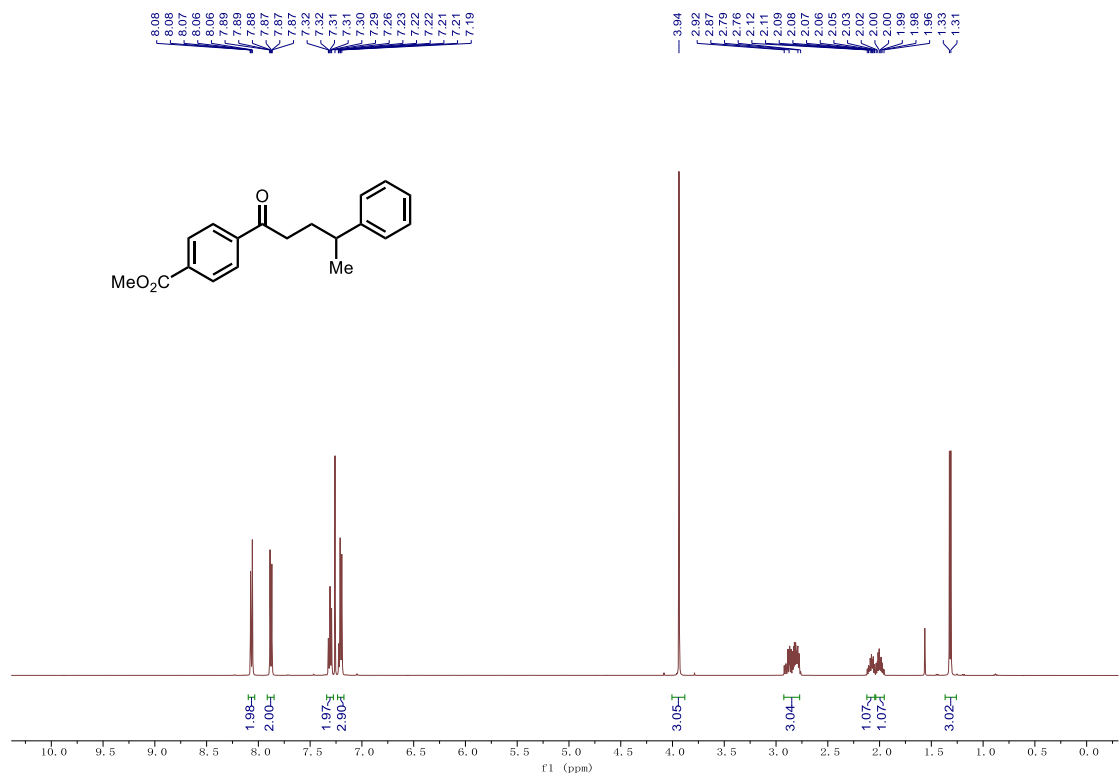


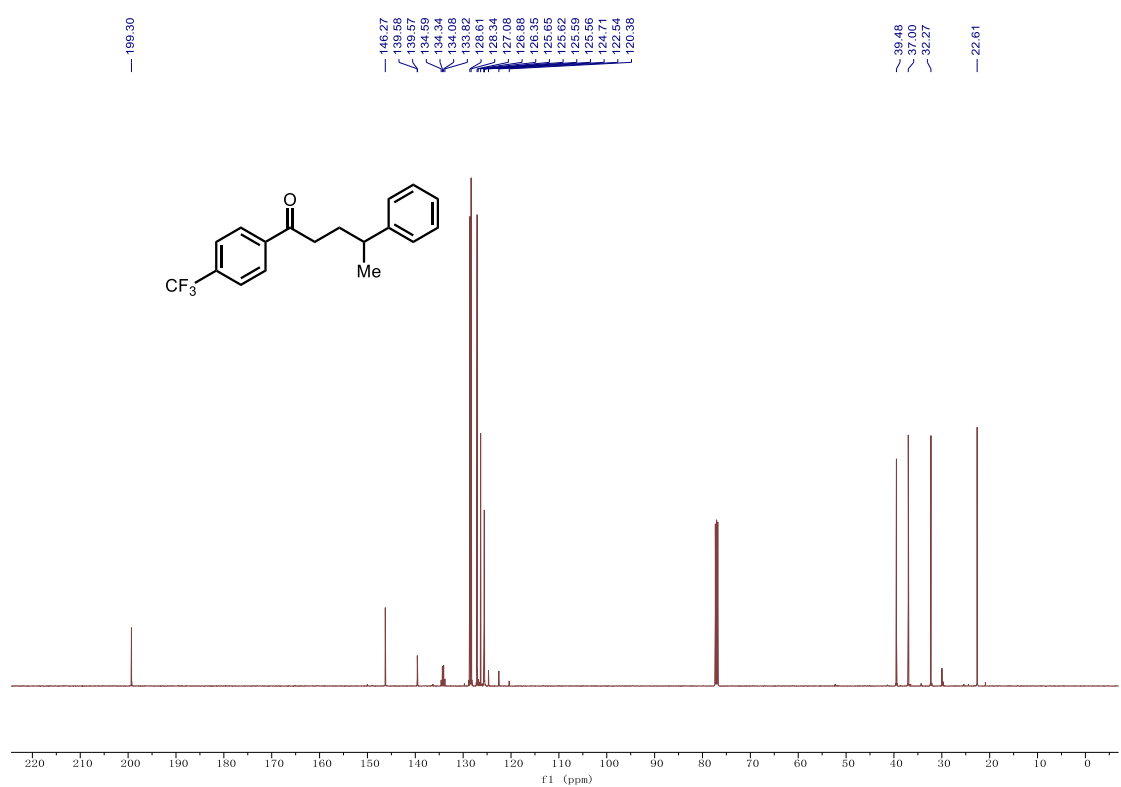
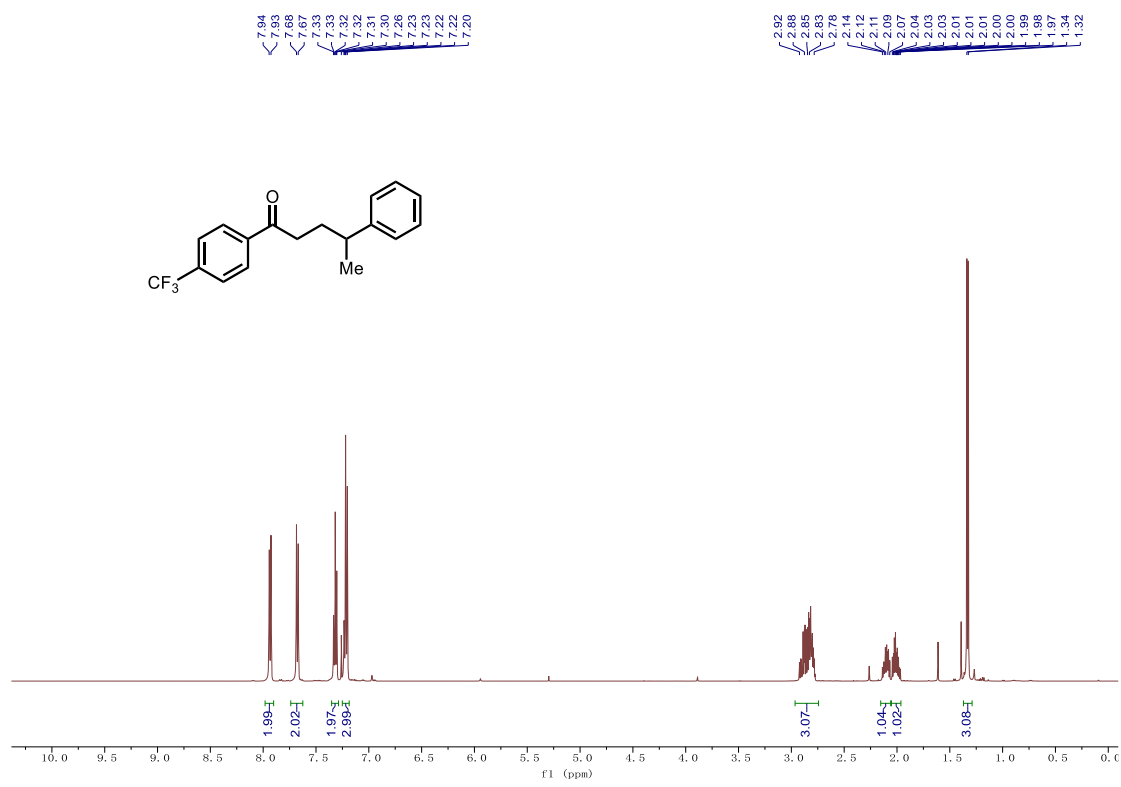




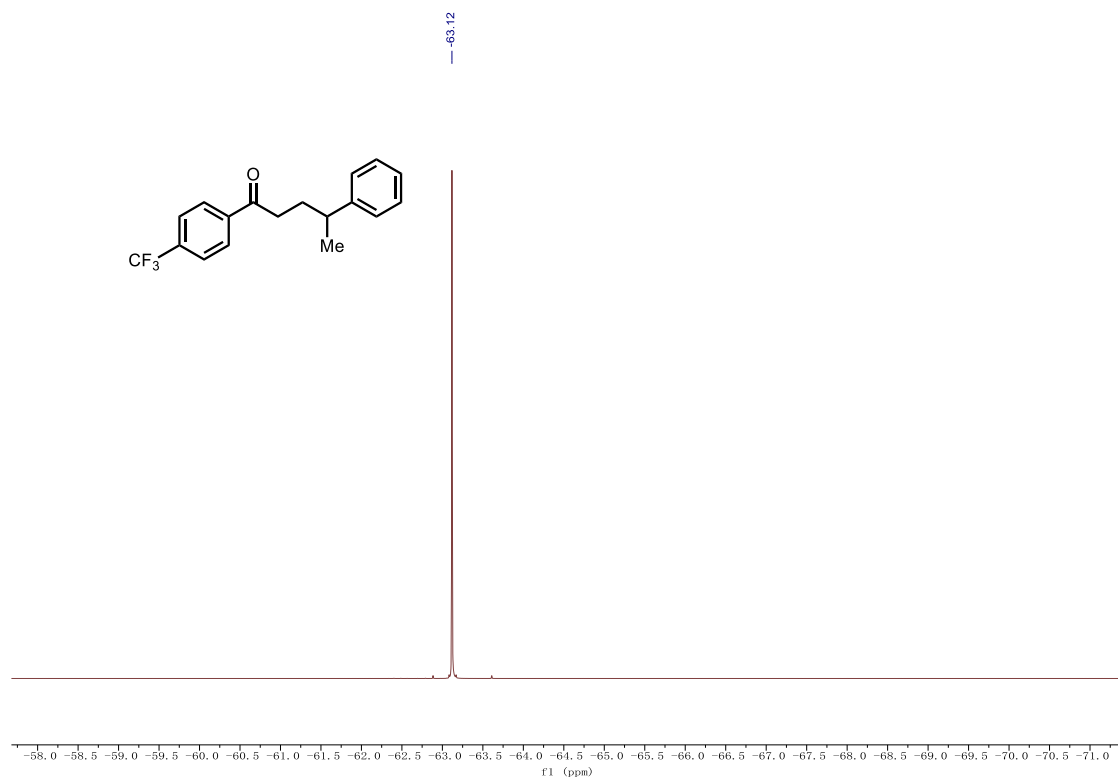


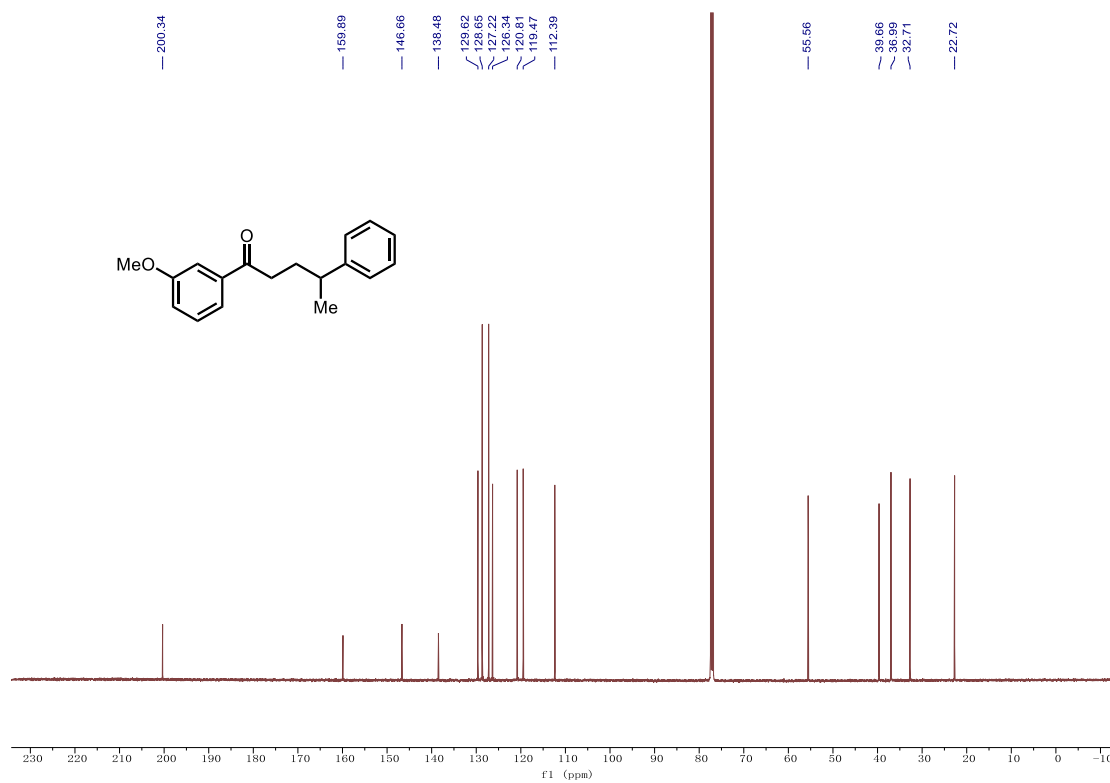
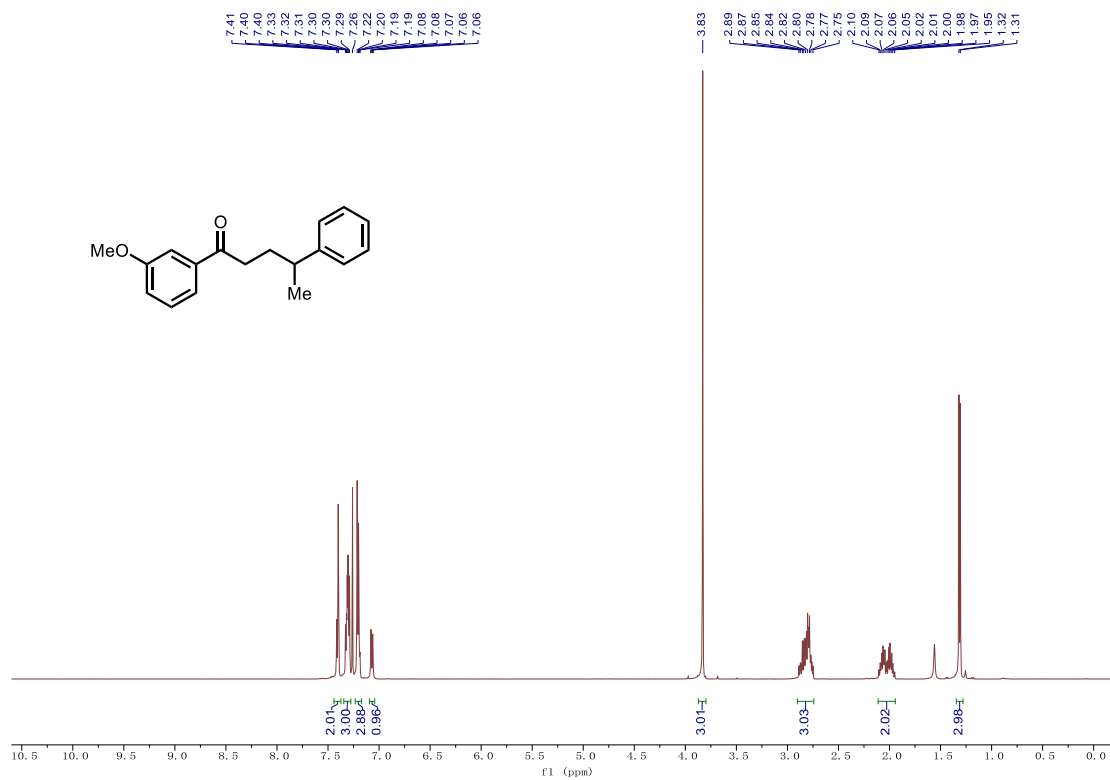


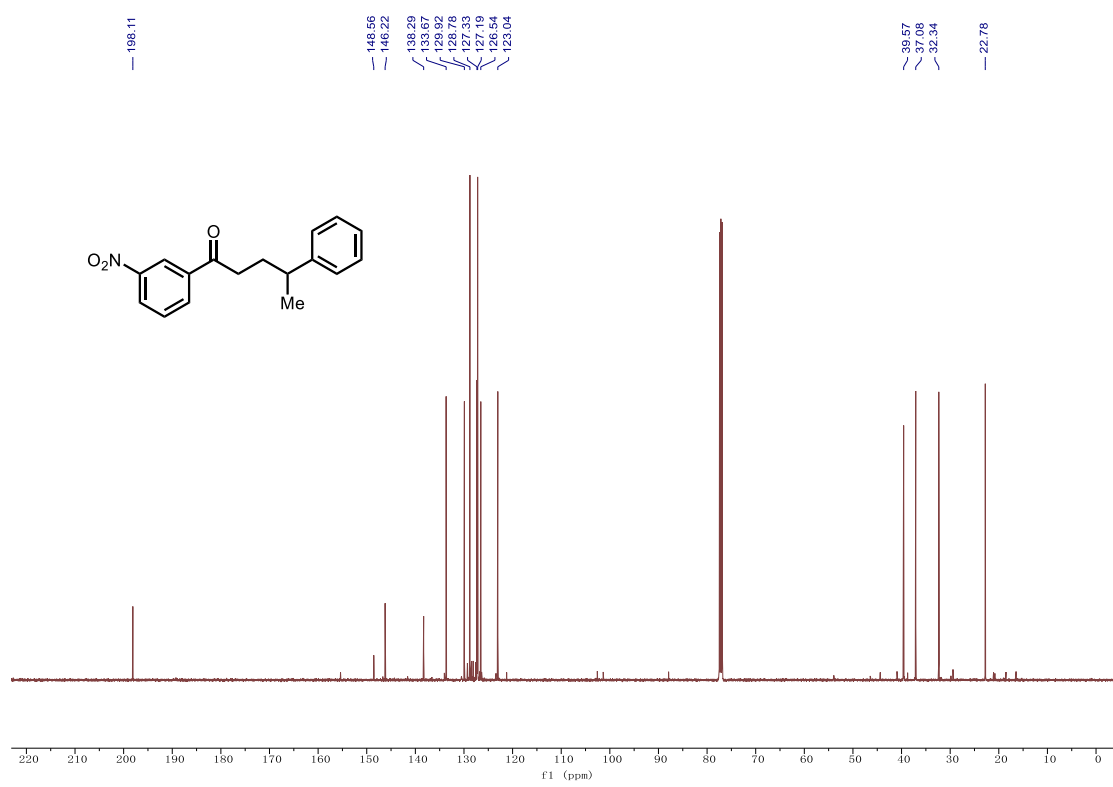
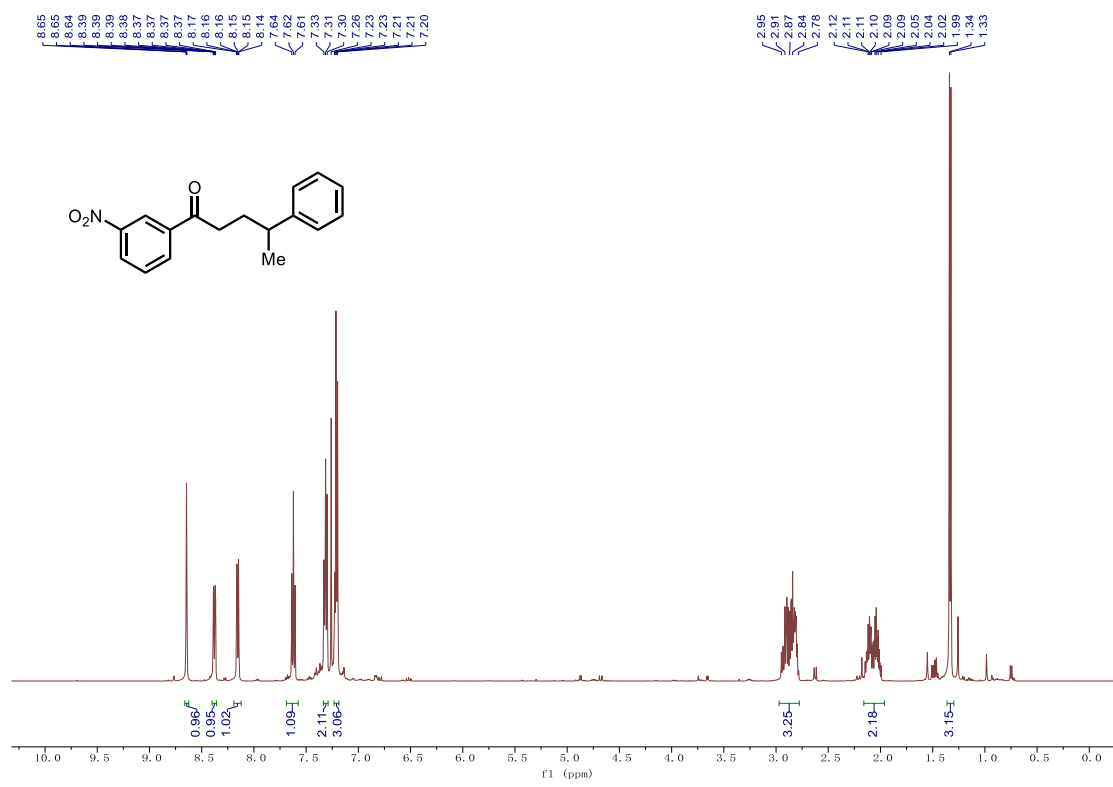


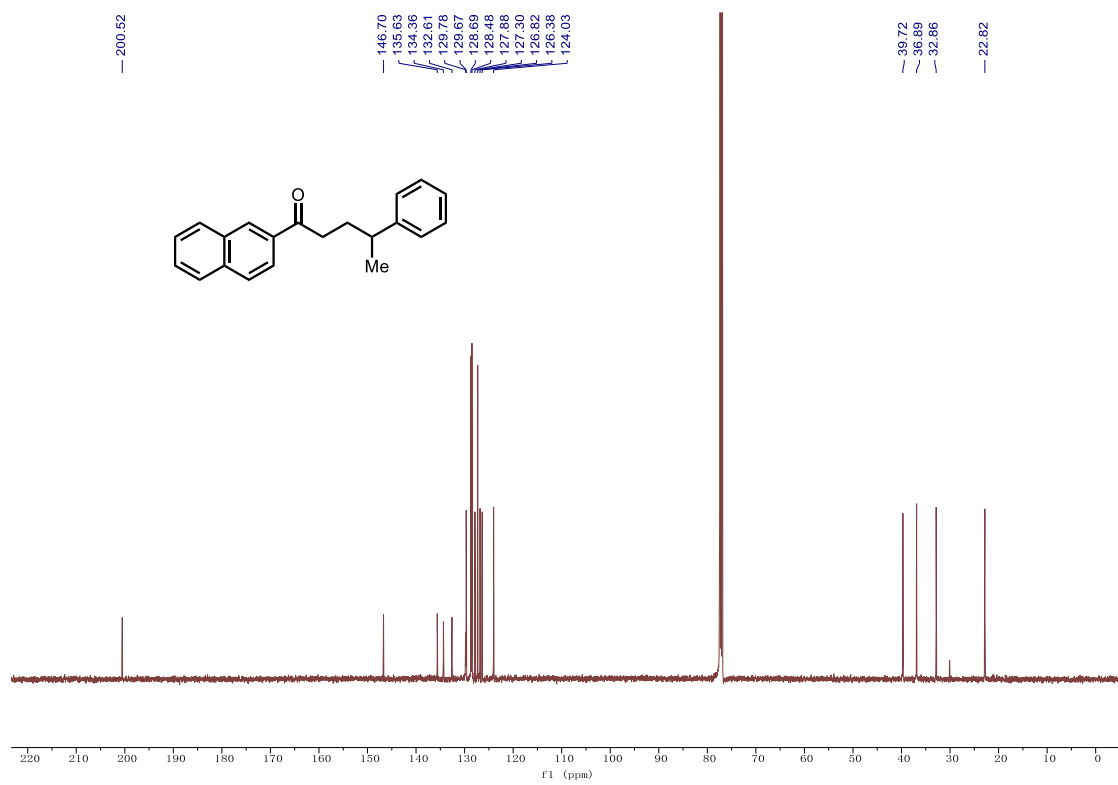
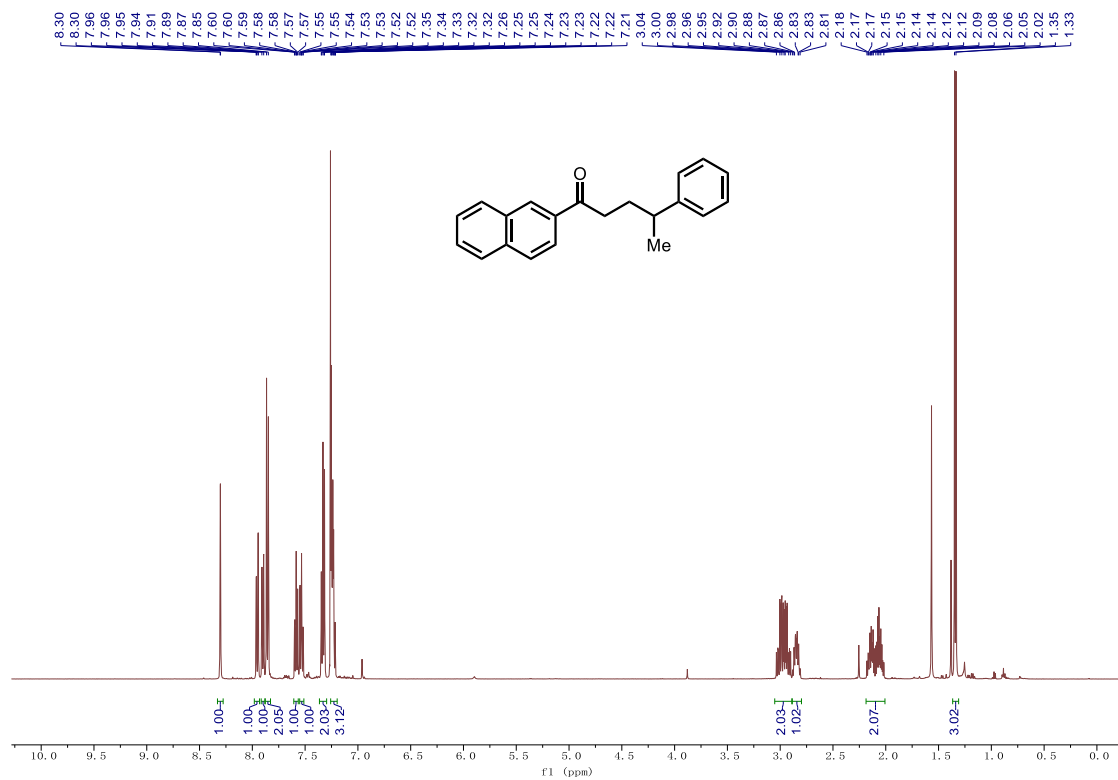


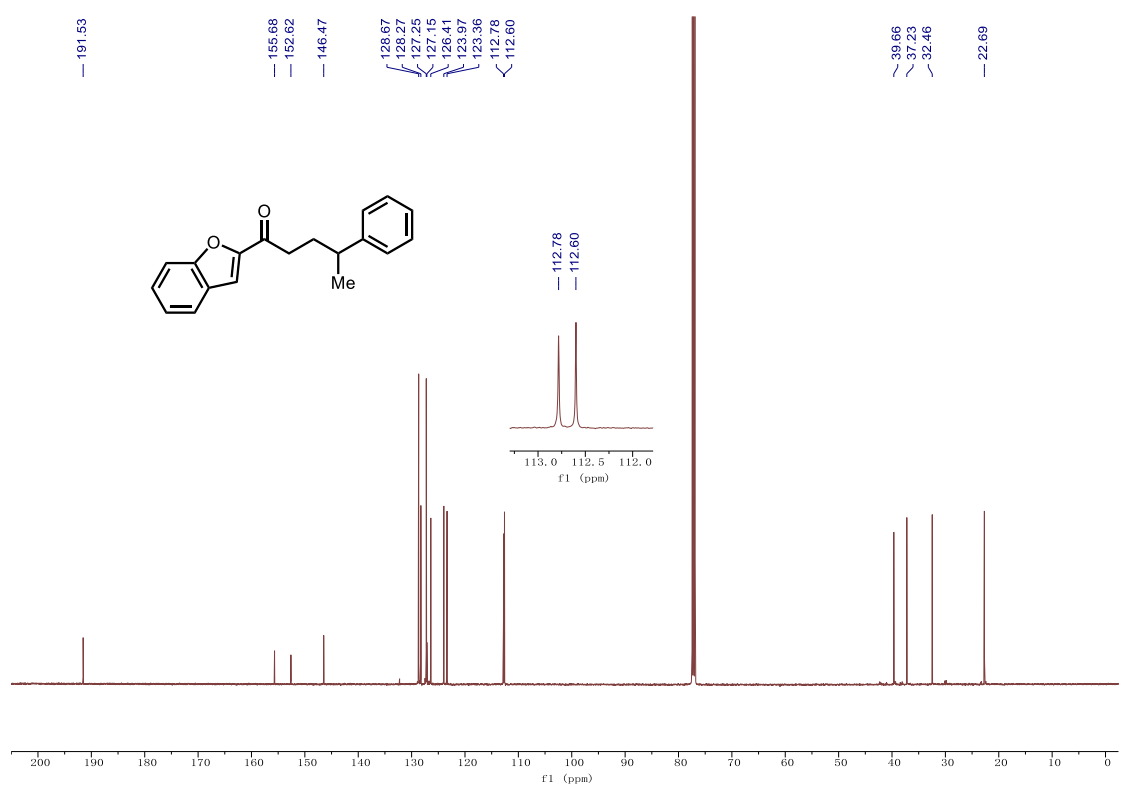
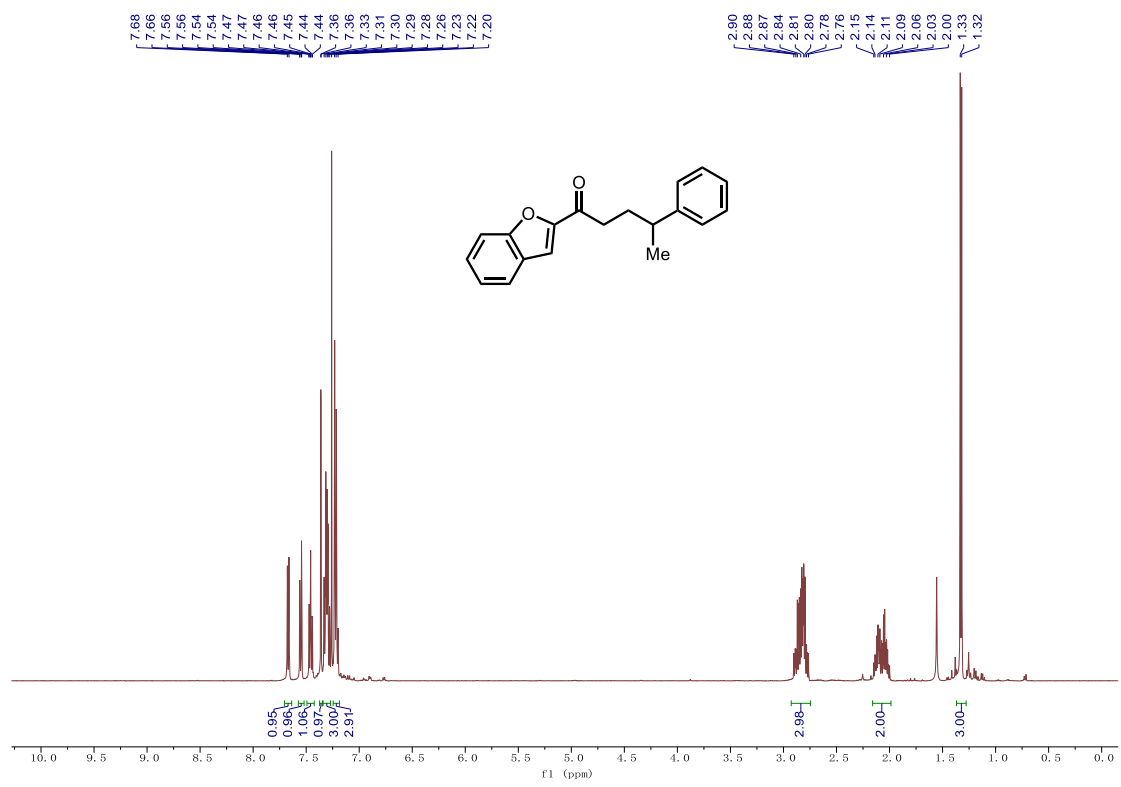


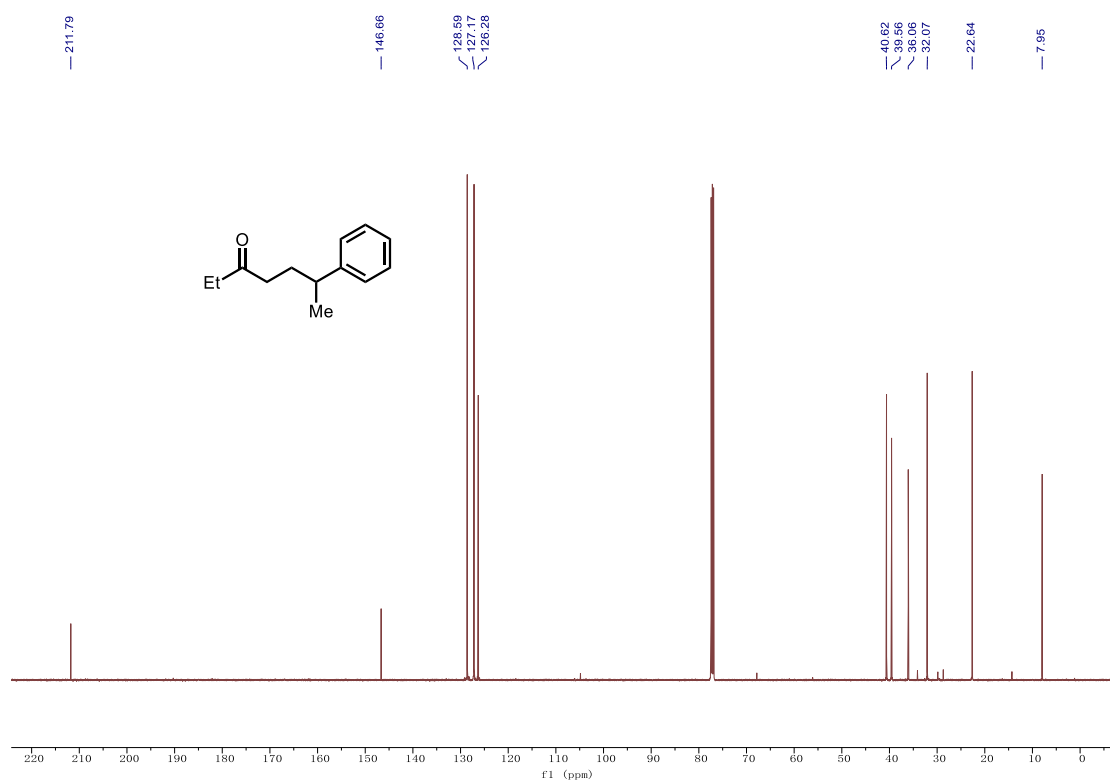
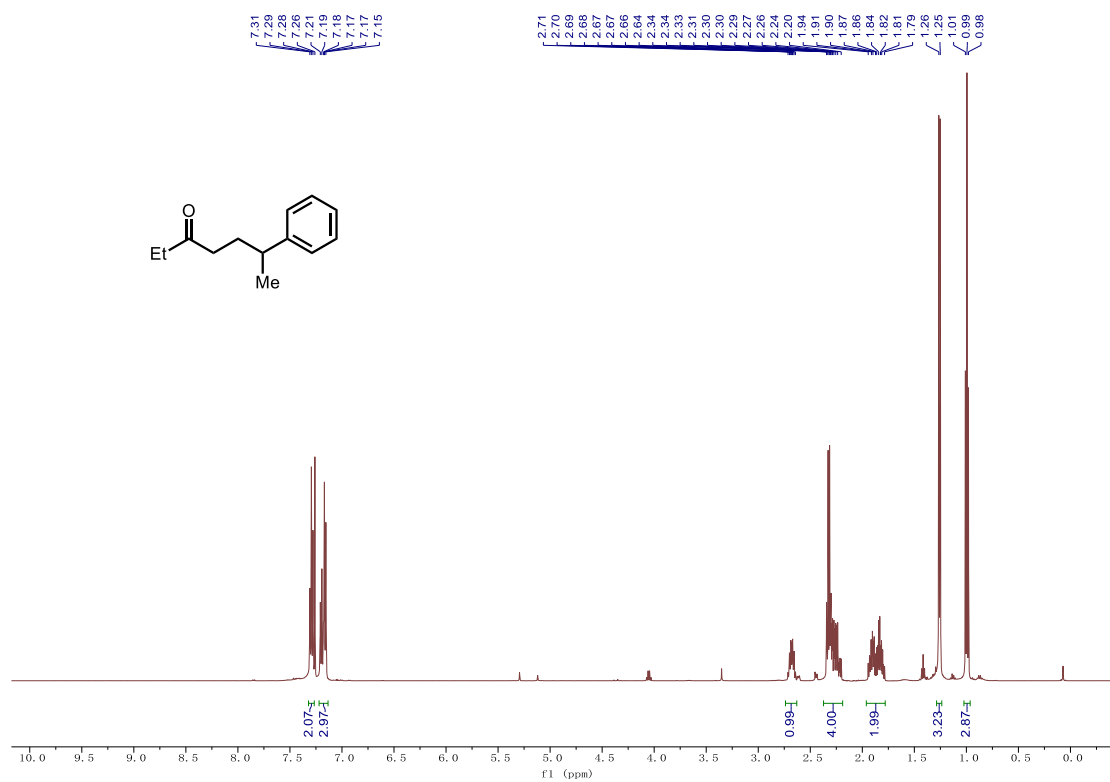


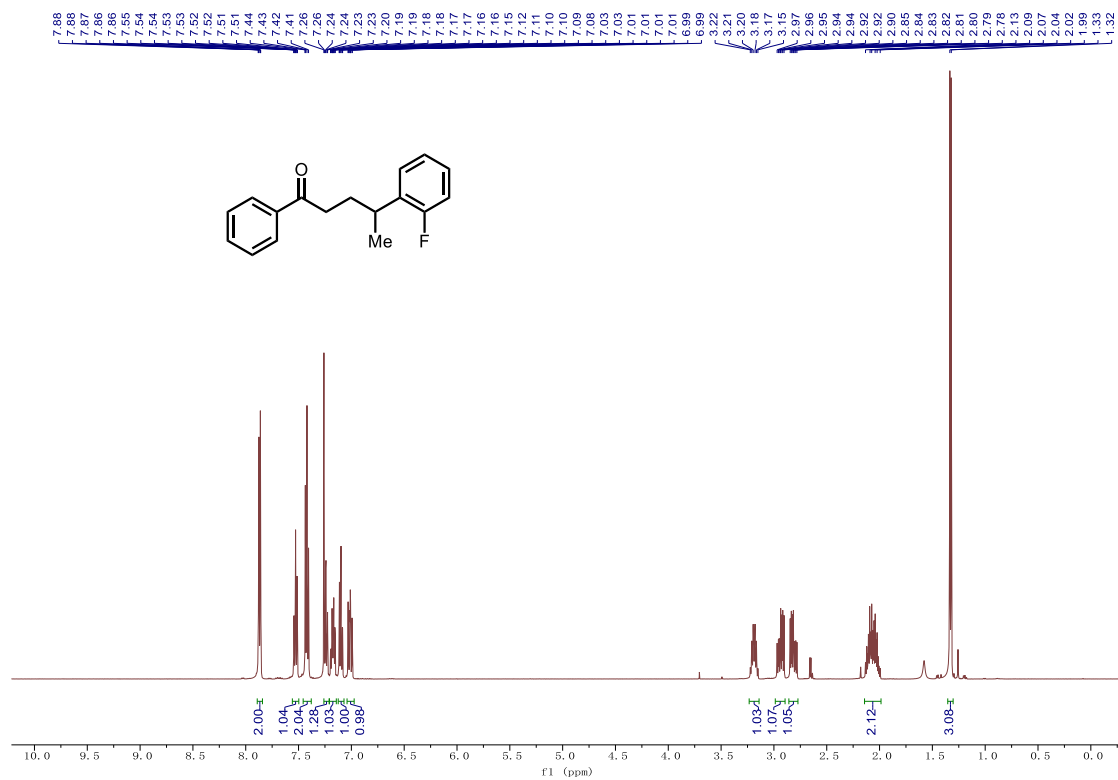


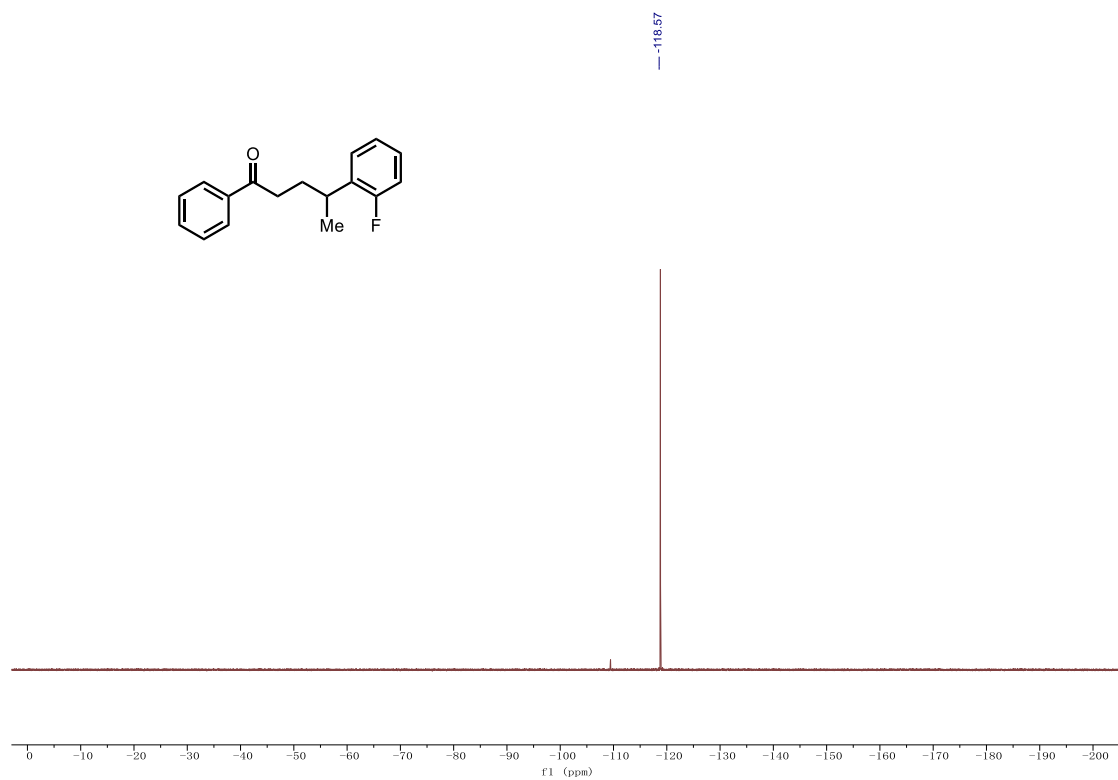




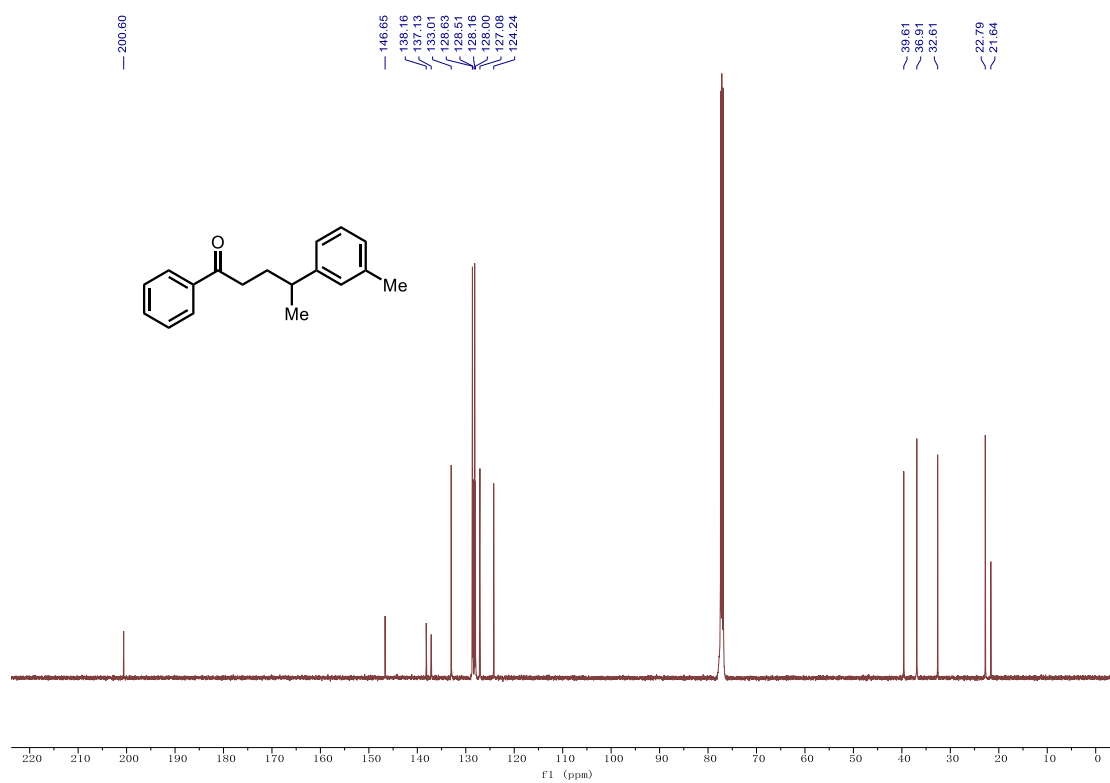
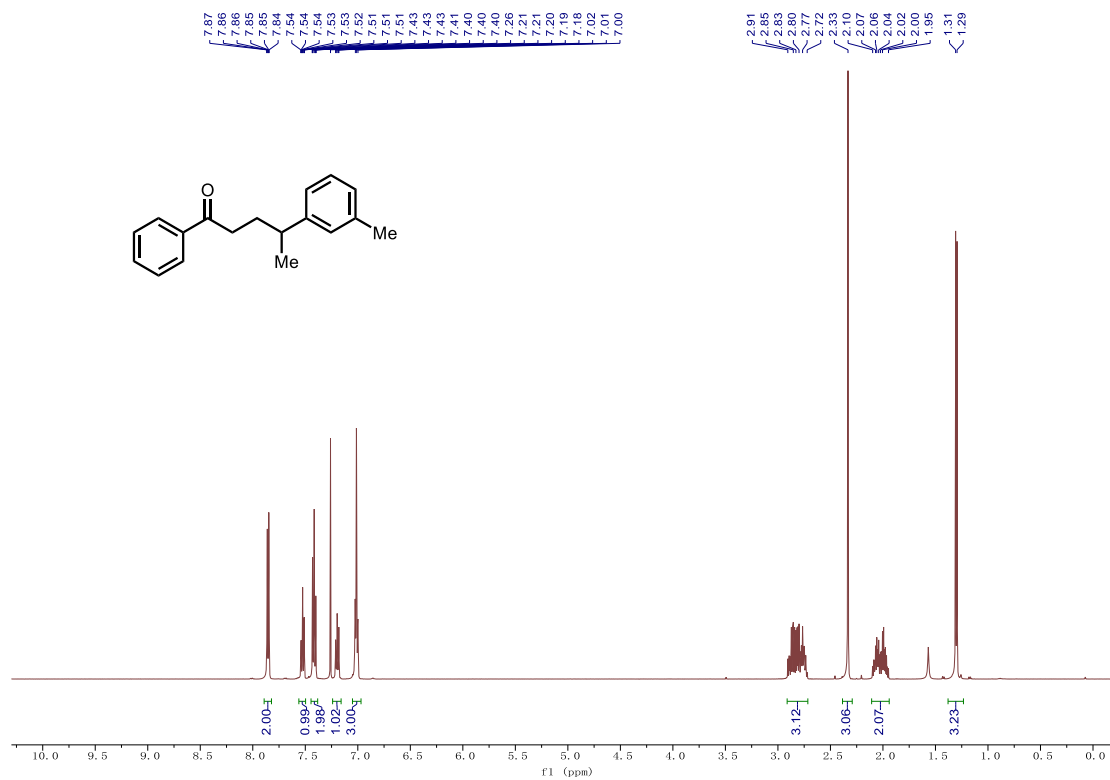


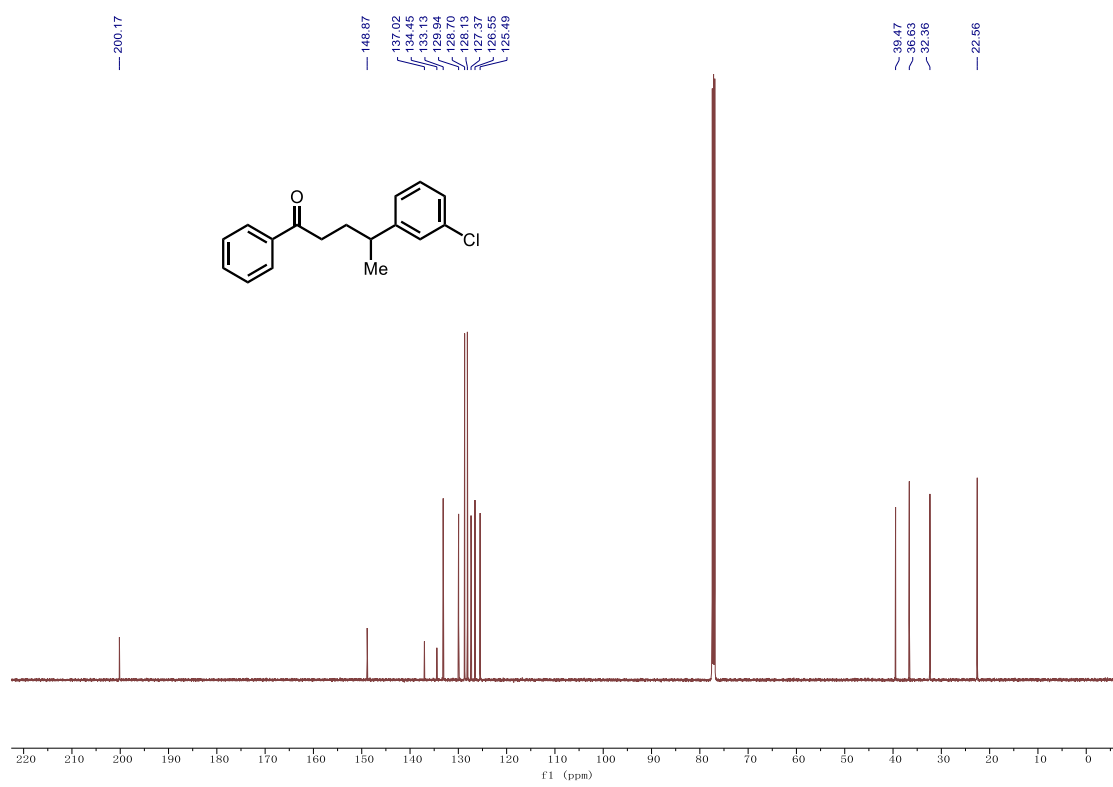
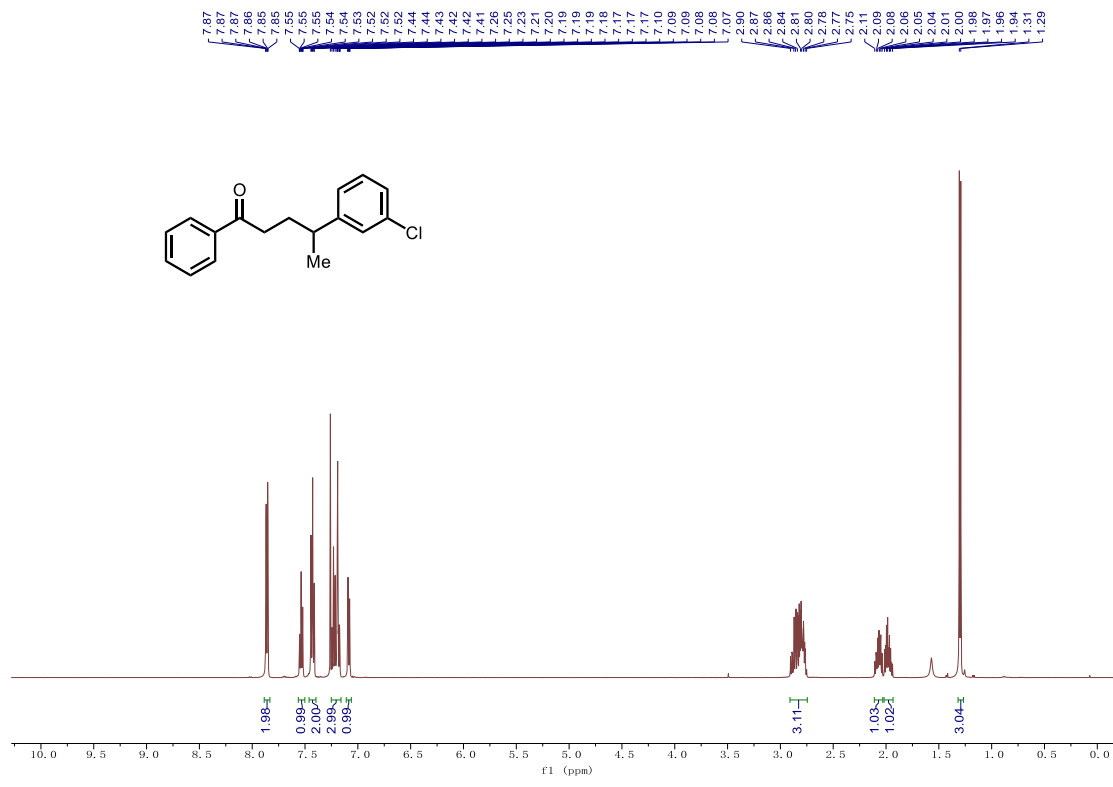


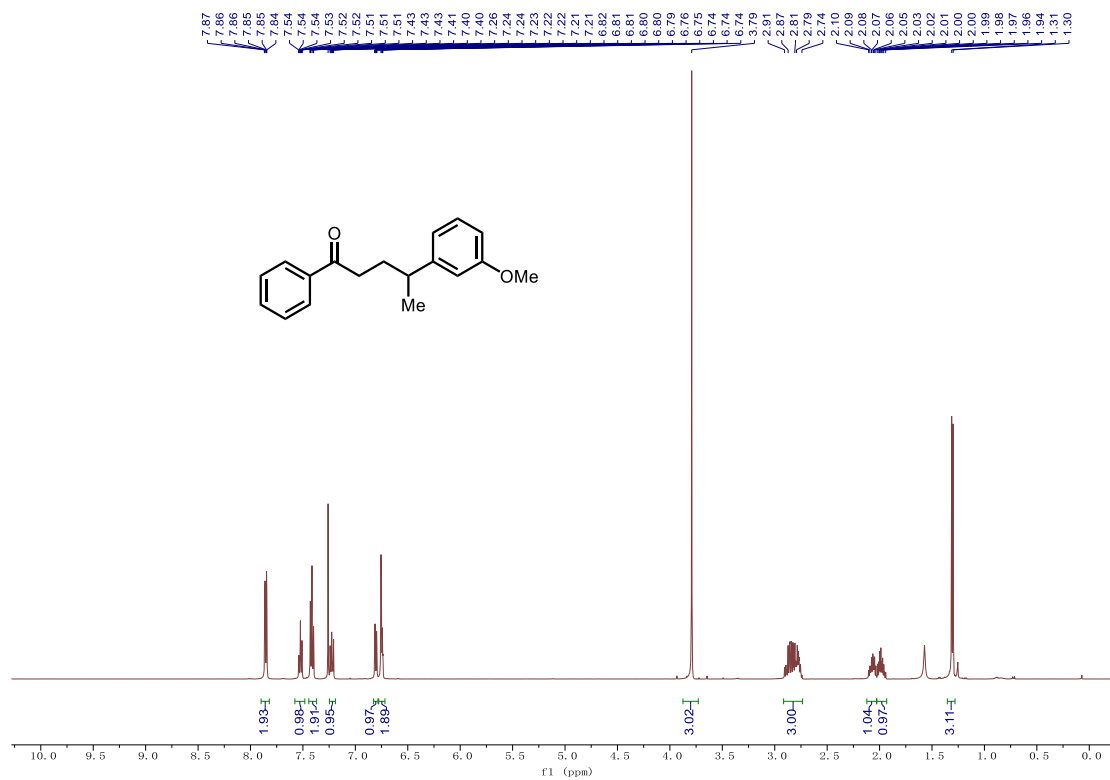


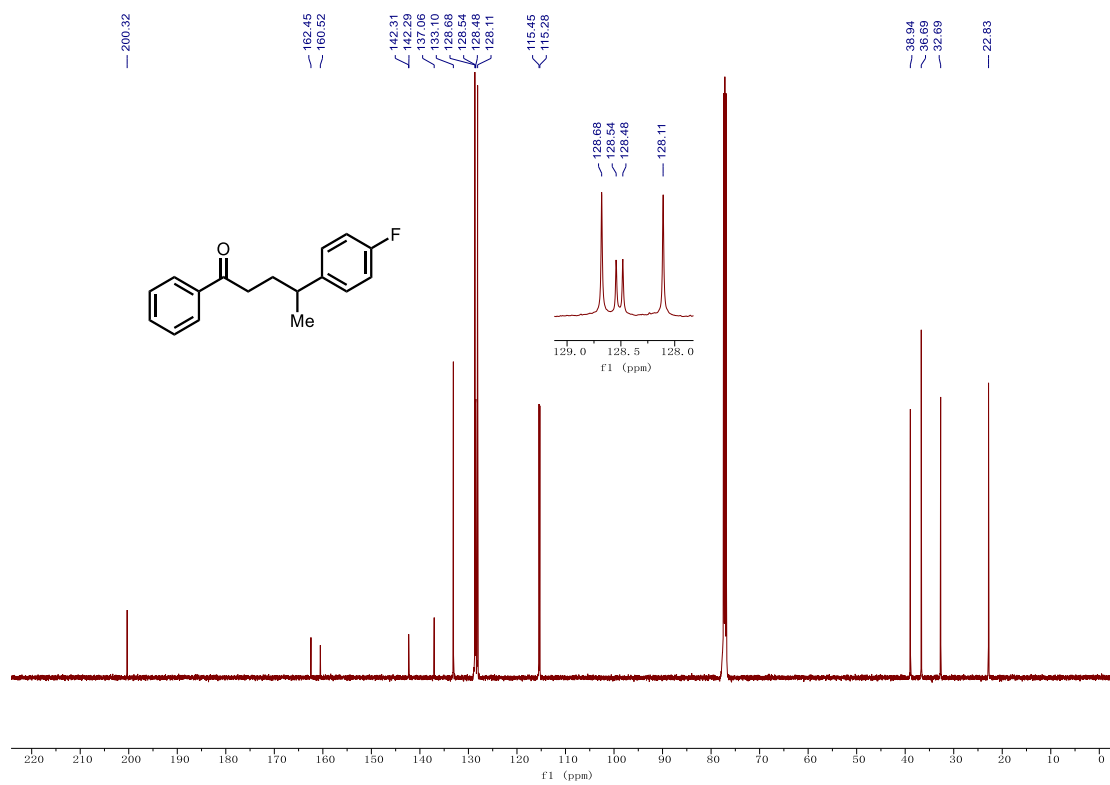
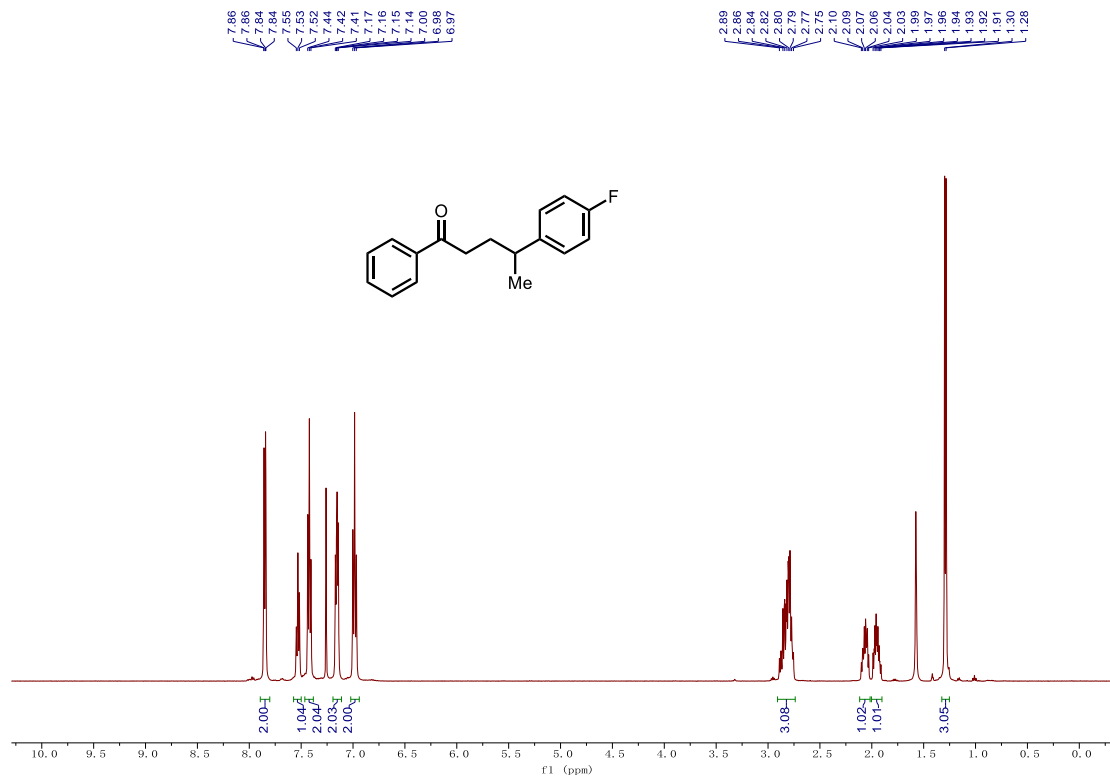


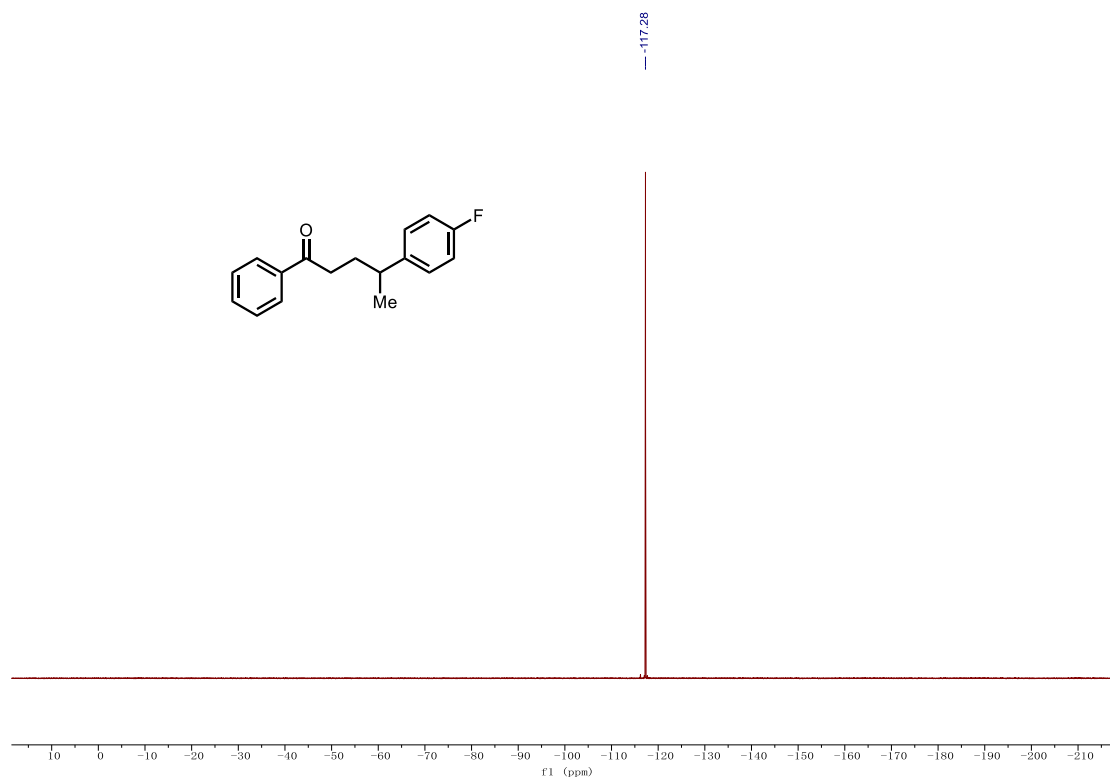


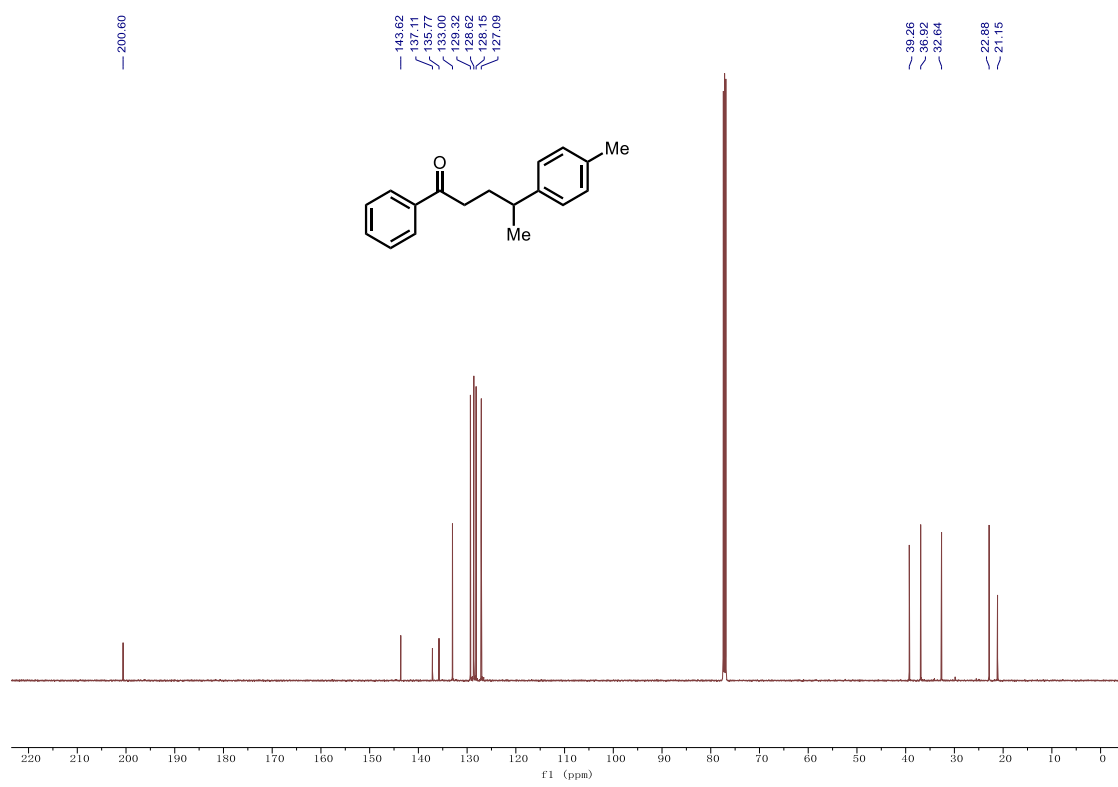
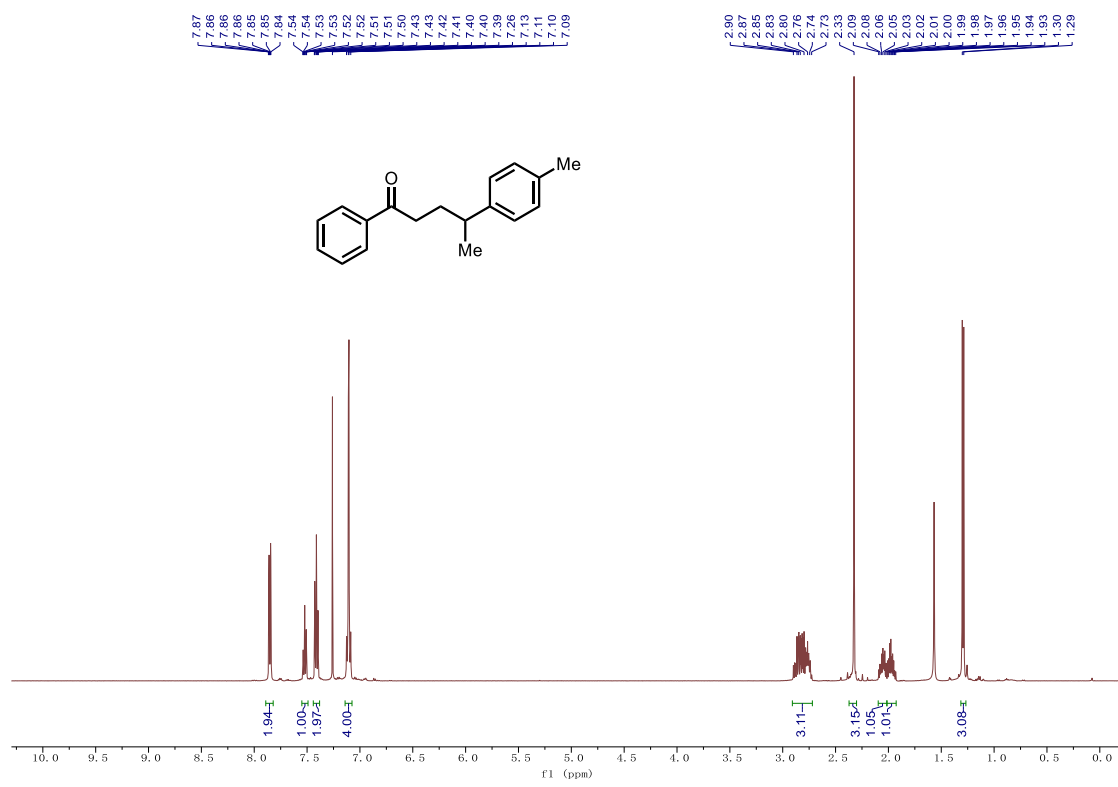


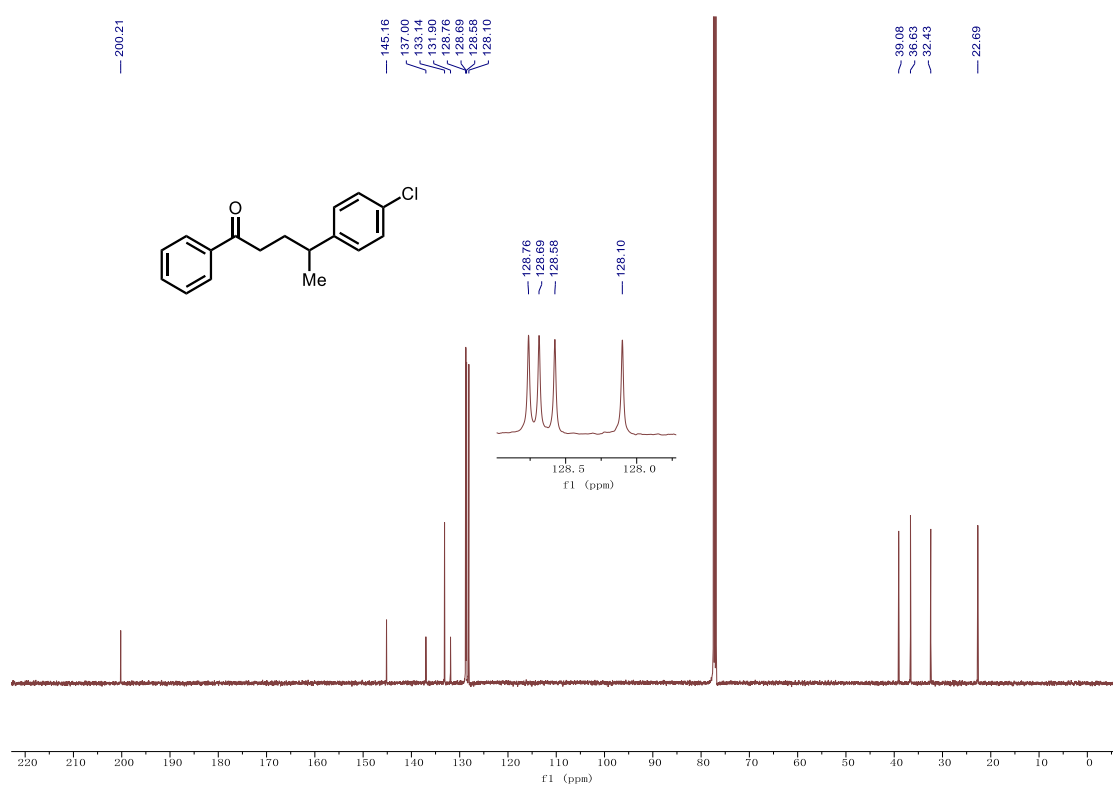
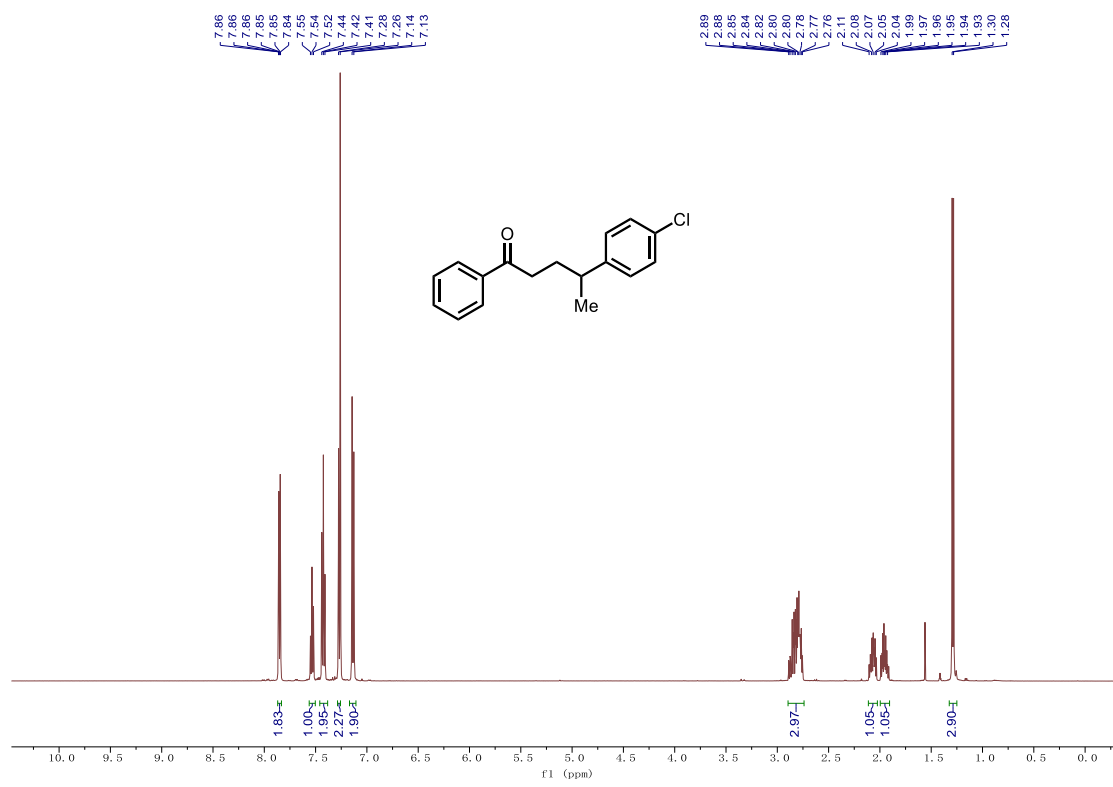


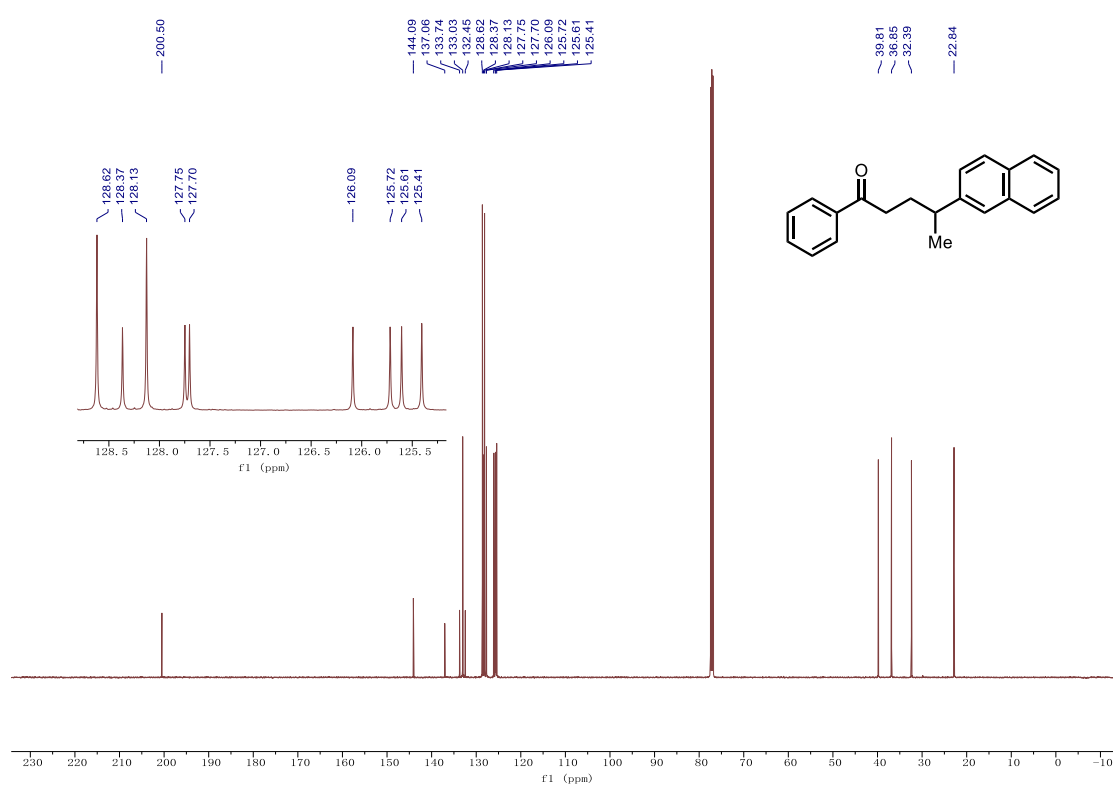
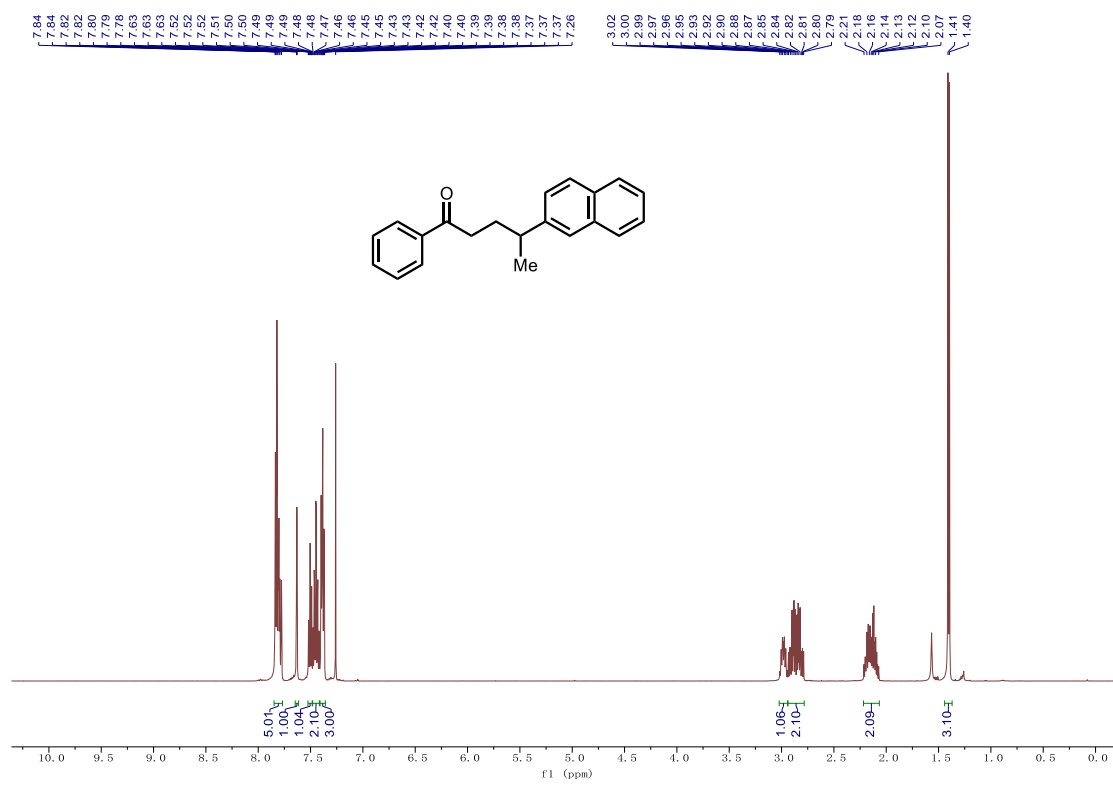




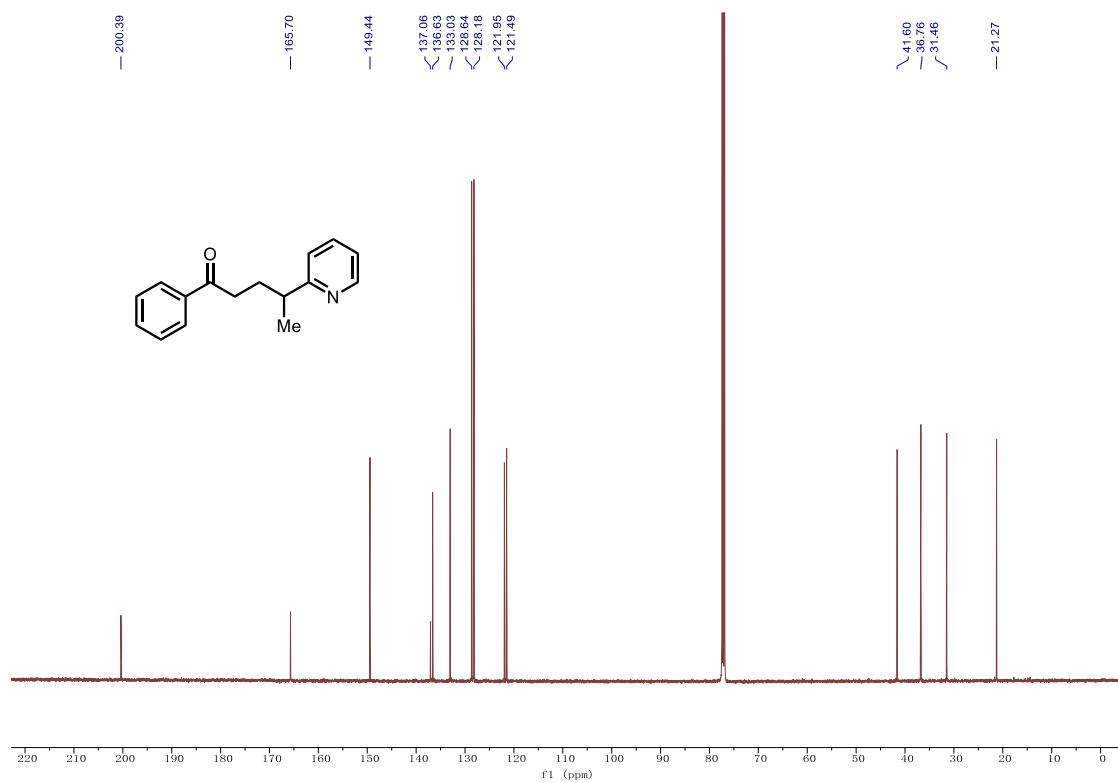
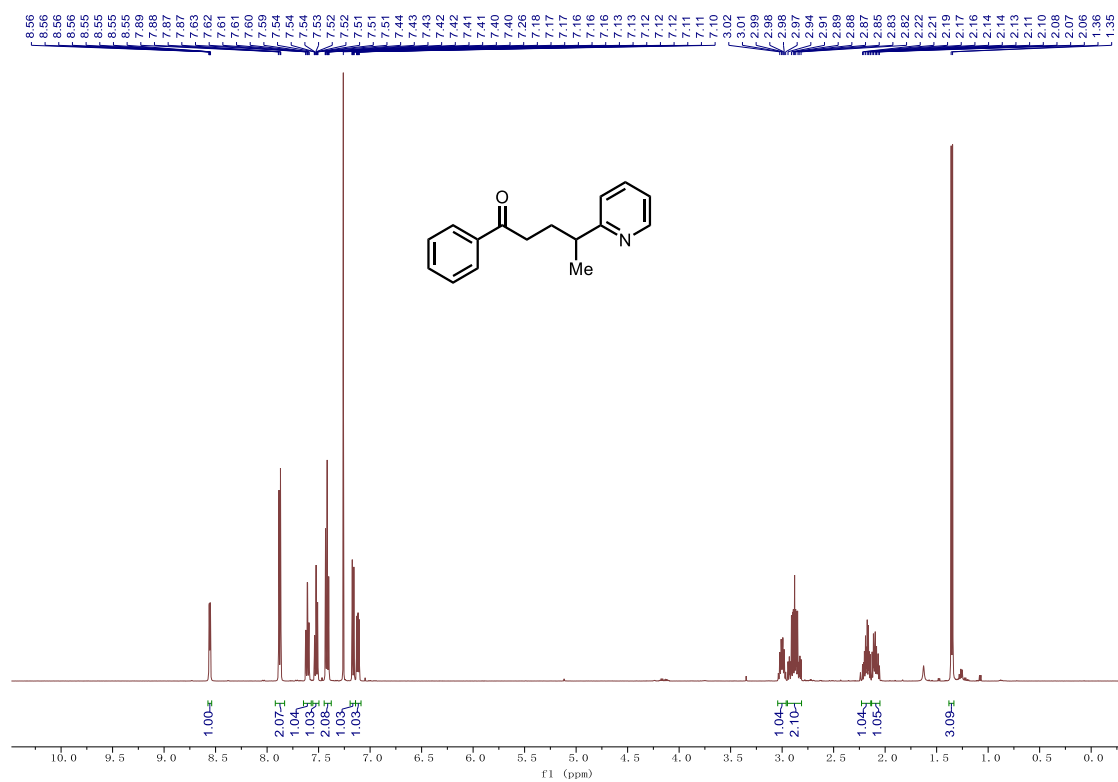


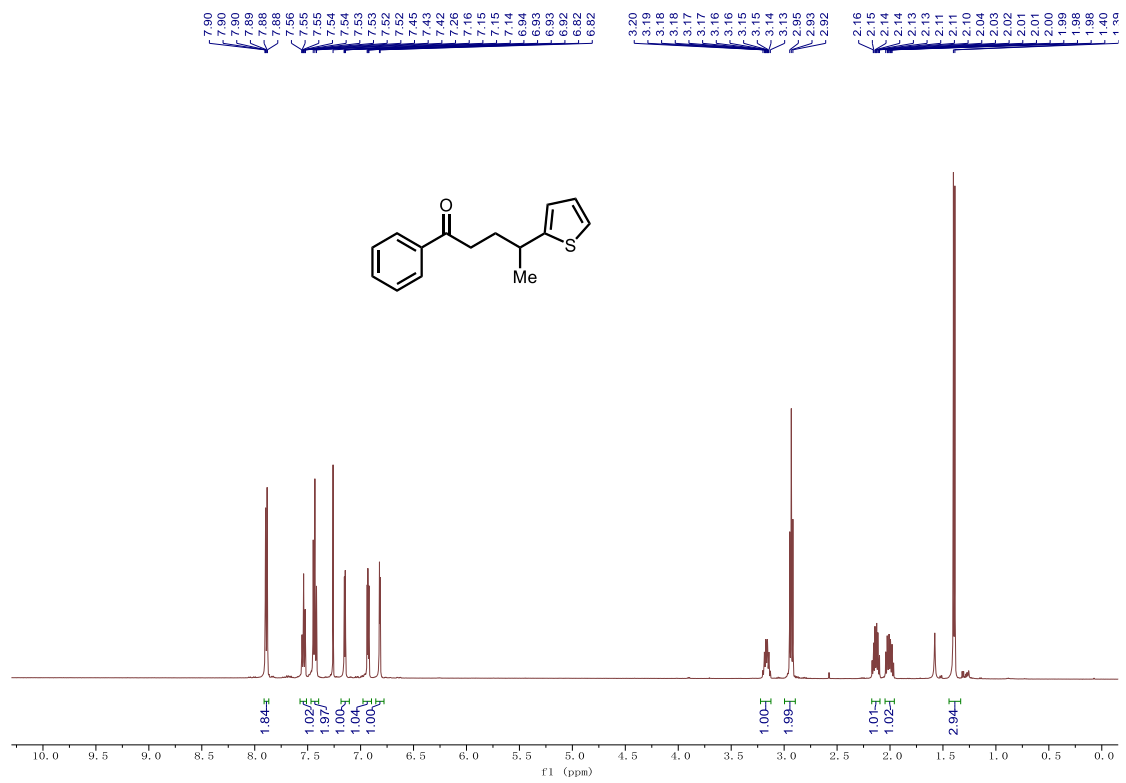


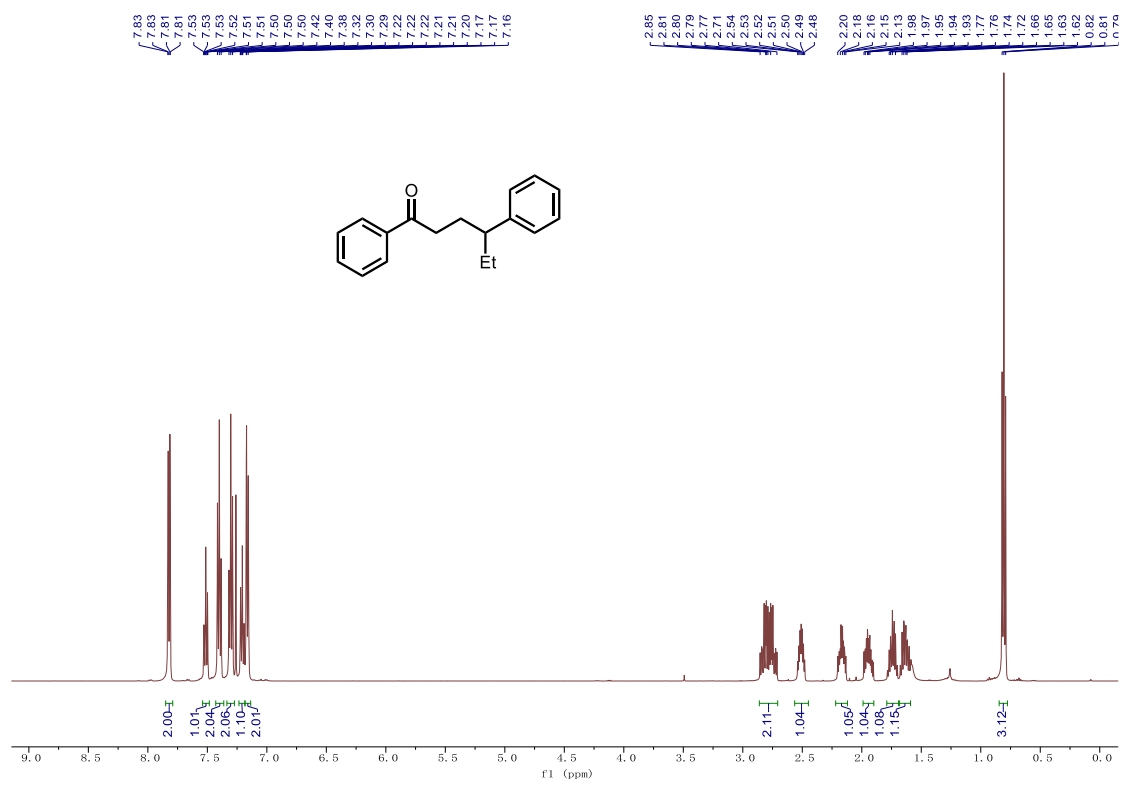


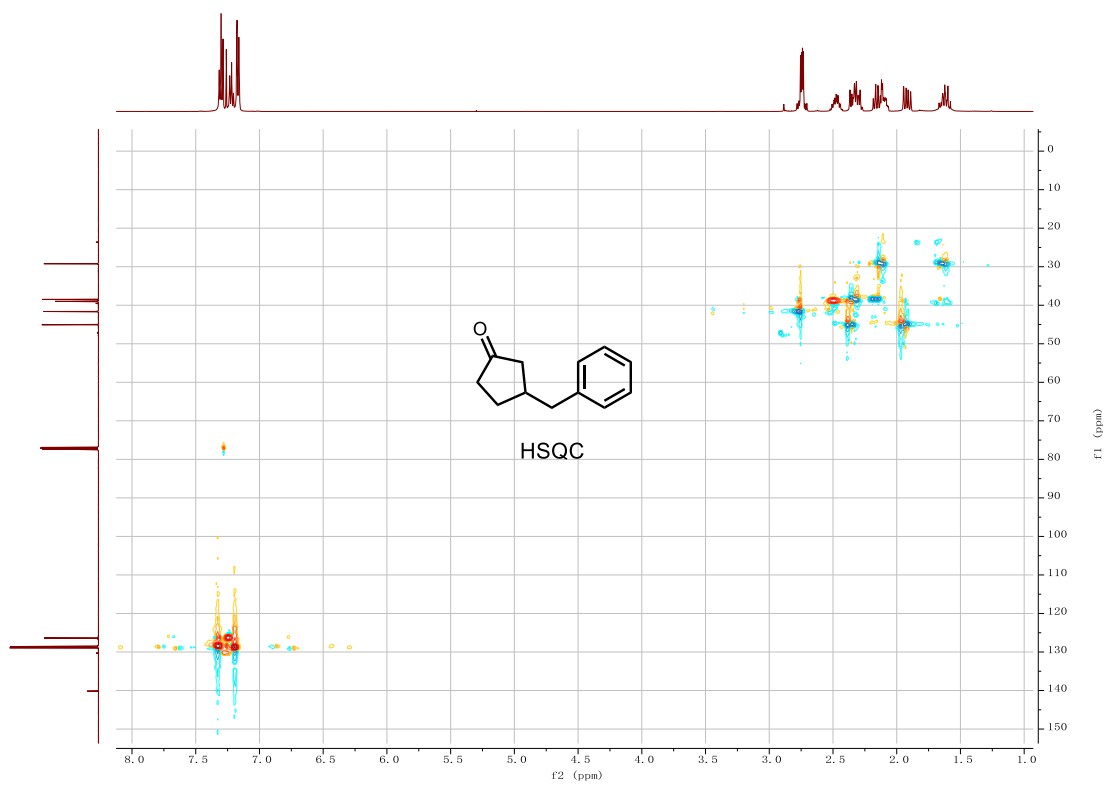
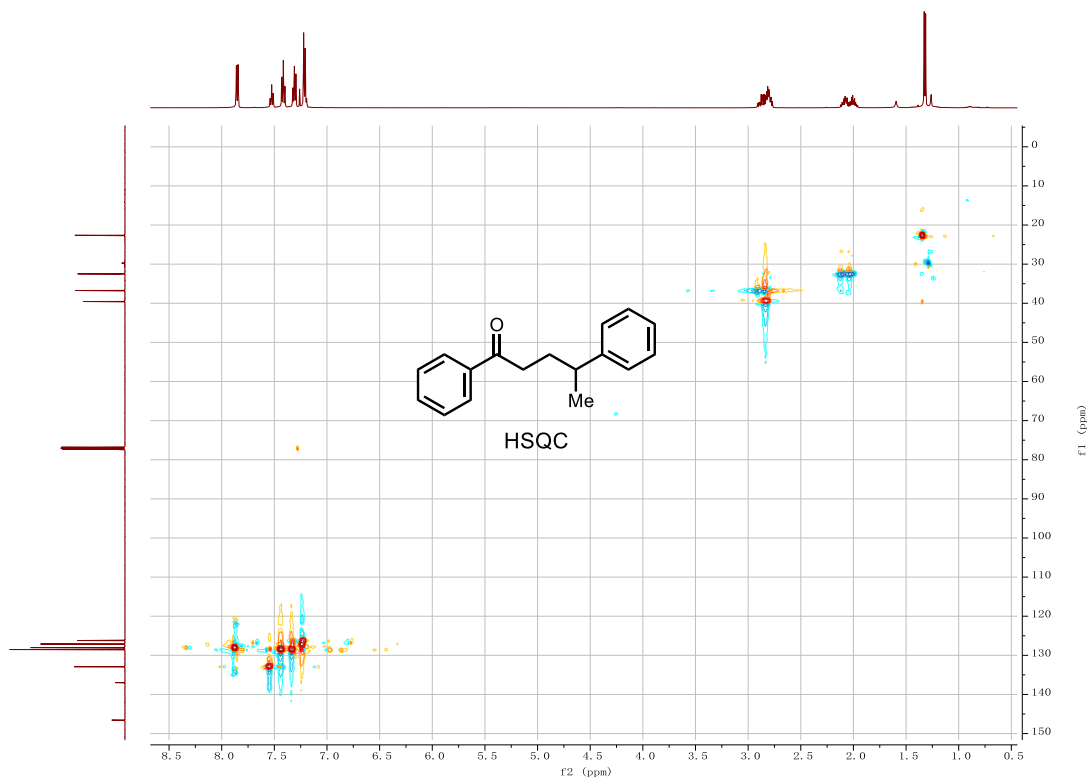












#### 4. Supplemental references

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