Supplementary Information

An Asymmetric sp^3–sp^3 Cross-Electrophile Coupling Using 'Ene'-Reductases

Haigen Fu,[1] Jingzhe Cao,[1,2] Tianzhang Qiao,[1] Yuyin Qi,[3] Simon J. Charnock,[3] Samuel Garfinkle,[2] and Todd K. Hyster[1*]

[1]Department of Chemistry and Chemical Biology, Cornell University, Ithaca, New York 14850, US

[2]Department of Chemistry, Princeton University, Princeton, New Jersey 08544, US

[3]Prozomix. Building 4, West End Ind. Estate, Haltwhistle (UK)

Correspondence to: thyster@cornell.edu.

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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). Glucose dehydrogenase GDH-105 (hereafter, GDH; 50 U/mg) 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}H and ^{13}C NMR spectra were recorded on Bruker UltraShield Plus (500 and 126 MHz, respectively) instrument, and are internally referenced to residual proton signals in $CDCl_3$ (7.26 ppm). ^{19}F NMR spectra were recorded on a Bruker 500 (470 MHz) or 400 (367 MHz) instruments. ^{1}H NMR data are reported as follows: chemical shift (δ 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}C NMR are reported in terms of chemical shift relative to $CDCl_3$ (77.16 ppm). High resolution mass spectra (HRMS) were obtained on a Thermo Fisher Scientific DART Mass Spectrometer. IR spectra were recorded on a Bruker Tensor II Infrared Spectrometer and peaks are reported in terms of frequency of absorption (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 μm) 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, and AS-H columns were used to separate enantiomers (4.6 x 250 mm, 5 μm).

LED Lamps.

The cyan LEDs lamps were constructed in house from Chanzon High Power 50 W Cyan LED Chips (497 nm/1500 mA/DC30-34 V/50 W, measured photon flux = 12,000 mM/m^2s) (Amazon 1DGL-JC-50W-490) powered by Mean Well HLG-320H-C1750A power supplies (320 W/183 V/1750 mA). Each LED chip was secured to a Nagulagu cooling aluminum LED heatsink equipped with a 12 V fan (Amazon B01K1Z6VP6).

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.[1] 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-α cells for storage, and *E. coli.* BL21 (DE3) electrocompetent cells for expression.

Protein and DNA Sequence.

Caulobacter segnis Alkene Reductase (**CsER**).

GenBank accession number: A0A2W5V2R8

CsER protein sequence

MPNLFDPLRVGDLNLPNRVVMAPLTRLRAGPTHIPNALMAEYYGQRASAGLLITEGVPVAPQ
GVGYAGVPGIWSKEQTEGWKQVTKAVHDKGGRIFMQIWHVGRISDPELLNGELPIAPSAIAA
KGHVSLLRPQRDYPTPRALSTEEVAGVVEAFRQGAENAQAAGFDGVQLHGANGYLLDQFLQ
DGSNQRTDQYGGSIENRARLLLEAADAAISVWGADRVGVHLAPRADSHSMGDSNLAATFGH
VAKALGERKIGFVSAREYEAADSLGPDLKKAFGGVYIANEKFDLASANAAIEAGKADAIAFGK
AYIANPDLVERLKAGAALNTPDPATFYGFENGPRGYTDYPTLAQVREPALEHHHHHH.

CsER DNA sequence

ATGCCGAATTTGTTTGATCCGCTTCGTGTGGGAGACCTTAATTTGCCTAATCGTGTCGTGA
TGGCACCCCTGACTCGCTTACGCGCTGGTCCTACACACATCCCGAACGCTCTGATGGCAGA
ATACTATGGGCAGCGTGCAAGTGCAGGCTTACTTATTACGGAGGGAGTTCCAGTGGCGCC
CCAAGGGGTTGGGTACGCTGGTGTTCCTGGAATTTGGTCCAAGGAACAGACCGAAGGCTG
GAAGCAAGTCACAAAAGCTGTCCACGACAAGGGCGGCCGCATCTTCATGCAAATCTGGCA
CGTTGGCCGCATCAGCGACCCGGAGTTGTTAAACGGAGAATTGCCGATTGCGCCAAGTGC
TATTGCCGCTAAAGGACATGTAAGCCTTTTACGCCCGCAACGCGATTACCCTACCCCCCGT
GCACTTTCAACCGAGGAGGTGGCAGGAGTAGTCGAAGCCTTCCGTCAGGGTGCTGAAAAT
GCTCAGGCAGCGGGCTTTGACGGGGTCCAGTTGCATGGAGCTAACGGCTACCTTTTGGAT
CAGTTTTTACAGGACGGGAGTAATCAACGCACGGATCAGTATGGGGGTTCGATTGAGAAC
CGTGCCCGCCTGCTGTTGGAGGCAGCCGATGCGGCAATTAGCGTCTGGGGAGCAGATCGC
GTAGGCGTGCACCTGGCCCCGCGTGCGGACTCCCATTCCATGGGTGACTCGAACCTGGCC
GCGACCTTTGGTCACGTAGCGAAGGCATTAGGGGAGCGCAAGATCGGTTTTGTCAGCGCA
CGCGAATATGAGGCCGCTGACTCTTTGGGACCGGATTTGAAGAAAGCATTCGGAGGAGTT
TATATTGCGAATGAGAAATTTGATCTTGCGTCTGCTAACGCCGCTATTGAGGCAGGCAAA
GCGGATGCCATCGCGTTTGGCAAAGCCTACATCGCAAATCCCGATTTAGTGGAACGTCTTA
AAGCCGGGGCAGCTTTAAACACCCCGGATCCGGCGACTTTCTATGGCTTCGAAAATGGTC
CTCGCGGGTATACGGATTACCCTACCTTGGCTCAGGTCCGCGAGCCCGCCCTCGAGCACCA
CCATCACCACCACTGA.

Old yellow enzyme 2 (**OYE2**) from *Saccharomyces cerevisiae*.
Genbank accession number: AAA83386.1

OYE2 protein sequence

MPFVKDFKPQALGDTNLFKPIKIGNNELLHRAVIPPLTRMRAQHPGNIPNRDWAVEYYAQRAQ
RPGTLIITEGTFPSPQSGGYDNAPGIWSEEQIKEWTKIFKAIHENKSFAWVQLWVLGWAAFPDT
LARDGLRYDSASDNVYMNAEQEEKAKKANNPQHSITKDEIKQYVKEYVQAAKNSIAAGADG
VEIHSANGYLLNQFLDPHSNNRTDEYGGSIENRARFTLEVVDAVVDAIGPEKVGLRLSPYGVF
NSMSGGAETGIVAQYAYVLGELERRAKAGKRLAFVHLVEPRVTNPFLTEGEGEYNGGSNKFAY
SIWKGPIIRAGNFALHPEVVREEVKDPRTLIGYGRFFISNPDLVDRLEKGLPLNKYDRDTFYKMS
AEGYIDYPTYEEALKLGWDKNHHHHHH.

OYE2 DNA sequence

ATGCCCTTCGTGAAAGACTTCAAACCTCAAGCCCTGGGCGATACTAATTTATTTAAGCCAAT
TAAAATTGGAAACAATGAGTTGTTACACCGCGCTGTAATTCCACCCTTAACCCGCATGCGCG
CCCAACATCCAGGGAACATCCCTAATCGCGATTGGGCAGTCGAGTACTATGCTCAGCGTGCT
CAGCGTCCGGGTACCCTTATCATCACGGAAGGAACGTTTCCGTCGCCGCAATCGGGAGGGT
ATGACAACGCTCCCGGTATCTGGTCGGAAGAACAGATTAAAGAATGGACCAAAATCTTTAA
AGCAATTCATGAGAATAAATCTTTCGCCTGGGTCCAACTTTGGGTCCTGGGCTGGGCAGCC
TTCCCTGACACATTGGCGCGTGACGGGCTTCGTTATGATAGTGCTTCGGATAACGTGTATATG
AATGCTGAACAAGAAGAAAAGGCAAAAAAAGCAAACAATCCACAGCATTCGATTACTAAA
GACGAGATTAAGCAGTATGTTAAGGAATACGTACAAGCAGCAAAGAATTCTATTGCCGCAG
GGGCGGACGGGGTAGAAATCCACTCTGCTAATGGGTACTTGCTTAACCAGTTCCTGGACCC
GCATTCAAACAACCGCACTGATGAGTACGGAGGGTCCATCGAAAATCGTGCACGTTTTACT
TTAGAGGTCGTAGATGCTGTAGTCGACGCGATTGGCCCTGAGAAGGTAGGTTTGCGTTTAA
GTCCTTATGGCGTGTTCAATTCAATGTCAGGGGGCGCTGAAACAGGTATCGTCGCGCAGTA
CGCATACGTCTTGGGAGAGCTGGAGCGTCGTGCTAAGGCTGGCAAGCGTTTAGCTTTTGTG
CATTTAGTTGAACCGCGCGTGACAAACCCCTTCTTGACGGAAGGCGAAGGAGAGTATAACG
GAGGATCGAATAAATTTGCGTATTCCATTGGAAGGGCCCGATCATTCGTGCCGGTAACTTTG
CCTTACATCCCGAAGTTGTTCGCGAGGAAGTAAAAGACCCACGTACCTTGATCGGGTATGG
CCGTTTCTTTATTTCAAACCCCGACTTGGTGGATCGCCTTGAAAAAGGTCTTCCCTTGAATA
AGTATGACCGTGATACGTTCTACAAAATGTCAGCCGAAGGTTACATCGACTACCCCACCTAC
GAAGAGGCTTTGAAACTTGGTTGGGACAAGAACCACCACCATCACCACCACTGA.

12-Oxophytodienoate reductase 1 (**OPR1**) from *Solanum lycopersicum*.
Genbank accession number: NP_001234781.1

OPR1 protein sequence

MENKVVEEKQVDKIPLMSPCKMGKFELCHRVVLAPLTRQRSYGYIPQPHAILHYSQRSTNGGL
LIGEATVISETGIGYKDVPGIWTKEQVEAWKPIVDAVHAKGGIFFCQIWHVGRVSNKDFQPNGE
DPISCTDRGLTPQIRSNGIDIAHFTRPRRLTTDEIPQIVNEFRVAARNAIEAGFDGVEIHGAHGYLI
DQFMKDQVNDRSDKYGGSLENRCRFALEIVEAVANEIGSDRVGIRISPFAHYNEAGDTNPTALG
LYMVESLNKYDLAYCHVVEPRMKTAWEKIECTESLVPMRKAYKGTFIVAGGYDREDGNRALI
EDRADLVAYGRLFISNPDLPKRFELNAPLNKYNRDTFYTSDPIVGYTDYPFLETMTLEHHHHHH.

OPR1 DNA sequence

ATGGAGAATAAAGTTGTGGAGGAGAAACAAGTCGATAAAATCCCCTTGATGTCACCGTGCA
AGATGGGAAAGTTTGAACTTTGCCACCGTGTTGTCCTGGCTCCGCTGACACGGCAACGCTC
CTACGGGTATATACCGCAGCCCCATGCAATCTTACATTACTCTCAGCGTTCAACCAACGGAG
GGCTGTTGATAGGTGAAGCAACAGTCATTAGCGAAACGGGTATAGGCTATAAGGACGTACC
CGGCATCTGGACTAAAGAACAAGTTGAGGCATGAAACCCATAGTAGACGCCGTACATGCAA
AGGGAGGGATCTTCTTCTGCCAGATATGGCATGTGGGTAGAGTGAGTAATAAGGACTTCCA
ACCTAACGGTGAGGATCCCATTAGCTGTACCGATCGGGGATTAACGCCACAGATACGGTCA
AATGGTATTGACATAGCTCATTTTACAAGACCTAGACGTCTTACCACGGACGAGATCCCACA
AATTGTCAACGAATTCCGCGTGGCGGCTAGAAATGCCATCGAAGCAGGATTCGACGGCGTA
GAGATACACGGAGCACACGGTTATCTGATAGACCAGTTCATGAAAGACCAAGTTAATGACC
GGTCCGATAAGTATGGAGGATCTCTGGAAAACCGGTGTCGGTTCGCCTTGGAGATTGTTGA
AGCCGTCGCTAATGAAATCGGAAGCGACCGTGTCGGAATACGCATTAGTCCATTCGCGCAC
TACAATGAGGCAGGGGATACCAATCCCACTGCGCTGGGTTTATATATGGTGGAGAGCCTGAA
TAAATACGATTTAGCATATTGTCATGTAGTGGAACCTCGCATGAAAACTGCTTGGGAAAAAA
TTGAATGCACTGAGAGTCTTGTTCCGATGCGTAAAGCGTACAAGGGAACGTTCATAGTAGC
TGGGGGTTATGATCGGGAGGACGGGAACGGGCCCTGATAGAAGACCGGGCCGACCTTGTC
GCATACGGACGTTTGTTCATATCCAACCCAGATTTACCGAAACGTTTTGAGTTAAACGCTCC
CCTGAATAAATACAATCGTGACACGTTCTATACTTCTGATCCAATCGTGGGTTATACGGACTA
TCCGTTTTTAGAGACGATGACGCTCGAGCACCACCACCACCACCACTGA.

Morphinone reductase (**MorB**) from *Pseudomonas putida*.
Genbank accession number: AAC43569

MorB protein sequence

MPDTSFSNPGLFTPLQLGSLSLPNRVIMAPLTRSRTPDSVPGRLQQIYYGQRASAGLIISEATNISP
TARGYVYTPGIWTDAQEAGWKGVVEAVHAKGGRIALQLWHVGRVSHELVQPDGQQPVAPSA
LKAEGAECFVEFEDGTAGLHPTSTPRALETDEIPGIVEDYRQAAQRAKRAGFDMVEVHAANA
CLPNQFLATGTNRRTDQYGGSIENRARFPLEVVDAVAEVFGPERVGIRLTPFLELFGLTDDEPEA
MAFYLAGELDRRGLAYLHFNEPDWIGGDITYPEGFREQMRQRFKGGLIYCGNYDAGRAQARL
DDNTADAVAFGRPFIANPDLPERFRLGAALNEPDPSTFYGGAEVGYTDYPFLDNGHDRLGHHH
HHH.

MorB DNA sequence

ATGCCCGACACTTCTTTTTCGAATCCAGGACTTTTTACTCCTCTTCAGTTGGGTAGTCTGTCT
CTTCCAAATCGTGTCATAATGGCACCTTTAACCCGCTCACGCACGCCAGATTCTGTACCTGG
ACGCCTTCAACAGATATACTATGGTCAACGCGCCAGCGCCGGGTTAATCATCTCCGAAGCGA
CAAATATCAGTCCCACCGCTCGGGGATACGTATACACGCCAGGCATTTGGACTGACGCTCAG
GAGGCCGGTTGGAAAGGTGTGGTCGAAGCTGTCCATGCTAAAGGGGGTCGTATAGCGTTGC
AGTTATGGCATGTCGGCCGGGTCTCTCATGAGCTGGTGCAGCCAGACGGCCAACAACCCGT
GGCACCATCCGCCTTAAAAGCCGAAGGGGCCGAGTGCTTTGTCGAATTCGAGGATGGGACT
GCTGGCCTGCACCCTACGTCAACTCCCAGAGCCCTGGAGACAGATGAGATACCCGGTATTG
TTGAAGATTACAGACAGGCCGCGCAGCGTGCGAAGCGGGCCGGATTCGATATGGTAGAGGT
CCACGCGGCAAATGCTTGTCTTCCTAATCAGTTCTTGGCGACAGGAACCAATCGTCGCACA
GACCAGTACGGTGGATCAATTGAGAACCGGGCTAGATTCCCATTAGAGGTTGTCGATGCTG
TAGCCGAGGTATTCGGGCCCGAAAGAGTGGGGATACGGCTGACTCCTTTCCTGGAGTTATTT
GGATTAACGGATGATGAACCCGAGGCAATGGCTTTTTACCTTGCGGGAGAATTAGACCGGC
GTGGTTTAGCGTATTTACACTTTAATGAACCCGATTGGATAGGTGGGGACATCACGTACCCG
GAAGGGTTTCGTGAGCAAATGCGTCAACGGTTCAAGGGGGGGCTTATATATTGTGGAAACT
ACGACGCAGGTCGGGCCCAAGCCCGGCTTGACGACAATACAGCAGATGCAGTGGCGTTTG
GGCGTCCATTTATTGCCAACCCCGACTTGCCAGAACGTTTCCGCTTAGGAGCAGCGCTGAA
CGAACCTGACCCCTCTACTTTTTACGGCGGGGCAGAGGTGGGGTACACAGACTACCCGTTC
CTGGACAACGGTCATGACCGCCTGGGACTCGAGCACCACCATCACCACCACTGA.

Gluconobacter oxydans enoate reductase (**GluER**) from *Gluconobacter oxydans* 621H.
Genbank accession number: AAW60280

GluER protein sequence

MHHHHHHPTLFDPIDFGPIHAKNRIVMSPLTRGRADKEAVPTPIMAEYYAQRASAGLIITEATGI
SREGLGWPFAPGIWSDAQVEAWKPIVAGVHAKGGKIVCQLWHMGRMVHSSVTGTQPVSSSAT
TAPGEVHTYEGKKPFEQARAIDAADISRILNDYENAARNAIRAGFDGVQIHAANGYLIDEFLRN
GTNHRTDEYGGVPENRIRFLKEVTERVIAAIGADRTGVRLSPNGDTQGCIDSAPETVFVPAAKL
LQDLGVAWLELREPGPNGTFGKTDQPKLSPQIRKVFLRPLVLNQDYTFEAAQTALAEGKADAI
AFGRKFISNPDLPERFARGIALQPDDMKTWYSQGPEGYTDYPSATSGPN.

GluER DNA sequence

ATGCACCACCATCACCACCACCCGACCCTTTTCGACCCCATCGATTTCGGACCTATCCACGC
CAAGAATCGTATCGTCATGTCCCCCCTGACTCGCGGTCGCGCTGACAAAGAGGCGGTTCCA
ACCCCCATTATGGCTGAATACTACGCCCAACGCGCTTCGGCGGGTTTAATTATCACTGAAGC
GACGGGGATTTCACGCGAAGGCTTAGGTTGGCCGTTTGCGCCGGGAATTTGGTCCGATGCA
CAGGTTGAGGCGTGGAAACCTATCGTCGCGGGTGTCCATGCAAAGGGCGGCAAGATCGTAT
GTCAGCTTTGGCATATGGGCCGTATGGTACATTCTTCAGTTACAGGGACGCAGCCCGTAAGC
AGTTCCGCCACTACTGCTCCAGGTGAGGTTCACACCTATGAGGGCAAGAAGCCCTTCGAAC
AAGCGCGTGCAATCGATGCTGCAGACATCTCCCGCATCCTTAACGATTACGAAAATGCAGC
ACGTAATGCAATCCGCGCGGGTTTCGATGGAGTGCAGATCCACGCAGCCAATGGCTACCTT
ATCGATGAGTTTTTGCGTAACGGAACCAATCATCGCACCGATGAGTATGGGGGGGTGCCGG
AGAACCGTATTCGTTTCTTGAAAGAGGTAACAGAACGCGTCATCGCGGCGATTGGCGCTGA
CCGTACGGGTGTGCGTCTGAGTCCAAACGGTGACACACAGGGTTGTATCGACAGTGCTCCC
GAAACCGTTTTTGTTCCTGCCGCAAAGCTTTTGCAAGATTTAGGGGTAGCGTGGCTTGAGC
TGCGTGAACCTGGTCCGAATGGTACGTTTGGAAAGACGGATCAACCAAAATTATCTCCACA
AATCCGTAAGGTATTCCTTCGTCCATTGGTCTTAAATCAAGACTATACTTTTGAGGCGGCAC
AGACGGCCCTGGCTGAGGGCAAGGCGGACGCTATTGCGTTTGGCCGTAAGTTCATTTCAAA
TCCAGACTTGCCTGAGCGCTTTGCCCGTGGCATCGCACTGCAACCAGACGATATGAAAACA
TGGTACTCCCAAGGCCCAGAGGGTTACACAGACTATCCATCCGCAACTTCTGGGCCGAACT
GA.

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

NCR protein sequence

MPSLFDPIRFGAFTAKNRIWMAPLTRGRATRDHVPTEIMAEYYAQRASAGLIISEATGISQEGLG
WPYAPGIWSDAQVEAWLPITQAVHDAGGLIFAQLWHMGRMVPSNVSGMQPVAPSASQAPGLG
HTYDGKKPYDVARALRLDEIPRLLDDYEKAARHALKAGFDGVQIHAANGYLIDEFIRDSTNHR
HDEYGGAVENRIRLLKDVTERVIATIGKERTAVRLSPNGEIQGTVDSHPEQVFIPAAKMLSDLDI
AFLGMREGAVDGTFGKTDQPKLSPEIRKVFKPPLVLNQDYTFETAQAALDSGVADAISFGRPFI
GNPDLPRRFFEKAPLTKDVIETWYTQTPKGYTDYPLLGDHHHHHH.

NCR DNA sequence

ATGCCGTCACTGTTCGATCCAATCCGCTTTGGGGCTTTCACTGCAAAAAATCGTATCTGGAT
GGCGCCGTTAACACGGGGTCGGGCAACCCGTGACCATGTCCCAACAGAGATAATGGCTGA
ATACTATGCCCAACGCGCATCCGCGGGCTTGATCATCAGCGAGGCGACCGGGATCAGCCAA
GAGGGCCTGGGCTGGCCCTATGCACCAGGAATCTGGAGTGATGCGCAGGTCGAGGCATGG
TTACCCATAACCCAAGCGGTACACGATGCCGGAGGTTTGATATTTGCACAACTGTGGCACAT
GGGGCGTATGGTGCCTTCCAACGTTTCTGGAATGCAACCTGTCGCACCTAGCGCTTCACAA
GCGCCCGGCTTGGGCCATACTTATGATGGCAAAAAGCCATACGATGTAGCCAGAGCATTGA
GACTTGACGAGATCCCACGGCTGCTGGACGACTATGAAAAGGCAGCTCGGCACGCACTGA
AAGCTGGGTTCGATGGAGTTCAGATTCATGCTGCCAACGGATACCTGATTGACGAGTTCATC
CGGGATTCAACAAATCATAGACACGACGAATACGGGGGGGCGGTTGAGAACAGAATACGG
TTATTGAAGGATGTCACTGAGCGGGTTATCGCAACCATCGGAAAGGAGCGCACAGCAGTGC
GTTTAAGTCCGAATGGAGAGATACAAGGCACAGTAGACTCGCATCCAGAACAGGTATTTAT
CCCGGCTGCAAAGATGTTATCTGATTTAGATATCGCGTTCCTTGGGATGCGCGAGGGTGCTG
TAGACGGGACATTTGGCAAAACAGACCAGCCCAAACTTTCGCCCGAGATCCGTAAAGTTTT
CAAGCCACCCCTTGTTCTGAATCAAGATTACACTTTCGAGACTGCCCAGGCTGCGTTAGATT
CGGGTGTAGCCGATGCAATCAGTTTTGGTCGTCCATTCATTGGGAATCCCGACTTACCGAGA
AGATTCTTTGAAAAGGCACCGTTAACTAAGGACGTAATTGAGACTTGGTACACTCAGACTC
CCAAAGGTTACACCGACTATCCACTGTTAGGTGATCTCGAGCACCACCATCACCACCACTG
A.

NADH-dependent flavin oxidoreductase from *Lacticaseibacillus paracasei* (**LacER**).
GenBank accession number: WP_013246060.1

LacER protein sequence

MSGYHFLKPFTFKHQTITLKNRIVIPPMTTRLSFEDGTVTRDEIRYYQQRAGGVGMFITGTANV
NALGKGFEGELSVADDRFIPGLSKLAAAMKTGGTKAILQIFSAGRMSNSKILRGEQPVSASAVA
APRAGYETPRALTSAEIEATIHDFGQAVRRAILAGFDGIELHGANTYLIQQFYSPNSNRRTDEWG
GDRDKRMRFPLAVVHEAEKVIATIADRPFLLGYRISPEELEQPGITLDDTLALIDALKQTKIDYL
HVSQSDVWRTSLRNPEDTAIMNEQIRDHVAGAFPVIVVGGIKTPADAEKAAESFDLVAIGHEMI
REPHWVQKVLDHDEKAIRYQIAPADLEELGIAPTFLDFIESISGGAKGVPLTTAQSVTSSNVTQD
LEHHHHHH.

LacER DNA sequence

ATGTCGGGCTACCACTTCCTGAAGCCATTTACTTTTAAGCACCAAACTATAACGCTTAAAAA
CCGCATCGTCATTCCACCCATGACTACGAGACTTTCCTTCGAGGATGGTACAGTTACCAGAG
ACGAGATTAGATACTATCAGCAACGGGCGGGTGGCGTCGGTATGTTTATAACTGGTACTGCA
AACGTCAACGCTCTTGGGAAAGGCTTTGAAGGAGAATTATCGGTCGCGGACGATCGGTTCA
TTCCGGGCTTGAGCAAATTGGCTGCAGCCATGAAGACTGGAGGGACCAAGGCTATTCTGCA
GATCTTTTCTGCCGGTCGCATGTCTAACAGCAAAATCTTGAGAGGGGAACAACCCGTGTCG
GCATCAGCTGTGGCGGCGCCAAGAGCCGGGTACGAAACACCTCGGGCGTTGACATCGGCT
GAGATCGAAGCCACGATCCACGACTTTGGGCAAGCTGTCCGTAGAGCAATCTTGGCGGGCT
TCGATGGGATAGAATTGCATGGCGCCAATACATATTTGATCCAGCAATTTTATTCCCCTAACA
GCAACCGGCGTACCGATGAATGGGGAGGGGATAGAGACAAACGCATGCGGTTTCCCTTAGC
AGTGGTCCACGAGGCTGAAAAGGTGATAGCAACCATCGCGGATCGCCCTTTCCTGCTTGGG
TATCGGATCTCTCCTGAAGAACTGGAGCAACCGGGGATAACTCTTGATGACACTCTGGCCTT
AATTGACGCTCTGAAACAAACGAAGATCGATTATTTACACGTTTCCCAGTCAGATGTCTGGA
GAACTTCACTGCGTAACCCCGAGGATACAGCTATTATGAATGAGCAAATCCGTGATCATGTC
GCAGGCGCCTTCCCAGTTATCGTAGTAGGAGGAATCAAGACTCCAGCCGACGCTGAGAAA
GCTGCGGAATCTTTTGATTTAGTTGCTATAGGTCATGAAATGATACGTGAGCCTCACTGGGTT
CAAAAAGTACTGGACCACS8GACGAAAAGGCTATCCGTTATCAAATTGCACCGGCGGACTT
GGAAGAACTGGGCATCGCCCCTACGTTTTTAGATTTTATCGAGAGCATCTCTGGTGGAGCCA
AGGGGGTGCCCTTGACGACGGCGCAGTCGGTCACTAGCAGTAACGTCACACAAGACCTCG
AGCACCACCATCACCACCACTGA.

CsER Protein Expression and Purification.

Caulobacter segnis Alkene Reductase (CsER) was produced in *E. coli* BL21 with a plasmid encoding CsER. Transformed glycerol stocks were used to initiate a 5 mL overnight culture in Luria-Bertani (LB) media with ampicillin (100 µg/mL) at 37 °C and 250 rpm. Expression culture (500 mL in a 2 L baffled shake flask) containing ampicillin (100 µg/mL) was inoculated with 5 mL of the overnight culture and grown until the culture reached an OD_{600} of 0.5-0.7 (37 °C, 250 rpm). Flasks were chilled on ice and protein expression was induced with 0.1 mM IPTG (25 °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.

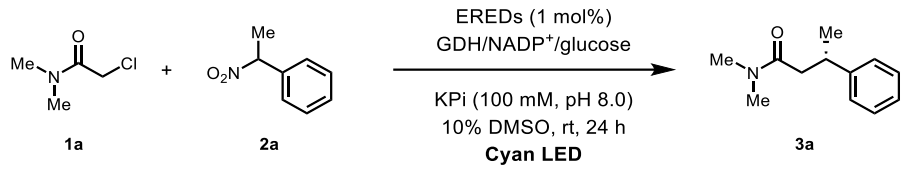
Frozen cells were thawed on ice and resuspended in buffer A (20 mM KPi pH 7.0, 300 mM NaCl, 25 mM imidazole) to a final concentration of 2 mL/g of wet cells. The resuspended cells were supplemented with lysozyme (1 mg/mL), FMN (1 mg/mL), DNase I (0.1 mg/mL), phenylmethylsulfonyl fluoride (PMSF, 1 mM) and allowed to shake for 30 min at 25 ºC. 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 AKTAStart purifier FPLC system (GE Healthcare). Enzymes were eluted with buffer B (20 mM KPi pH 7.0, 300 mM NaCl, 250 mM imidazole) over five column volumes. Yellow fractions containing CsER enzymes were pooled, concentrated, and subjected to three buffer exchanges into an imidazole-free storage buffer (100 mM KPi pH 8.0). Concentrated enzymes were aliquoted, flash-frozen in liquid N_2, 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^{-1} cm^{-1} at 446 nm) for free FMN released after protein denaturation. Extinction coefficient for CsER: ε = 10.2 x mM^{-1} cm^{-1} at 466 nm.

The detailed protein expression and purification of other tested ‘ene’-reductases in this study, including old yellow enzyme 2 (OYE2), 12-oxophytodienoate reductase 1 (OPR1), morphinone reductase (MorB), *Gluconobacter oxydans* enoate reductase (GluER), Nicotinamide-dependent cyclohexanone reductase from *Zymomonas mobiles* (NCR), and NADH-dependent flavin oxidoreductase from *Lacticaseibacillus paracasei* (LacER), were reported elsewhere.[2–4]

2. Detailed experimental procedures

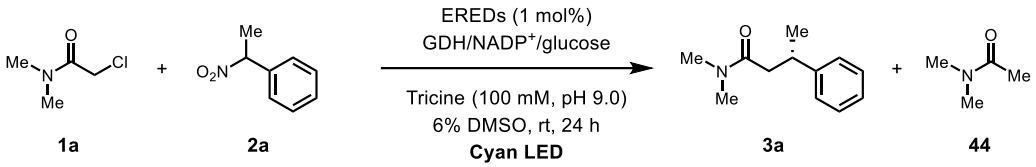
Supplementary Table 1. Initial panel of 'ene'-reductases screened for cross-electrophile couplings.



Entry	'Ene'-reductases	Light	Yield of **3a**[a]	er[b]
1	MorB	Cyan	20%	80:20
2	GluER-T36A	Cyan	13%	11:89
3	CsER	Cyan	28%	95:5
4	NCR	Cyan	11%	13:87
5	OYE2	Cyan	0%	n.d.[c]
6	OPR1	Cyan	2%	n.d.
7	LacER	Cyan	7%	46:54
8	CsER	No light	0%	n.d.
9	No enzyme	Cyan	0%	n.d.

Reaction conditions: α-chloroamide (**1a**, 1.2 mg, 10 μmol, 2 equiv), 1-nitroethylbenzene (**2a**, 0.76 mg, 5 μmol, 1 equiv), GDH (0.3 mg), $NADP^+$ (0.05 μmol, 1 mol%), glucose (25 μmol) and purified 'ene'-reductases (0.05 μmol, 1 mol% based on nitroalkane) in KPi buffer (100 mM, pH 8.0), with 10% DMSO as cosolvent, final total volume is 500 μL. Reaction mixtures were irradiated with cyan LEDs under anaerobic conditions at room temperature for 24 h. [a] Yield (average of duplicate) determined *via* LCMS relative to an internal standard (TBB). [b] Enantiomeric ratio (er, *S*:*R*) determined by HPLC on a chiral stationary phase. [c] n.d., not determined.

Supplementary Table 2. Reaction optimization and control experiments.

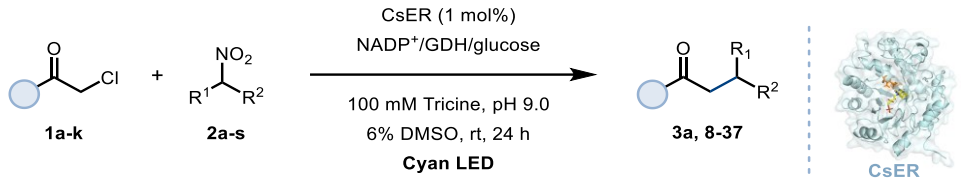


1a **2a** **3a** **44**

Entry	'Ene'-reductases	Light	Yield of **3a**[a]	er[b]	Yield of **44**[c]
1	MorB	Cyan	23%	83:17	13%
2	GluER-T36A	Cyan	51%	10:90	9%
3	CsER	Cyan	92%	95:5	15%
4	NCR	Cyan	39%	10:90	8%
5	OYE2	Cyan	0%	n.d.	3%
6	OPR1	Cyan	3%	n.d.	n.d.
7	LacER	Cyan	15%	46:54	23%
8	CsER	456 nm	33%	91:9	6%
9	CsER	390 nm	20%	90:10	6%
10	CsER	No light	0%	n.d.	0%
11	No enzyme	Cyan	0%	n.d.	0%
12	CsER without turnover system	Cyan	11%	92:8	4%

Reaction conditions: α-chloroamide (**1a**, 1.2 mg, 10 μmol, 2 equiv), 1-nitroethylbenzene (**2a**, 0.76 mg, 5 μmol, 1 equiv), GDH (0.3 mg), $NADP^+$ (0.05 μmol, 1 mol%), glucose (25 μmol) and purified 'ene'-reductases (0.05 μmol, 1 mol% based on nitroalkane) in Tricine buffer (100 mM, pH 9.0), with 6% DMSO as cosolvent, final total volume is 800 μL. Reaction mixtures were irradiated with cyan LEDs under anaerobic conditions at room temperature for 24 h. [a] Yield (average of duplicate) of **3a** (based on nitroalkane **2a**) determined *via* LCMS relative to an internal standard (TBB). [b] Enantiomeric ratio (er, *S*:*R*) determined by HPLC on a chiral stationary phase. [c] Yield (average of duplicate) of **44** based on α-chloroamide **1a**.

Photoenzymatic cross-electrophile couplings of alkyl halides with nitroalkanes



General procedure 1.

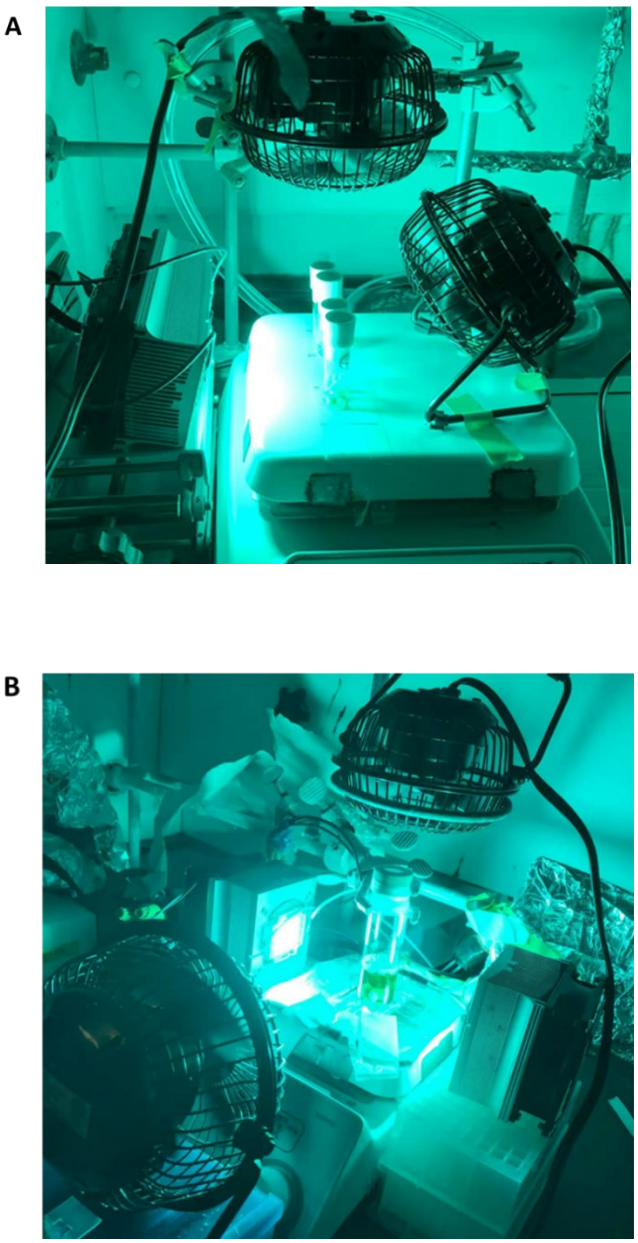
In the Coy® chamber (Vinyl Anaerobic Chamber, Type A), a 1 dram shell vial (15 x 45 mm, Fisherbrand® 03-339-26B) was charged with GDH (100 µL, 3 mg/mL stock solution in 100 mM Tricine buffer pH 9.0), glucose (100 µL, 45 mg/mL stock solution in 100 mM Tricine buffer pH 9.0), $NADP^+$ (9.2 µL, 5 mg/mL stock solution in 100 mM Tricine buffer pH 9.0, 1 mol%), CsER wild-type protein (1 mol% based on nitroalkane), α-chloroamide (25 µL, 400 mM stock in DMSO, 10 µmol, 2 equiv) and nitroalkane (25 µL, 200 mM stock in DMSO, 5 µmol, 1 equiv). Tricine buffer (100 mM pH 9.0) was added to bring the total volume to 800 µL with 6% DMSO (*v*/*v*) as cosolvent. The vial was sealed with a rubber septum and brought out of the Coy® chamber where it is placed on a stir plate at 200 rpm under a fan and irradiated with cyan LEDs for 24 hours (reaction setup see Supplementary Fig. 1A). The reaction mixture was placed approximately 10 cm away from the single light source (energy output 31.0 mW/cm^2). Upon completion, the reaction was quenched with 1.6 mL of acetonitrile and 50 µL 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_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude residue was dissolved in 10% isopropanol/hexanes (*v*/*v*) for chiral HPLC analysis.

Note: The tested α-chloroamide, α-chloroketone, α-bromoester and nitroalkane substrates are stable at room temperature (store at 4-degree fridge), we observed hydrolyzed products for α-bromoesters after enzymatic reaction. All substrate stock solutions were freshly prepared using degassed DMSO in the Coy® chamber before setup of reactions.

General procedure 2 for preparative scale reaction.

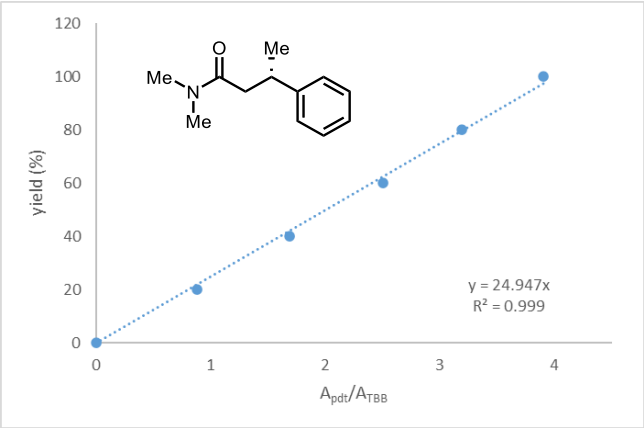
In the Coy® chamber (Vinyl Anaerobic Chamber, Type A), a 20 mL glass vial with screw cap was charged with GDH (2 mL, 3 mg/mL stock solution in 100 mM Tricine buffer pH 9.0), glucose (2 mL, 45 mg/mL stock solution in 100 mM Tricine buffer pH 9.0), $NADP^+$ (184 µL, 5 mg/mL stock solution in 100 mM Tricine buffer pH 9.0), CsER wild-type protein (1 mol% based on nitroalkane), α-chloroamide (500 µL, 400 mM stock in DMSO, 0.20 mmol, 2 equiv) and nitroalkane (500 µL, 200 mM stock in DMSO, 0.10 mmol, 1 equiv). Tricine buffer (100 mM pH 9.0) was added to bring the total volume to 16 mL with 6% DMSO (*v*/*v*) as cosolvent. The vial was sealed with a screw cap and brought out of the Coy® chamber where it is placed on a stir plate at 200 rpm under a fan and irradiated with cyan LEDs for 24 hours (reaction setup see Supplementary Fig. 1B). The reaction mixture was placed

approximately 10 cm away from the dual light source (energy output around 62.0 mW/cm^2). Upon completion, the reaction was quenched with 32 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 DCM (3 x 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to provide the crude product, which was purified by preparative TLC (EtOAc/Hexanes, 50%, *v*/*v*).



Supplementary Fig. 1. (**A**) Reaction light setup for general procedure 1. (B) Reaction light setup for general procedure 2.

(*S*)-*N*,*N*-Dimethyl-3-phenylbutanamide (**3a**)

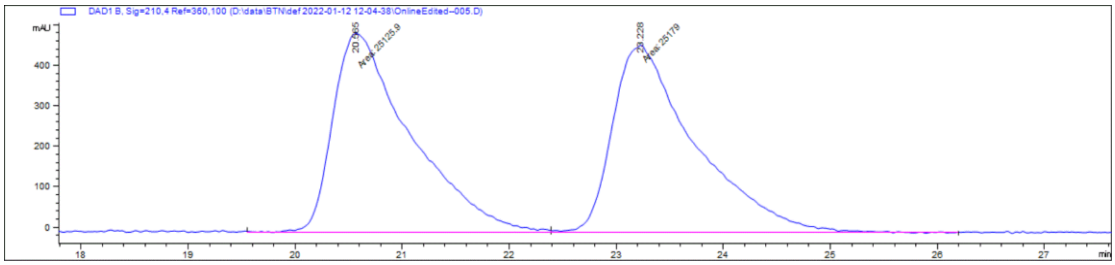


Prepared according to the general procedure 1 using α-chloro-*N*,*N*-dimethylacetamide (**1a**, 10 μmol, 2 equiv) and 1-nitroethylbenzene (**2a**, 5 μmol, 1 equiv) catalyzed by CsER (1 mol%).

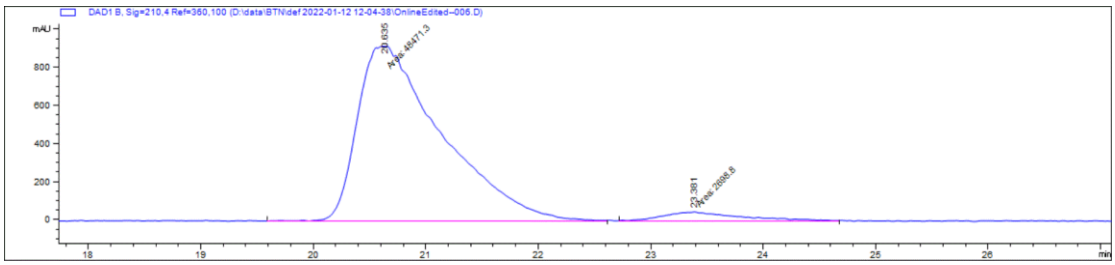
Yields: run 1: 94%, run 2: 90%, average yield 92%.

Preparative enzymatic synthesis was conducted according to the general procedure 2 using α-chloro-*N*,*N*-dimethylacetamide (**1a**, 0.20 mmol, 2 equiv) and 1-nitroethylbenzene (**2a**, 0.10 mmol, 1 equiv) catalyzed by CsER (1 mol%). Isolated yield: 74% (clear oil, 14 mg).

Enantioselectivity: 95:5 er. Chiral HPLC method: OD-H column, 210 nm, 5% isopropanol/n-heptane, flow rate 0.5 mL/min, room temperature, t_R (major) = 20.64 min, t_R (minor) = 23.38 min. **Absolute configuration** of the enzymatic product **3a** is assigned as ***S*** by comparison with the previously reported chiral HPLC data.[5]

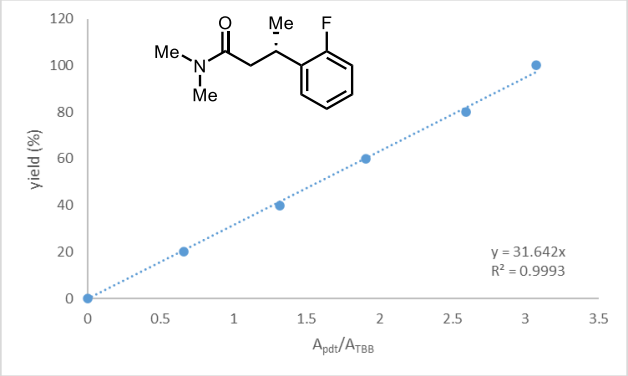


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	20.565	MF	24870.6	492.3	0.842	50.080	0.421
2	23.228	FM	24791	462.8	0.8928	49.920	0.518



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	20.635	MM	48471.3	921.5	0.8767	94.726	0.475
2	23.381	MM	2698.8	51.2	0.8777	5.274	0.617

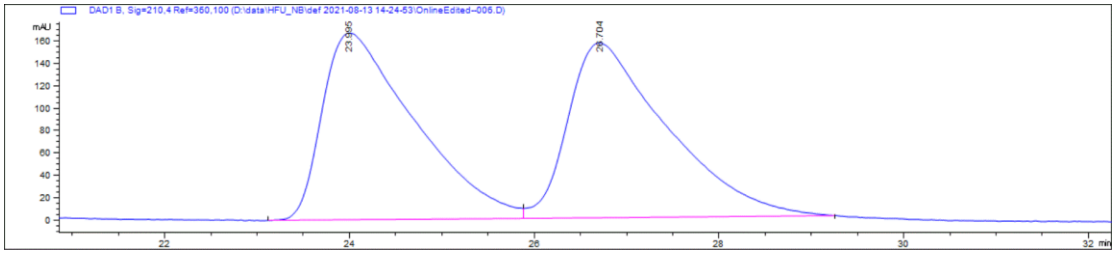
(*S*)-3-(2-Fluorophenyl)-*N*,*N*-dimethylbutanamide (**8**)



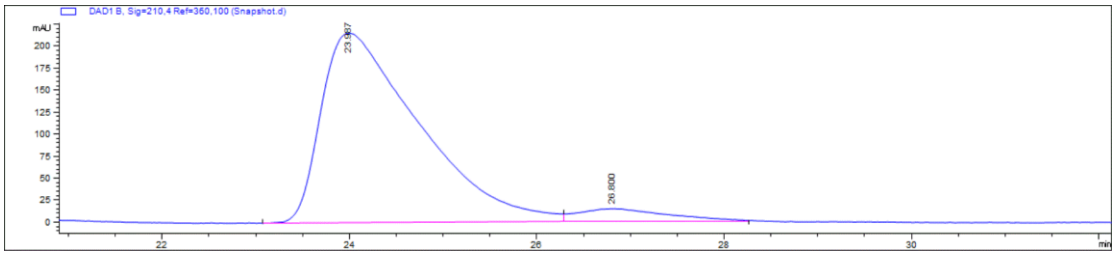
Prepared according to the general procedure 1 using α-chloro-*N*,*N*-dimethylacetamide (**1a**, 10 µmol, 2 equiv) and 1-fluoro-2-(1-nitroethyl)benzene (**2b**, 5 µmol, 1 equiv) catalyzed by CsER (1 mol%).

Yields: run 1: 28%, run 2: 29%, average yield 28%.

Enantioselectivity: 94:6 er. Chiral HPLC method: OD-H column, 210 nm, 1% isopropanol/hexanes, flow rate 1.0 mL/min, room temperature, t_R (major) = 23.99 min, t_R (minor) = 26.80 min.

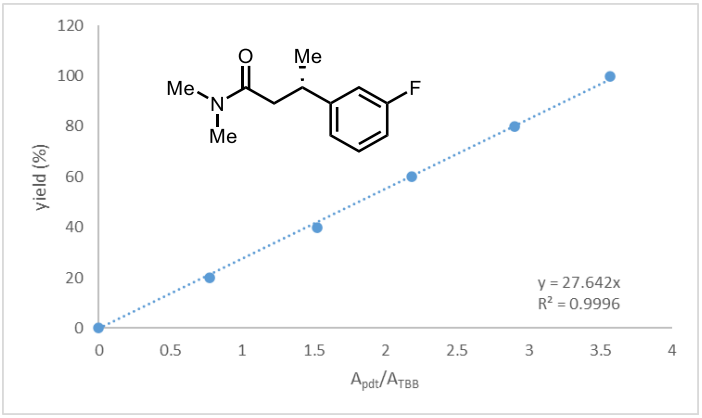


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	23.995	BV	11679	168.2	0.9262	49.600	0.387
2	26.704	VB	11867.5	157.7	0.9741	50.400	0.429



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	23.987	VB	15755	216	0.8909	93.917	0.358
2	26.8	BV	1020.5	15.1	0.7961	6.083	0.58

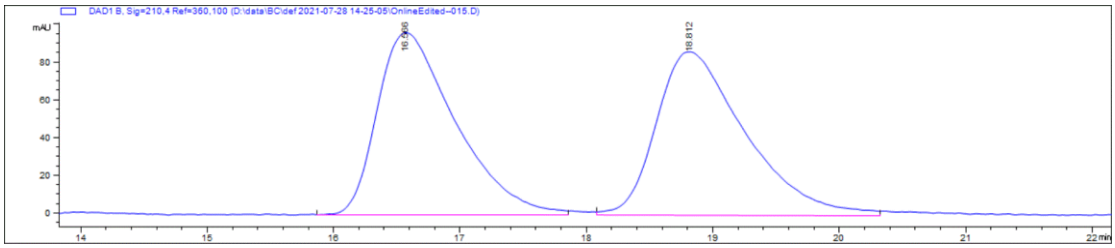
(*S*)-3-(3-Fluorophenyl)-*N*,*N*-dimethylbutanamide (**9**)



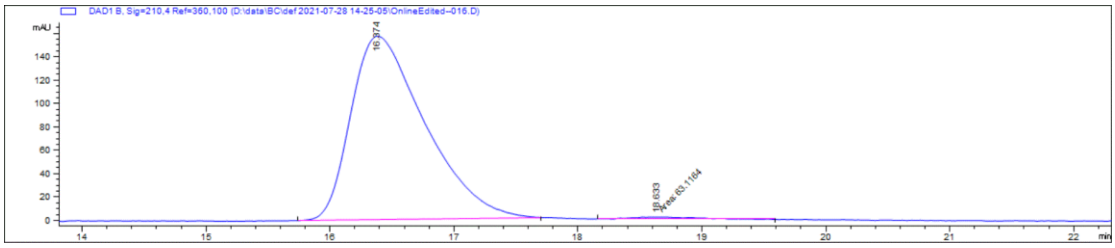
Prepared according to the general procedure 1 using α-chloro-*N*,*N*-dimethylacetamide (**1a**, 10 μmol, 2 equiv) and 1-fluoro-3-(1-nitroethyl)benzene (**2c**, 5 μmol, 1 equiv) catalyzed by CsER (1 mol%).

Yields: run 1: 93%, run 2: 94%, average yield 93%.

Enantioselectivity: 99:1 er. Chiral HPLC method: OD-H column, 210 nm, 2% isopropanol/hexanes, flow rate 1.0 mL/min, room temperature, t_R (major) = 16.37 min, t_R (minor) = 18.63 min.

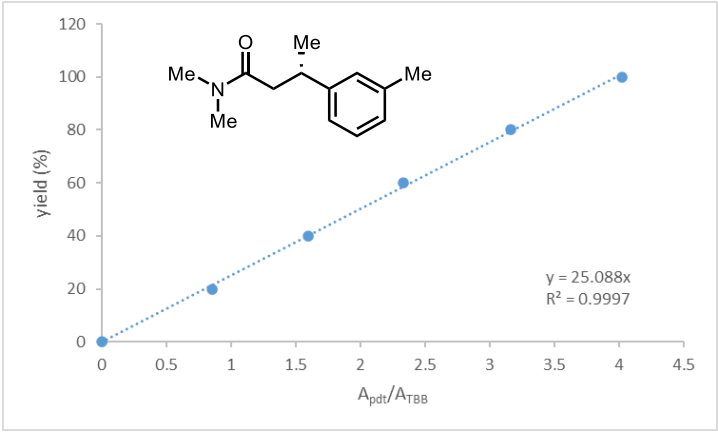


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	16.566	VV	4184.1	97	0.5935	49.355	0.54
2	18.812	BB	4293.5	87.2	0.5907	50.645	0.592



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	16.374	BB	6515.5	156.8	0.6027	99.041	0.526
2	18.633	MM	63.1	1.7	0.6266	0.959	0.546

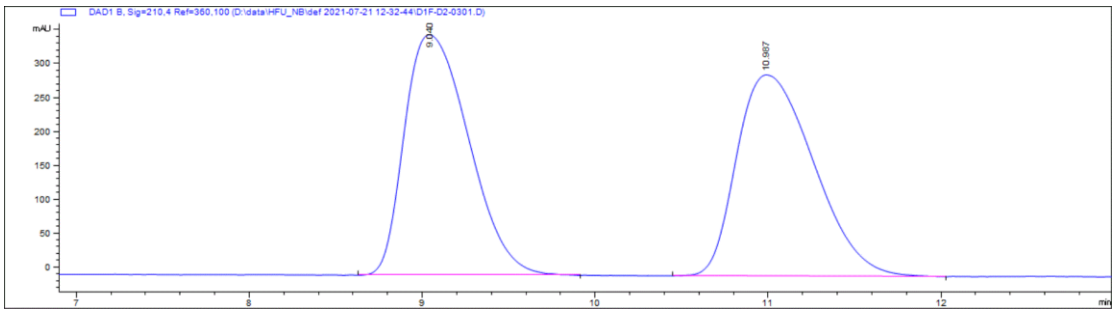
(*S*)-*N*,*N*-Dimethyl-3-(m-tolyl)butanamide (**10**)



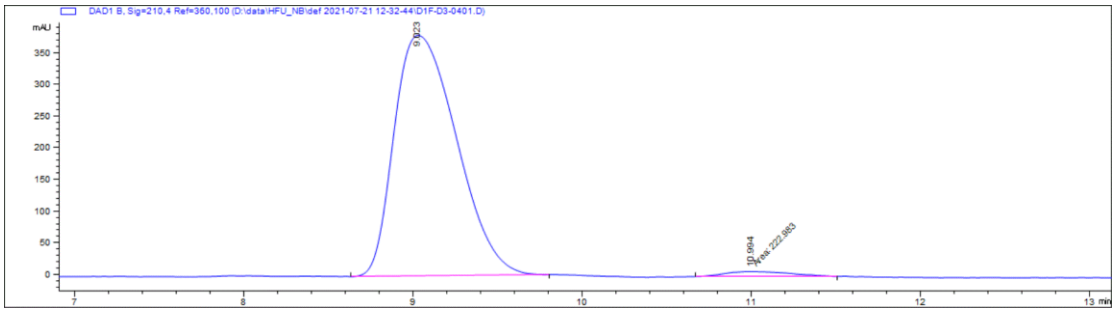
Prepared according to the general procedure 1 using α-chloro-*N*,*N*-dimethylacetamide (**1a**, 10 µmol, 2 equiv) and 1-methyl-3-(1-nitroethyl)benzene (**2d**, 5 µmol, 1 equiv) catalyzed by CsER (1 mol%).

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

Enantioselectivity: 98:2 er. Chiral HPLC method: OD-H column, 210 nm, 5% isopropanol/hexanes, flow rate 1.0 mL/min, room temperature, t_R (major) = 9.02 min, t_R (minor) = 10.99 min.

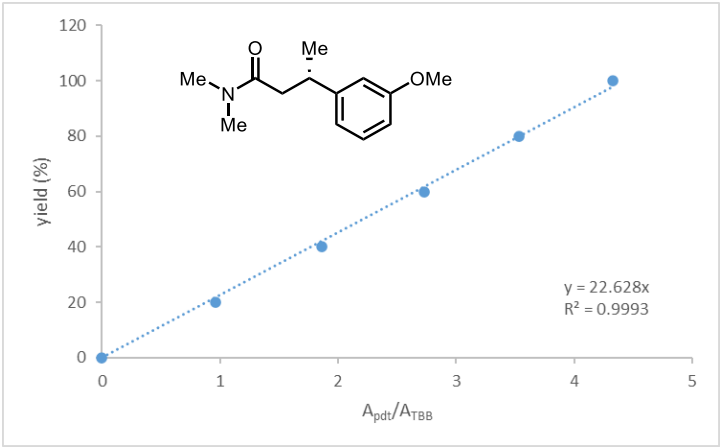


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	9.04	VB	9143.6	353.1	0.4101	49.961	0.606
2	10.987	BV	9157.8	295.5	0.4916	50.039	0.601



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	9.023	VB	9806.1	382.3	0.4133	97.777	0.595
2	10.994	MM	223	8.1	0.4615	2.223	0.655

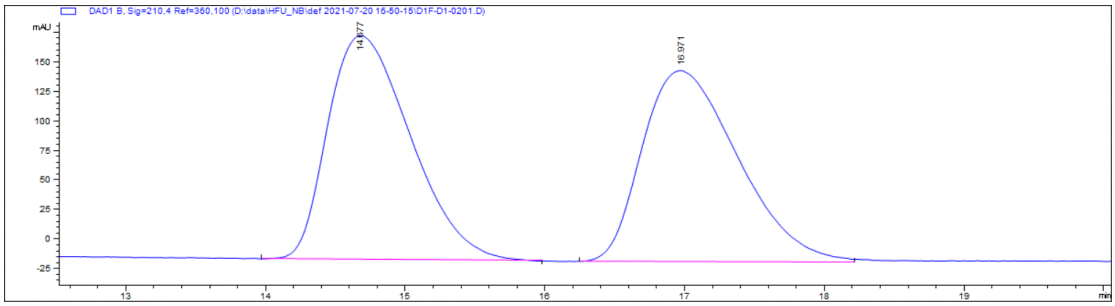
(*S*)-3-(3-Methoxyphenyl)-*N*,*N*-dimethylbutanamide (**11**)



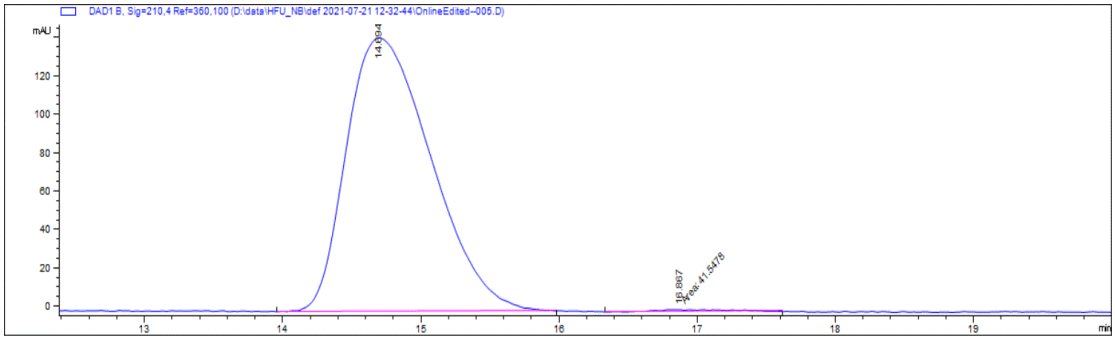
Prepared according to the general procedure 1 using α-chloro-*N*,*N*-dimethylacetamide (**1a**, 10 µmol, 2 equiv) and 1-methoxy-3-(1-nitroethyl)benzene (**2e**, 5 µmol, 1 equiv) catalyzed by CsER (1 mol%).

Yields: run 1: 82%, run 2: 78%, average yield 80%.

Enantioselectivity: 99:1 er. Chiral HPLC method: OD-H column, 210 nm, 5% isopropanol/hexanes, flow rate 1.0 mL/min, room temperature, t_R (major) = 14.69 min, t_R (minor) = 16.88 min.

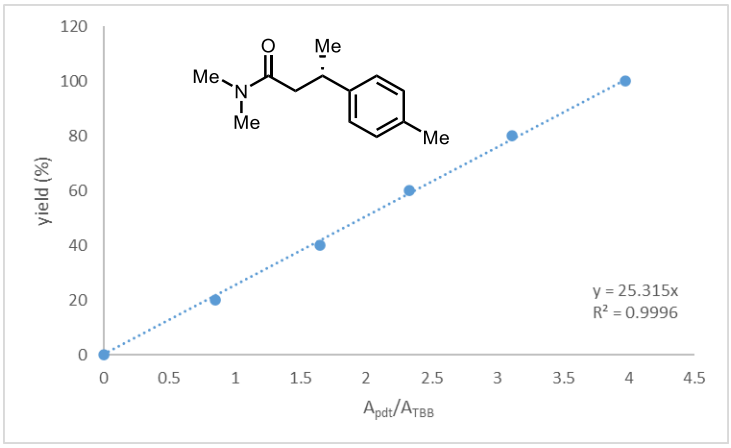


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	14.677	VB	7871.3	190.5	0.588	50.312	0.627
2	16.971	BV	7773.5	162.6	0.6897	49.688	0.637



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	14.694	VB	6062.1	142.1	0.6057	99.319	0.599
2	16.867	MM	41.5	1.1	0.64	0.681	0.488

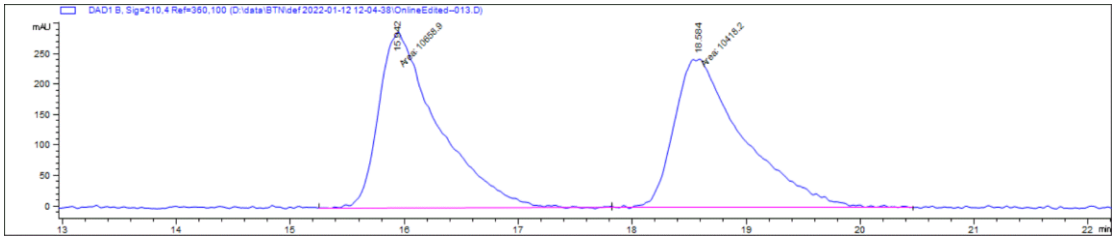
(*S*)-*N*,*N*-Dimethyl-3-(*p*-tolyl)butanamide (**12**)



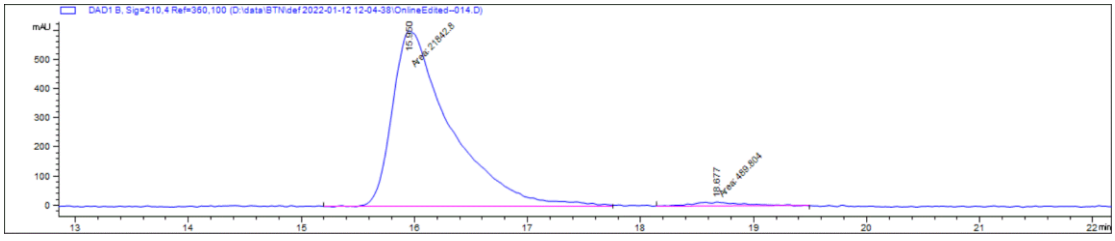
Prepared according to the general procedure 1 using α-chloro-*N*,*N*-dimethylacetamide (**1a**, 10 µmol, 2 equiv) and 1-methyl-4-(1-nitroethyl)benzene (**2f**, 5 µmol, 1 equiv) catalyzed by CsER (1 mol%).

Yields: run 1: 98%, run 2: 94%, average yield 96%.

Enantioselectivity: 98:2 er. Chiral HPLC method: OD-H column, 210 nm, 5% isopropanol/n-heptane, flow rate 0.5 mL/min, room temperature, t_R (major) = 15.95 min, t_R (minor) = 18.68 min. **Absolute configuration** of the enzymatic product **12** is assigned as ***S*** by comparison with the previously reported chiral HPLC data [5].

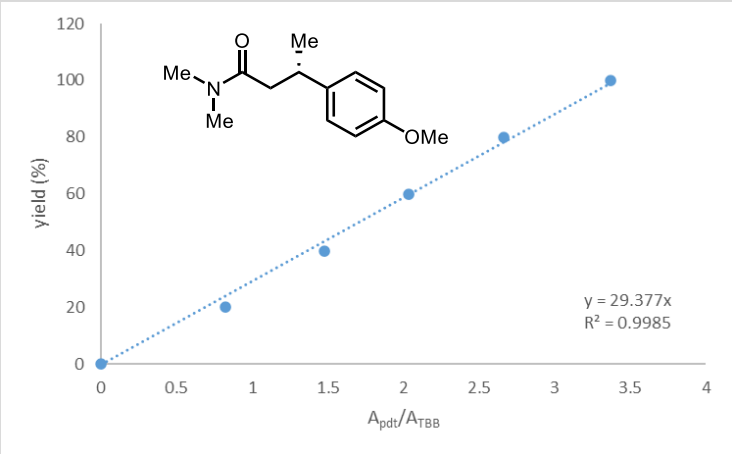


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	15.942	MF	10658.9	291.4	0.6096	50.571	0.476
2	18.584	FM	10418.2	245.4	0.7074	49.429	0.556



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	15.95	MM	21842.8	602.9	0.6038	97.807	0.386
2	18.677	MM	489.8	14.9	0.5488	2.193	1.026

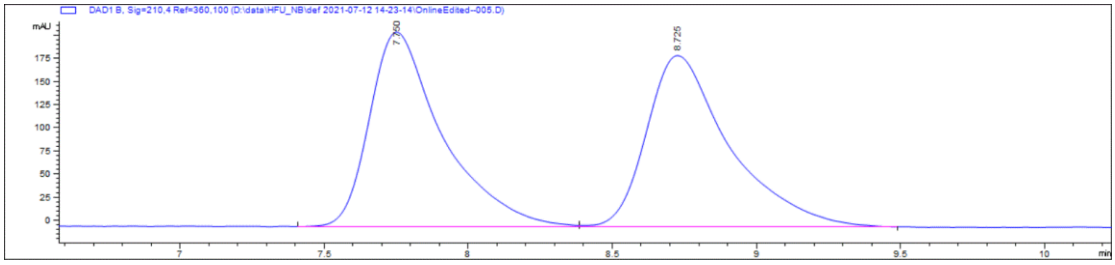
(*S*)-3-(4-Methoxyphenyl)-*N*,*N*-dimethylbutanamide (**13**)



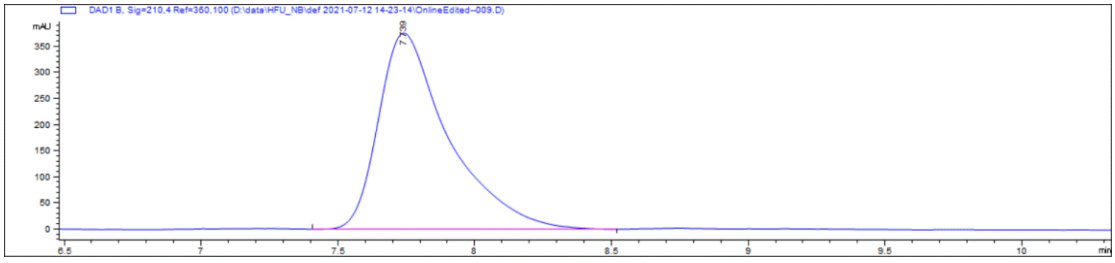
Prepared according to the general procedure 1 using α-chloro-*N*,*N*-dimethylacetamide (**1a**, 10 μmol, 2 equiv) and 1-methoxy-4-(1-nitroethyl)benzene (**2g**, 5 μmol, 1 equiv) catalyzed by CsER (1 mol%).

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

Enantioselectivity: >99:1 er. Chiral HPLC method: OD-H column, 210 nm, 10% isopropanol/hexanes, flow rate 1.0 mL/min, room temperature, t_R (major) = 7.74 min.

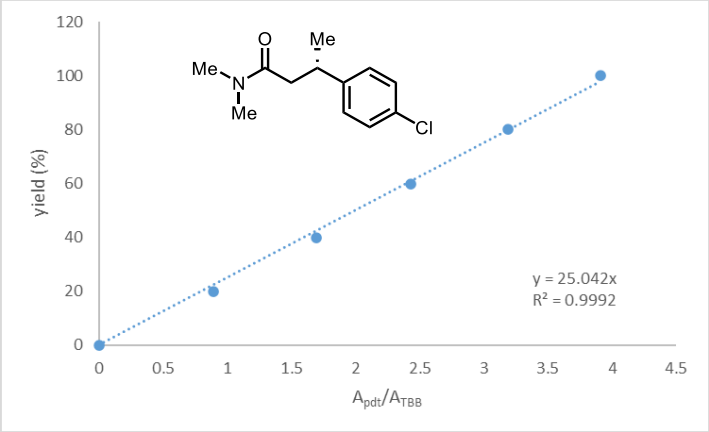


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	7.75	VV	3722.5	210.6	0.2582	49.908	0.548
2	8.725	VV	3736.2	185.6	0.2949	50.092	0.558



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	7.739	VV	6794.7	379.3	0.261	100.000	0.523

(*S*)-3-(4-Chlorophenyl)-*N*,*N*-dimethylbutanamide (**14**)

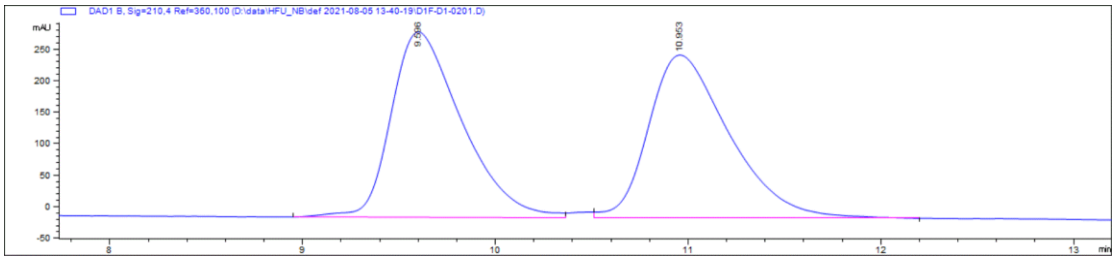


Prepared according to the general procedure 1 using α-chloro-*N*,*N*-dimethylacetamide (**1a**, 10 µmol, 2 equiv) and 1-chloro-4-(1-nitroethyl)benzene (**2h**, 5 µmol, 1 equiv) catalyzed by CsER (1 mol%).

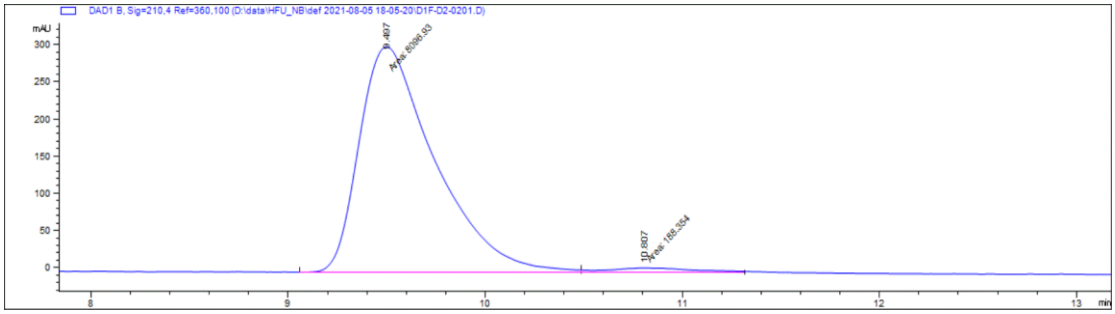
Yields: run 1: 98%, run 2: 96%, average yield 97%.

Preparative enzymatic synthesis was conducted according to the general procedure 2 using α-chloro-*N*,*N*-dimethylacetamide (**1a**, 0.20 mmol, 2 equiv) and 1-chloro-4-(1-nitroethyl)benzene (**2h**, 0.10 mmol, 1 equiv) catalyzed by CsER (1 mol%). Isolated yield: 76% (white solid, 17 mg).

Enantioselectivity: 98:2 er. Chiral HPLC method: OD-H column, 210 nm, 5% isopropanol/hexanes, flow rate 1.0 mL/min, room temperature, t_R (major) = 9.50 min, t_R (minor) = 10.81 min.

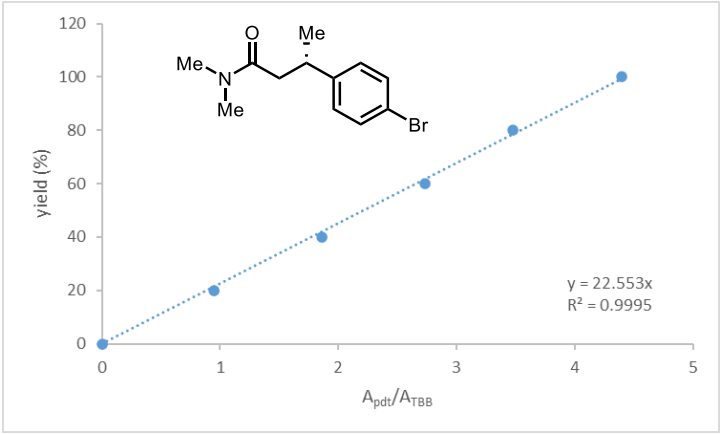


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	9.596	BV	7489.3	293.2	0.388	49.922	0.606
2	10.953	VB	7512.7	257.6	0.4343	50.078	0.609



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	9.497	MF	8096.9	303.4	0.4448	97.727	0.543
2	10.807	FM	188.4	6.1	0.5135	2.273	0.703

(*S*)-3-(4-Bromophenyl)-*N*,*N*-dimethylbutanamide (**15**)

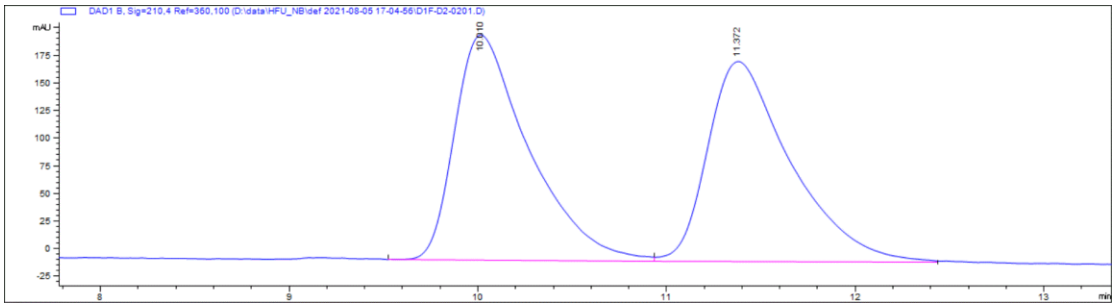


Prepared according to the general procedure 1 using α-chloro-*N*,*N*-dimethylacetamide (**1a**, 10 µmol, 2 equiv) and 1-bromo-4-(1-nitroethyl)benzene (**2i**, 5 µmol, 1 equiv) catalyzed by CsER (1 mol%).

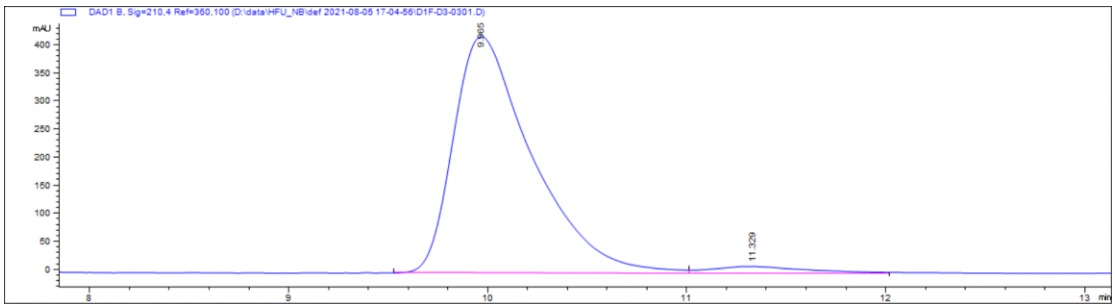
Yields: run 1: 94%, run 2: 93%, average yield 93%.

Preparative enzymatic synthesis was conducted according to the general procedure 2 using α-chloro-*N*,*N*-dimethylacetamide (**1a**, 0.20 mmol, 2 equiv) and 1-bromo-4-(1-nitroethyl)benzene (**2i**, 0.10 mmol, 1 equiv) catalyzed by CsER (1 mol%). Isolated yield: 70% (white solid, 19 mg).

Enantioselectivity: 97:3 er. Chiral HPLC method: OD-H column, 210 nm, 5% isopropanol/hexanes, flow rate 1.0 mL/min, room temperature, t_R (major) = 9.96 min, t_R (minor) = 11.33 min.

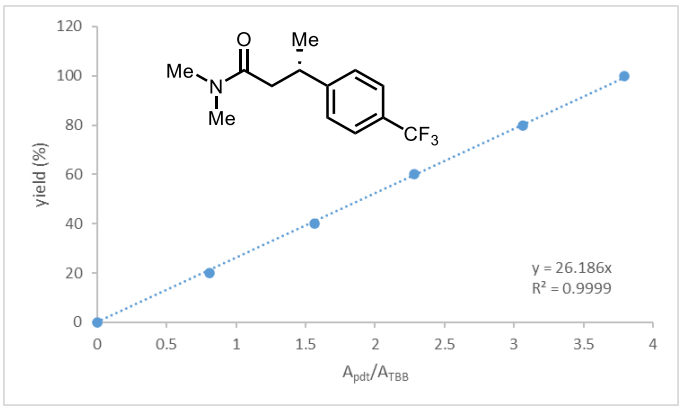


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	10.01	BV	5591.4	204.3	0.3993	50.123	0.508
2	11.372	VV	5564	181.4	0.4377	49.877	0.552



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	9.965	VV	11650	423.1	0.4012	96.552	0.518
2	11.329	VV	416.1	12.4	0.4027	3.448	0.708

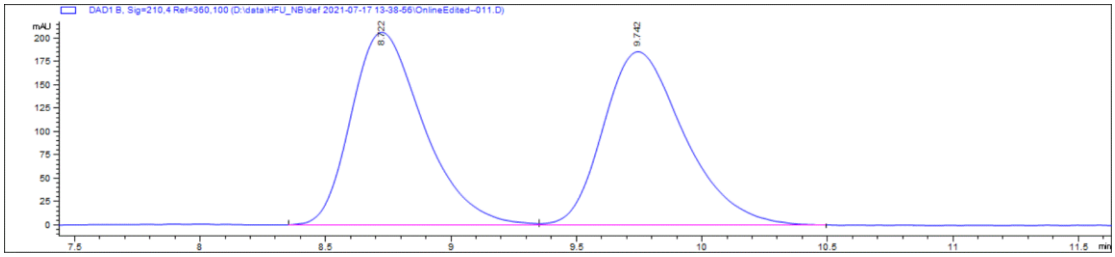
(*S*)-*N*,*N*-Dimethyl-3-[4-(trifluoromethyl)phenyl]butanamide (**16**)



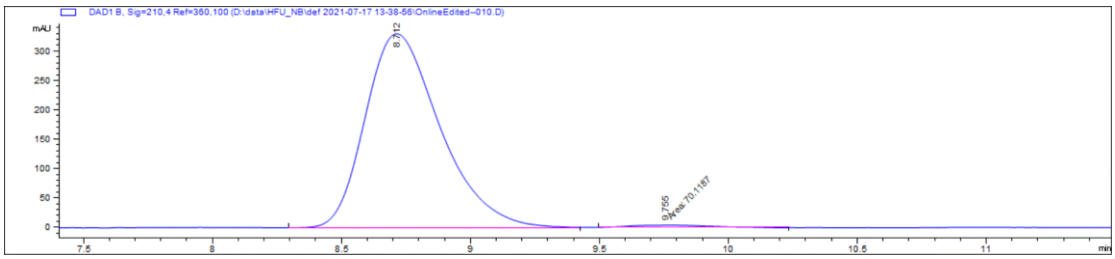
Prepared according to the general procedure 1 using α-chloro-*N*,*N*-dimethylacetamide (**1a**, 10 µmol, 2 equiv) and 1-(1-nitroethyl)-4-(trifluoromethyl)benzene (**2j**, 5 µmol, 1 equiv) catalyzed by CsER (1 mol%). **Yields**: run 1: 98%, run 2: 97%, average yield 98%.

Preparative enzymatic synthesis was conducted according to the general procedure 2 using α-chloro-*N*,*N*-dimethylacetamide (**1a**, 0.20 mmol, 2 equiv) and 1-(1-nitroethyl)-4-(trifluoromethyl)benzene (**2j**, 0.10 mmol, 1 equiv) catalyzed by CsER (1 mol%). Isolated yield: 77% (clear oil, 20 mg).

Enantioselectivity: 99:1 er. Chiral HPLC method: OD-H column, 210 nm, 5% isopropanol/hexanes, flow rate 1.0 mL/min, room temperature, t_R (major) = 8.71 min, t_R (minor) = 9.76 min.

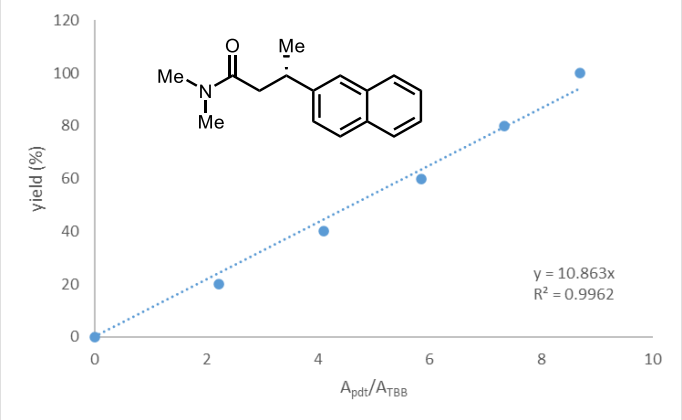


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	8.722	BV	4209.3	208	0.3121	49.853	0.69
2	9.742	VB	4234.1	187.2	0.3479	50.147	0.708



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	8.712	VV	6697.5	331.3	0.3159	98.964	0.686
2	9.755	MM	70.1	3.7	0.3147	1.036	0.861

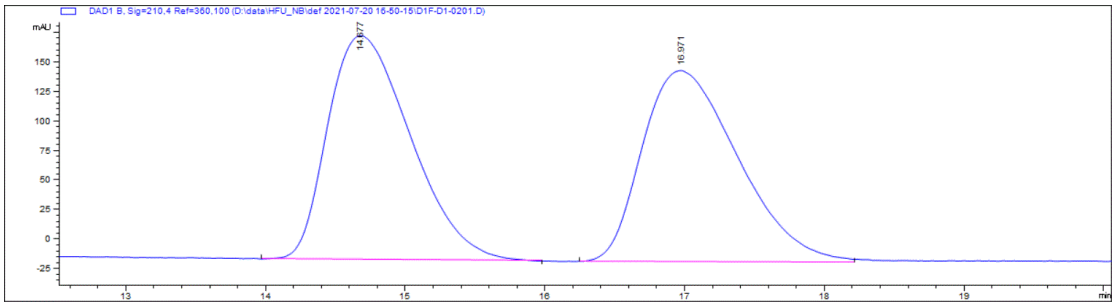
(*S*)-*N*,*N*-Dimethyl-3-(naphthalen-2-yl)butanamide (**17**)



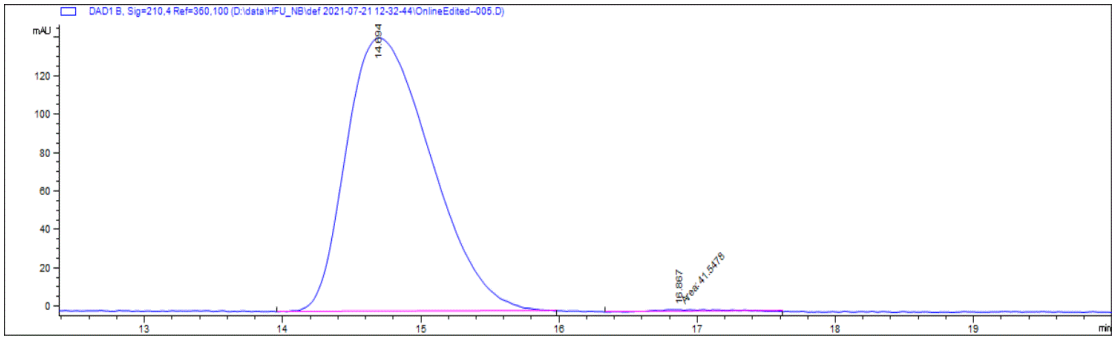
Prepared according to the general procedure 1 using α-chloro-*N*,*N*-dimethylacetamide (**1a**, 10 µmol, 2 equiv) and 2-(1-nitroethyl)naphthalene (**2k**, 5 µmol, 1 equiv) catalyzed by CsER (1 mol%).

Yields: run 1: 58%, run 2: 58%, average yield 58%.

Enantioselectivity: 99:1 er. Chiral HPLC method: OD-H column, 210 nm, 5% isopropanol/hexanes, flow rate 1.0 mL/min, room temperature, t_R (major) = 14.69 min, t_R (minor) = 16.88 min.

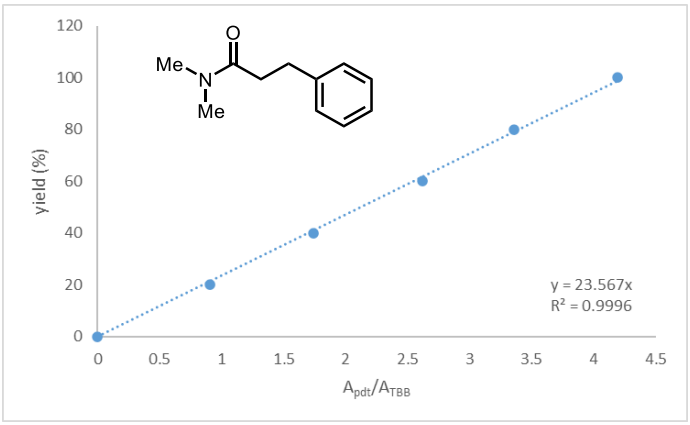


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	14.677	VB	7871.3	190.5	0.588	50.312	0.627
2	16.971	BV	7773.5	162.6	0.6897	49.688	0.637



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	14.694	VB	6062.1	142.1	0.6057	99.319	0.599
2	16.867	MM	41.5	1.1	0.64	0.681	0.488

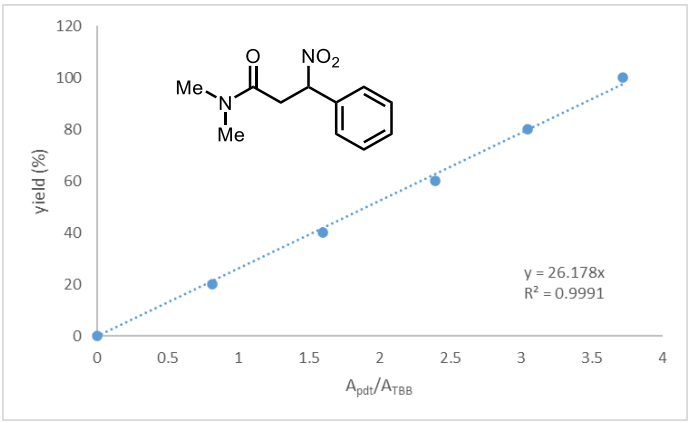
N,*N*-Dimethyl-3-phenylpropanamide (**18**)



Prepared according to the general procedure 1 using α-chloro-*N*,*N*-dimethylacetamide (**1a**, 10 µmol, 2 equiv) and (nitromethyl)benzene (**2l**, 5 µmol, 1 equiv) catalyzed by CsER (1 mol%).

Yields: run 1: 27%, run 2: 29%, average yield 28%.

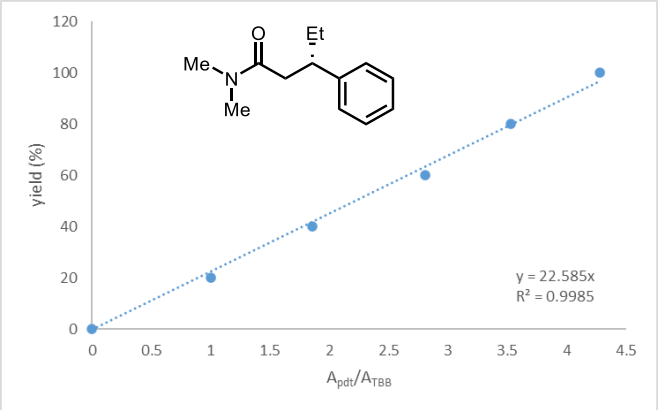
N,N-Dimethyl-3-nitro-3-phenylpropanamide (**40**)



Prepared according to the general procedure 1 using α-chloro-*N*,*N*-dimethylacetamide (**1a**, 10 µmol, 2 equiv) and (nitromethyl)benzene (**2l**, 5 µmol, 1 equiv) catalyzed by CsER (1 mol%).

Yields: run 1: 28%, run 2: 29%, average yield 29%.

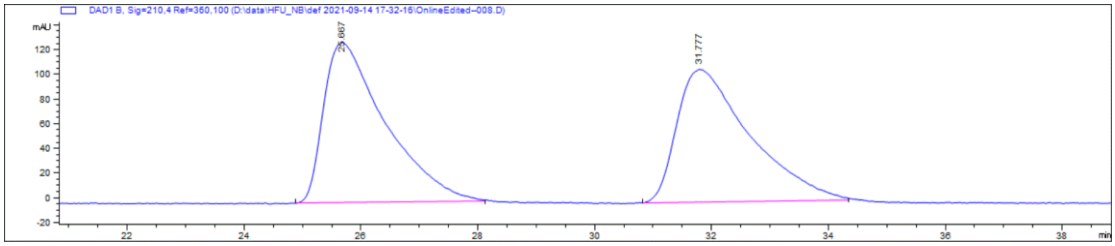
(*S*)-*N*,*N*-Dimethyl-3-phenylpentanamide (**19**)



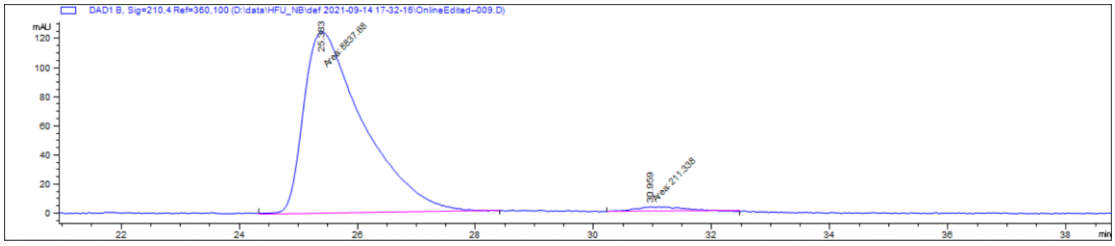
Prepared according to the general procedure 1 using α-chloro-*N*,*N*-dimethylacetamide (**1a**, 10 µmol, 2 equiv) and (1-nitropropyl)benzene (**2m**, 5 µmol, 1 equiv) catalyzed by CsER (1 mol%).

Yields: run 1: 63%, run 2: 65%, average yield 64%.

Enantioselectivity: 98:2 er. Chiral HPLC method: OD-H column, 210 nm, 1% isopropanol/hexanes, flow rate 1.0 mL/min, room temperature, t_R (major) = 25.38 min, t_R (minor) = 30.96 min.

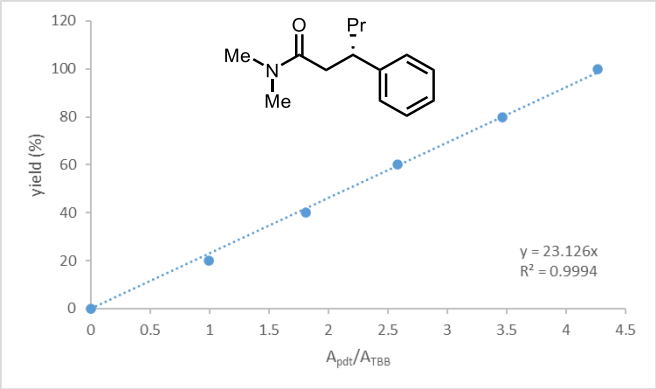


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	25.667	BB	9530	130.1	0.8708	50.440	0.412
2	31.777	VV	9363.9	108	1.0254	49.560	0.436



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	25.383	MM	8837.7	125.3	1.1757	97.665	0.411
2	30.959	MM	211.3	3.5	1.0111	2.335	0.545

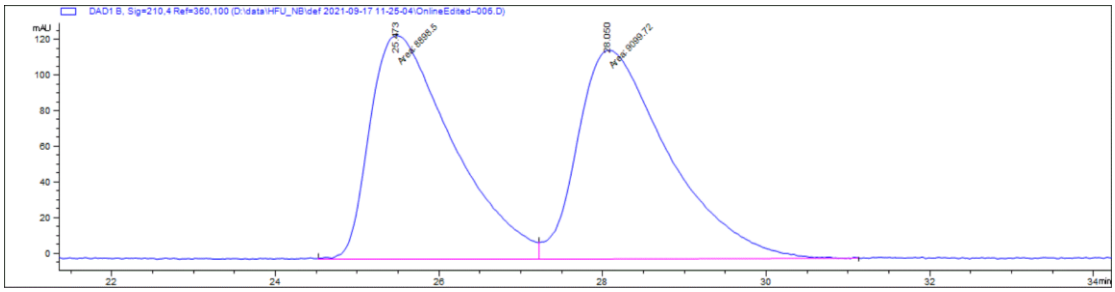
(*S*)-*N*,*N*-Dimethyl-3-phenylhexanamide (**20**)



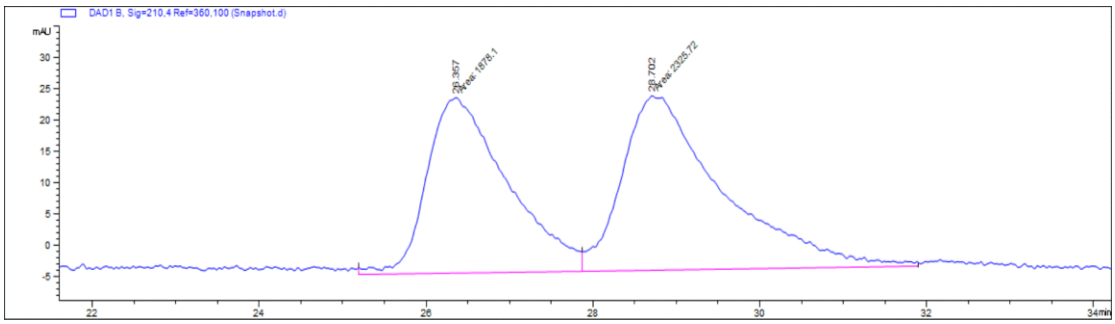
Prepared according to the general procedure 1 using α-chloro-*N*,*N*-dimethylacetamide (**1a**, 10 µmol, 2 equiv) and (1-nitrobutyl)benzene (**2n**, 5 µmol, 1 equiv) catalyzed by CsER (2 mol%).

Yields: run 1: 14%, run 2: 16%, average yield 15%.

Enantioselectivity: 55:45 er. Chiral HPLC method: OD-H column, 210 nm, 1% isopropanol/hexanes, flow rate 1.0 mL/min, room temperature, t_R (minor) = 26.35min, t_R (major) = 28.70 min.

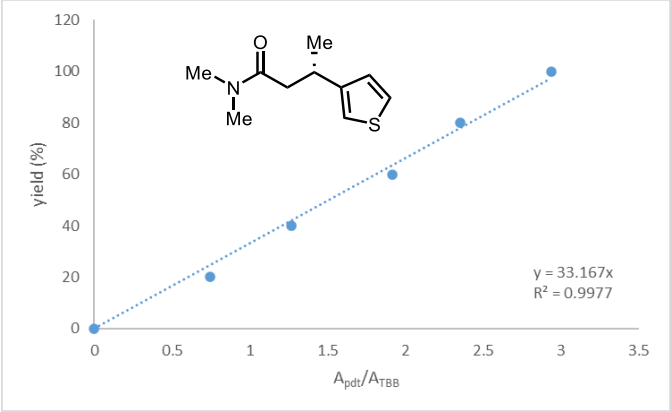


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	25.473	MF	8898.5	126.4	1.1734	49.441	0
2	28.05	FM	9099.7	117.7	1.2888	50.559	0.479



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	26.357	MF	1878.1	28	1.1181	44.676	0.564
2	28.702	FM	2325.7	27.8	1.393	55.324	0.421

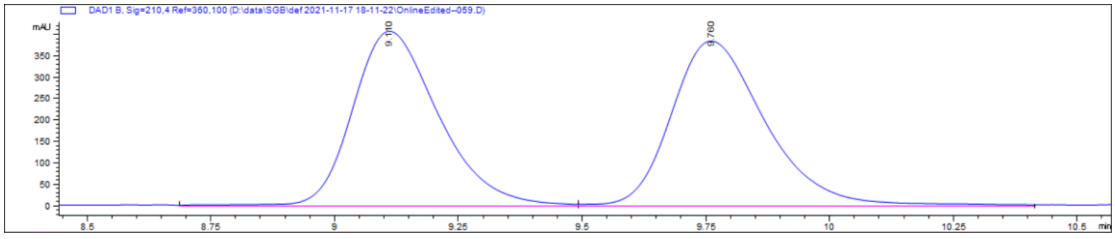
(*S*)-*N*,*N*-Dimethyl-3-(thiophen-3-yl)butanamide (**22**)



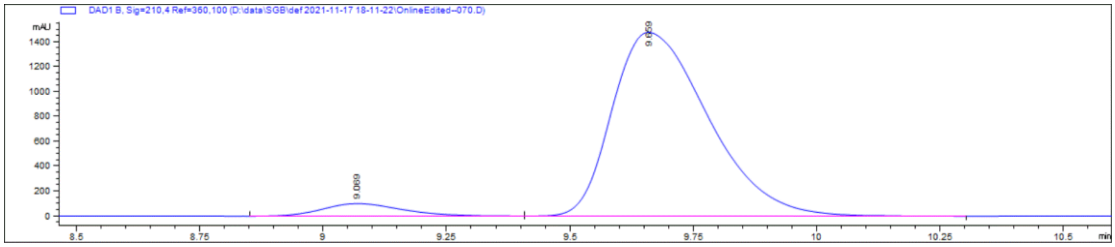
Prepared according to the general procedure 1 using α-chloro-*N*,*N*-dimethylacetamide (**1a**, 10 µmol, 2 equiv) and 3-(1-nitroethyl)thiophene (**2p**, 5 µmol, 1 equiv) catalyzed by CsER (1 mol%).

Yields: run 1: 75%, run 2: 76%, average yield 76%.

Enantioselectivity: 94:6 er. Chiral HPLC method: OJ-H column, 210 nm, 1% isopropanol/hexanes, flow rate 1.0 mL/min, room temperature, t_R (minor) = 9.07 min, t_R (major) = 9.66 min.

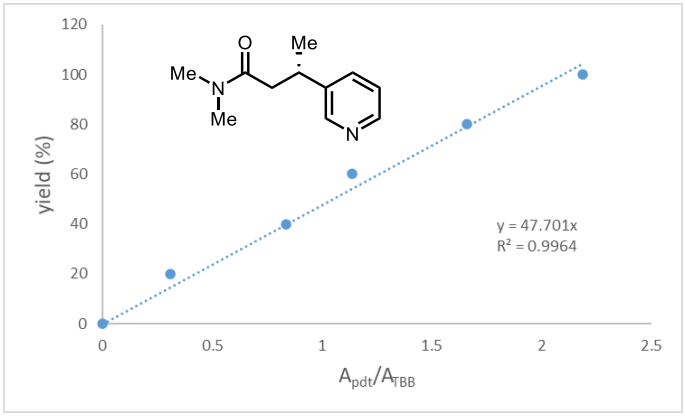


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	9.11	VV	5022.3	410	0.1889	49.102	0.723
2	9.76	VB	5205.9	387.1	0.2029	50.898	0.681



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	9.069	VV	1201	102.9	0.1762	5.617	0.733
2	9.659	VV	20180.7	1488	0.2082	94.383	0.581

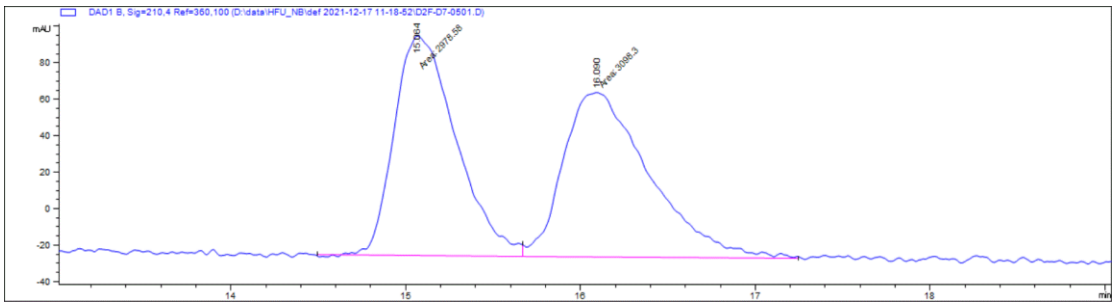
(*S*)-*N*,*N*-Dimethyl-3-(pyridin-3-yl)butanamide (**23**)



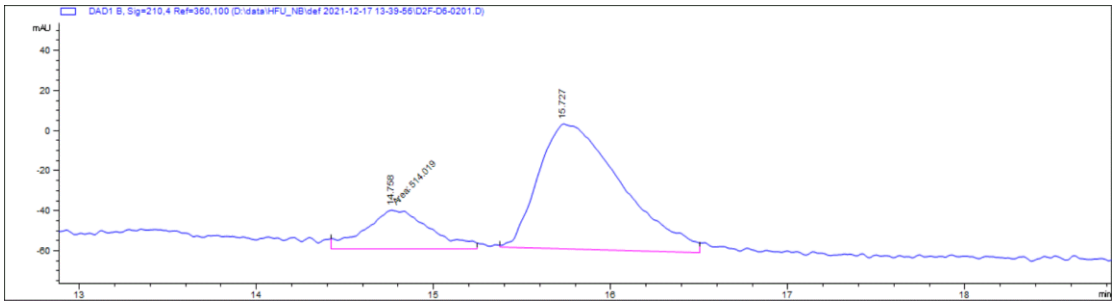
Prepared according to the general procedure 1 using α-chloro-*N*,*N*-dimethylacetamide (**1a**, 10 µmol, 2 equiv) and 3-(1-nitroethyl)pyridine (**2q,** 5 µmol, 1 equiv) catalyzed by CsER (1 mol%). The product standard curve was made using a AS-H column, with 20% isopropanol/hexanes as mobile phase, due to the high polarity of the enzymatic product **23**.

Yields: run 1: 42%, run 2: 38%, average yield 40%.

Enantioselectivity: 80:20 er. Chiral HPLC method: AS-H column, 210 nm, 15% isopropanol/hexanes, flow rate 1.0 mL/min, room temperature, t_R (minor) = 14.76 min, t_R (major) = 15.73 min.

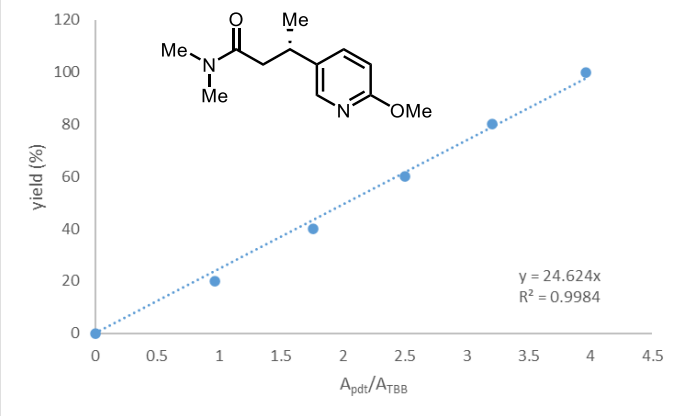


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	15.064	MF	2978.6	120.4	0.4123	49.015	0.593
2	16.09	FM	3098.3	90.1	0.573	50.985	0.616



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	14.758	MM	514	19.7	0.4338	20.081	0.684
2	15.727	VV	2045.7	62.6	0.3893	79.919	0.433

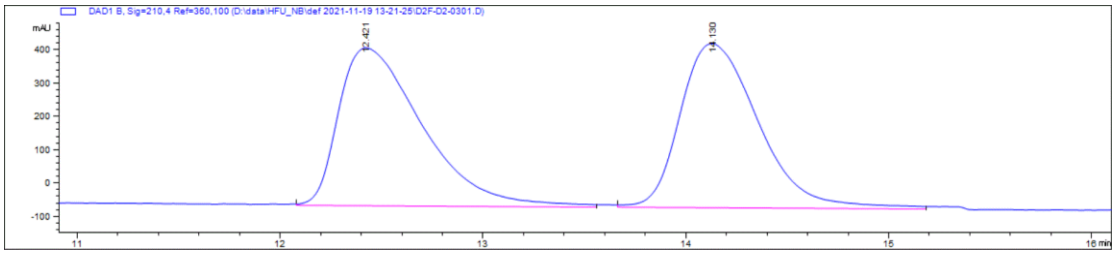
(*S*)-3-(6-Methoxypyridin-3-yl)-*N*,*N*-dimethylbutanamide (**24**)



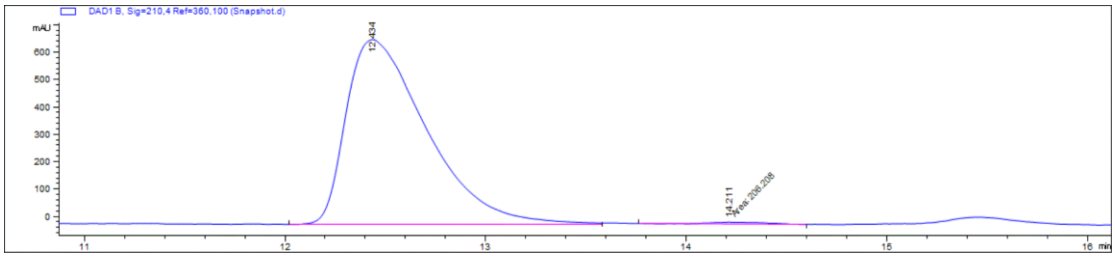
Prepared according to the general procedure 1 using α-chloro-*N*,*N*-dimethylacetamide (**1a,** 10 µmol, 2 equiv) and 2-methoxy-5-(1-nitroethyl)pyridine (**2r**, 5 µmol, 1 equiv) catalyzed by CsER (1 mol%).

Yields: run 1: 96%, run 2: 95%, average yield 95%.

Enantioselectivity: 99:1 er. Chiral HPLC method: AS-H column, 210 nm, 15% isopropanol/hexanes, flow rate 1.0 mL/min, room temperature, t_R (major) = 12.43 min, t_R (minor) = 14.21 min.

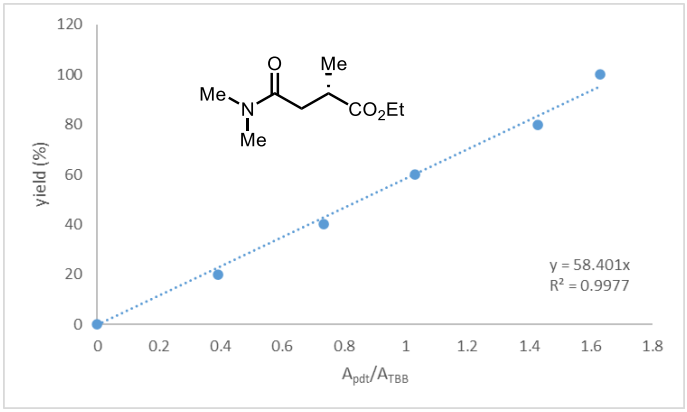


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	12.421	VV	13620	473.6	0.4035	50.556	0.451
2	14.13	VV	13320.3	492.3	0.4237	49.444	0.639



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	12.434	VV	18991.5	677.2	0.3952	98.926	0.458
2	14.211	MM	206.2	8.2	0.419	1.074	0.648

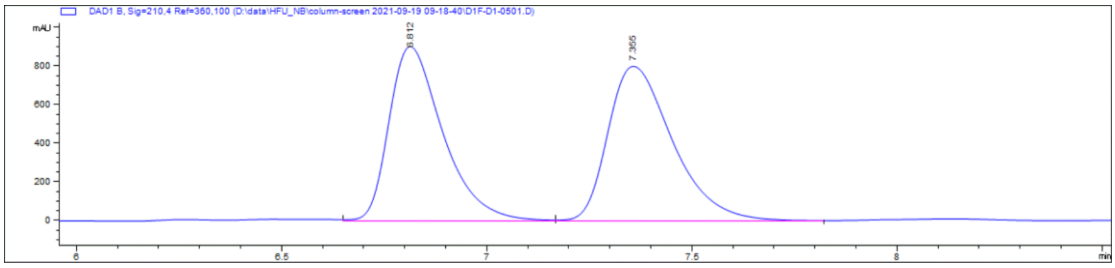
(*S*)-Ethyl 4-(dimethylamino)-2-methyl-4-oxobutanoate (**25**)



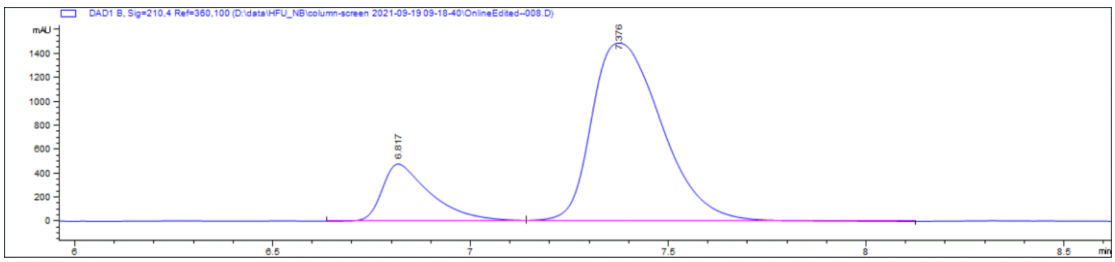
Prepared according to the general procedure 1 using α-chloro-*N*,*N*-dimethylacetamide (**1a**, 10 µmol, 2 equiv) and ethyl 2-nitropropanoate (**2s**, 5 µmol, 1 equiv) catalyzed by CsER (1 mol%).

Yields: run 1: 97%, run 2: 95%, average yield 96%.

Enantioselectivity: 82:18 er. Chiral HPLC method: OJ-H column, 210 nm, 10% isopropanol/hexanes, flow rate 1.0 mL/min, room temperature, t_R (minor) = 6.82 min, t_R (major) = 7.38 min.

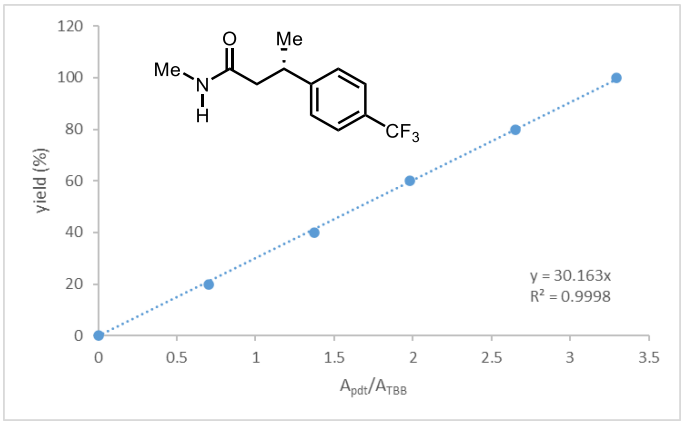


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	6.812	VV	8415.3	913.2	0.1395	48.308	0.603
2	7.355	VB	9004.9	809.8	0.1697	51.692	0.601



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	6.817	VV	4198.7	485.3	0.1249	18.374	0.461
2	7.376	VB	18652.8	1503	0.1968	81.626	0.603

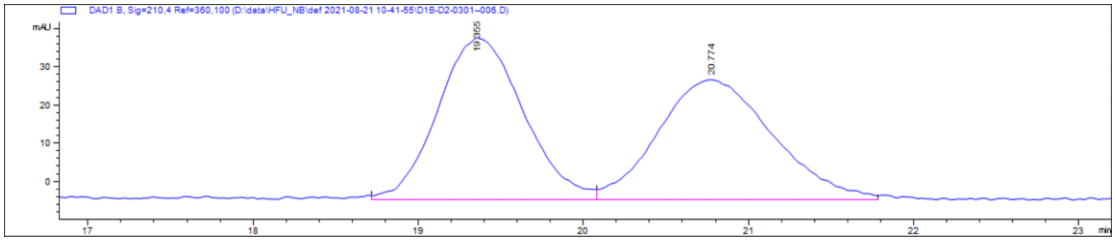
(*S*)-*N*-Methyl-3-[4-(trifluoromethyl)phenyl]butanamide (**26**)



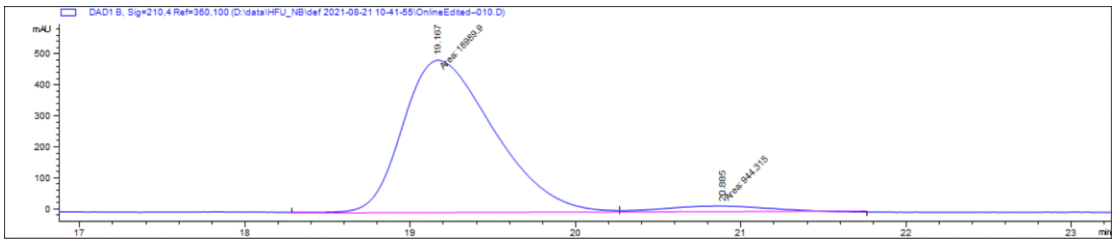
Prepared according to the general procedure 1 using α-chloro-*N*-methylacetamide (**1b**,10 µmol, 2 equiv) and 1-(1-nitroethyl)-4-(trifluoromethyl)benzene (**2j**, 5 µmol, 1 equiv) catalyzed by CsER (1 mol%).

Yields: run 1: 76%, run 2: 73%, average yield 75%.

Enantioselectivity: 95:5 er. Chiral HPLC method: AS-H column, 210 nm, 10% isopropanol/hexanes, flow rate 1.0 mL/min, room temperature, t_R (major) = 19.17 min, t_R (minor) = 20.88 min.

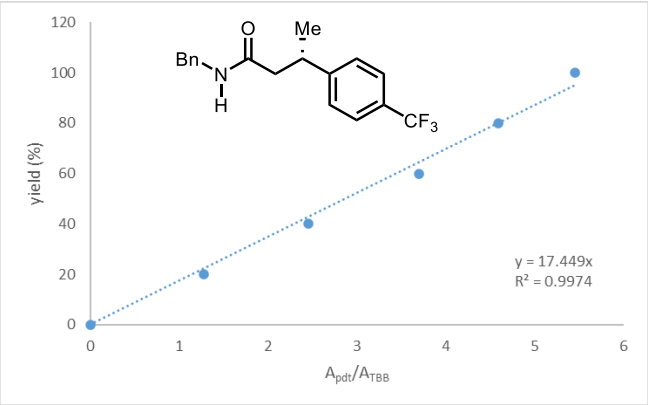


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	19.355	VV	1539.8	42.7	0.4351	50.082	0.846
2	20.774	VV	1534.7	31.7	0.6035	49.918	0.837



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	19.167	MF	18989.9	493.4	0.6415	95.263	0.621
2	20.885	FM	944.3	20.3	0.7736	4.737	1.126

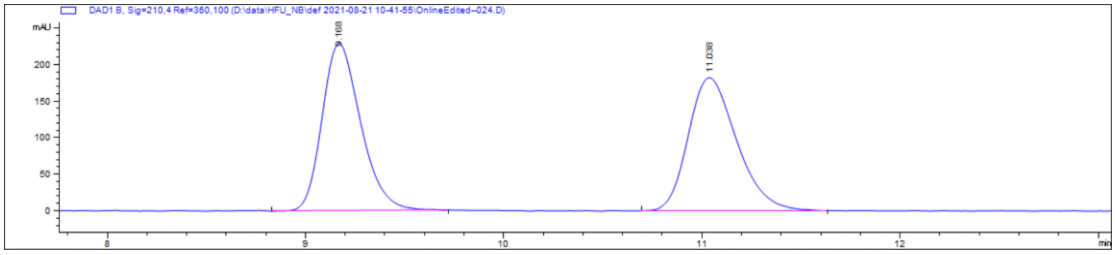
(*S*)-*N*-Benzyl-3-[4-(trifluoromethyl)phenyl]butanamide (**27**)



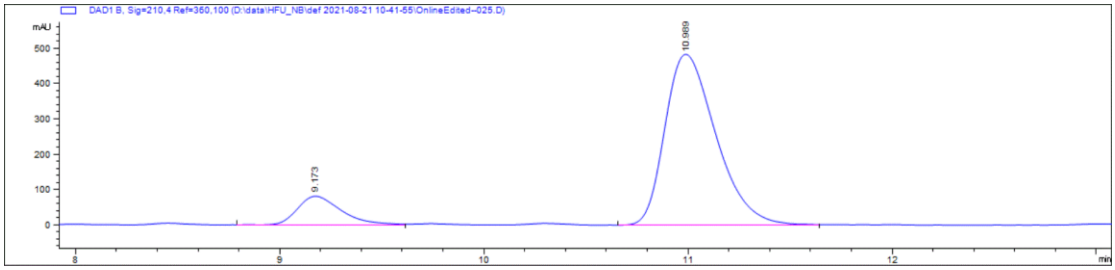
Prepared according to the general procedure 1 using α-chloro-*N*-benzylacetamide (**1c**, 10 µmol, 2 equiv) and 1-(1-nitroethyl)-4-(trifluoromethyl)benzene (**2j**, 5 µmol, 1 equiv) catalyzed by CsER (1 mol%).

Yields: run 1: 55%, run 2: 51%, average yield 53%.

Enantioselectivity: 87:13 er. Chiral HPLC method: OJ-H column, 210 nm, 10% isopropanol/hexanes, flow rate 1.0 mL/min, room temperature, t_R (minor) = 9.17 min, t_R (major) = 10.99 min.

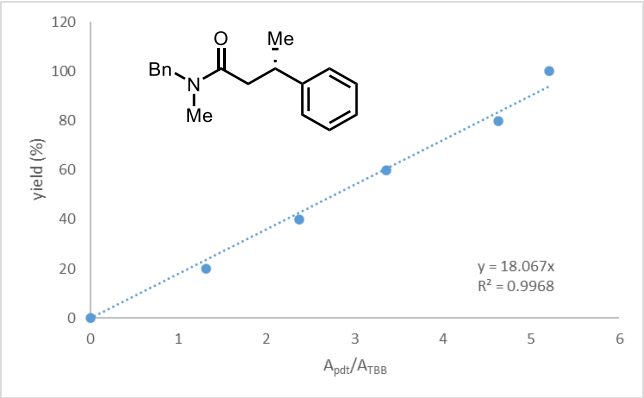


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	9.168	VB	3105.7	229.1	0.2082	49.827	0.739
2	11.038	BB	3127.2	182.5	0.2619	50.173	0.73



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	9.173	VV	1296.8	83	0.2382	13.278	0.662
2	10.989	VV	8469.7	484.9	0.2678	86.722	0.652

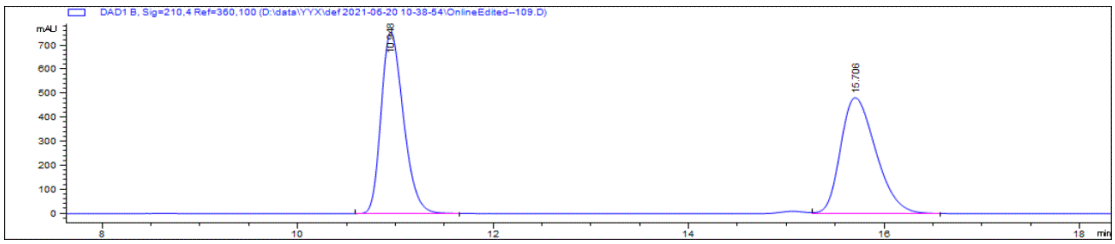
(*S*)-*N*-Benzyl-*N*-methyl-3-phenylbutanamide (**28**)



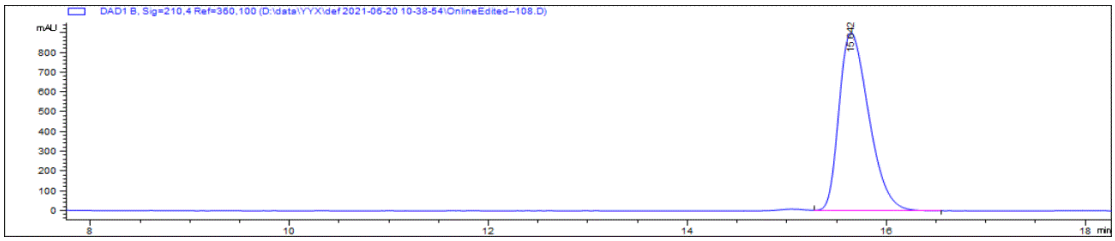
Prepared according to the general procedure 1 using α-chloro-*N*-benzyl-*N*-methylacetamide (**1d**, 5 μmol, 1 equiv) and 1-nitroethylbenzene (**2a**, 10 μmol, 2 equiv) catalyzed by CsER (1 mol%).

Yields: run 1: 46%, run 2: 48%, average yield 47%.

Enantioselectivity: >99:1 er. Chiral HPLC method: OJ-H column, 210 nm, 10% isopropanol/hexanes, flow rate 1.0 mL/min, room temperature, t_R (major) = 15.64 min.

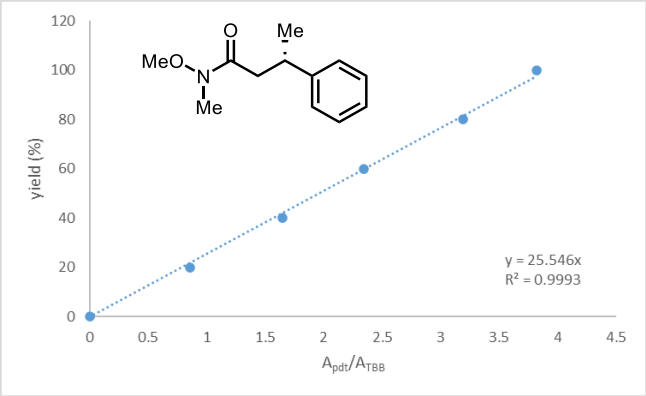


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	10.948	VB	11965.1	752.3	0.2476	49.816	0.714
2	15.706	VB	12053.4	480.1	0.3889	50.184	0.677



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	15.642	VB	18871	905.7	0.3251	100.000	0.638

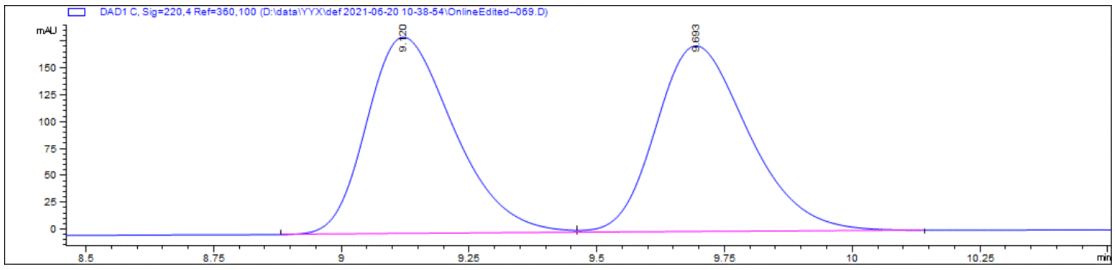
(*S*)-*N*-Methoxy-*N*-methyl-3-phenylbutanamide (**29**)



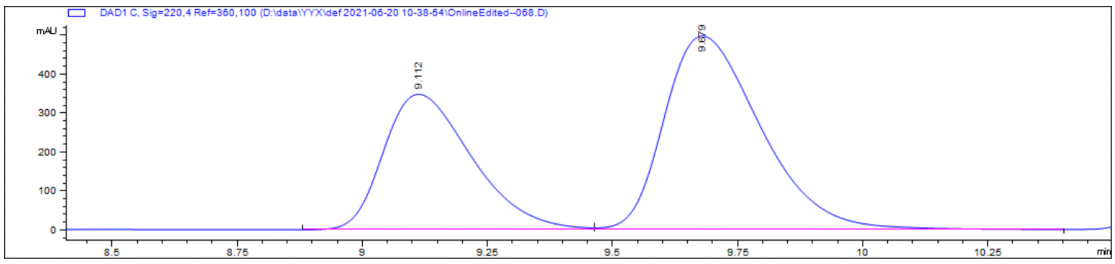
Prepared according to the general procedure 1 using α-chloro-*N*-methoxy-*N*-methylacetamide (**1e**, 5 μmol, 1 equiv) and 1-nitroethylbenzene (**2a**, 10 μmol, 2 equiv) catalyzed by CsER (1 mol%).

Yields: run 1: 54%, run 2: 52%, average yield 53%.

Enantioselectivity: 61:39 er. Chiral HPLC method: OJ-H column, 220 nm, 10% isopropanol/hexanes, flow rate 1.0 mL/min, room temperature, t_R (minor) = 9.11 min, t_R (major) = 9.68 min.

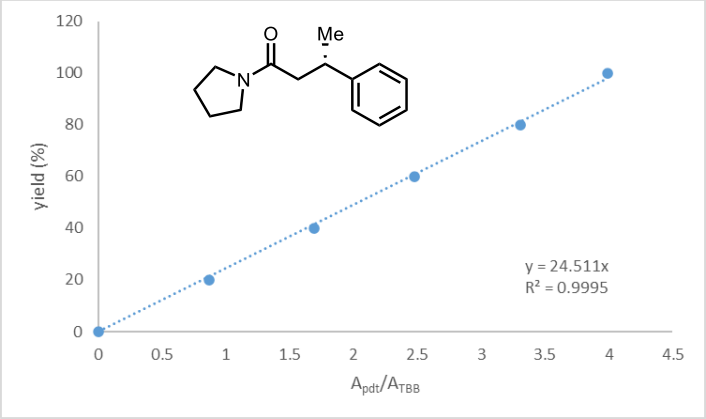


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	9.12	BV	2194.6	184.8	0.1846	49.766	0.688
2	9.693	VB	2215.3	174.9	0.1938	50.234	0.727



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	9.112	BV	4280	348.7	0.1912	38.949	0.621
2	9.679	VB	6708.7	498.9	0.2089	61.051	0.615

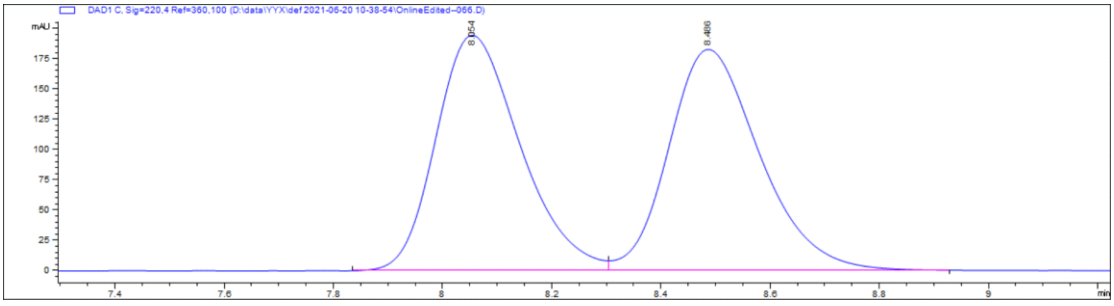
(*S*)-3-Phenyl-1-(pyrrolidin-1-yl)butan-1-one (**30**)



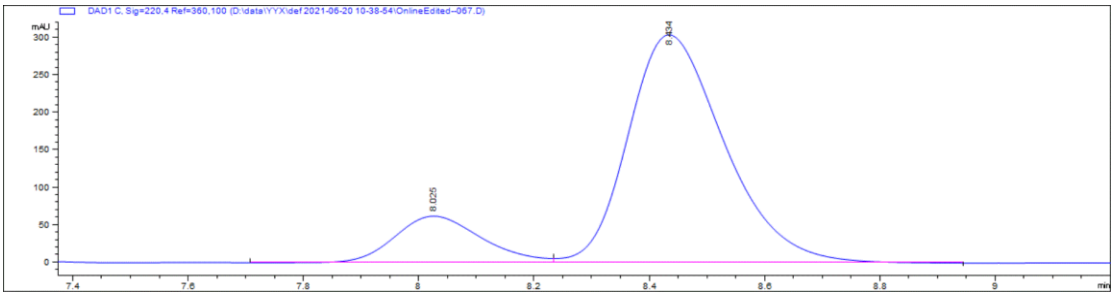
Prepared according to the general procedure 1 using α-chloro-1-(pyrrolidin-1-yl)ethan-1-one (**1f**, 10 μmol, 2 equiv) and 1-nitroethylbenzene (**2a**, 5 μmol, 1 equiv) catalyzed by CsER (1 mol%).

Yields: run 1: 95%, run 2: 96%, average yield 95%.

Enantioselectivity: 84:16 er. Chiral HPLC method: OJ-H column, 220 nm, 10% isopropanol/hexanes, flow rate 1.0 mL/min, room temperature, t_R (minor) = 8.02 min, t_R (major) = 8.43 min.

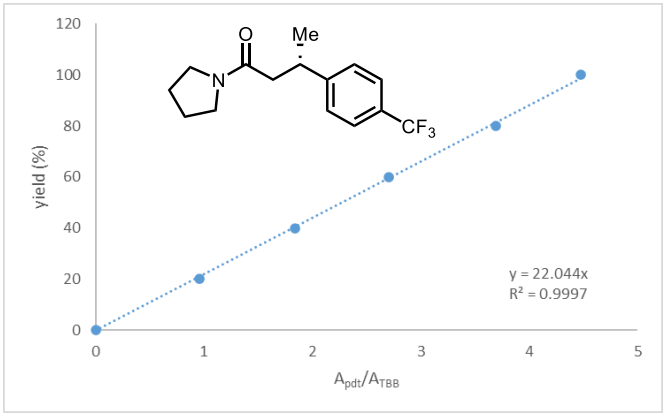


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	8.054	BV	2101.9	196	0.1671	49.643	0.719
2	8.486	VB	2132.1	184.1	0.1791	50.357	0.734



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	8.025	VV	662	62.7	0.1612	15.707	0.784
2	8.434	VB	3552.4	305.9	0.1795	84.293	0.703

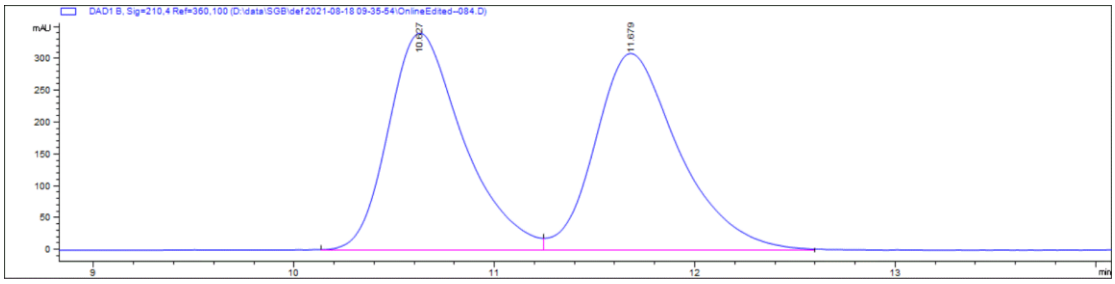
(*S*)-1-(Pyrrolidin-1-yl)-3-[4-(trifluoromethyl)phenyl]butan-1-one (**31**)



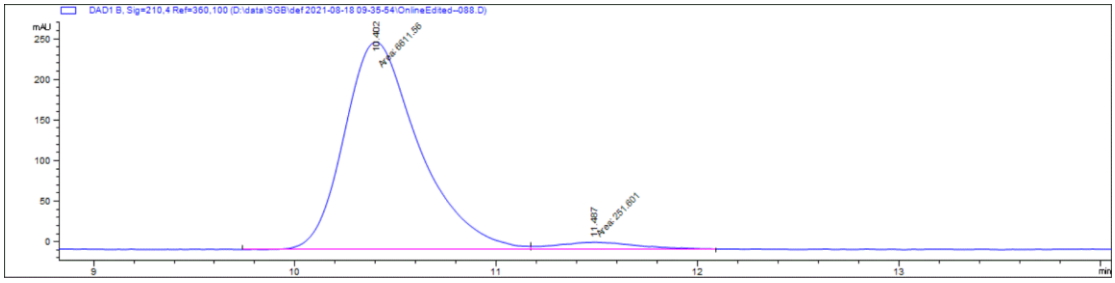
Prepared according to the general procedure 1 using α-chloro-1-(pyrrolidin-1-yl)ethan-1-one (**1f**, 10 µmol, 2 equiv) and 1-(1-nitroethyl)-4-(trifluoromethyl)benzene (**2j**, 5 µmol, 1 equiv) catalyzed by CsER (1 mol%).

Yields: run 1: 87%, run 2: 87%, average yield 87%.

Enantioselectivity: 96:4 er. Chiral HPLC method: OD-H column, 210 nm, 5% isopropanol/hexanes, flow rate 1.0 mL/min, room temperature, t_R (major) = 10.40 min, t_R (minor) = 11.49 min.

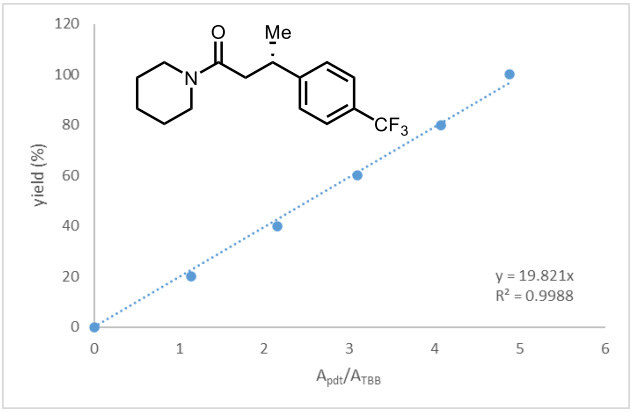


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	10.627	VV	8984.1	343.3	0.3953	49.643	0.689
2	11.679	VV	9113.4	311.3	0.4396	50.357	0.693



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	10.402	MF	6611.6	255.4	0.4314	96.334	0.716
2	11.487	FM	251.6	8.8	0.4759	3.666	0.844

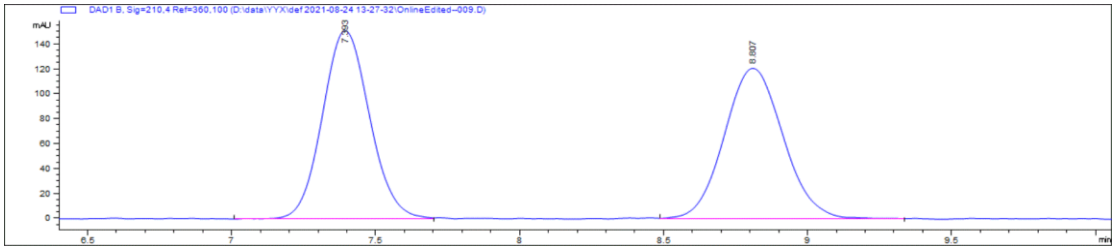
(*S*)-1-(Piperidin-1-yl)-3-(4-(trifluoromethyl)phenyl)butan-1-one (**32**)



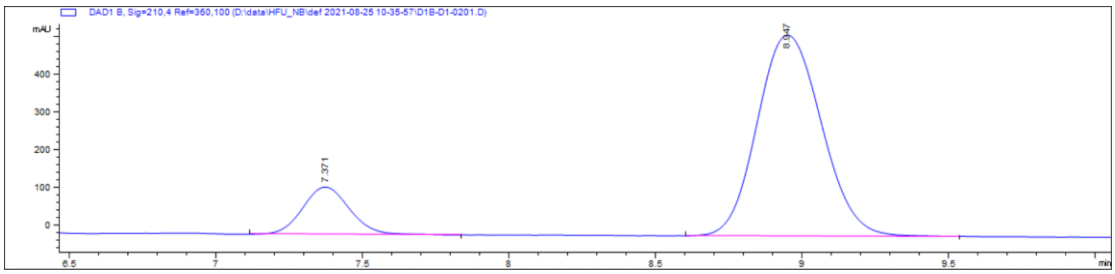
Prepared according to the general procedure 1 using α-chloro-1-(piperidin-1-yl)ethan-1-one (**1g**, 10 μmol, 2 equiv) and 1-(1-nitroethyl)-4-(trifluoromethyl)benzene (**2j** 5 μmol, 1 equiv) catalyzed by CsER (1 mol%).

Yields: run 1: 41%, run 2: 42%, average yield 42%.

Enantioselectivity: 85:15 er. Chiral HPLC method: AS-H column, 210 nm, 10% isopropanol/hexanes, flow rate 1.0 mL/min, room temperature, t_R (minor) = 7.37 min, t_R (major) = 8.95 min.

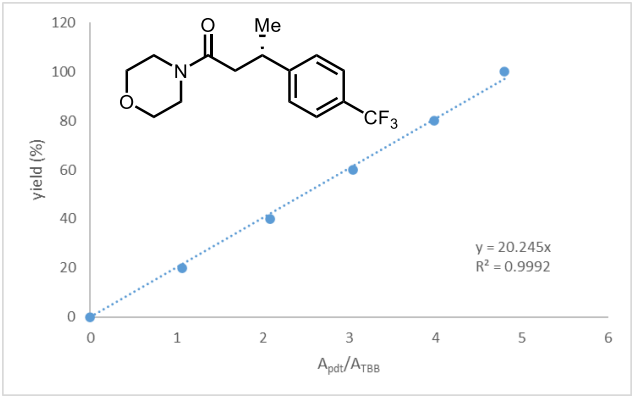


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	7.393	VV	1737.7	151.8	0.1755	49.905	0.902
2	8.807	VB	1744.3	121.5	0.2256	50.095	0.9



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	7.371	VB	1415.7	126	0.1751	14.816	0.879
2	8.947	VB	8139.7	533.4	0.24	85.184	0.863

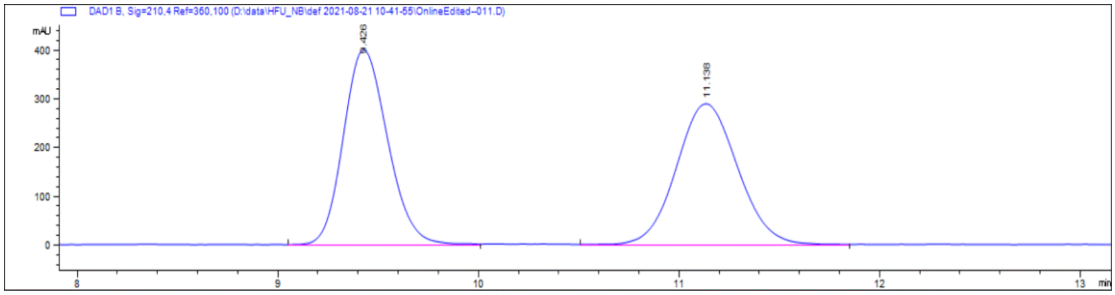
(*S*)-Morpholino-3-[4-(trifluoromethyl)phenyl]butan-1-one (**33**)



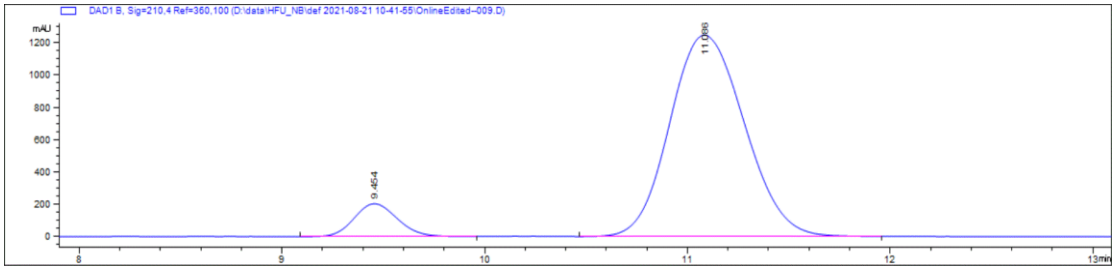
Prepared according to the general procedure 1 using α-chloro-1-morpholinoethan-1-one (**1h**, 10 µmol, 2 equiv) and 1-(1-nitroethyl)-4-(trifluoromethyl)benzene (**2j**, 5 µmol, 1 equiv) catalyzed by CsER (1 mol%).

Yields: run 1: 77%, run 2: 68%, average yield 73%.

Enantioselectivity: 91:9 er. Chiral HPLC method: AS-H column, 210 nm, 10% isopropanol/hexanes, flow rate 1.0 mL/min, room temperature, t_R (minor) = 9.45 min, t_R (major) = 11.09 min.

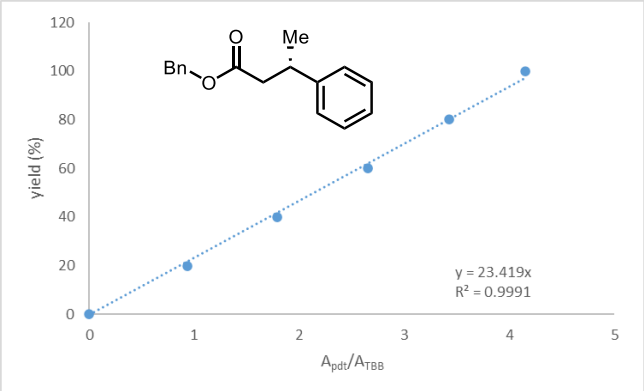


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	9.426	VV	6215.6	400.9	0.2429	49.867	0.801
2	11.138	VV	6248.8	289.9	0.3315	50.133	0.911



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	9.454	VV	3151.2	206.6	0.2379	8.879	0.841
2	11.086	VV	32339	1257.6	0.398	91.121	0.84

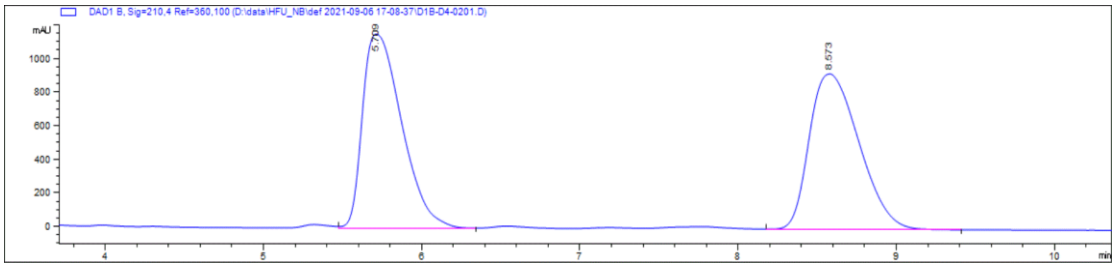
(*S*)-Benzyl 3-phenylbutanoate (**34**)



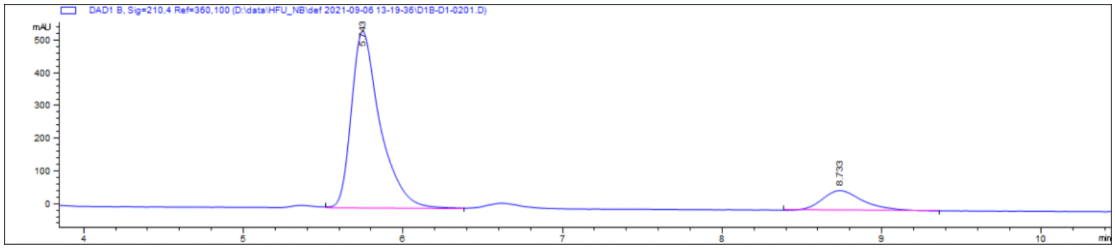
Prepared according to the general procedure 1 using benzyl 2-bromoacetate (**1i**, 15 µmol, 3 equiv) and 1-nitroethylbenzene (**2a**, 5 µmol, 1 equiv) catalyzed by CsER (1 mol%).

Yields: run 1: 37%, run 2: 39%, average yield 38%.

Enantioselectivity: 86:14 er. Chiral HPLC method: OD-H column, 210 nm, 5% isopropanol/hexanes, flow rate 1.0 mL/min, room temperature, t_R (major) = 5.74 min, t_R (minor) = 8.73 min.

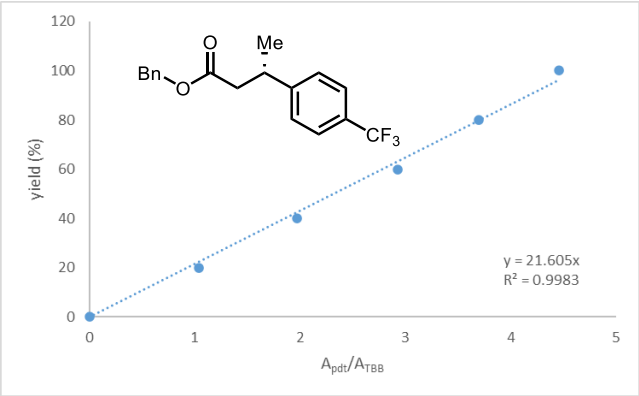


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	5.709	VV	20005.4	1154.7	0.2701	49.808	0.51
2	8.573	VB	20159.7	924	0.3505	50.192	0.653



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	5.743	VV	6783	540.8	0.1863	85.976	0.594
2	8.733	VV	1106.4	61.2	0.273	14.024	0.707

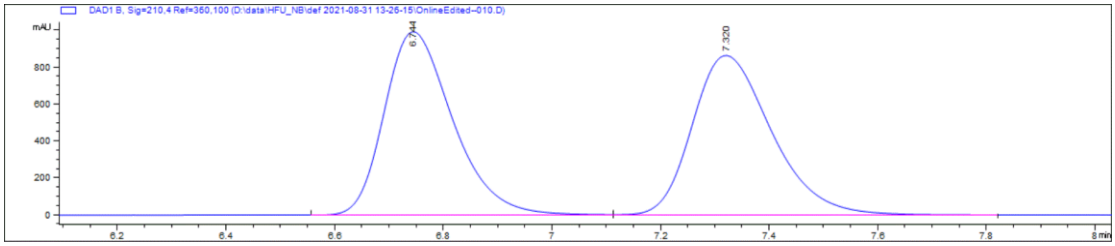
(*S*)-Benzyl 3-[4-(trifluoromethyl)phenyl]butanoate (**35**)



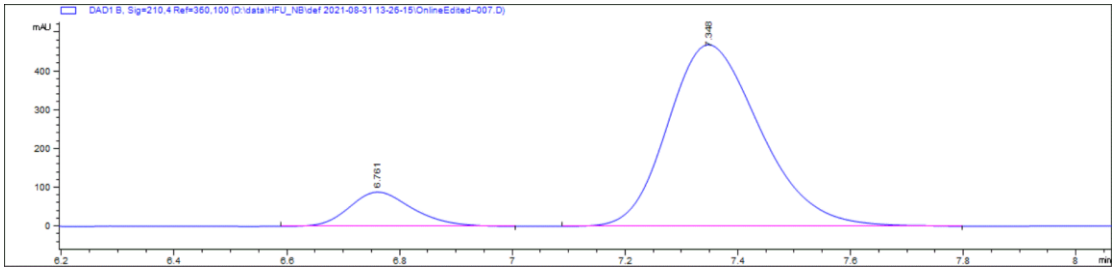
Prepared according to the general procedure 1 using benzyl 2-bromoacetate (**1i**, 15 µmol, 3 equiv) and 1-(1-nitroethyl)-4-(trifluoromethyl)benzene (**2j**, 5 µmol, 1 equiv) catalyzed by CsER (1 mol%).

Yields: run 1: 32%, run 2: 30%, average yield 31%.

Enantioselectivity: 88:12 er. Chiral HPLC method: OJ-H column, 210 nm, 10% isopropanol/hexanes, flow rate 1.0 mL/min, room temperature, t_R (minor) = 6.76 min, t_R (major) = 7.35 min.

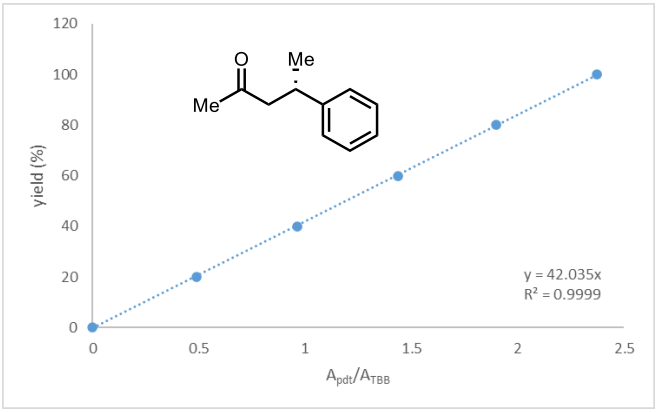


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	6.744	VV	8763.3	996.6	0.1346	49.724	0.688
2	7.32	VV	8860.6	867.3	0.1572	50.276	0.693



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	6.761	VV	710.9	89.1	0.1211	11.650	0.769
2	7.348	VV	5391.4	468.7	0.1782	88.350	0.745

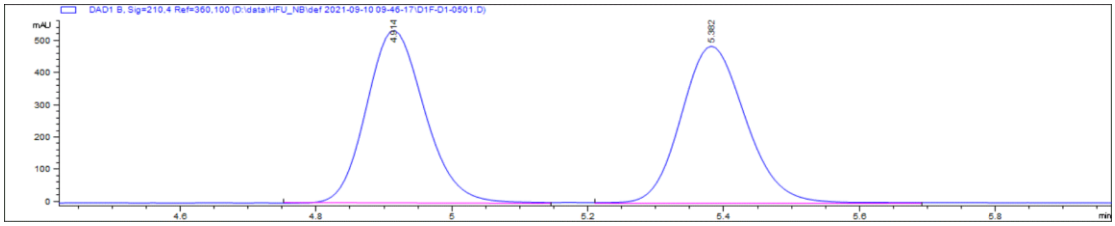
(*S*)-4-Phenylpentan-2-one (**36**)



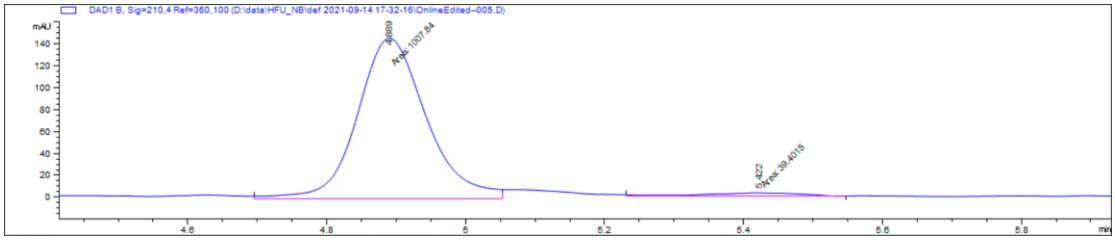
Prepared according to the general procedure 1 using chloroacetone (**1j**, 15 µmol, 2 equiv) and 1-nitroethylbenzene (**2a**, 5 µmol, 1 equiv) catalyzed by CsER (1 mol%).

Yields: run 1: 59%, run 2: 48%, average yield 54%.

Enantioselectivity: 96:4 er. Chiral HPLC method: AS-H column, 210 nm, 10% isopropanol/hexanes, flow rate 1.0 mL/min, room temperature, t_R (major) = 4.89 min, t_R (minor) = 5.42 min. **Absolute configuration** of the enzymatic product is assigned as ***S*** by comparison with the previously reported chiral HPLC data.[6]

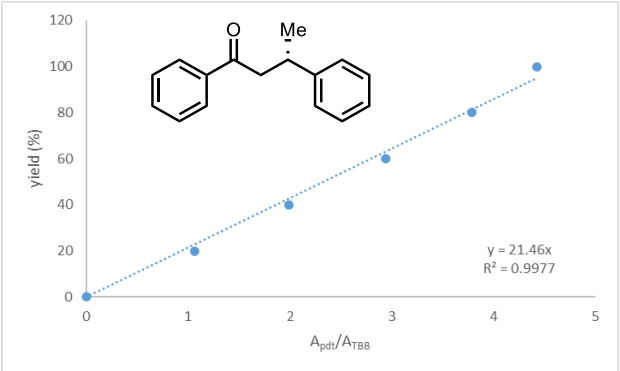


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	4.914	VV	3252.7	540.2	0.0942	49.771	0.833
2	5.382	VV	3282.6	490.9	0.104	50.229	0.834



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	4.889	MF	1007.8	146.3	0.1148	96.238	0.855
2	5.422	MM	39.4	3.4	0.1933	3.762	1.443

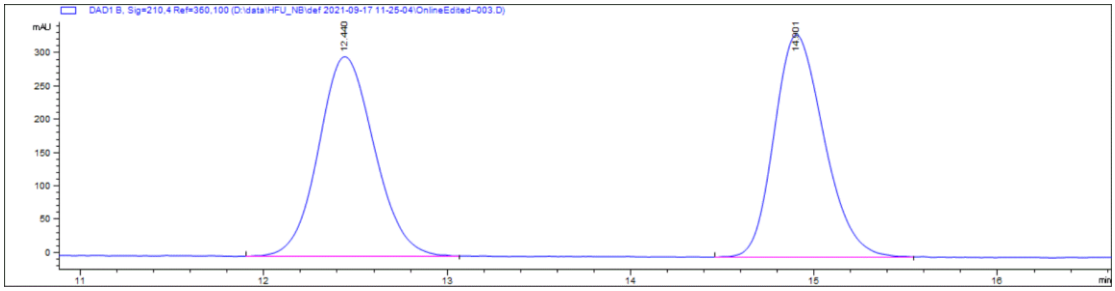
(*S*)-1,3-Diphenylbutan-1-one (**37**)



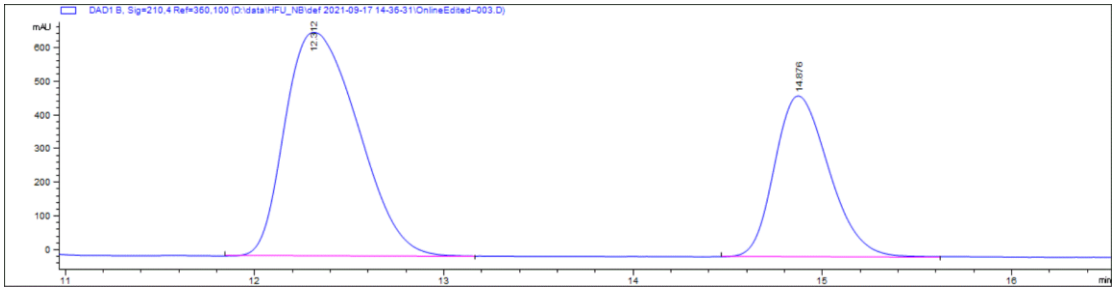
Prepared according to the general procedure 1 using 2-chloro-1-phenylethan-1-one (**1k**, 10 µmol, 2 equiv) and 1-nitroethylbenzene (**2a**, 5 µmol, 1 equiv) catalyzed by CsER (1 mol%).

Yields: run 1: 17%, run 2: 16%, average yield 16%.

Enantioselectivity: 65:35 er. Chiral HPLC method: OJ-H column, 210 nm, 5% isopropanol/hexanes, flow rate 1.0 mL/min, room temperature, t_R (major) = 12.31 min, t_R (minor) = 14.88 min.

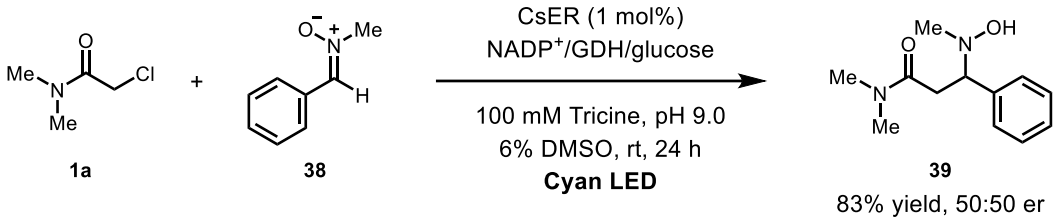


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	12.44	VB	6471.7	303	0.3272	50.307	0.856
2	14.901	VV	6392.7	336.8	0.2915	49.693	0.761



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	12.312	BV	17788.6	661	0.432	65.066	0.625
2	14.876	VV	9550.7	476	0.3141	34.934	0.726

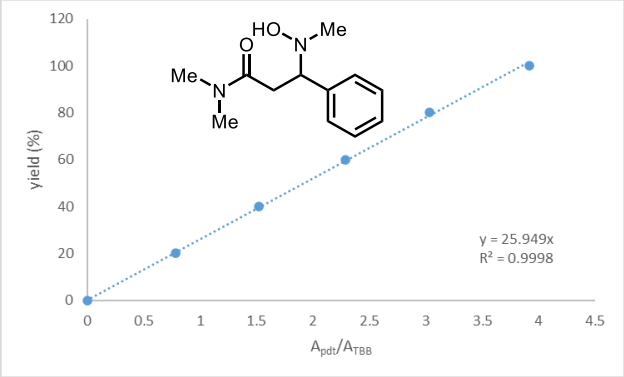
Photoenzymatic reaction of α-chloroamide with nitrone



1a + **38** → **39**

83% yield, 50:50 er

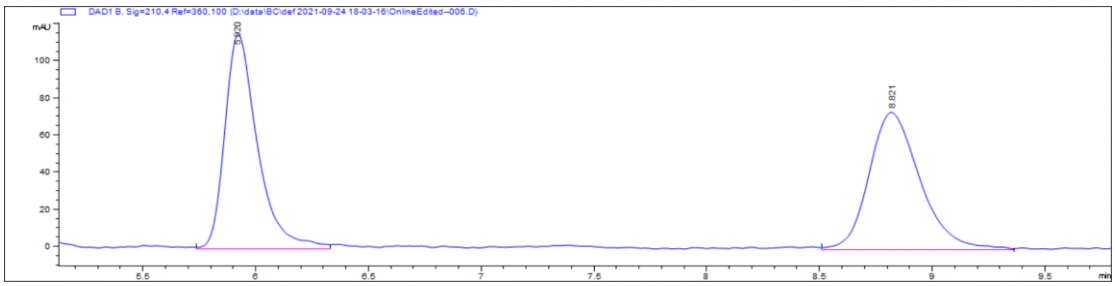
3-[Hydroxy(methyl)amino]-*N*,*N*-dimethyl-3-phenylpropanamide (**39**)



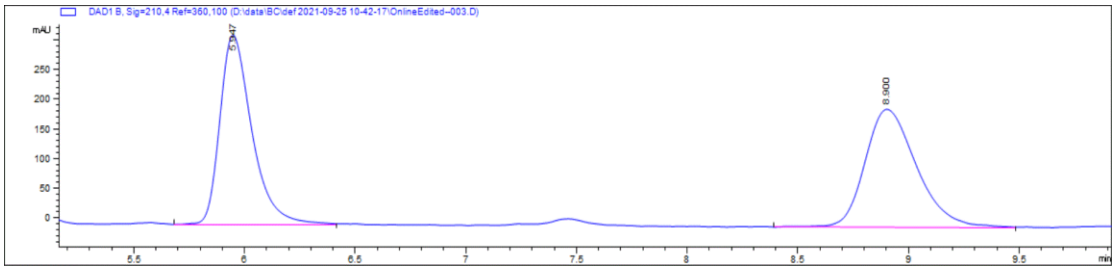
Prepared according to the general procedure 1 using α-chloro-*N*,*N*-dimethylacetamide (**1a**, 10 µmol, 2 equiv) and *C*-Phenyl-*N*-methyl-nitrone (**38**, 5 µmol, 1 equiv) catalyzed by CsER (1 mol%).

Yields: run 1: 84%, run 2: 82%, average yield 83%.

Enantioselectivity: 50:50 er. Chiral HPLC method: OJ-H column, 210 nm, 20% isopropanol/hexanes, flow rate 1.0 mL/min, room temperature, t_R (peak 1) = 5.95 min, t_R (peak 2) = 8.90 min.

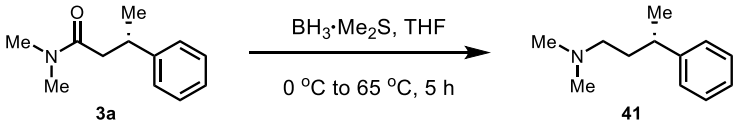


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	5.92	VV	1183	116.1	0.1509	49.881	0.636
2	8.821	VV	1188.7	74.5	0.2441	50.119	0.737



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	5.947	VV	3266.8	321.1	0.1547	50.082	0.638
2	8.9	VV	3256.1	199.3	0.2526	49.918	0.712

Derivatization of enzymatic products.

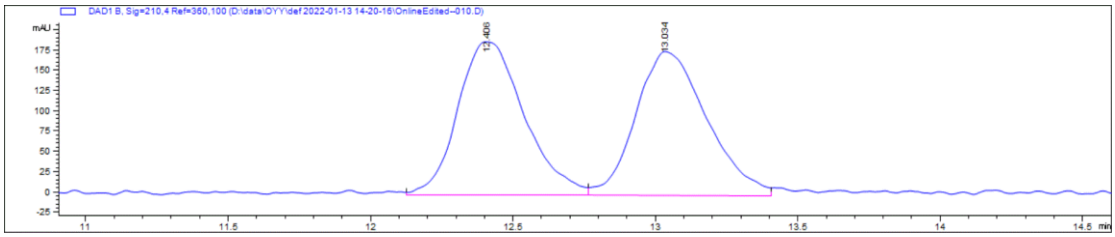


3a
95:5 er

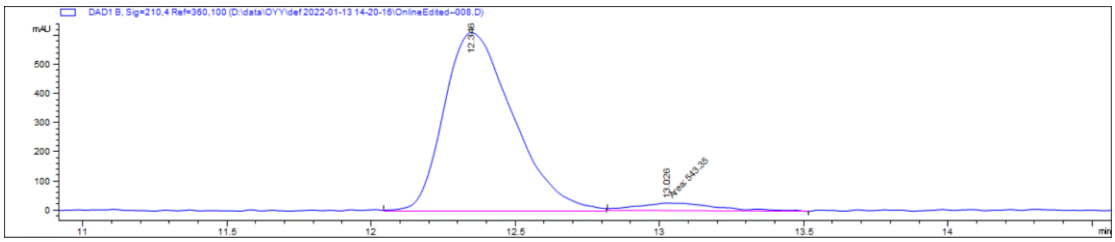
41
70% yield, 95:5 er

To a stirred solution of enzymatic product **3a** (16 mg, 0.08 mmol, 1 equiv) in dry THF (1 mL) was slowly added $BH_3 \cdot Me_2S$ (2 M solution in THF, 0.12 mL, 0.24 mmol, 3 equiv) under N_2 atmosphere and cooling with ice bath. The reaction mixture was allowed to warm up to room temperature and then stirred at 65 °C for 5 hours. After completion of the reaction, the reaction mixture was quenched with saturated NH_4Cl aqueous solution (5 mL) and extracted with EtOAc (3 x 10 mL). The organic layer was collected and dried over Na_2SO_4, filtered and concentrated to give crude product **41**, which was purified by preparative thin layer chromatography (EtOAc/Hexanes, 20%, *v*/*v*). Clear oil. 10 mg, 70% yield.

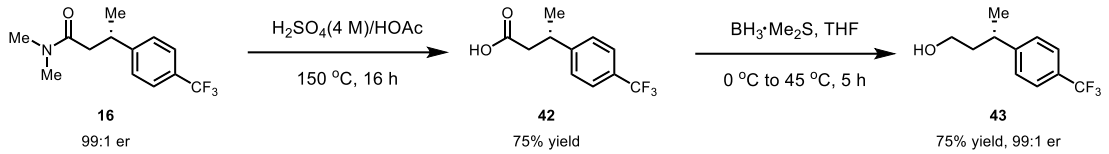
Enantioselectivity: 95:5 er. Chiral HPLC method: OJ-H column, 210 nm, 5% isopropanol/hexanes, flow rate 1.0 mL/min, room temperature, t_R (major) = 12.35 min, t_R (minor) = 13.03 min.



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	12.406	VV	3092.4	189.1	0.2427	49.986	0.749
2	13.034	VV	3094.1	177.3	0.2216	50.014	0.696



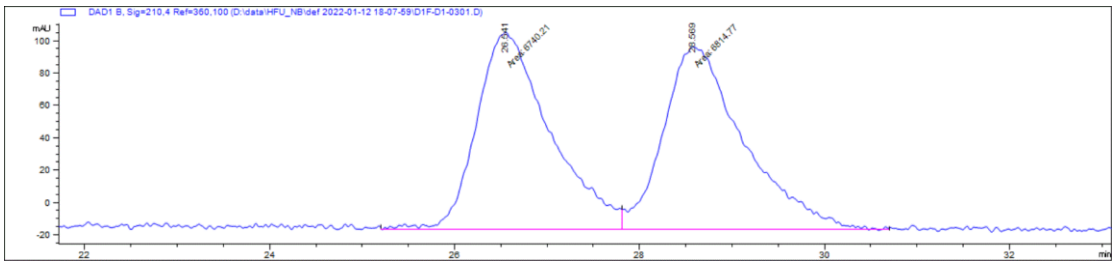
#	Time	Type	Area	Height	Width	Area%	Symmetry
1	12.346	VV	10261	614.3	0.2449	94.971	0.627
2	13.026	MM	543.3	26.6	0.3402	5.029	0.533



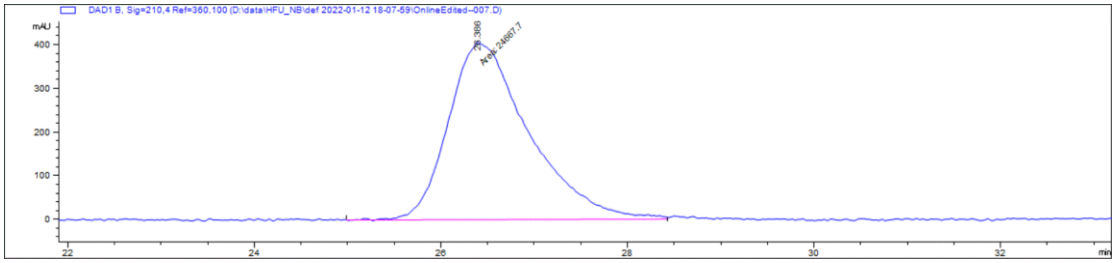
Adapted from the method by A. Link *et al*.[7] The enzymatic product **16** (18 mg, 0.07 mmol) was dissolved in 0.5 mL of mixed acid solution (0.25 mL of 4 M H_2SO_4 and 0.25 mL of acetic acid) at room temperature. The reaction mixture was stirred at 150 °C for 16 hours. After completion of the reaction, the reaction mixture was diluted with water (2 mL) and basified with saturated Na_2CO_3 solution, the mixture was extracted with DCM (2 mL). The aqueous layer was acidified using 1 M HCl to pH 2.0 and extracted with EtOAc (4 x 10 mL), the organic layers were collected and dried over Na_2SO_4, filtered and concentrated to give the acid product **42**. Light yellow solid. 12 mg, 75% yield.

To a stirred solution of acid **42** (12 mg, 0.05 mmol, 1 equiv) in dry THF (1 mL) was slowly added $BH_3{\cdot}Me_2S$ (2 M solution in THF, 0.15 mL, 0.15 mmol, 3 equiv) under N_2 atmosphere and cooling with an ice bath. The reaction mixture was allowed to warm up to room temperature and then stirred at 45 °C for 5 hours. After completion of the reaction, the reaction mixture was quenched with saturated NH_4Cl aqueous solution (5 mL) and extracted with EtOAc (3 x 10 mL). The organic layer was collected and dried over Na_2SO_4, filtered and concentrated to give crude product **43**, which was purified by preparative thin layer chromatography (EtOAc/Hexanes, 50%, *v*/*v*). Clear oil. 8 mg, 75% yield.

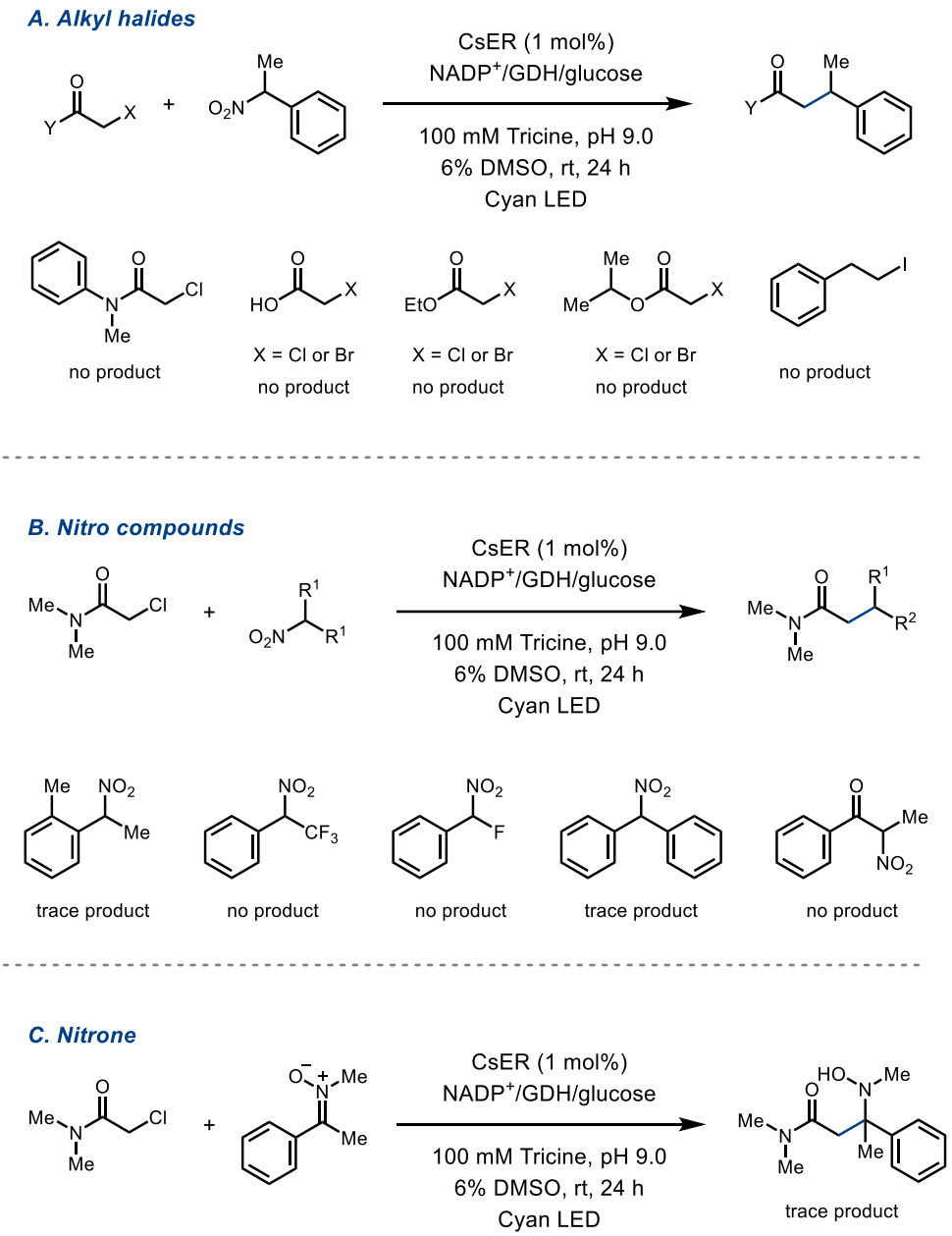
Enantioselectivity: 99:1 er. Chiral HPLC method: OD-H column, 210 nm, 2% isopropanol/hexanes, flow rate 0.5 mL/min, room temperature, t_R (major) = 26.39 min, t_R (minor) = 28.57 min. **Absolute configuration** of the derivatized product **43** is assigned as ***S*** by comparison with the previously reported chiral HPLC data.[8]



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	26.541	MF	6740.2	121.9	0.9214	49.725	0.633
2	28.569	FM	6814.8	112.7	1.0074	50.275	0.571



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	26.386	MM	24667.7	409.9	1.0029	100.000	0.56



Supplementary Fig. 2. (**A**) Alkyl halides, (**B**) nitro compounds or (**C**) nitrone substrates not accepted by CsER under standard conditions.

Protein crystallography and docking

X-ray crystallographic data of CsER (PDB: 7TNB)

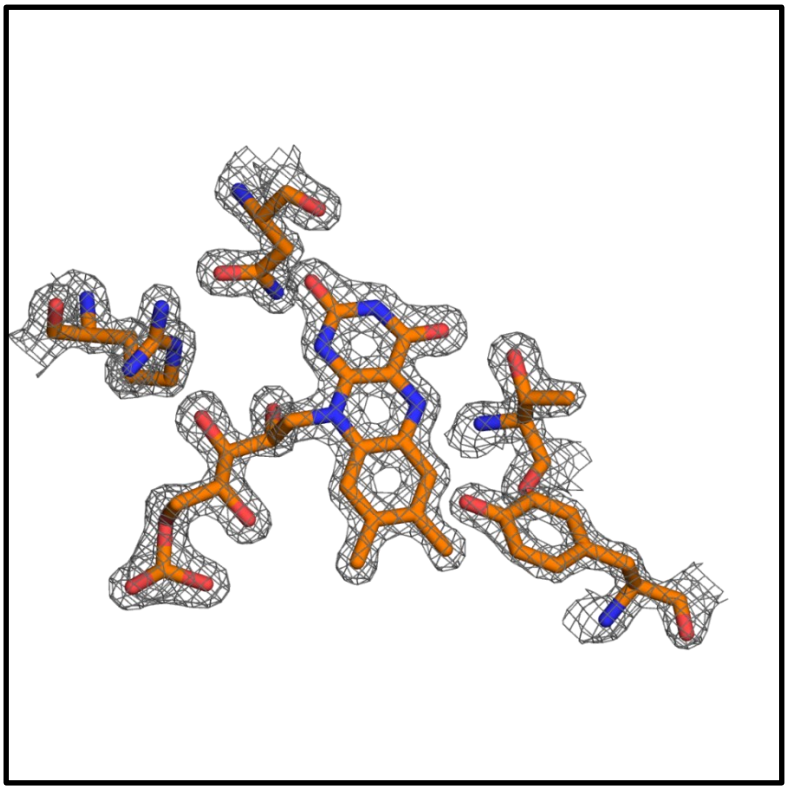
The expression and purification of wild-type CsER was described above. The purified proteins were concentrated to a final concentration of 1.0 mM, approximately 40 mg/mL. Initial crystallization screens were carried out using Crystal Screen 1 in hanging drop vapor-diffusion crystallization trays (Hampton Research). Crystals grew in 0.15 M ammonium sulfate, 0.1 M sodium acetate, and 25% (w/v) PEG 4000 (Hampton Research). Initial crystals appeared after 7-10 days and continued to grow for the next 14 days. Crystals were cryoprotected in well solution (0.15 M ammonium sulfate, 0.1 M sodium acetate pH 4.6, 20-30% (w/v) PEG 4000) with an additional 20% glycerol and frozen in liquid nitrogen prior to data collection. Diffraction data for wild-type CsER was obtained at the 17-ID-1 (AMX) beamline of NSLS-II using 0.9201 Å wavelength at 100 K to a maximum resolution of 1.79 Å.

All data was integrated with the program XDS[9] and scaled with the program AIMLESS.[10] The structure for wild-type CsER was determined by the method of molecular replacement using the PDB entry 6MYW and the program PHASER.[11] There is one molecule in the asymmetric unit for wild-type CsER. Clear electron density was observed for amino acids 2-354. COOT was used for model building, while structure refinement was carried out with REFMAC 5.8.[12] The final model for wild-type CsER has excellent agreement with the data with an R-factor of 16.8% and an R-free of 19.7% for 3099 atoms. Ramachandran statistics for wild-type CsER show 96% (349) of residues favored, 3% (11) allowed, and less than 1% (2) as outliers. Outliers for wild-type CsER (E55, E286) are well supported by the density.

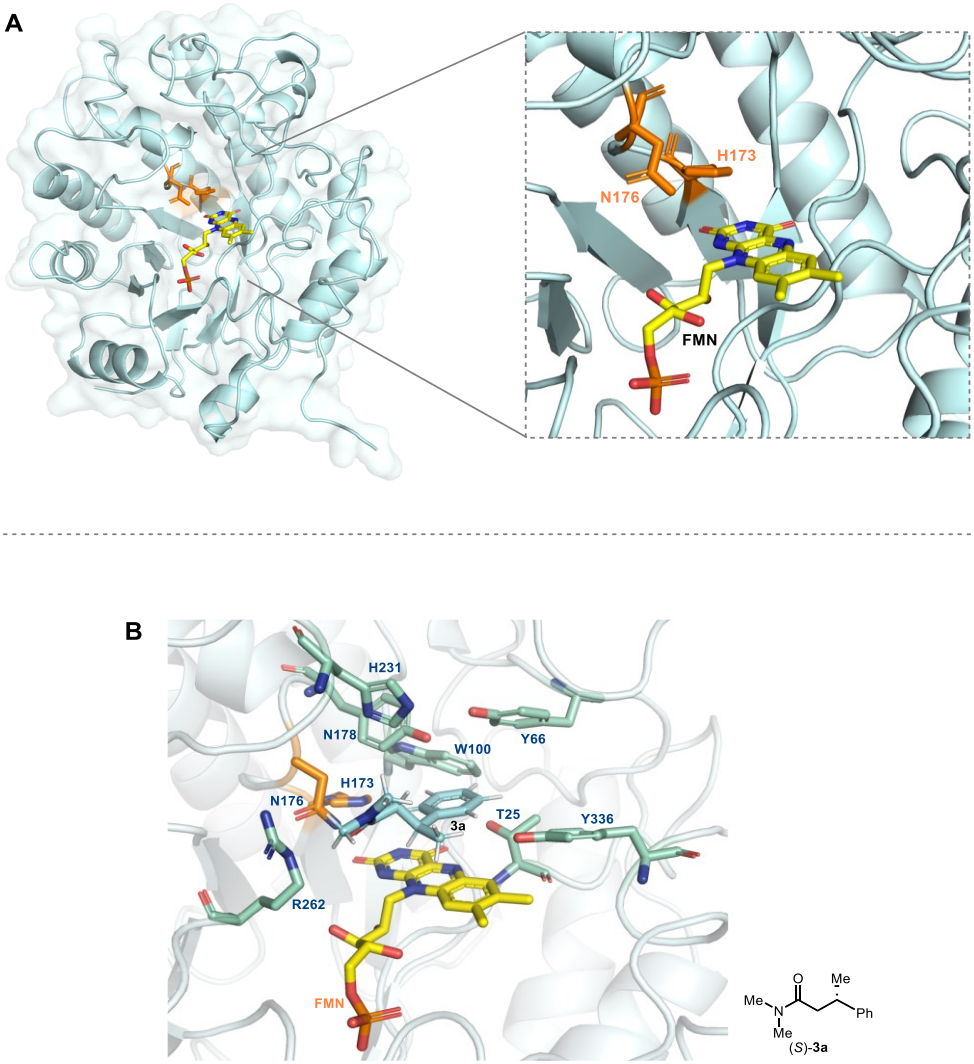
Supplementary Table 3. Data collection and refinement statistics (molecular replacement) of CsER.

	wild-type CsER PDB: 7TNB
Data collection	
Data collection wavelength (Å)	0.9201
Space group	C 2 2 2_1
Unit cell dimensions	
a, *b*, *c* (Å)	46.47, 104.18, 144.33
a, b, g (°)	90.00, 90.00, 90.00
X-ray diffraction data	
Resolution range (Å)	30-1.79 (1.83-1.79)*
No. of observed reflections	450763 (23517)
No. of unique reflections	33499 (1909)
Redundancy	13.3 (12.3)
Completeness (%)	99.8 (97.3)
CC(1/2)	0.998 (0.745)
R_{merge}	0.147 (1.390)
R_{meas}	0.159 (1.513)
R_{pim}	0.043 (0.425)
I / sI	12.9 (1.9)
Refinement	
Resolution (Å)	30-1.8
Reflections used in refinement	31797 (2315)
Reflections used for R-free	1666 (92)
R_{work}	0.168 (0.34)
R_{free}	0.197 (0.37)
No. atoms	
Protein	2723
Ligand/ion	82
Water	294
B-factors	
All	19.46
Protein	18.97
Ligand/ion	35.49
Water	29.61
R.m.s. deviations	
Bond lengths (Å)	0.011
Bond angles (°)	1.592
Ramachandran Statistics	
Favored (%)	96
Allowed (%)	3
Outliers (%)	<1
Rotamer outliers (%)	2
Clashscore	3

*One crystal was used to generate this structure. Values in parentheses are for highest-resolution shell.

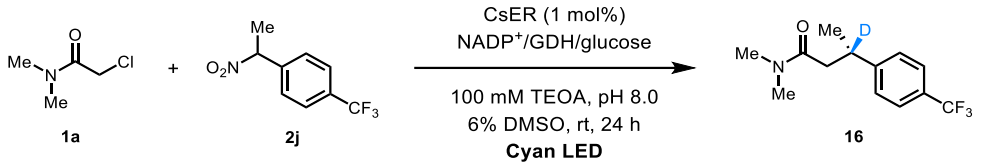


Supplementary Fig. 3. A sample electron density map (2FO-FC) for WT CsER (PDB: 7TNB). The quality of the map is high, and the FMN is well-supported by electron density.

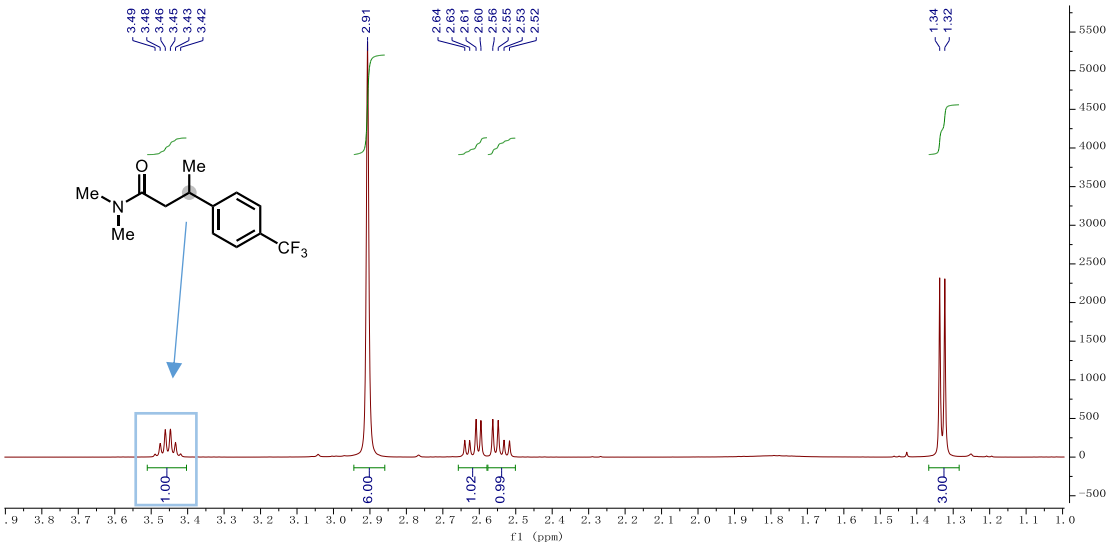


Supplementary Fig. 4. (**A**) Overall crystal structure and active site of wild-type CsER (PDB code: 7TNB). Residues H173 and N176 responsible for substrate binding and cofactor FMN are labeled. (**B**) A close-up of the active site of wild-type CsER using the docking model of CsER with the product (*S*)-**3a**. Docking was performed with AutoDock Vina.[13] PyMOL was used for graph preparation.

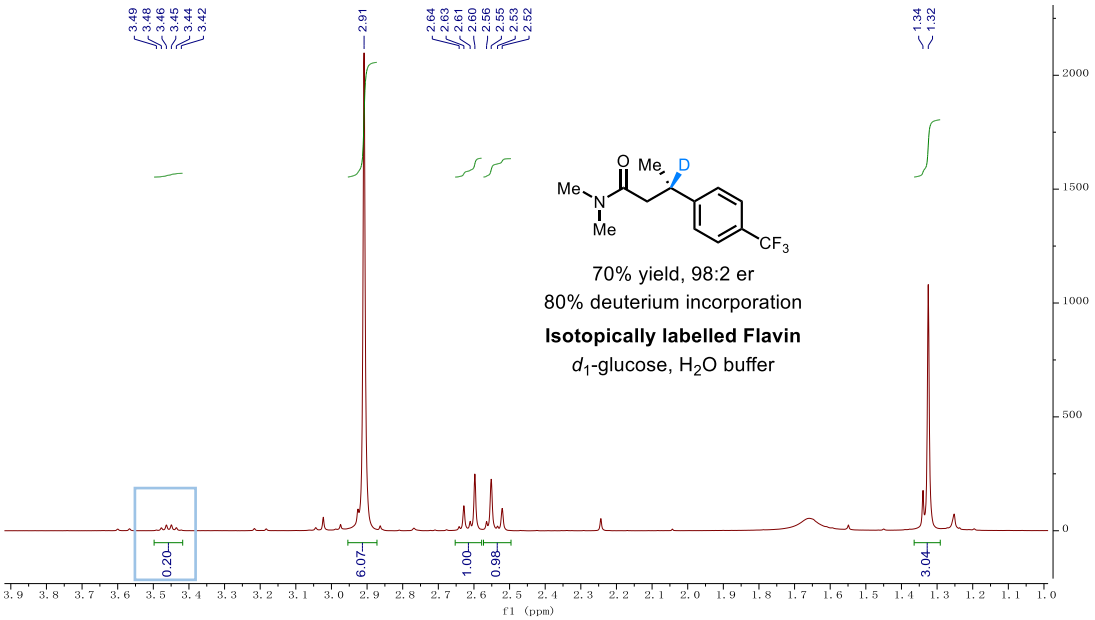
Deuterium labeling experiments



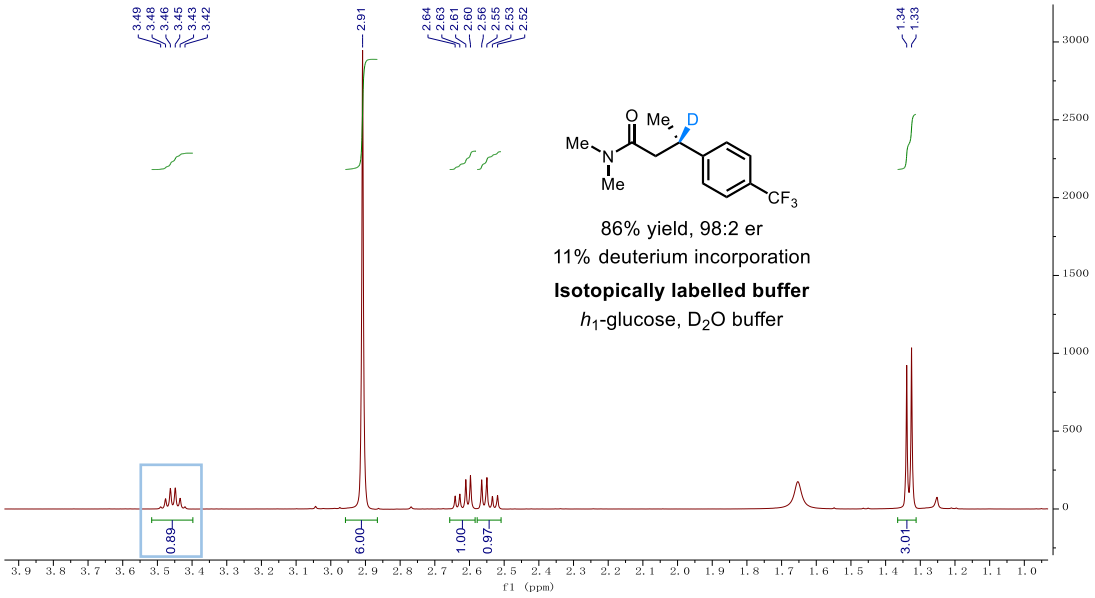
In the Coy® chamber (Vinyl Anaerobic Chamber, Type A), a 20 mL glass vial with screw cap was charged with GDH (3 mg), either d_1-glucose or h_1-glucose (45 mg), $NADP^+$ (0.5 mg), CsER (1 mol%), α-chloroamide (**1a**, 250 µL, 800 mM stock in DMSO, 0.20 mmol, 4 equiv) and 1-(1-nitroethyl)-4-(trifluoromethyl)benzene (**2j**, 250 µL, 200 mM stock in DMSO, 0.05 mmol, 1 equiv). Triethanolamine (TEOA) buffer (100 mM pH 8.0, in either H_2O or D_2O) was added to bring the total volume to 8 mL with 6% DMSO (*v*/*v*) as cosolvent. The vial was sealed with a screw cap and brought out of the Coy® chamber where it is placed on a stir plate at 200 rpm under a fan and irradiated with cyan LEDs for 24 hours (reaction setup see Supplementary Fig. 1B). Upon completion, the reaction was quenched with 16 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 DCM (3 x 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to provide the crude product, which was purified by preparative TLC (EtOAc/Hexanes, 50%, *v*/*v*). The purified enzymatic product was dissolved in $CDCl_3$ for quantitative ^1H NMR analysis. The benzylic proton peaks were integrated from 3.42 – 3.49 ppm. Other aliphatic protons were used as references.



Supplementary Fig. 5. ^1H NMR of the aliphatic region of product standard.



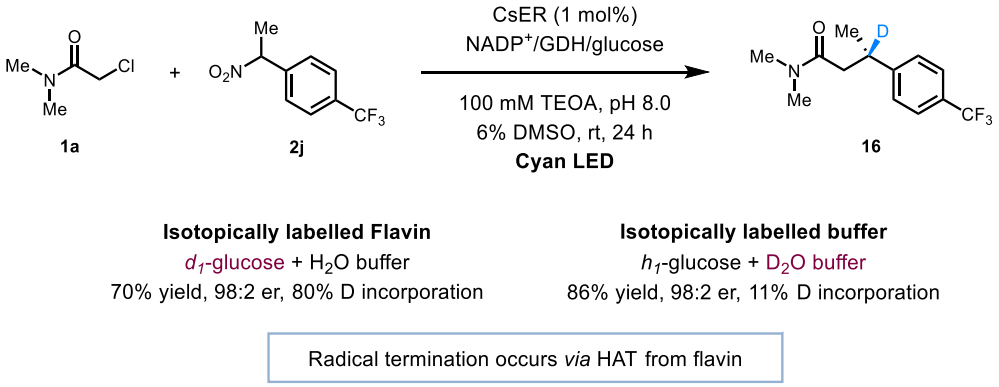
Supplementary Fig. 6. ^{1}H NMR of the aliphatic region of the enzymatic product obtained from d_1-glucose in H_2O buffer (100 mM TEOA, pH 8.0). 80% deuterium incorporation was observed at the benzylic position.



Supplementary Fig. 7. ^{1}H NMR of the aliphatic region of the enzymatic product obtained from h_1-glucose in D_2O buffer (100 mM TEOA, pH 8.0). 11% deuterium incorporation was observed at the benzylic position.

Summary and discussion of the results of deuterium labeling experiments

To elucidate the terminal hydrogen atom source, we conducted a set of deuterium-labeling experiments. When flavin was labeled *in situ* using d_1-glucose with the turnover system, deuterium (80% incorporation) was labeled exclusively at the benzylic position of **16** with good yield and excellent enantioselectivity (70% yield, 98:2 er, Supplementary Fig. 6). In contrast, when the reaction was carried out with h_1-glucose in deuterated buffer, only 11% deuterium incorporation at the benzylic position of **16** was observed with 86% yield, 98:2 er Supplementary Fig. 7). Collectively, these results suggest with CsER, the radical termination occurs primarily through hydrogen atom transfer (HAT) from flavin (FMN_{sq}).



Supplementary Fig. 8. Summary of the results of deuterium labeling experiments.

Spectroscopic experiments

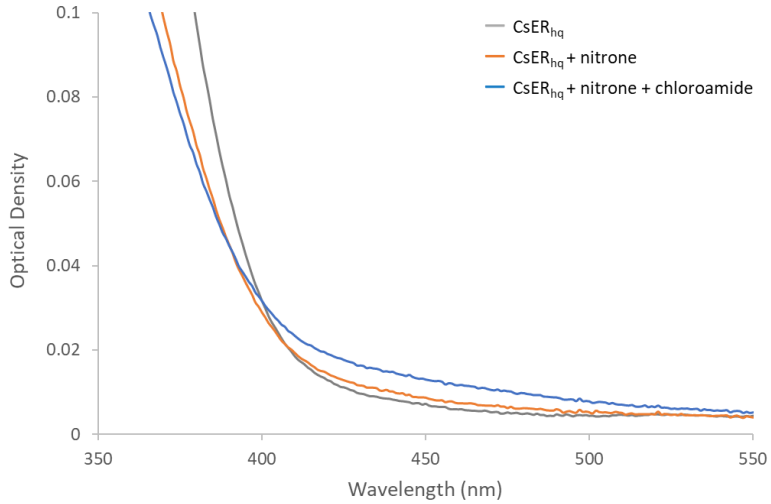
General comments. All samples were prepared in an MBraun® glovebox with O_2 level less than 1 ppm. Custom designed quartz cuvettes with a 10 mm path length and a JY valve were used to maintain oxygen-free conditions for the duration of the experiments. At each distinct stage for measuring CT complexes, solutions were filtered through a 0.2 µm syringe filter. Spectra were obtained on a Cary 60 UV-Vis spectrophotometer.

UV-Vis spectra of reduced CsER with α-chloroamide 1a + nitrone 38

A blank solution of degassed Tricine buffer (100 mM, pH 9.0) was prepared and used to obtain a baseline spectrum. A 50 µM solution of enzyme was prepared by mixing CsER (200 nmol, 1 equiv) with degassed Tricine buffer (the total volume is 4 mL) in an anaerobic chamber and filtered through a syringe filter before a spectrum was taken of the oxidized CsER. The oxidized FMN cofactor was reduced by the addition of 60 µL of 4 mM sodium dithionite (240 nmol, 1.2 equiv) in Tricine buffer (100 mM, pH 9.0). Following filtration through a syringe filter, a spectrum of the reduced CsER was obtained. To detect the presence of a charge-transfer complex, 100 µmol of α-chloroamide (12.1 mg, 500 equiv) was added to the reduced CsER solution and filtered through a syringe filter. A spectrum of reduced CsER (FMN_{hq}) with α-chloroamide was then obtained. Subsequently, 40 µmol of nitrone (5.5 mg, 200 equiv) dissolved in isopropanol (150 µL) was added to the system and filtered through a syringe filter. A spectrum of reduced CsER (FMN_{hq}) with both α-chloroamide and nitrone was then obtained. The overlayed spectra are shown in the main text in Fig. 4a.

UV-Vis spectra of reduced CsER with nitrone 38 + α-chloroamide 1a

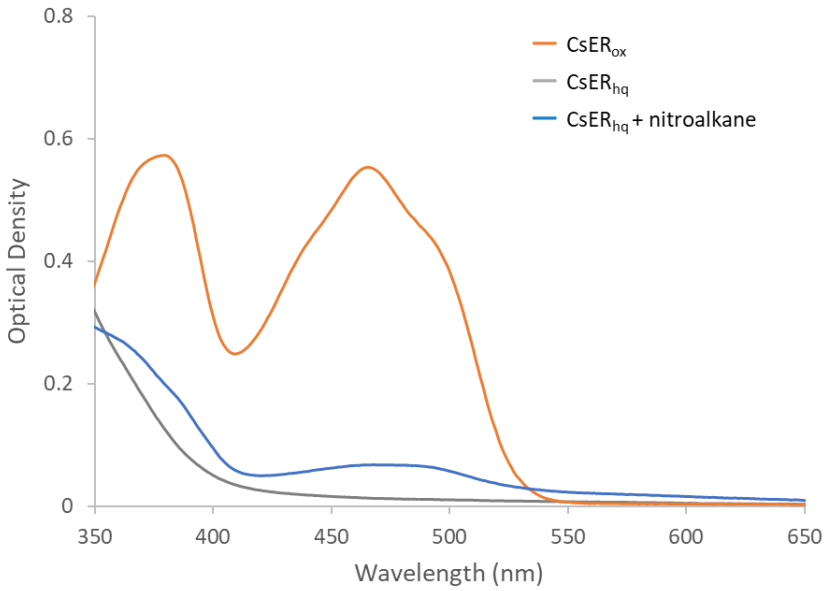
A blank solution of degassed Tricine buffer (100 mM, pH 9.0) was prepared and used to obtain a baseline spectrum. A 50 µM solution of enzyme was prepared by mixing CsER (200 nmol, 1 equiv) with degassed Tricine buffer (the total volume is 4 mL) in an anaerobic chamber and filtered through a syringe filter before a spectrum was taken of the oxidized CsER. The oxidized FMN cofactor was reduced by the addition of 60 µL of 4 mM sodium dithionite (240 nmol, 1.2 equiv) in Tricine buffer (100 mM, pH 9.0). Following filtration through a syringe filter, a spectrum of the reduced CsER was obtained. To detect the presence of a charge transfer-complex, 40 µmol of nitrone (5.5 mg, 200 equiv) dissolved in isopropanol (150 µL) was added to the reduced CsER solution and filtered through a syringe filter. A spectrum of reduced CsER (FMN_{hq}) with nitrone was then obtained. Subsequently, 100 µmol of α-chloroamide (12.1 mg, 500 equiv) was added to the system and filtered through a syringe filter. A spectrum of reduced CsER (FMN_{hq}) with both nitrone and α-chloroamide was then obtained. The overlayed spectra are shown in Supplementary Fig. 9. Although no CT complex was observed between reduced $CsER_{hq}$ with nitrone, a CT complex was observed between reduced $CsER_{hq}$ with both nitrone and α-chloroamide.



Supplementary Fig. 9. UV-Vis absorption traces of CsER in the presence of nitrone and α-chloroamide.

UV-Vis spectra of reduced CsER with nitroalkane 2a

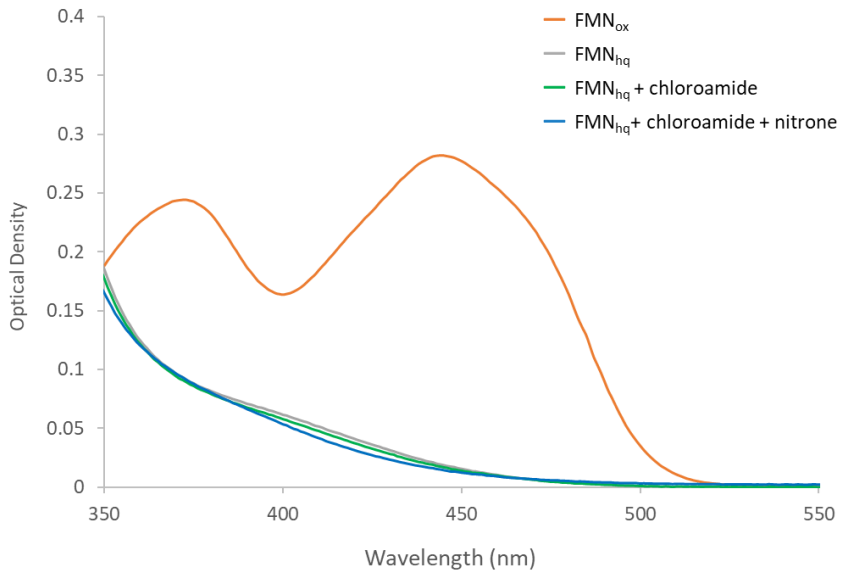
A blank solution of degassed Tricine buffer (100 mM, pH 9.0) was prepared and used to obtain a baseline spectrum. A 50 µM solution of enzyme was prepared by mixing CsER (200 nmol, 1 equiv) with degassed Tricine buffer (the total volume is 4 mL) in an anaerobic chamber and filtered through a syringe filter before and a spectrum was taken of the oxidized CsER. The oxidized FMN cofactor was reduced by the addition of 60 µL of 4 mM sodium dithionite (240 nmol, 1.2 equiv) in Tricine buffer (100 mM, pH 9.0). Following filtration through a syringe filter, a spectrum of the reduced CsER was obtained. Subsequently, 20 µmol of nitroalkane (**2a**, 3.0 mg, 100 equiv) dissolved in isopropanol (150 µL) was added to the reduced CsER solution and filtered through a syringe filter. A spectrum of reduced CsER (FMN_{hq}) with nitroalkane was then obtained. The overlayed spectra are shown in Supplementary Fig. 10. We attribute the absorption band around 450 nm – 500 nm of the reduced CsER with nitroalkane (blue line) to a mixture of flavin quinone and flavin semiquinone.



Supplementary Fig. 10. UV-Vis absorption traces of CsER in the presence of nitroalkane.

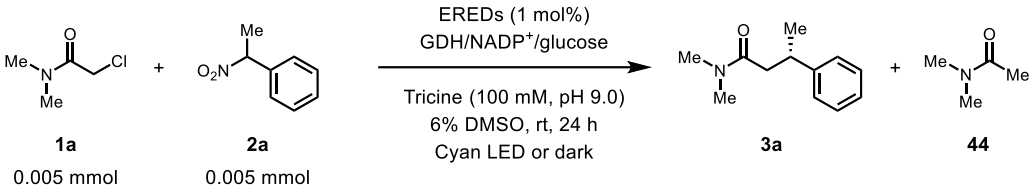
UV-Vis spectra of free FMN with α-chloroamide 1a and nitrone 38

A blank solution of degassed Tricine buffer (100 mM, pH 9.0) was prepared and used to obtain a baseline spectrum. A 30 µM solution of FMN was prepared by FMN (120 nmol, 1 equiv) with degassed Tricine buffer (the total volume is 4 mL) in an anaerobic chamber and filtered through a syringe filter before and a spectrum was taken of the oxidized FMN. The oxidized FMN cofactor was reduced by the addition of 36 µL of 4 mM sodium dithionite (144 nmol, 1.2 equiv) in Tricine buffer (100 mM, pH 9.0). Following filtration through a syringe filter, a spectrum of the reduced FMN was obtained. To detect the presence of a charge-transfer complex, 100 µmol of α-chloroamide (11.7 mg, 800 equiv) was added to the reduced CsER solution and filtered through a syringe filter. A spectrum of reduced FMN_{hq} with α-chloroamide was then obtained. Subsequently, 40 µmol of nitrone (5.0 mg, 300 equiv) dissolved in isopropanol (150 µL) was added to the system and filtered through a syringe filter. A spectrum of reduced FMN_{hq} with both α-chloroamide and nitrone was then obtained. The overlayed spectra are shown in the main text in Supplementary Fig. 11. No CT complex was observed between reduced FMN_{hq} with α-chloroamide and nitrone.



Supplementary Fig. 11. UV-Vis absorption traces of free FMN in the presence of α-chloroamide and nitrone.

Supplementary Table 4. Direction reduction of α-chloroamide by EREDs.

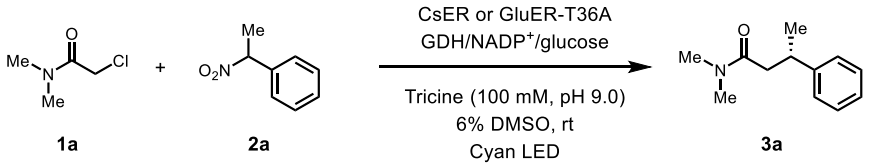


1a 0.005 mmol + **2a** 0.005 mmol → **3a** + **44**

Entry	ERED	Substrate	Light	Yield[a] of **3a**	Yield of **44**
1	CsER	**1a** + **2a**	cyan	51%	21%
2	CsER	**1a** + **2a**	dark	0%	0%
3	GluER-T36A	**1a** + **2a**	cyan	38%	16%
4	GluER-T36A	**1a** + **2a**	dark	0%	0%
5	CsER	**1a**	cyan	0%	48%
6	CsER	**1a**	dark	0%	0%
7	GluER-T36A	**1a**	cyan	0%	15%
8	GluER-T36A	**1a**	dark	0%	0%

Reaction conditions: α-chloroamide (**1a**, 0.6 mg, 5 μmol, 1 equiv), 1-nitroethylbenzene (**2a**, 0.76 mg, 5 μmol, 1 equiv), GDH (0.3 mg), $NADP^+$ (0.05 μmol, 1 mol%), glucose (25 μmol) and purified enzyme (0.05 μmol, 1 mol%) in tricine buffer (100 mM, pH 9.0), with 6% DMSO as cosolvent, final total volume is 800 μL. Reaction mixtures were irradiated with cyan LEDs or covered by aluminum foil under anaerobic conditions at room temperature for 24 h. [a] Yields (average of duplicate) of **3a** and **44** were determined *via* LCMS relative to an internal standard (TBB).

Supplementary Table 5. Specific activity of CsER and GluER-T36A for the model reaction.



Entry	ERED	Initial velocity[a] (μmol/min)	Specific activity[b] (U/mg)
1	CsER	0.0178 ± 0.0002	0.0116 ± 0.0002
2	GluER-T36A	0.0046 ± 0.0001	0.0023 ± 0.0001

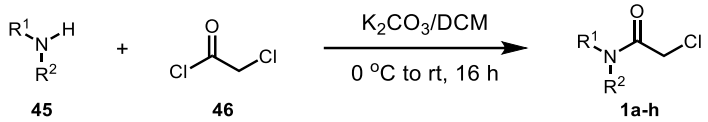
Reaction conditions: α-chloroamide (**1a**, 0.12 mg, 10 μmol, 2 equiv), 1-nitroethylbenzene (**2a**, 0.76 mg, 5 μmol, 1 equiv), GDH (0.3 mg), $NADP^+$ (0.05 μmol, 1 mol%), glucose (25 μmol) and purified CsER (0.04 μmol, 0.8 mol%) or GluER-T36A (0.05 μmol, 1 mol%) in tricine buffer (100 mM, pH 9.0), with 6% DMSO as cosolvent, final total volume is 800 μL. Reaction mixtures were irradiated with cyan LEDs under anaerobic conditions at room temperature. Yield (triplicate) of **3a** was determined *via* LCMS relative to an internal standard (TBB).

Note: [a] Initial rate of the enzymatic reaction was calculated over the time period of 0–30 min for CsER and 0–20 min for GluER-T36A respectively. [b]For calculation of specific activity, one unit (μmol/min) was defined as the amount of biocatalyst required for forming 1 μmol of product **3a** per minute.

Synthesis of substrates

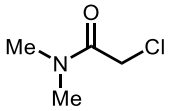
Substrates 2-chloro-*N*-methylacetamide (**1b**), benzyl 2-bromoacetate (**1i**), 1-chloropropan-2-one (**1j**), 2-chloro-1-phenylethan-1-one (**1k**), (nitromethyl)benzene (**2l**), ethyl 2-nitropropanoate (**2s**) are commercially available from Sigma-Aldrich.

Synthesis of α-chloroamide substrates



General procedure. To a stirred solution of amine (**45**, 5 mmol, 1 equiv) in dry DCM (20 mL) was added K_2CO_3 (15 mmol, 3 equiv), then α-chloroacetyl chloride (**46**, 6 mmol, 1.2 equiv) was added dropwise to the reaction mixture under nitrogen atmosphere at 0 °C, the reaction mixture was warmed up to room temperature and further stirred over 16 hours. After completion of the reaction, the mixture was filtered, and the filtrate was collected and concentrated *in vacuo* to give a crude product, which was further purified by flash chromatography (EtOAc/Hexanes, 30–70%, *v*/*v*).

2-Chloro-*N*,*N*-dimethylacetamide (**1a**)



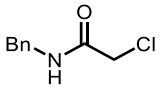
Clear oil. 540 mg, 89% yield.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.07 (s, 2H), 3.09 (s, 3H), 2.98 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 166.6, 41.3, 37.7, 36.1.

The NMR spectra is in agreement with published data.[14]

N-Benzyl-2-chloroacetamide (**1c**)



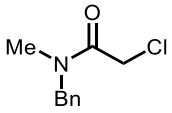
White solid. 730 mg, 80% yield.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 – 7.33 (m, 2H), 7.33 – 7.27 (m, 3H), 6.90 (s, 1H), 4.49 (d, J = 5.8 Hz, 2H), 4.09 (s, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 165.9, 137.4, 129.0, 127.9, 127.9, 44.0, 42.7.

The NMR spectra is in agreement with published data.[15]

N-Benzyl-2-chloro-*N*-methylacetamide (**1d**)



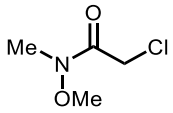
White solid. 837 mg, 85% yield.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 – 7.28 (m, 3H), 7.26 – 7.17 (m, 2H), 4.61 (s, 2H), 4.15 (s, 1.2H), 4.11 (s, 0.8H), 3.00 (s, 1.8H), 2.97 (s, 1.2H). Major rotamer:minor rotamer = 1.5:1.

^{13}C NMR (126 MHz, $CDCl_3$) δ 167.1, 166.8, 136.6, 135.9, 129.2, 128.9, 128.2, 128.1, 127.8, 126.6, 53.8, 51.5, 41.5, 41.2, 35.2, 34.5.

The NMR spectra is in agreement with published data.[16]

2-Chloro-*N*-methoxy-*N*-methylacetamide (**1e**)



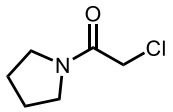
Clear oil. 356 mg, 52% yield.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.23 (s, 2H), 3.74 (s, 3H), 3.22 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 167.7, 61.8, 40.9, 32.7.

The NMR spectra is in agreement with published data.[16]

2-Chloro-1-(pyrrolidin-1-yl)ethan-1-one (**1f**)



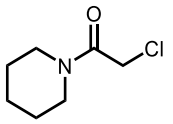
Clear oil. 478 mg, 65% yield.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.01 (s, 2H), 3.51 (dt, J = 9.2, 6.9 Hz, 4H), 1.99 (p, J = 6.9 Hz, 2H), 1.88 (p, J = 6.9 Hz, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 164.9, 46.8, 46.5, 42.2, 26.3, 24.3.

The NMR spectra is in agreement with published data.[16]

2-Chloro-1-(piperidin-1-yl)ethan-1-one (**1g**)



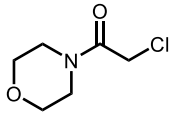
White solid. 603 mg, 75% yield.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.06 (s, 2H), 3.59 – 3.52 (m, 2H), 3.48 – 3.39 (m, 2H), 1.69 – 1.60 (m, 4H), 1.60 – 1.53 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 165.0, 47.6, 43.4, 41.3, 26.5, 25.5, 24.4.

The NMR spectra is in agreement with published data.[17]

2-Chloro-1-morpholinoethan-1-one (**1h**)



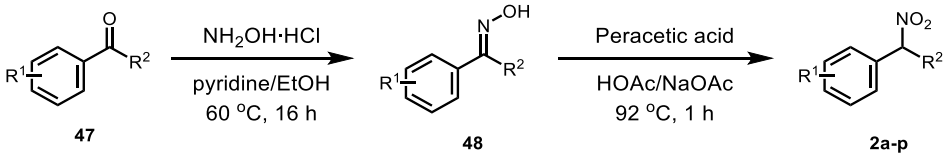
White solid. 570 mg, 70% yield.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.06 (s, 2H), 3.71 (dt, J = 12.9, 4.8 Hz, 4H), 3.63 (t, J = 4.8 Hz, 2H), 3.53 (t, J = 4.8 Hz, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 165.4, 66.8, 66.6, 46.9, 42.6, 40.7.

The NMR spectra is in agreement with published data.[17]

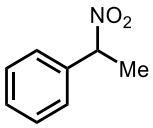
Synthesis of nitroalkane substrates



General procedure. Adapted from the method by S.V. Tsukanov *et al*.[18] To a stirred solution of ketone (**47**, 10 mmol, 1 equiv) in dry ethanol (10 mL) was added hydroxylamine hydrochloride (15 mmol, 1.5 equiv) and pyridine (20 mmol, 2 equiv), the reaction mixture was stirred at 60 °C for 16 hours. After completion of the reaction, the solvent was removed under reduced pressure. The resulting mixture was dissolved in EtOAc (50 mL), washed with aqueous 1 M HCl (50 mL), saturated aqueous $NaHCO_3$ (50 mL), and brine (50 mL). The organic layer was collected and dried over Na_2SO_4, filtered and concentrated to give the oxime product **48**, which was used in the next step without further purification.

The oxime (**48**, 5 mmol, 1 equiv) was dissolved in glacial acetic acid (5 mL) and the reaction mixture was heated to 92 °C. Sodium acetate (2 mmol, 0.4 equiv) was dissolved in a solution of peracetic acid (3.0 equiv), and the mixture was added to the oxime solution in a dropwise manner over 20 min. The temperature of the reaction was maintained carefully around 92 °C for 1 hour. After completion of the reaction, the reaction mixture was cooled to room temperature and diluted with water (50 mL). The resulting solution was extracted with DCM (2 x 30 mL). The combined organic layers were washed with water (50 mL), saturated aqueous $NaHCO_3$ (50 mL), saturated aqueous Na_2SO_3 (50 mL), and brine (50 mL). The resulting solution was dried over Na_2SO_4, filtered, and concentrated to provide a crude product, which was further purified by flash chromatography (EtOAc/Hexanes, 5%, *v*/*v*) to provide the pure nitro compounds **2a-q**.

1-Nitroethylbenzene (**2a**)



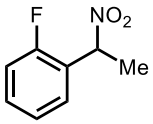
Clear oil. 340 mg, 45% yield.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50 – 7.44 (m, 2H), 7.44 – 7.37 (m, 3H), 5.62 (q, J = 7.0 Hz, 1H), 1.90 (d, J = 7.0 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 135.7, 129.9, 129.2, 127.5, 86.3, 19.6.

The NMR spectra is in agreement with published data.[18]

1-Fluoro-2-(1-nitroethyl)benzene (**2b**)



Clear oil. 296 mg, 35% yield.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 – 7.37 (m, 2H), 7.24 – 7.18 (m, 1H), 7.15 – 7.08 (m, 1H), 5.92 (q, J = 7.0 Hz, 1H), 1.92 (d, J = 7.0 Hz, 3H).

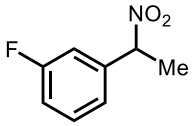
^{13}C NMR (126 MHz, $CDCl_3$) δ 160.4 (d, J = 249.7 Hz), 131.6 (d, J = 8.6 Hz), 128.2 (d, J = 2.7 Hz), 124.9 (d, J = 3.7 Hz), 123.2 (d, J = 13.6 Hz), 116.1 (d, J = 21.7 Hz), 79.1 (d, J = 3.7 Hz), 19.0.

^{19}F NMR (470 MHz, $CDCl_3$) δ -117.3.

HRMS (DART-MS): m/z calcd for C_8H_8F $[M–NO_2]^+$: 123.0604, found 123.0606.

IR: 2995, 1731, 1616, 1492, 1458, 1386, 1356, 1236, 757, 741(cm^{-1}).

1-Fluoro-3-(1-nitroethyl)benzene (**2c**)



Clear oil. 304 mg, 36% yield.

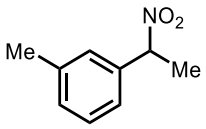
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 – 7.37 (m, 1H), 7.30 – 7.18 (m, 2H), 7.17 – 7.11 (m, 1H), 5.63 (q, J = 7.0 Hz, 1H), 1.92 (d, J = 7.0 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 163.0 (d, J = 247.9 Hz), 137.7 (d, J = 7.5 Hz), 130.8 (d, J = 8.2 Hz), 123.4 (d, J = 3.1 Hz), 117.0 (d, J = 21.0 Hz), 114.7 (d, J = 22.7 Hz), 85.6, 19.5.

^{19}F NMR (470 MHz, $CDCl_3$) δ -111.4.

The NMR spectra is in agreement with published data.[19]

1-Methyl-3-(1-nitroethyl)benzene (**2d**)



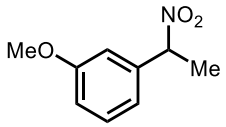
Light yellow oil. 313 mg, 38% yield.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 – 7.23 (m, 4H), 5.62 (q, J = 6.9 Hz, 1H), 2.41 (s, 3H), 1.92 (d, J = 7.0 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 139.0, 135.7, 130.6, 129.0, 128.1, 124.5, 86.3, 21.5, 19.6.

The NMR spectra is in agreement with published data.[20]

1-Methoxy-3-(1-nitroethyl)benzene (**2e**)



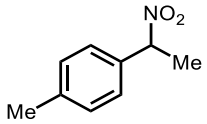
Light yellow oil. 298 mg, 33% yield.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (t, J = 8.0 Hz, 1H), 7.03 (d, J = 7.7 Hz, 1H), 7.00 – 6.97 (m, 1H), 6.96 – 6.91 (m, 1H), 5.58 (q, J = 6.9 Hz, 1H), 3.82 (s, 3H), 1.88 (d, J = 6.9 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 160.1, 137.1, 130.2, 119.7, 115.2, 113.2, 86.2, 55.5, 19.6.

The NMR spectra is in agreement with published data.[20]

1-Methyl-4-(1-nitroethyl)benzene (**2f**)



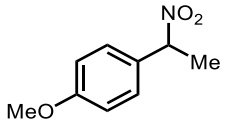
Light yellow oil. 247 mg, 30% yield.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 (d, J = 8.1 Hz, 2H), 7.21 (d, J = 7.8 Hz, 2H), 5.59 (q, J = 7.0 Hz, 1H), 2.37 (s, 3H), 1.88 (d, J = 6.9 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 140.0, 132.8, 129.8, 127.4, 86.1, 21.3, 19.5.

The NMR spectra is in agreement with published data.[20]

1-Methoxy-4-(1-nitroethyl)benzene (**2g**)



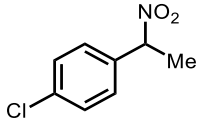
Yellow oil. 153 mg, 17% yield.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (d, J = 8.9 Hz, 2H), 6.92 (d, J = 8.8 Hz, 2H), 5.57 (q, J = 7.0 Hz, 1H), 3.82 (s, 3H), 1.88 (d, J = 7.0 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 160.8, 129.1, 127.8, 114.4, 85.9, 55.5, 19.5.

The NMR spectra is in agreement with published data.[20]

1-Chloro-4-(1-nitroethyl)benzene (**2h**)



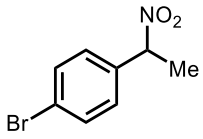
Light yellow oil. 315 mg, 38% yield.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 – 7.37 (m, 4H), 5.59 (q, J = 7.0 Hz, 1H), 1.88 (d, J = 7.0 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 136.0, 134.0, 129.4, 129.0, 85.5, 19.5.

The NMR spectra is in agreement with published data.[20]

1-Bromo-4-(1-nitroethyl)benzene (**2i**)



Light yellow oil. 483 mg, 42% yield.

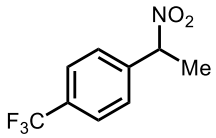
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (d, J = 8.5 Hz, 2H), 7.34 (d, J = 8.5 Hz, 2H), 5.57 (q, J = 7.0 Hz, 1H), 1.88 (d, J = 7.0 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 134.5, 132.4, 129.2, 124.2, 85.6, 19.5.

HRMS (DART-MS): m/z calcd for C_8H_8Br $[M–NO_2]^+$: 182.9804, found 182.9804.

IR: 2991, 1593, 1546, 1489, 1408, 1385, 1355, 1284, 1073, 1011, 863, 747, 702 (cm^{-1}).

1-(1-Nitroethyl)-4-(trifluoromethyl)benzene (**2j**)



Clear oil. 330 mg, 30% yield.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (d, J = 8.1 Hz, 2H), 7.59 (d, J = 8.1 Hz, 2H), 5.67 (q, J = 6.9 Hz, 1H), 1.93 (d, J = 7.0 Hz, 3H).

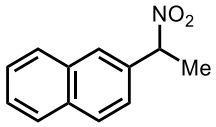
^{13}C NMR (126 MHz, $CDCl_3$) δ 139.2 (d, J = 1.5 Hz), 132.1 (q, J = 32.8 Hz), 128.0, 126.2 (q, J = 3.8 Hz), 123.8 (q, J = 272.4 Hz), 85.6, 19.6.

^{19}F NMR (470 MHz, $CDCl_3$) δ -62.9.

HRMS (DART-MS): m/z calcd for $C_9H_9NO_2F_3$ $[M+H]^+$: 220.0580, found 220.0578.

IR: 2981, 1690, 1556, 1428, 1410, 1361, 1262, 1125, 1060, 837, 718, 607 (cm^{-1}).

2-(1-nitroethyl)naphthalene (**2k**)



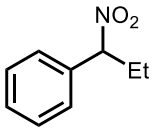
Clear oil. 281 mg, 28% yield.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 – 7.82 (m, 4H), 7.59 – 7.50 (m, 3H), 5.79 (q, J = 6.9 Hz, 1H), 2.00 (d, J = 6.9 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 133.8, 133.1, 133.0, 129.2, 128.4, 127.9, 127.5, 127.2, 126.9, 124.3, 86.5, 19.7.

The NMR spectra is in agreement with published data.[20]

1-Nitropropylbenzene (**2m**)



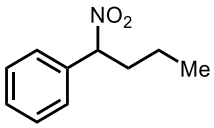
Clear oil. 255 mg, 31% yield.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50 – 7.45 (m, 2H), 7.43 – 7.37 (m, 3H), 5.37 (dd, J = 8.8, 6.4 Hz, 1H), 2.58 – 2.46 (m, 1H), 2.19 – 2.05 (m, 1H), 0.99 (t, J = 7.4 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 134.6, 129.9, 129.1, 127.9, 93.2, 27.5, 10.8.

The NMR spectra is in agreement with published data.[21]

1-Nitrobutylbenzene (**2n**)



Clear oil. 134 mg, 15% yield.

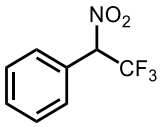
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 – 7.44 (m, 2H), 7.42 – 7.38 (m, 3H), 5.46 (dd, J = 8.8, 6.4 Hz, 1H), 2.54 – 2.42 (m, 1H), 2.11 – 1.99 (m, 1H), 1.43 – 1.30 (m, 2H), 0.98 (t, J = 7.4 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 134.8, 129.9, 129.1, 127.9, 91.5, 36.0, 19.5, 13.6.

HRMS (DART-MS): m/z calcd for $C_{10}H_{14}NO_2$ $[M+H]^+$: 180.1019, found 180.1019.

IR: 2970, 1552, 1491, 1457, 1363, 1073, 951, 750, 695 (cm^{-1}).

(2,2,2-Trifluoro-1-nitroethyl)benzene (**2o**)



White solid. 380 mg, 37% yield.

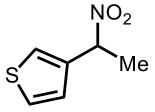
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.86 (s, 1H), 7.57 – 7.46 (m, 5H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 148.0 (q, J = 32.5 Hz), 130.8, 128.8, 128.7, 126.0, 120.7 (q, J = 274.8 Hz).

^{19}F NMR (376 MHz, $CDCl_3$) δ -66.8.

The NMR spectra is in agreement with published data.[18]

3-(1-Nitroethyl)thiophene (**2p**)



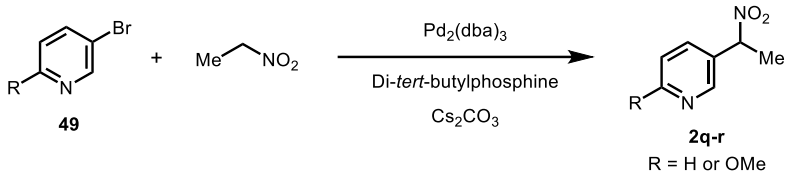
Clear oil. 87 mg, 11% yield.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 – 7.42 (m, 1H), 7.36 (dd, J = 5.1, 3.0 Hz, 1H), 7.20 (dd, J = 5.0, 1.4 Hz, 1H), 5.72 (q, J = 7.0 Hz, 1H), 1.91 (d, J = 6.9 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 136.4, 127.1, 126.3, 125.1, 81.6, 19.6.

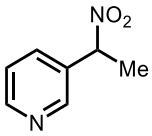
HRMS (DART-MS): m/z calcd for $C_6H_8NO_2S$ $[M+H]^+$: 158.0270, found 158.0271.

IR: 3108, 2991, 1546, 1546, 1416, 1408, 1383, 1312, 1164, 1084, 916, 829, 756, 670 (cm^{-1}).



General procedure. Adapted from the method by E. M. Vogl *et al*.[22] In a flame-dried round bottle flask equipped with a stir bar under nitrogen was charged with the aryl bromide **49** (3 mmol, 1 equiv), nitroethane (6 mmol, 450 mg, 2 equiv), $Pd_2(dba)_3$ (0.09 mmol, 82 mg, 3 mol%), di-tert-butylphosphine ligand (0.18 mmol, 26 mg, 6 mol%), Cs_2CO_3 (3.6 mmol, 1.17 g, 1.2 equiv) in dry dioxane. The reaction mixture was purged with N_2 for 15 min and heated at 60 °C for 24 hours. After completion of the reaction, the reaction mixture was filtered through Celite and washed with DCM (15 mL). The filtrate was concentrated under vacuum to provide the crude product, which was purified by flash chromatography. For compound **2q**, additional reverse phase C18 flash chromatography was needed.

3-(1-Nitroethyl)pyridine (**2q**)



Clear oil. 80 mg, 17% yield.

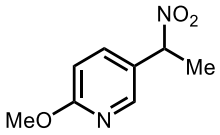
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.71 (s, 1H), 8.67 (d, J = 4.8 Hz, 1H), 7.84 (dd, J = 7.7, 2.1 Hz, 1H), 7.38 (dd, J = 8.1, 4.9 Hz, 1H), 5.65 (q, J = 7.0 Hz, 1H), 1.94 (d, J = 7.0 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 151.1, 149.1, 135.1, 131.4, 124.1, 83.9, 19.5.

HRMS (DART-MS): m/z calcd for $C_7H_9N_2O_2$ $[M+H]^+$: 153.0658, found 153.0659.

IR: 2993, 1688, 1547, 1428, 1360, 1273, 1091, 1064, 863 (cm^{-1}).

2-Methoxy-5-(1-nitroethyl)pyridine (**2r**)



Clear oil. 218 mg, 40% yield.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.22 (d, J = 2.5 Hz, 1H), 7.70 (dd, J = 8.7, 2.6 Hz, 1H), 6.77 (d, J = 8.7

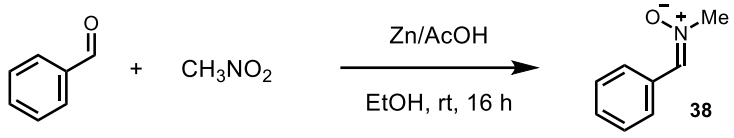
Hz, 1H), 5.56 (q, J = 7.0 Hz, 1H), 3.93 (s, 3H), 1.87 (d, J = 7.0 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 165.2, 146.8, 137.4, 124.3, 111.6, 83.6, 53.8, 19.3.

HRMS (DART-MS): m/z calcd for $C_8H_{11}N_2O_3$ $[M+H]^+$: 183.0764, found 183.0767.

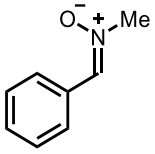
IR: 2980, 1610, 1554, 1385, 1135, 904, 724, 649 (cm^{-1}).

Synthesis of nitrone 38



To a solution of benzyl aldehyde (1.06 g, 10 mmol, 1.0 equiv), CH_3NO_2 (2.44 g, 40 mmol, 4.0 equiv) and zinc powder (3.93 g, 60 mmol 6 equiv) in 95% ethanol (20 mL) was added glacial acetic acid (4 mL, 70 mmol, 7 equiv) dropwise at 0 °C. The reaction mixture was allowed to stir at room temperature for 16 h. The suspension was filtered, and the filtrate was collected and concentrated under vacuum, the crude mixture was purified by flash column chromatography using EtOAc as eluent to give the nitrone product.

C-Phenyl-*N*-methyl-nitrone (**38**)



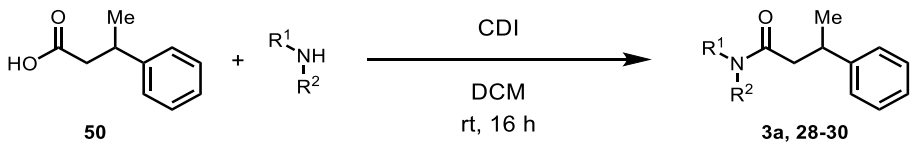
White solid. 590 mg, 44% yield.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.24 – 8.18 (m, 2H), 7.46 – 7.39 (m, 3H), 7.37 (s, 1H), 3.88 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 135.3, 130.6, 128.6, 128.5, 54.6.

The NMR spectra is in agreement with published data.[23]

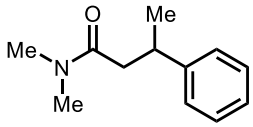
Synthesis of reference compounds



General procedure. To a stirred solution of acid **50** (328 mg, 2 mmol, 1 equiv) in dry DCM (10 mL) was added carbonyldiimidazole (CDI, 356 mg, 2.2 mmol, 1.2 equiv) under N_2 atmosphere and the reaction mixture was stirred at room temperature for 1 hour. Amine (2.6 mmol, 1.3 equiv) was added to the reaction mixture, and the mixture was further stirred at room temperature for 16 h. After completion of the reaction, the reaction mixture was diluted with DCM (10 mL), washed with aqueous 1 M HCl (10 mL), saturated aqueous $NaHCO_3$ (20 mL) and brine (20 mL). The organic layer was collected and dried

over Na_2SO_4, filtered and concentrated to give crude amide product, which was purified by flash chromatography (EtOAc/Hexanes, 30–50%, *v*/*v*).

N,*N*-Dimethyl-3-phenylbutanamide (**3a**)



Clear oil. 263 mg, 69% yield.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 – 7.19 (m, 5H), 3.38 (h, J = 7.0 Hz, 1H), 2.92 (s, 3H), 2.89 (s, 3H), 2.63 (dd, J = 15.0, 6.2 Hz, 1H), 2.53 (dd, J = 15.0, 8.1 Hz, 1H), 1.35 (d, J = 6.9 Hz, 3H).

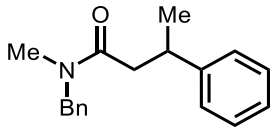
^{13}C NMR (126 MHz, $CDCl_3$) δ 171.9, 146.7, 128.5, 127.0, 126.3, 42.0, 37.4, 36.6, 35.5, 21.7.

The NMR spectra is in agreement with published data [24].

HRMS (DART-MS): m/z calcd for $C_{12}H_{18}NO$ $[M+H]^+$: 192.1383, found 192.1379.

IR: 3026, 2929, 1638, 1493, 1395, 1264, 1143, 1016, 763, 700 (cm^{-1}).

N-Benzyl-*N*-methyl-3-phenylbutanamide (**28**)



Clear oil. 402 mg, 75% yield.

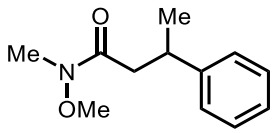
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 – 7.21 (m, 8H), 7.10 (dd, J = 19.3, 7.1 Hz, 2H), 4.66 (d, J = 14.7 Hz, 0.6H), 4.50 (d, J = 14.7 Hz, 0.6H), 4.46 (d, J = 17.2 Hz, 0.4H), 4.41 (d, J = 16.8 Hz, 0.4H), 3.52 – 3.42 (m, 1H), 2.92 (s, 1.2H), 2.83 (s, 1.8H), 2.77 – 2.67 (m, 1H), 2.64 – 2.56 (m, 1H), 1.40 (d, J = 6.9 Hz, 1.8H), 1.34 (d, J = 6.9 Hz, 1.2H). Two rotamers, major rotamer : minor rotamer = 1.5:1.

^{13}C NMR (126 MHz, $CDCl_3$) δ 172.1, 171.8, 146.5, 146.4, 137.4, 136.6, 128.9, 128.5, 127.9, 127.6, 127.2, 127.0, 126.9, 126.3, 53.2, 50.8, 41.8, 41.6, 36.7, 36.5, 35.0, 33.9, 21.8, 21.6. Observed complexity is due to rotamers.

HRMS (DART-MS): m/z calcd for $C_{18}H_{22}NO$ $[M+H]^+$: 268.1596, found 268.1693.

IR: 3027, 2961, 1638, 1493, 1451, 1356, 1181, 1121, 1016, 733, 698 (cm^{-1}).

N-Methoxy-*N*-methyl-3-phenylbutanamide (**29**)



Clear oil. 190 mg, 46% yield.

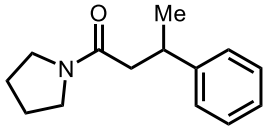
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 – 7.24 (m, 4H), 7.22 – 7.17 (m, 1H), 3.58 (s, 3H), 3.42 – 3.33 (m, 1H), 3.14 (s, 3H), 2.74 (dd, J = 10.2 Hz, 1H), 2.65 (dd, J = 15.1, 8.3 Hz, 1H), 1.32 (d, J = 7.0 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 173.3, 146.7, 128.6, 127.0, 126.4, 61.3, 40.5, 35.9, 32.2, 21.8.

HRMS (DART-MS): m/z calcd for $C_{12}H_{18}NO_2$ $[M+H]^+$: 208.1332, found 208.1330.

IR: 3027, 2958, 1603, 1451, 1389, 1196, 909, 761, 699 (cm^{-1}).

3-Phenyl-1-(pyrrolidin-1-yl)butan-1-one (**30**)



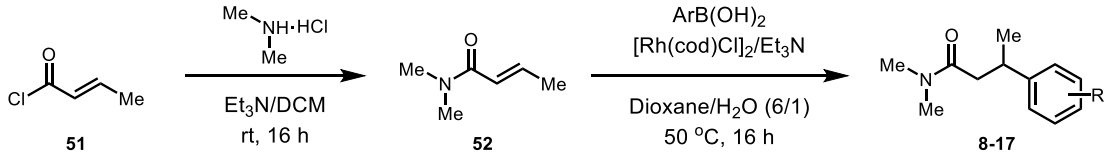
Clear oil. 262 mg, 60% yield.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 – 7.26 (m, 4H), 7.23 – 7.18 (m, 1H), 3.50 – 3.37 (m, 3H), 3.36 – 3.30 (m, 1H), 3.19 – 3.09 (m, 1H), 2.55 (dd, J = 14.7, 6.5 Hz, 1H), 2.49 (dd, J = 14.7, 7.9 Hz, 1H), 1.90 – 1.74 (m, 4H), 1.36 (d, J = 6.9 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.4, 146.7, 128.5, 127.0, 126.3, 46.8, 45.7, 43.8, 36.5, 26.2, 24.5, 21.5.

HRMS (DART-MS): m/z calcd for $C_{14}H_{20}NO$ $[M+H]^+$: 218.1339, found 218.1334.

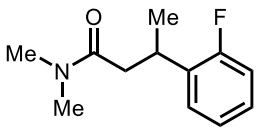
IR: 3026, 2964, 2871, 1631, 1425, 1339, 1252, 1087, 761, 700 (cm^{-1}).



General procedure.

(*E*)-*N*,*N*-dimethylbut-2-enamide **52** was prepared according to published procedure.[25] Adapted from the method by R. Itooka *et al.*[26] To a stirred solution of $ArB(OH)_2$ (2.25 mmol, 1.5 equiv) and $[Rh(cod)Cl]_2$ (1 mol%) in degassed dioxane/H_2O (6/1, *v*/*v*, 3 mL) was added the α,β-unsaturated amide (**52**, 1.5 mmol, 1.0 equiv) and triethylamine (1.5 mmol, 1.0 equiv) under N_2 atmosphere. The reaction mixture was heated at 50 °C for 16 hours. After completion of the reaction, the mixture was concentrated *in vacuo*, the resulting mixture was dissolved in DCM (20 mL), washed with aqueous 1 M HCl (10 mL), saturated aqueous $NaHCO_3$ (20 mL) and brine (20 mL). The organic layer was collected and dried over Na_2SO_4, filtered and concentrated to give the crude product, which was purified by flash chromatography (EtOAc/Hexanes, 30–50%, *v*/*v*).

3-(2-Fluorophenyl)-*N*,*N*-dimethylbutanamide (**8**)



Clear oil. 49 mg, 16% yield.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 – 7.23 (m, 2H), 7.20 – 7.14 (m, 1H), 7.10 – 7.05 (m, 1H), 7.03 – 6.97 (m, 1H), 3.59 (h, J = 13.9, 7.0 Hz, 1H), 2.96 (s, 3H), 2.92 (s,3H), 2.70 (dd, J = 15.2, 5.8 Hz, 1H), 2.56 (dd, J = 15.2, 8.5 Hz, 1H), 1.35 (d, J = 7.0 Hz, 3H).

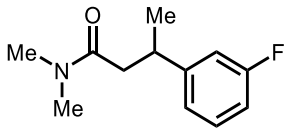
^{13}C NMR (126 MHz, $CDCl_3$) δ 171.6, 161.0 (d, J = 245.2 Hz), 133.2 (d, J = 14.0 Hz), 128.8 (d, J = 5.4 Hz), 127.8 (d, J = 8.4 Hz), 124.3 (d, J = 3.4 Hz), 115.7 (d, J = 22.8 Hz), 40.2, 37.4, 35.6, 31.10, 20.4.

^{19}F NMR (470 MHz, $CDCl_3$) δ -117.8.

HRMS (DART-MS): m/z calcd for $C_{13}H_{17}NOF$ $[M+H]^+$: 210.1289, found 210.1284.

IR: 2970, 2883, 2871, 1636, 1466, 1340, 1159, 950, 816 (cm^{-1}).

3-(3-Fluorophenyl)-*N*,*N*-dimethylbutanamide (**9**)



Clear oil. 120 mg, 38% yield.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 – 7.21 (m, 1H), 7.02 (dd, J = 7.5, 1.5 Hz, 1H), 6.97 – 6.84 (m, 2H), 3.38 (h, J = 7.0 Hz, 1H), 2.90 (s, 6H), 2.60 (dd, J = 15.2, 6.3 Hz, 1H), 2.50 (dd, J = 15.2, 7.8 Hz, 1H), 1.31 (d, J = 6.9 Hz, 3H).

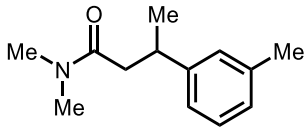
^{13}C NMR (126 MHz, $CDCl_3$) δ 171.5, 163.1 (d, J = 245.3 Hz), 149.5 (d, J = 6.7 Hz), 130.0 (d, J = 8.3 Hz), 122.8 (d, J = 2.7 Hz), 113.8 (d, J = 21.0 Hz), 113.2 (d, J = 21.0 Hz), 41.6, 37.4, 36.3, 35.6, 21.7.

^{19}F NMR (470 MHz, $CDCl_3$) δ -113.4.

HRMS (DART-MS): m/z calcd for $C_{13}H_{17}NOF$ $[M+H]^+$: 210.1289, found 210.1286.

IR: 2931, 1638, 1587, 1486, 1397, 1139, 869, 783, 698 (cm^{-1}).

N,*N*-Dimethyl-3-(m-tolyl)butanamide (**10**)



Light yellow oil. 141 mg, 45% yield.

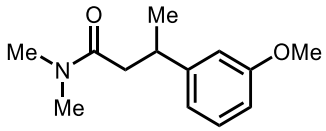
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.18 (t, J = 7.5 Hz, 1H), 7.08 – 6.99 (m, 3H), 3.32 (h, J = 6.9 Hz, 1H), 2.91 (s, 3H), 2.88 (s, 3H), 2.60 (dd, J = 14.9, 6.0 Hz, 1H), 2.50 (dd, J = 15.0, 8.3 Hz, 1H), 2.33 (s, 3H), 1.32 (d, J = 7.0 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 172.0, 146.7, 138.1, 128.5, 127.8, 127.1, 123.9, 42.0, 37.4, 36.6, 35.6, 21.7, 21.6.

HRMS (DART-MS): m/z calcd for $C_{13}H_{20}NO$ $[M+H]^+$: 206.1539, found 206.1538.

IR: 2925, 1638, 1489, 1395, 1261, 1142, 783, 704 (cm^{-1}).

3-(3-Methoxyphenyl)-*N*,*N*-dimethylbutanamide (**11**)



Light yellow oil. 105 mg, 31% yield.

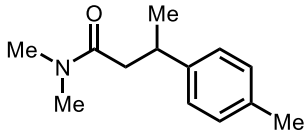
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.21 (t, J = 7.9 Hz, 1H), 6.84 (d, J = 7.6 Hz, 1H), 6.81 – 6.77 (m, 1H), 6.76 – 6.72 (m, 1H), 3.79 (s, 3H), 3.34 (h, J = 6.9 Hz, 1H), 2.91 (s, 3H), 2.89 (s,3H), 2.60 (dd, J = 15.0, 6.0 Hz, 1H), 2.50 (dd, J = 15.0, 8.3 Hz, 1H), 1.32 (d, J = 6.9 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 171.9, 159.8, 148.6, 129.5, 119.4, 113.0, 111.4, 55.3, 41.9, 37.4, 36.7, 35.6, 21.7.

HRMS (DART-MS): m/z calcd for $C_{13}H_{20}NO_2$ $[M+H]^+$: 222.1489, found 222.1486.

IR: 2932, 2835, 1637, 1583, 1486, 1396, 1260, 1144, 780, 700 (cm^{-1}).

N,*N*-Dimethyl-3-(*p*-tolyl)butanamide (**12**)



Clear oil. 95 mg, 31% yield.

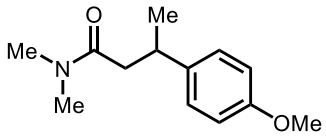
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.17 – 7.12 (m, 2H), 7.12 – 7.08 (m, 2H), 3.32 (h, J = 6.9 Hz, 1H), 2.90 (s, 3H), 2.88 (s, 3H), 2.59 (dd, J = 15.0, 6.1 Hz, 1H), 2.50 (dd, J = 15.0, 8.2 Hz, 1H), 2.31 (s, 3H), 1.31 (d, J = 6.9 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 172.0, 143.8, 135.8, 129.2, 126.8, 42.1, 37.4, 36.2, 35.5, 21.8, 21.1.

HRMS (DART-MS): m/z calcd for $C_{13}H_{20}NO$ $[M+H]^+$: 206.1539, found 206.1536.

IR: 2925, 1638, 1514, 1455, 1395, 1264, 1143, 1017, 816, 721 (cm^{-1}).

3-(4-Methoxyphenyl)-*N*,*N*-dimethylbutanamide (**13**)



Light yellow oil. 135 mg, 41% yield.

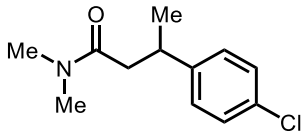
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.16 (d, J = 8.7 Hz, 2H), 6.83 (d, J = 8.7 Hz, 2H), 3.78 (s, 3H), 3.32 (h, J = 7.0 Hz, 1H), 2.89 (s, 3H), 2.87 (s, 3H), 2.58 (dd, J = 14.9, 6.5 Hz, 1H), 2.49 (dd, J = 14.9, 7.9 Hz, 1H), 1.30 (d, J = 7.0 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 172.0, 158.1, 138.8, 127.9, 113.9, 55.4, 42.2, 37.5, 35.9, 35.5, 21.9.

HRMS (DART-MS): m/z calcd for $C_{13}H_{20}NO_2$ $[M+H]^+$: 222.1489, found 222.1488.

IR: 2957, 1636, 1511, 1369, 1244, 1264, 1178, 1035, 830, 703 (cm^{-1}).

3-(4-Chlorophenyl)-*N*,*N*-dimethylbutanamide (**14**)



White solid. 140 mg, 41% yield.

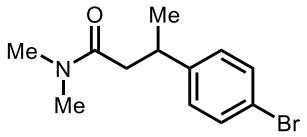
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 (d, J = 8.3 Hz, 2H), 7.20 (d, J = 8.3 Hz, 2H), 3.38 (h, J = 7.0 Hz, 1H), 2.92 (s, 6H), 2.60 (dd, J = 15.2, 6.7 Hz, 1H), 2.52 (dd, J = 15.2, 7.5 Hz, 1H), 1.32 (d, J = 6.9 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 171.5, 145.2, 131.9, 128.6, 128.4, 41.8, 37.4, 36.0, 35.6, 21.8.

HRMS (DART-MS): m/z calcd for $C_{12}H_{17}NOCl$ $[M+H]^+$: 226.0993, found 226.0991.

IR: 2960, 1638, 1492, 1396, 1263, 1144, 1092, 1012, 825, 719 (cm^{-1}).

3-(4-Bromophenyl)-*N*,*N*-dimethylbutanamide (**15**)



Light yellow solid. 121 mg, 30% yield.

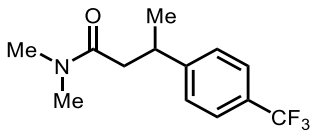
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (d, J = 8.5 Hz, 2H), 7.12 (d, J = 8.2 Hz, 2H), 3.35 (h, J = 7.0 Hz, 1H), 2.89 (s, 6H), 2.57 (dd, J = 15.2, 6.6 Hz, 1H), 2.49 (dd, J = 15.2, 7.5 Hz, 1H), 1.30 (d, J = 7.0 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 171.5, 145.8, 131.6, 128.8, 120.0, 41.7, 37.4, 36.0, 35.6, 21.8.

HRMS (DART-MS): m/z calcd for $C_{12}H_{17}NOBr$ $[M+H]^+$: 270.0488, found 270.0484.

IR: 2960, 2929, 1637, 1488, 1396, 1263, 1106, 1008, 821, 716 (cm^{-1}).

N,*N*-Dimethyl-3-[4-(trifluoromethyl)phenyl]butanamide (**16**)



White solid. 140 mg, 36% yield.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 (d, J = 8.0 Hz, 2H), 7.36 (d, J = 8.0 Hz, 2H), 3.45 (h, J = 7.0 Hz, 1H), 2.91 (s, 6H), 2.62 (dd, J = 15.4, 6.7 Hz, 1H), 2.54 (dd, J = 15.4, 7.5 Hz, 1H), 1.33 (d, J = 7.0 Hz, 3H).

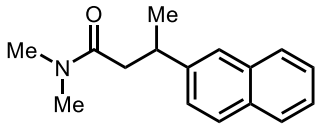
^{13}C NMR (126 MHz, $CDCl_3$) δ 171.3, 150.9 (d, J = 1.5 Hz), 128.6 (q, J = 32.3 Hz), 127.4, 125.5 (q, J = 3.8 Hz), 124.4 (q, J = 273.4 Hz), 41.5, 37.4, 36.4, 35.6, 21.8.

^{19}F NMR (470 MHz, $CDCl_3$) δ -62.4.

HRMS (DART-MS): m/z calcd for $C_{13}H_{17}NOF_3$ $[M+H]^+$: 260.1257, found 260.1254.

IR: 2933, 1641, 1496, 1398, 1323, 1266, 1160, 1111, 1066, 840, 733 (cm^{-1}).

N,*N*-Dimethyl-3-(naphthalen-2-yl)butanamide (**17**)



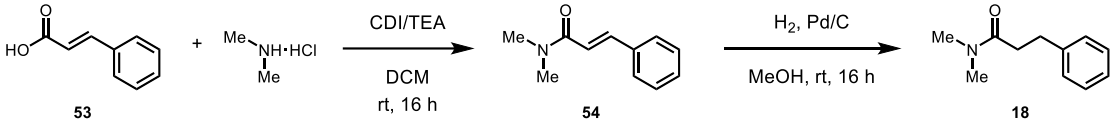
White solid. 146 mg, 40% yield.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 – 7.77 (m, 3H), 7.68 (d, J = 1.7 Hz, 1H), 7.48 – 7.39 (m, 3H), 3.55 (h, J = 6.9 Hz, 1H), 2.90 (s, 3H), 2.88 (s,3H), 2.72 (dd, J = 15.0, 6.2 Hz, 1H), 2.60 (dd, J = 15.0, 7.9 Hz, 1H), 1.43 (d, J = 6.9 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 171.8, 144.2, 133.7, 132.4, 128.1, 127.8, 127.7, 126.0, 125.9, 125.4, 125.0, 41.9, 37.5, 36.7, 35.6, 21.8.

HRMS (DART-MS): m/z calcd for $C_{16}H_{20}NO$ $[M+H]^+$: 242.1539, found 242.1537.

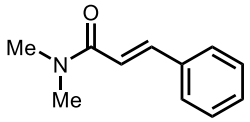
IR: 2926, 1632, 1491, 1370, 1269, 1143, 1010, 826, 751 (cm^{-1}).



To a stirred solution of cinnamic acid **53** (740 mg, 5 mmol, 1 equiv) in dry DCM (10 mL) was added carbonyldiimidazole (CDI, 972 mg, 6 mmol, 1.2 equiv) under N_2 atmosphere and the reaction mixture was stirred at room temperature for 1 hour. Dimethylamine hydrochloride (530 mg, 6.5 mmol, 1.3 equiv) and triethylamine (760 mg, 1.5 equiv) were added to the reaction mixture, and the mixture was further stirred at room temperature for 16 hours. After completion of the reaction, the reaction mixture was diluted with DCM (20 mL), washed with aqueous 1 M HCl (20 mL), saturated aqueous $NaHCO_3$ (30 mL) and brine (30 mL). The organic layer was collected and dried over Na_2SO_4, filtered and concentrated to give crude product **54**, which was purified by flash chromatography (EtOAc/Hexanes, 40%, *v*/*v*).

The *N*,*N*-dimethylcinnamamide **54** (350 mg, 2 mmol) was dissolved in MeOH (10 mL), followed by the addition of Pd/C (10 wt%, 20 mg), and the reaction was stirred under H_2 atmosphere (balloon) for 16 h at room temperature. After completion of the reaction, the reaction mixture was filtered through Celite and washed with MeOH (5 mL). The filtrate was concentrated under vacuum to provide the product **18**.

N,*N*-Dimethylcinnamamide (**54**)



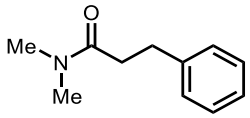
White solid. 620 mg, 71% yield.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (d, J = 15.4 Hz, 1H), 7.57 – 7.52 (m, 2H), 7.42 – 7.34 (m, 3H), 6.91 (d, J = 15.4 Hz, 1H), 3.19 (s, 3H), 3.10 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 166.8, 142.4, 135.5, 129.6, 128.9, 127.9, 117.6, 37.5, 36.0.

The NMR spectra is in agreement with published data.[27]

N,*N*-Dimethyl-3-phenylpropanamide (**18**)

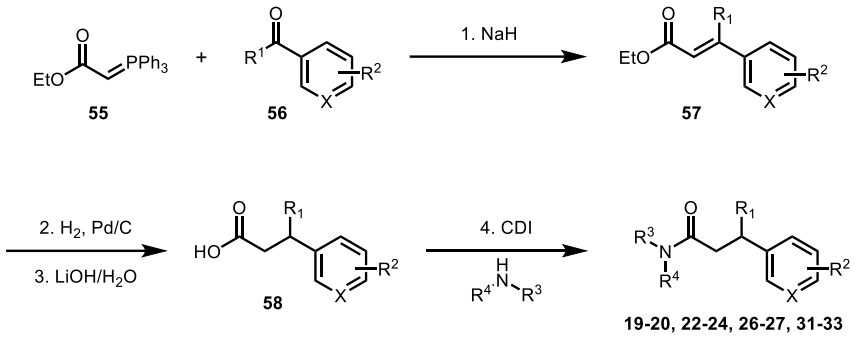


Clear oil. 310 mg, 87% yield.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 – 7.27 (m, 2H), 7.24 – 7.18 (m, 3H), 2.97 (t, J = 7.7 Hz, 2H), 2.95 (s, 3H), 2.93 (s,3H), 2.62 (t, J = 7.7 Hz, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 172.3, 141.6, 128.6, 128.6, 126.2, 37.3, 35.6, 35.4, 31.5.

The NMR spectra is in agreement with published data.[28]



General procedure. In a round bottle flask equipped with a stir bar under nitrogen was charged with the 60% NaH in mineral oil (7.5 mmol, 300 mg, 1.5 equiv) and ethyl (triphenylphosphoranylidene)acetate **55** (7.5 mmol, 2.61 g, 1.5 equiv) in dry THF (25 mL) and cooled to 0 °C. Acetophenone derivatives **56** (5 mmol, 1 equiv) are dissolved in dry THF (5 mL) and added dropwise to the reaction and stirred the resulting mixture overnight at room temperature. Upon completion, the reaction mixture was filtered, and the filtrate was concentrated under vacuum. The residue was purified by silica gel column chromatography to afford the ester products **57** (82~95% yield).

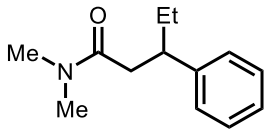
The ester **57** was dissolved in MeOH (10 mL), followed by the addition of Pd/C (10 wt%, 30 mg), and the reaction was stirred under H_2 atmosphere (balloon) for 16 hours at room temperature. After completion of the reaction, the reaction mixture was filtered through Celite and washed with MeOH (5 mL). The filtrate was concentrated under vacuum to provide the crude product, which was purified by flash chromatography (EtOAc/Hexanes, 50%, *v*/*v*).

In a round bottle flask equipped with a stir bar was charged with the hydrogenation products from the previous step. Aqueous LiOH (1 M, 50 mL) and THF (10% v/v) were added via syringe. The reaction mixture was allowed to stir at room temperature overnight. Upon completion as determined by TLC

analysis, concentrated HCl was added (until pH = 1) under ice-bath. The aqueous layer was extracted with DCM (35 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated to give crude product. The residue was purified by silica gel column chromatography to afford the free acid product **58** (90~95% yield).

To a stirred solution of acid **58** (5 mmol, 1 equiv) in dry DCM (30 mL) was added carbonyldiimidazole (CDI, 892 mg, 5.5 mmol, 1.1 equiv) under N_2 atmosphere and the reaction mixture was stirred at room temperature for 1 hour. Amine (6.5 mmol, 1.3 equiv) was added to the reaction mixture, and the mixture was further stirred at room temperature for 16 hours. After completion of the reaction, the reaction mixture was washed with aqueous 1 M HCl (30 mL), saturated aqueous $NaHCO_3$ (30 mL) and brine (30 mL). The organic layer was collected and dried over Na_2SO_4, filtered, and concentrated to give crude product. Then it was purified by silica gel column chromatography to afford the amide product (65~95% yield).

N,N-Dimethyl-3-phenylpentanamide (**19**)



Colorless oil. 234 mg, 42% yield.

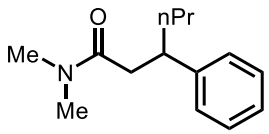
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 – 7.25 (m, 2H), 7.23 – 7.16 (m, 3H), 3.18 – 2.99 (m, 1H), 2.87 (s, 3H), 2.84 (s, 3H), 2.64 – 2.51 (m, 2H), 1.86 – 1.73 (m, 1H), 1.68 – 1.55 (m, 1H), 0.79 (t, J = 7.3 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 171.9, 144.8, 128.3, 127.7, 126.2, 44.1, 40.5, 37.3, 35.4, 28.8, 12.1.

HRMS (DART-MS): m/z calcd for $C_{13}H_{20}NO$ $[M+H]^+$: 206.1539, found 206.1537.

IR: 3026, 2960, 1638, 1493, 1452, 1395, 1264, 1142, 1076, 700 (cm^{-1}).

N,N-Dimethyl-3-phenylhexanamide (**20**)



White solid. 198 mg, 38% yield.

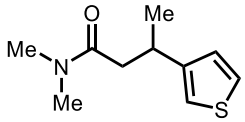
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 – 7.24 (m, 2H), 7.23 – 7.14 (m, 3H), 3.23 – 3.12 (m, 1H), 2.87 (s, 3H), 2.83 (s, 3H), 2.57 (h, J = 7.8, 7.4 Hz, 2H), 1.76 – 1.67 (m, 1H), 1.65 – 1.54 (m, 1H), 1.26 – 1.08 (m, 2H), 0.84 (t, J = 7.3 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 171.9, 145.0, 128.3, 127.6, 126.2, 42.1, 40.8, 38.1, 37.3, 35.4, 20.7, 14.0.

HRMS (DART-MS): m/z calcd for $C_{14}H_{22}NO$ $[M+H]^+$: 220.1696, found 220.1694.

IR: 2965, 2924, 1630, 1494, 1450, 1420, 1394, 1360, 1335, 1147, 772, 735 (cm^{-1}).

N,N-Dimethyl-3-(thiophen-3-yl)butanamide (**22**)



Colorless oil. 135 mg, 40% yield.

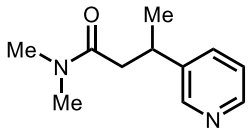
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 – 7.24 (m, 1H), 7.04 – 6.98 (m, 2H), 3.51 (h, J = 6.9 Hz, 1H), 2.94 (s, 3H), 2.90 (s, 3H), 2.63 (dd, J = 14.9, 6.2 Hz, 1H), 2.49 (dd, J = 15.0, 7.9 Hz, 1H), 1.35 (d, J = 6.9 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 171.7, 147.5, 126.9, 125.4, 119.2, 41.7, 37.3, 35.5, 32.0, 21.4.

HRMS (DART-MS): m/z calcd for $C_{10}H_{16}NOS$ $[M+H]^+$: 198.0947, found 198.0946.

IR: 2966, 1629, 1457, 1398, 1320, 1265, 1140, 1100, 1061, 953, 961, 777, 654 (cm^{-1}).

N,N-Dimethyl-3-(pyridin-3-yl)butanamide (**23**)



Yellow oil. 98 mg, 16% yield.

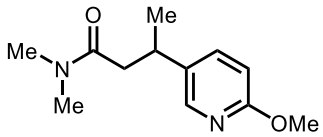
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (d, J = 30.9 Hz, 2H), 7.54 (d, J = 7.8 Hz, 1H), 7.19 (dd, J = 7.9, 4.7 Hz, 1H), 3.38 (h, J = 7.1 Hz, 1H), 2.89 (s, 3H), 2.87 (s, 3H), 2.63 – 2.45 (m, 2H), 1.31 (d, J = 7.0 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 171.0, 148.7, 147.7, 141.8, 134.6, 123.4, 41.3, 37.2, 35.4, 34.1, 21.6.

HRMS (DART-MS): m/z calcd for $C_{11}H_{17}N_2O$ $[M+H]^+$: 193.1335, found 193.1333.

IR: 2962, 1698, 1637, 1575, 1396, 1329, 1262, 1146, 1107, 716, 657 (cm^{-1}).

3-(6-Methoxypyridin-3-yl)-*N,N*-dimethylbutanamide (**24**)



Colorless oil. 112 mg, 34% yield.

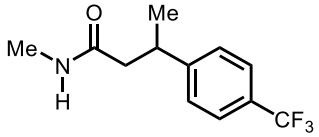
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01 – 7.89 (m, 1H), 7.47 – 7.33 (m, 1H), 6.60 (dd, J = 8.6, 1.6 Hz, 1H), 3.82 (s, 3H), 3.26 (h, J = 7.0 Hz, 1H), 2.84 (s, 3H), 2.82 (s, 3H), 2.54 – 2.37 (m, 2H), 1.22 (d, J = 7.0 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 171.2, 162.8, 144.9, 137.5, 134.4, 110.4, 53.2, 41.5, 37.2, 35.3, 33.2, 21.7.

HRMS (DART-MS): m/z calcd for $C_{12}H_{19}N_2O_2$ $[M+H]^+$: 223.1440, found 223.1431.

IR: 2945, 1699, 1639, 1606, 1573, 1490, 1393, 1325, 1285, 1144, 1062, 830 (cm^{-1}).

N-Methyl-3-[4-(trifluoromethyl)phenyl]butanamide (**26**)



White solid. 150 mg, 42% yield.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 (d, J = 8.0 Hz, 2H), 7.33 (d, J = 8.0 Hz, 2H), 5.41 (brs, 1H), 3.40 (h, J = 7.1 Hz, 1H), 2.72 (d, J = 4.8 Hz, 3H), 2.47 – 2.31 (m, 2H), 1.31 (d, J = 6.9 Hz, 3H).

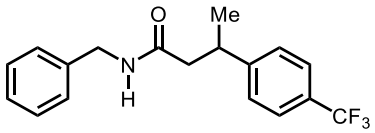
^{13}C NMR (126 MHz, $CDCl_3$) δ 171.7, 150.1, 128.7 (q, J = 32.3 Hz), 127.2, 125.5 (q, J = 3.8 Hz), 124.2 (q, J = 271.7 Hz), 45.2, 36.6, 26.3, 21.4.

^{19}F NMR (470 MHz, $CDCl_3$) δ -62.2.

HRMS (DART-MS): m/z calcd for $C_{12}H_{15}F_3NO$ $[M+H]^+$: 246.1100, found 246.1099.

IR: 3306, 2964, 1637, 1560, 1330, 1286, 1216, 1183, 1156, 1111, 897 (cm^{-1}).

N-Benzyl-3-[4-(trifluoromethyl)phenyl]butanamide (**27**)



White solid. 122 mg, 29% yield.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (d, J = 8.0 Hz, 2H), 7.35 (d, J = 8.0 Hz, 2H), 7.31 – 7.22 (m, 3H), 7.11 – 6.97 (m, 2H), 5.71 (brs, 1H), 4.42 (dd, J = 14.8, 6.1 Hz, 1H), 4.28 (dd, J = 14.8, 5.3 Hz, 1H), 3.45 (h, J = 7.2 Hz, 1H), 2.51 (dd, J = 14.1, 6.9 Hz, 1H), 2.45 (dd, J = 14.1, 8.2 Hz, 1H), 1.35 (d, J = 7.0 Hz, 3H).

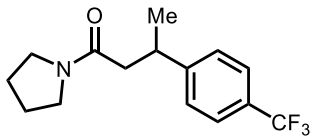
^{13}C NMR (126 MHz, $CDCl_3$) δ 170.9, 149.8 (d, J = 1.5 Hz), 138.0, 130.9 (q, J = 3.7 Hz), 128.7, 127.6, 127.5, 127.3, 125.5 (q, J = 3.7 Hz), 124.3 (d, J = 271.8 Hz), 45.4, 43.5, 36.9, 21.6.

^{19}F NMR (470 MHz, $CDCl_3$) δ -62.3.

HRMS (DART-MS): m/z calcd for $C_{18}H_{19}F_3NO$ $[M+H]^+$: 322.1413, found 322.1412.

IR: 3258, 3080, 2980, 1644, 1564, 1496, 1366, 1175, 1152, 1116, 1014 (cm^{-1}).

1-(Pyrrolidin-1-yl)-3-[4-(trifluoromethyl)phenyl]butan-1-one (**31**)



Colorless oil. 166 mg, 41% yield.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (d, J = 8.1 Hz, 2H), 7.30 (d, J = 8.1 Hz, 2H), 3.45 – 3.21 (m, 4H), 3.18 – 3.05 (m, 1H), 2.46 (h, J = 7.8, 7.4 Hz, 2H), 1.88 – 1.59 (m, 4H), 1.26 (d, J = 7.0 Hz, 3H).

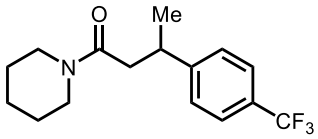
^{13}C NMR (126 MHz, $CDCl_3$) δ 169.6, 150.8, 128.3 (q, J = 32.2 Hz), 127.3, 125.2 (q, J = 3.8 Hz), 124.5 (q, J = 271.7 Hz), 46.5, 45.5, 42.9, 36.0, 25.9, 24.2, 21.4.

^{19}F NMR (470 MHz, $CDCl_3$) δ -62.4.

HRMS (DART-MS): m/z calcd for $C_{15}H_{19}F_3NO$ $[M+H]^+$: 286.1413, found 286.1406.

IR: 2969, 2876, 1627, 1436, 1325, 1155, 1114, 1066, 1014, 840, 637 (cm^{-1}).

1-(Piperidin-1-yl)-3-[4-(trifluoromethyl)phenyl]butan-1-one (**32**)



Colorless oil. 145 mg, 38% yield.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 (d, J = 8.1 Hz, 2H), 7.36 (d, J = 8.0 Hz, 2H), 3.59 – 3.51 (m, 1H), 3.50 – 3.39 (m, 2H), 3.36 – 3.23 (m, 2H), 2.62 (dd, J = 15.1, 6.8 Hz, 1H), 2.53 (dd, J = 15.1, 7.5 Hz, 1H), 1.63 – 1.55 (m, 2H), 1.54 – 1.42 (m, 3H), 1.36 – 1.29 (m, 4H).

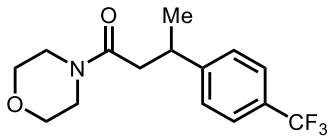
^{13}C NMR (126 MHz, $CDCl_3$) δ 169.6, 150.8, 150.8, 128.53 (q, J = 32.3 Hz), 127.3, 125.40 (q, J = 3.8 Hz), 124.5 (q, J = 271.7 Hz), 46.5, 45.5, 42.9, 36.0, 25.9, 24.2, 21.4.

^{19}F NMR (470 MHz, $CDCl_3$) δ -62.4.

HRMS (DART-MS): m/z calcd for $C_{16}H_{21}F_3NO$ $[M+H]^+$: 300.1570, found 300.1565.

IR: 2936, 2857, 1634, 1438, 1323, 1267, 1217, 1160, 1112, 1067, 837 (cm^{-1}).

1-Morpholino-3-[4-(trifluoromethyl)phenyl]butan-1-one (**33**)



Colorless oil. 151 mg, 37% yield.

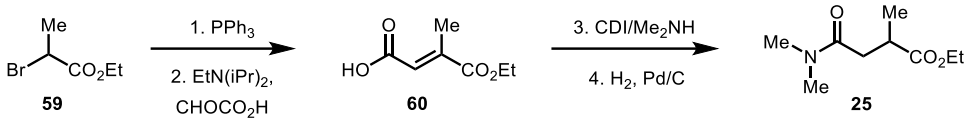
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 (d, J = 8.0 Hz, 2H), 7.34 (d, J = 7.9 Hz, 2H), 3.66 – 3.49 (m, 5H), 3.47 – 3.35 (m, 3H), 3.34 – 3.24 (m, 1H), 2.61 (dd, J = 15.2, 7.0 Hz, 1H), 2.52 (dd, J = 15.2, 7.3 Hz, 1H), 1.33 (d, J = 7.0 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 169.8, 150.4, 128.7 (q, J = 32.3 Hz), 127.3, 125.5 (q, J = 3.8 Hz), 124.2 (q, J = 271.9 Hz), 66.9, 66.5, 46.1, 41.9, 40.9, 36.4, 21.7.

^{19}F NMR (470 MHz, $CDCl_3$) δ -62.4.

HRMS (DART-MS): m/z calcd for $C_{15}H_{19}F_3NO_2$ $[M+H]^+$: 302.1362, found 302.1360.

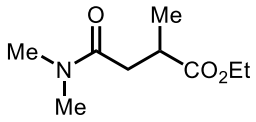
IR: 2966, 2858, 1638, 1421, 1360, 1324, 1273, 1161, 1110, 1015, 840 (cm^{-1}).



(*E*)-4-ethoxy-3-methyl-4-oxobut-2-enoic acid **60** was prepared according to the published procedure.[29] To a stirred solution of acid **60** (475 mg, 3 mmol, 1 equiv) in dry DCM (15 mL) was added carbonyldiimidazole (CDI, 535 mg, 3.3 mmol, 1.1 equiv) under N_2 atmosphere and the reaction mixture was stirred at room temperature for 1 hour. Dimethylamine solution (1.95 mL, 2 M in THF, 3.9 mmol, 1.3 equiv) was added to the reaction mixture, and the mixture was further stirred at room temperature for 16 hours. After completion of the reaction, the reaction mixture was washed with aqueous 1 M HCl (15 mL), saturated aqueous $NaHCO_3$ (20 mL) and brine (20 mL). The organic layer was collected and dried over Na_2SO_4, filtered and concentrated to give crude amide product, which was used in the next step.

The crude material was dissolved in MeOH (10 mL), followed by the addition of Pd/C (10 wt%, 20 mg), and the reaction was stirred under H_2 atmosphere (balloon) for 16 hours at room temperature. After completion of the reaction, the reaction mixture was filtered through Celite and washed with MeOH (5 mL). The filtrate was concentrated under vacuum to provide the crude product, which was purified by flash chromatography (EtOAc/Hexanes, 70%, *v*/*v*).

Ethyl 4-(dimethylamino)-2-methyl-4-oxobutanoate (**25**)



Clear oil. 360 mg, 65% yield over two steps.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.21 – 4.07 (m, 2H), 3.08 – 2.83 (m, 7H), 2.77 (dd, J = 16.2, 8.5 Hz, 1H), 2.31 (dd, J = 16.2, 5.4 Hz, 1H), 1.25 (t, J = 7.1 Hz, 3H), 1.21 (d, J = 7.2 Hz, 3H).

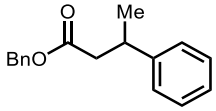
^{13}C NMR (126 MHz, $CDCl_3$) δ 176.5, 171.1, 60.6, 37.2, 36.8, 36.1, 35.5, 17.6, 14.3.

HRMS (DART-MS): m/z calcd for $C_9H_{18}NO_3$ $[M+H]^+$: 188.1281, found 188.1291.

IR: 2980, 1729, 1644, 1461, 1398, 1372, 1176, 1149, 1025, 805, 755 (cm^{-1}).

General procedure. To a stirred solution of acid **61** (1 mmol, 1 equiv) in dry DCM (10 mL) was added thionyl chloride (2 mmol, 236 mg) and one drop of DMF under N_2 atmosphere and the reaction mixture was stirred at room temperature for 3 hours. The solvent was evaporated to provide acid chloride, which was directly used in the next step. The resulting crude oil was dissolved in dry DCM (10 mL), triethylamine (121 mg, 1.2 mmol, 1.2 equiv) and benzyl alcohol (130 mg, 1.2 mmol, 1.2 equiv) were added at 0 °C, and the reaction mixture was further stirred at room temperature for 16 hours. After completion of the reaction, the reaction mixture was washed with aqueous 1 M HCl (10 mL), saturated aqueous $NaHCO_3$ (10 mL) and brine (10 mL). The organic layer was collected and dried over Na_2SO_4, filtered and concentrated to give crude ester product, which was purified by flash chromatography (EtOAc/Hexanes, 20%, *v*/*v*).

Benzyl 3-phenylbutanoate (**34**)



Colorless oil. 95 mg, 37% yield.

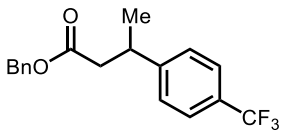
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 – 7.16 (m, 10H), 5.08 (s, 2H), 3.33 (h, J = 7.2 Hz, 1H), 2.75 – 2.58 (m, 2H), 1.33 (d, J = 7.0 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 172.2, 145.6, 135.9, 128.5, 128.5, 128.2, 126.8, 126.4, 66.2, 42.9, 36.6, 21.9. The NMR spectra is in agreement with published data.[30]

HRMS (DART-MS): m/z calcd for $C_{17}H_{18}O_2$ $[M+H]^+$: 255.1379, found 255.1378.

IR: 2980, 2253, 1731, 1456, 1380, 1265, 1161, 1086, 904, 727 (cm^{-1}).

Benzyl 3-[4-(trifluoromethyl)phenyl]butanoate (**35**)



Colorless oil. 104 mg, 32% yield.

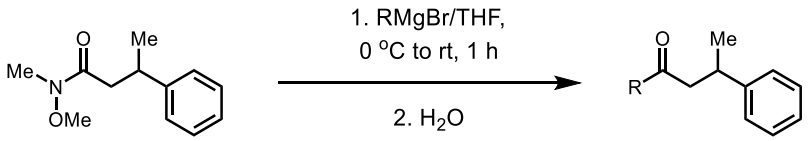
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (d, J = 8.1 Hz, 2H), 7.38 – 7.31 (m, 5H), 7.24 (dd, J = 6.6, 2.7 Hz, 2H), 5.08 (s, 2H), 3.39 (h, J = 7.2 Hz, 1H), 2.76 – 2.62 (m, 2H), 1.34 (d, J = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 171.7, 149.5, 135.7, 128.8 (q, J = 32.4 Hz), 128.5, 128.3, 128.2, 127.2, 125.5 (q, J = 3.8 Hz), 124.2 (q, J = 271.8 Hz), 66.3, 42.5, 36.5, 21.9.

^{19}F NMR (470 MHz, $CDCl_3$) δ -62.4.

HRMS (DART-MS): m/z calcd for $C_{18}H_{17}O_2F_3$ $[M+H]^+$: 323.1253, found 323.1253.

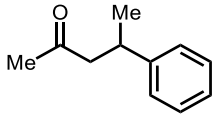
IR: 2970, 1731, 1619, 1498, 1456, 1421, 1324, 1161, 1115, 907, 729 (cm^{-1}).



29 **36-37**

To a stirred solution of Weinreb amide **29** (0.4 mmol, 1.0 equiv) in dry THF (5 mL) was added Grignard reagent (MeMgBr or PhMgBr, 0.44 mmol, 1.1 equiv) dropwise at 0 °C. The reaction mixture was allowed to stir at room temperature for 1 hour. After completion of the reaction, the reaction mixture was quenched with saturated aqueous NH_4Cl followed by extraction with Et_2O (3 x 10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated to give the crude product, which was purified by flash chromatography (EtOAc/Hexanes, 10%, *v*/*v*).

4-Phenylpentan-2-one (**36**)



Clear oil. 45 mg, 69% yield.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 – 7.14 (m, 5H), 3.31 (h, J = 7.0 Hz, 1H), 2.76 (dd, J = 16.3, 6.5 Hz, 1H), 2.66 (dd, J = 16.3, 7.8 Hz, 1H), 2.07 (s, 3H), 1.27 (d, J = 6.9 Hz, 3H).

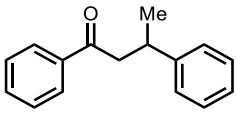
^{13}C NMR (126 MHz, $CDCl_3$) δ 208.0, 146.3, 128.7, 126.9, 126.5, 52.1, 35.6, 30.7, 22.1.

The NMR spectra is in agreement with published data.[6]

HRMS (DART-MS): m/z calcd for $C_{11}H_{15}O$ $[M+H]^+$: 163.1117, found 163.1116.

IR: 2962, 1714, 1494, 1452, 1357, 1161, 1025, 758, 699 (cm^{-1}).

1,3-Diphenylbutan-1-one (**37**)



Light yellow solid. 60 mg, 67% yield.

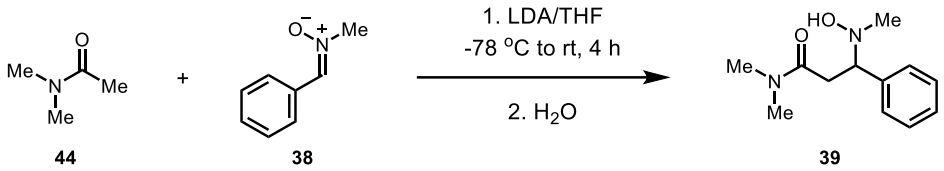
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94 (dd, J = 8.3, 1.4 Hz, 2H), 7.58 – 7.53 (m, 1H), 7.48 – 7.42 (m, 2H), 7.34 – 7.27 (m, 4H), 7.24 – 7.18 (m, 1H), 3.52 (h, J = 6.9 Hz, 1H), 3.31 (dd, J = 16.5, 5.7 Hz, 1H), 3.20 (dd, J = 16.5, 8.4 Hz, 1H), 1.36 (d, J = 6.9 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 199.2, 146.7, 137.3, 133.1, 128.7, 128.7, 128.2, 127.0, 126.4, 47.2, 35.7, 22.0.

The NMR spectra is in agreement with published data.[31]

HRMS (DART-MS): m/z calcd for $C_{16}H_{17}O$ $[M+H]^+$: 225.1274, found 225.1275.

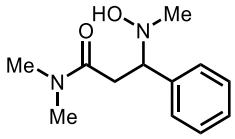
IR: 2970, 1662, 1597, 1581, 1449, 1270, 1202, 990, 753, 690 (cm^{-1}).



44 38 39

To a stirred solution of *N*,*N*-dimethylacetamide **44** (261 mg, 3 mmol, 1.5 equiv) in dry THF (5 mL) was added lithium diisopropylamide (LDA, 3 mmol, 1.5 equiv) under N_2 atmosphere and cooling with dry ice/acetone bath, the reaction mixture was stirred at -78 ºC for 20 min. *C*-Phenyl-*N*-methyl-nitrone **38** (270 mg, 1 mmol, 1 equiv) was added to the reaction mixture, the mixture was then warmed up to room temperature and further stirred for 4 hours. After completion of the reaction, the reaction mixture was quenched with saturated NH_4Cl aqueous solution, and then the organic solvents were evaporated under reduced pressure. The resulting mixture was extracted with DCM and washed with brine. The organic layer was collected and dried over Na_2SO_4, filtered and concentrated to give crude product **39**, which was purified by flash chromatography (MeOH/DCM, 5%, *v*/*v*).

3-[Hydroxy(methyl)amino]-*N*,*N*-dimethyl-3-phenylpropanamide (**39**)



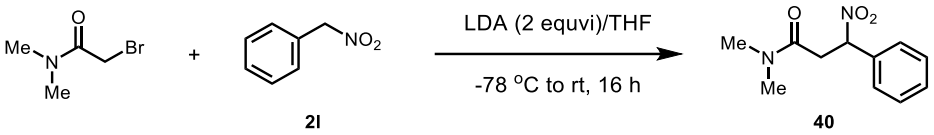
White solid. 240 mg, 54% yield.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 – 7.26 (m, 5H), 6.30 (s, 1H), 4.07 (t, J = 6.1 Hz, 1H), 3.10 (dd, J = 15.0, 6.3 Hz, 1H), 2.91 (s, 3H), 2.85 – 2.76 (m, 4H), 2.50 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 171.6, 128.6, 128.4, 127.9, 70.7, 46.3, 38.3, 37.6, 35.7.

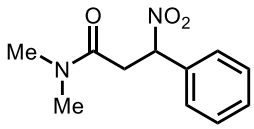
HRMS (DART-MS): m/z calcd for $C_{12}H_{19}N_2O_2$ $[M+H]^+$: 223.1441, found 223.1439.

IR: 2964, 2876, 1634, 1394, 1142, 1046, 837, 778, 617 (cm^{-1}).



To a stirred solution of (nitromethyl)benzene **2l** (69 mg, 0.5 mmol, 1 equiv) in dry THF (2 mL) was added lithium diisopropylamide (LDA, 1 mmol, 2 equiv) under N_2 atmosphere and cooling with dry ice/acetone bath, the reaction mixture was stirred at -78 °C for 1 hour. 2-Bromo-*N*,*N*-dimethylacetamide (83 mg, 0.5 mmol, 1 equiv) was added to the reaction mixture, the mixture was then warmed up to room temperature and further stirred for 16 hours. After completion of the reaction, the reaction mixture was quenched with acetic acid (120 mg, 4 equiv). Solvents were evaporated under reduced pressure to give a crude oil, which was purified by flash chromatography (EtOAc/Hexanes, 50%, *v*/*v*).

N,*N*-Dimethyl-3-nitro-3-phenylpropanamide (**40**)



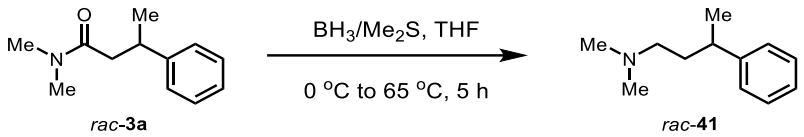
Light yellow oil. 25 mg, 23% yield.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 – 7.36 (m, 5H), 6.05 (dd, J = 10.4, 3.4 Hz, 1H), 3.72 (dd, J = 17.0, 10.4 Hz, 1H), 3.05 (s, 3H), 2.95 (s, 3H), 2.80 (dd, J = 17.0, 3.5 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 168.1, 134.7, 130.0, 129.3, 127.5, 86.6, 37.6, 37.1, 35.6.

HRMS (DART-MS): m/z calcd for $C_{11}H_{14}NO$ $[M\text{-}HNO_2+H]^+$: 176.1070, found 176.1069.

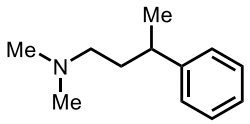
IR: 2933, 1642, 1549, 1497, 1419, 1369, 1266, 1146, 860, 719, 695 (cm^{-1}).



rac-**3a** *rac*-**41**

To a stirred solution of *N*,*N*-Dimethyl-3-phenylbutanamide (50 mg, 0.26 mmol, 1 equiv) in dry THF (3 mL) was slowly added $BH_3 \cdot Me_2S$ (2 M solution in THF, 0.39 mL, 0.78 mmol, 3 equiv) under N_2 atmosphere and cooling with an ice bath. The reaction mixture was allowed to warm up to room temperature and then stirred at 65 °C for 5 hours. After completion of the reaction, the reaction mixture was quenched with saturated NH_4Cl aqueous solution (10 mL) and extracted with EtOAc (3 x 15 mL). The organic layer was collected and dried over Na_2SO_4, filtered and concentrated to give the crude product, which was purified by preparative thin layer chromatography (EtOAc/Hexanes, 20%, *v*/*v*).

N,*N*-Dimethyl-3-phenylbutan-1-amine (*rac*-**41**)



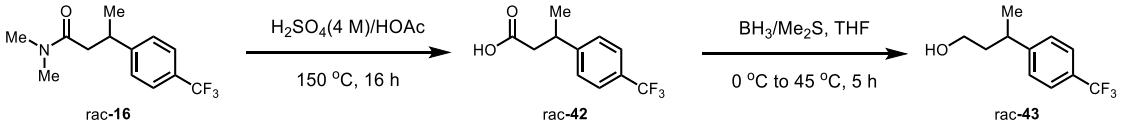
Clear oil. 35 mg, 76% yield.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 (t, J = 7.6 Hz, 2H), 7.24 – 7.16 (m, 3H), 2.78 – 2.62 (m, 2H), 2.55 – 2.49 (m, 1H), 2.51 (s, 3H), 2.50 (s, 3H), 2.09 – 1.96 (m, 2H), 1.30 (d, J = 7.0 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 145.9, 128.8, 126.9, 126.6, 63.5, 51.9, 51.2, 38.5, 32.0, 23.0.

HRMS (DART-MS): m/z calcd for $C_{12}H_{20}N$ $[M+H]^+$: 178.1590, found 178.1592.

IR: 2969, 1630, 1494, 1453, 1378, 1246, 1166, 1024, 763, 701 (cm^{-1}).



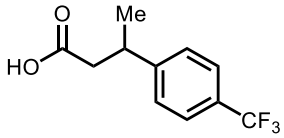
rac-**16** rac-**42** rac-**43**

Adapted from the method by A. Link *et al*.[7] The amide *rac*-**16** (130 mg, 0.5 mmol) was dissolved in 2 mL of mixed acid solution (1 mL of 4 M H_2SO_4 and 1 mL of acetic acid) at room temperature. The reaction mixture was stirred at 150 °C for 16 hours. After completion of the reaction, the reaction mixture was diluted with water (5 mL) and basified with saturated Na_2CO_3 solution, the mixture was extracted with DCM (5 mL). The aqueous layer was acidified using 1 M HCl to pH 2.0 and extracted with EtOAc (3 x 10 mL), the organic layers were collected and dried over Na_2SO_4, filtered and concentrated to give the acid product *rac*-**42**.

To a stirred solution of acid *rac*-**42** (52 mg, 0.2 mmol, 1 equiv) in dry THF (3 mL) was slowly added $BH_3 \cdot Me_2S$ (2 M solution in THF, 0.3 mL, 0.6 mmol, 3 equiv) under N_2 atmosphere and cooling with an ice bath. The reaction mixture was allowed to warm up to room temperature and then stirred at 45 °C for 5 hours. After completion of the reaction, the reaction mixture was quenched with saturated NH_4Cl

aqueous solution (10 mL) and extracted with EtOAc (3 x 15 mL). The organic layer was collected and dried over Na_2SO_4, filtered and concentrated to give crude product *rac*-**43**, which was purified by preparative thin layer chromatography (EtOAc/Hexanes, 50%, *v*/*v*).

3-[4-(Trifluoromethyl)phenyl]butanoic acid (*rac*-**42**)



White solid. 82 mg, 71% yield.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (d, J = 8.1 Hz, 2H), 7.34 (d, J = 8.0 Hz, 2H), 3.34 (h, J = 7.2 Hz, 1H), 2.65 (qd, J = 15.9, 7.5 Hz, 2H), 1.33 (d, J = 7.0 Hz, 3H).

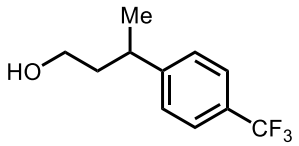
^{13}C NMR (126 MHz, $CDCl_3$) δ 177.7 (d, J = 7.4 Hz), 149.5, 129.0 (q, J = 32.4 Hz), 127.3, 125.7 (q, J = 3.8 Hz), 124.3 (q, J = 271.9 Hz), 42.2, 36.2, 21.9.

^{19}F NMR (470 MHz, $CDCl_3$) δ -62.43.

HRMS (DART-MS): m/z calcd for $C_{11}H_{12}O_2F_3$ $[M+H]^+$: 233.0784, found 233.0788.

IR: 2981, 1704, 1618, 1436, 1327, 1285, 1121, 1017, 940, 876, 836, 693 (cm^{-1}).

3-[4-(Trifluoromethyl)phenyl]butan-1-ol (*rac*-**43**)



Clear oil. 32 mg, 73% yield.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (d, J = 8.1 Hz, 2H), 7.32 (d, J = 8.0 Hz, 2H), 3.63 – 3.48 (m, 2H), 3.04 – 2.93 (m, 1H), 1.94 – 1.78 (m, 2H), 1.29 (d, J = 7.0 Hz, 3H), 1.28 (brs, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 151.1 (d, J = 1.5 Hz), 128.6 (q, J = 32.3 Hz), 127.5, 125.6 (q, J = 3.7 Hz), 124.4 (q, J = 272.1 Hz), 60.9, 40.8, 36.4, 22.2.

^{19}F NMR (470 MHz, $CDCl_3$) δ -62.3.

The NMR spectra is in agreement with published data.[8]

HRMS (DART-MS): m/z calcd for $C_{11}H_{14}OF_3$ $[M+H]^+$: 219.0991, found 219.0993.

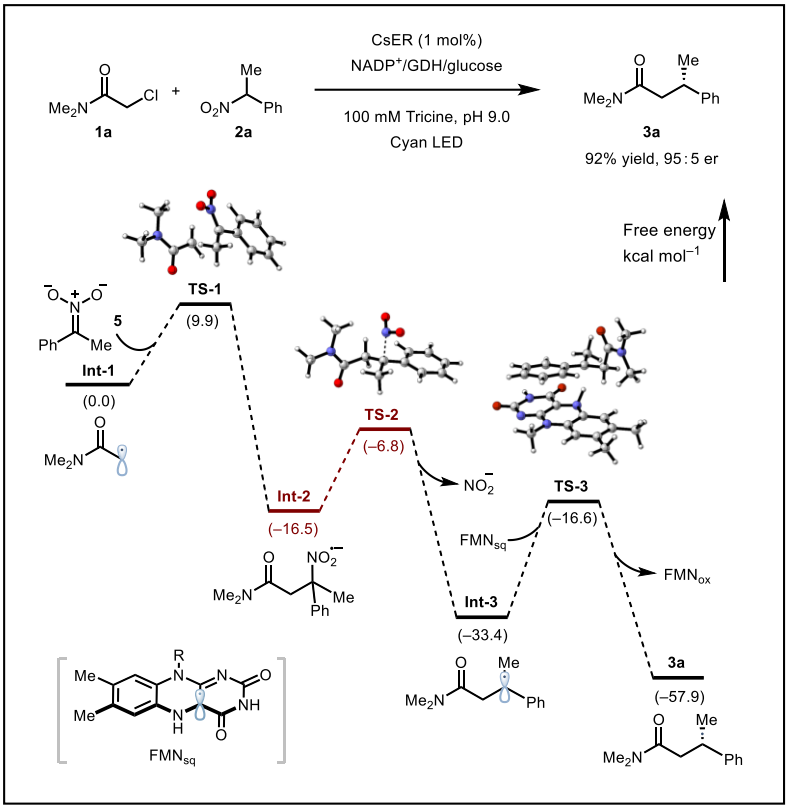
IR: 2970, 1619, 1420, 1379, 1323, 1161, 1117, 1016, 837, 606 (cm^{-1}).

Density functional theory (DFT) calculations

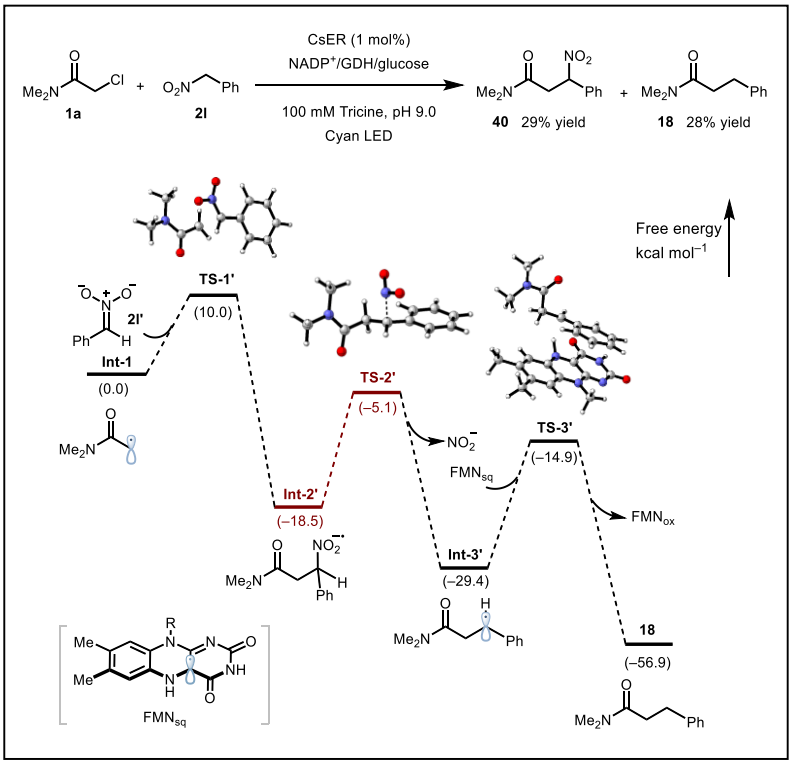
All DFT computations were carried out using the Gaussian 16, Revision C.01 program[32] and the ωB97X-D functional.[33] All structures were optimized at the ωB97X-D/6-311+G(d,p) level of theory.[33] Higher level of theory single point calculations were performed at the ωB97X-D/6-311+G(d,p) level of theory[33] with polarizable continuum model (IEFPCM) in water.[34–36] Computed structures were illustrated with CYLview20.[37] Simplified model of FMN_{sq} and FMN were used as previous computational works.[38,39]

For the photoenzymatic reactions showed in Supplementary Fig. 12 (the model reaction, α-chloroamide **1a** couple with nitroalkane **2a**) and Supplementary Fig. 13 (α-chloroamide **1a** couple with nitroalkane **2l**), the common radical species **Int-1** was initiated via SET from the photoexcited FMN_{hq} in the enzyme active-site by forming a CT complex (Supplementary Fig. 4a).[16] For the model reaction, the addition step of radical **Int-1** to nitronate **5** give rise to the key intermediate radical anion **Int-2** with a free energy barrier of 9.9 kcal mol^{-1}. Subsequently, the radical anion **Int-2** could readily undergo a rapid and irreversible C–N bond cleavage to generate a nitrite ion and a benzylic radical **Int-3** (free energy barrier 9.6 kcal/mol), which is then terminated through HAT by FMN_{sq} to provide the final product **3a** (Supplementary Fig. 12).

For the enzymatic reaction of α-chloroamide **1a** with nitroalkane **2l** (Supplementary Fig. 13), the radical addition of **Int-1** to nitronate **2l′** provide the key intermediate radical anion **Int-2′** with a free energy barrier of 10.0 kcal mol^{-1}, which is very close to that of the model reaction. Similarly, the radical anion **Int-2′** undergo irreversible C–N bond cleavage to generate a nitrite ion and a benzylic radical **Int-3′** with a free energy barrier of 13.4 kcal/mol, which is higher than that of the corresponding step (9.6 kcal/mol) in the model reaction, indicating a relative slower denitration step when compared to the model reaction. The resulting radical **Int-3′** is then quenched through HAT by FMN_{sq} to provide the cross-coupling product **18**. Alternatively, due to the relative slower denitration step of **Int-2′**, the radical anion **Int-2′** could also be partially oxidized by FMN_{sq} to provide the other product **40**.



Supplementary Fig. 12. Energy diagram of the model reaction (**1a** reacts with **2a**).



Supplementary Fig. 13. Energy diagram of **1a** reacts with **2l**.

Atomic coordinates

Note: energies reported below are in units of hartrees.

Int-1

Electronic Energy: -287.161196

Thermal correction to Enthalpy: 0.125355

Thermal correction to Gibbs Free Energy: 0.084403

C	0.78351800	-0.18928000	-0.02121800
O	1.24359700	-1.32928100	-0.01084500
N	-0.56842600	0.05163200	-0.07091100
C	-1.48471900	-1.06659600	0.04155900
H	-2.00588400	-1.05048300	1.00630100
H	-2.22917400	-1.02633600	-0.75927500
H	-0.91864900	-1.99162200	-0.03875600
C	-1.14798700	1.37964500	-0.00992800
H	-2.18246600	1.32125100	-0.35159400
H	-1.15024100	1.79001600	1.00772100
H	-0.62794000	2.07274100	-0.67275300
C	1.68714400	0.95230000	0.02901700
H	2.74273900	0.72302000	-0.01430800
H	1.37409100	1.97781900	0.16922000

5

Electronic Energy: -514.871271

Thermal correction to Enthalpy: 0.156779

Thermal correction to Gibbs Free Energy: 0.110289

C	-1.07151700	0.46059500	0.00125400
C	0.34040500	0.14796000	0.00053200
C	1.26906600	1.22324100	-0.00187800
C	0.91680500	-1.14945100	0.00229500
C	2.64122200	1.02371100	-0.00237900
H	0.90658700	2.24336700	-0.00376700
C	2.29149500	-1.33369100	0.00181400
H	0.25243000	-1.99878300	0.00396900
C	3.17811700	-0.25979300	-0.00048800
H	3.29922400	1.88896800	-0.00440000
H	2.67759300	-2.34991300	0.00333300
H	4.25186600	-0.41789600	-0.00089700
C	-1.51686600	1.89479800	0.00315800
H	-1.14891200	2.43793200	0.88538800
H	-1.15788100	2.43827100	-0.88266100
H	-2.60334500	1.92989800	0.00836300
N	-2.05503700	-0.48601400	-0.00081500
O	-1.77722800	-1.71641600	-0.00166400
O	-3.27085600	-0.13533000	-0.00202100

TS-1

Electronic Energy: -802.041681

Thermal correction to Enthalpy: 0.284632

Thermal correction to Gibbs Free Energy: 0.219639

C	-1.97042800	-1.15547200	-0.68982800
O	-2.14746300	-2.31080900	-0.27060700
N	-3.03533900	-0.26374000	-0.71932500
C	-4.23398200	-0.60611100	0.00877900
H	-4.28211600	-0.06392200	0.96462200
H	-5.12199200	-0.34258700	-0.57940900
H	-4.23225200	-1.67605300	0.20645200
C	-2.91165000	1.14388600	-1.04421000
H	-3.85568100	1.48289400	-1.48694400
H	-2.69002800	1.75067500	-0.15827100
H	-2.12361800	1.31321200	-1.77427800
C	-0.66873700	-0.71056600	-1.11987200
H	0.05926100	-1.50064800	-1.24451500
H	-0.49505800	0.21311700	-1.65365000
C	0.38699600	0.19840800	0.77964700
C	1.75504800	0.03902200	0.25911000
C	2.56003600	-0.99437900	0.77771000
C	2.32362600	0.82160200	-0.76604400
C	3.84687800	-1.22857000	0.31299100
H	2.17732700	-1.62789800	1.56715000
C	3.61222600	0.58335200	-1.22409600
H	1.73603200	1.62234700	-1.18700600
C	4.39009300	-0.44050900	-0.69460300
H	4.42881600	-2.03559200	0.74823500
H	4.01074200	1.21104900	-2.01583100
H	5.39542500	-0.62202500	-1.06066800
C	-0.11126600	-0.74419800	1.83679400
H	0.04765600	-1.77916900	1.52872800
H	0.37852400	-0.57406600	2.80570500
H	-1.17999400	-0.60310600	1.97854100
N	-0.20813900	1.44928400	0.79136800
O	0.11074000	2.32292200	-0.05638100
O	-1.14099500	1.67465900	1.60680900

Int-2

Electronic Energy: -802.087790

Thermal correction to Enthalpy: 0.287803

Thermal correction to Gibbs Free Energy: 0.223776

C	-2.06453100	-0.85551700	-0.39178700
O	-2.46795800	-1.85514100	0.18825100
N	-2.94511100	0.00605700	-1.00494100
C	-4.34725700	-0.19979700	-0.70199500
H	-4.61100200	0.25206900	0.26381700
H	-4.95311600	0.26281700	-1.48696200
H	-4.56055100	-1.26576900	-0.65200500
C	-2.62321400	1.38441700	-1.33076100
H	-3.22770900	1.69182800	-2.19237000
H	-2.80961500	2.03468900	-0.47137000
H	-1.57317300	1.49941200	-1.58454400
C	-0.57476400	-0.66576800	-0.61978300
H	-0.21436800	-1.64651900	-0.94432700
H	-0.36662300	0.03124900	-1.43172100
C	0.27920100	-0.25026300	0.60566700
C	1.71122900	-0.15001000	0.08200200
C	2.54127500	-1.26798000	0.03570500
C	2.19080000	1.04603100	-0.45961200
C	3.81256100	-1.20253700	-0.53022800
H	2.19786600	-2.20938300	0.44929300
C	3.45512300	1.11472800	-1.02724900
H	1.56841400	1.92939500	-0.39527200
C	4.27615500	-0.00961300	-1.06660800
H	4.43908300	-2.08911500	-0.54759000
H	3.80920200	2.05844700	-1.43062400
H	5.26738500	0.04793900	-1.50537400
C	0.14032300	-1.23823400	1.76940500
H	0.28824200	-2.27393800	1.45311400
H	0.86303700	-0.97571800	2.54469200
H	-0.86885400	-1.15284000	2.17121300
N	-0.17223700	1.08922700	1.09571500
O	0.65047200	1.67713300	1.90118000
O	-1.45853900	1.16622100	1.27757900

TS-2

Electronic Energy: -802.069332

Thermal correction to Enthalpy: 0.285368

Thermal correction to Gibbs Free Energy: 0.220736

C	-2.16443100	-1.10121200	-0.28335500
O	-2.39799200	-2.25278100	0.07034900
N	-3.15239300	-0.15357700	-0.28023000
C	-4.45496800	-0.50524000	0.23997900
H	-4.65943800	0.04410600	1.16825200
H	-5.23419600	-0.24735200	-0.48724800
H	-4.48121800	-1.57374800	0.44166000
C	-2.99055600	1.24895400	-0.61234300
H	-3.78701500	1.54725300	-1.30534100
H	-3.06653800	1.86813500	0.28946600
H	-2.02553900	1.45861000	-1.06743200
C	-0.76966900	-0.71763900	-0.74202100
H	-0.36034200	-1.64900700	-1.14312200
H	-0.78256400	0.01578200	-1.55533800
C	0.14933000	-0.19730400	0.35918000
C	1.57126700	-0.38322400	0.11072600
C	2.08233800	-0.47601900	-1.20249900
C	2.51776300	-0.37687200	1.15664900
C	3.44158800	-0.58797000	-1.44605500
H	1.40324100	-0.43054300	-2.04465100
C	3.87623800	-0.49270700	0.90723300
H	2.18187000	-0.27848700	2.18089300
C	4.35607700	-0.60628200	-0.39533200
H	3.79382900	-0.65088900	-2.47164900
H	4.57148400	-0.48829800	1.74188600
H	5.42034000	-0.69374900	-0.58840300
C	-0.33210600	-0.32295200	1.77995500
H	-0.16968800	-1.33104700	2.18159900
H	0.18324900	0.40695400	2.40841300
H	-1.40028000	-0.10329800	1.84863000
N	0.01288700	1.76786600	0.13979000
O	0.08436900	2.11196500	-1.06546200
O	0.65013700	2.38036100	1.01420800

Int-3

Electronic Energy: -596.833152

Thermal correction to Enthalpy: 0.271720

Thermal correction to Gibbs Free Energy: 0.211307

C	-1.84181400	0.26914800	0.29670300
O	-1.54086100	0.61948000	1.42259900
N	-3.02336900	-0.36078100	0.01635300
C	-3.89616800	-0.74483600	1.11078900
H	-3.52249600	-0.30039300	2.03004400
H	-4.91421500	-0.39055700	0.92281600
H	-3.91955500	-1.83493100	1.22395300
C	-3.37277600	-0.88687600	-1.28868300
H	-3.00734000	-1.91209900	-1.43133300
H	-4.46100100	-0.89998300	-1.38150700
H	-2.98434600	-0.26151800	-2.09086400

C	-0.90860300	0.54075900	-0.89277900
H	-0.77782300	-0.37337800	-1.47693800
H	-1.41280800	1.25402000	-1.55652300
C	1.53509600	0.27568600	-0.22117400
C	2.79919200	0.83313300	0.09967700
C	1.46164900	-1.13925600	-0.27913100
C	3.90492900	0.03408800	0.32529800
H	2.90766200	1.90881700	0.16580800
C	2.57214900	-1.93006500	-0.04878000
H	0.51530300	-1.62540800	-0.48341500
C	3.80548400	-1.35405700	0.25096900
H	4.85698200	0.49576600	0.56395200
H	2.47691900	-3.00959800	-0.09437700
H	4.67343500	-1.97763800	0.43101600
C	0.40521700	1.11038900	-0.45827900
C	0.46961000	2.58554800	-0.21075300
H	-0.50856800	3.04907400	-0.34838700
H	0.78933000	2.80008200	0.81440800
H	1.17521000	3.08540400	-0.88705400

NO_2^-

Electronic Energy: -205.253707

Thermal correction to Enthalpy: 0.012047

Thermal correction to Gibbs Free Energy: -0.015457

N	0.00000000	0.45604800	0.00000000
O	1.06261900	-0.19961700	0.00000000
O	-1.06261900	-0.19942500	0.00000000

FMN_{sq}

Electronic Energy: -872.679196

Thermal correction to Enthalpy: 0.270196

Thermal correction to Gibbs Free Energy: 0.208394

C	3.40675900	0.58772000	0.00000900
C	2.19865900	1.27540900	0.00007900
C	0.97003200	0.61355900	0.00008000
C	0.98475000	-0.79096400	0.00005500
C	2.19300500	-1.48414600	0.00001100
C	3.40768600	-0.81900000	-0.00002500
C	-1.40023900	-0.78472400	0.00002700
C	-1.45438900	0.63173500	-0.00002600
C	-2.62361100	-1.55490300	-0.00001400
H	2.22189600	2.35691300	0.00013300
H	2.16857500	-2.56958300	0.00000100
C	4.70371400	1.35045900	-0.00002600
H	5.30682400	1.10603300	0.87973300
H	5.30668700	1.10617700	-0.87991900
H	4.53032600	2.42743800	0.00007200
C	4.69940800	-1.59002100	-0.00009200
H	5.30384400	-1.35055900	-0.88015100
H	5.30394100	-1.35057200	0.87990500
H	4.51749900	-2.66567000	-0.00008900
N	-0.24762300	1.30592300	0.00013300
C	-0.24794100	2.76158000	-0.00004900
H	0.25624000	3.13915400	0.89309300
H	0.25655700	3.13891800	-0.89311100
H	-1.28289200	3.09154200	-0.00027000
N	-2.56892300	1.31296700	-0.00006600
C	-3.77246800	0.64859300	-0.00005600
O	-4.84718100	1.20295100	0.00009600
N	-3.74373700	-0.76625700	-0.00027300
H	-4.64286800	-1.22674100	0.00003100
N	-0.22424600	-1.45388800	0.00006600
H	-0.28282800	-2.46567100	0.00012000
O	-2.63585500	-2.77800000	0.00010300

TS-3

Electronic Energy: -1469.513468

Thermal correction to Enthalpy: 0.542288

Thermal correction to Gibbs Free Energy: 0.447655

C	-2.92561600	-2.32560400	0.12104400
O	-2.62868800	-3.44896600	0.48101500
N	-4.10470600	-1.72527900	0.46126000
C	-5.01979900	-2.41256100	1.35598400
H	-4.59855800	-3.38353400	1.60540100
H	-5.99232600	-2.55513100	0.87485000
H	-5.16171000	-1.83548600	2.27565900
C	-4.46722500	-0.37966900	0.04974400
H	-3.92166000	0.39162500	0.60851500
H	-5.53313600	-0.24007400	0.23334700
H	-4.29511600	-0.22023000	-1.01648800
C	-1.99361400	-1.49249800	-0.76696200
H	-2.09504700	-0.43734700	-0.51717800
H	-2.34885900	-1.60119700	-1.79841200
C	0.17011600	-1.63071200	0.51422600
C	1.51726400	-2.03572400	0.67925500
C	-0.37208200	-0.79628400	1.53104000
C	2.25448400	-1.67674100	1.80238800
H	1.97404400	-2.68670900	-0.05358900

C	0.37418400	-0.42747100	2.62660300
H	-1.39844600	-0.45693600	1.46792000
C	1.69892500	-0.85739700	2.76830800
H	3.28066900	-2.01192600	1.89731400
H	-0.07295600	0.20182800	3.38868800
H	2.28327000	-0.55590400	3.62950300
C	-0.55269700	-1.91642900	-0.68044000
C	-0.17881900	-3.04202600	-1.60692900
H	-0.48459300	-2.81705700	-2.63267600
H	-0.72821100	-3.93532600	-1.28366800
H	0.88500500	-3.25898100	-1.63375700
C	-1.83691400	3.23103000	0.00163600
C	-0.57940400	3.02948700	0.55127300
C	0.31039600	2.07776100	0.03774000
C	-0.11025100	1.30358400	-1.05291500
C	-1.36012400	1.53914800	-1.62704800
C	-2.23687200	2.48193600	-1.12173100
C	1.95228100	0.18352600	-1.06525500
C	2.45097000	0.99423500	-0.00381600
C	2.86076100	-0.76472600	-1.69489700
H	-0.28472500	3.62979900	1.40168900
H	-1.63166300	0.95102800	-2.49775800
C	-2.76016600	4.25954200	0.59658200
H	-3.70182300	3.80596000	0.92174500
H	-3.01431200	5.03271500	-0.13484100
H	-2.30643500	4.74878400	1.45947500
C	-3.58109400	2.70036400	-1.76203100
H	-3.68586100	3.72477900	-2.13217400
H	-4.39663200	2.53434900	-1.05038200
H	-3.72799700	2.02502700	-2.60680200
N	1.58098100	1.90242800	0.56576300
C	2.01701900	2.70798100	1.69579400
H	1.34187500	2.55776600	2.54166200
H	2.03851300	3.76749400	1.42590400
H	3.01848200	2.38357300	1.96297900
N	3.66766400	0.93198500	0.46669700
C	4.55354100	0.02278600	-0.05456700
O	5.67606600	-0.14336600	0.37119500
N	4.12194600	-0.75301600	-1.14677000
H	4.79332800	-1.40927900	-1.51925000
N	0.70397500	0.29877900	-1.58010800
H	0.17698800	-0.66537900	-1.60560800
O	2.53853300	-1.52138600	-2.59597300

3a

Electronic Energy: -597.482722

Thermal correction to Enthalpy: 0.285611

Thermal correction to Gibbs Free Energy: 0.226755

C	-2.14609900	-0.36033600	-0.21807900
O	-2.33832200	-1.55638300	-0.36288100
N	-3.16891600	0.54634000	-0.25386900
C	-4.53699900	0.07141300	-0.34590100
H	-4.52447900	-1.00694800	-0.48470100
H	-5.04523700	0.54006000	-1.19435400
H	-5.09047100	0.31040500	0.56935200
C	-3.00122000	1.96871000	-0.02629300
H	-3.05487000	2.22488200	1.03946700
H	-3.80194600	2.50173600	-0.54337700
H	-2.05569700	2.33068900	-0.42719100
C	-0.74259200	0.20273100	-0.01946800
H	-0.73832000	0.92175100	0.80686700
H	-0.47631600	0.76939600	-0.91943700
C	1.70361500	-0.31362700	0.03581200
C	2.51102900	-0.76397100	-1.00717200
C	2.20845900	0.67862500	0.87923400
C	3.78542700	-0.24260200	-1.20557100
H	2.13647700	-1.53590500	-1.67243700
C	3.47924600	1.20430700	0.68514600
H	1.60380400	1.04485900	1.70327400
C	4.27401900	0.74472400	-0.35982600
H	4.39676500	-0.61047700	-2.02236500
H	3.85221000	1.97339900	1.35284700
H	5.26703800	1.15275700	-0.51107500
C	0.31187600	-0.88268500	0.23306800
C	0.14480700	-1.52025000	1.61646600
H	-0.83644100	-1.99036300	1.70011100
H	0.24265900	-0.77344700	2.41141700
H	0.90847000	-2.28387800	1.78175900
H	0.15593100	-1.66445900	-0.51453100

FMN_{ox}

Electronic Energy: -872.073647

Thermal correction to Enthalpy: 0.258414

Thermal correction to Gibbs Free Energy: 0.197996

C	3.39001800	-0.56629700	0.00001500
C	2.20320200	-1.27879900	0.00000800
C	0.96666600	-0.62049900	0.00000200
C	0.94704500	0.78466300	-0.00000100

C	2.15803300	1.49429700	0.00000900
C	3.37490400	0.85120300	0.00001600
C	-1.33224000	0.83176800	-0.00003000
C	-1.43223000	-0.62711700	-0.00002100
C	-2.62174200	1.59828100	0.00000100
H	2.24455900	-2.35988200	0.00000500
H	2.09194400	2.57664600	0.00000800
C	4.70074400	-1.30246800	0.00002300
H	5.29672200	-1.04020800	-0.87914500
H	5.29669200	-1.04023700	0.87922200
H	4.55223400	-2.38286200	0.00000300
C	4.66083200	1.63210300	0.00002500
H	5.26768900	1.40016400	0.88044300
H	5.26769700	1.40017300	-0.88038900
H	4.46468700	2.70484000	0.00003000
N	-0.23835800	-1.30273800	0.00000200
C	-0.24764600	-2.76367400	0.00001800
H	0.25697400	-3.13617200	-0.89337300
H	0.25700300	-3.13615100	0.89340000
H	-1.28342800	-3.08927600	0.00003700
N	-2.54215100	-1.30056900	-0.00003900
C	-3.74864100	-0.63364200	-0.00013000
O	-4.81617200	-1.19516700	0.00001400
N	-3.72300200	0.77650000	0.00008500
H	-4.62822200	1.22691000	0.00009000
N	-0.22686700	1.48826200	-0.00001400
O	-2.69452600	2.80103600	-0.00003700

2I′

Electronic Energy: -475.562387

Thermal correction to Enthalpy: 0.127513

Thermal correction to Gibbs Free Energy: 0.085563

C	1.14762900	-0.76327200	0.00018800
C	-0.21405900	-0.32321900	0.00007300
C	-1.22141600	-1.32163200	-0.00001800
C	-0.66416400	1.01867700	0.00009100
C	-2.56886900	-1.00931800	-0.00007500
H	-0.91721400	-2.36501200	-0.00005900
C	-2.02027000	1.31758200	0.00002300
H	0.07848300	1.80328500	0.00013100
C	-2.99196000	0.32051700	-0.00005300
H	-3.30126300	-1.81250400	-0.00014900
H	-2.32339600	2.36159700	0.00003900
H	-4.04831700	0.56906000	-0.00009800
N	2.25799400	0.01208700	-0.00001500
O	2.17906000	1.26941900	-0.00008700
O	3.38774900	-0.55153400	-0.00008100
H	1.36993400	-1.82011600	0.00021400

TS-1′

Electronic Energy: -762.730258

Thermal correction to Enthalpy: 0.255118

Thermal correction to Gibbs Free Energy: 0.192571

C	-1.95836300	-1.25419000	-0.39622600
O	-2.08855600	-2.26823800	0.30520100
N	-3.03781200	-0.40286600	-0.59536700
C	-4.12298300	-0.46462800	0.35938100
H	-3.99185900	0.29601900	1.14153200
H	-5.07944800	-0.29191000	-0.14824400
H	-4.12906900	-1.45053500	0.81943000
C	-2.92041600	0.86452100	-1.29108000
H	-3.92436700	1.18364500	-1.59020700
H	-2.47489300	1.64590300	-0.66434500
H	-2.33019000	0.75383400	-2.20094000
C	-0.68613200	-0.91599500	-0.98685500
H	0.04350800	-1.71390200	-1.00184100
H	-0.54195900	-0.09390200	-1.67356500
C	0.36743500	0.21609600	0.76423500
C	1.74716500	0.04866400	0.33906100
C	2.38360800	-1.15023200	0.71731100
C	2.48640400	0.95258800	-0.44339900
C	3.68870600	-1.42866800	0.34761100
H	1.82646700	-1.87247200	1.30649500
C	3.79849700	0.66781400	-0.80414800
H	2.01234800	1.87339300	-0.75099700
C	4.41399800	-0.51720500	-0.41732200
H	4.14450100	-2.36409700	0.65804000
H	4.34627000	1.38851700	-1.40448200
H	5.43722700	-0.73110100	-0.70848800
N	-0.30540000	1.40928300	0.76936100
O	0.03900800	2.35023100	0.00769200
O	-1.33848200	1.50376700	1.48232700
H	-0.01931600	-0.46698400	1.50648700

Int-2′

Electronic Energy: -762.780306

Thermal correction to Enthalpy: 0.258910

Thermal correction to Gibbs Free Energy: 0.197134

C	2.04819900	-1.08376500	0.14395900
O	2.15880300	-2.18073500	-0.39994500
N	3.12093700	-0.25726400	0.29561800
C	4.41130000	-0.69246900	-0.19194100
H	4.71494800	-0.09936500	-1.06351400
H	5.16700400	-0.56146400	0.59175000
H	4.35299700	-1.74069400	-0.47720400
C	3.09416500	1.08802900	0.84498700
H	3.64060800	1.11606600	1.79777700
H	3.59250400	1.76603500	0.14396400
H	2.07763200	1.46981400	0.97710000
C	0.69002200	-0.65029600	0.66760800
H	0.20354900	-1.57826800	0.97032500
H	0.73409100	0.02155400	1.52511500
C	-0.16859400	0.03259300	-0.41481100
C	-1.65327500	-0.16576900	-0.13726700
C	-2.46790700	0.87850900	0.29676300
C	-2.22034500	-1.42546000	-0.33298000
C	-3.82038400	0.65730500	0.53352000
H	-2.01588200	1.85371600	0.44489100
C	-3.57173700	-1.64757100	-0.09386300
H	-1.59169600	-2.24094500	-0.68154000
C	-4.37894000	-0.60277600	0.34363900
H	-4.44448700	1.48033900	0.86797900
H	-3.99485800	-2.63448700	-0.25482100
H	-5.43558000	-0.76863900	0.52983400
N	0.19880300	1.45288200	-0.55480400
O	0.21475000	2.14296100	0.56165500
O	-0.13137500	1.99257900	-1.67796700
H	0.04853600	-0.42140500	-1.38498600

TS-2′

Electronic Energy: -762.754746

Thermal correction to Enthalpy: 0.255719

Thermal correction to Gibbs Free Energy: 0.192936

C	2.16343100	-1.09252000	-0.09158200
O	2.36042400	-2.04984800	-0.83316700
N	3.16961300	-0.21481000	0.20355100
C	4.47325800	-0.42916900	-0.38563200
H	4.68210600	0.32688000	-1.15328200
H	5.24629600	-0.35400500	0.38825000
H	4.50230400	-1.41591800	-0.84242000
C	3.04983600	1.00718900	0.97626600
H	3.67901700	0.94687800	1.87451800
H	3.39503200	1.85372400	0.37215700
H	2.02146500	1.22389300	1.25781300
C	0.79171100	-0.89398200	0.52758900
H	0.46906600	-1.90194100	0.81355700
H	0.80996900	-0.28276300	1.43471600
C	-0.19255800	-0.29691800	-0.44698400
C	-1.60091800	-0.41809900	-0.19094400
C	-2.12145900	-0.70320300	1.08998600
C	-2.53276900	-0.14303500	-1.21697800
C	-3.48892500	-0.74607300	1.31632100
H	-1.44198400	-0.88219100	1.91580000
C	-3.89482600	-0.18445900	-0.98271300
H	-2.15608700	0.12300600	-2.19872900
C	-4.39156300	-0.49423500	0.28553400
H	-3.85703800	-0.97042400	2.31356100
H	-4.58326600	0.03376500	-1.79410600
H	-5.46083100	-0.52558600	0.46763400
N	0.12942000	1.66258100	-0.24538500
O	0.04245200	2.03839200	0.94596200
O	-0.40605100	2.31034800	-1.15648600
H	0.09480800	-0.33381800	-1.49228300

Int-3′

Electronic Energy: -557.517499

Thermal correction to Enthalpy: 0.242257

Thermal correction to Gibbs Free Energy: 0.186215

C	-2.32219000	-0.60428400	-0.33299800
O	-3.14752100	-1.49980100	-0.27905100
N	-2.52353600	0.61634200	0.24331400
C	-3.80809000	0.90747300	0.85230300
H	-3.67020200	1.23046800	1.88887600
H	-4.32124400	1.70488800	0.30299500
H	-4.41910800	0.00826100	0.83216400
C	-1.60222000	1.73303400	0.14633500
H	-1.82978400	2.37399800	-0.71481900
H	-1.68957000	2.33821500	1.05157600
H	-0.56917000	1.39825100	0.08169600
C	-0.98286400	-0.83648500	-1.03807100
H	-1.15315400	-1.71397900	-1.66927800
H	-0.73697500	-0.00146900	-1.69657400
C	0.10328600	-1.12018200	-0.05182400
C	1.39112300	-0.54281100	-0.02469000
C	1.84956000	0.40014900	-0.98168100
C	2.29621500	-0.90535400	1.00909200

C	3.11891000	0.94204900	-0.89788700
H	1.20451200	0.69864900	-1.80002800
C	3.56108200	-0.35847400	1.08183300
H	1.97437500	-1.62743100	1.75245000
C	3.98493500	0.57220700	0.13075000
H	3.44367700	1.65893600	-1.64407000
H	4.22871200	-0.65458400	1.88339800
H	4.97861400	1.00059200	0.18927200
H	-0.13424800	-1.85471100	0.71257500

TS-3′

Electronic Energy: -1430.198859

Thermal correction to Enthalpy: 0.512782

Thermal correction to Gibbs Free Energy: 0.419880

C	3.18614400	-2.29184900	0.08254500
O	2.84022400	-3.28845800	0.68434200
N	4.48019800	-1.84575000	0.06926600
C	5.46608300	-2.51782400	0.89735900
H	5.02993300	-3.43586900	1.28373300
H	6.35371700	-2.75880700	0.30540100
H	5.76538300	-1.88366600	1.73973900
C	4.88911600	-0.59418400	-0.54026400
H	4.65788200	0.27321600	0.09195000
H	5.96868700	-0.62050600	-0.69655400
H	4.42255000	-0.44889100	-1.51511300
C	2.19172500	-1.45336600	-0.73366700
H	2.33838200	-0.39828200	-0.48681600
H	2.45366800	-1.56188200	-1.79231300
C	0.04758500	-1.52910200	0.64717300
C	-1.25434400	-2.06146400	0.82911400
C	0.49487700	-0.56352100	1.59190800
C	-2.04483000	-1.68689400	1.90921500
H	-1.59828300	-2.83138000	0.14815100
C	-0.30756400	-0.18476900	2.64274400
H	1.48410600	-0.13113100	1.49688900
C	-1.58802000	-0.73336400	2.80282400
H	-3.03145600	-2.11866800	2.02953100
H	0.05477300	0.55010900	3.35376200
H	-2.21316200	-0.42193400	3.63157100
C	0.76813200	-1.85286400	-0.51904200
C	1.32470600	3.41689400	0.09228500
C	0.04192700	3.09178200	0.50571800
C	-0.66102300	2.01080000	-0.03937900
C	-0.02951400	1.24945300	-1.03277000
C	1.24753600	1.60200400	-1.47122300
C	1.94452500	2.66234100	-0.92355200
C	-1.90798000	-0.14816200	-1.15723600
C	-2.61906200	0.63191700	-0.19912600
C	-2.57087000	-1.29749700	-1.75259700
H	-0.41964000	3.69163000	1.27860300
H	1.68567700	1.01640800	-2.27267900
C	2.04357500	4.57995800	0.71998900
H	2.98262800	4.26150000	1.18310000
H	2.29664500	5.33773200	-0.02777800
H	1.43326800	5.05610100	1.48846100
C	3.32859800	3.00042900	-1.40761200
H	3.37360100	4.01480100	-1.81543300
H	4.05975400	2.95101700	-0.59421400
H	3.64919700	2.31163100	-2.19114500
N	-1.94807800	1.69178300	0.37319100
C	-2.61090800	2.50223600	1.38491300
H	-2.02334400	2.50307900	2.30536800
H	-2.73868000	3.52767000	1.02750500
H	-3.58489700	2.06010700	1.57313100
N	-3.84976200	0.40030500	0.16828300
C	-4.52508500	-0.67779500	-0.35003700
O	-5.65073200	-0.98445300	-0.02499400
N	-3.85943500	-1.46861000	-1.30876900
H	-4.37391800	-2.26141100	-1.66516400
N	-0.66388400	0.14252300	-1.59098200
H	-0.02828100	-0.73973600	-1.62282300
O	-2.02036300	-2.05463100	-2.53560800
H	0.40351900	-2.69521700	-1.09939800

18

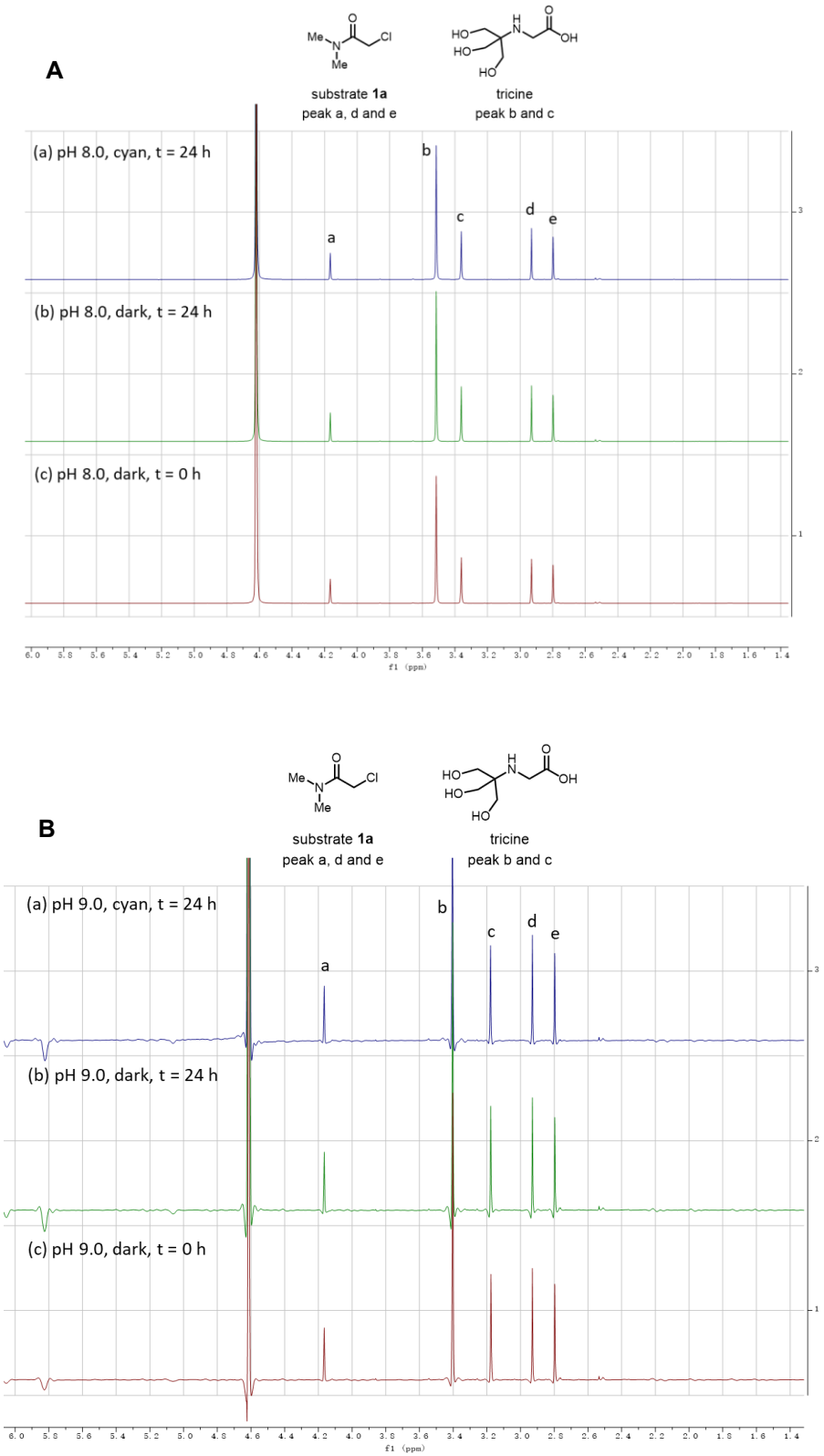
Electronic Energy: -558.169844

Thermal correction to Enthalpy: 0.255988

Thermal correction to Gibbs Free Energy: 0.199523

C	-2.14939200	-0.47720300	-0.01520400
O	-2.37320200	-1.66394400	-0.18340400
N	-3.15682000	0.43722100	0.13401600
C	-4.53206800	0.00478100	-0.03072800
H	-4.56122600	-1.08203000	-0.03883700
H	-5.14327300	0.38057000	0.79513600
H	-4.94889100	0.37974700	-0.97316200
C	-2.95124500	1.87108200	0.18400800
H	-2.99971000	2.32493800	-0.81436000
H	-3.73506000	2.31999500	0.79891800

H	-1.99382000	2.12354200	0.63501500
C	-0.72259500	0.05237500	0.05276800
H	-0.58357600	0.83391800	-0.70250400
H	-0.55830900	0.53567400	1.02250200
C	1.71646800	-0.49884200	-0.07699600
C	2.38977100	-0.41791000	1.14193200
C	2.35343200	-0.01377900	-1.21927800
C	3.66322100	0.13370300	1.21972400
H	1.91183200	-0.79885900	2.03981400
C	3.62670500	0.53897100	-1.14763900
H	1.84673400	-0.07702000	-2.17794100
C	4.28586000	0.61553600	0.07396100
H	4.17247700	0.18262200	2.17602200
H	4.10725900	0.90567500	-2.04810500
H	5.28061400	1.04279500	0.13179300
C	0.31541200	-1.05230200	-0.15018200
H	0.16980800	-1.82594500	0.60671100
H	0.14508100	-1.53308600	-1.11607900



Supplementary Fig. 14. Stability of the model substrate **1a**. (A) ^{1}H NMR (water suppression, 500 MHz) comparison of substrate **1a** in pH 8.0 tricine buffer (100 mM). (B) ^{1}H NMR comparison of substrate **1a** in pH 9.0 tricine buffer (100 mM). (a) Cyan light irradiation, t = 24 h. (b) Dark condition, t = 24 h. (c) Dark condition, t = 0 h. **Note**: Higher pH (9.0) value does not affect model substrate's stability.

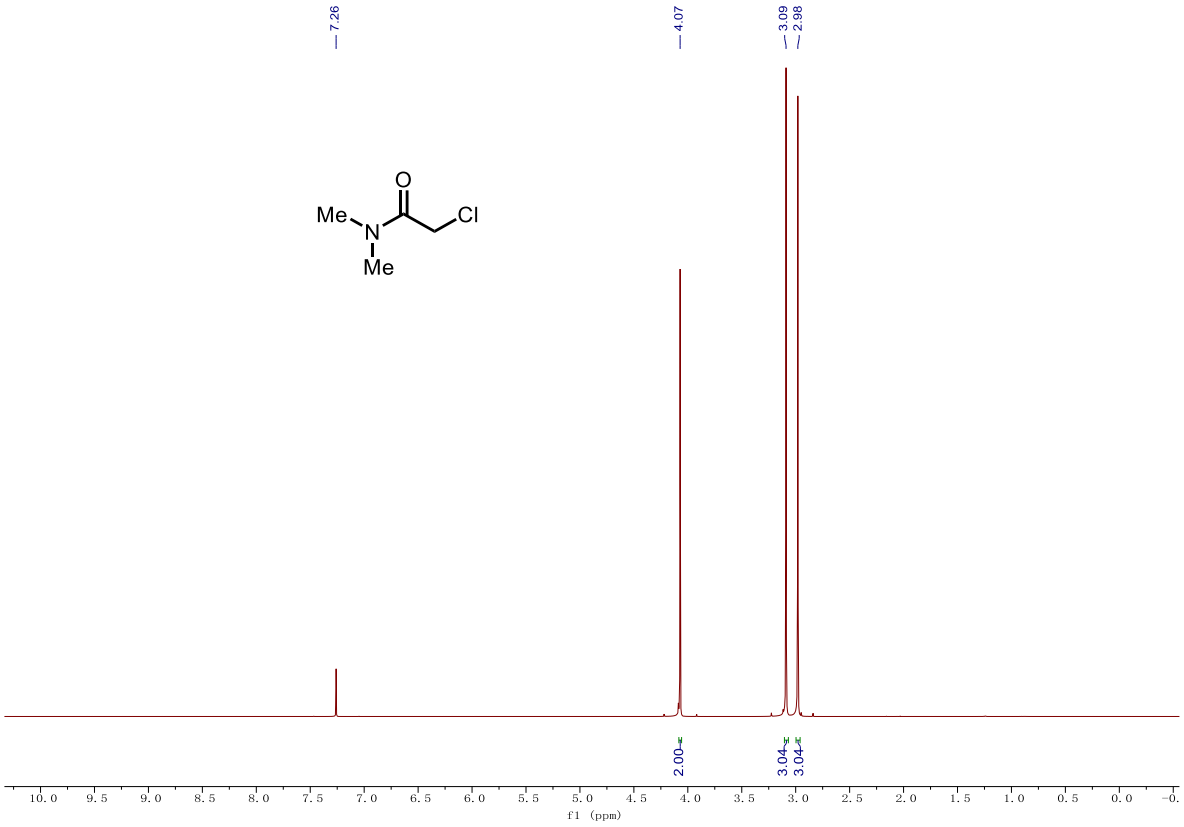
Supplementary Table 6. Reduction potential of CsER (FMN_{hq}/FMN_{ox}) at different pH value.

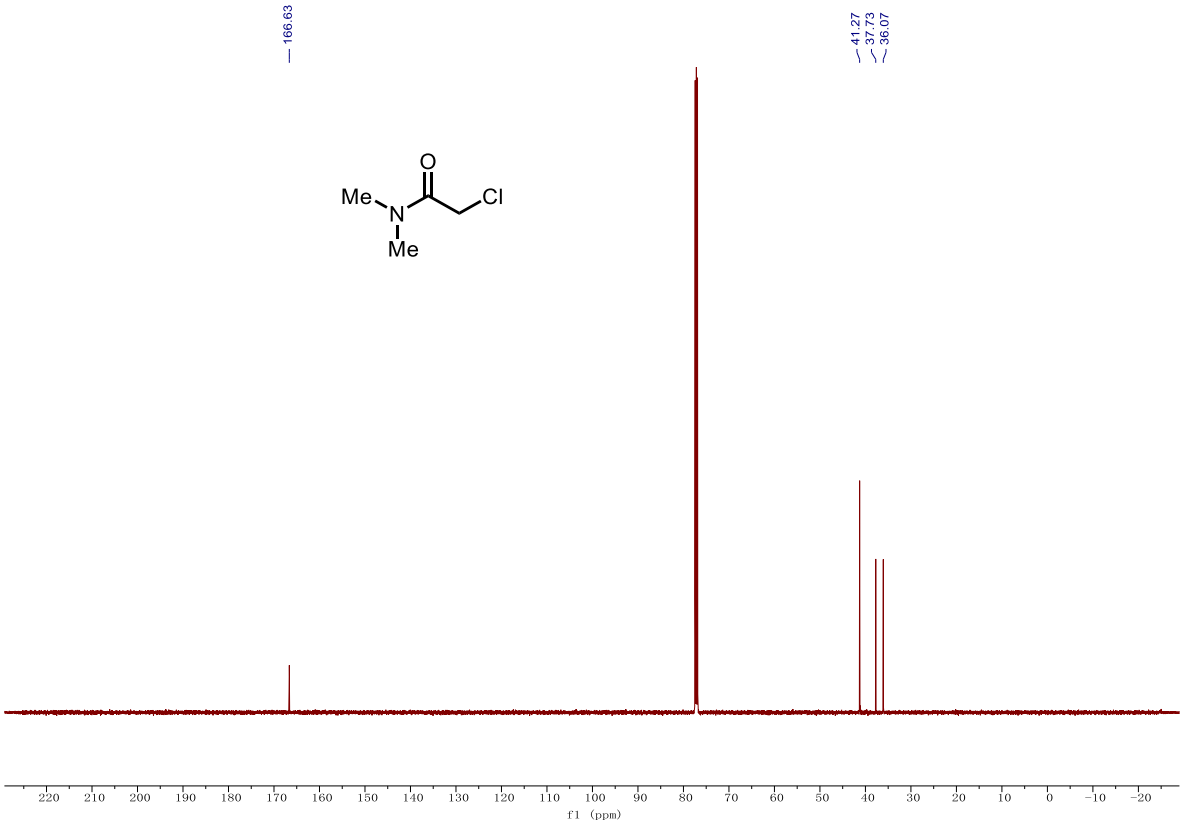
Entry	pH	E^{red} (mV vs SCE)
1	7.0	-504 ± 2
2	8.0	-516 ± 2
3	9.0	-524 ± 2

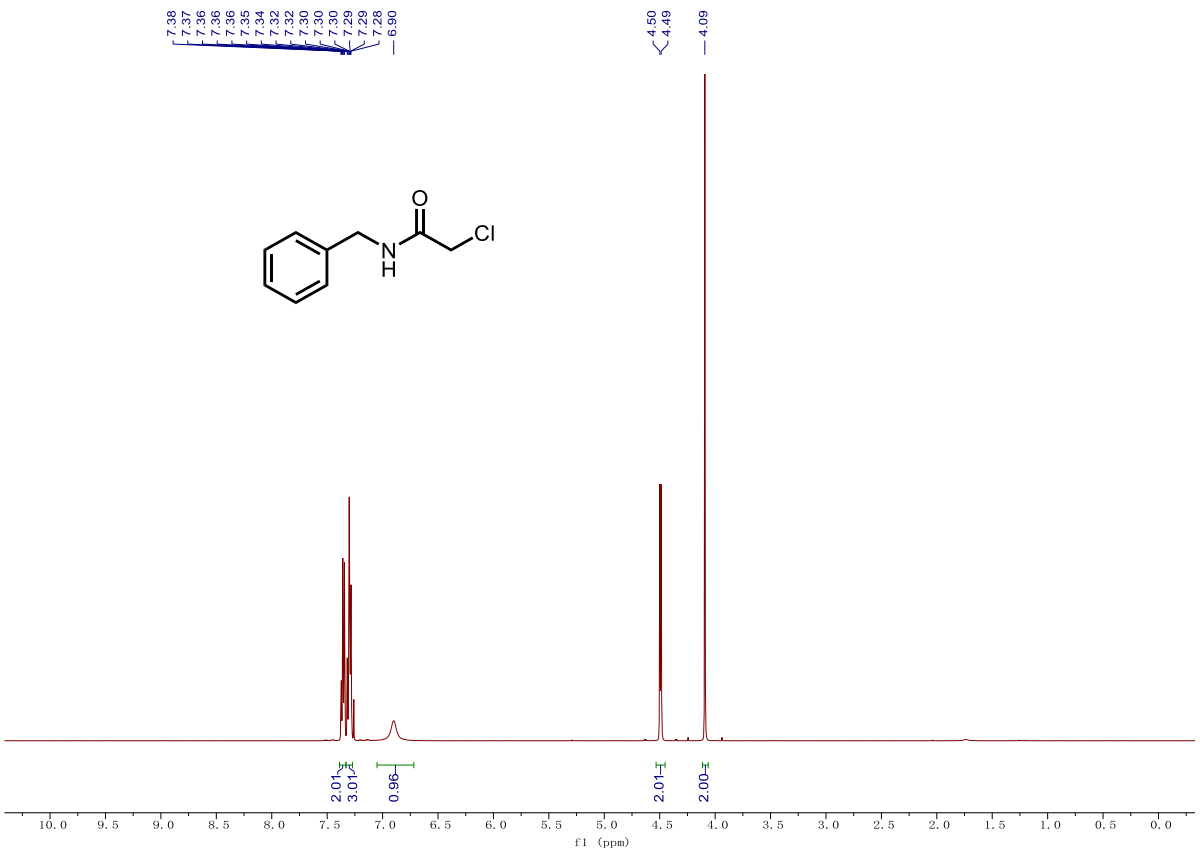
Note: pH value has minor effect on the reduction potential of CsER, indicating pH value has minor effect on flavin electron transfer rate.

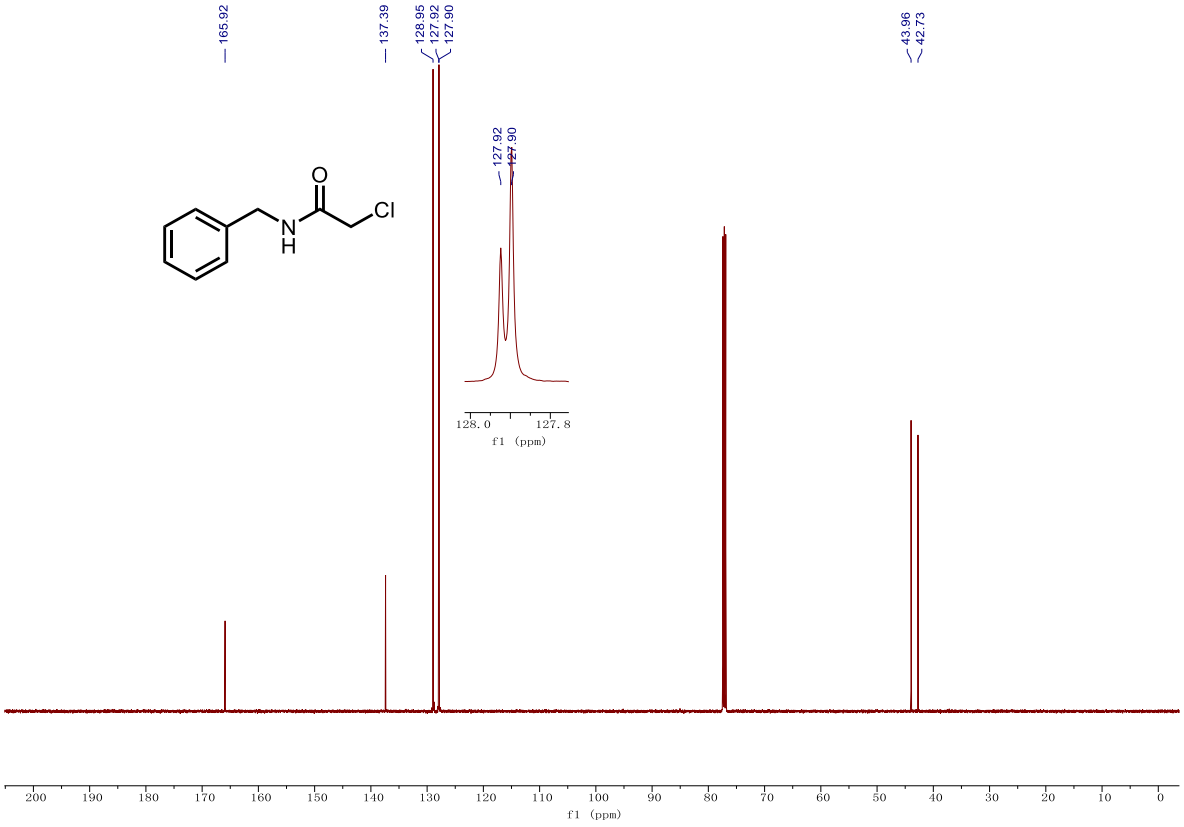
Procedure was adapted from a literature example.[40,41] Prepare stock solutions of 20 μM benzyl viologen dichloride (communicator dye), 150 μM of phenosaphranin (reference dye), and 150 μM of CsER in 100 mM tricine buffer (pH 7.0, 8.0 and 9.0). Prepare 1.0 mM of xanthine in 0.1 mM NaOH. Mix 200 μL of benzyl viologen stock, 200 μL of phenosaphranin stock, 200 μL of CsER stock, 200 μL of xanthine, and 1.2 mL of tricine buffer in the bulb portion of a freeze-pump-thaw cuvette and degas. Import into an anaerobic chamber (MBraun® glovebox with O_2 level less than 1 ppm) and transfer the CsER solution into the cuvette portion of the freeze-pump-thaw cuvette. In anaerobic chamber, prepare 200 nM of xanthine oxidase and place 200 μL of xanthine oxidase stock in the bulb portion of the freeze-pump-thaw cuvette, ensuring that the CsER solution and xanthine oxidase solution do not mix. The cuvette was sealed and removed from the anaerobic chamber. The cuvette was brought to the UV-Vis spectrophotometer, and the two solutions were mixed and specta were taken from 250-650 nm every 30 seconds for 2 hours. Calculation of reduction potential of CsER was adapted from literature example.[41]

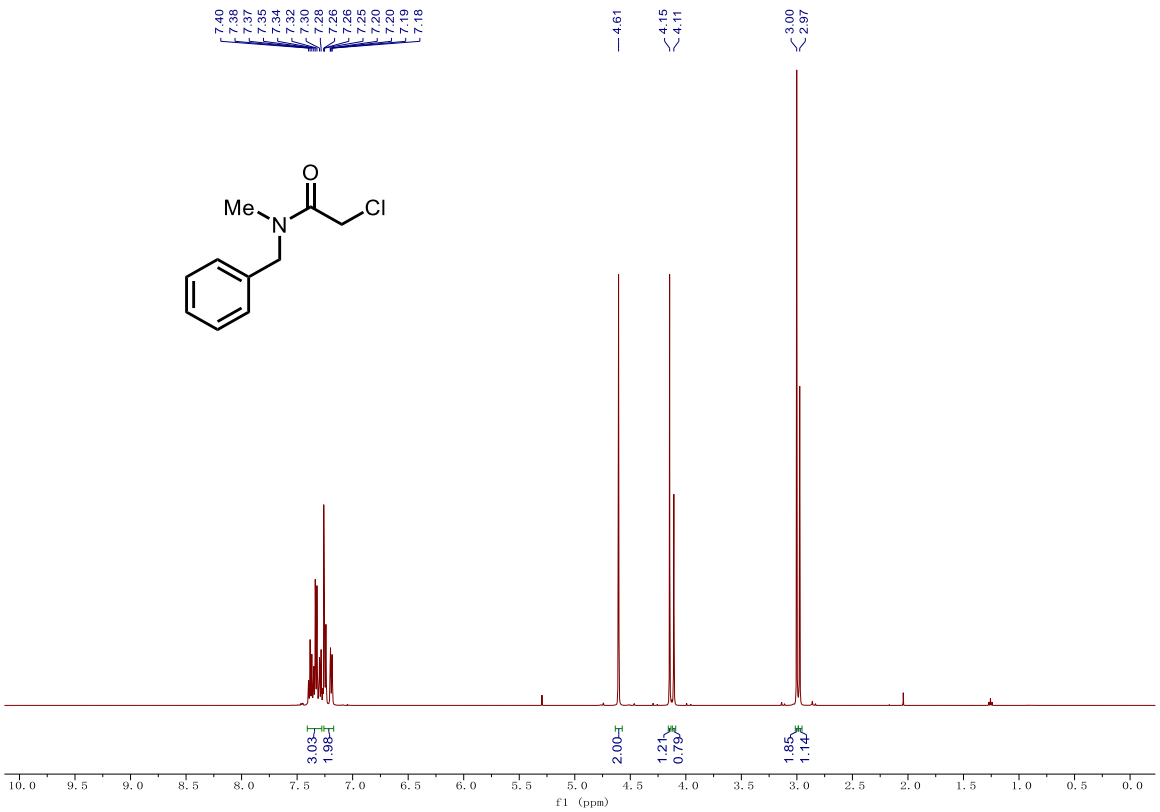
3. NMR spectra

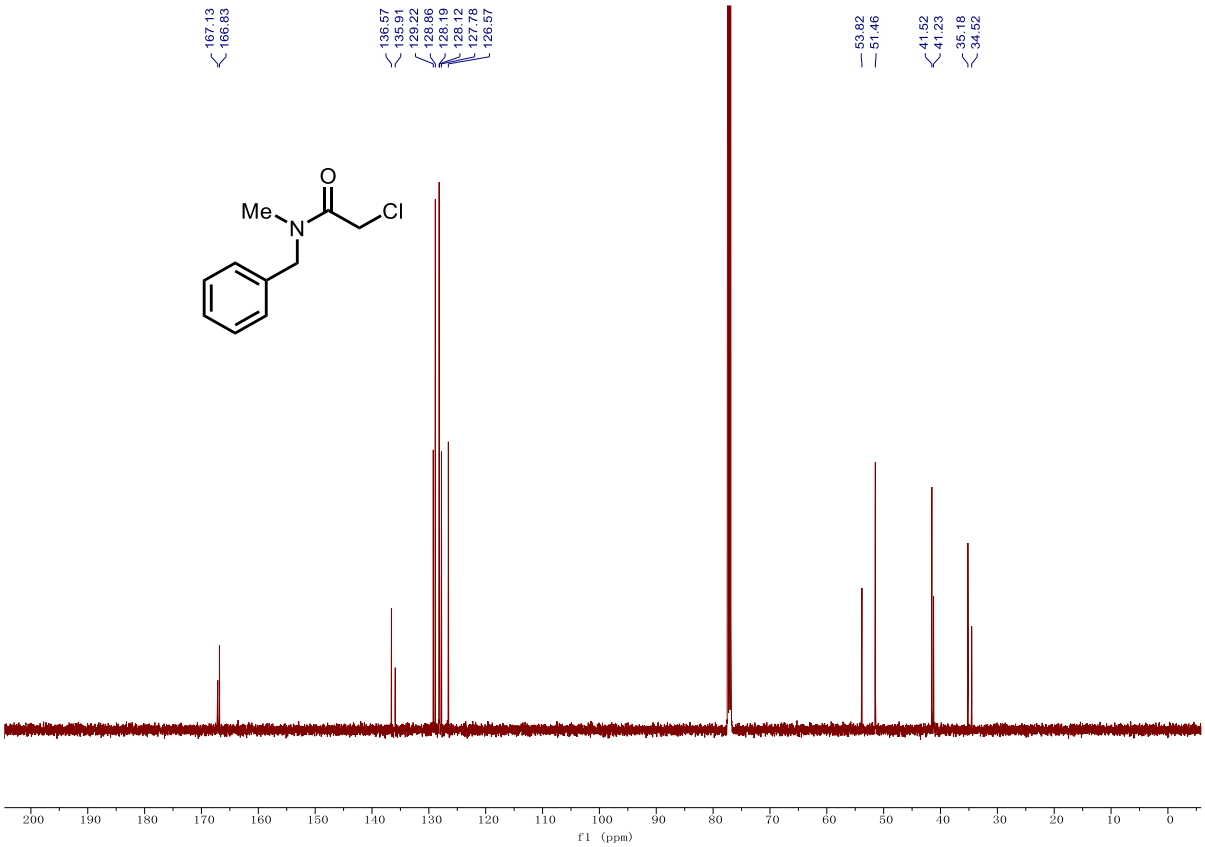


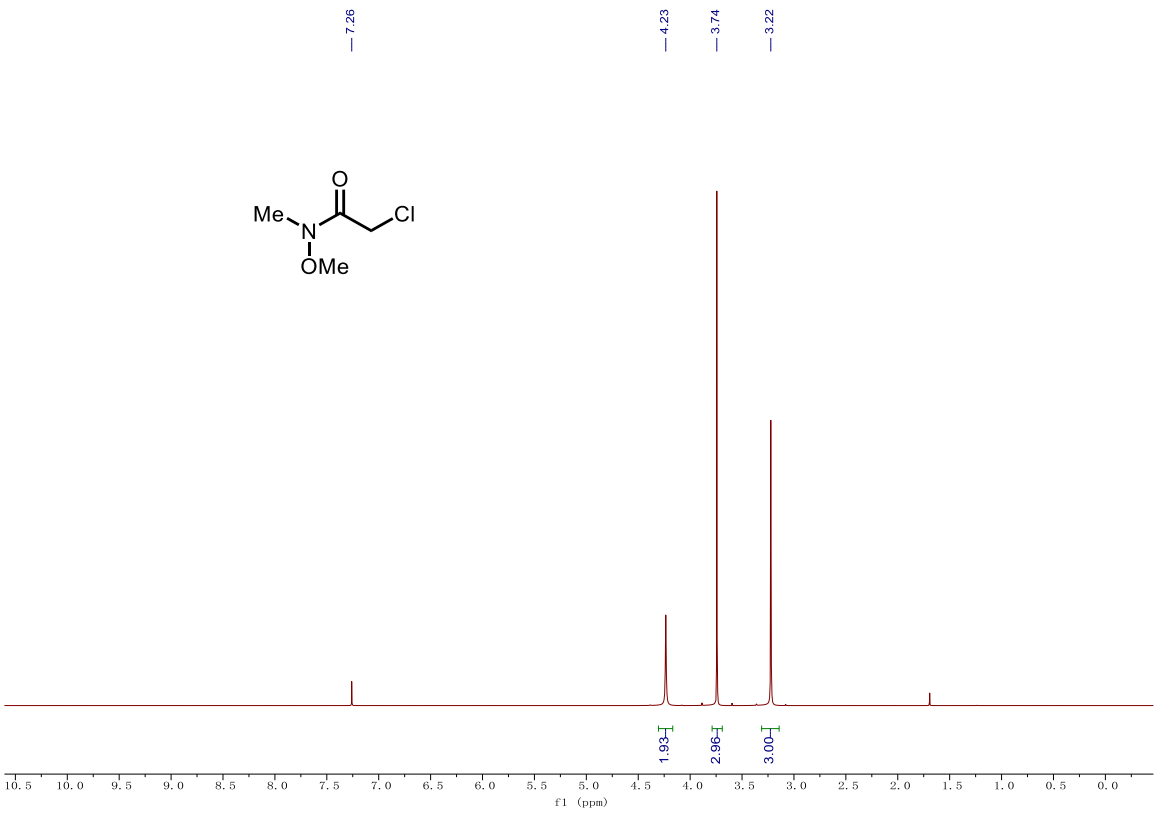



7.38
7.37
7.36
7.36
7.36
7.35
7.34
7.32
7.32
7.30
7.30
7.30
7.29
7.29
7.28
6.90
4.50
4.49
4.09
O
Cl
N
H
2.01
3.01
0.96
2.01
2.00
f1 (ppm)


165.92
137.39
128.95
127.92
127.90
43.96
42.73
127.92
127.90
O
Cl
N
H
128.0
127.8
f1 (ppm)
f1 (ppm)


7.40
7.38
7.37
7.35
7.34
7.32
7.30
7.28
7.26
7.26
7.25
7.20
7.20
7.19
7.18
4.61
4.15
4.11
3.00
2.97
Me
N
O
Cl
3.03
1.98
2.00
1.21
0.79
1.85
1.14
f1 (ppm)


167.13
166.83
136.57
135.91
129.22
128.86
128.19
128.12
127.78
126.57
53.82
51.46
41.52
41.23
35.18
34.52
Me
N
O
Cl
f1 (ppm)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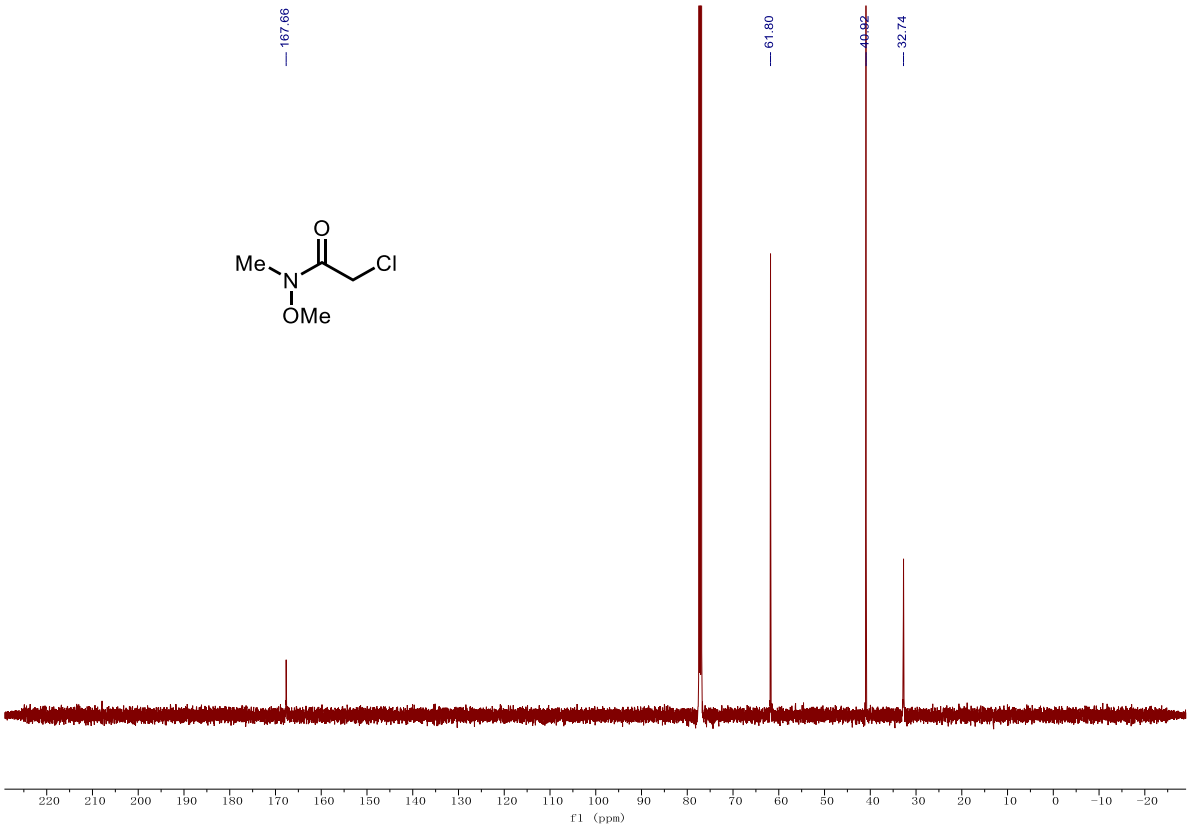
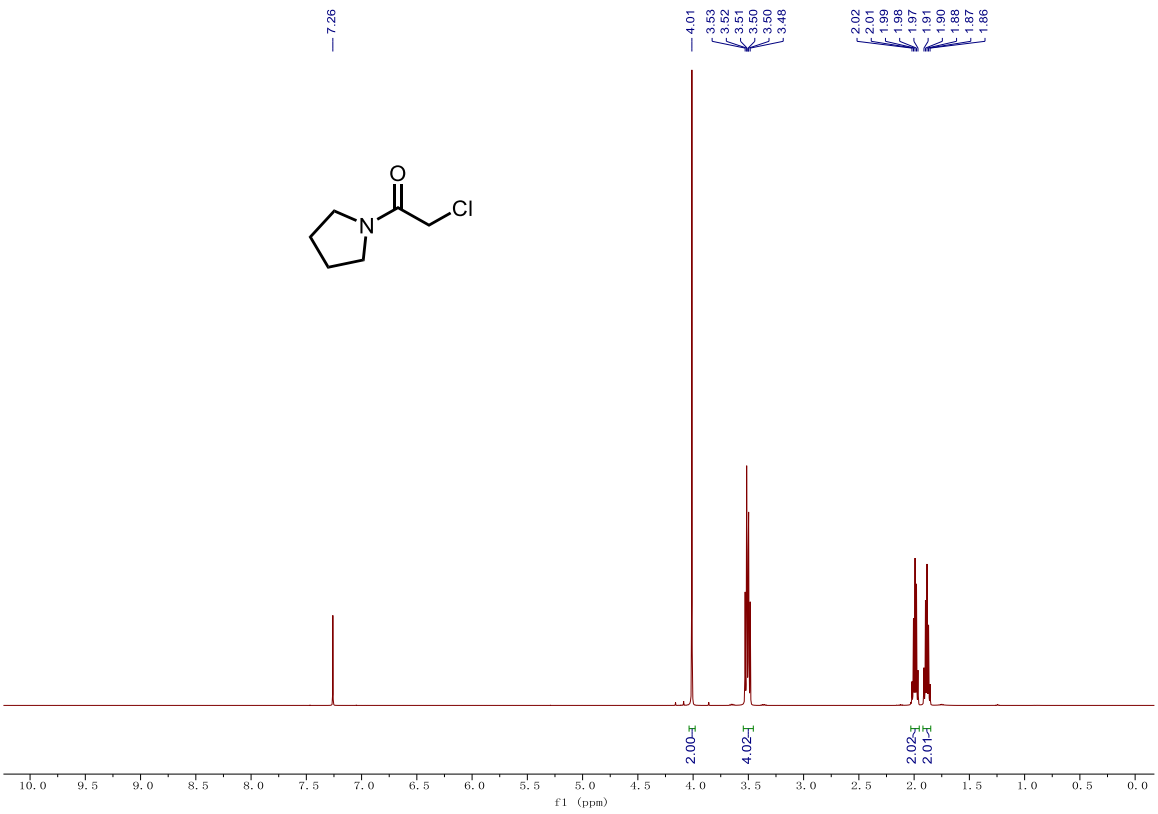
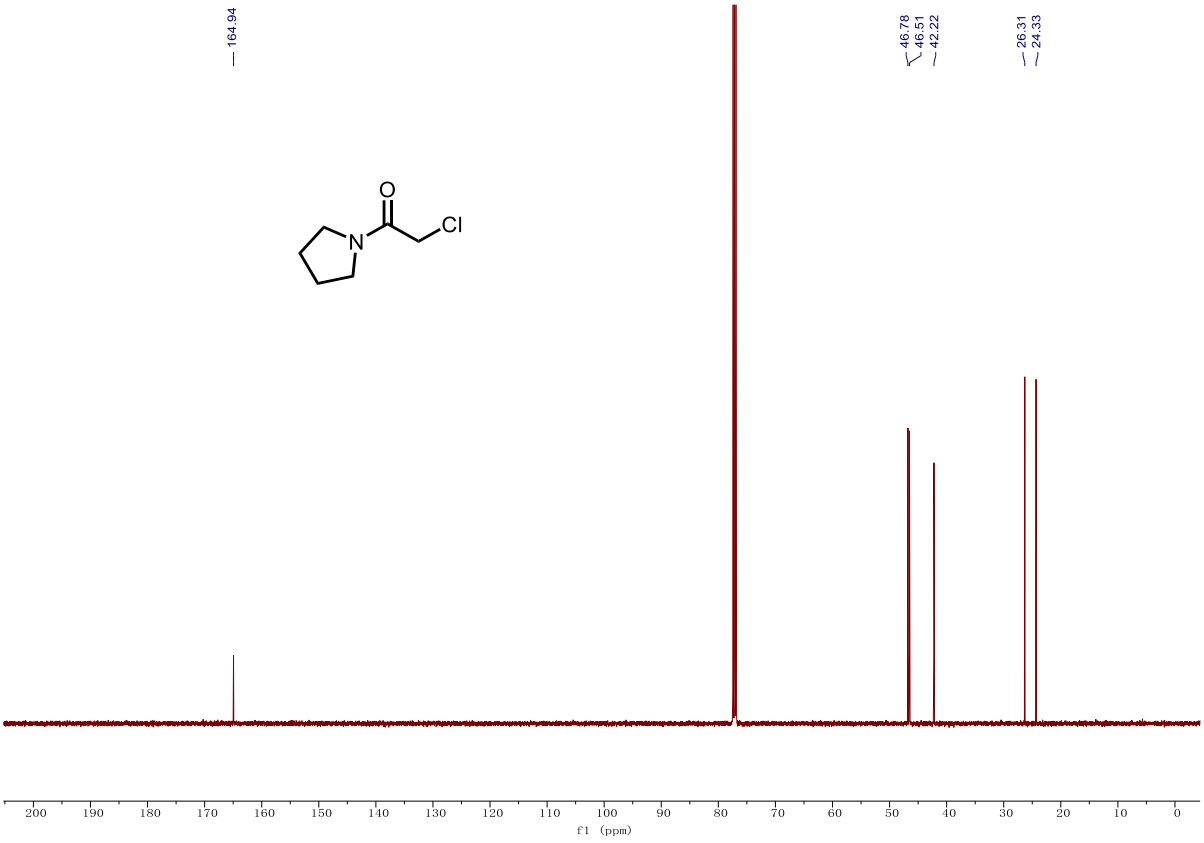
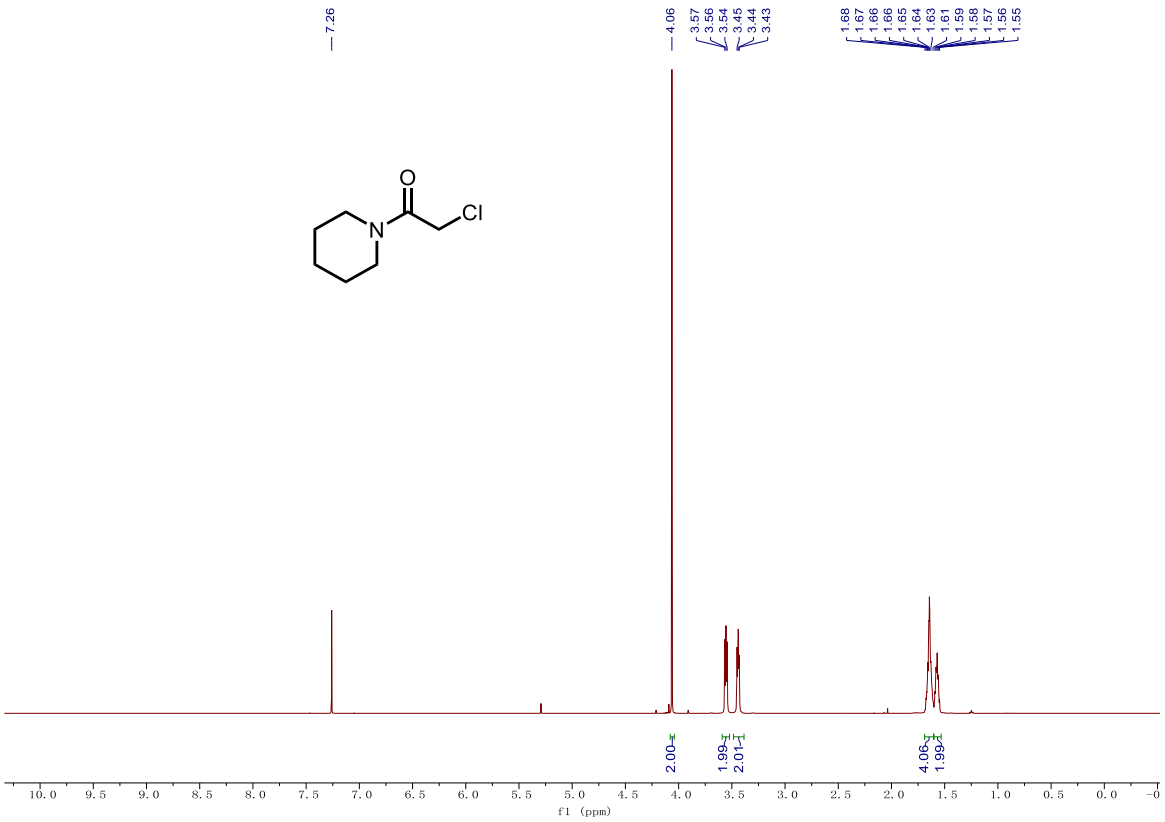
4.23
3.74
3.22
Me
N
O
OMe
Cl
1.93
2.96
3.00
f1 (ppm)


167.66
61.80
40.92
32.74
Me
N
O
OMe
Cl
f1 (ppm)


7.26
4.01
3.53
3.52
3.51
3.50
3.50
3.48
2.02
2.01
1.99
1.98
1.97
1.91
1.90
1.88
1.87
1.86
O
N
Cl
2.00
4.02
2.02
2.01
f1 (ppm)


164.94
46.78
46.51
42.22
26.31
24.33
O
N
Cl
f1 (ppm)


7.26
4.06
3.57
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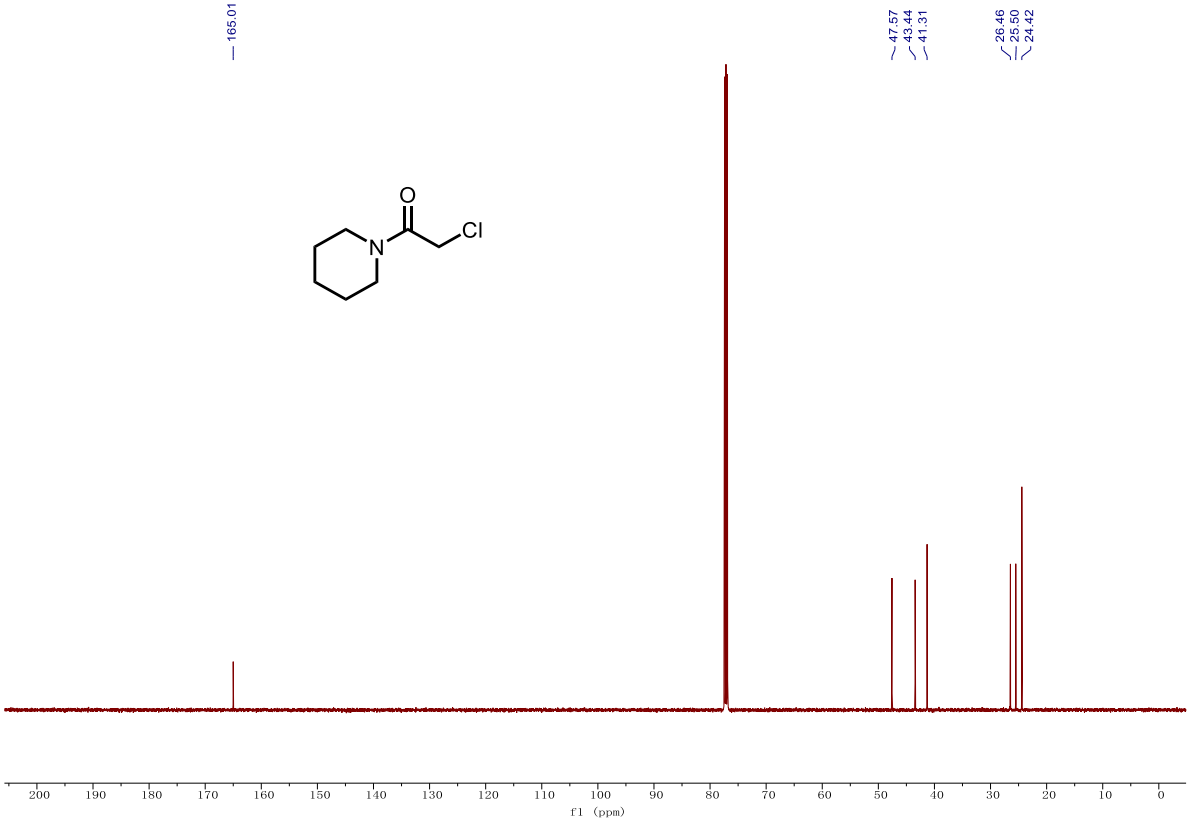
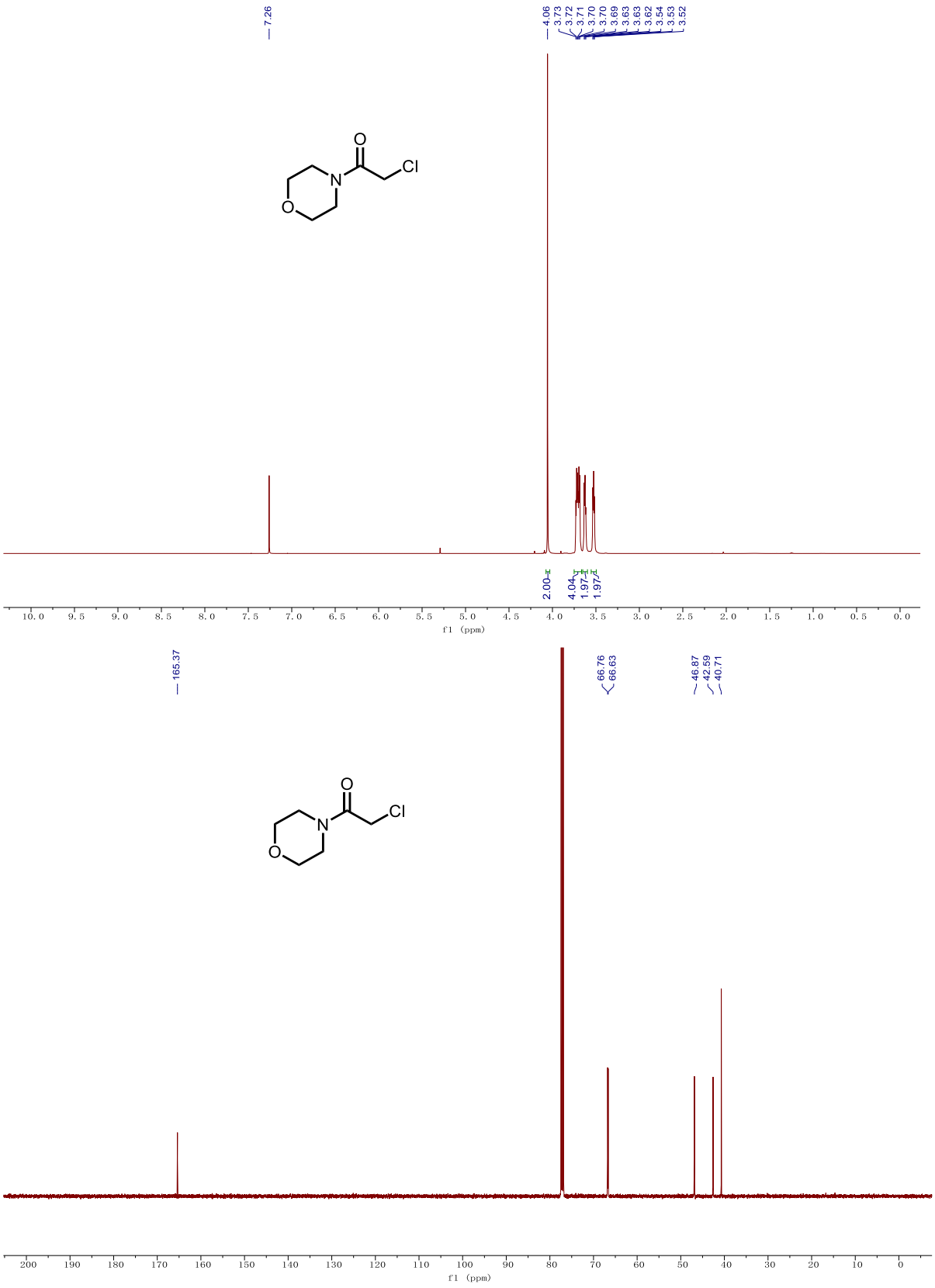
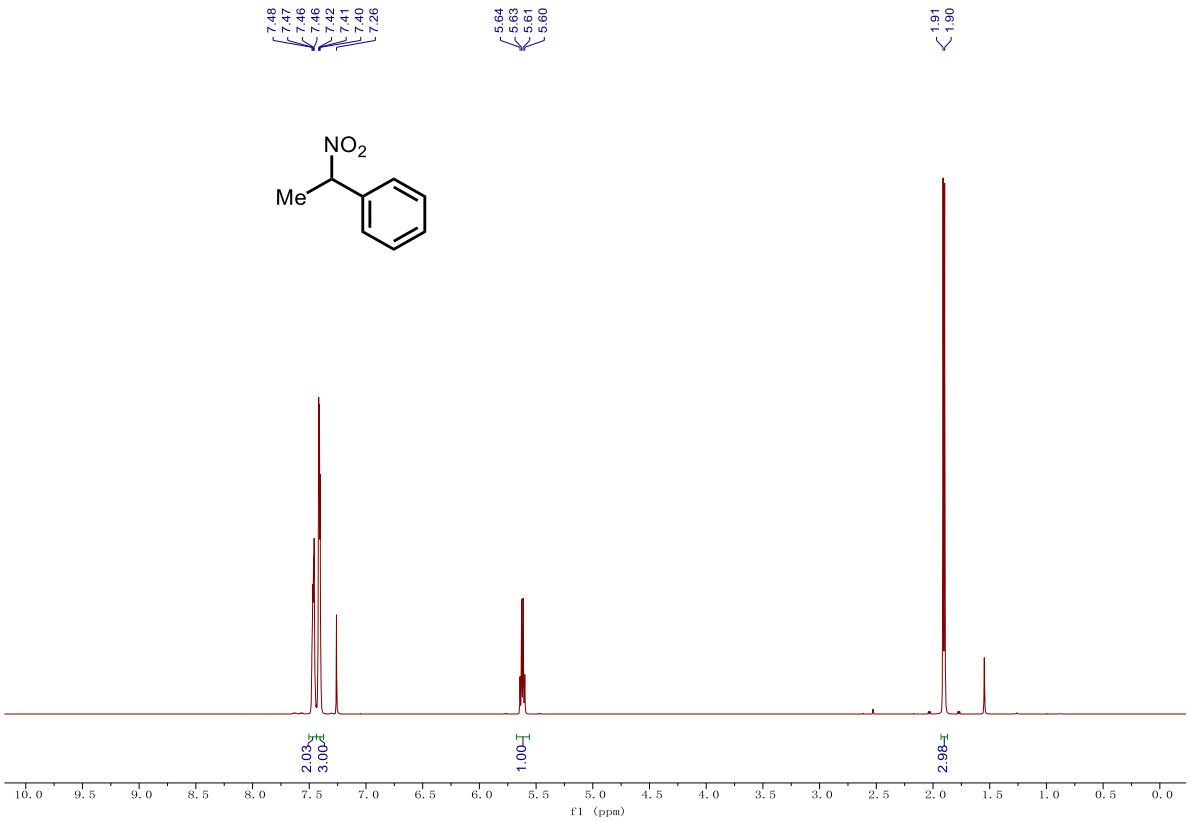
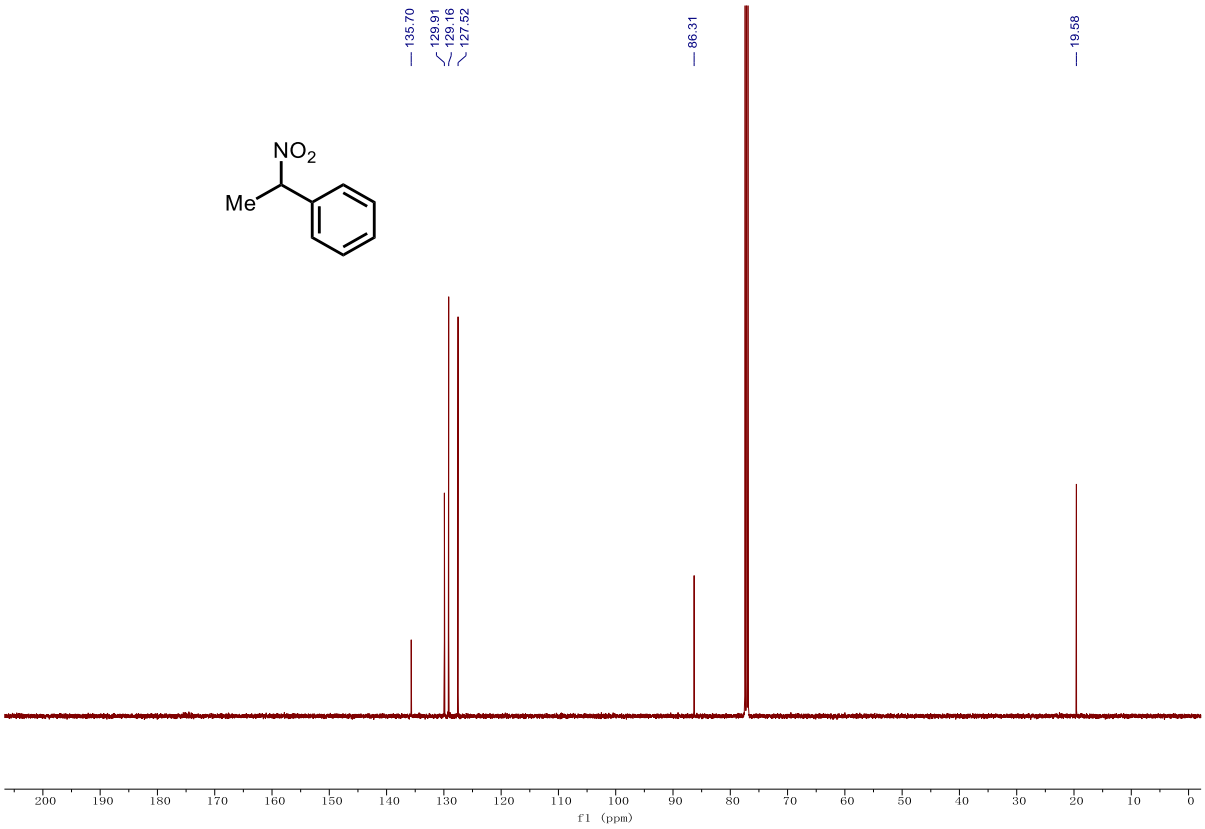
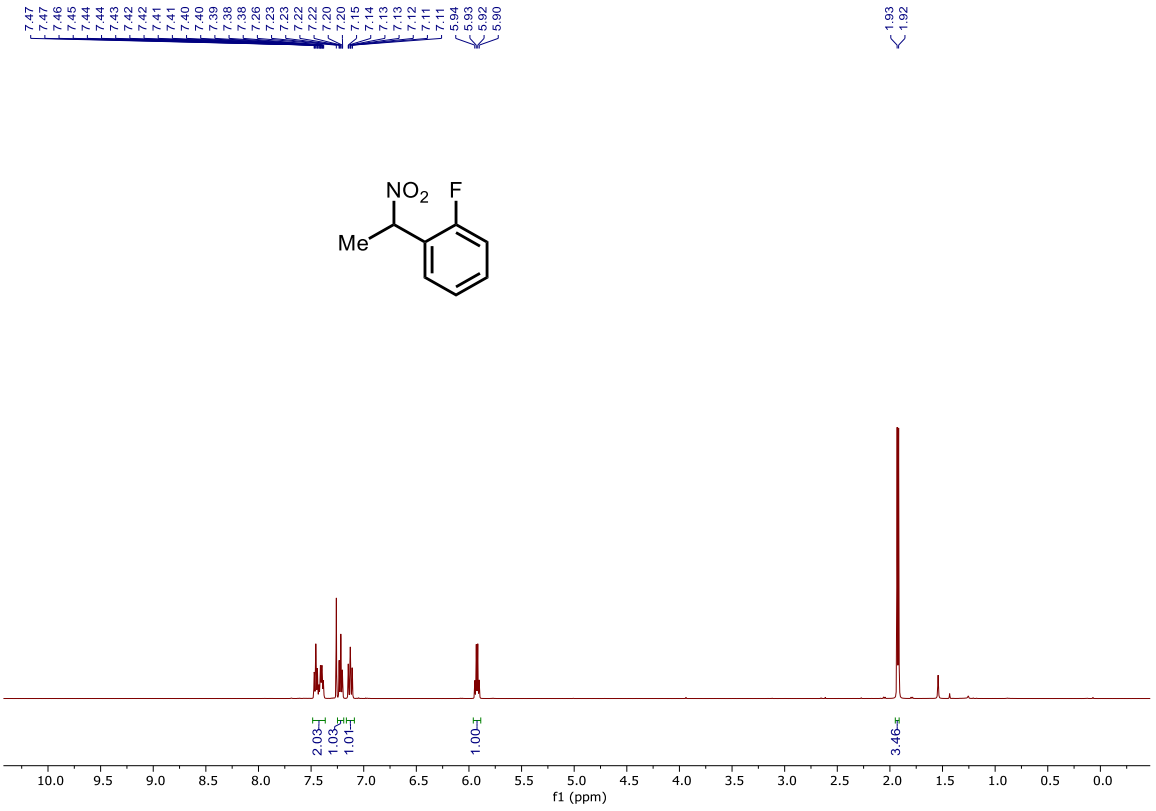
3.54
3.45
3.44
3.43
1.68
1.67
1.66
1.66
1.65
1.64
1.63
1.61
1.59
1.58
1.57
1.56
1.55
O
N
Cl
2.00
1.99
2.01
4.06
1.99
f1 (ppm)

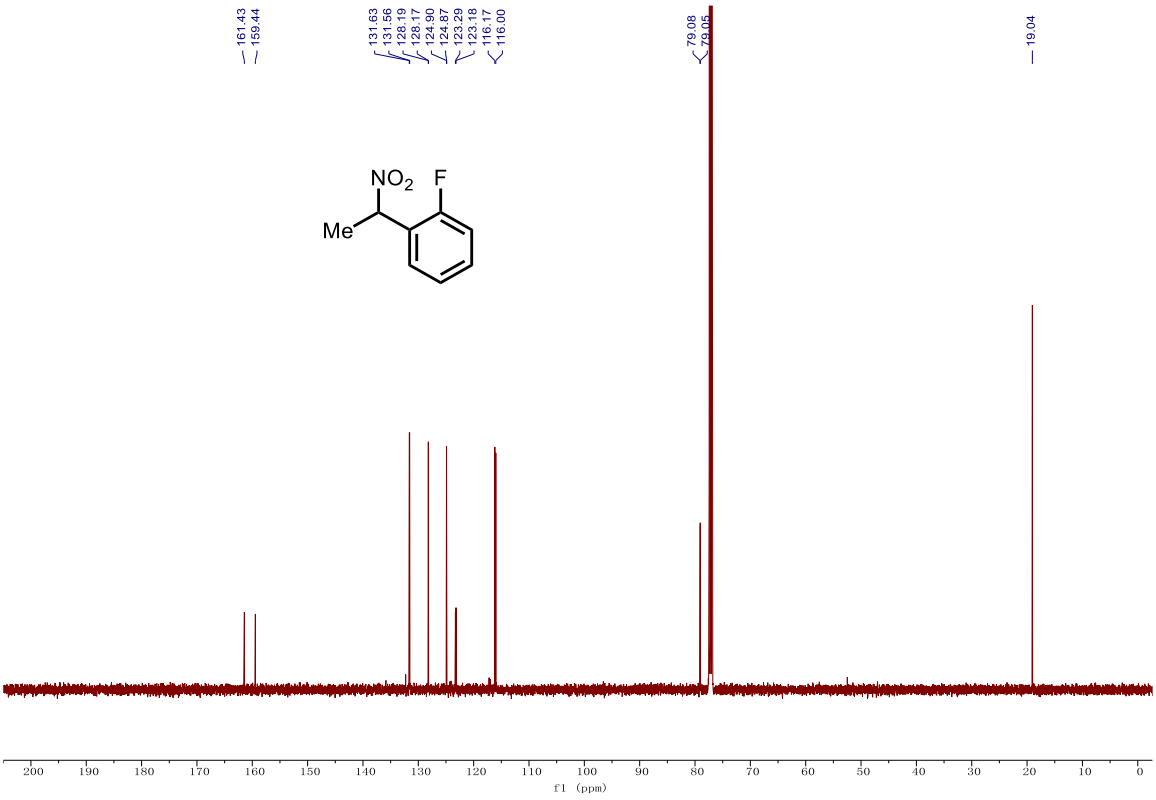

165.01
47.57
43.44
41.31
26.46
25.50
24.42
O
N
Cl
f1 (ppm)

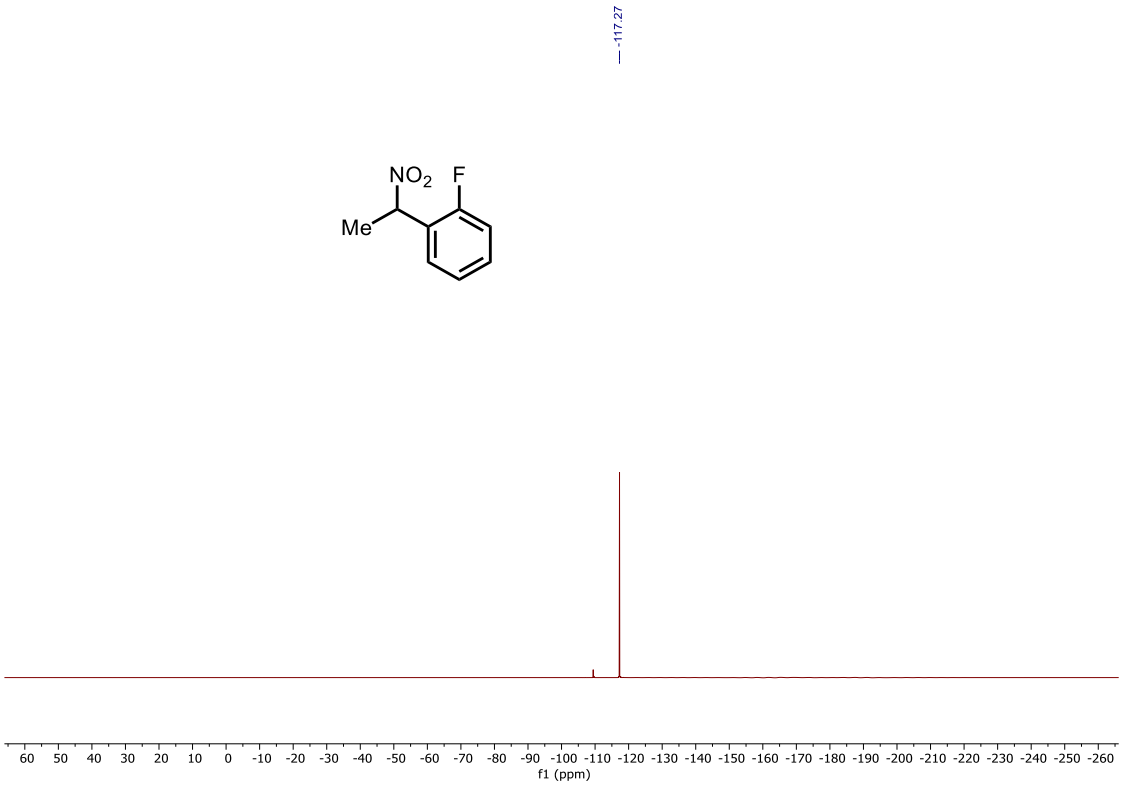

7.26
4.06
3.73
3.72
3.71
3.70
3.70
3.69
3.63
3.63
3.62
3.54
3.53
3.52
O
N
O
Cl
2.00
4.04
1.97
1.97
f1 (ppm)
165.37
66.76
66.63
46.87
42.59
40.71
O
N
O
Cl
f1 (ppm)

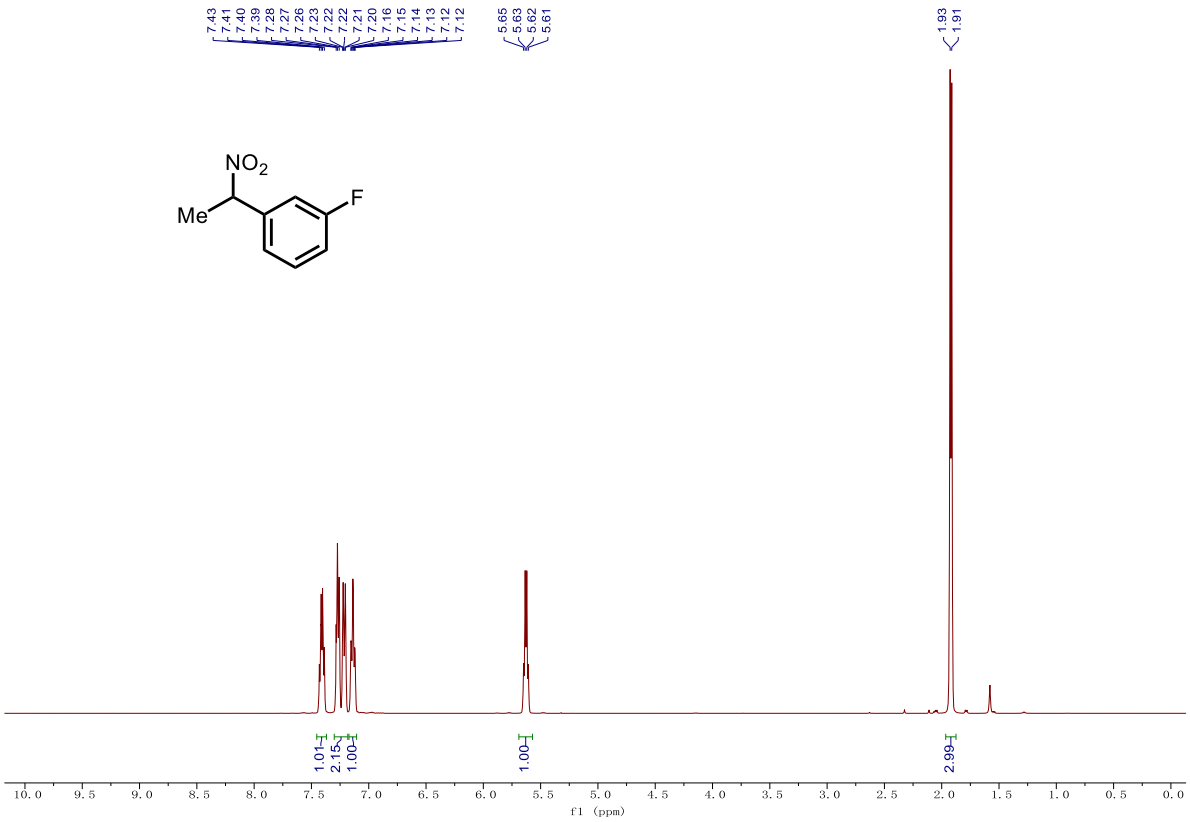

7.48
7.47
7.46
7.46
7.42
7.41
7.40
7.26
5.64
5.63
5.61
5.60
1.91
1.90
NO2
Me
2.03
3.00
1.00
2.98
f1 (ppm)

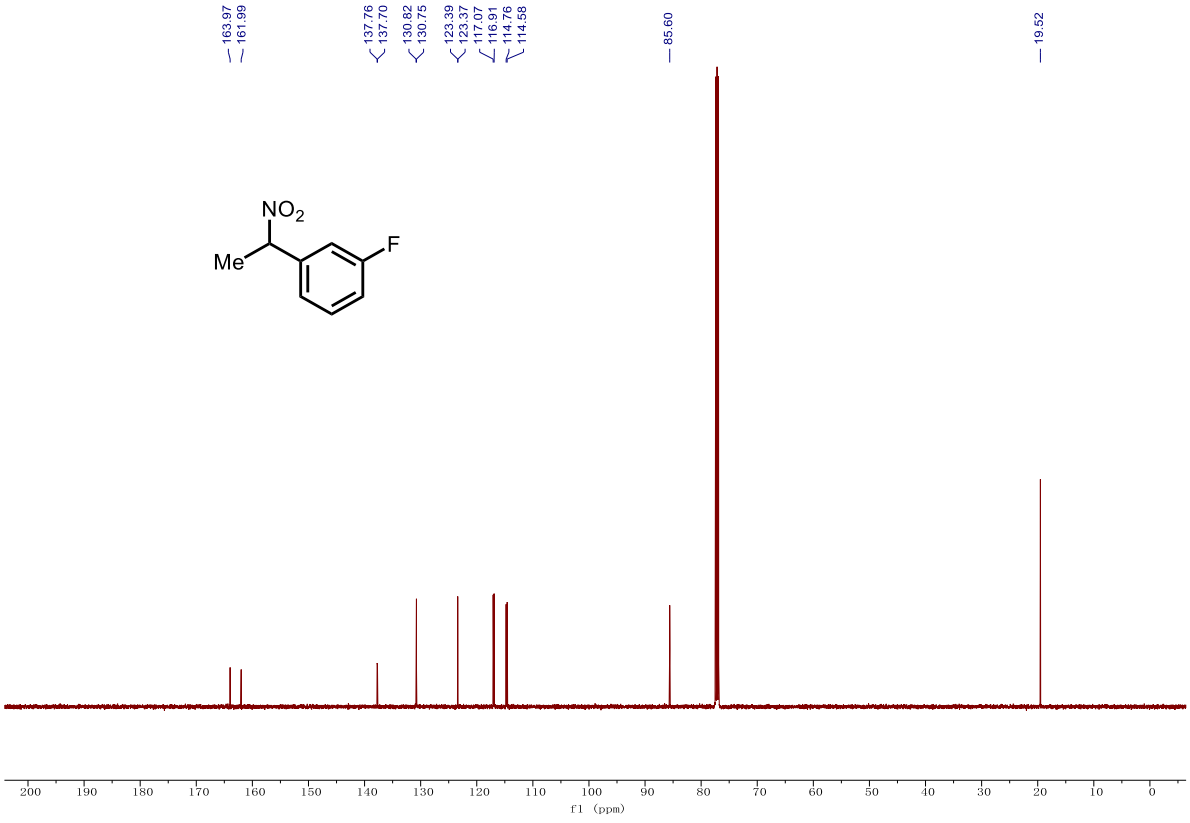

135.70
129.91
129.16
127.52
86.31
19.58
NO2
Me
f1 (ppm)

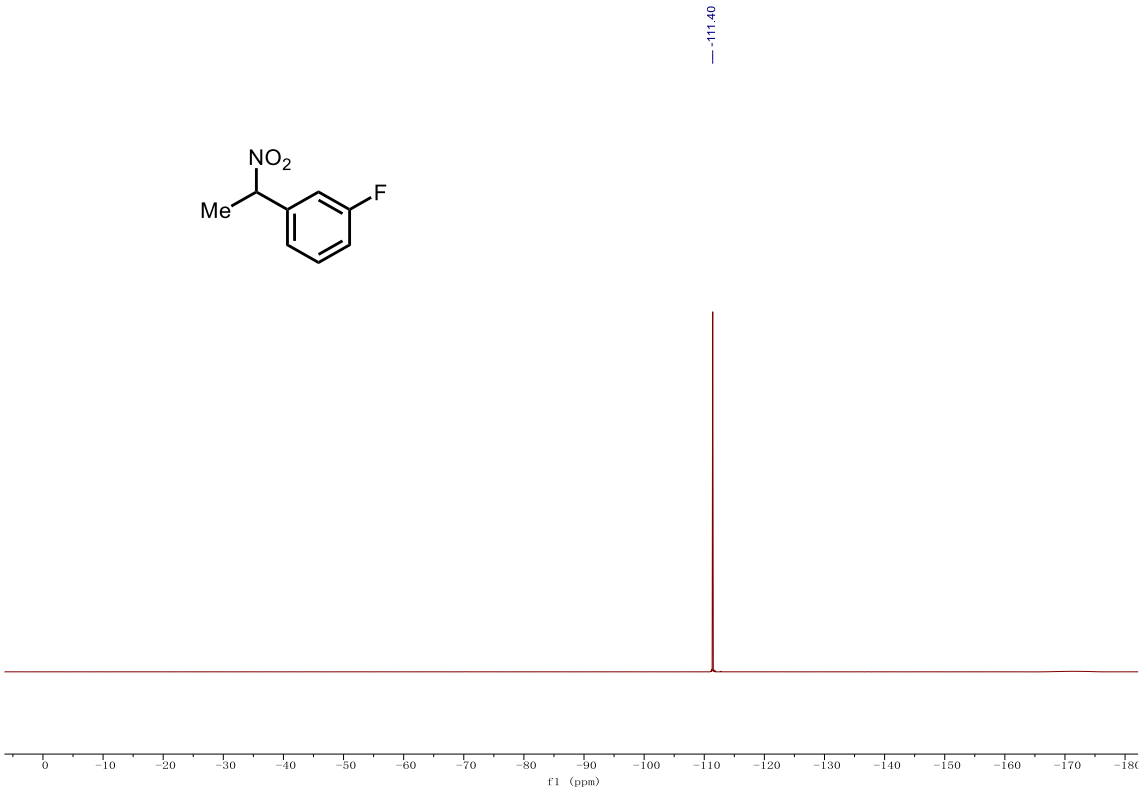

7.47
7.47
7.46
7.45
7.44
7.44
7.43
7.42
7.42
7.41
7.41
7.40
7.40
7.39
7.38
7.38
7.26
7.23
7.23
7.22
7.22
7.20
7.20
7.15
7.14
7.13
7.13
7.12
7.11
7.11
5.94
5.93
5.92
5.90
1.93
1.92
NO2
F
Me
2.03
1.03
1.01
1.00
3.46
f1 (ppm)


161.43
159.44
131.63
131.56
128.19
128.17
124.90
124.87
123.29
123.18
116.17
116.00
79.08
79.05
19.04
NO2
F
Me
f1 (ppm)


-117.27
NO2
F
Me
60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240 -250 -260
f1 (ppm)


7.43
7.41
7.40
7.39
7.28
7.27
7.26
7.23
7.22
7.22
7.21
7.20
7.16
7.15
7.14
7.13
7.12
7.12
5.65
5.63
5.62
5.61
1.93
1.91
NO2
Me
F
1.01
2.15
1.00
1.00
2.99
f1 (ppm)


163.97
161.99
137.76
137.70
130.82
130.75
123.39
123.37
117.07
116.91
114.76
114.58
85.60
19.52
NO2
Me
F
f1 (ppm)


-111.40
NO2
Me
F
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
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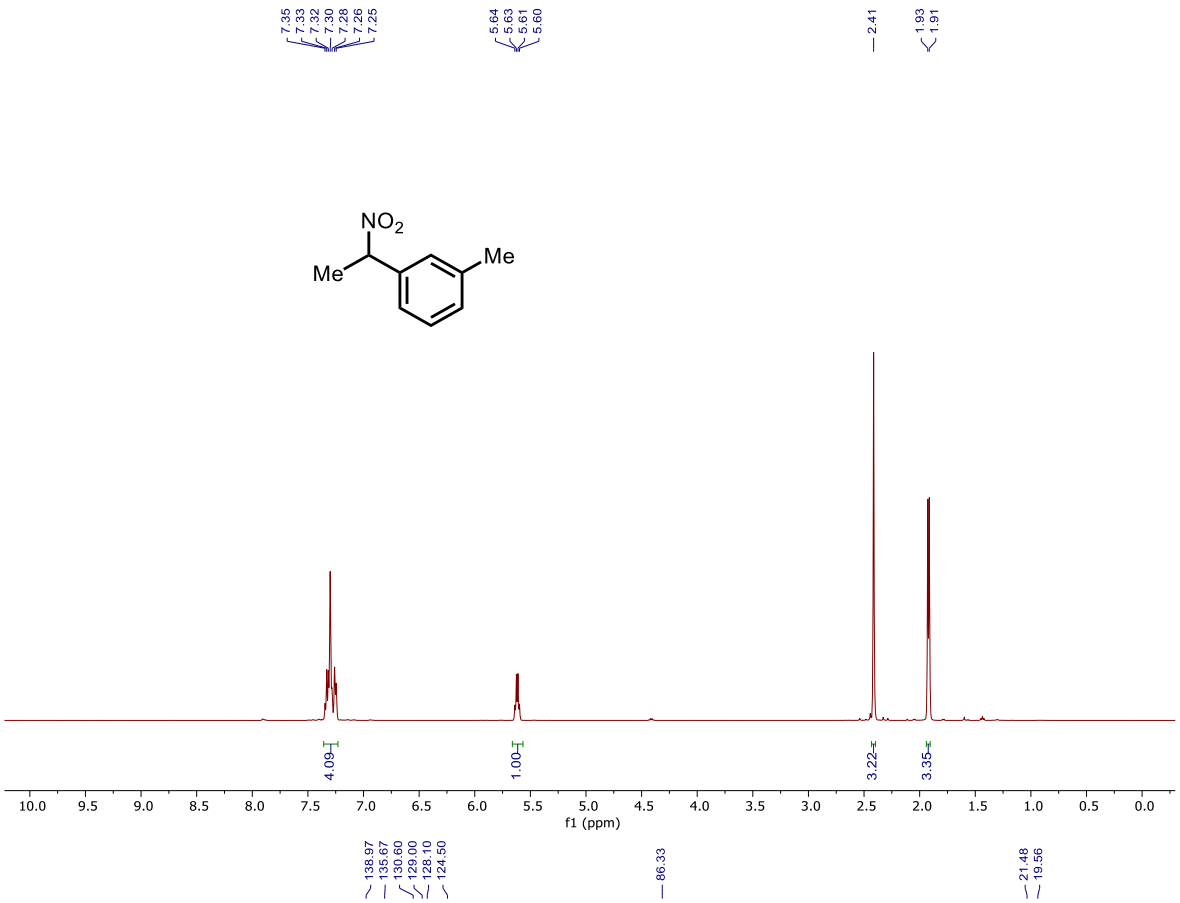
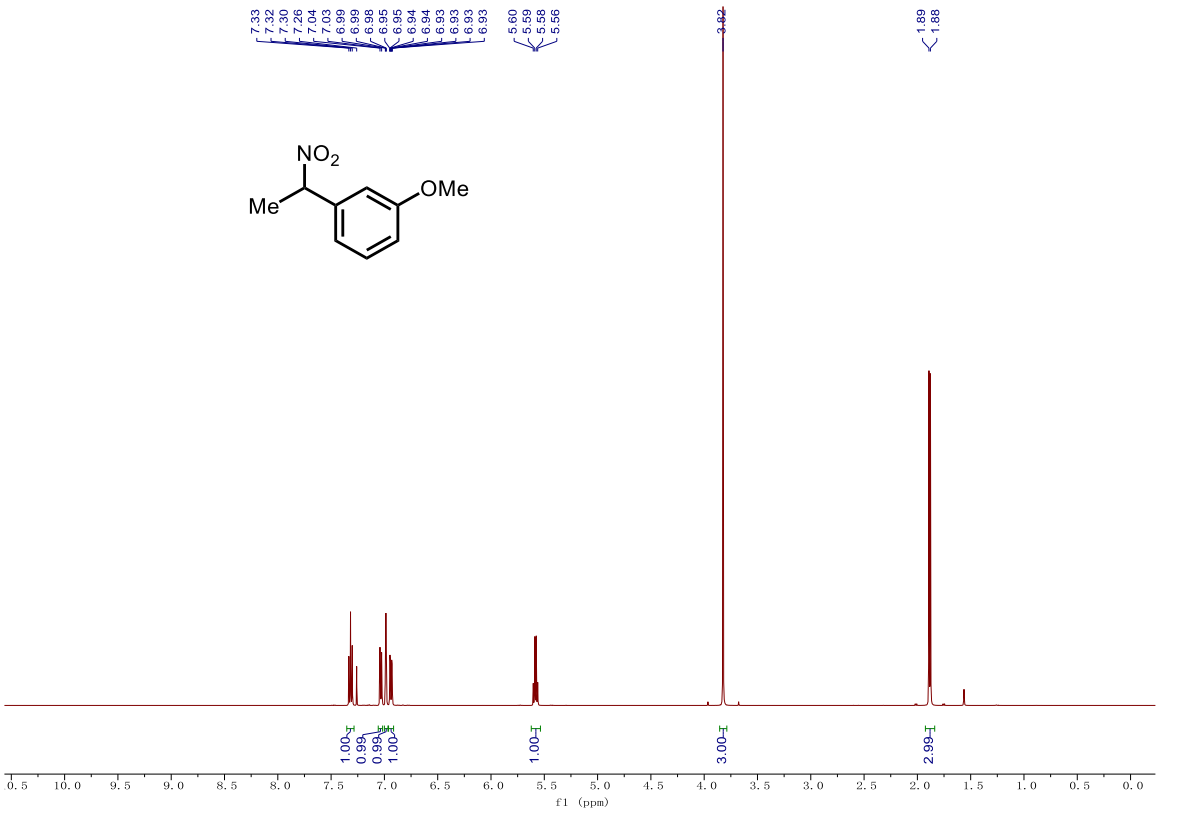
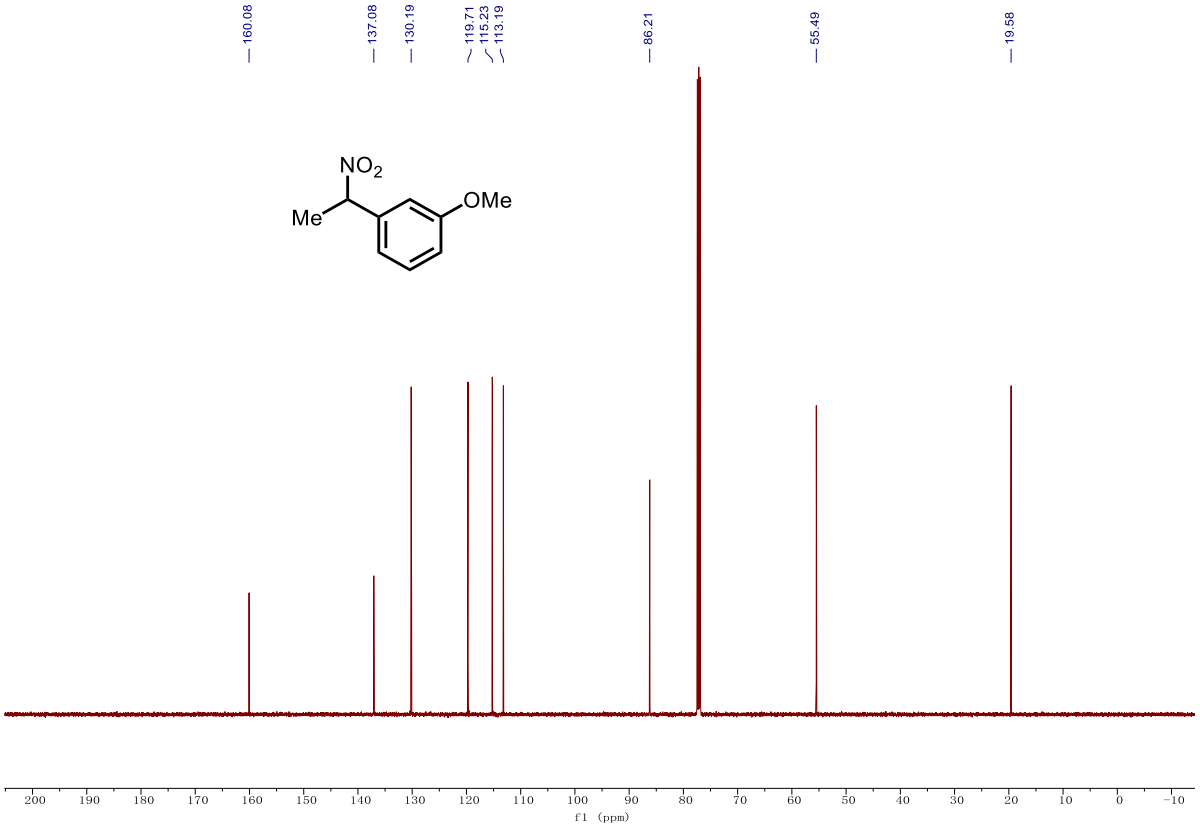
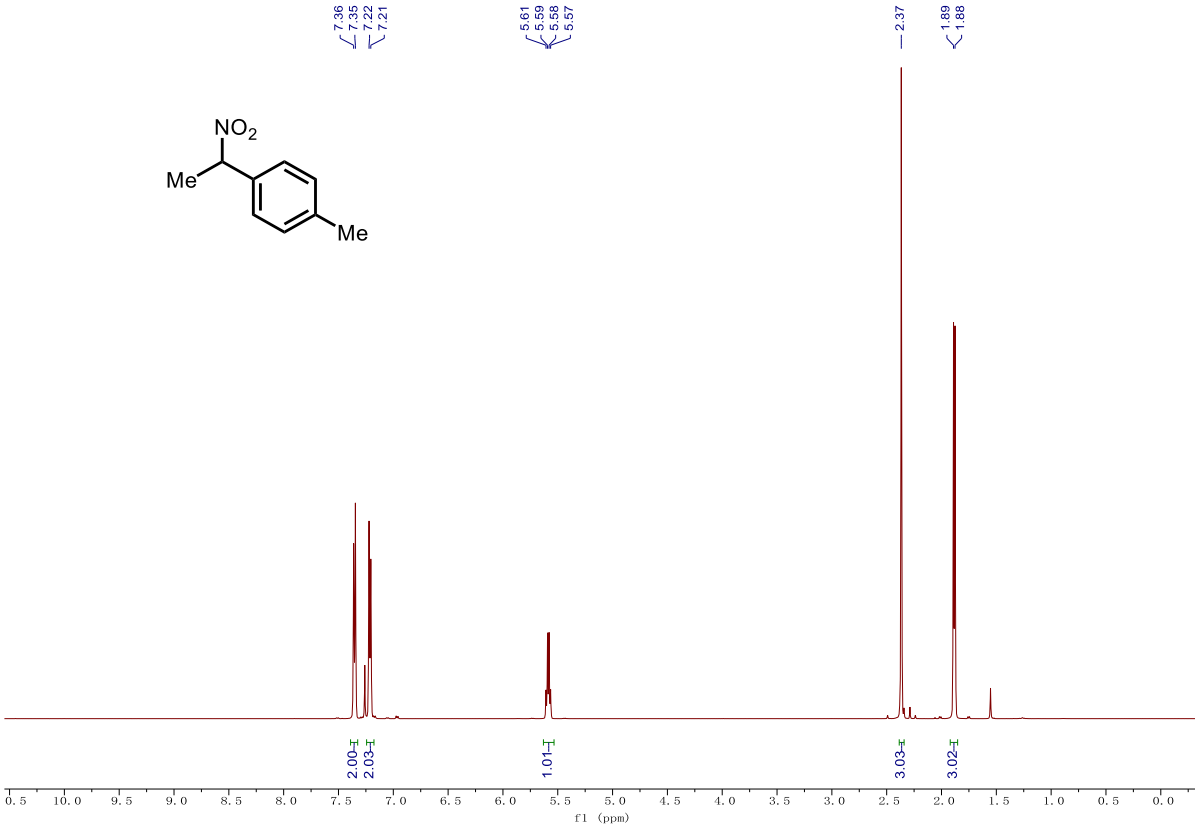
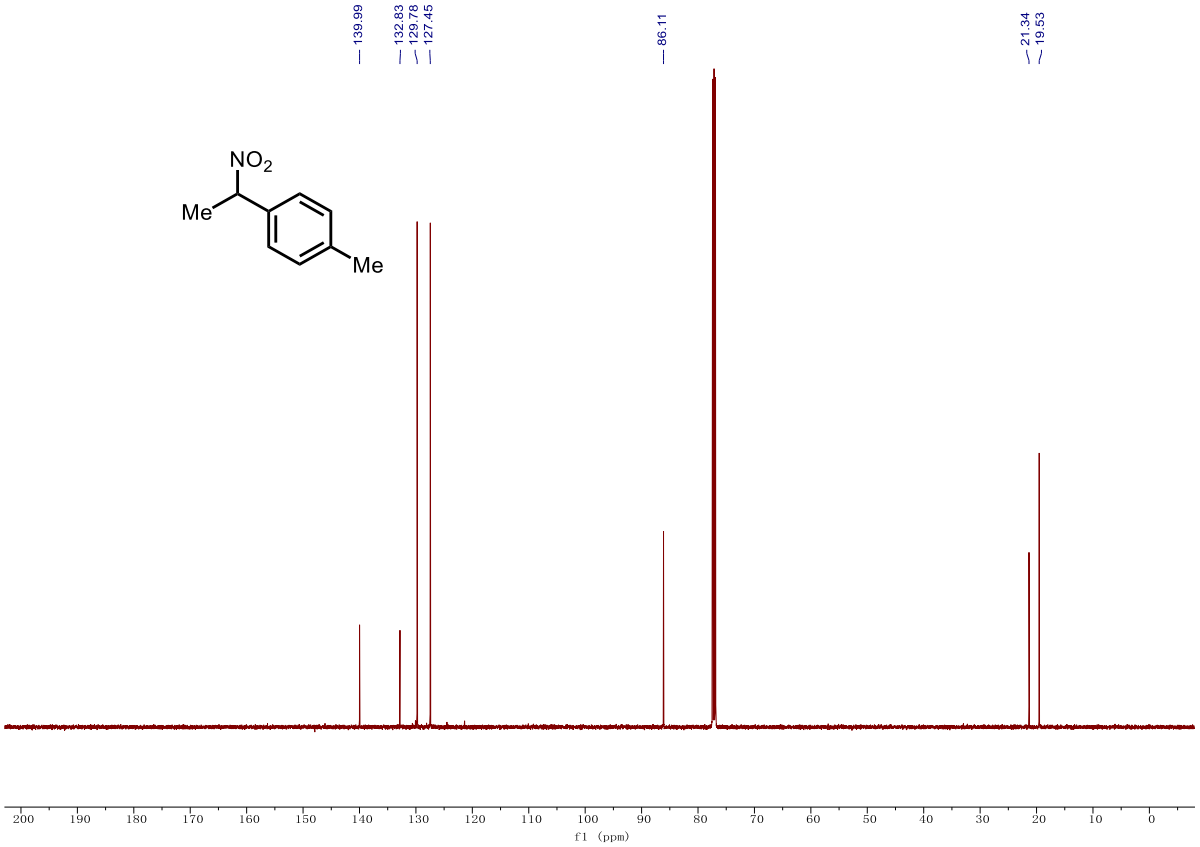
-120
-130
-140
-150
-160
-170
f1 (ppm)

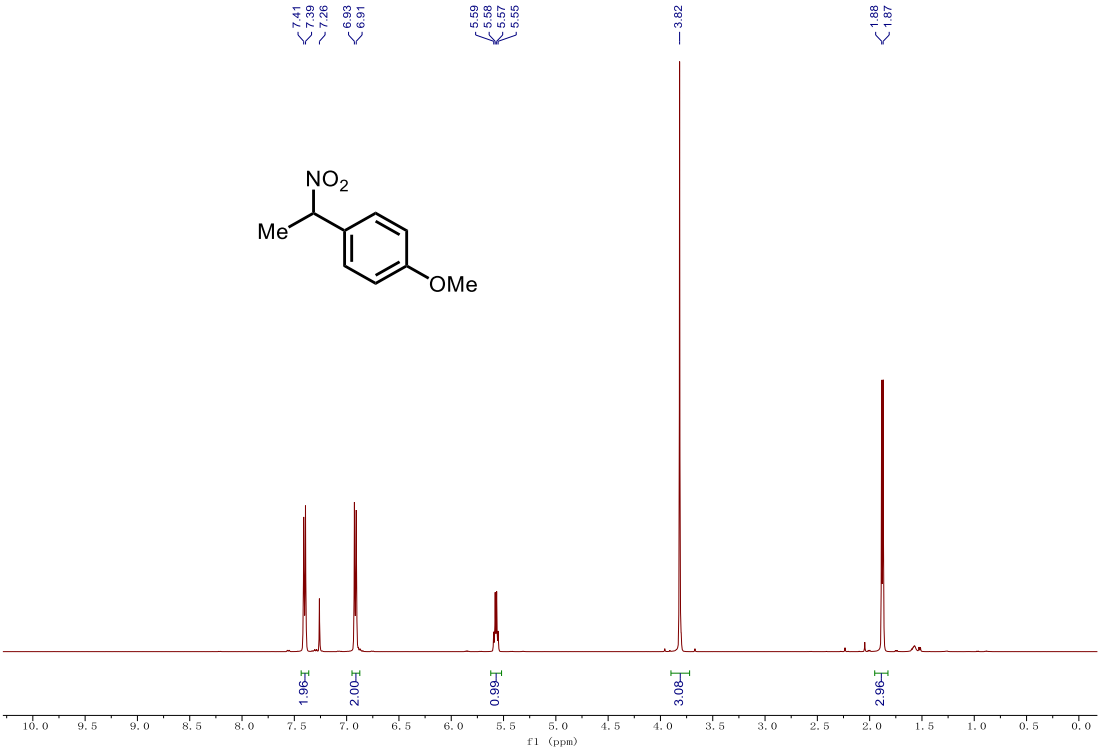

7.35
7.33
7.32
7.30
7.28
7.26
7.25
5.64
5.63
5.61
5.60
2.41
1.93
1.91
NO2
Me
Me
4.09
1.00
3.22
3.35
f1 (ppm)
138.97
135.67
130.60
129.00
128.10
124.50
86.33
21.48
19.56
NO2
Me
Me
f1 (ppm)

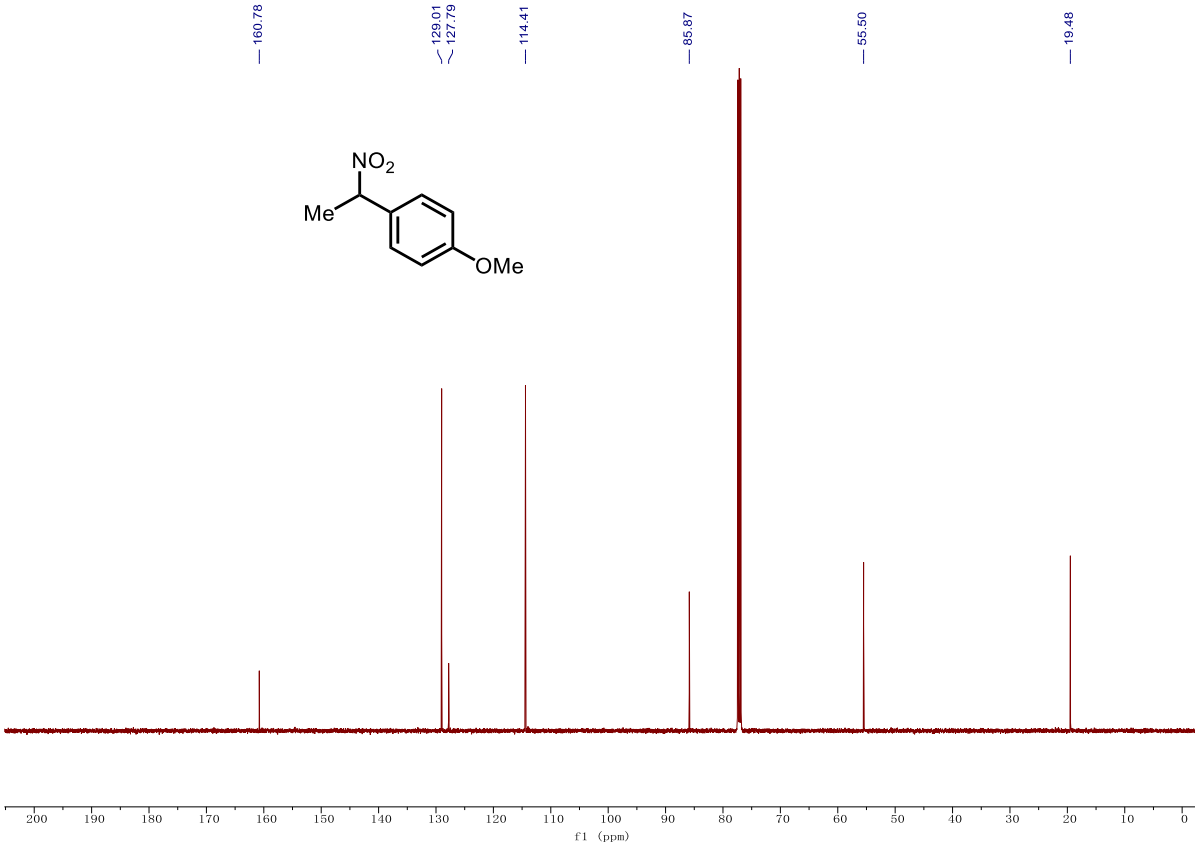

7.33
7.32
7.30
7.26
7.04
7.03
6.99
6.99
6.98
6.95
6.95
6.94
6.94
6.93
6.93
6.93
6.93
5.60
5.59
5.58
5.56
3.82
1.89
1.88
NO2
Me
OMe
1.00
0.99
0.99
1.00
1.00
3.00
2.99
f1 (ppm)

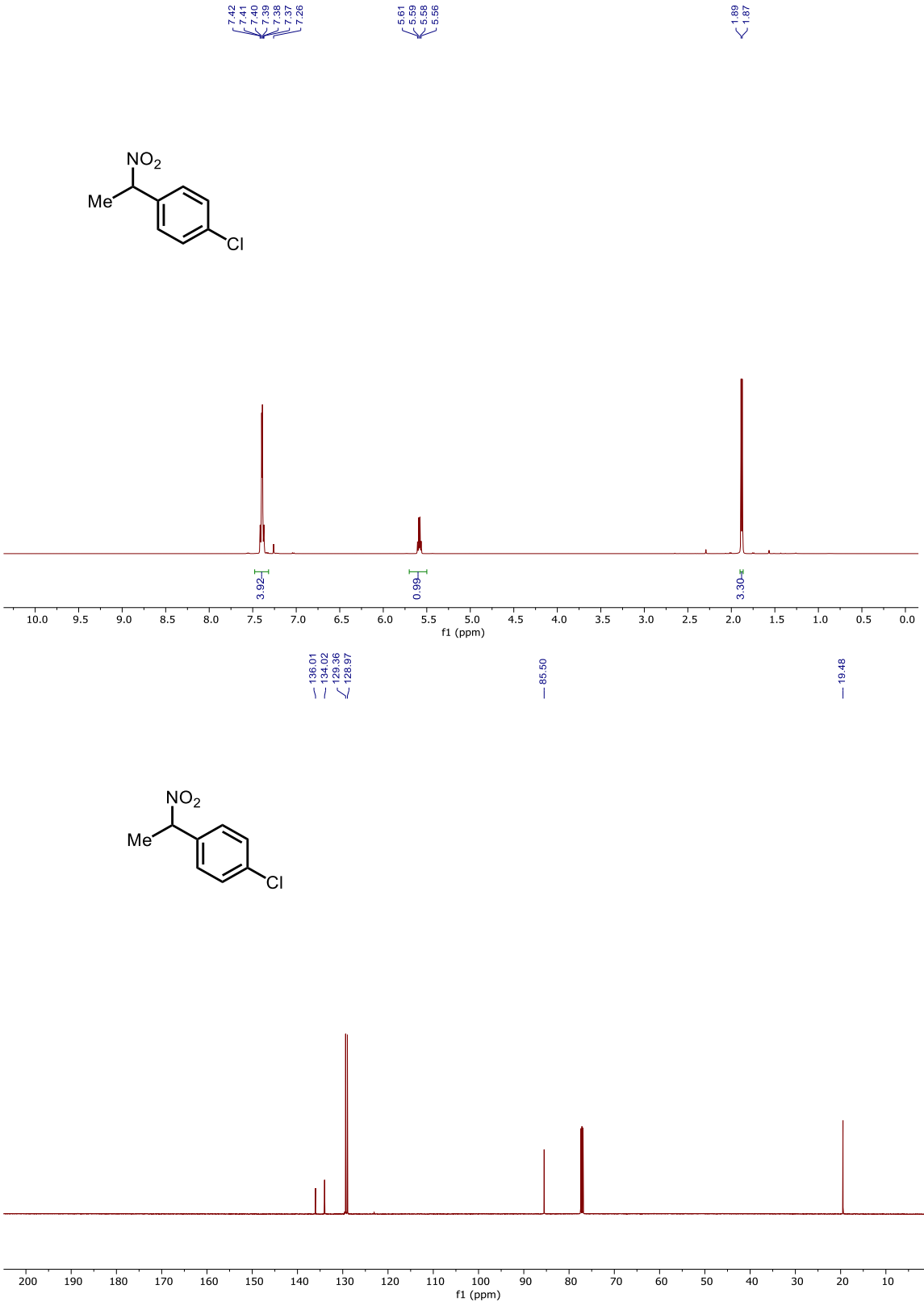

160.08
137.08
130.19
119.71
115.23
113.19
86.21
55.49
19.58
NO2
Me
OMe
f1 (ppm)

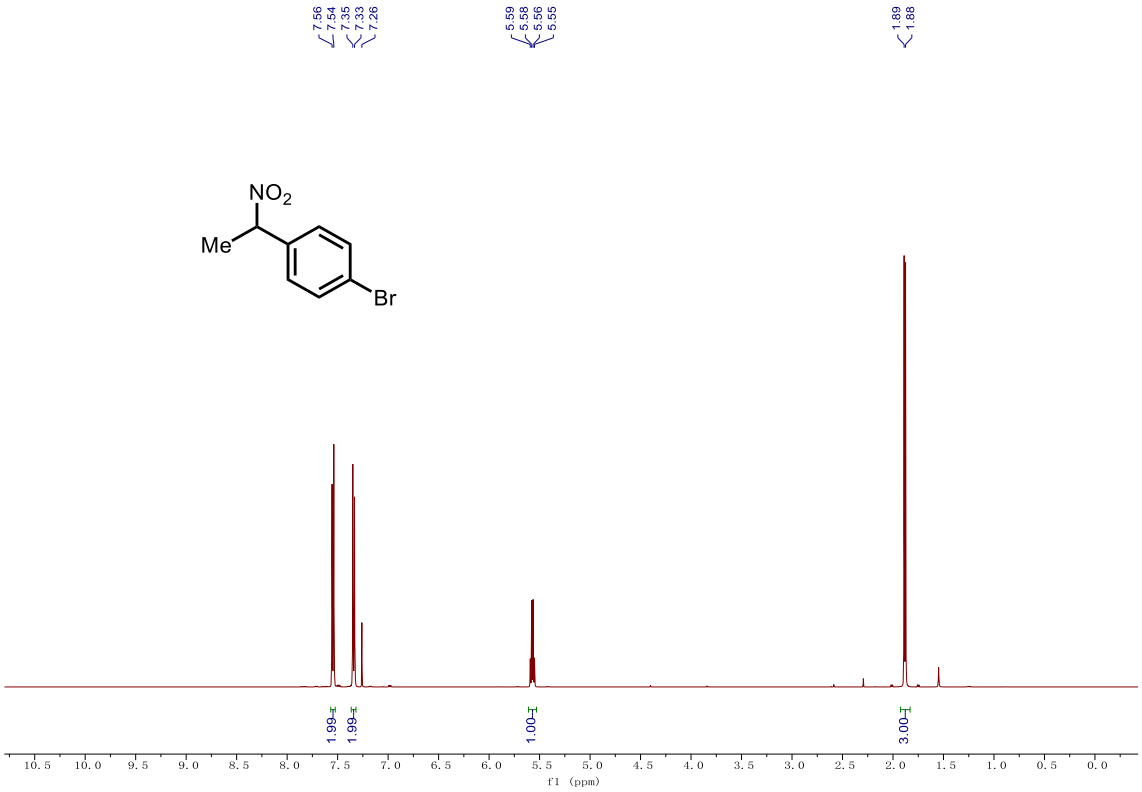

7.36
7.35
7.22
7.21
5.61
5.59
5.58
5.57
2.37
1.89
1.88
NO2
Me
Me
2.00
2.03
1.01
3.03
3.02
f1 (ppm)


139.99
132.83
129.78
127.45
86.11
21.34
19.53
NO2
Me
Me
f1 (ppm)

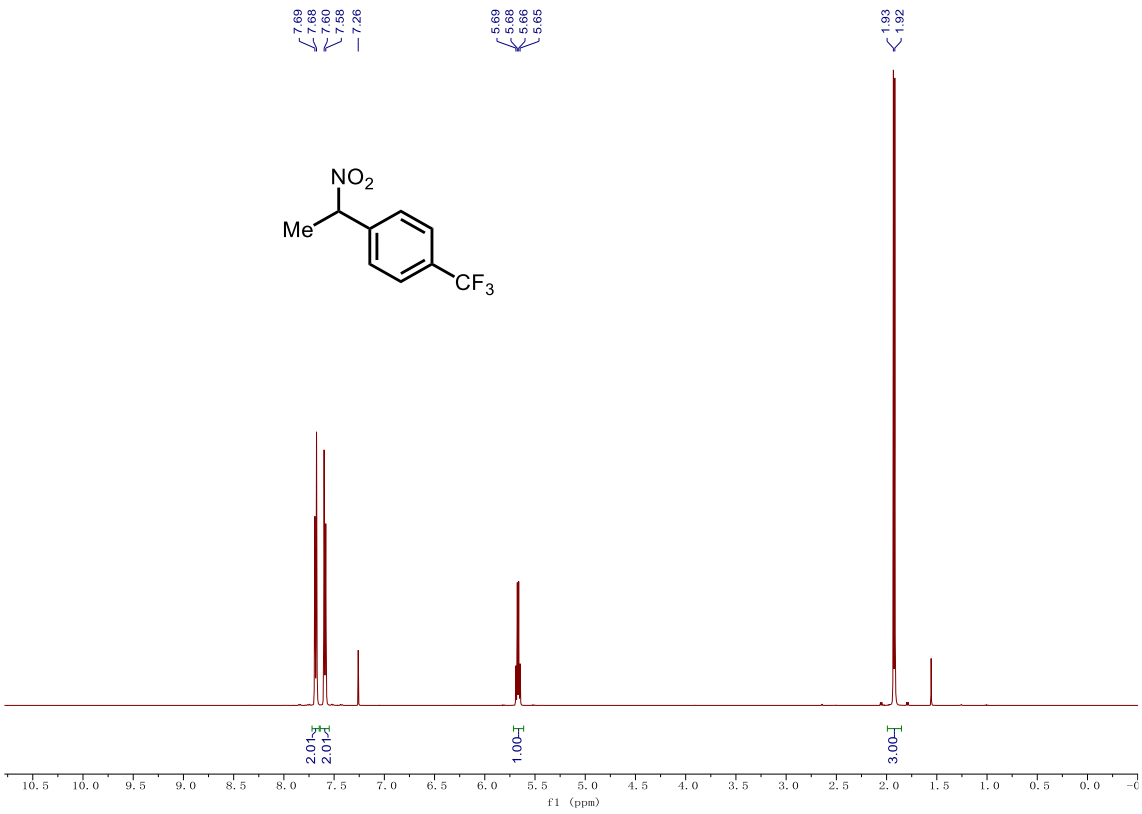

7.41
7.39
7.26
6.93
6.91
5.59
5.58
5.57
5.55
3.82
1.88
1.87
NO2
Me
OMe
1.96
2.00
0.99
3.08
2.96
f1 (ppm)

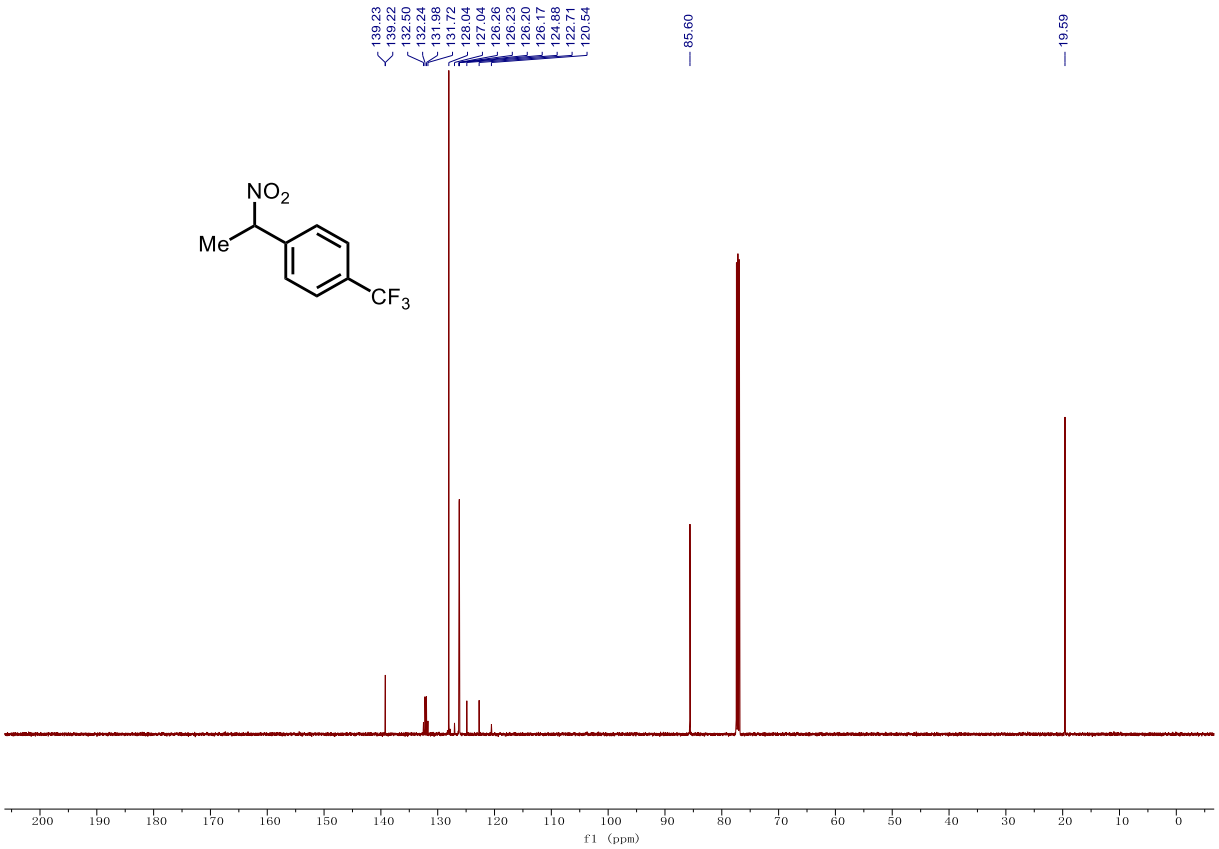

160.78
129.01
127.79
114.41
85.87
55.50
19.48
NO2
Me
OMe
f1 (ppm)

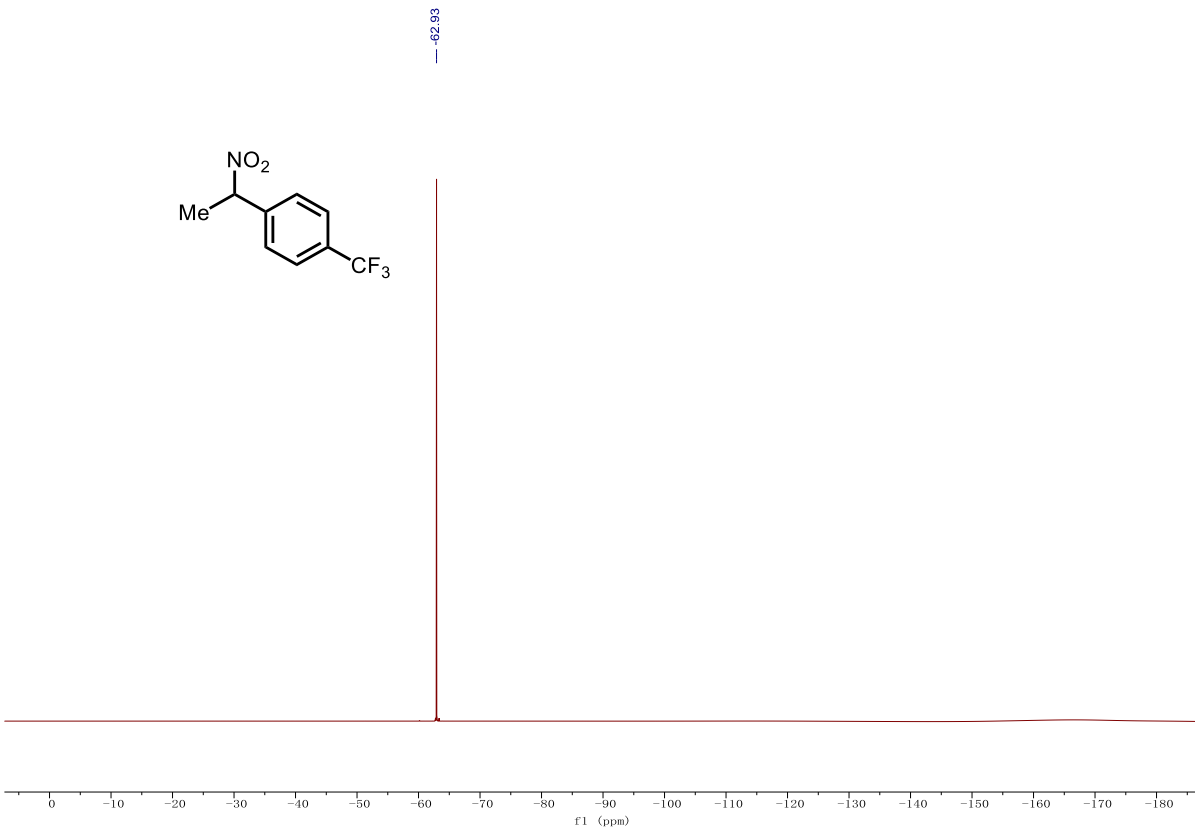

7.42
7.41
7.40
7.39
7.38
7.37
7.26
5.61
5.59
5.58
5.56
1.89
1.87
NO2
Me
Cl
3.92
0.99
3.30
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)
136.01
134.02
129.36
128.97
85.50
19.48
NO2
Me
Cl
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


7.56
7.54
7.35
7.33
7.26
5.59
5.58
5.56
5.55
1.89
1.88
NO2
Me
Br
1.99
1.99
1.00
3.00
f1 (ppm)


134.53
132.37
129.24
124.25
85.59
19.48
NO2
Me
Br
f1 (ppm)


7.69
7.68
7.60
7.58
7.26
5.69
5.68
5.66
5.65
1.93
1.92
NO2
Me
CF3
2.01
2.01
1.00
3.00
f1 (ppm)


139.23
139.22
132.50
132.24
131.98
131.72
128.04
127.04
126.26
126.23
126.20
126.17
124.88
122.71
120.54
85.60
19.59
NO2
Me
CF3
f1 (ppm)


-62.93
NO2
Me
CF3
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
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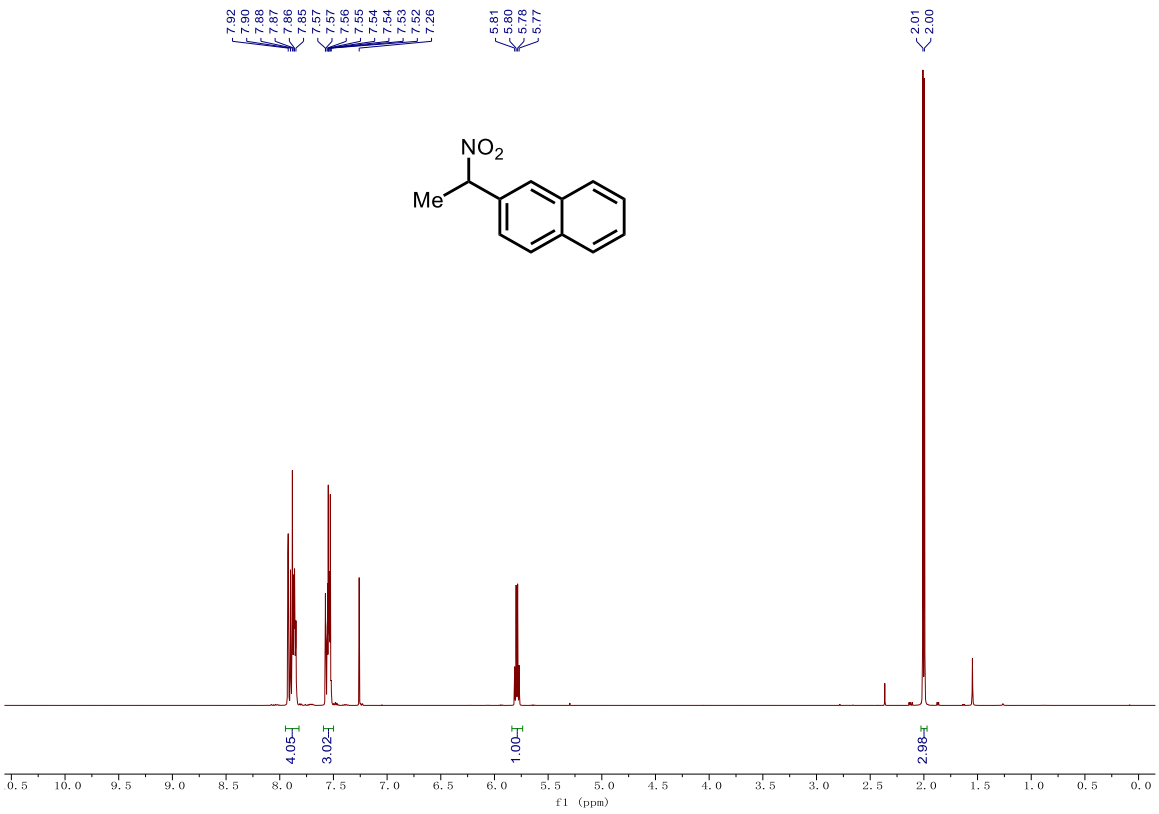
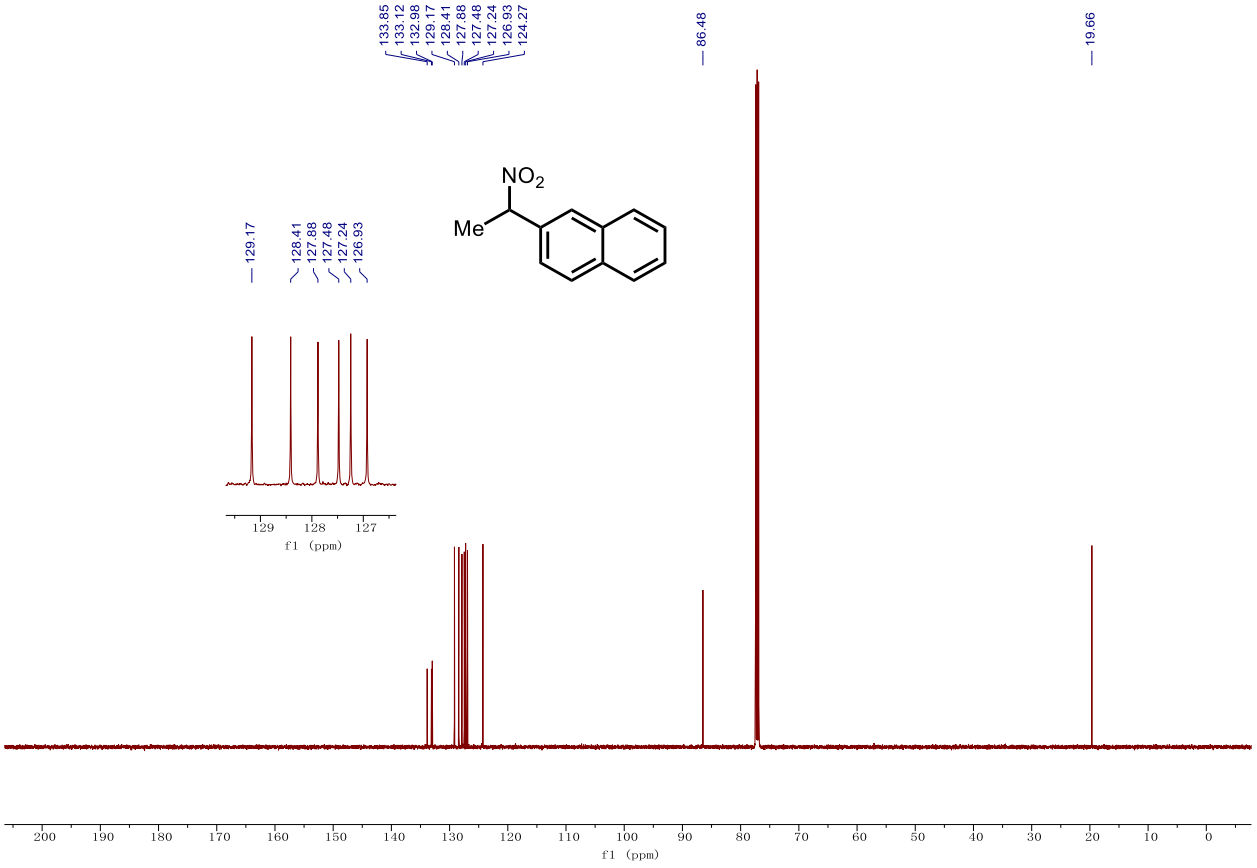
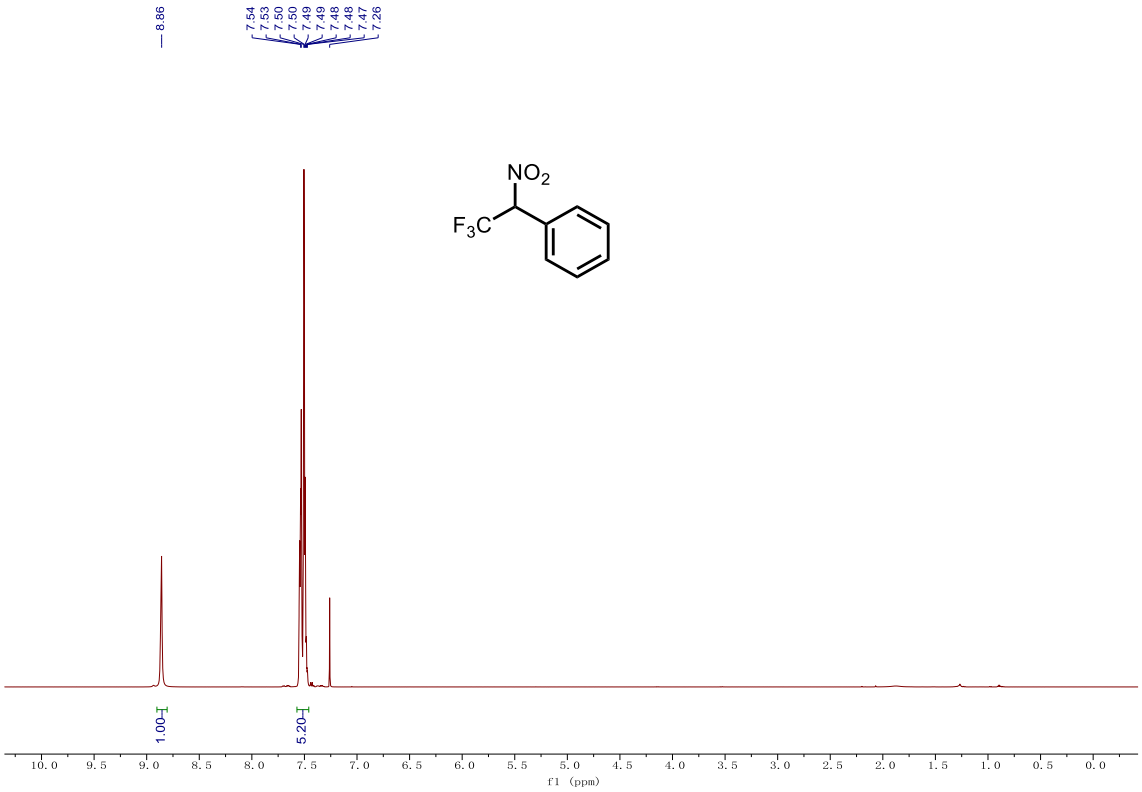
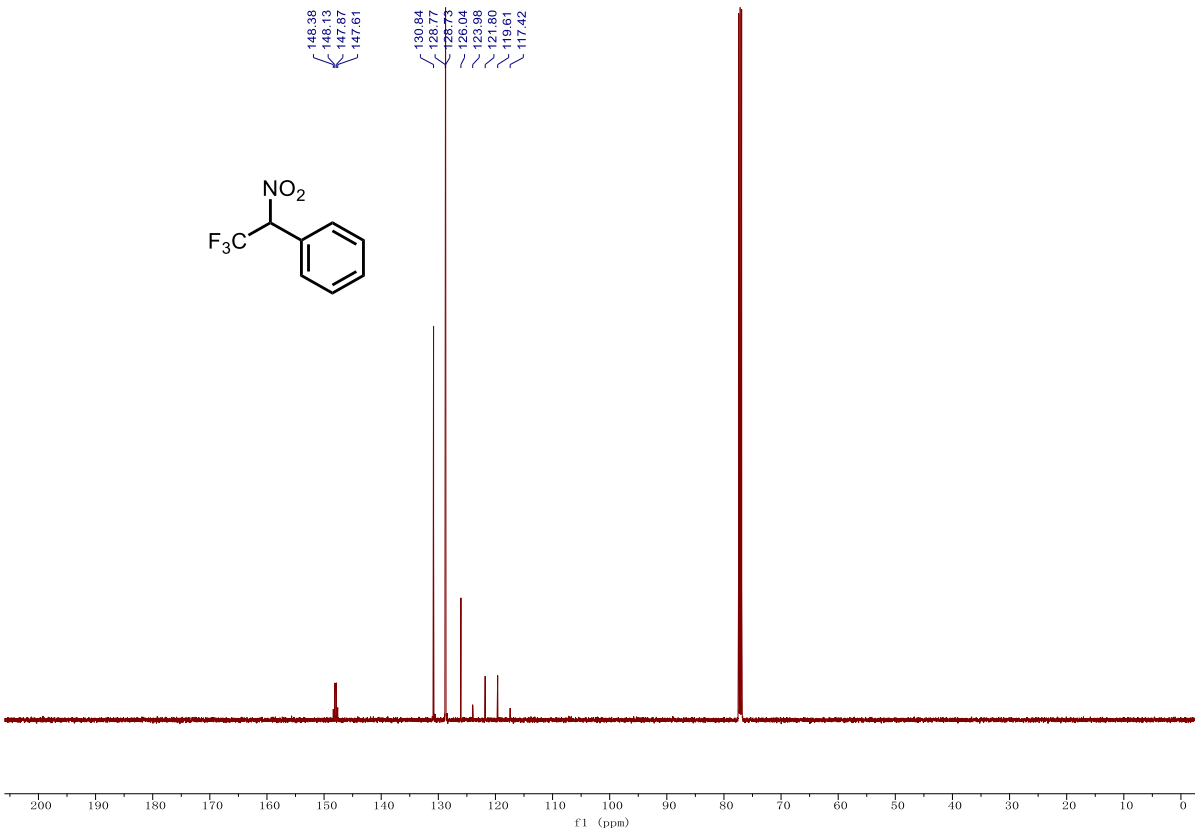
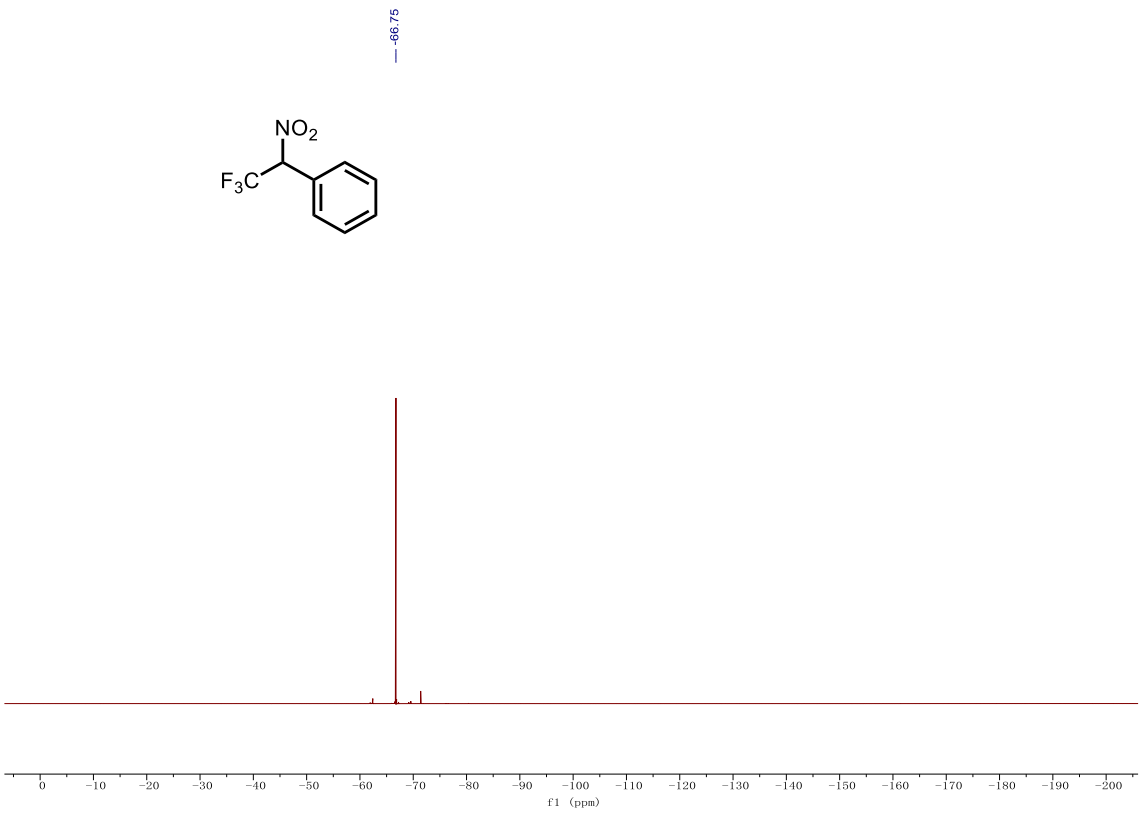
-110
-120
-130
-140
-150
-160
-170
-180
f1 (ppm)

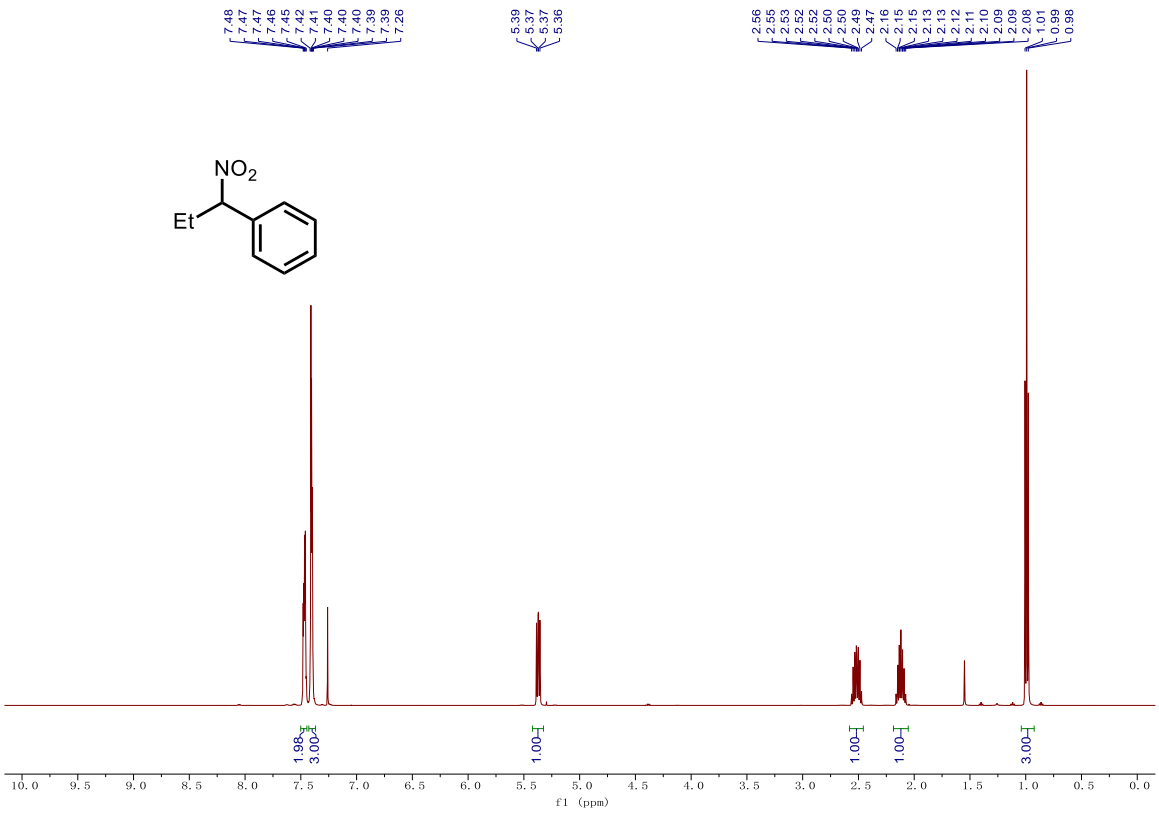

7.92
7.90
7.88
7.87
7.86
7.85
7.57
7.57
7.56
7.55
7.54
7.54
7.53
7.52
7.26
5.81
5.80
5.78
5.77
2.01
2.00
NO2
Me
4.05
3.02
1.00
2.98
f1 (ppm)


133.85
133.12
132.98
129.17
128.41
127.88
127.48
127.24
126.93
124.27
86.48
19.66
NO2
Me
129.17
128.41
127.88
127.48
127.24
126.93
129
128
127
f1 (ppm)
f1 (ppm)


8.86
7.54
7.53
7.50
7.50
7.49
7.49
7.48
7.48
7.47
7.26
NO2
F3C
1.00
5.20
f1 (ppm)


148.38
148.13
147.87
147.61
130.84
128.77
128.73
126.04
123.98
121.80
119.61
117.42
NO2
F3C
f1 (ppm)


-66.75
NO2
F3C
0
−10
−20
−30
−40
−50
−60
−70
−80
−90
−100
−110
−120
−130
−140
−150
−160
−170
−180
−190
−200
f1 (ppm)


7.48
7.47
7.47
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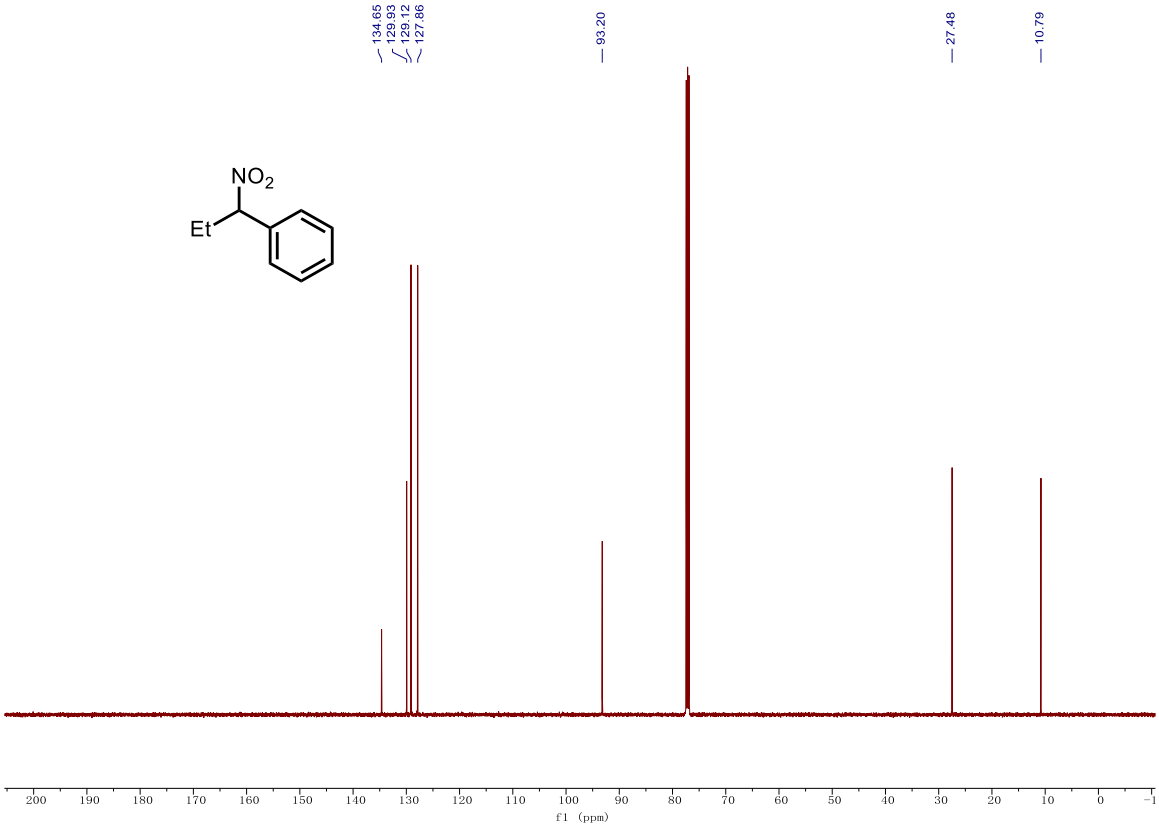
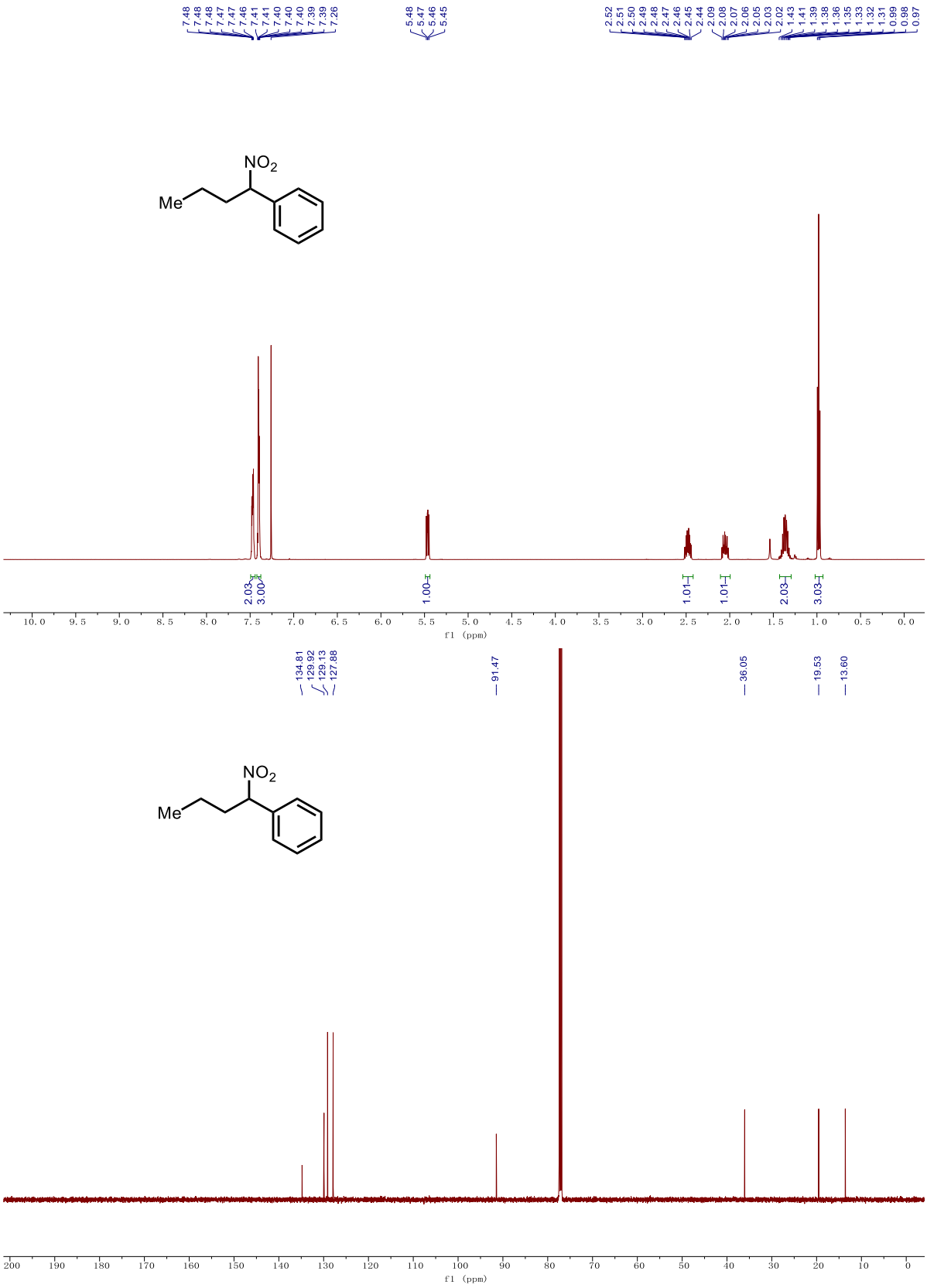
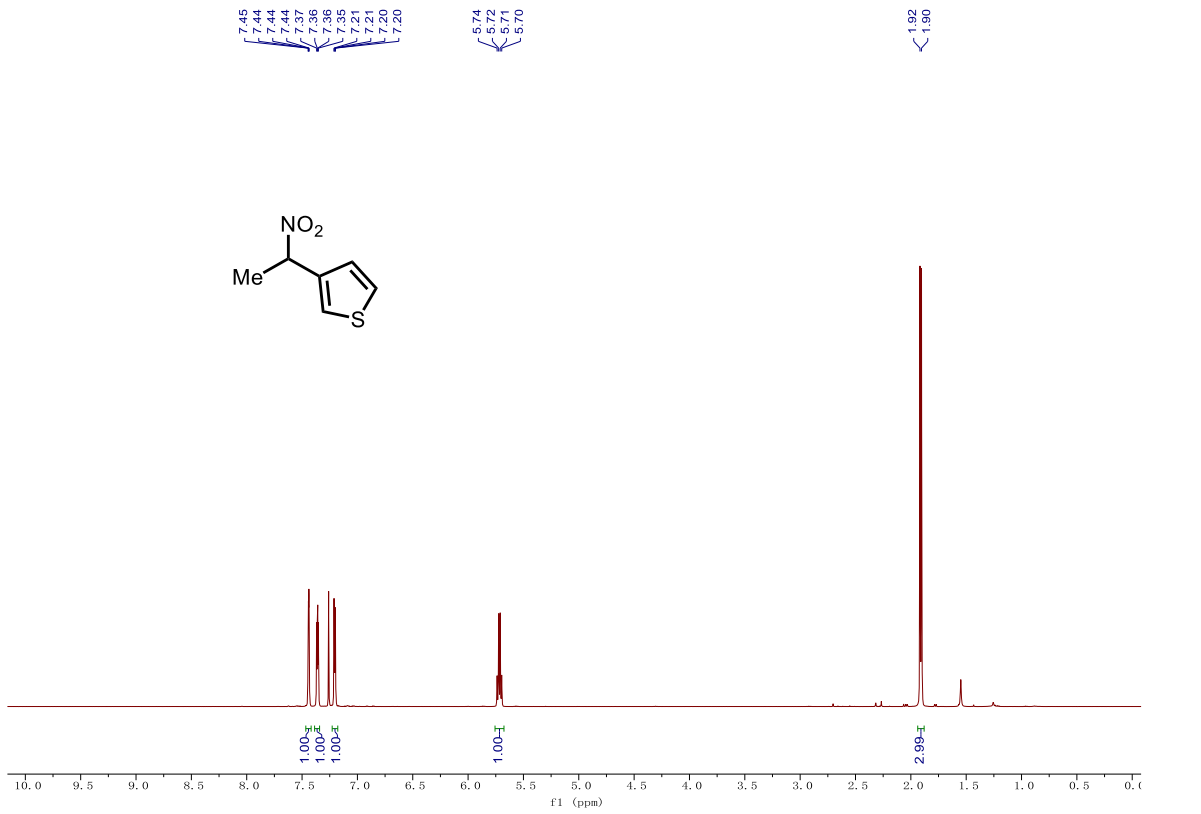
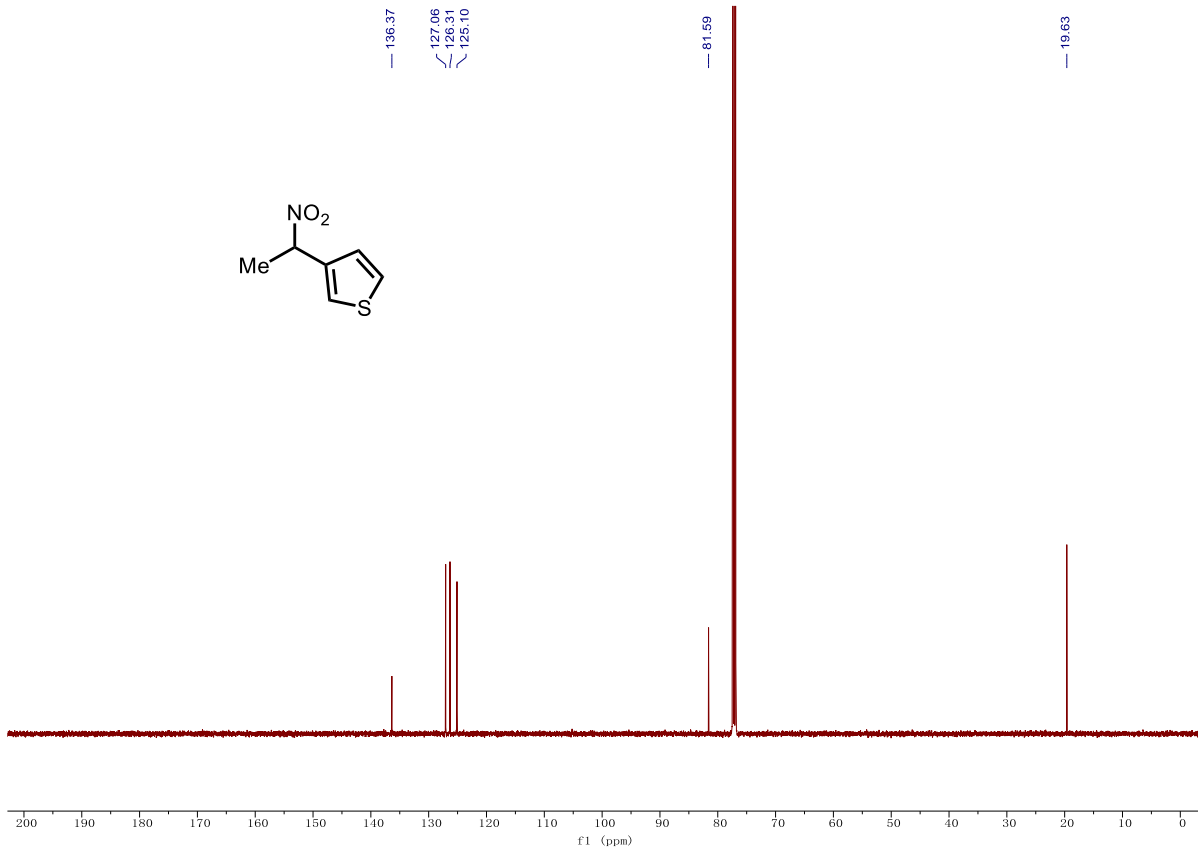
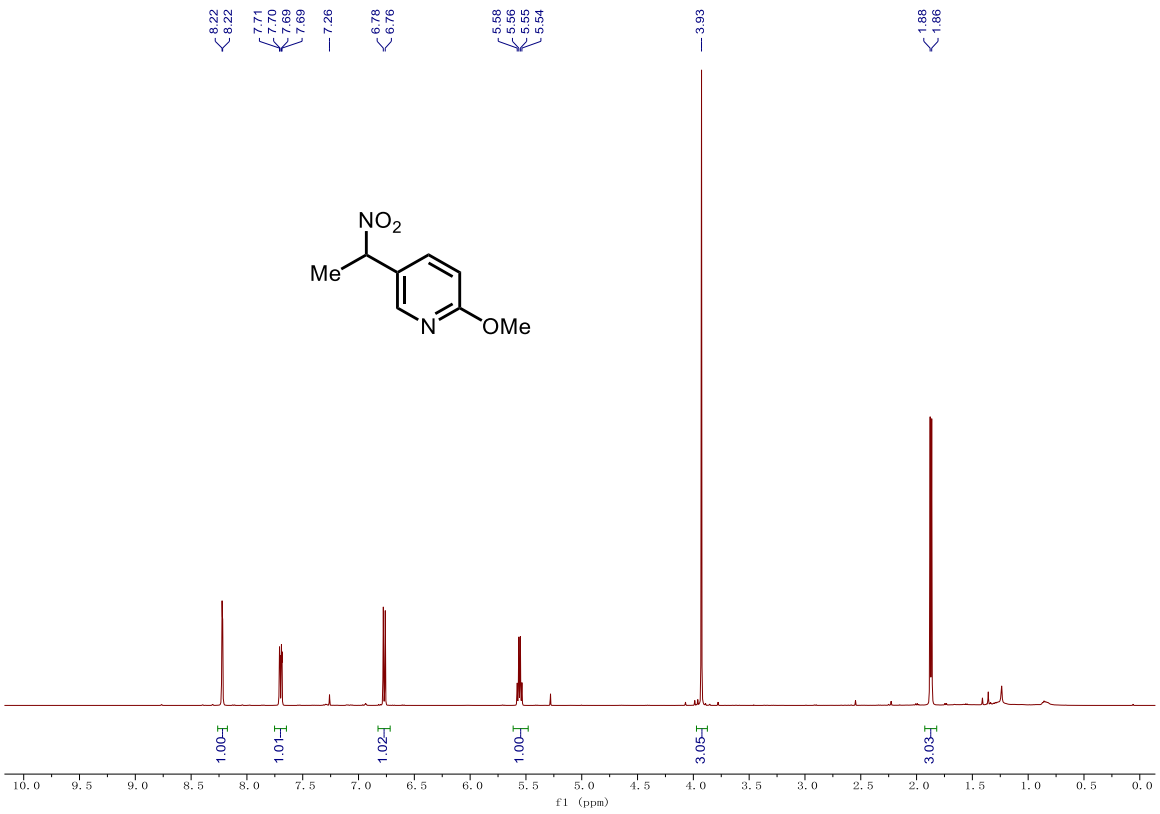
7.42
7.41
7.40
7.40
7.40
7.39
7.39
7.26
5.39
5.37
5.37
5.36
2.56
2.55
2.53
2.52
2.52
2.50
2.50
2.49
2.47
2.16
2.15
2.15
2.13
2.12
2.11
2.10
2.09
2.09
2.08
1.01
0.99
0.98
NO2
Et
1.98
3.00
1.00
1.00
1.00
3.00
f1 (ppm)

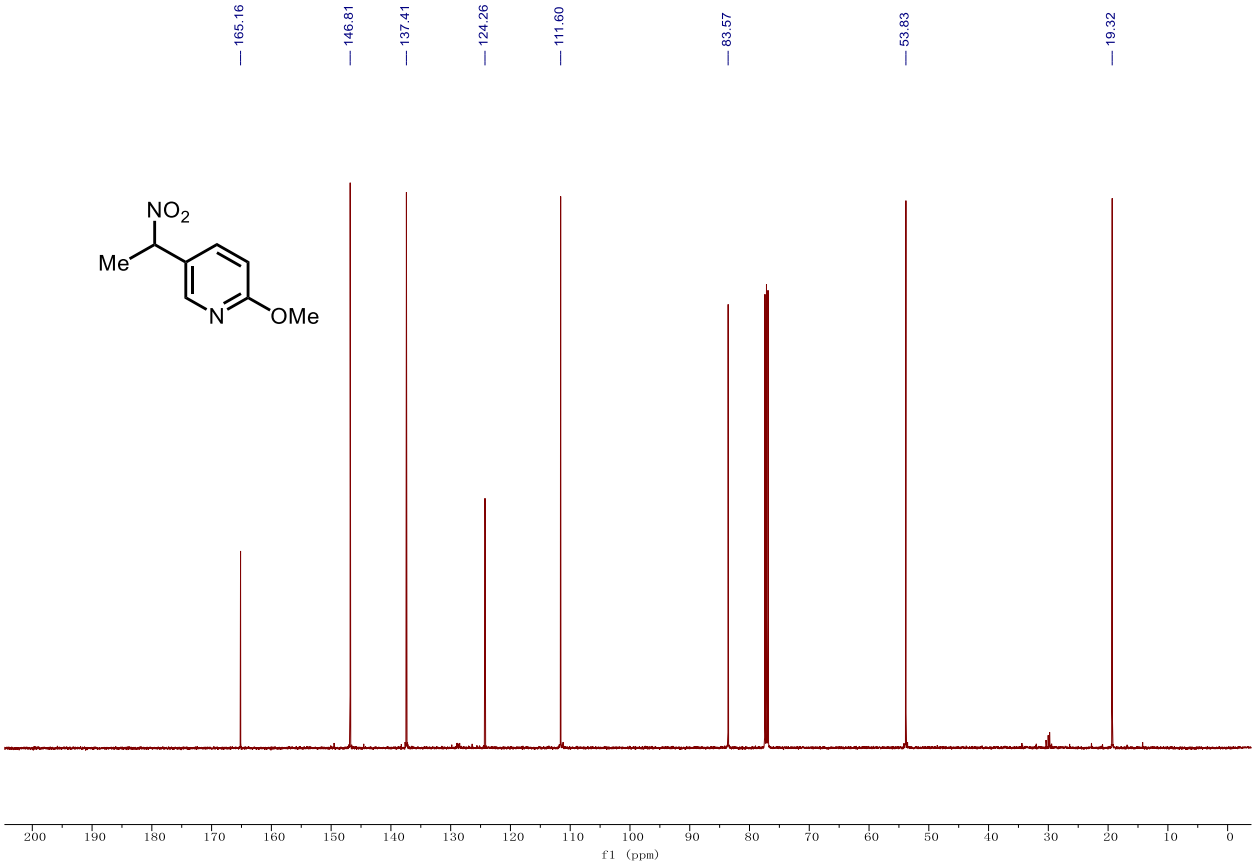

134.65
129.93
129.12
127.86
93.20
27.48
10.79
NO2
Et
f1 (ppm)

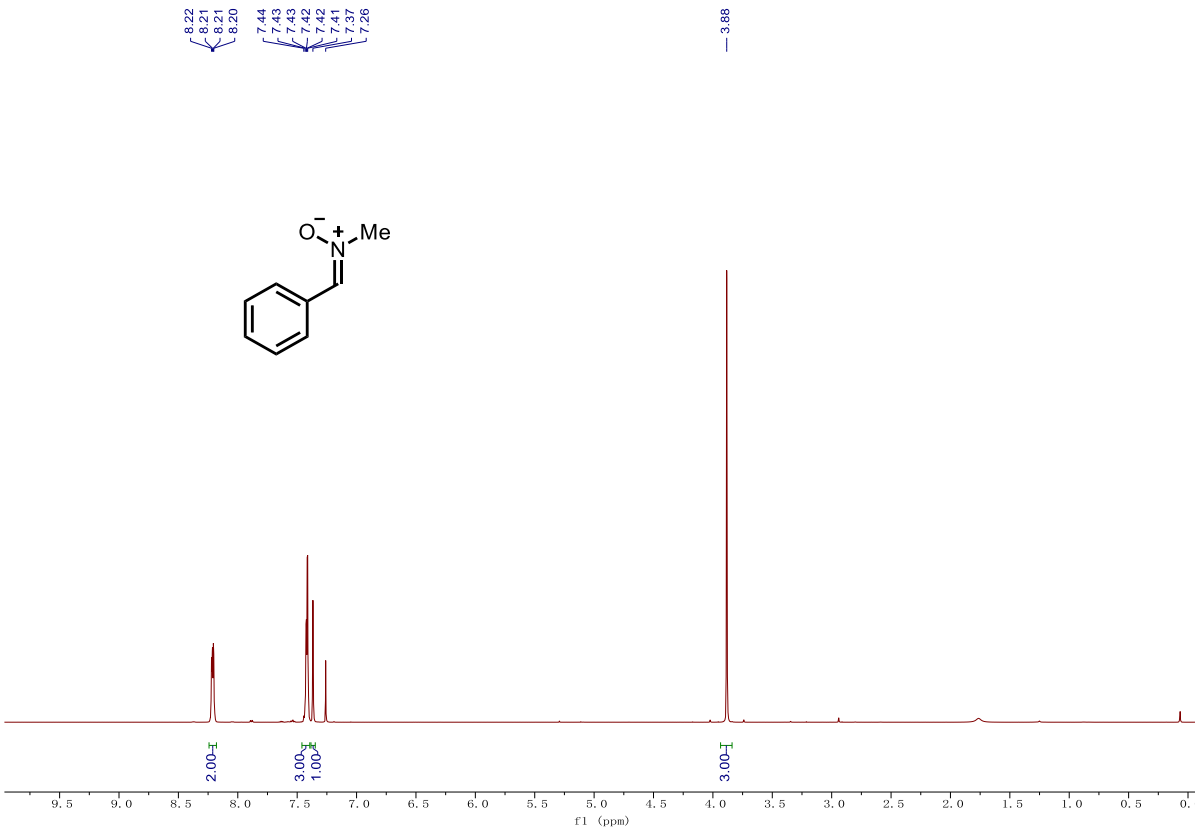

7.48
7.46
7.48
7.47
7.47
7.46
7.41
7.41
7.40
7.40
7.40
7.39
7.39
7.26
5.48
5.47
5.46
5.45
2.52
2.51
2.50
2.49
2.48
2.47
2.46
2.45
2.44
2.09
2.08
2.07
2.06
2.05
2.03
2.02
1.43
1.41
1.39
1.38
1.36
1.35
1.33
1.32
1.31
0.99
0.98
0.97
NO2
Me
2.03
3.00
1.00
1.01
1.01
2.03
3.03
f1 (ppm)
134.81
129.92
129.13
127.88
91.47
36.05
19.53
13.60
NO2
Me
f1 (ppm)

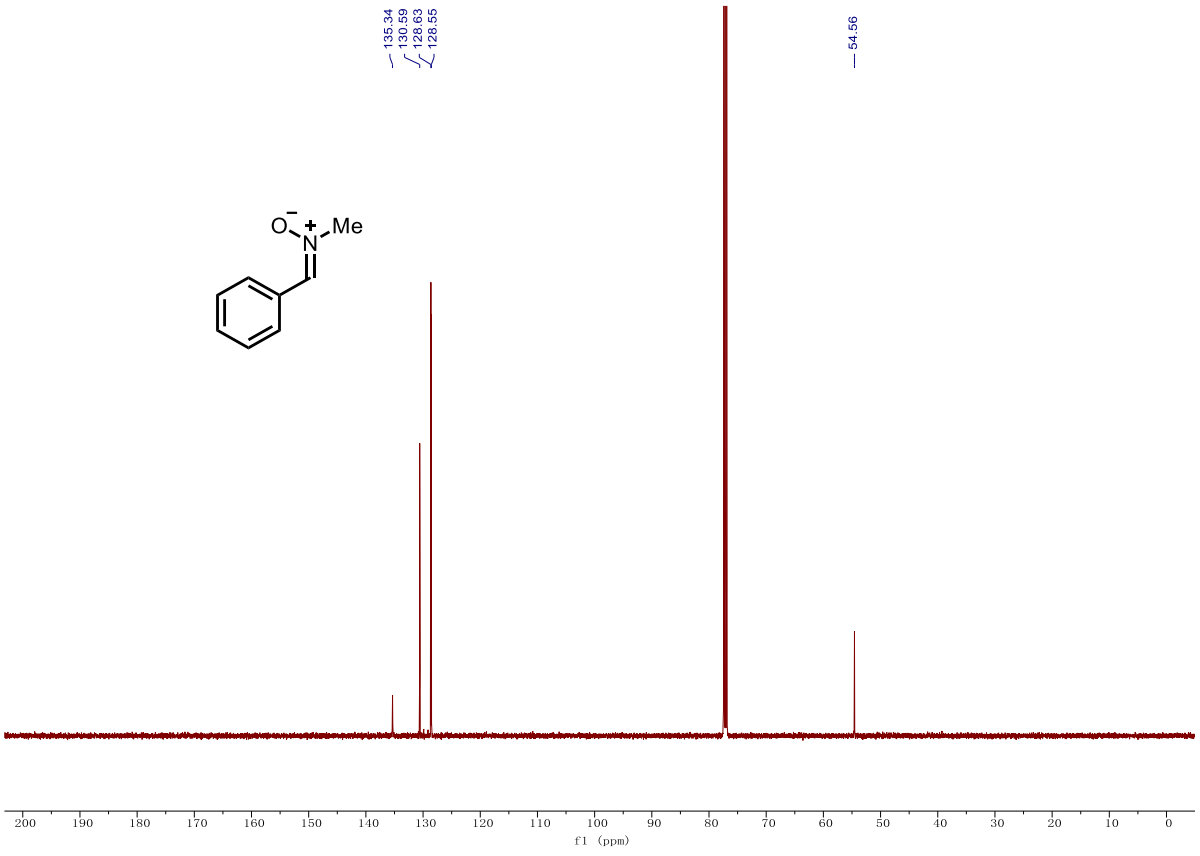

7.45
7.44
7.44
7.44
7.37
7.36
7.36
7.35
7.21
7.21
7.20
7.20
5.74
5.72
5.71
5.70
1.92
1.90
NO2
Me
S
1.00
1.00
1.00
1.00
2.99
f1 (ppm)

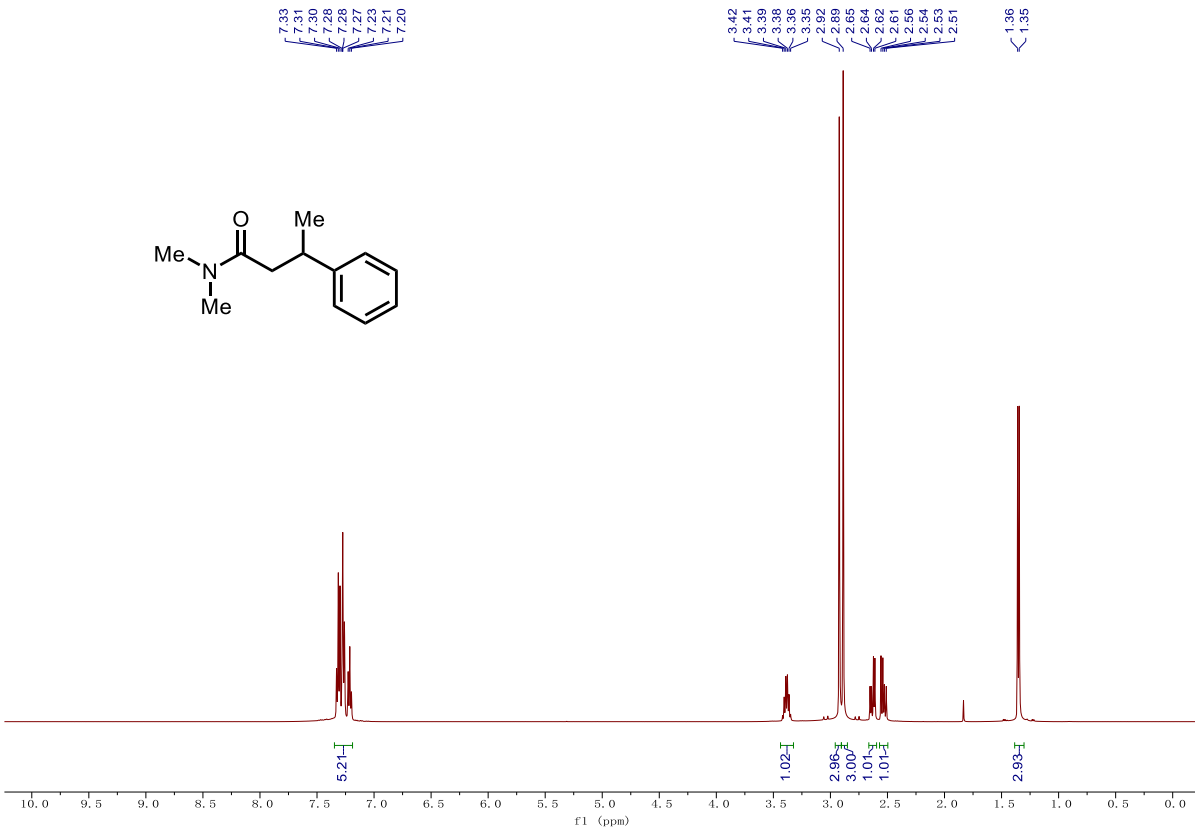

136.37
127.06
126.31
125.10
81.59
19.63
NO2
Me
S
f1 (ppm)

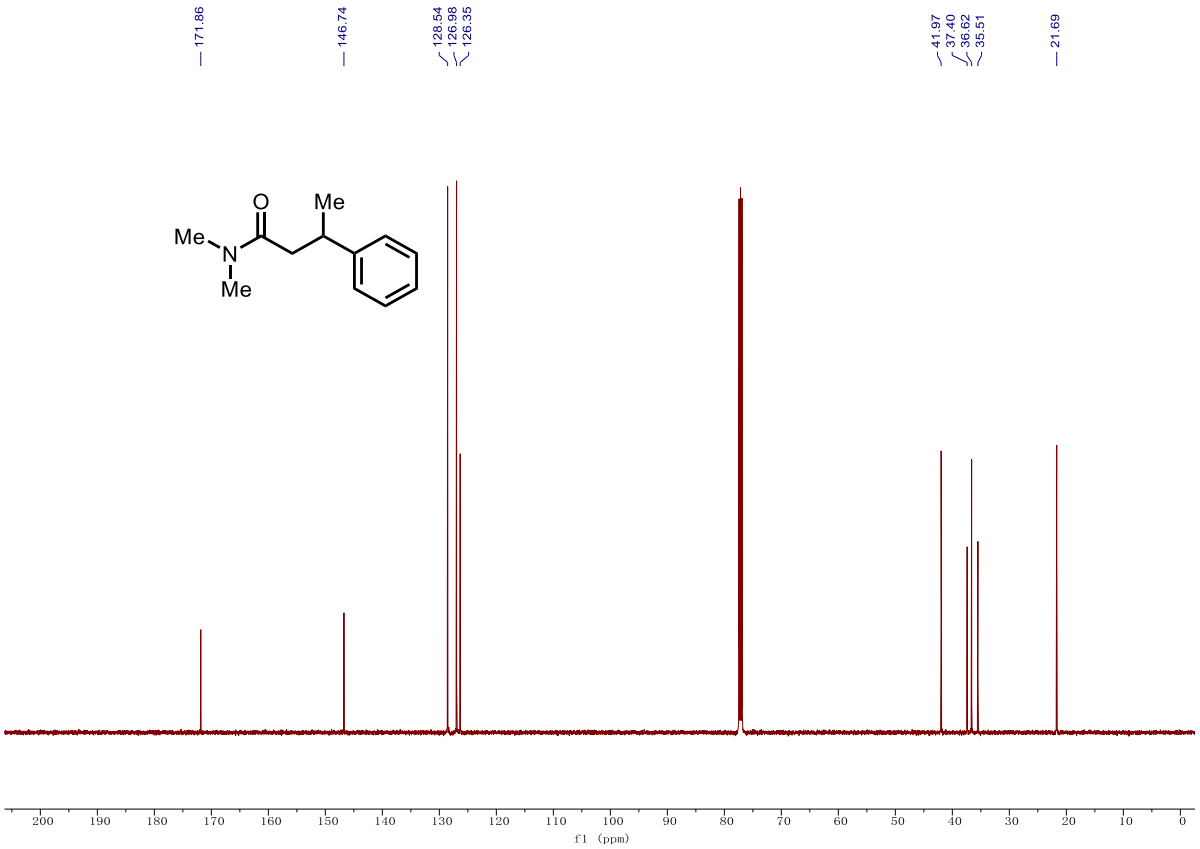

8.22
8.22
7.71
7.70
7.69
7.69
7.26
6.78
6.76
5.58
5.56
5.55
5.54
3.93
1.88
1.86
NO2
Me
N
OMe
1.00
1.01
1.02
1.00
3.05
3.03
f1 (ppm)


165.16
146.81
137.41
124.26
111.60
83.57
53.83
19.32
NO2
Me
N
OMe
f1 (ppm)


8.22
8.21
8.21
8.20
7.44
7.43
7.43
7.42
7.42
7.41
7.37
7.26
3.88
O
N
Me
2.00
3.00
1.00
3.00
f1 (ppm)


135.34
130.59
128.63
128.55
54.56
O
N
Me
f1 (ppm)

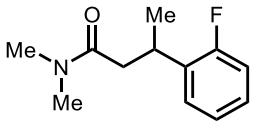

7.33
7.31
7.30
7.28
7.28
7.27
7.23
7.21
7.20
3.42
3.41
3.39
3.38
3.36
3.35
2.92
2.89
2.65
2.64
2.62
2.61
2.56
2.54
2.53
2.51
1.36
1.35
O
Me
Me
N
Me
5.21
1.02
2.96
3.00
1.01
1.01
2.93
f1 (ppm)

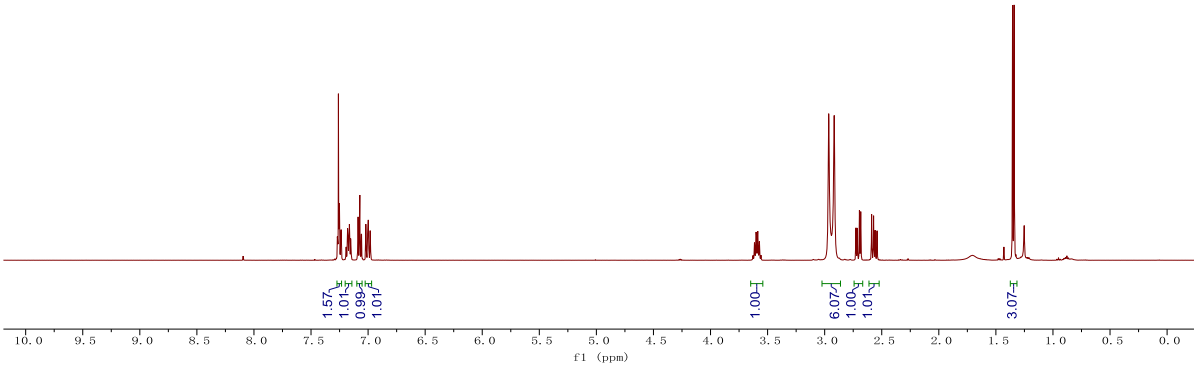

171.86
146.74
128.54
126.98
126.35
41.97
37.40
36.62
35.51
21.69
O
Me
Me
N
Me
f1 (ppm)

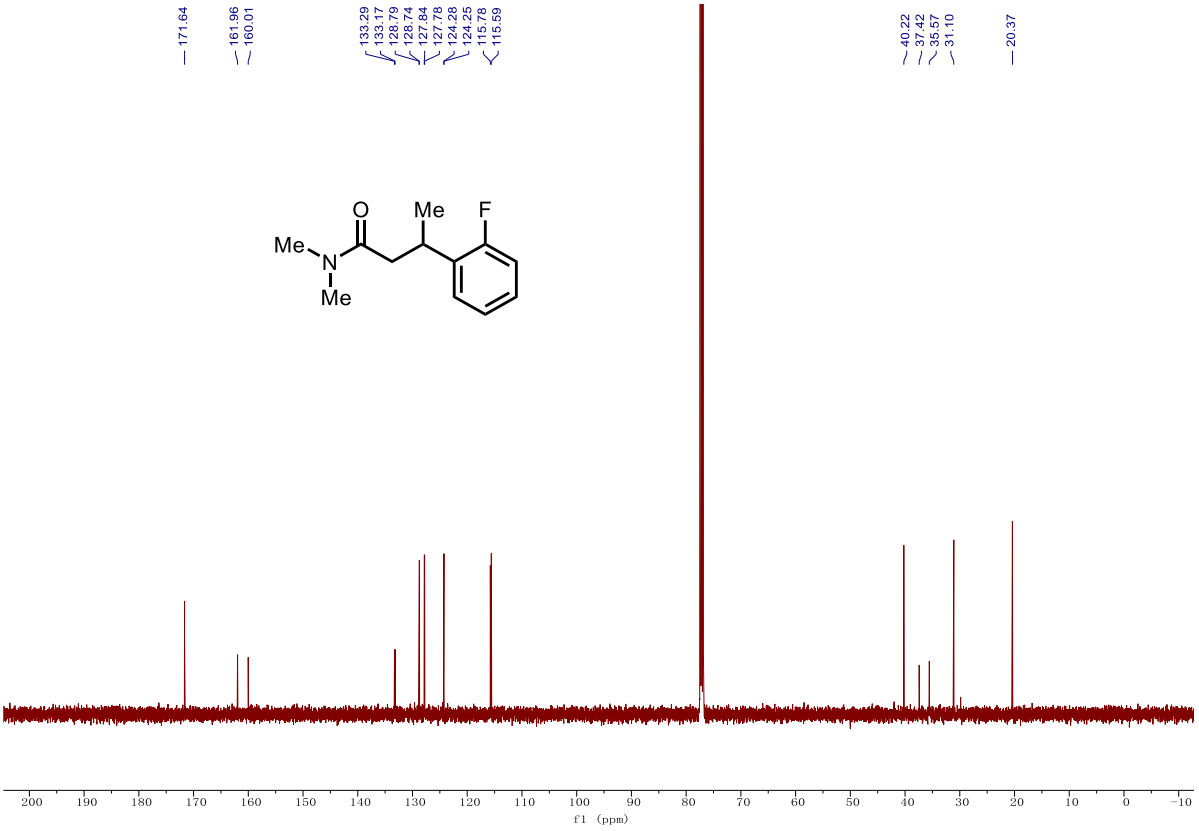

7.27
7.27
7.26
7.25
7.25
7.24
7.24
7.19
7.19
7.18
7.18
7.18
7.18
7.17
7.16
7.16
7.15
7.15
7.09
7.09
7.08
7.07
7.06
7.06
7.02
7.02
7.00
7.00
7.00
7.00
6.98
6.98


3.63
3.61
3.60
3.59
3.57
3.56
2.96
2.92
2.73
2.71
2.70
2.68
2.59
2.57
2.56
2.54

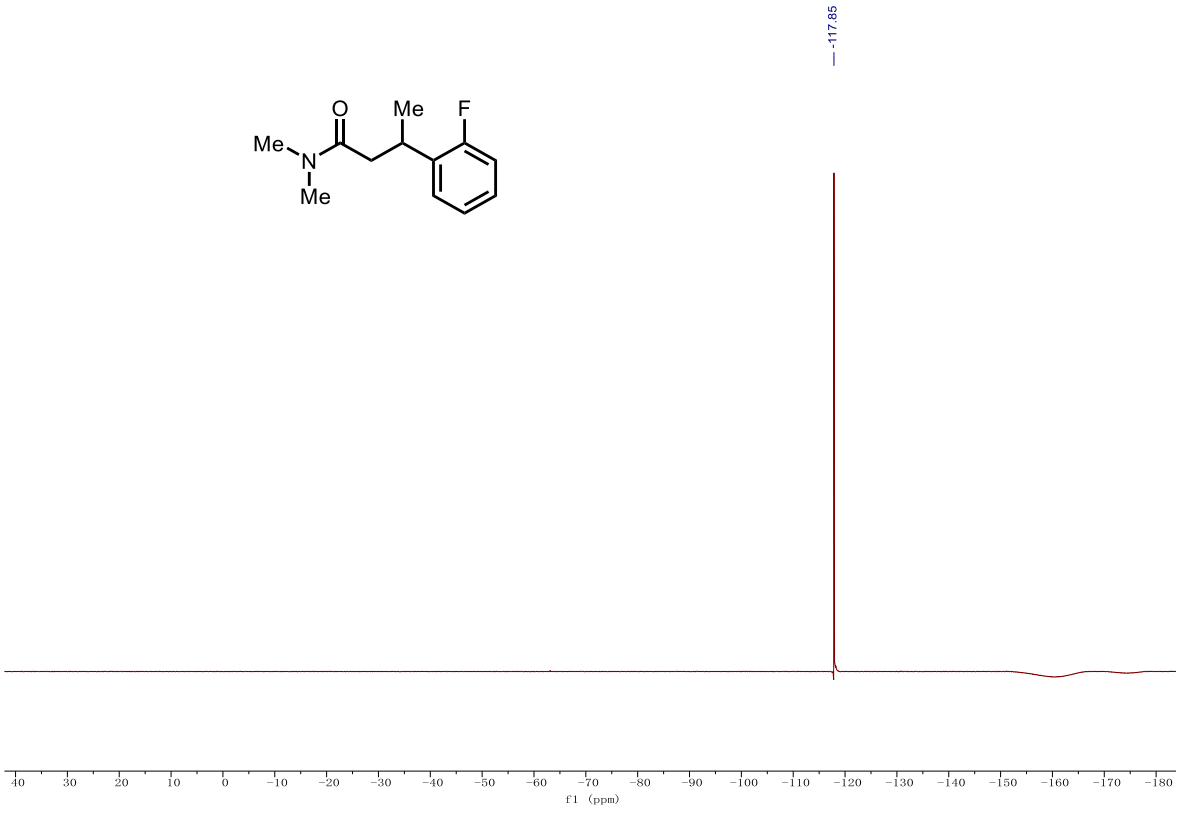
1.35
1.34

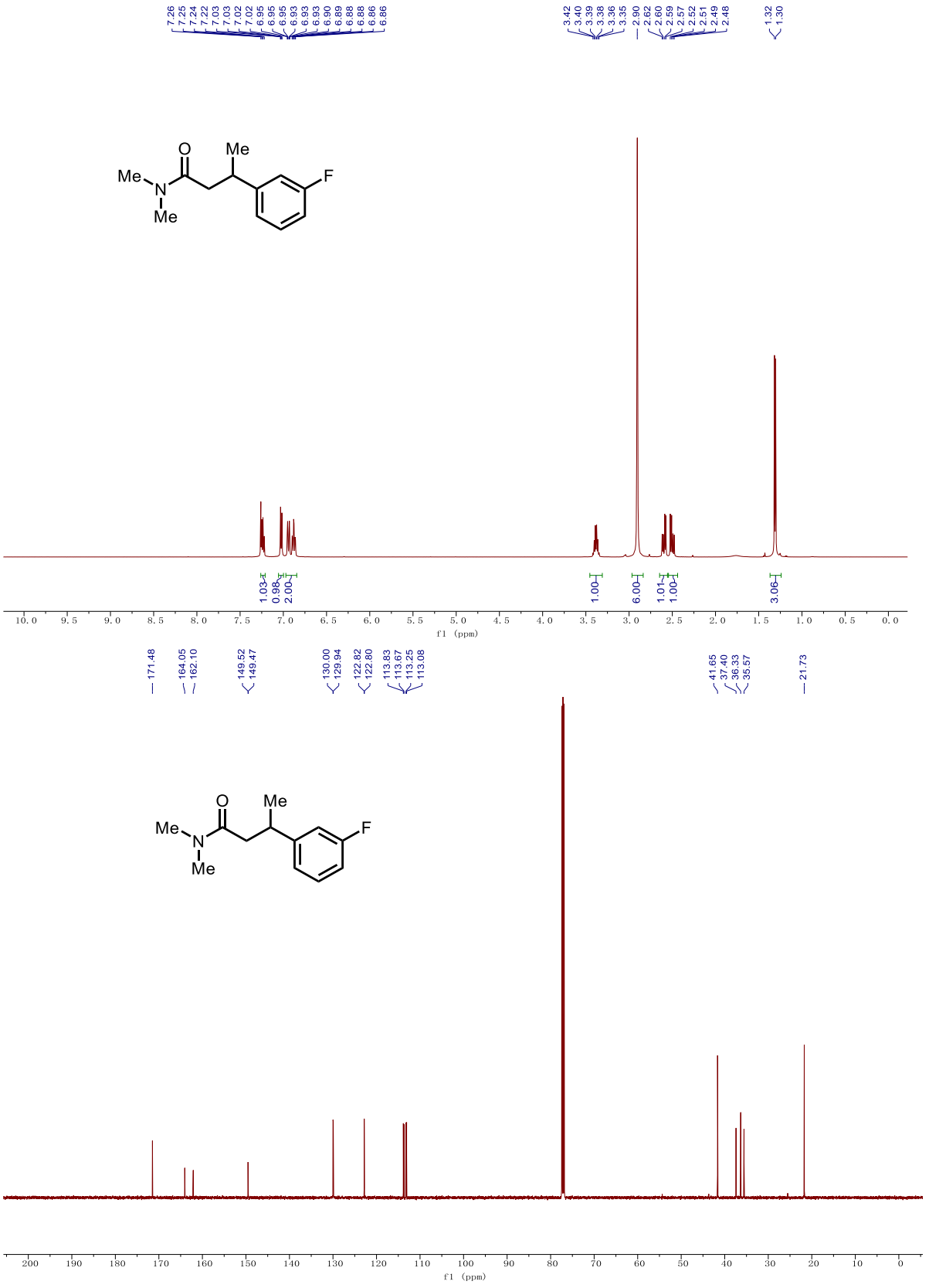

O
Me
F
Me
N
Me

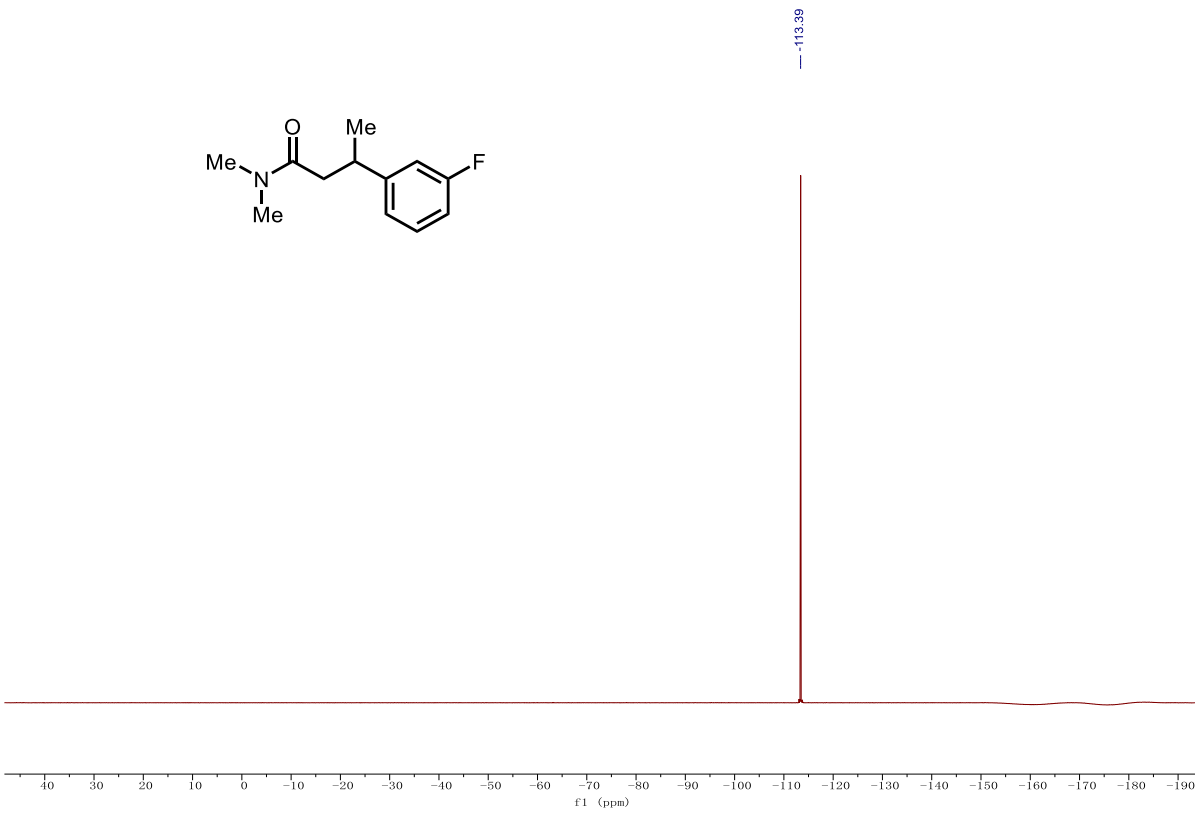

1.57
1.01
0.99
1.01
1.00
6.07
1.00
1.01
3.07
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

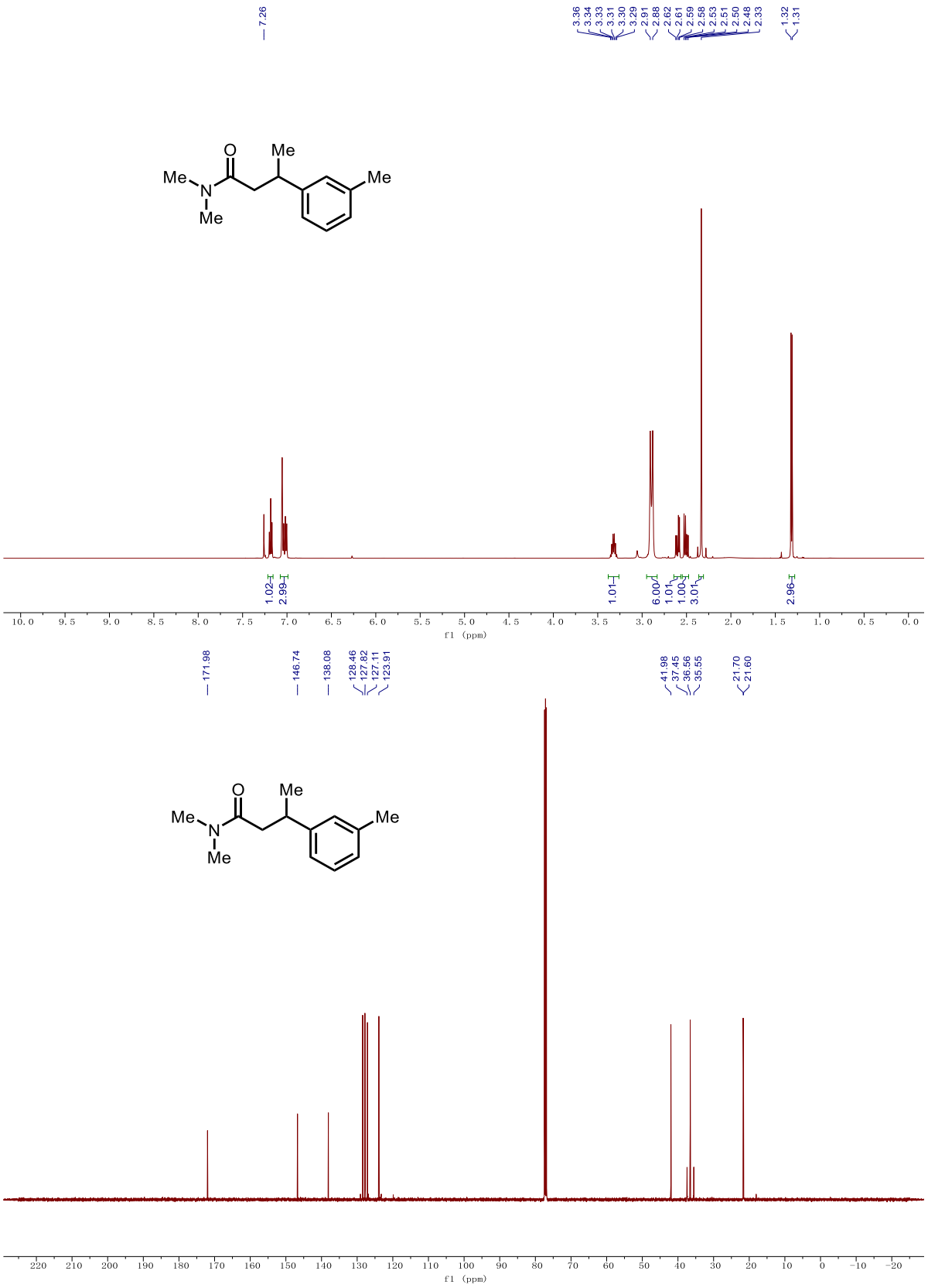

171.64
161.96
160.01
133.29
133.17
128.79
128.74
127.84
127.78
124.28
124.25
115.78
115.59
40.22
37.42
35.57
31.10
20.37
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
−10
f1 (ppm)

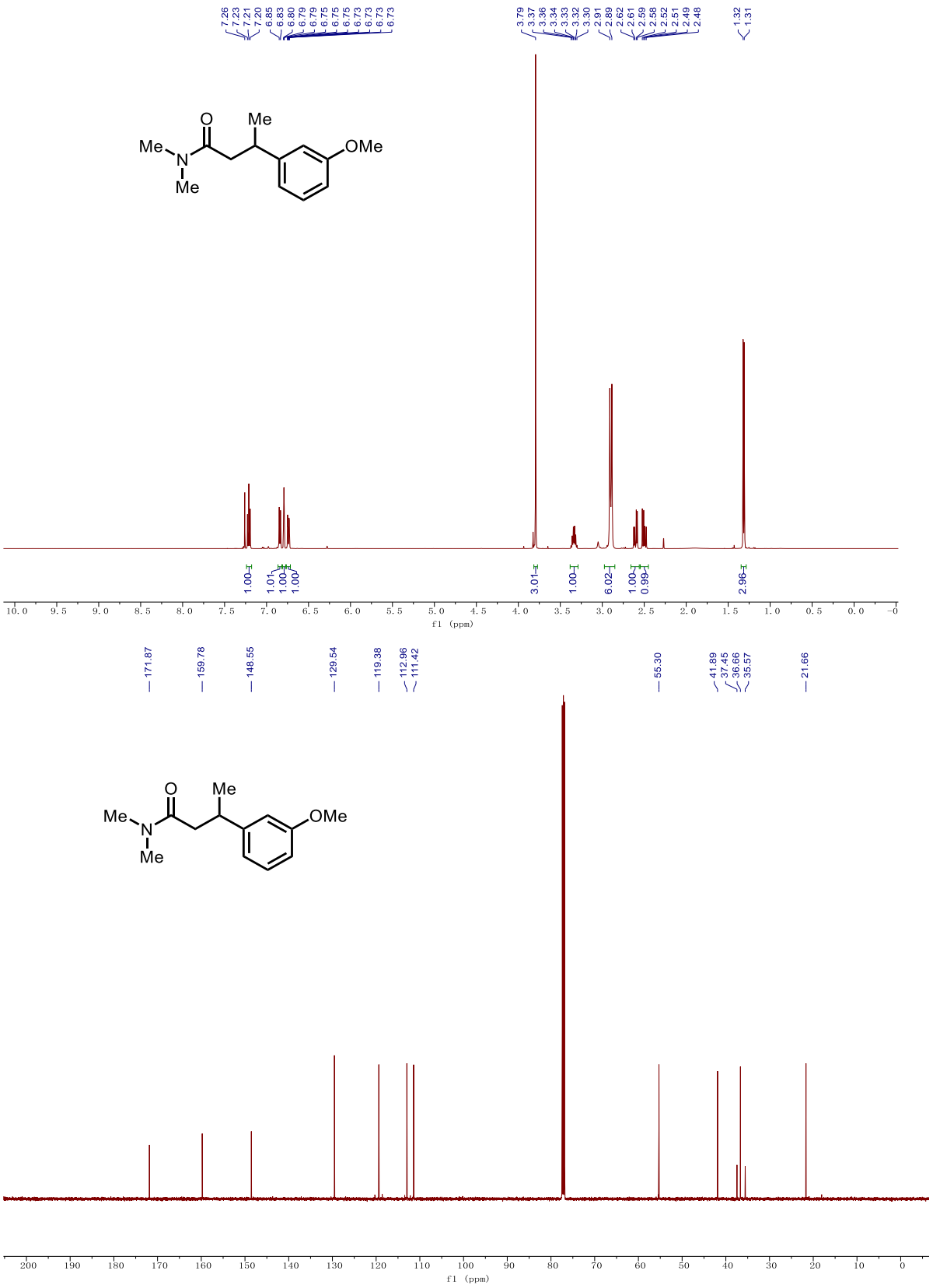
O
Me
F
Me
N
Me


-117.85
O
Me
F
Me
N
Me
40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180
f1 (ppm)


7.26
7.25
7.24
7.22
7.03
7.03
7.02
7.02
6.95
6.95
6.95
6.93
6.93
6.90
6.89
6.88
6.88
6.86
6.86
3.42
3.40
3.39
3.38
3.36
3.35
2.90
2.62
2.60
2.59
2.57
2.52
2.51
2.49
2.48
1.32
1.30
O
Me
Me
N
Me
F
1.03
0.98
2.00
1.00
6.00
1.01
1.00
3.06
f1 (ppm)
171.48
164.05
162.10
149.52
149.47
130.00
129.94
122.82
122.80
113.83
113.67
113.25
113.08
41.65
37.40
36.33
35.57
21.73
f1 (ppm)


-113.39
O
Me
Me
N
Me
F
40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190
f1 (ppm)


7.26
3.36
3.34
3.33
3.31
3.30
3.29
2.91
2.88
2.62
2.61
2.59
2.58
2.53
2.51
2.50
2.48
2.33
1.32
1.31
O
Me
Me
N
Me
Me
1.02
2.99
1.01
6.00
1.01
1.00
3.01
2.96
f1 (ppm)
171.98
146.74
138.08
128.46
127.82
127.11
123.91
41.98
37.45
36.56
35.55
21.70
21.60
O
Me
Me
N
Me
Me
f1 (ppm)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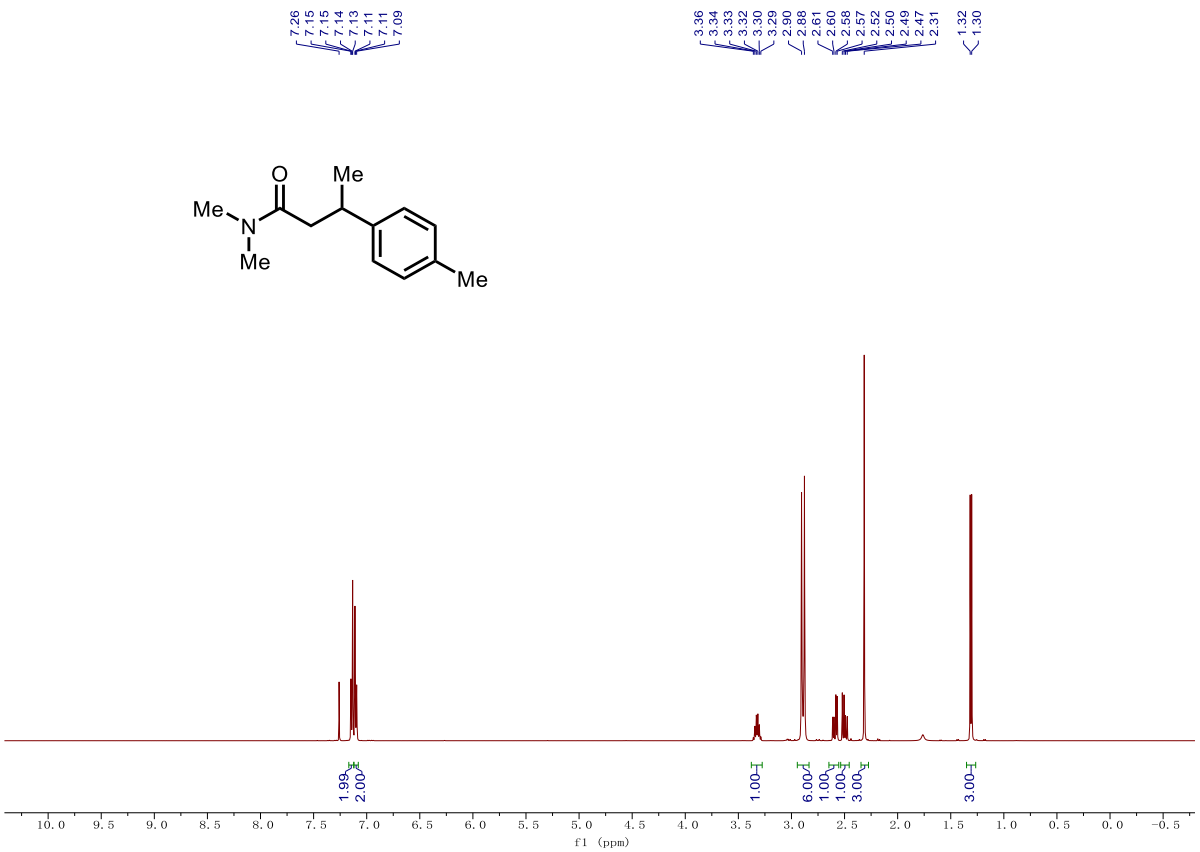
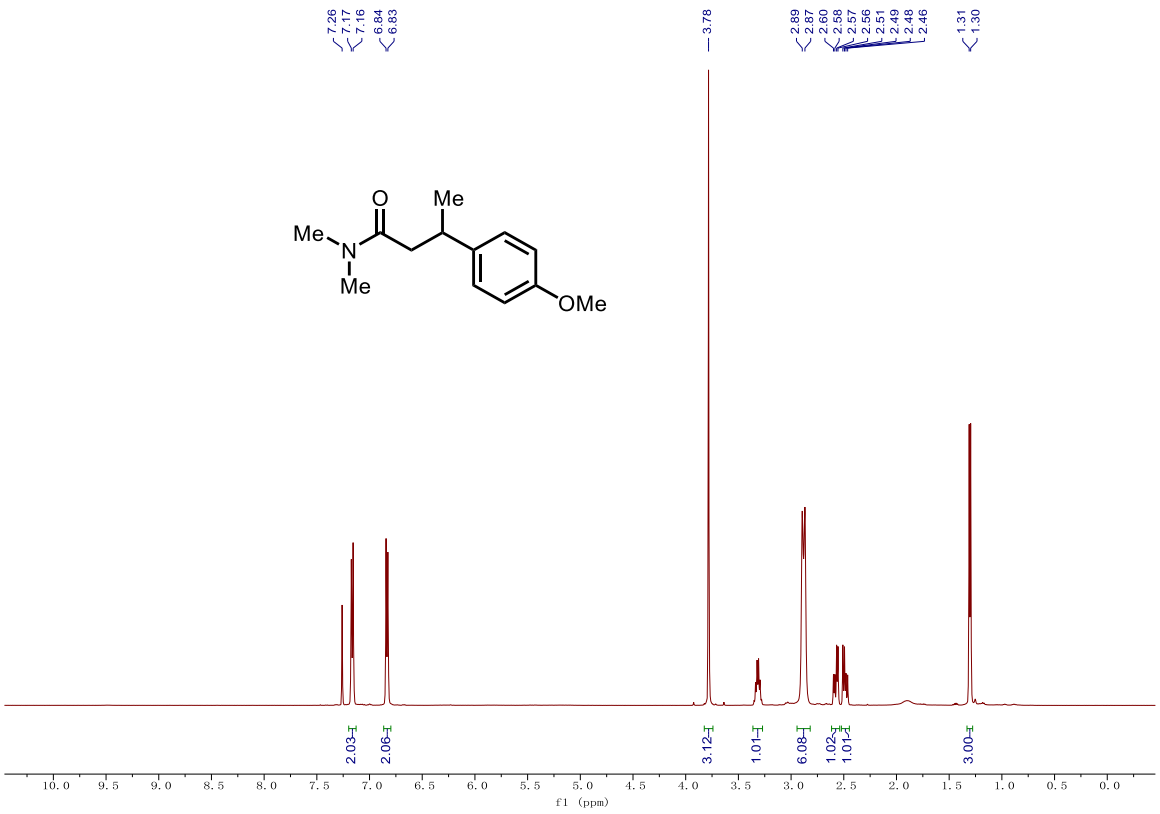
7.23
7.21
7.20
6.85
6.83
6.80
6.79
6.79
6.75
6.75
6.75
6.73
6.73
6.73
6.73
3.79
3.37
3.36
3.34
3.33
3.32
3.30
2.91
2.89
2.62
2.61
2.59
2.58
2.52
2.51
2.49
2.48
1.32
1.31
O
Me
Me
N
OMe
Me
1.00
1.01
1.00
1.00
3.01
1.00
6.02
1.00
0.99
2.96
f1 (ppm)
171.87
159.78
148.55
129.54
119.38
112.96
111.42
55.30
41.89
37.45
36.66
35.57
21.66
O
Me
Me
N
OMe
Me
f1 (ppm)


7.26
7.15
7.15
7.14
7.13
7.11
7.11
7.09
3.36
3.34
3.33
3.32
3.30
3.29
2.90
2.88
2.61
2.60
2.58
2.57
2.52
2.50
2.49
2.47
2.31
1.32
1.30
O
Me
Me
N
Me
Me
1.99
2.00
1.00
6.00
1.00
1.00
3.00
3.00
f1 (ppm)


171.99
143.76
135.82
129.24
126.85
42.08
37.45
36.20
35.54
21.80
21.12
O
Me
Me
N
Me
Me
f1 (ppm)


7.26
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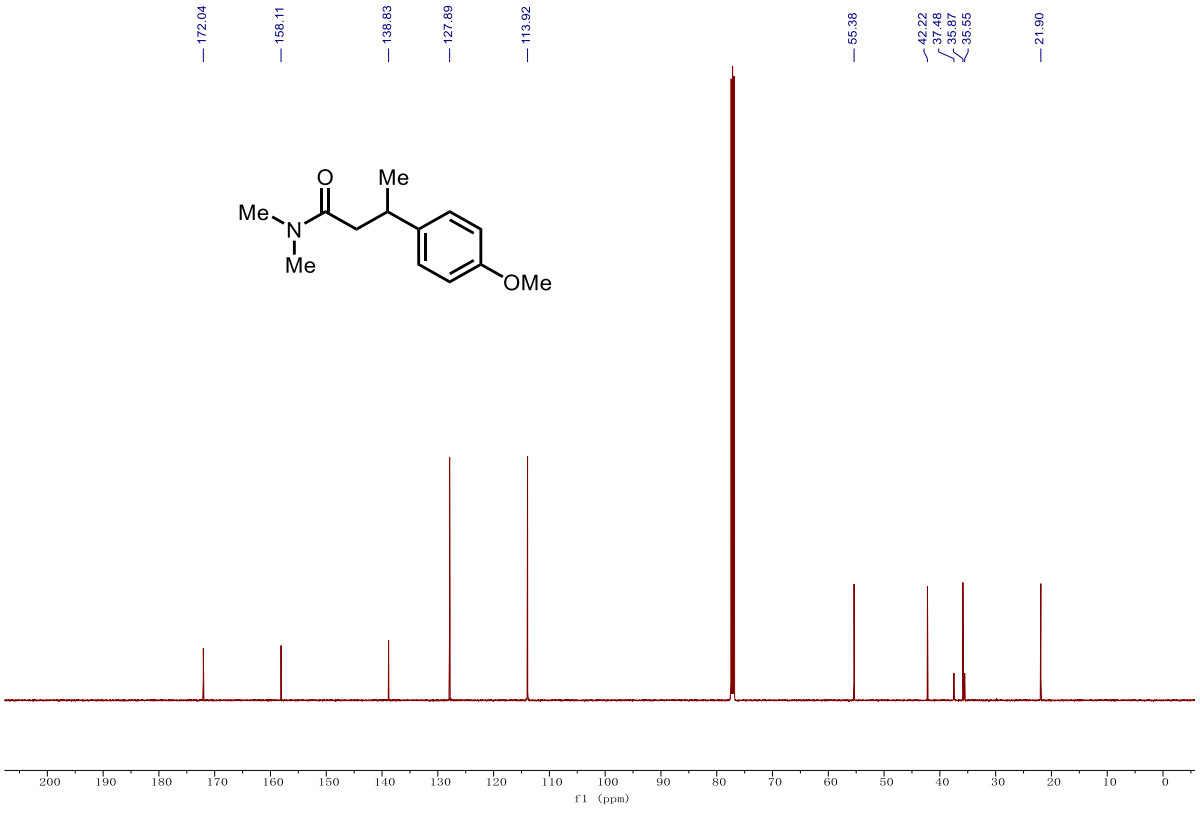
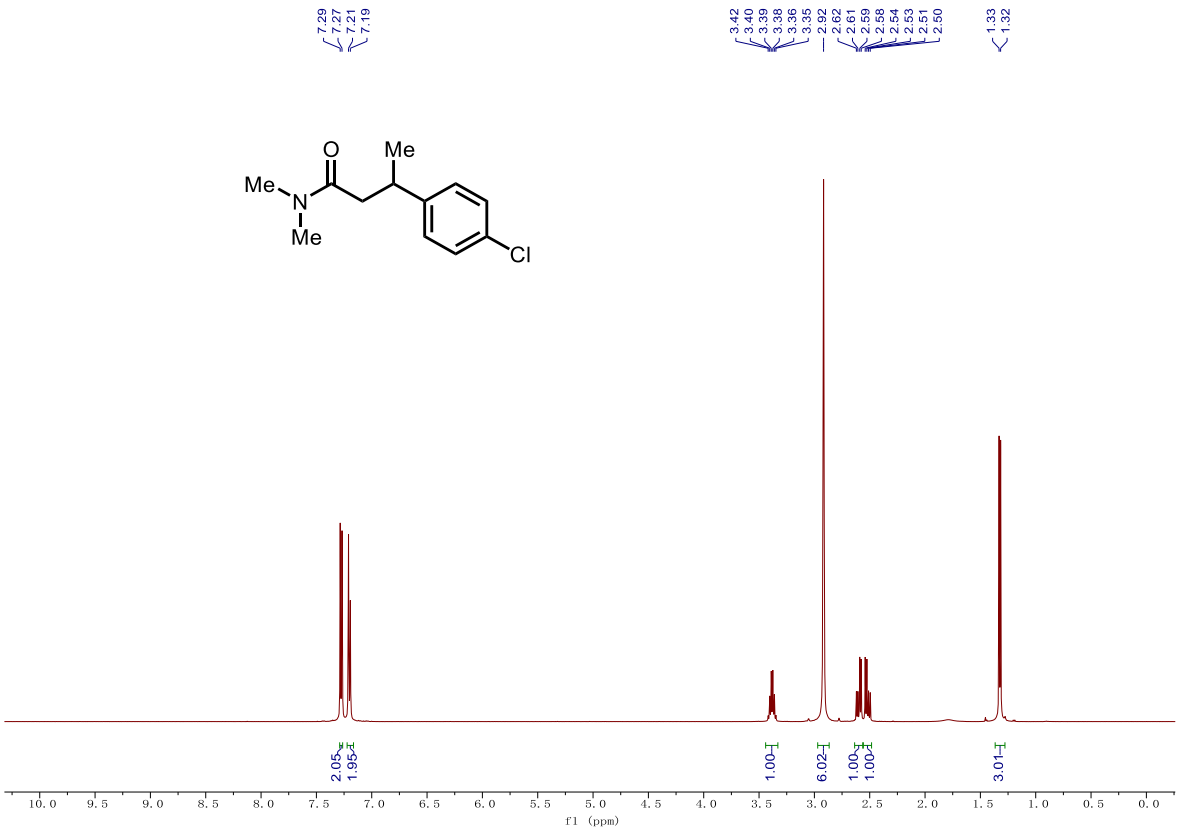
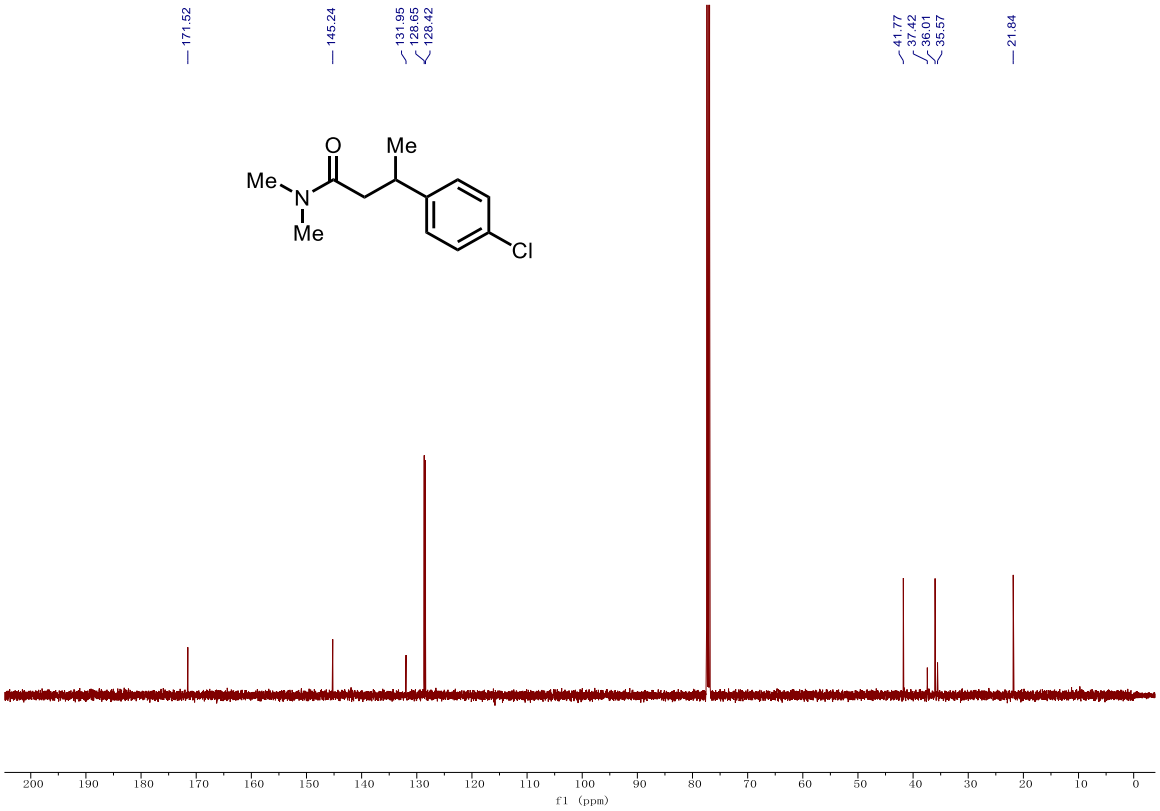
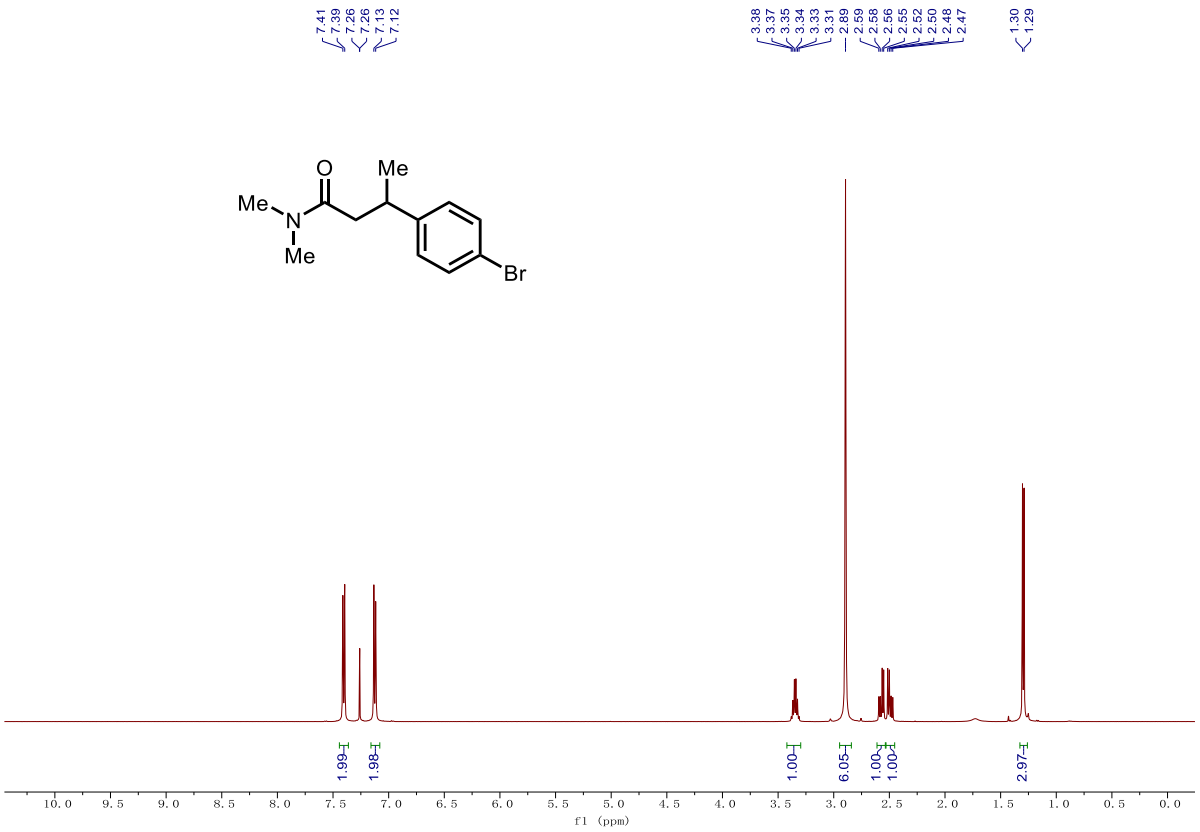
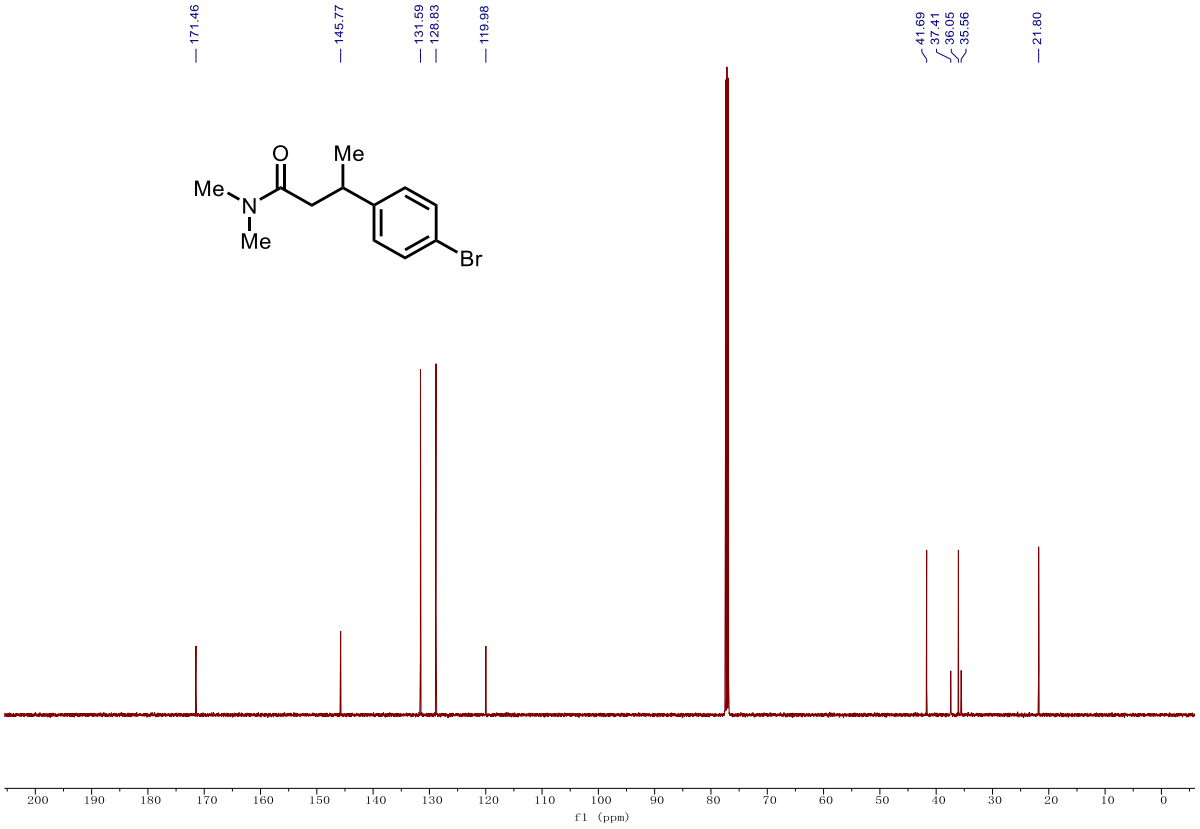
7.16
6.84
6.83
3.78
2.89
2.87
2.60
2.58
2.57
2.56
2.51
2.49
2.48
2.46
1.31
1.30
O
Me
Me
N
Me
OMe
2.03
2.06
3.12
1.01
6.08
1.02
1.01
3.00
f1 (ppm)

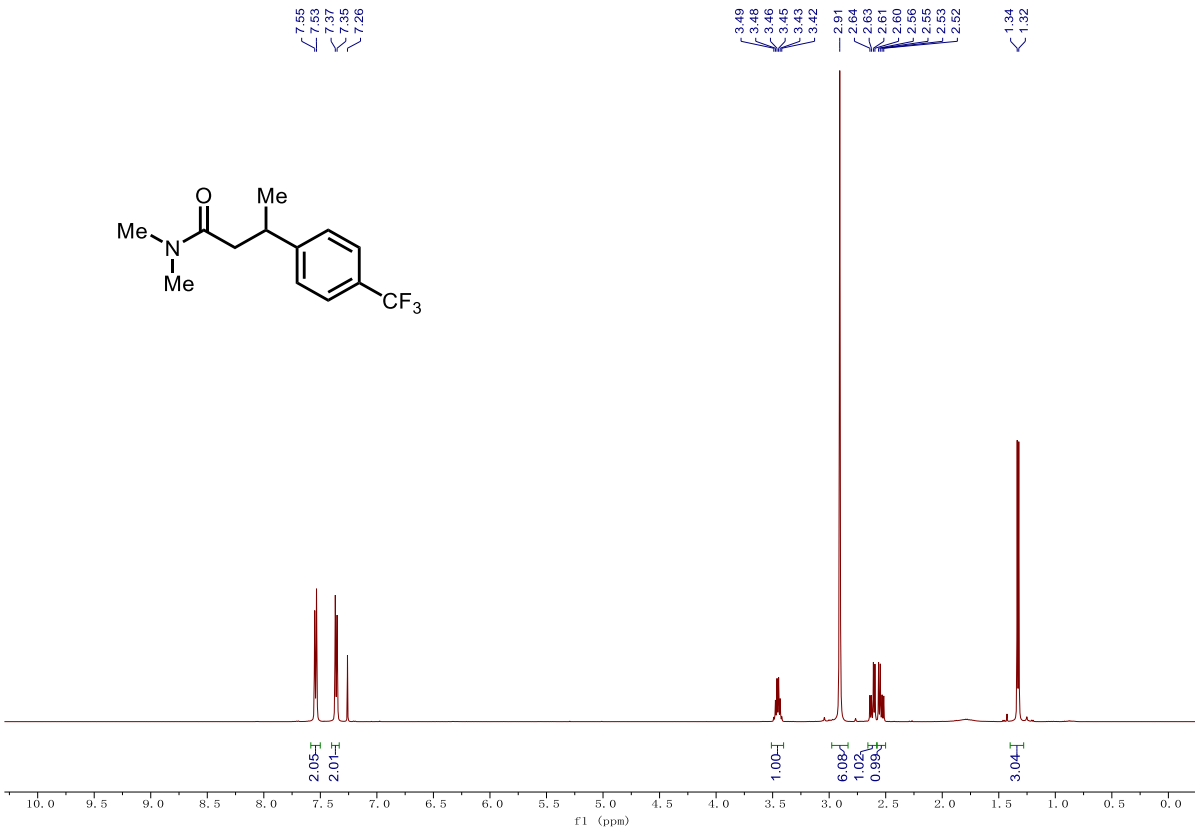

172.04
158.11
138.83
127.89
113.92
55.38
42.22
37.48
35.87
35.55
21.90
O
Me
Me
N
Me
OMe
f1 (ppm)

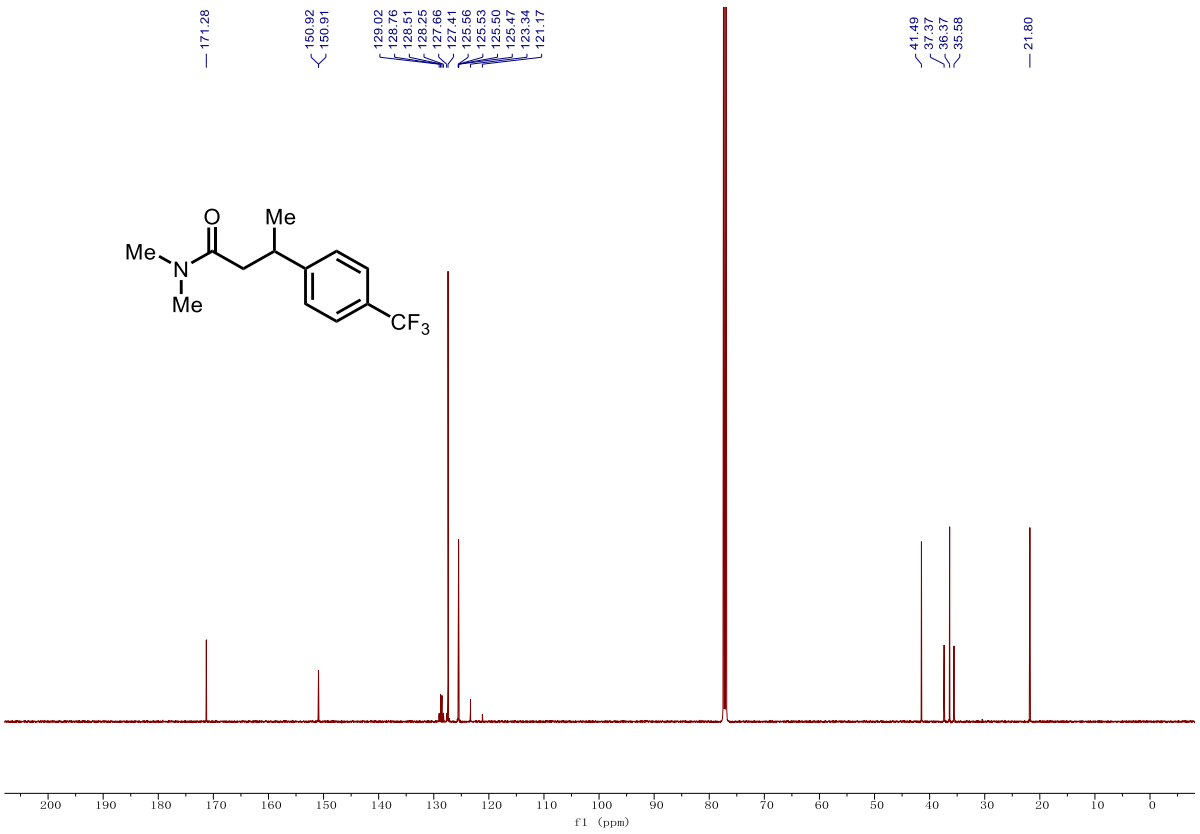

7.29
7.27
7.21
7.19
3.42
3.40
3.39
3.38
3.36
3.35
2.92
2.62
2.61
2.59
2.58
2.54
2.53
2.51
2.50
1.33
1.32
O
Me
Me
N
Me
Cl
2.05
1.95
1.00
6.02
1.00
1.00
3.01
f1 (ppm)


171.52
145.24
131.95
128.65
128.42
41.77
37.42
36.01
35.57
21.84
O
Me
Me
N
Me
Cl
f1 (ppm)


7.41
7.39
7.26
7.26
7.13
7.12
3.38
3.37
3.35
3.34
3.33
3.31
2.89
2.59
2.58
2.56
2.55
2.52
2.50
2.48
2.47
1.30
1.29
O
Me
Me
N
Me
Br
1.99
1.98
1.00
6.05
1.00
1.00
2.97
f1 (ppm)


171.46
145.77
131.59
128.83
119.98
41.69
37.41
36.05
35.56
21.80
O
Me
Me
N
Me
Br
f1 (ppm)


7.55
7.53
7.37
7.35
7.26
3.49
3.48
3.46
3.45
3.43
3.42
2.91
2.64
2.63
2.61
2.60
2.56
2.55
2.53
2.52
1.34
1.32
O
Me
Me
N
Me
CF3
2.05
2.01
1.00
6.08
1.02
0.99
3.04
f1 (ppm)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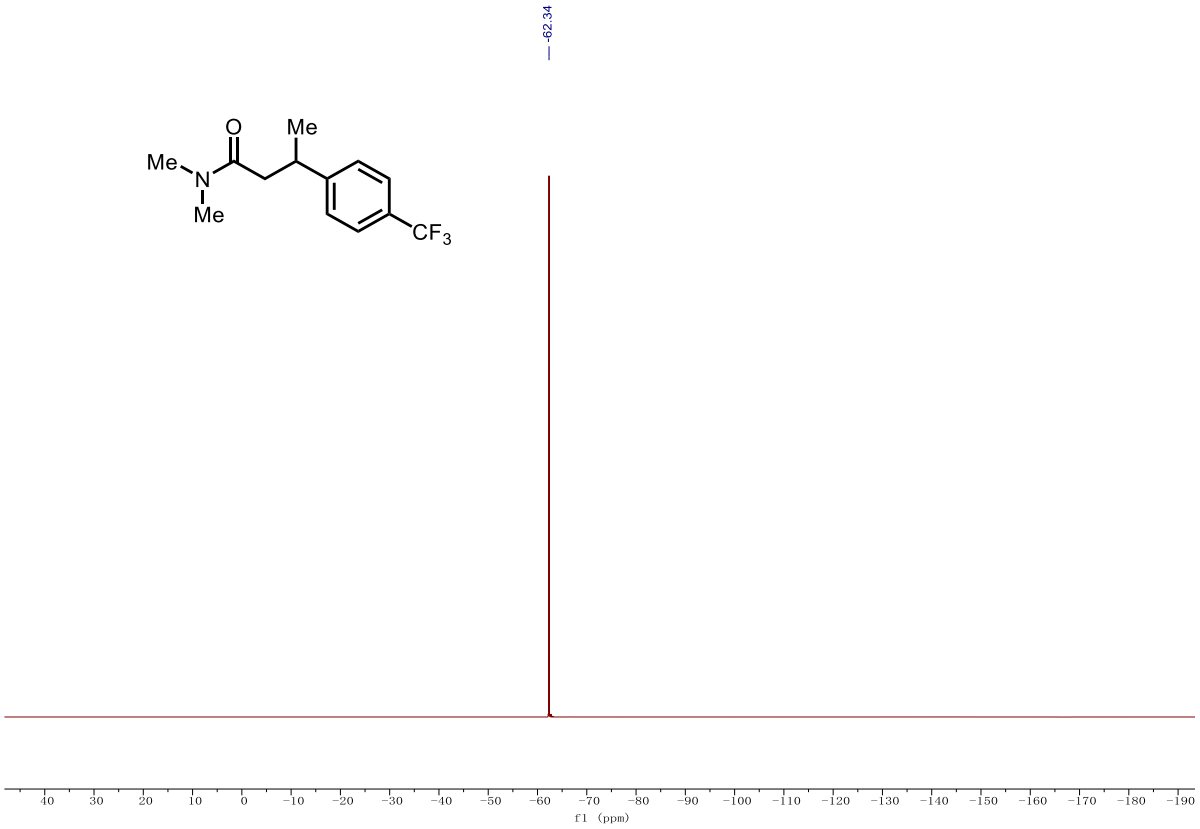
150.92
150.91
129.02
128.76
128.51
128.25
127.66
127.41
125.56
125.53
125.50
125.47
123.34
121.17
41.49
37.37
36.37
35.58
21.80
O
Me
Me
N
Me
CF3
f1 (ppm)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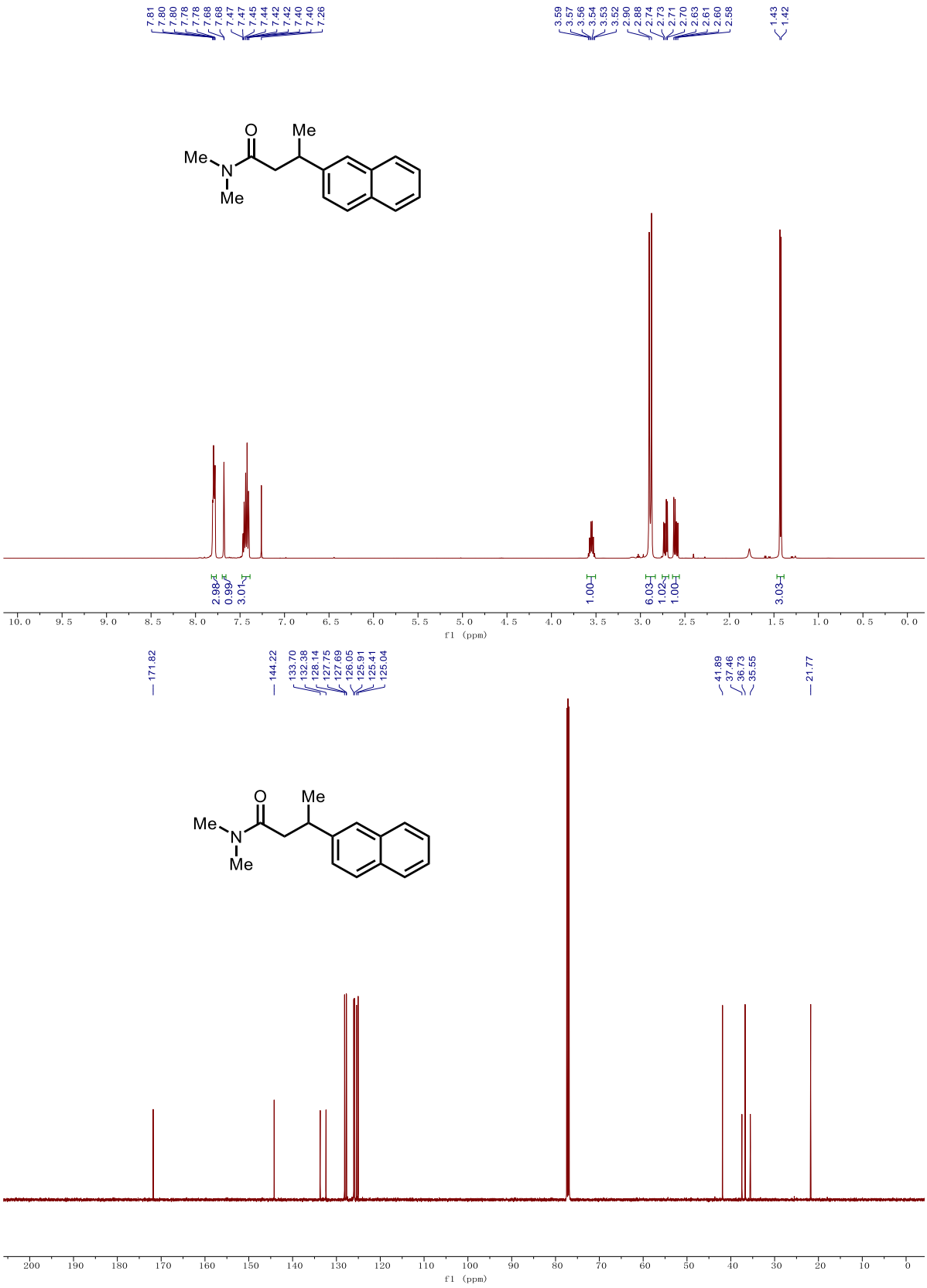
O
Me
Me
N
Me
CF3
40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190
f1 (ppm)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7.80
7.80
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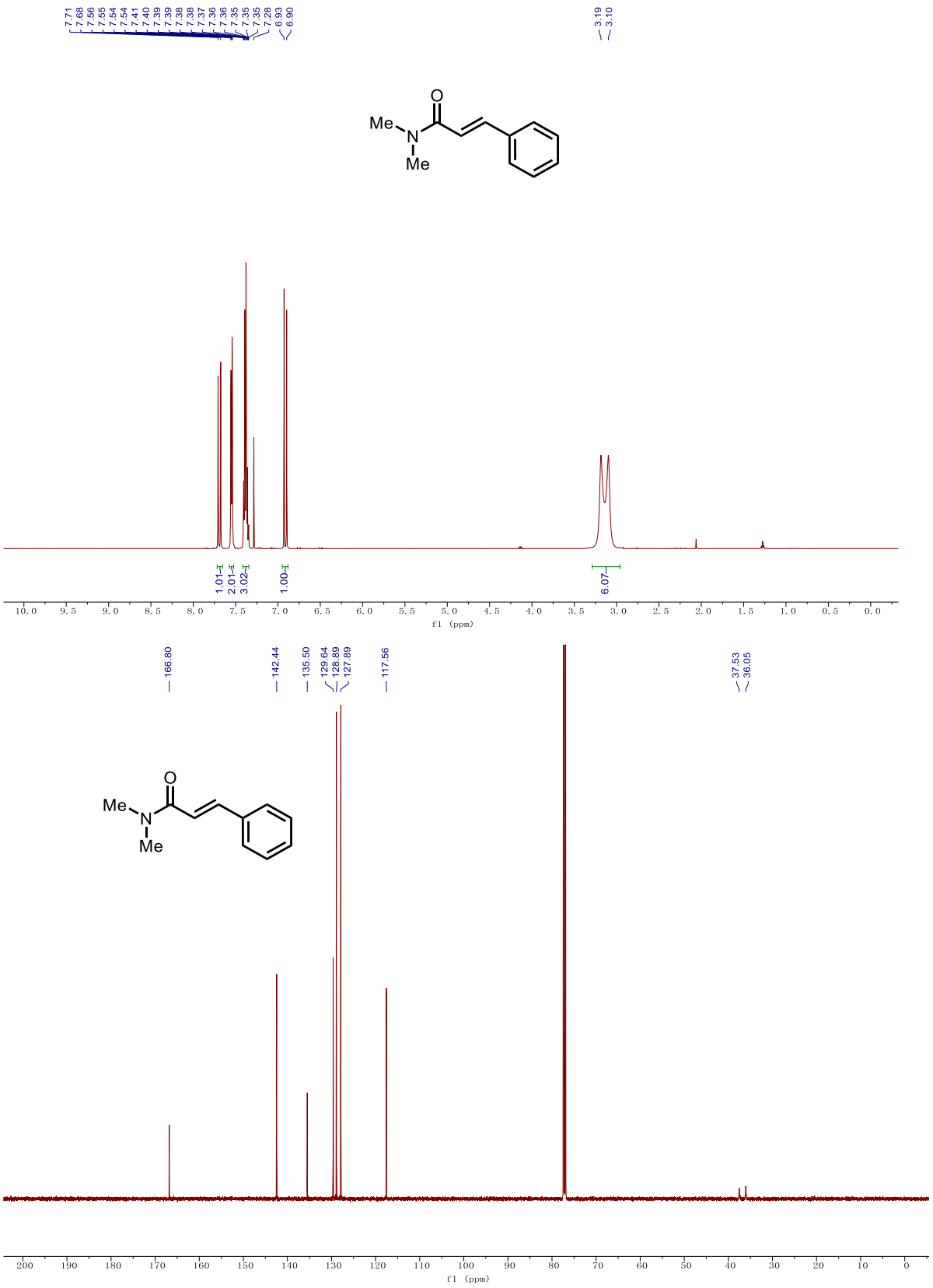
7.78
7.68
7.68
7.47
7.47
7.45
7.44
7.42
7.42
7.40
7.40
7.26
3.59
3.57
3.56
3.54
3.53
3.52
2.90
2.88
2.74
2.73
2.71
2.70
2.63
2.61
2.60
2.58
1.43
1.42
O
Me
Me
N
Me
2.98
0.99
3.01
1.00
6.03
1.02
1.00
3.03
f1 (ppm)
171.82
144.22
133.70
132.38
128.14
127.75
127.69
126.05
125.91
125.41
125.04
41.89
37.46
36.73
35.55
21.77
O
Me
Me
N
Me
f1 (ppm)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7.41
7.40
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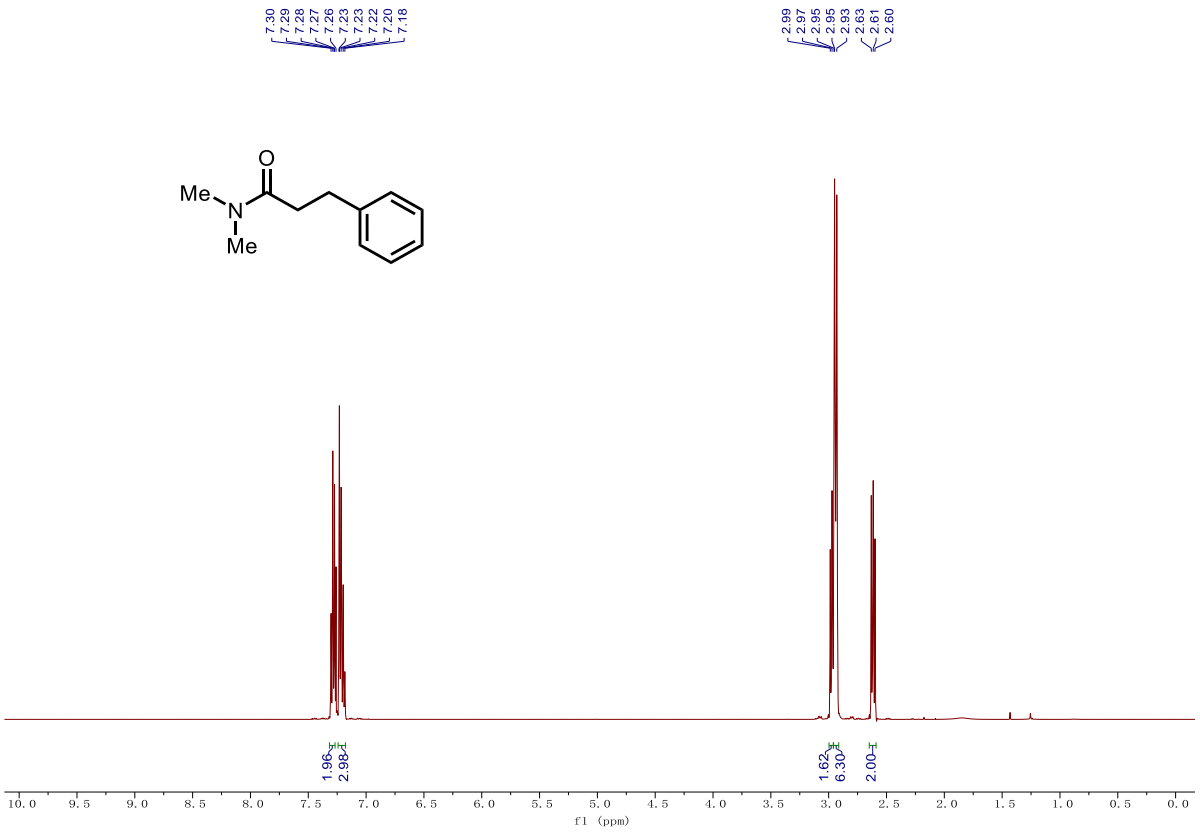
7.39
7.38
7.38
7.37
7.36
7.36
7.35
7.35
7.35
7.28
6.93
6.90
3.19
3.10
Me
N
Me
O
1.01
2.01
3.02
1.00
6.07
f1 (ppm)
166.80
142.44
135.50
129.64
128.89
127.89
117.56
37.53
36.05
Me
N
Me
O
f1 (ppm)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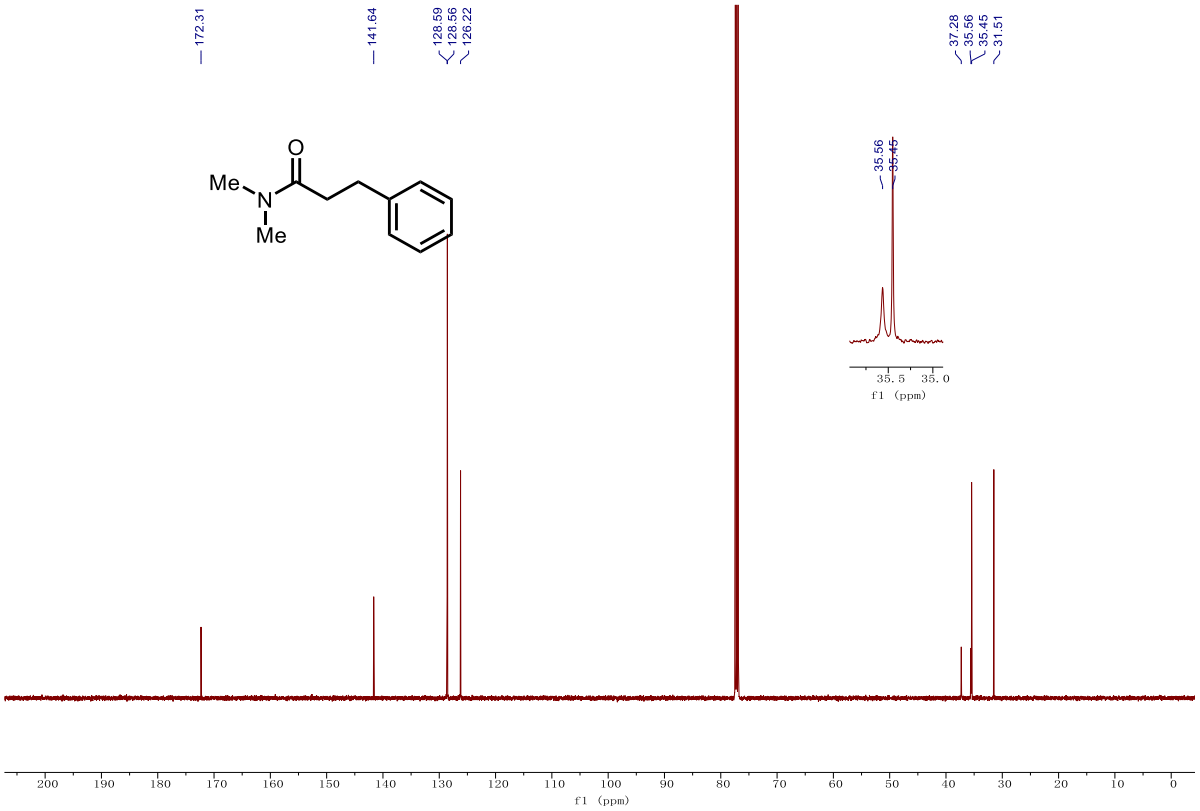
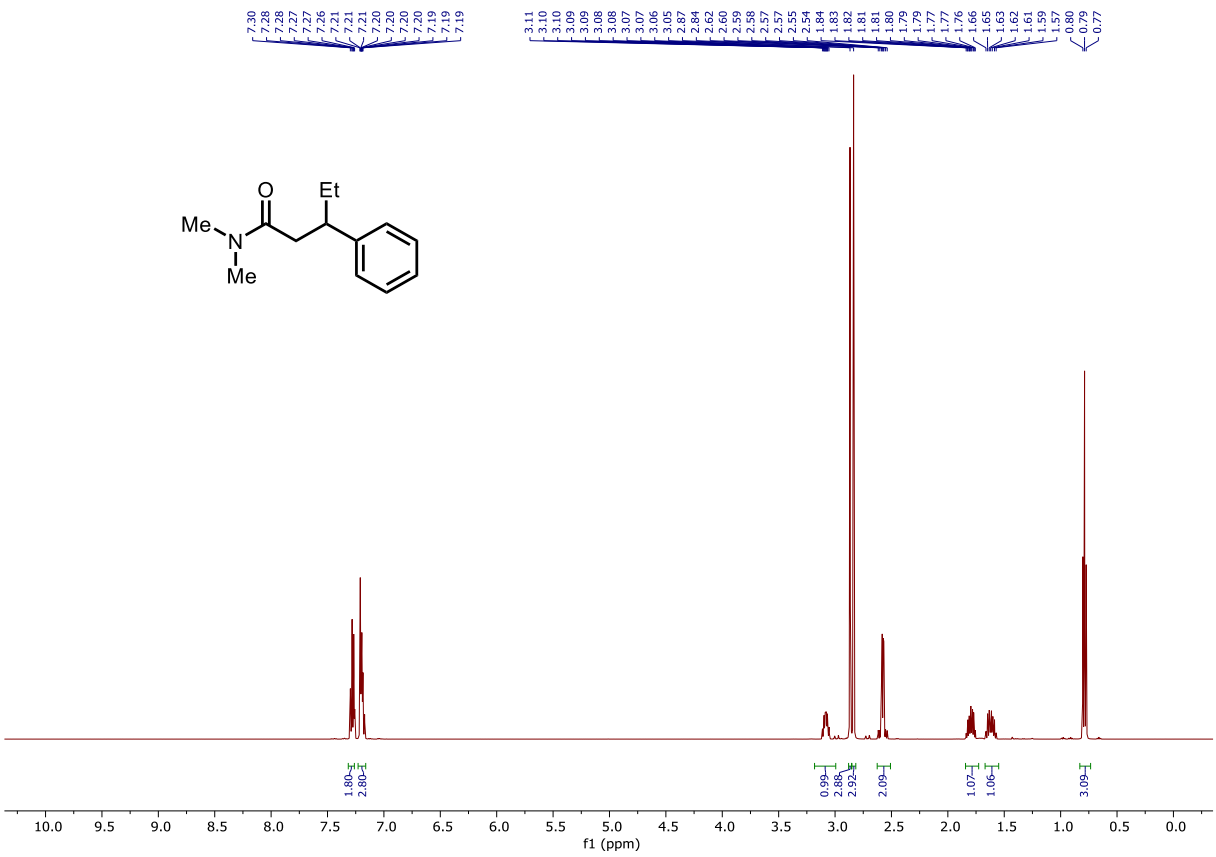
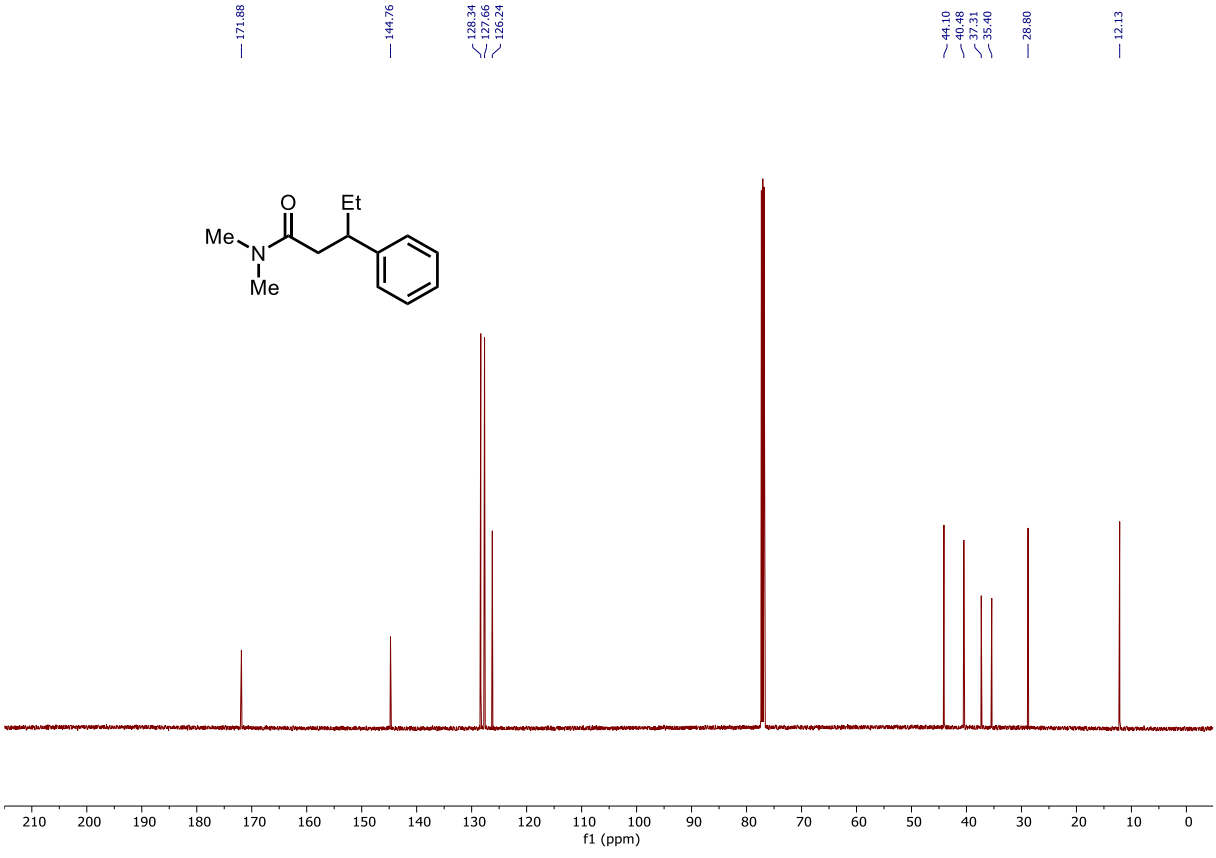
7.29
7.28
7.27
7.26
7.23
7.23
7.22
7.20
7.18
2.99
2.97
2.95
2.95
2.93
2.63
2.61
2.60
Me
N
Me
O
1.96
2.98
1.62
6.30
2.00
f1 (ppm)


172.31
141.64
128.59
128.56
126.22
37.28
35.56
35.45
31.51
35.56
35.45
Me
N
Me
O
f1 (ppm)


7.30 7.28 7.28 7.27 7.27 7.26 7.21 7.21 7.20 7.20 7.20 7.19 7.19 7.19
3.11 3.10 3.10 3.09 3.09 3.08 3.08 3.07 3.07 3.06 3.05 2.87 2.84 2.62 2.60 2.59 2.58 2.57 2.57 2.55 2.54 1.84 1.83 1.82 1.81 1.81 1.80 1.79 1.79 1.77 1.77 1.76 1.66 1.65 1.63 1.62 1.61 1.59 1.57 0.80 0.79 0.77
O
Et
Me
N
Me
1.80
2.80
0.99
2.88
2.92
2.09
1.07
1.06
3.09
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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144.76
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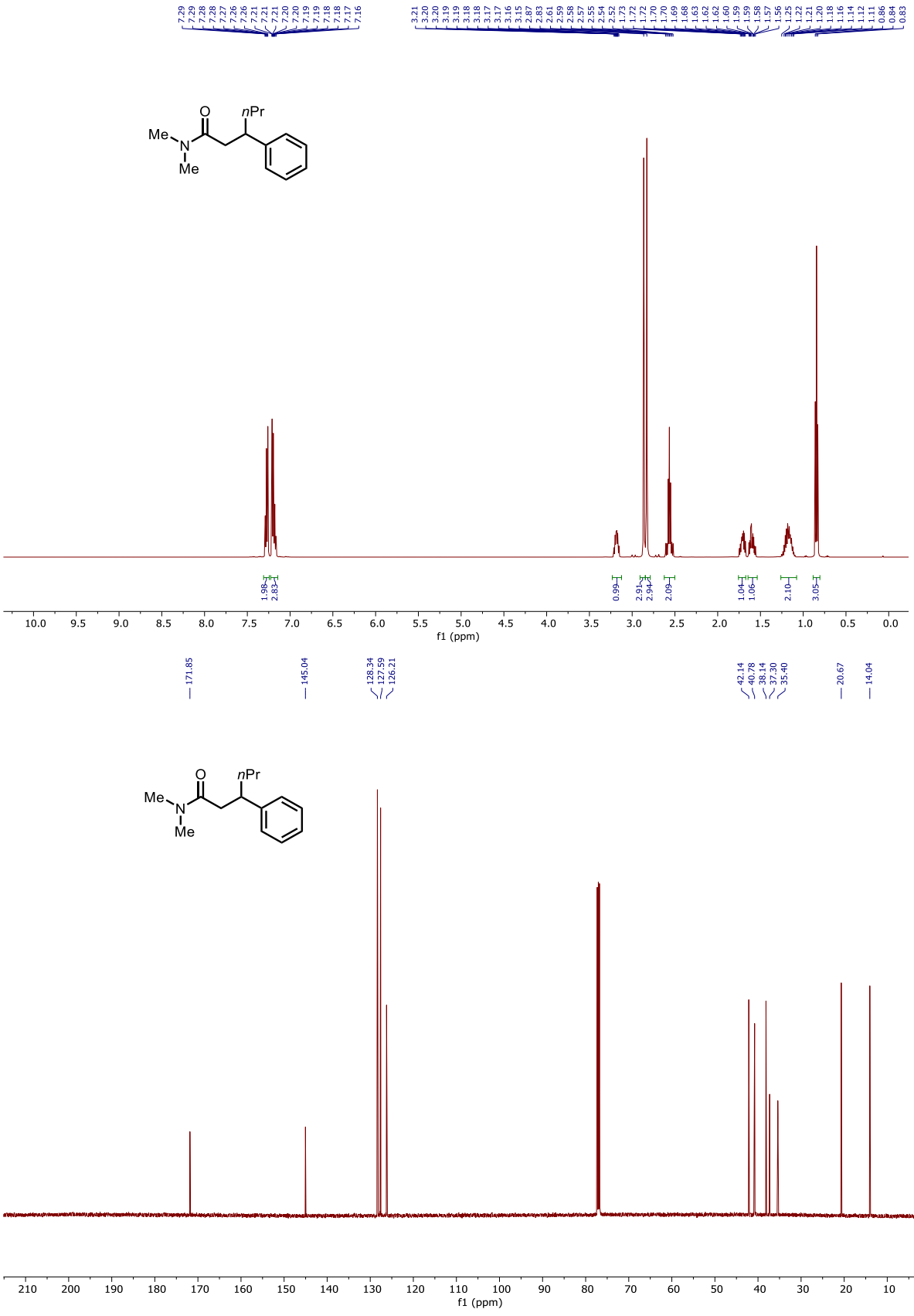
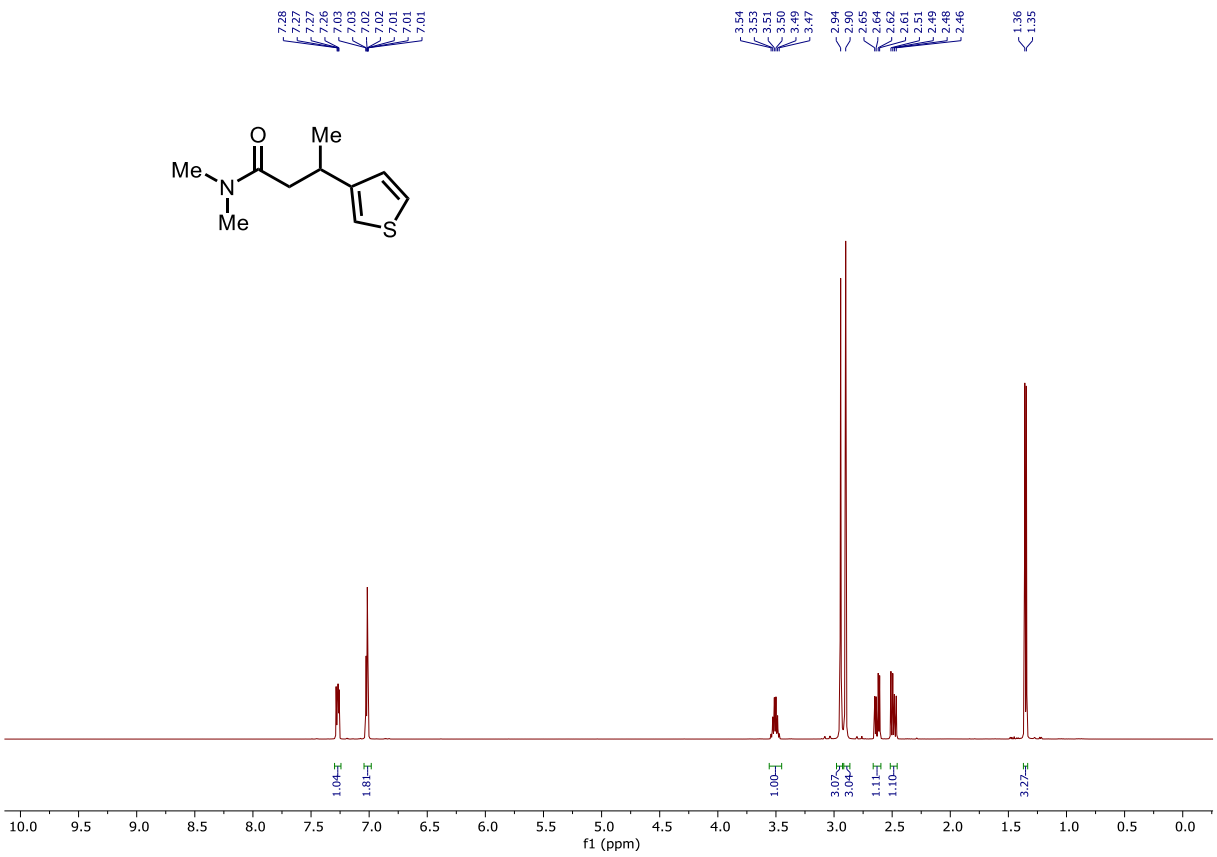
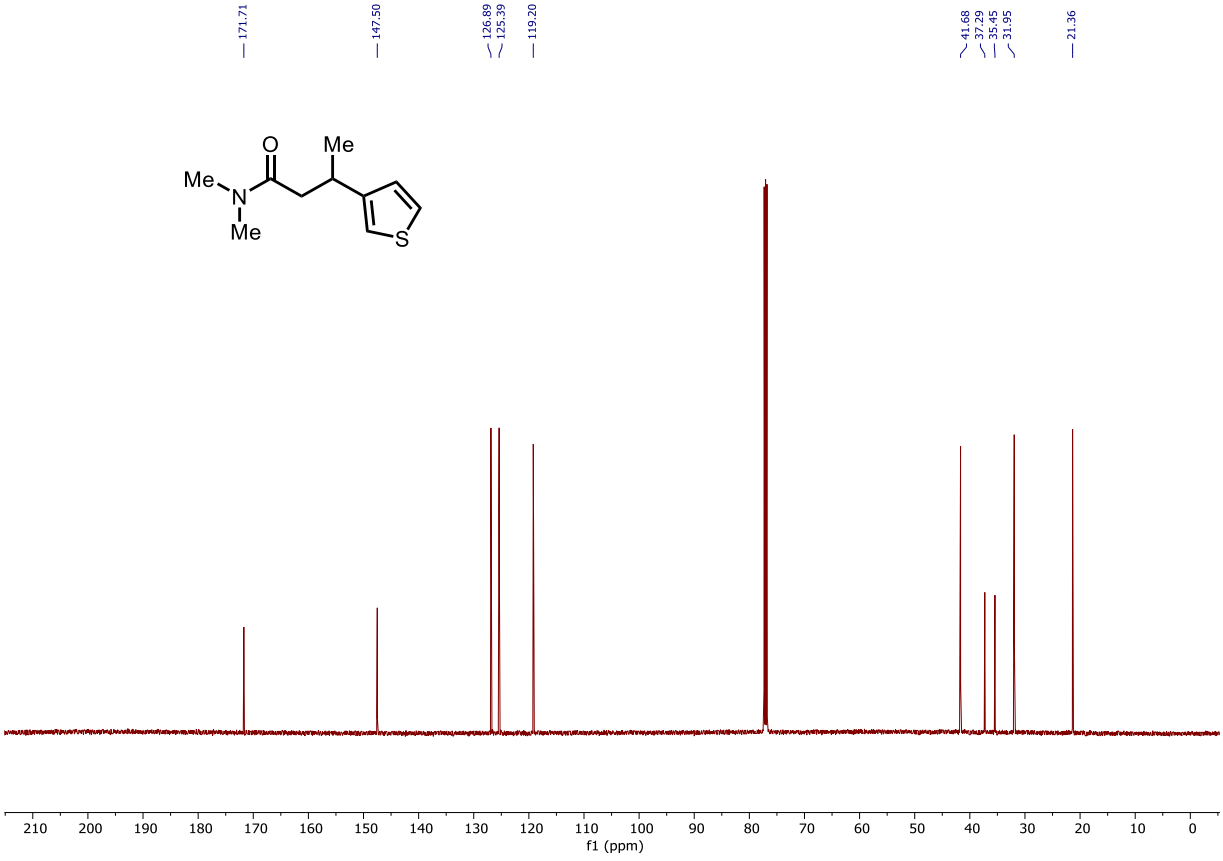
127.66
126.24
44.10
40.48
37.31
35.40
28.80
12.13
O
Et
Me
N
Me
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


7.29 7.29 7.28 7.28 7.27 7.26 7.26 7.21 7.21 7.21 7.20 7.20 7.19 7.19 7.18 7.18 7.17 7.16
3.21 3.20 3.20 3.19 3.19 3.18 3.18 3.17 3.17 3.16 3.15 2.87 2.83 2.61 2.59 2.58 2.57 2.55 2.54 2.52 1.73 1.72 1.72 1.70 1.70 1.69 1.68 1.63 1.62 1.62 1.60 1.59 1.59 1.58 1.57 1.56 1.25 1.22 1.21 1.20 1.18 1.16 1.14 1.12 1.11 0.86 0.84 0.83
O
nPr
Me
N
Me
1.98
2.83
0.99
2.91
2.94
2.09
1.04
1.06
2.10
3.05
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)
171.85
145.04
128.34
127.59
126.21
42.14
40.78
38.14
37.30
35.40
20.67
14.04
O
nPr
Me
N
Me
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


7.28
7.27
7.27
7.26
7.03
7.02
7.02
7.01
7.01
7.01
3.54
3.53
3.51
3.50
3.49
3.47
2.94
2.90
2.65
2.64
2.62
2.61
2.51
2.49
2.48
2.46
1.36
1.35
O
Me
Me
N
Me
S
1.04
1.81
1.00
3.07
3.04
1.11
1.10
3.27
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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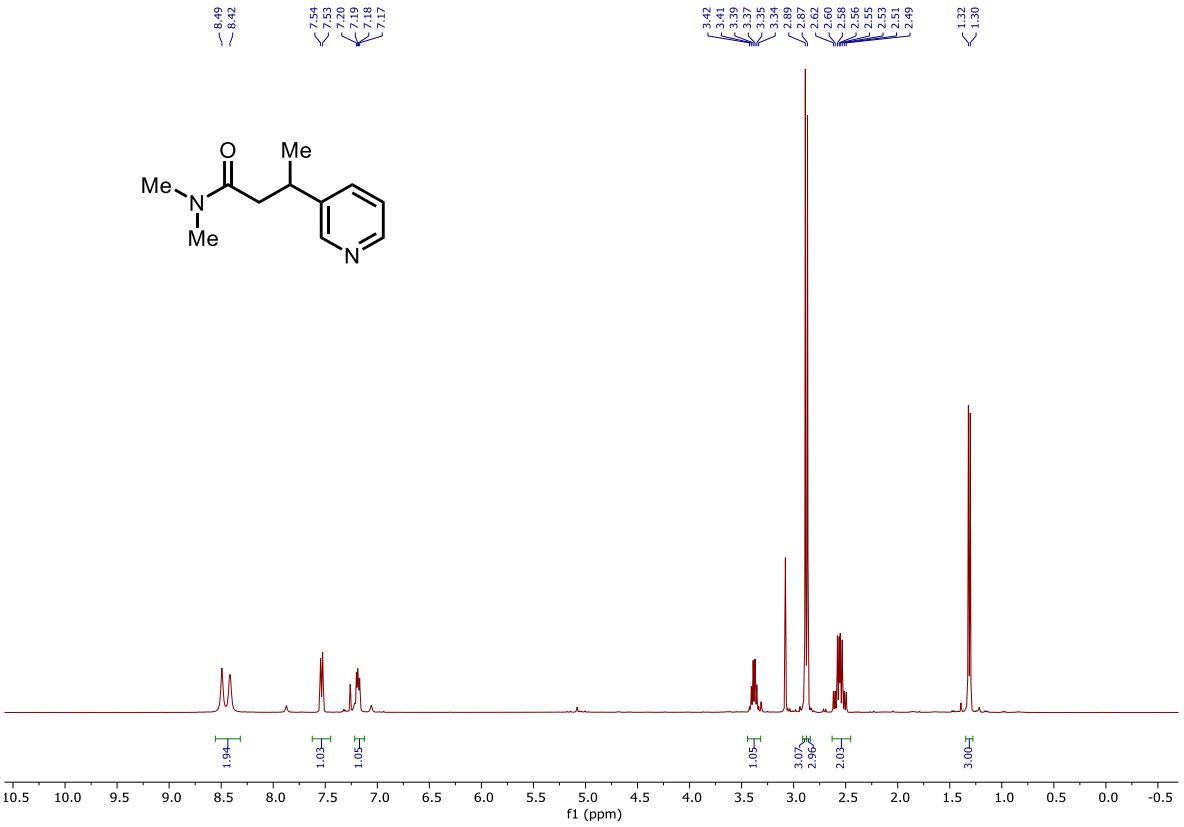
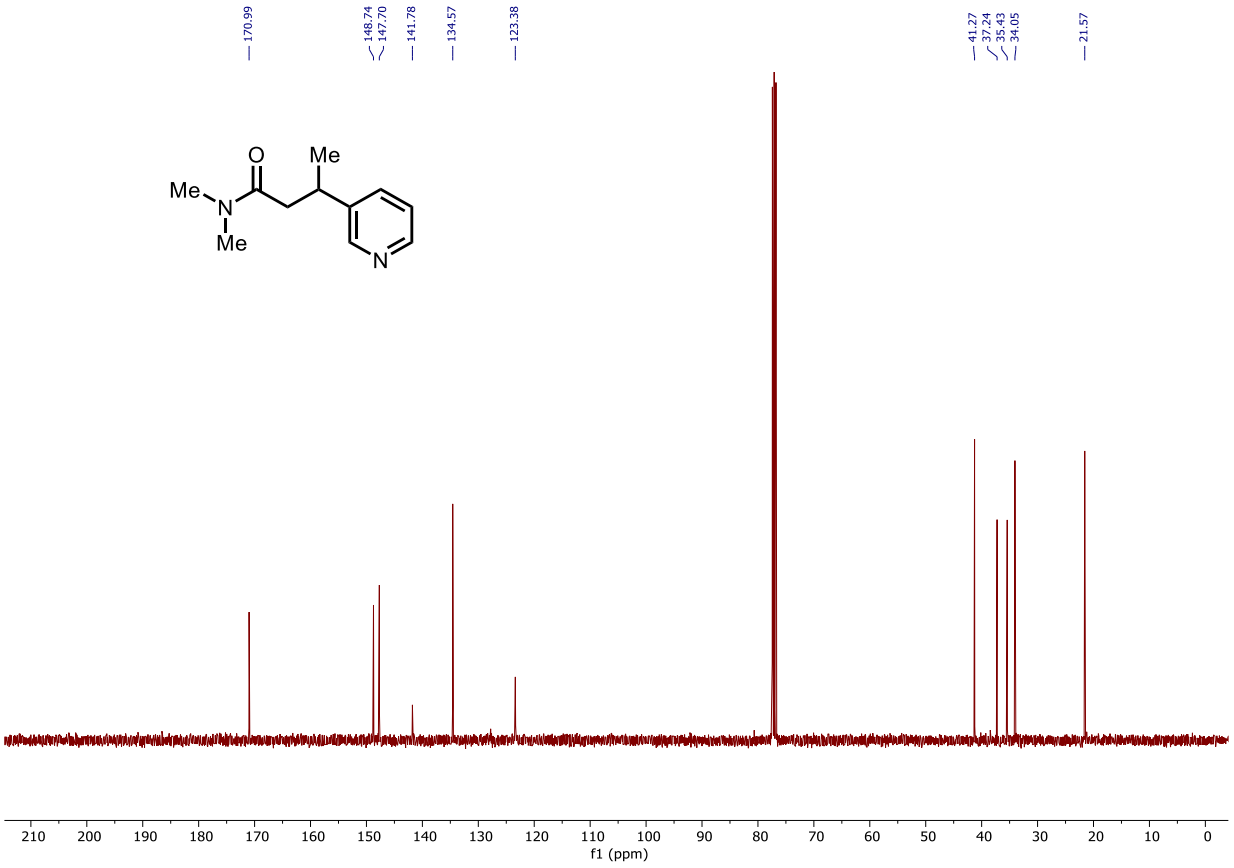
147.50
126.89
125.39
119.20
41.68
37.29
35.45
31.95
21.36
O
Me
Me
N
Me
S
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


8.49
8.42
7.54
7.53
7.20
7.19
7.18
7.17
3.42
3.41
3.39
3.37
3.35
3.34
2.89
2.87
2.62
2.60
2.58
2.56
2.55
2.53
2.51
2.49
1.32
1.30
O
Me
Me
N
Me
N
1.94
1.03
1.05
1.05
3.07
2.96
2.03
3.00
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)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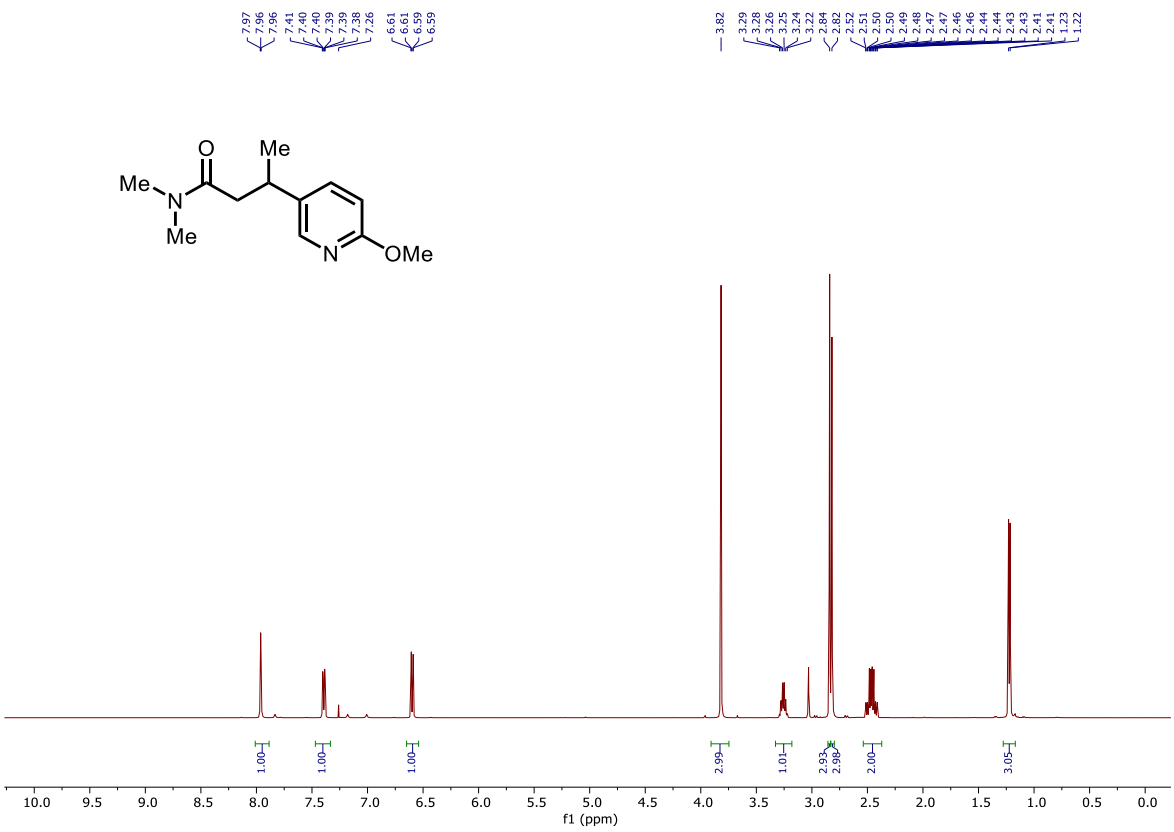
148.74
147.70
141.78
134.57
123.38
41.27
37.24
35.43
34.05
21.57
O
Me
Me
N
Me
N
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)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7.96
7.96
7.41
7.40
7.40
7.39
7.39
7.38
7.26
6.61
6.61
6.59
6.59
3.82
3.29
3.28
3.26
3.25
3.24
3.22
2.84
2.82
2.52
2.51
2.50
2.50
2.49
2.48
2.47
2.47
2.46
2.46
2.44
2.44
2.43
2.43
2.41
2.41
1.23
1.22
O
Me
Me
N
Me
N
OMe
1.00
1.00
1.00
2.99
1.01
2.93
2.98
2.00
3.05
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
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4.5
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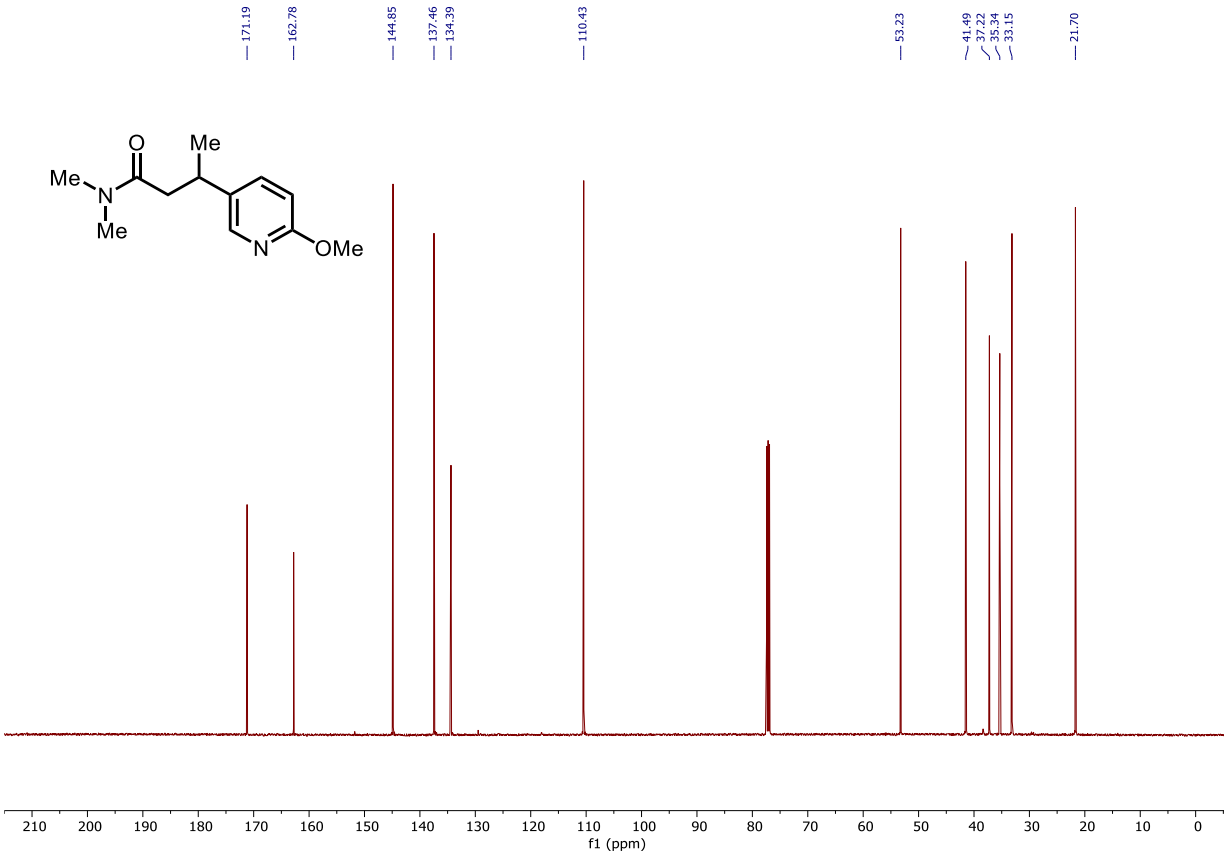
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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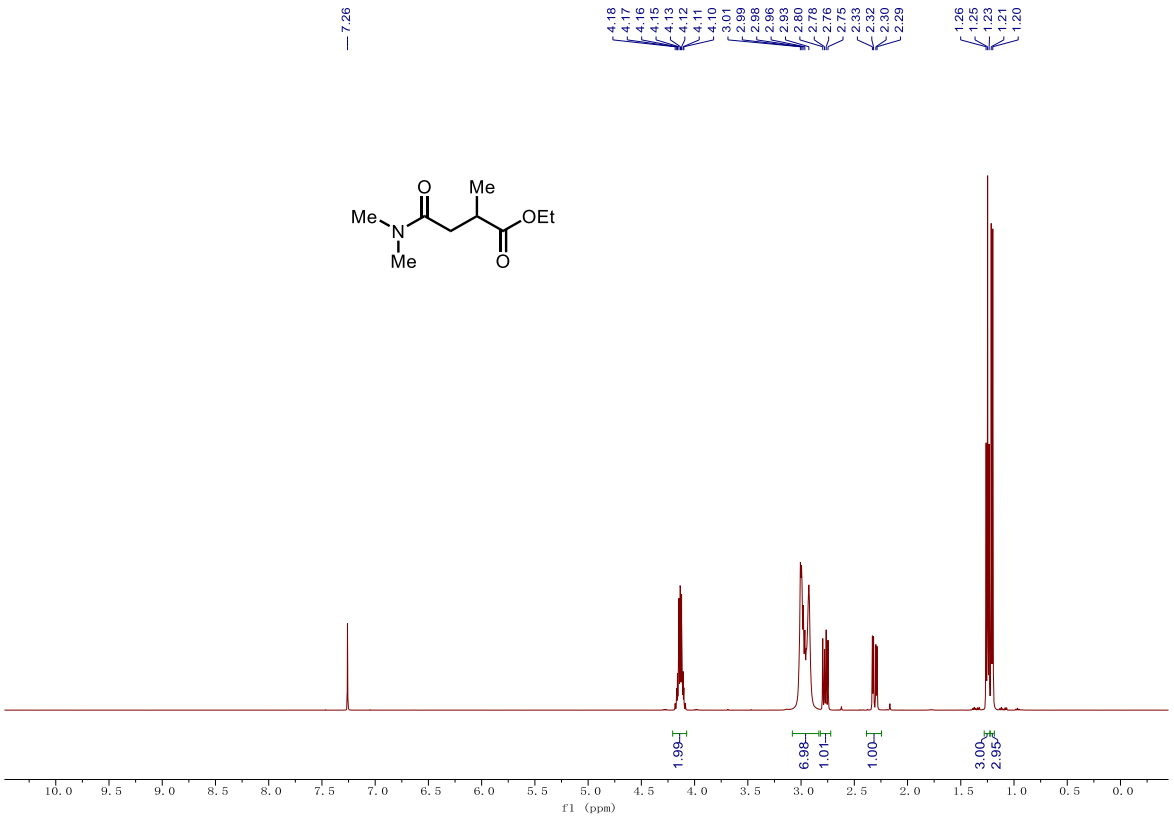
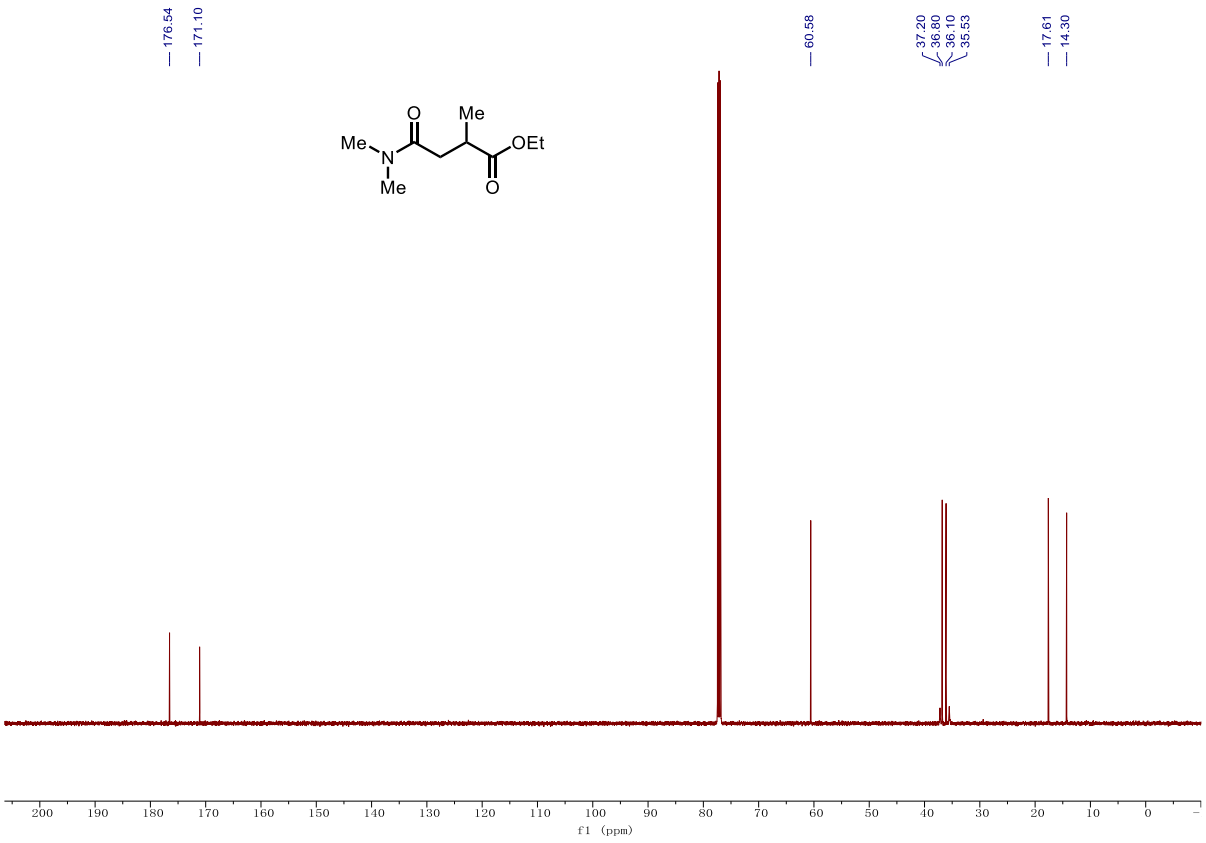
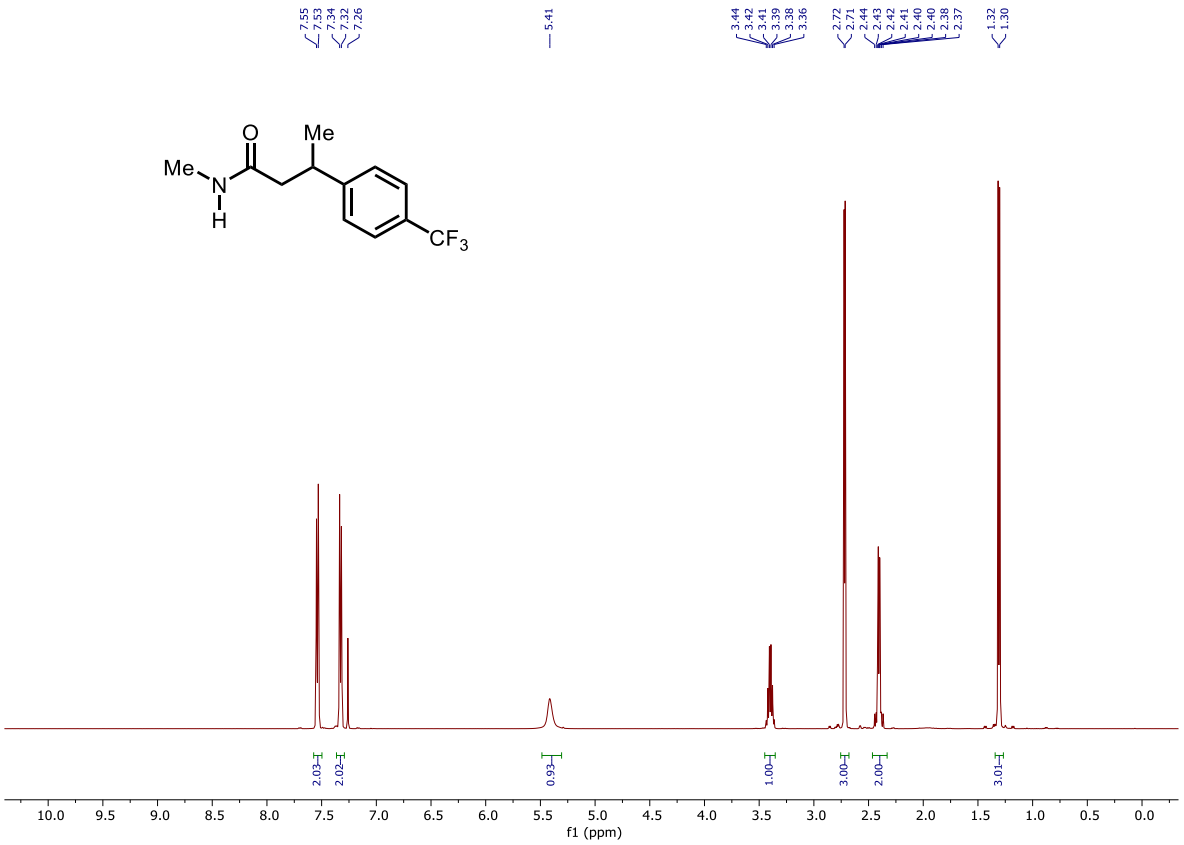
162.78
144.85
137.46
134.39
110.43
53.23
41.49
37.22
35.34
33.15
21.70
O
Me
Me
N
Me
N
OMe
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


7.26
4.18
4.17
4.16
4.15
4.13
4.12
4.11
4.10
3.01
2.99
2.98
2.96
2.93
2.80
2.78
2.76
2.75
2.33
2.32
2.30
2.29
1.26
1.25
1.23
1.21
1.20
Me
O
Me
N
Me
OEt
O
1.99
6.98
1.01
1.00
3.00
2.95
f1 (ppm)


176.54
171.10
60.58
37.20
36.80
36.10
35.53
17.61
14.30
Me
O
Me
N
Me
OEt
O
f1 (ppm)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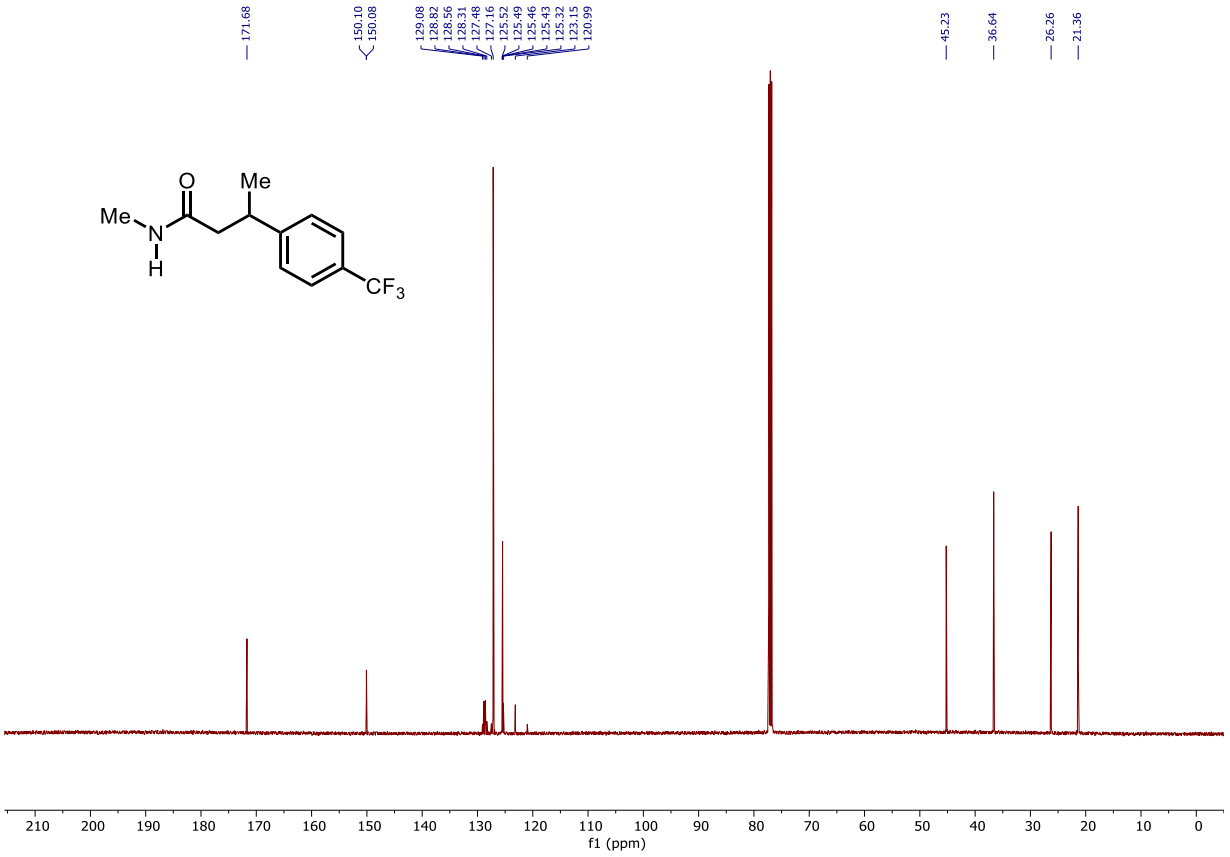
7.53
7.34
7.32
7.26
5.41
3.44
3.42
3.41
3.39
3.38
3.36
2.72
2.71
2.44
2.43
2.42
2.41
2.40
2.40
2.38
2.37
1.32
1.30
O
Me
Me
N
H
CF3
2.03
2.02
0.93
1.00
3.00
2.00
3.01
f1 (ppm)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127.48
127.16
125.52
125.49
125.46
125.43
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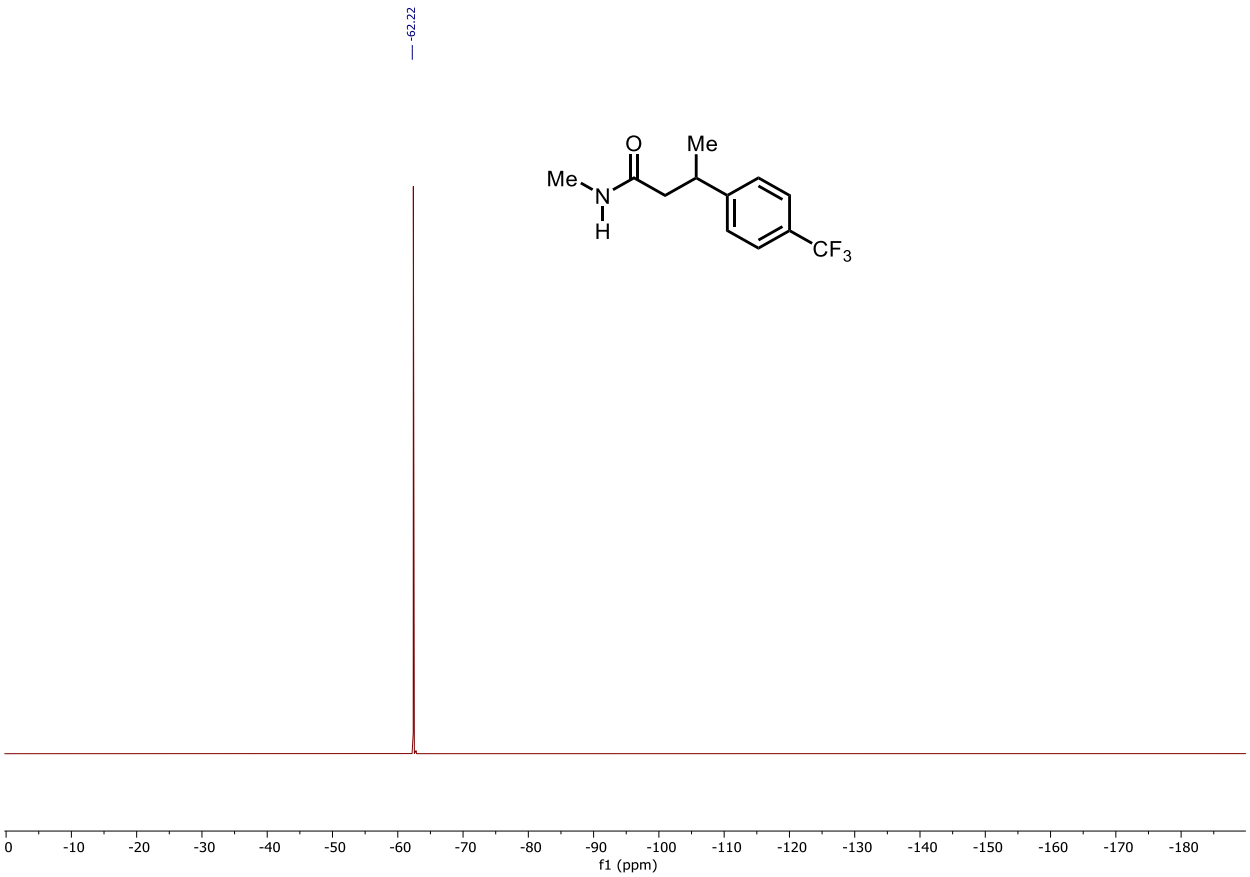
21.36
O
Me
Me
N
H
CF3
f1 (ppm)


-62.22
O
Me
Me
N
H
CF3
0
-10
-20
-30
-40
-50
-60
-70
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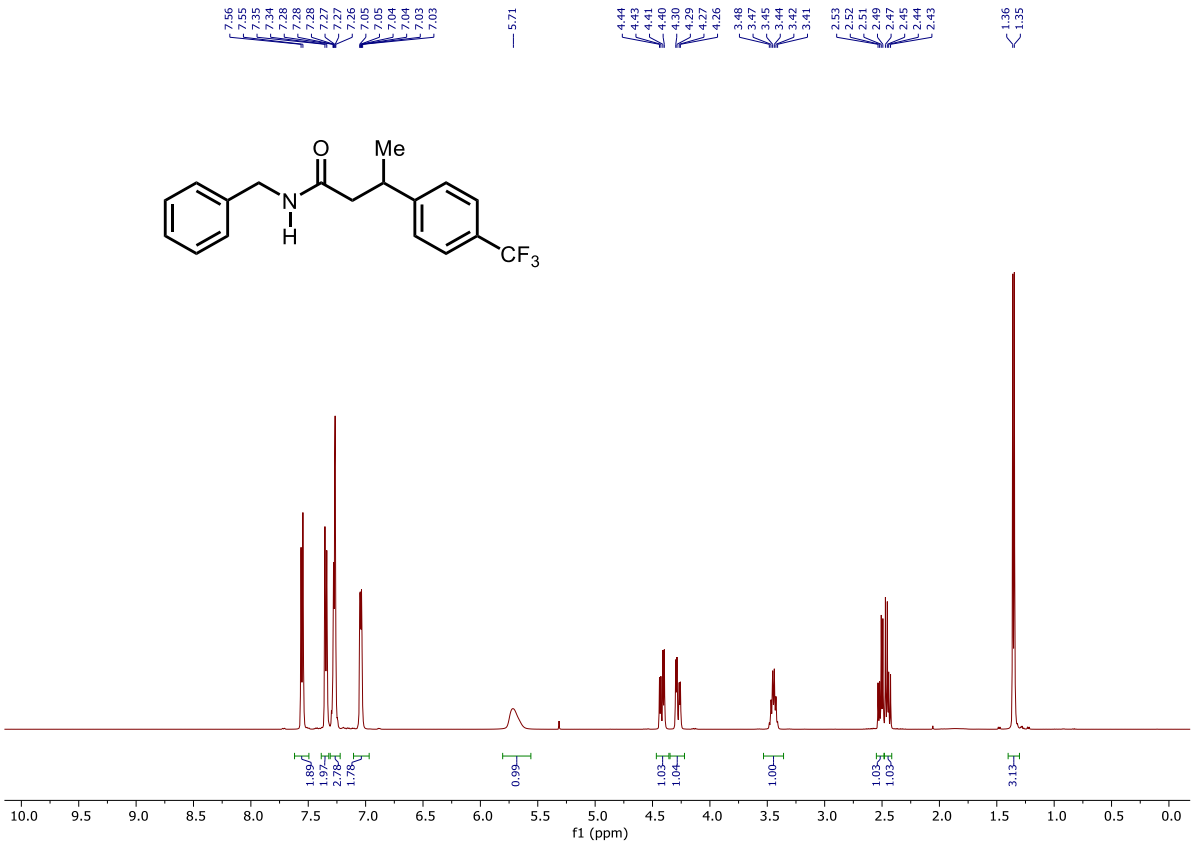
-130
-140
-150
-160
-170
-180
f1 (ppm)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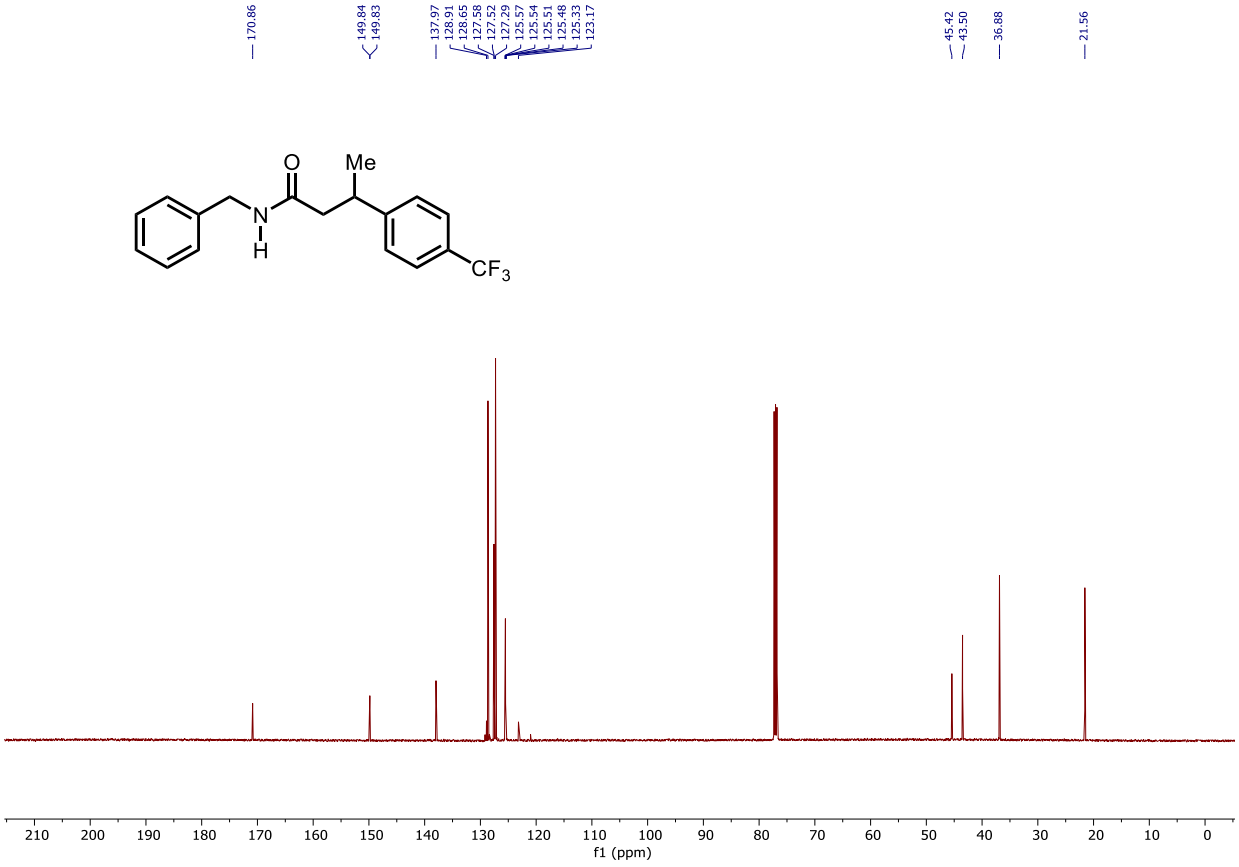
7.26
7.05
7.05
7.04
7.04
7.03
7.03
5.71
4.44
4.43
4.41
4.40
4.30
4.29
4.27
4.26
3.48
3.47
3.45
3.44
3.42
3.41
2.53
2.52
2.51
2.49
2.47
2.45
2.44
2.43
1.36
1.35
O
Me
N
H
CF3
1.89
1.97
2.78
1.78
0.99
1.03
1.04
1.00
1.03
1.03
3.13
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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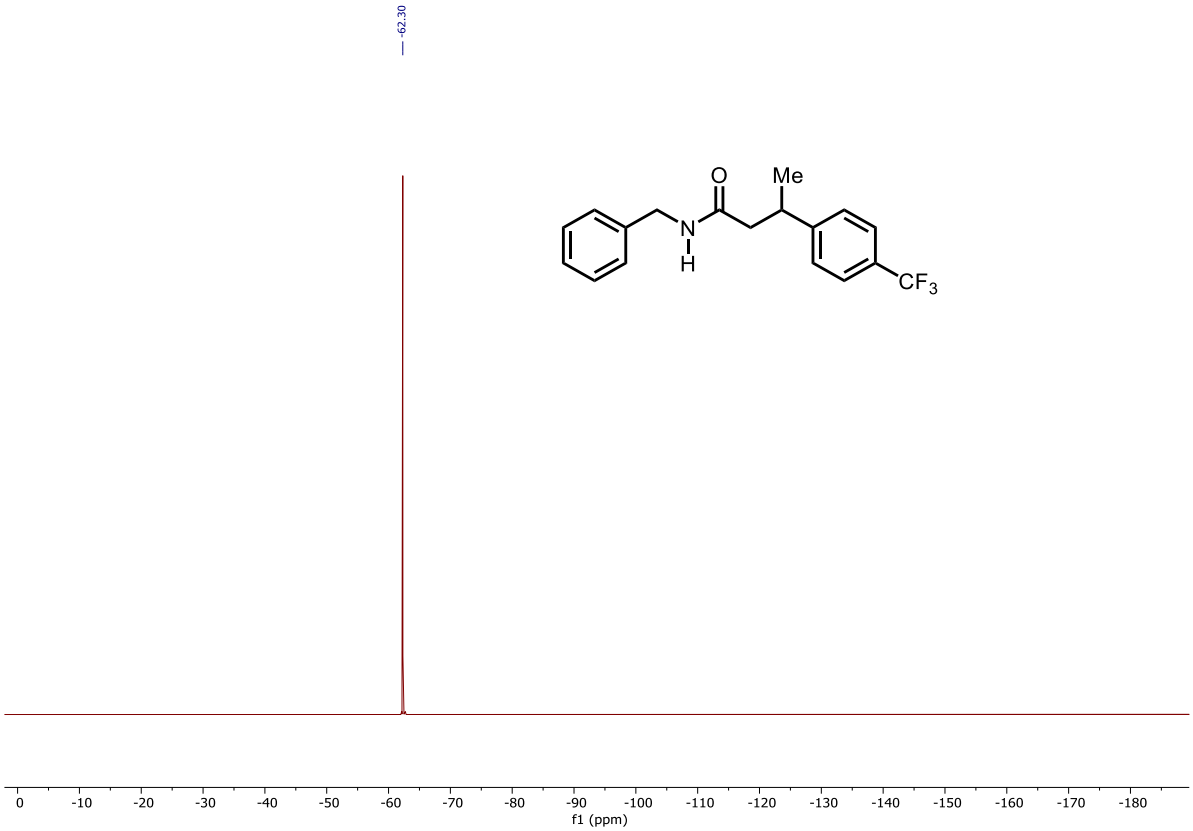
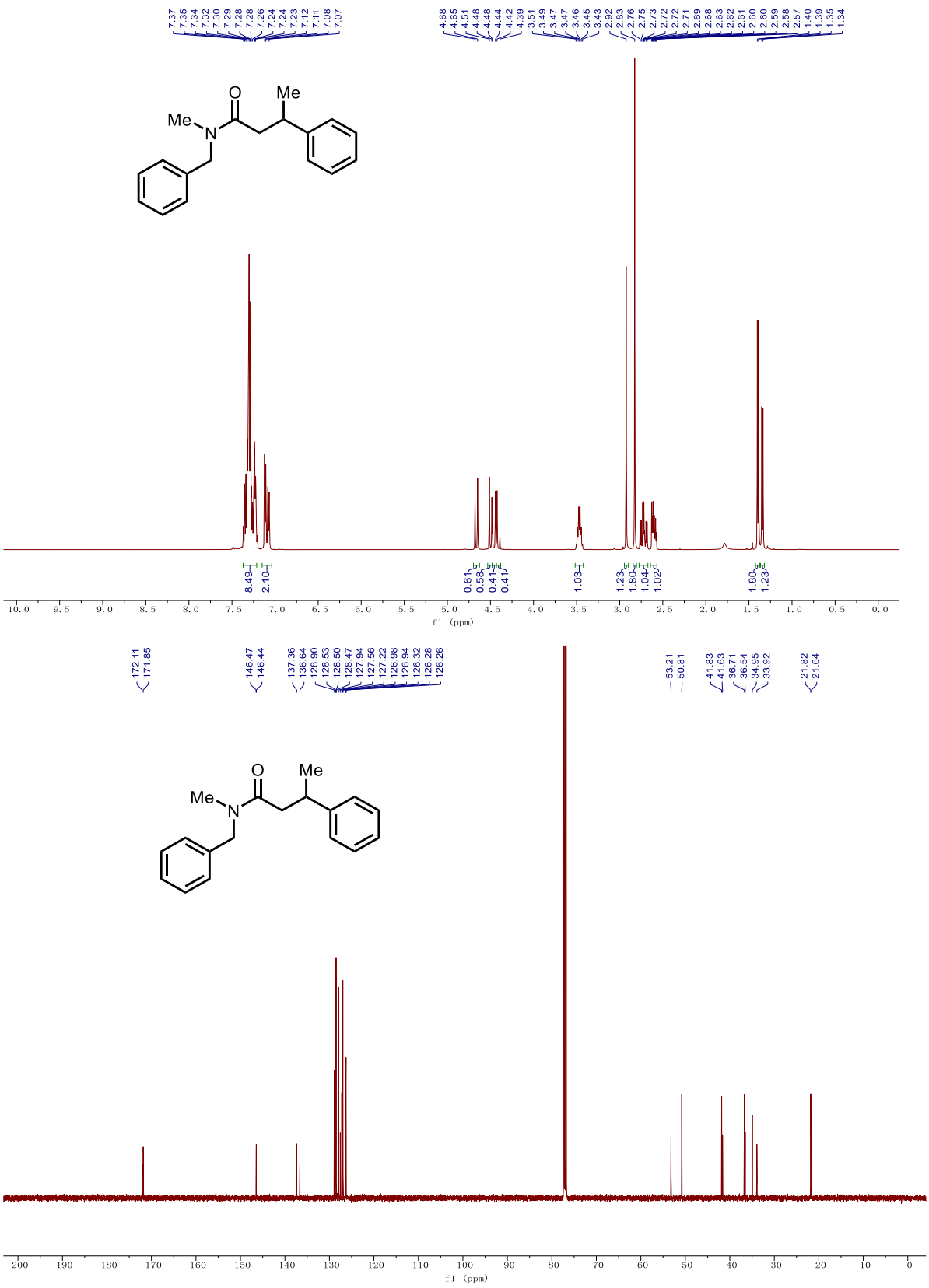
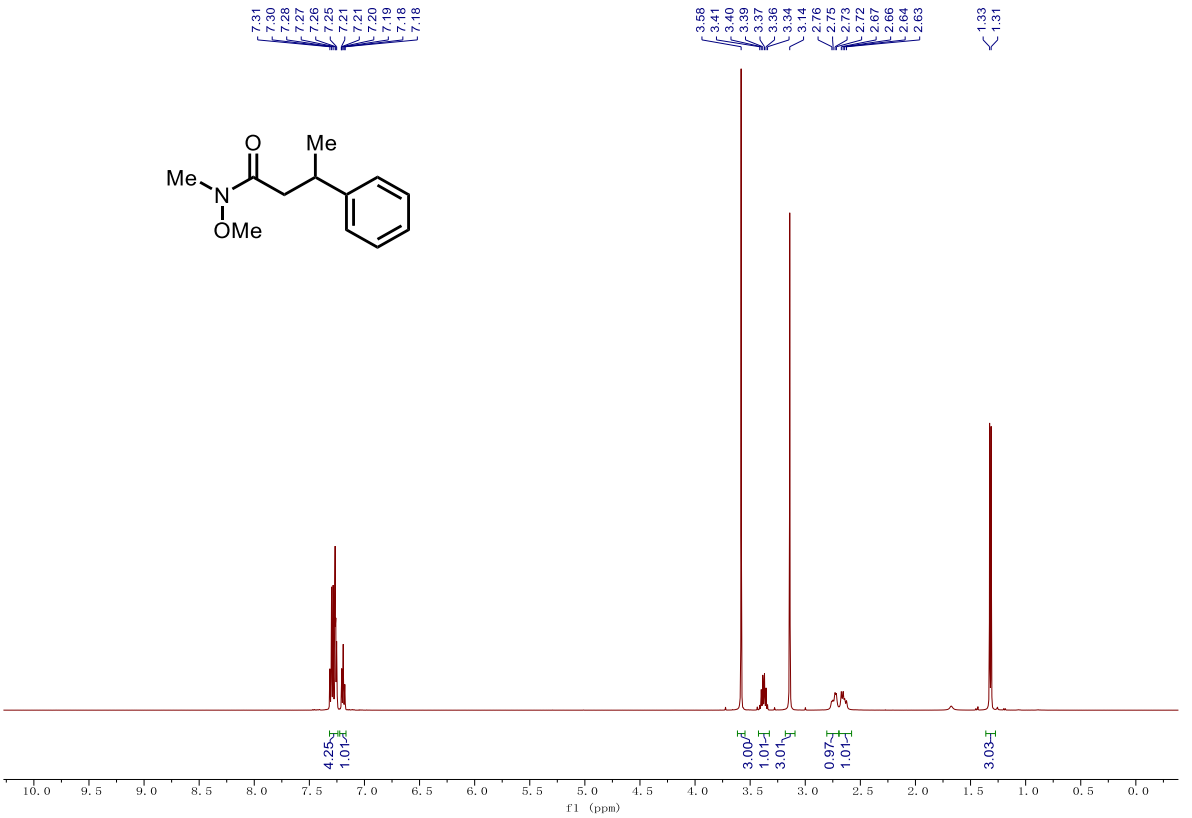
128.91
128.65
127.58
127.52
127.29
125.57
125.54
125.51
125.48
125.33
123.17
45.42
43.50
36.88
21.56
O
Me
N
H
CF3
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


-62.30
O
Me
N
H
CF3
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
f1 (ppm)


7.37 7.35 7.34 7.32 7.30 7.29 7.28 7.28 7.26 7.24 7.24 7.23 7.12 7.11 7.08 7.07
4.68 4.65 4.51 4.48 4.48 4.44 4.42 4.39 3.51 3.49 3.47 3.47 3.46 3.45 3.43 2.92 2.83 2.76 2.75 2.73 2.72 2.72 2.71 2.69 2.68 2.63 2.62 2.61 2.60 2.60 2.59 2.58 2.57 1.40 1.39 1.35 1.34
O
Me
Me
N
8.49
2.10
0.61
0.58
0.41
0.41
1.03
1.23
1.80
1.04
1.02
1.80
1.23
f1 (ppm)
172.11
171.85
146.47
146.44
137.36
136.64
128.90
128.53
128.50
128.47
127.94
127.56
127.22
126.98
126.94
126.32
126.28
126.26
53.21
50.81
41.83
41.63
38.71
36.54
34.95
33.92
21.82
21.64
f1 (ppm)


7.31
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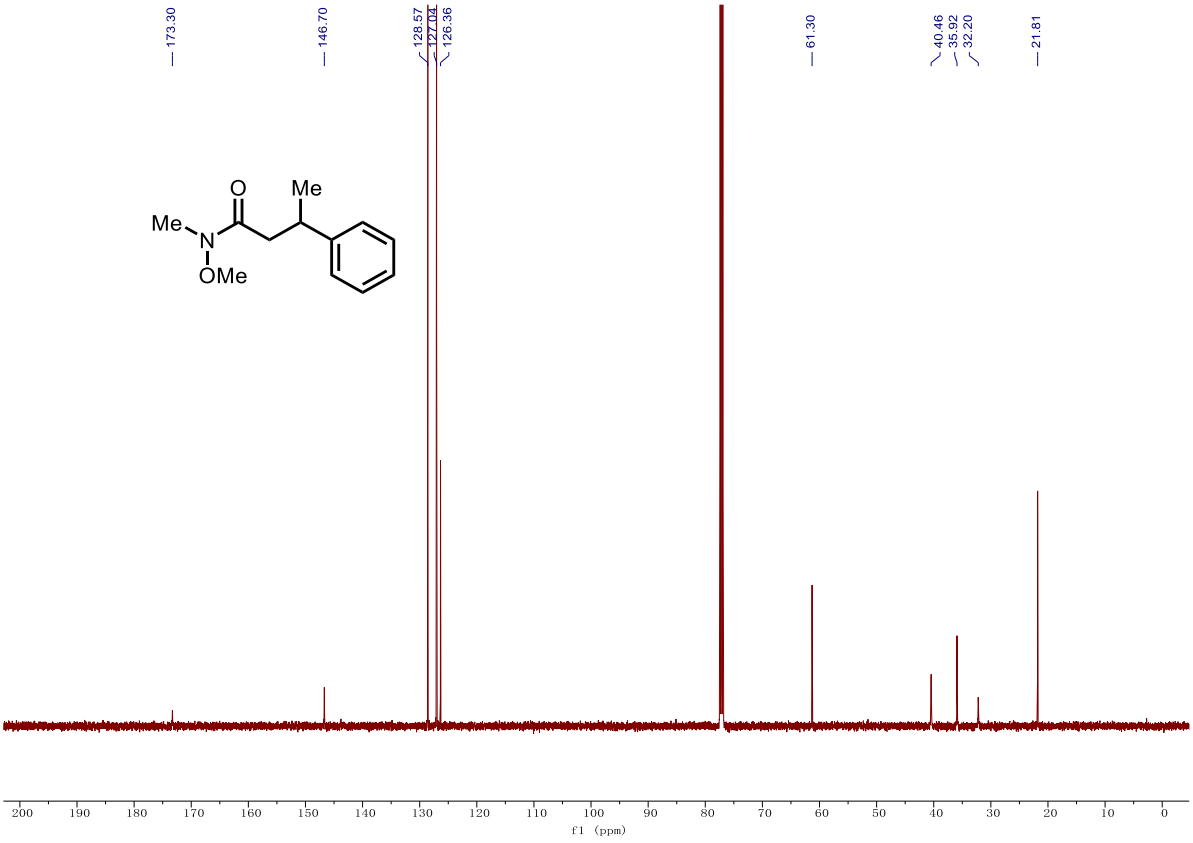
7.28
7.27
7.26
7.25
7.21
7.20
7.19
7.18
7.18
3.58
3.41
3.40
3.39
3.37
3.36
3.34
3.14
2.76
2.75
2.73
2.72
2.67
2.66
2.64
2.63
1.33
1.31
O
Me
Me
N
OMe
4.25
1.01
3.00
1.01
3.01
0.97
1.01
3.03
f1 (ppm)


173.30
146.70
128.57
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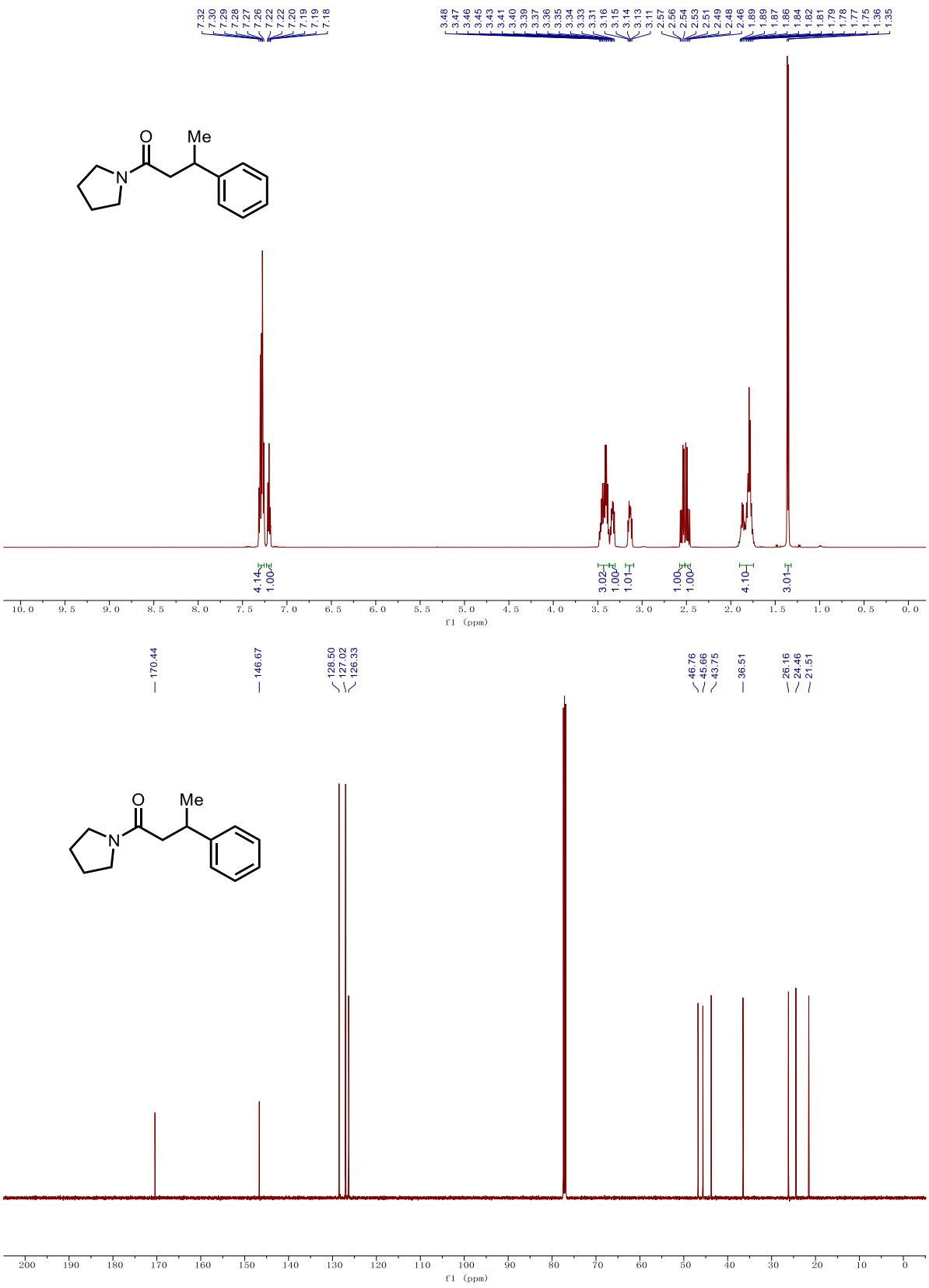
61.30
40.46
35.92
32.20
21.81
O
Me
Me
N
OMe
f1 (ppm)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7.22
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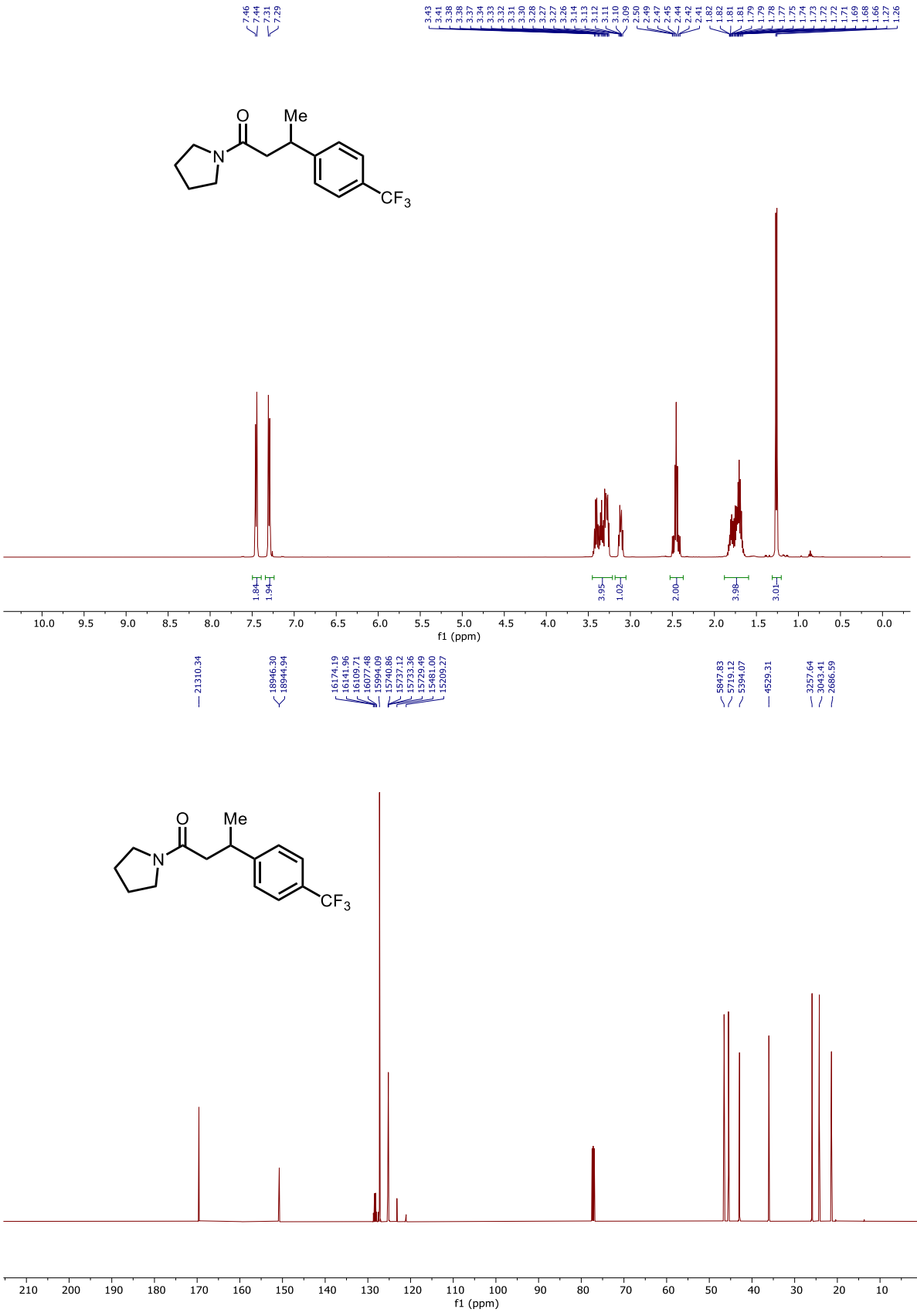
7.19
7.19
7.18
3.48
3.47
3.46
3.45
3.43
3.41
3.40
3.39
3.37
3.36
3.35
3.34
3.33
3.31
3.16
3.15
3.14
3.13
3.11
2.57
2.56
2.54
2.53
2.51
2.49
2.48
2.46
1.89
1.89
1.87
1.86
1.84
1.82
1.81
1.79
1.78
1.77
1.75
1.36
1.35
O
Me
N
4.14
1.00
3.02
1.00
1.01
1.00
1.00
4.10
3.01
f1 (ppm)
170.44
146.67
128.50
127.02
126.33
46.76
45.66
43.75
36.51
26.16
24.46
21.51
O
Me
N
f1 (ppm)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3.41
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3.38
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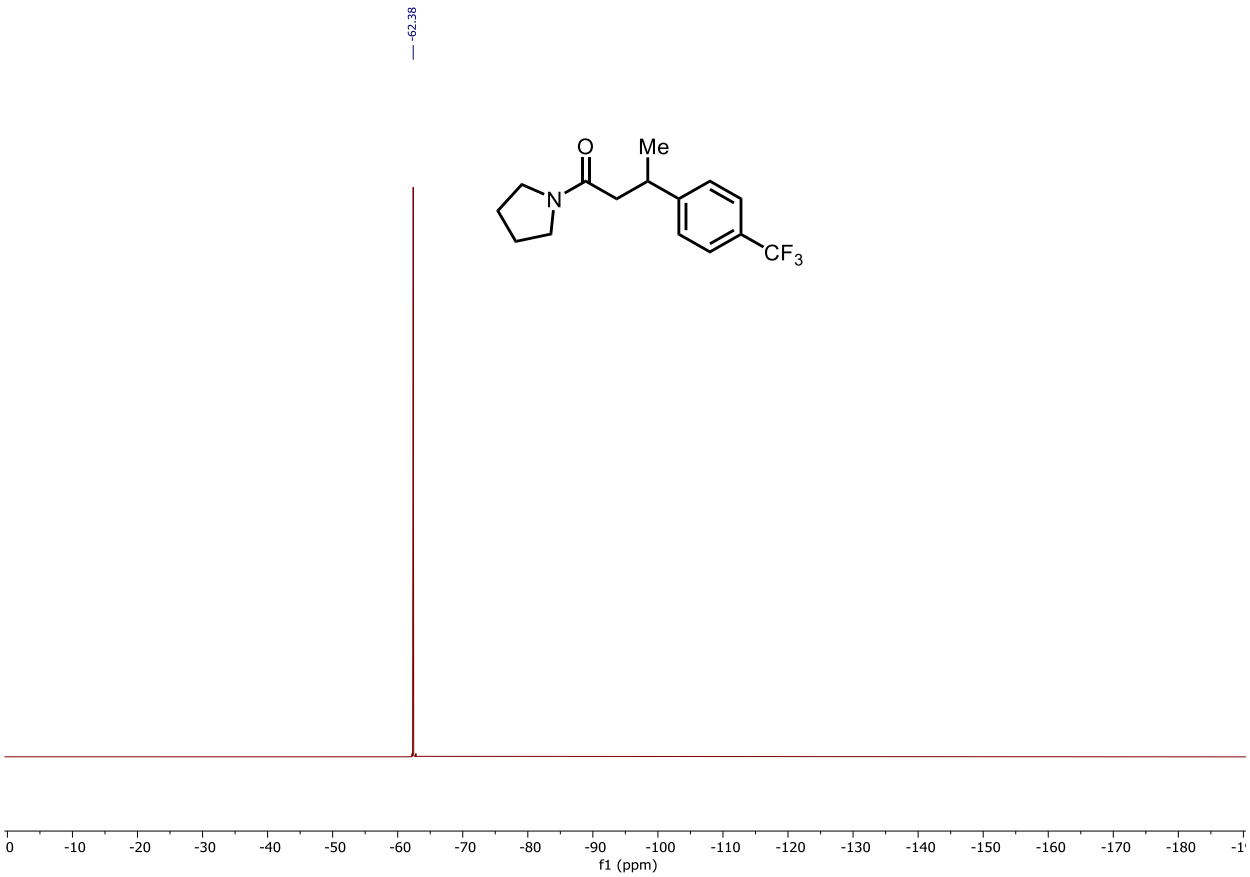
3.34
3.33
3.32
3.31
3.30
3.28
3.27
3.27
3.26
3.14
3.13
3.12
3.11
3.10
3.09
2.50
2.49
2.47
2.45
2.44
2.42
2.41
1.82
1.82
1.81
1.81
1.79
1.79
1.78
1.77
1.75
1.74
1.73
1.72
1.72
1.71
1.69
1.68
1.66
1.27
1.26
O
Me
N
CF3
1.84
1.94
3.95
1.02
2.00
3.98
3.01
f1 (ppm)
21310.34
18946.30
18944.94
16174.19
16141.96
16109.71
16077.48
15994.09
15740.86
15737.12
15733.36
15729.49
15481.00
15209.27
5847.83
5719.12
5394.07
4529.31
3257.64
3043.41
2686.59
O
Me
N
CF3
f1 (ppm)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O
Me
N
CF3
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-20
-30
-40
-50
-60
-70
-80
-90
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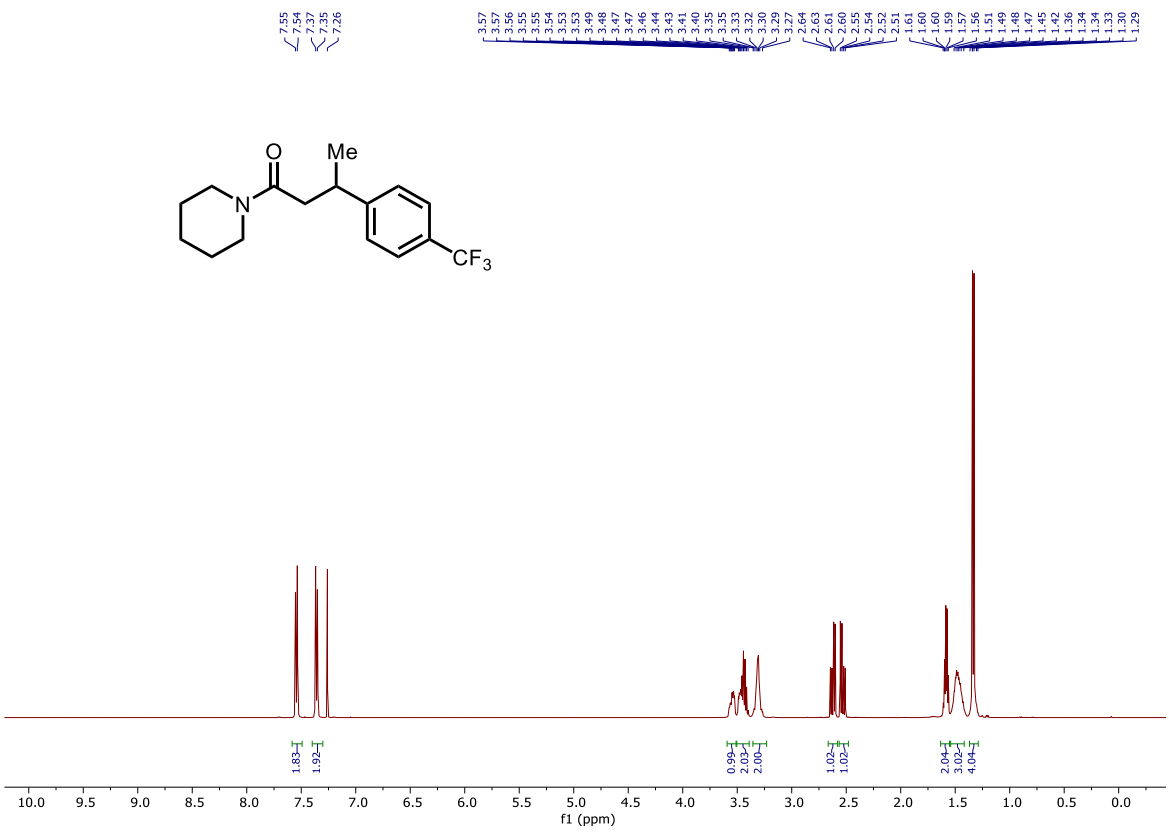
-130
-140
-150
-160
-170
-180
f1 (ppm)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7.54
7.37
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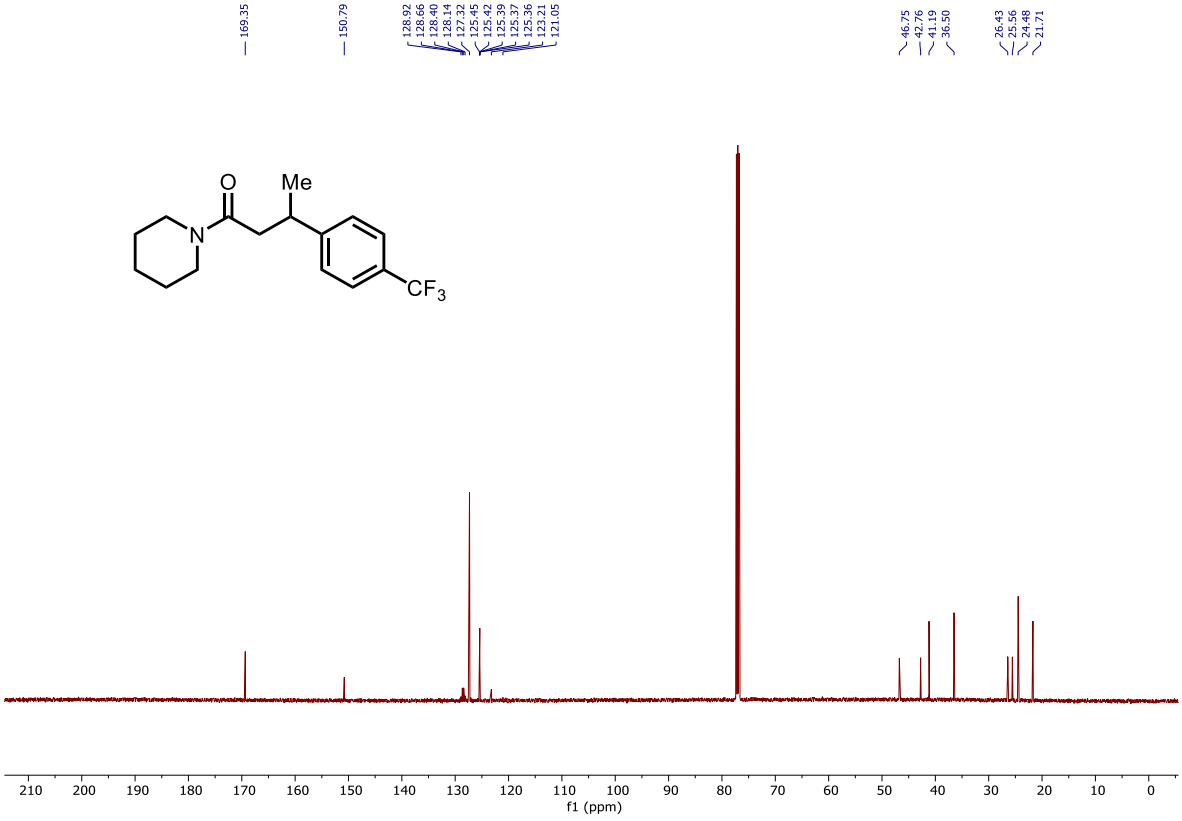
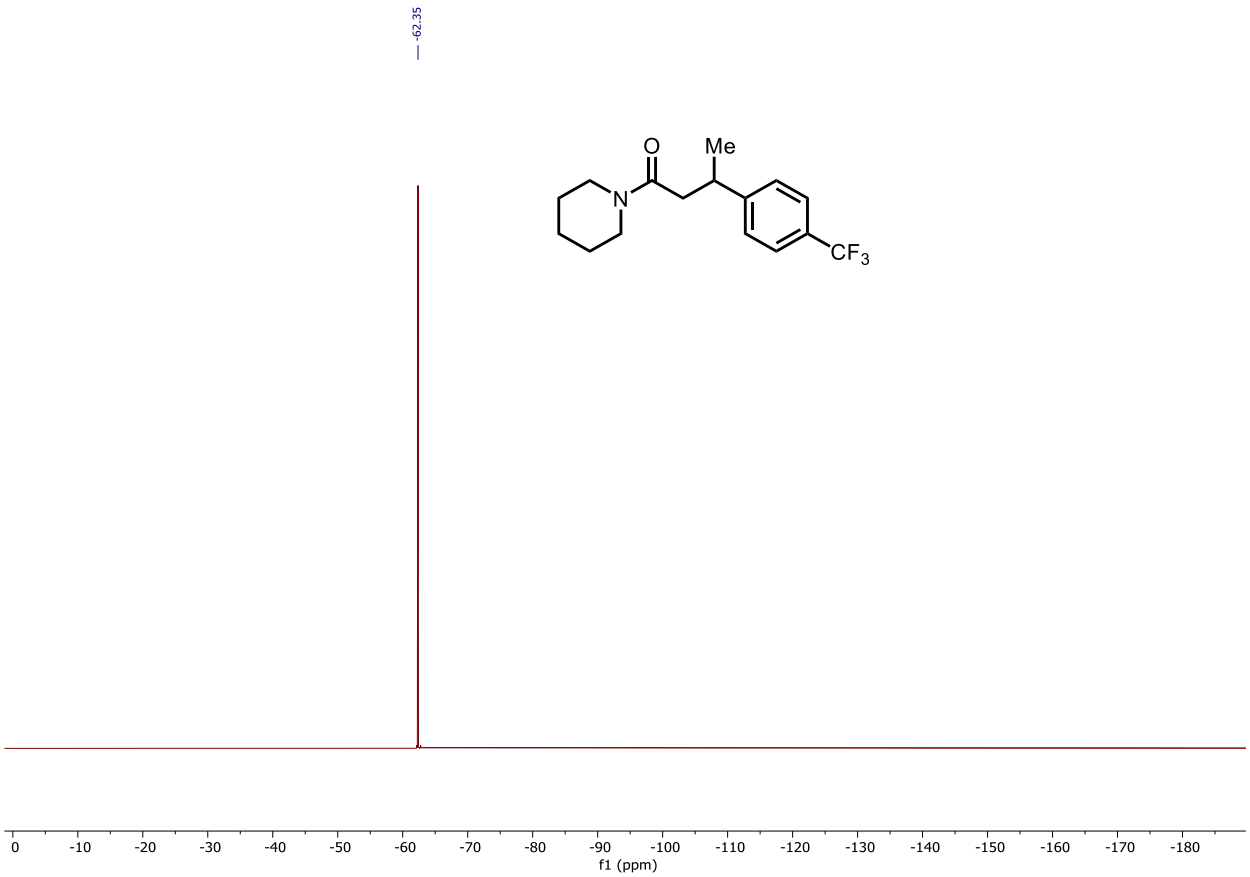
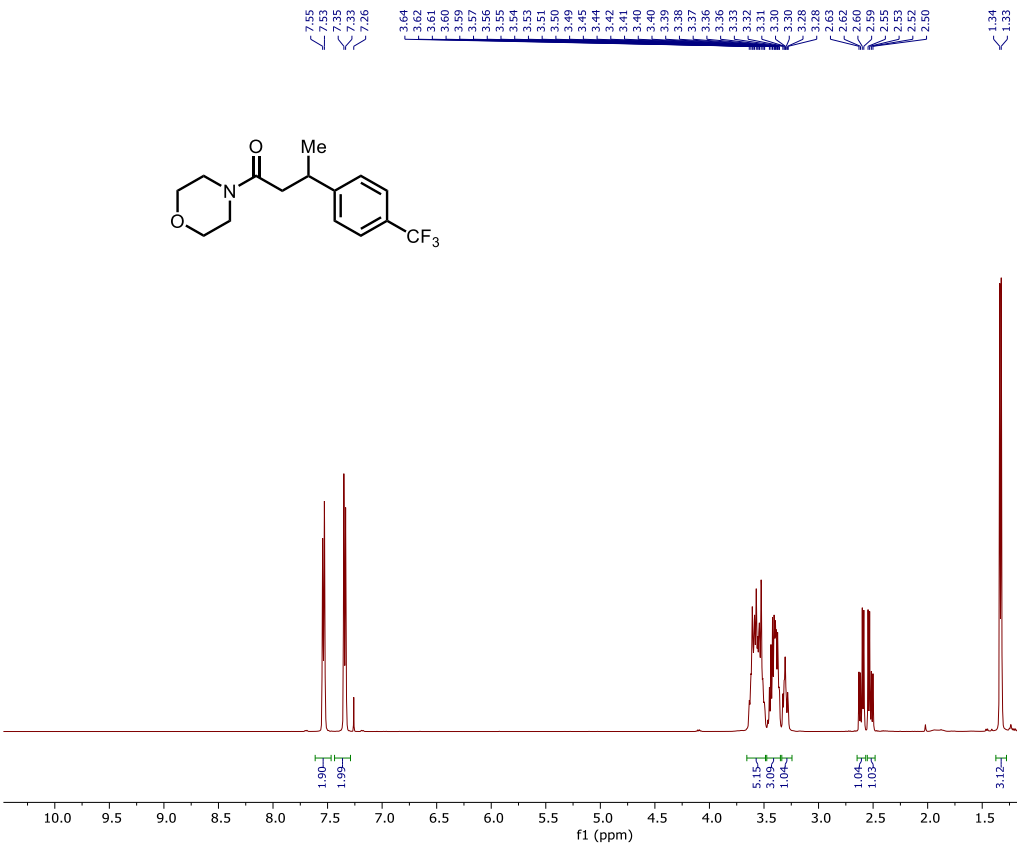
3.57
3.57
3.56
3.55
3.55
3.54
3.53
3.53
3.49
3.48
3.47
3.47
3.46
3.44
3.43
3.41
3.40
3.35
3.33
3.32
3.30
3.29
3.27
2.64
2.63
2.61
2.60
2.55
2.54
2.52
2.51
1.61
1.60
1.60
1.59
1.57
1.56
1.51
1.49
1.48
1.47
1.45
1.42
1.36
1.34
1.34
1.33
1.30
1.29
O
Me
N
CF3
1.83
1.92
0.99
2.03
2.00
1.02
1.02
2.04
3.02
4.04
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


169.35
150.79
128.92
128.66
128.40
128.14
127.32
125.45
125.42
125.39
125.37
125.36
123.21
121.05
46.75
42.76
41.19
36.50
26.43
25.56
24.48
21.71
O
Me
N
CF3
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


-62.35
O
Me
N
CF3
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
f1 (ppm)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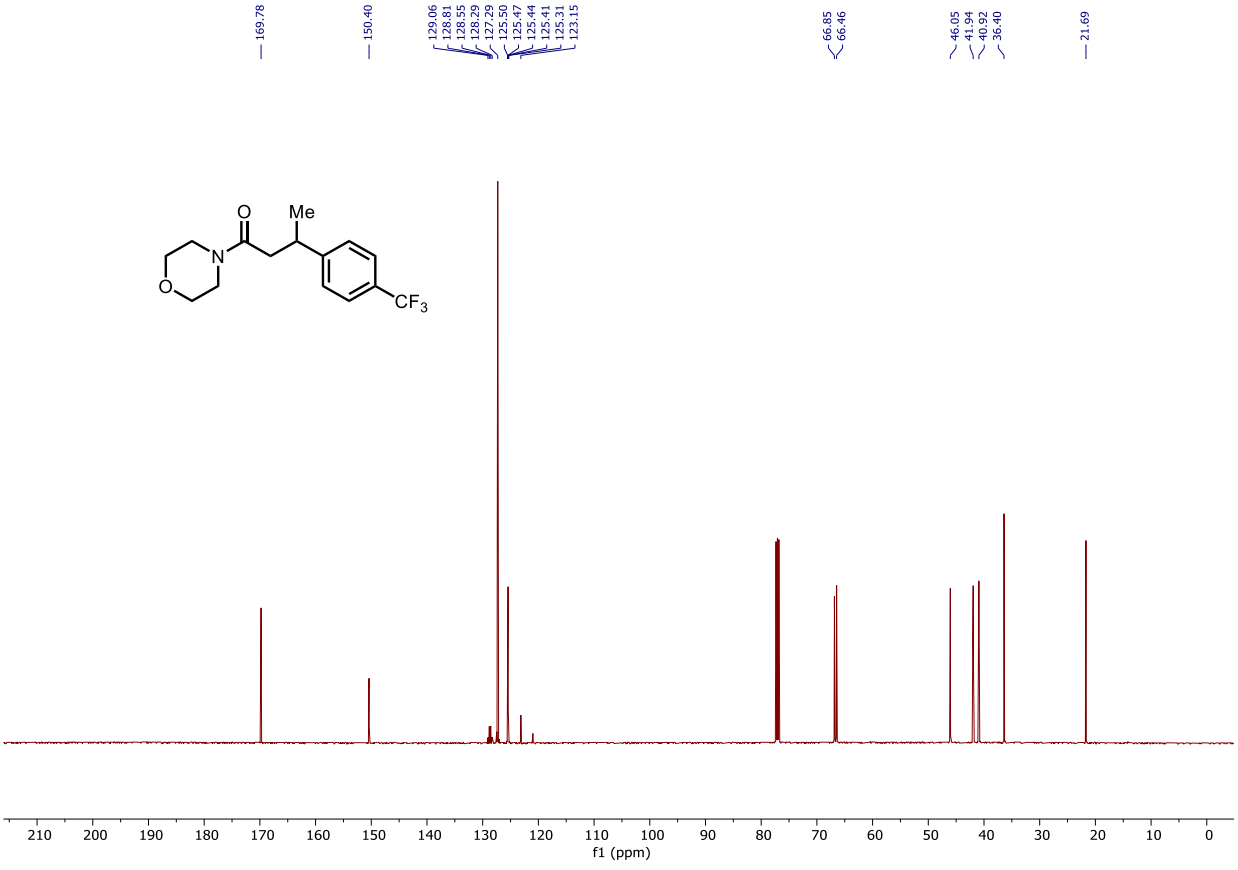
7.53
7.35
7.33
7.26
3.64
3.62
3.61
3.60
3.59
3.57
3.56
3.55
3.54
3.53
3.51
3.50
3.49
3.45
3.44
3.42
3.41
3.40
3.40
3.39
3.38
3.37
3.36
3.36
3.33
3.32
3.31
3.30
3.30
3.28
3.28
2.63
2.62
2.60
2.59
2.55
2.53
2.52
2.50
1.34
1.33
O
Me
N
O
CF3
1.90
1.99
5.15
3.09
1.04
1.04
1.03
3.12
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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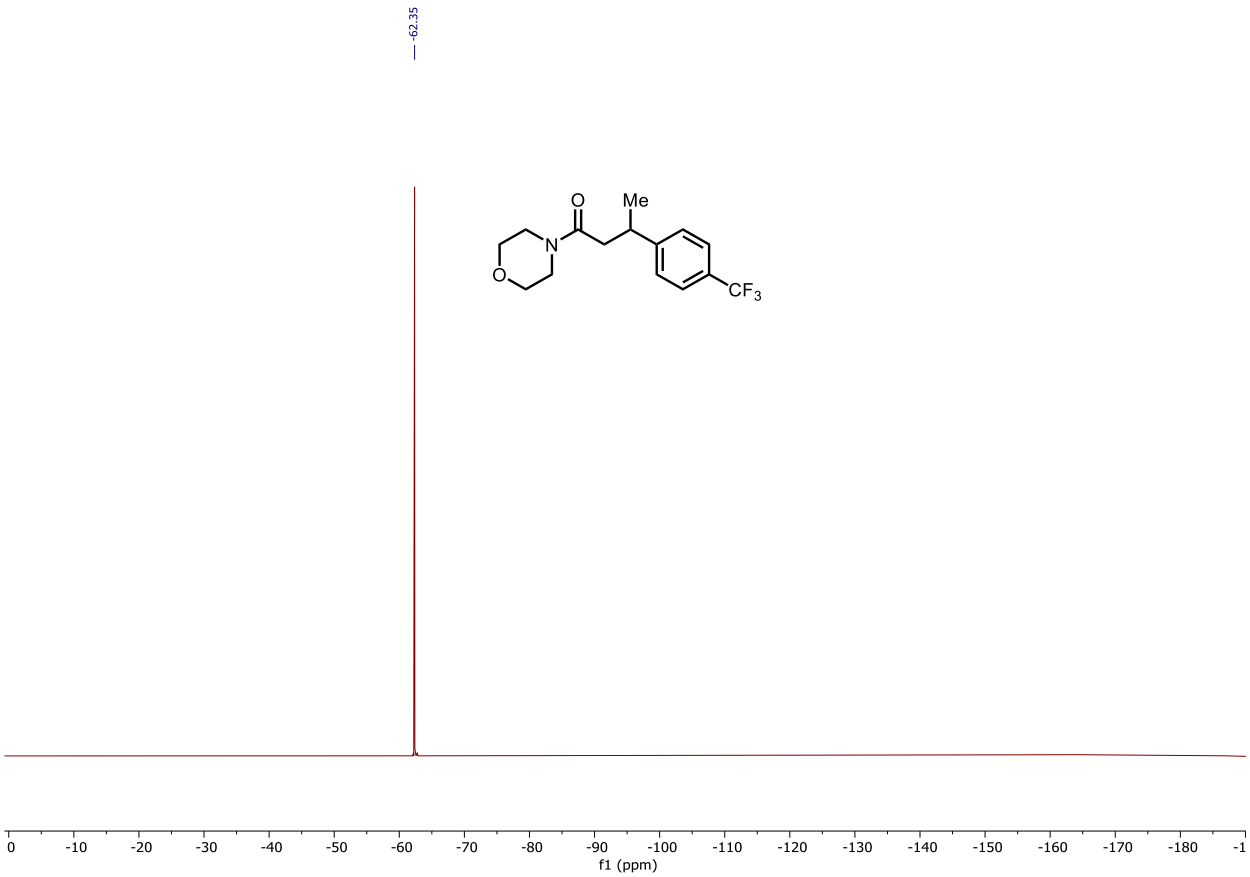
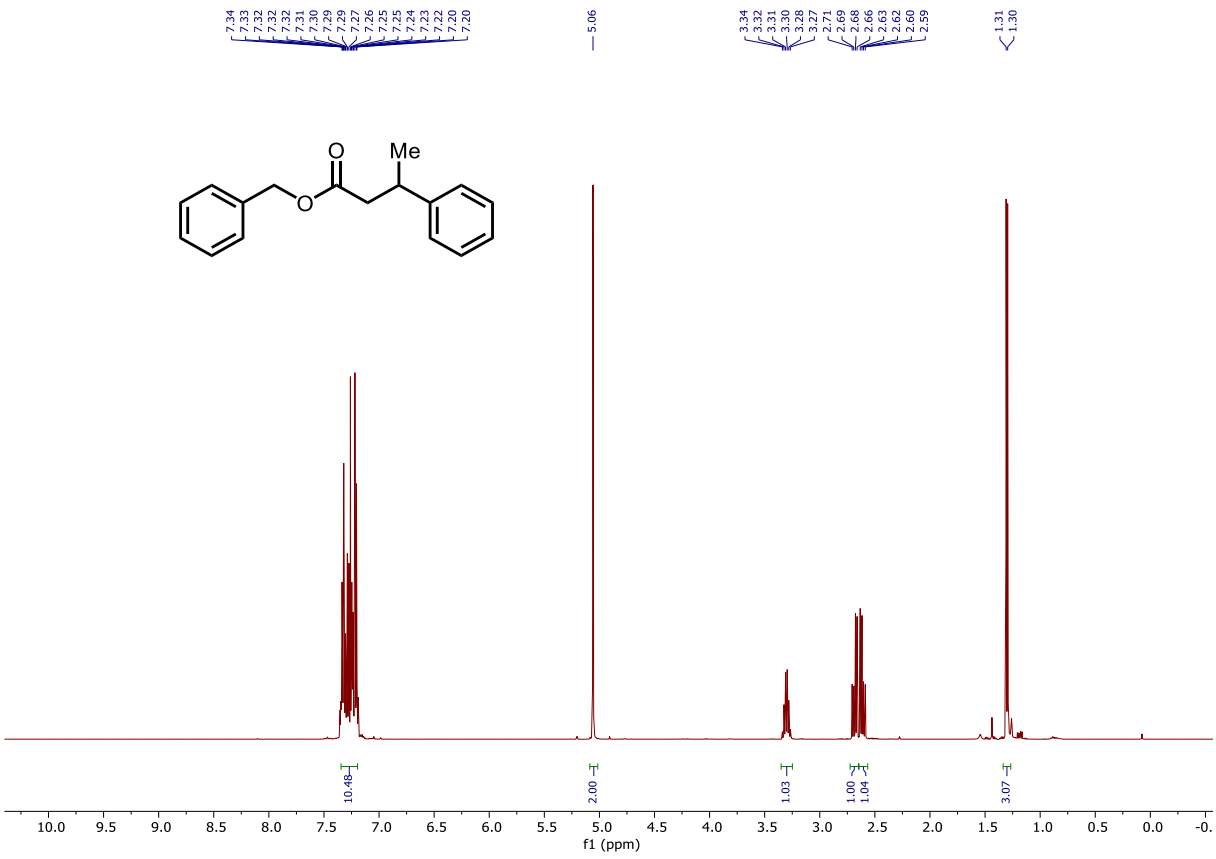
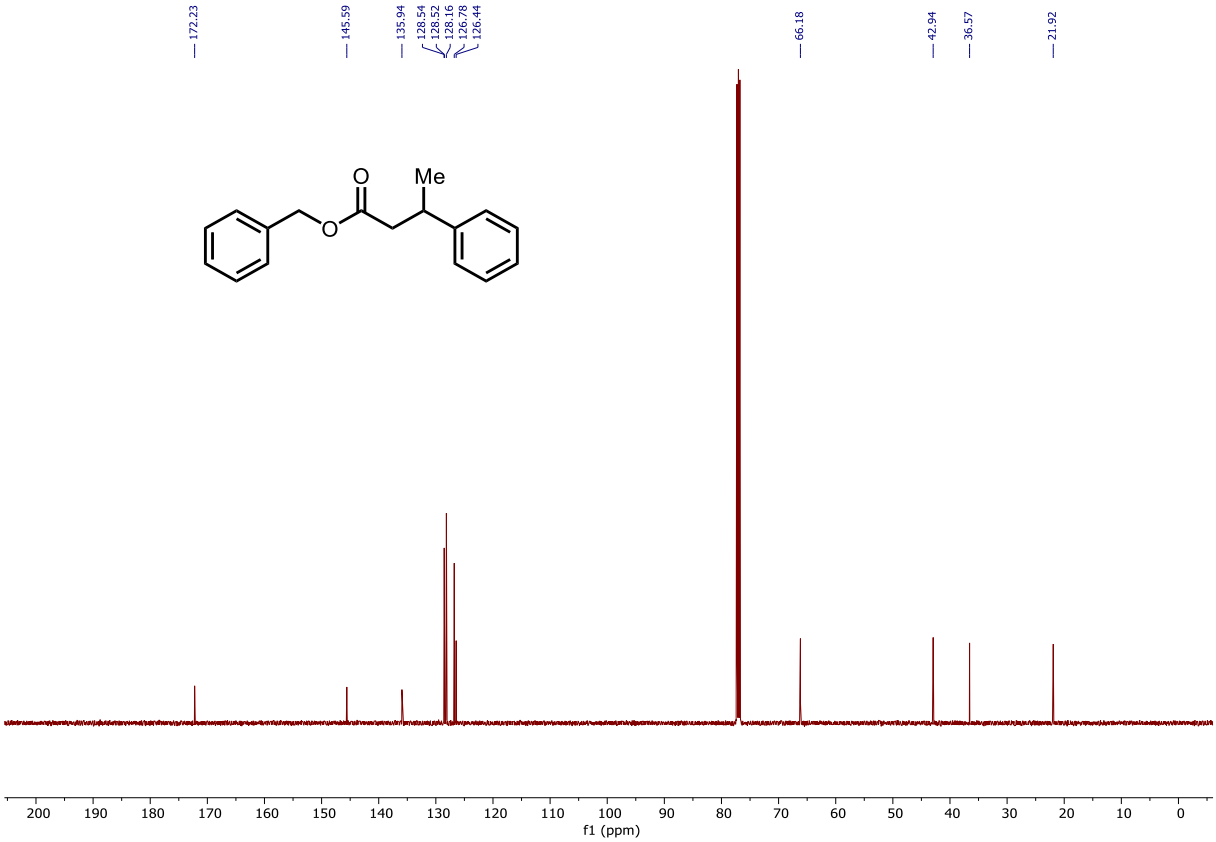
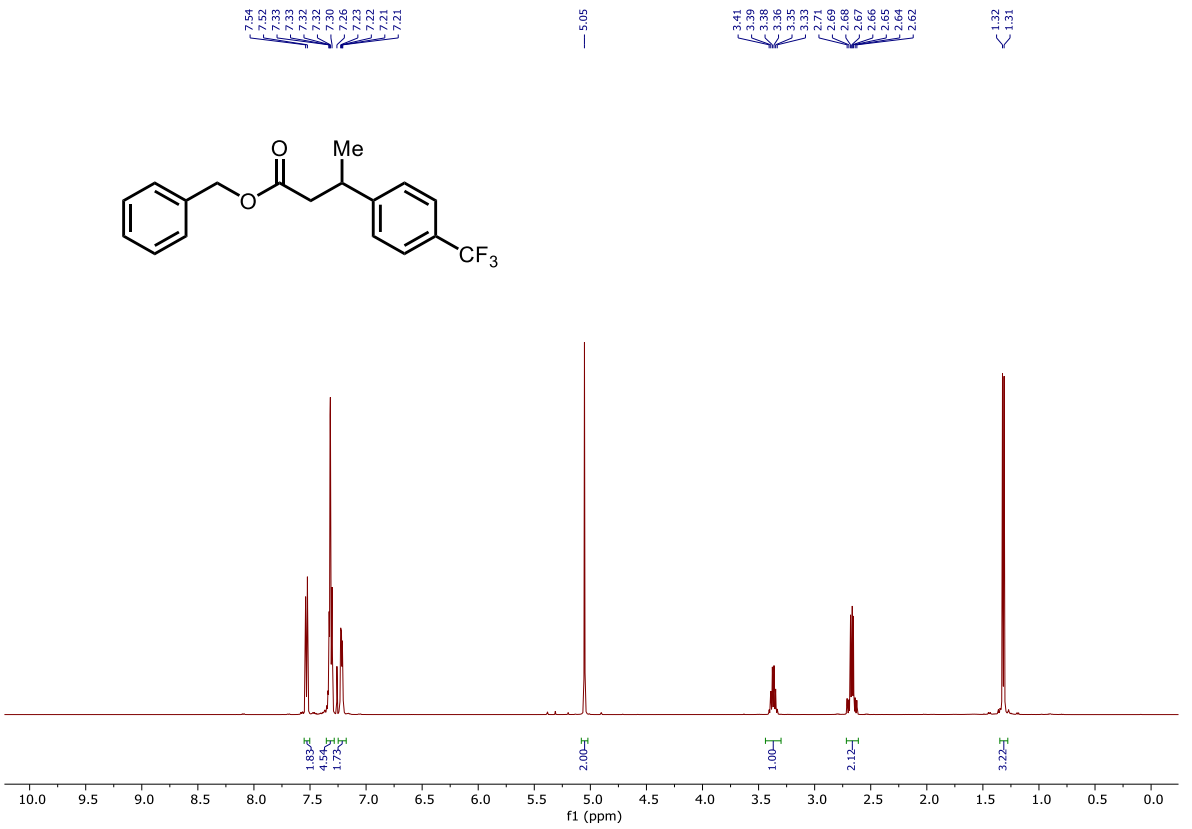
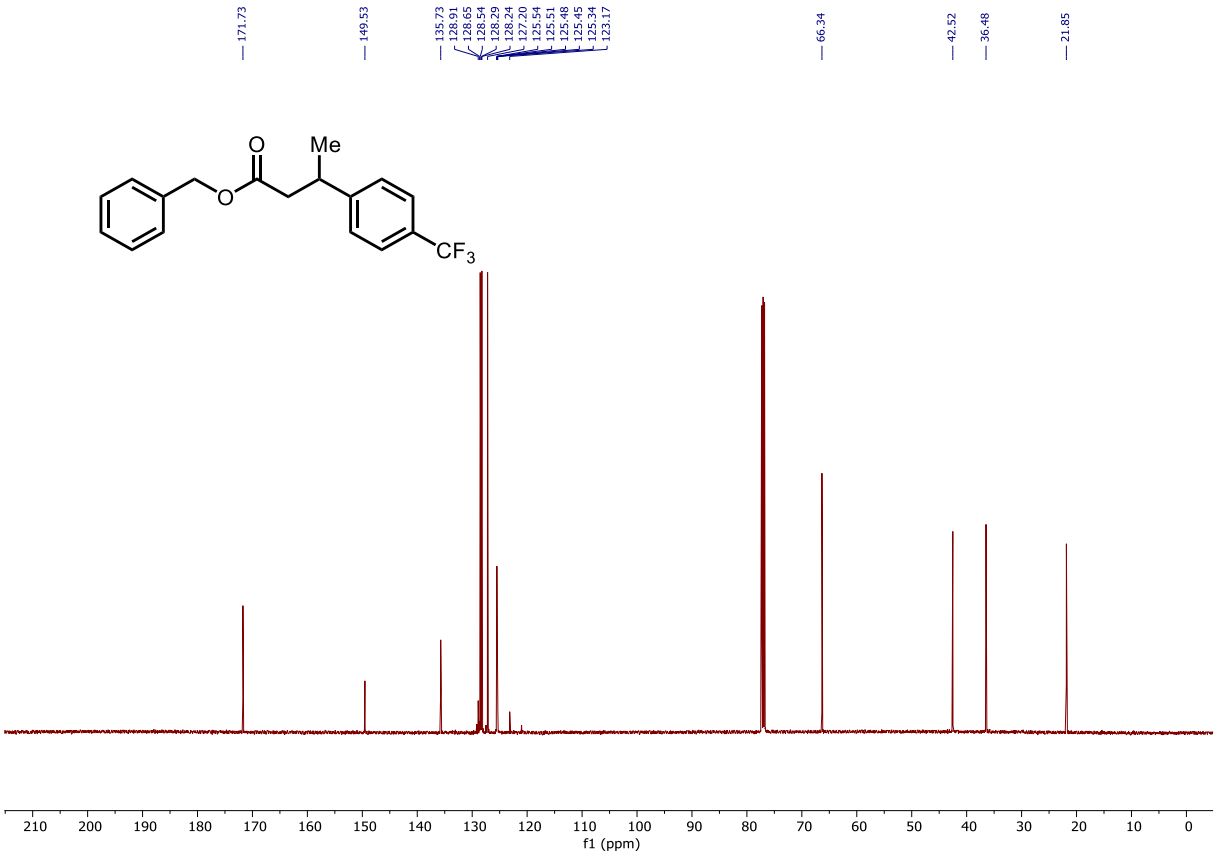
150.40
129.06
128.81
128.55
128.29
127.29
125.50
125.47
125.44
125.41
125.31
123.15
66.85
66.46
46.05
41.94
40.92
36.40
21.69
O
Me
N
O
CF3
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

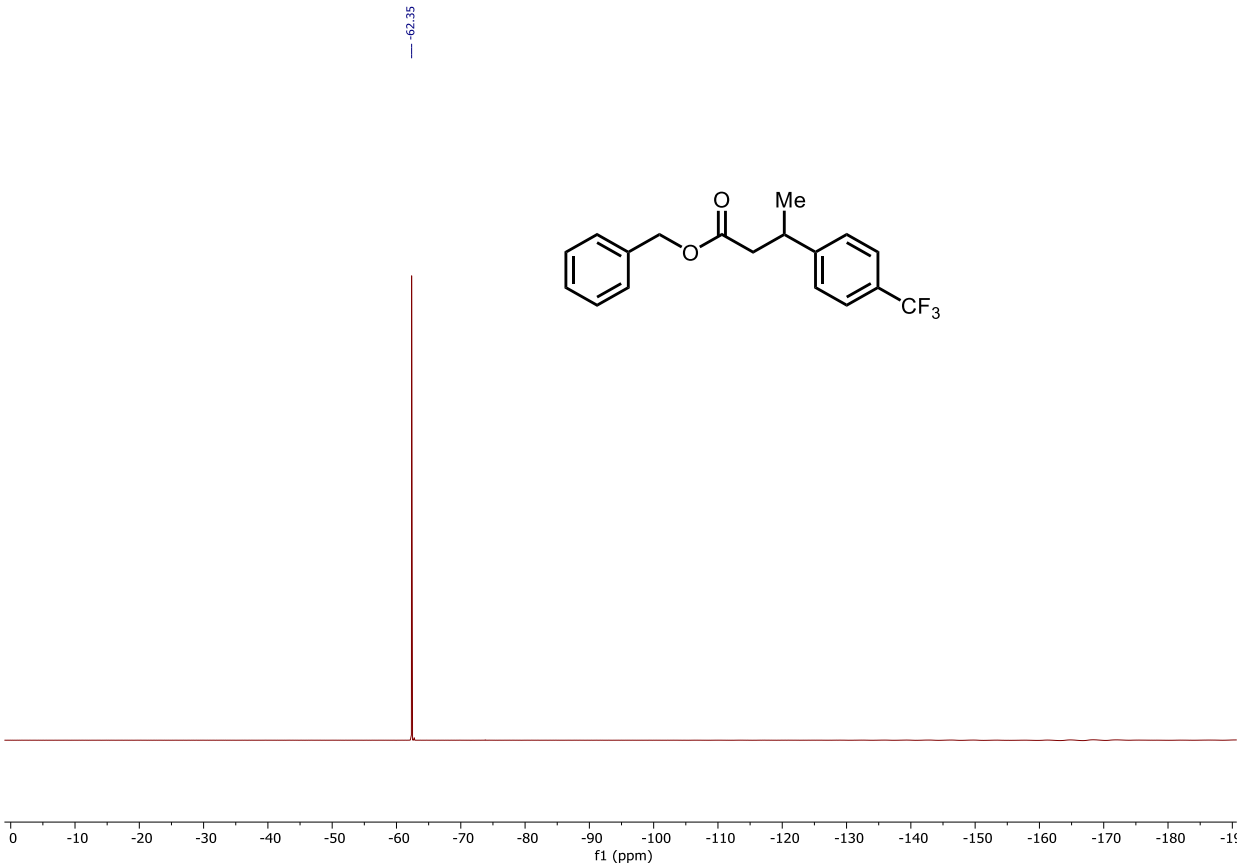

-62.35
O
Me
N
O
CF3
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
f1 (ppm)

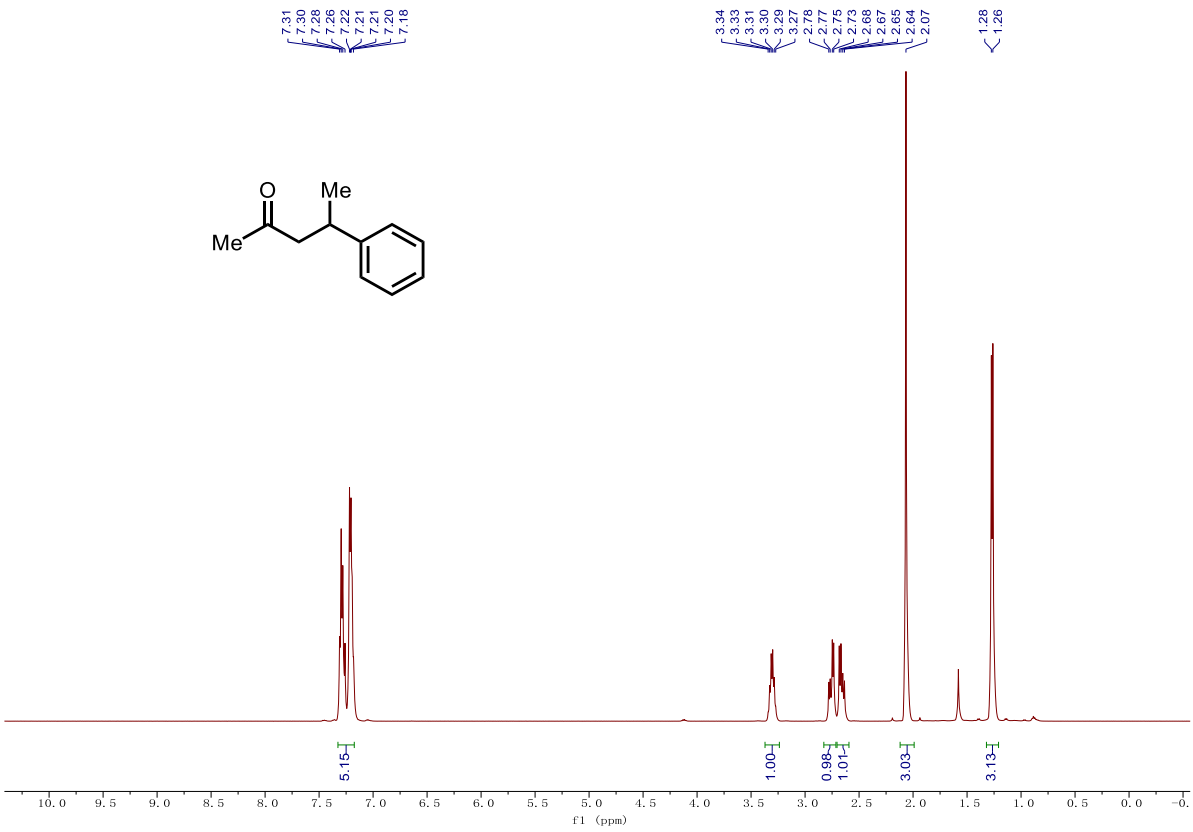

7.34
7.33
7.32
7.32
7.32
7.31
7.30
7.29
7.29
7.27
7.26
7.25
7.25
7.24
7.23
7.22
7.20
7.20
5.06
3.34
3.32
3.31
3.30
3.28
3.27
2.71
2.69
2.68
2.66
2.63
2.62
2.60
2.59
1.31
1.30
O
Me
O
10.48
2.00
1.03
1.00
1.04
3.07
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.
f1 (ppm)


172.23
145.59
135.94
128.54
128.52
128.16
126.78
126.44
66.18
42.94
36.57
21.92
O
Me
O
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


7.54
7.52
7.33
7.33
7.32
7.32
7.30
7.26
7.23
7.22
7.21
7.21
5.05
3.41
3.39
3.38
3.36
3.35
3.33
2.71
2.69
2.68
2.67
2.66
2.65
2.64
2.62
1.32
1.31
O
Me
O
CF3
1.83
4.64
1.73
2.00
1.00
2.12
3.22
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


171.73
149.53
135.73
128.91
128.65
128.54
128.29
128.24
127.20
125.54
125.51
125.48
125.45
125.34
123.17
66.34
42.52
36.48
21.85
O
Me
O
CF3
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


-62.35
O
Me
O
CF3
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
f1 (ppm)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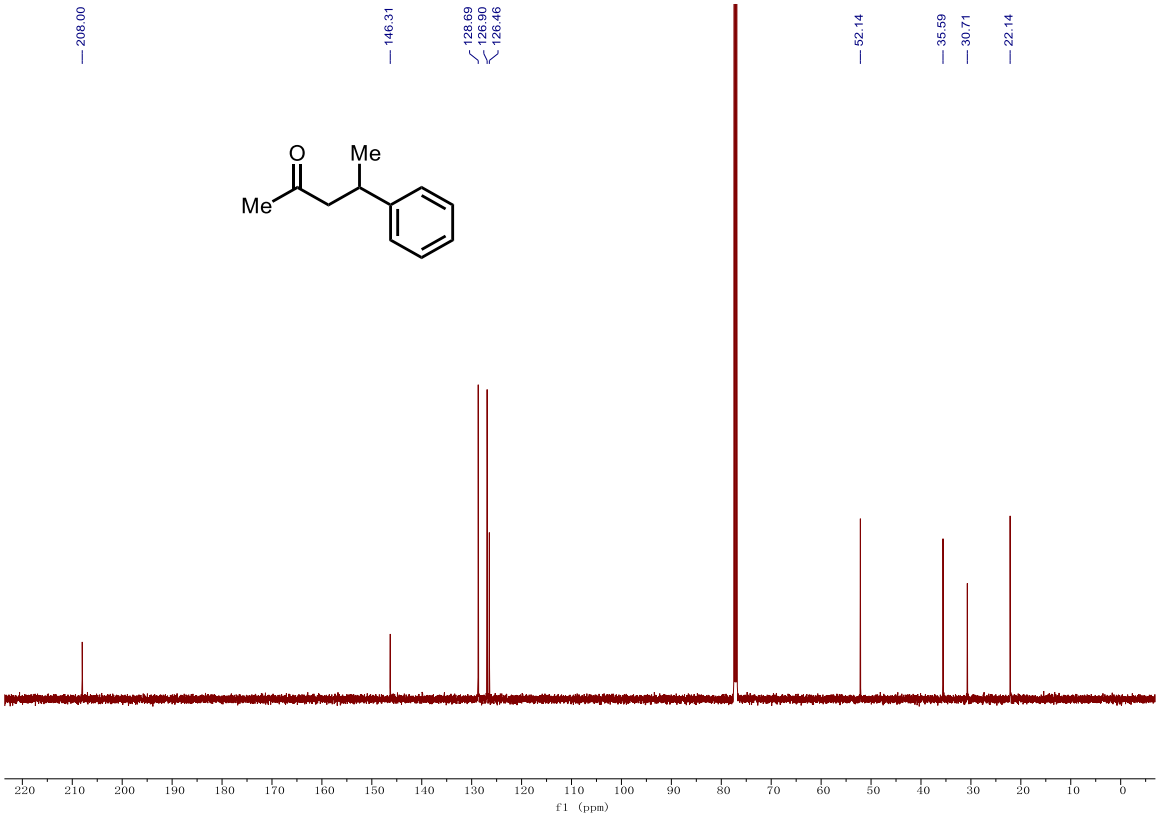
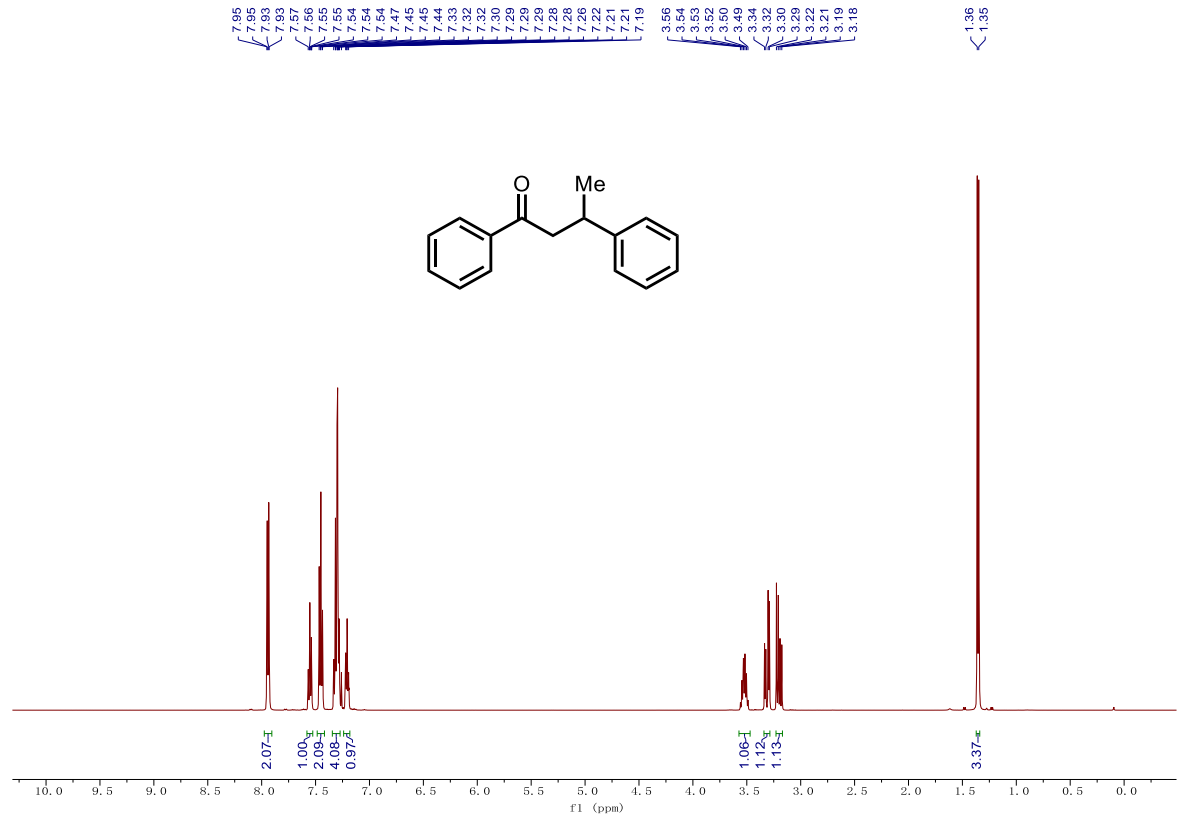
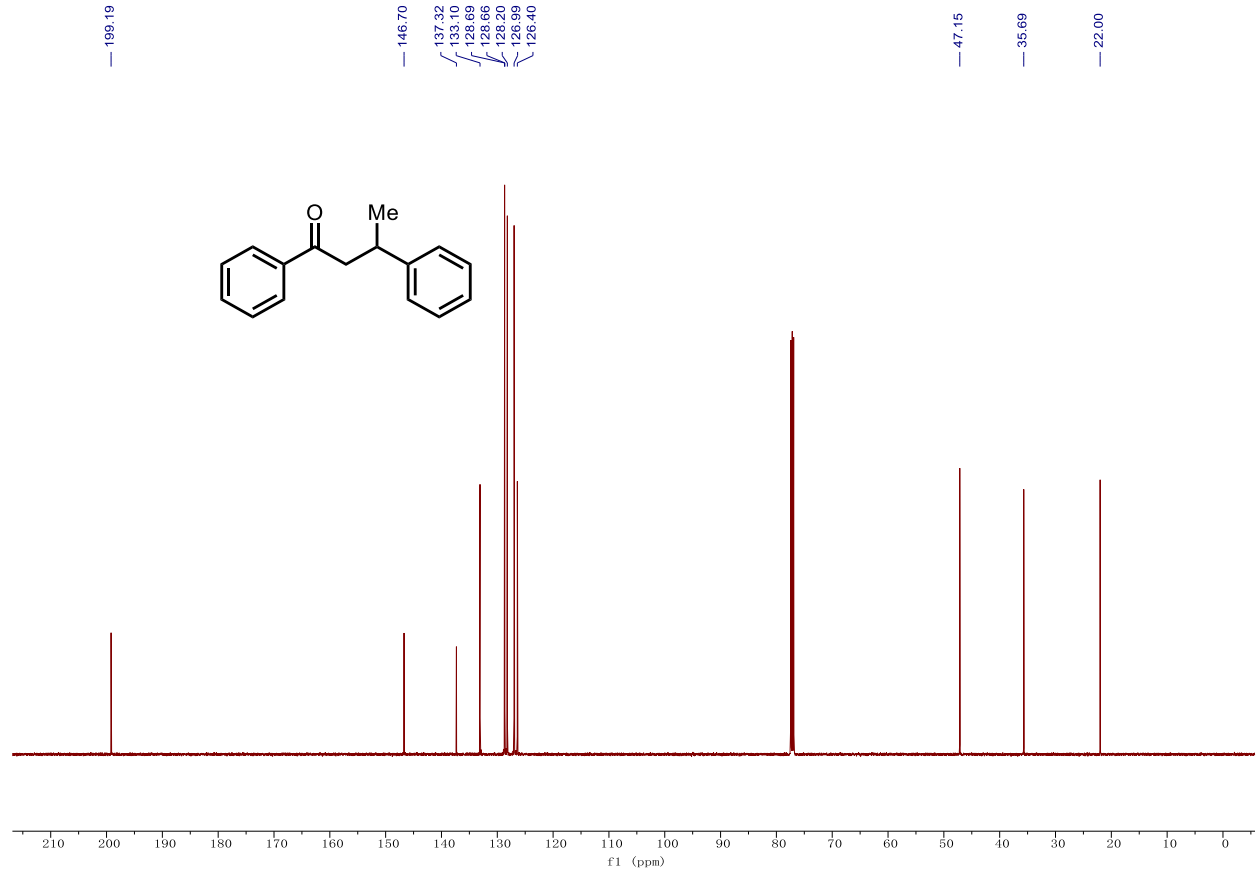
7.30
7.28
7.26
7.22
7.21
7.21
7.20
7.18
3.34
3.33
3.31
3.30
3.29
3.27
2.78
2.77
2.75
2.73
2.68
2.67
2.65
2.64
2.07
1.28
1.26
O
Me
Me
5.15
1.00
0.98
1.01
3.03
3.13
f1 (ppm)


208.00
146.31
128.69
126.90
126.46
52.14
35.59
30.71
22.14
O
Me
Me
f1 (ppm)


7.95
7.95
7.93
7.93
7.57
7.56
7.55
7.55
7.54
7.54
7.54
7.47
7.45
7.45
7.44
7.33
7.32
7.30
7.29
7.29
7.28
7.26
7.22
7.21
7.21
7.19
3.56
3.54
3.53
3.52
3.50
3.49
3.34
3.32
3.30
3.29
3.22
3.21
3.19
3.18
1.36
1.35
O
Me
2.07
1.00
2.09
4.08
0.97
1.06
1.12
1.13
3.37
f1 (ppm)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146.70
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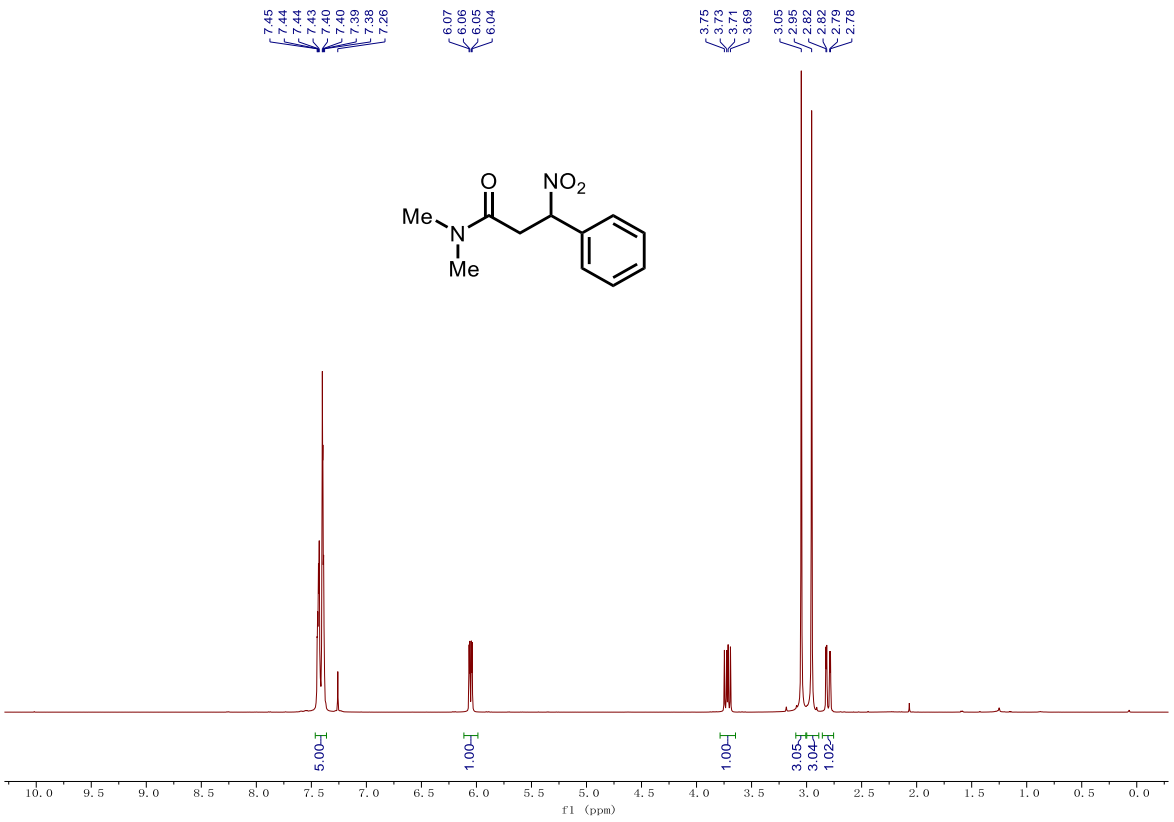
133.10
128.69
128.66
128.20
126.99
126.40
47.15
35.69
22.00
O
Me
f1 (ppm)


7.45
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7.44
7.43
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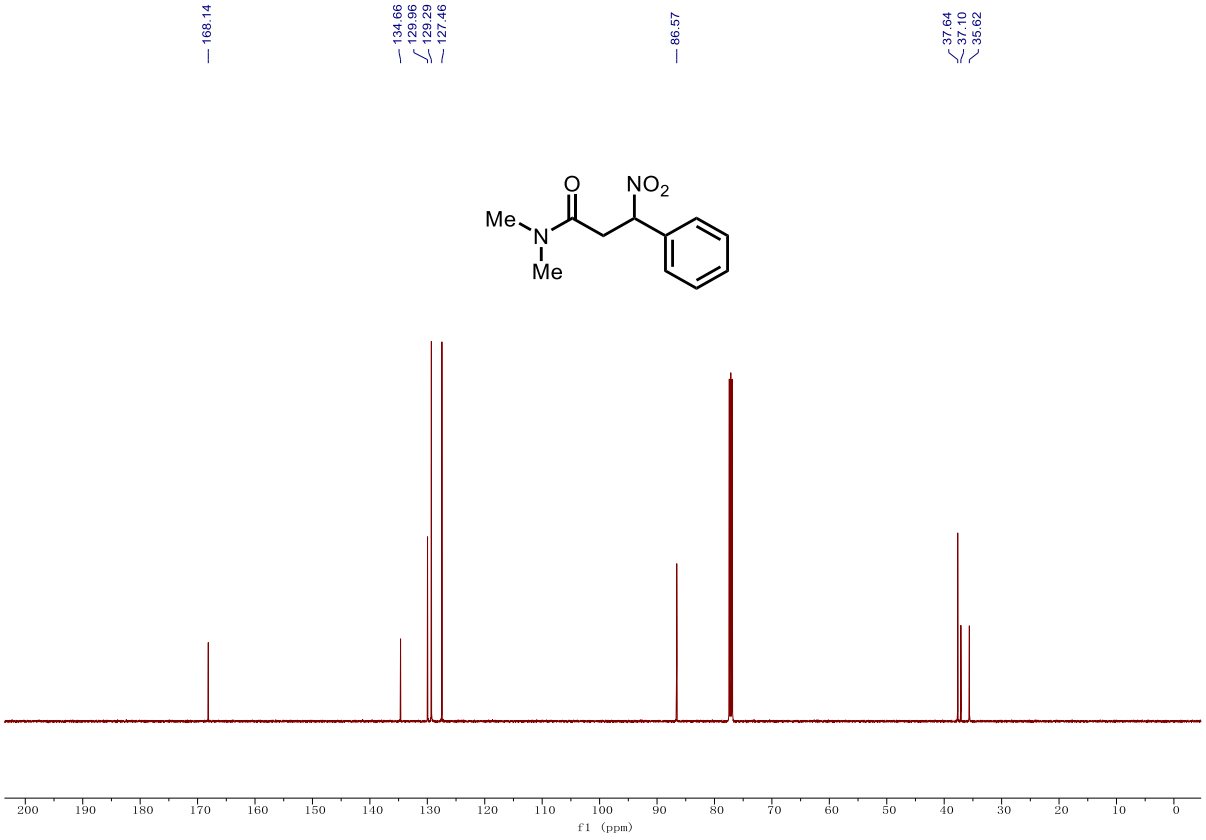
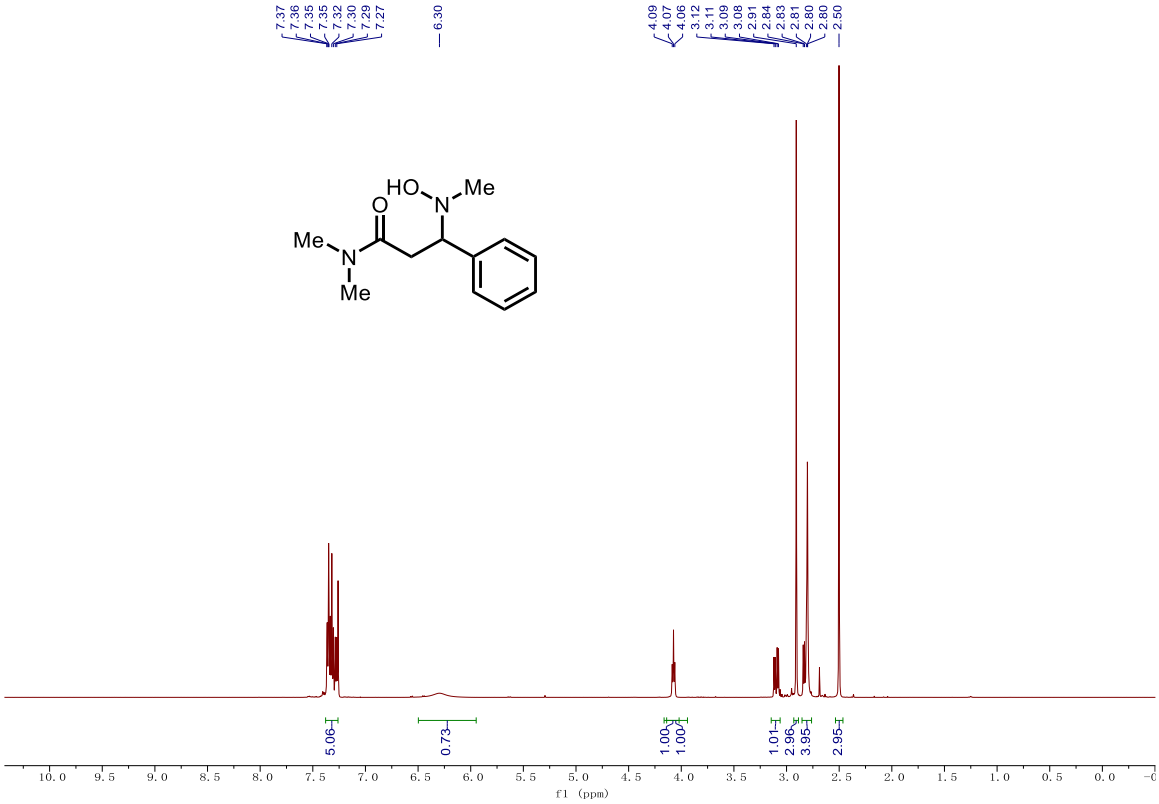
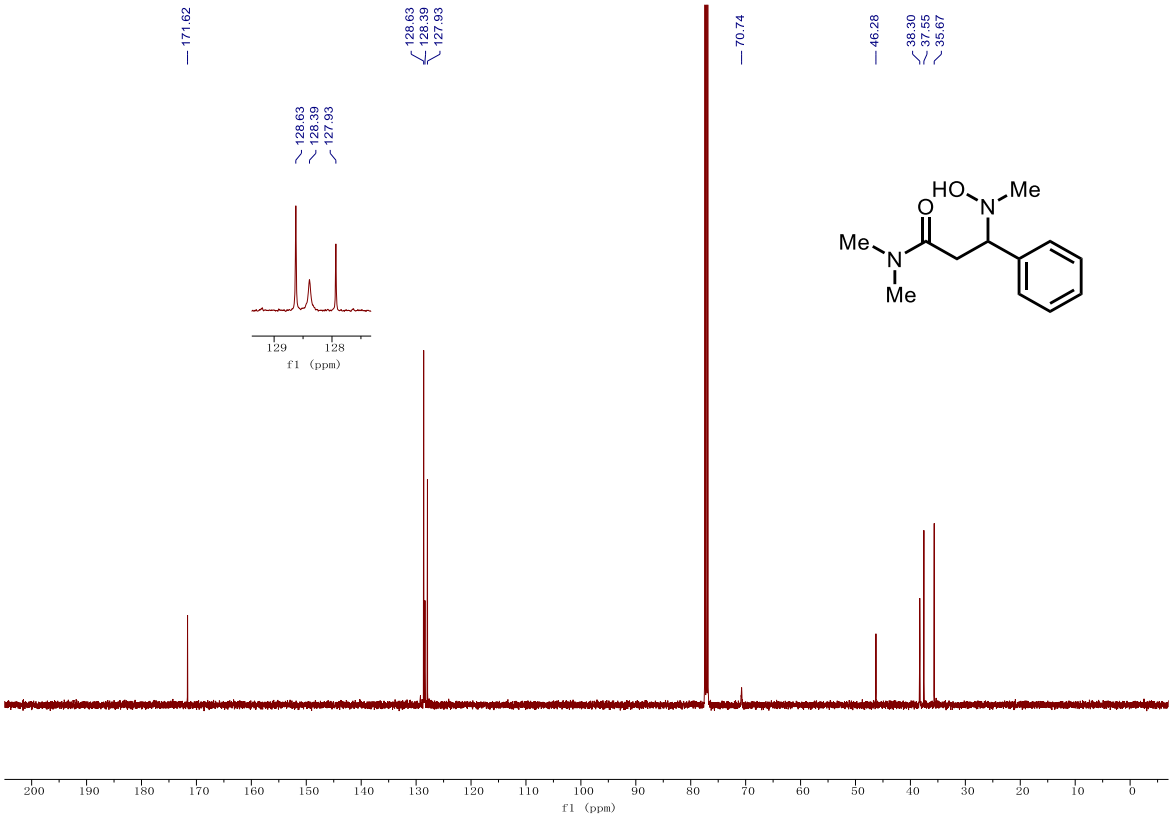
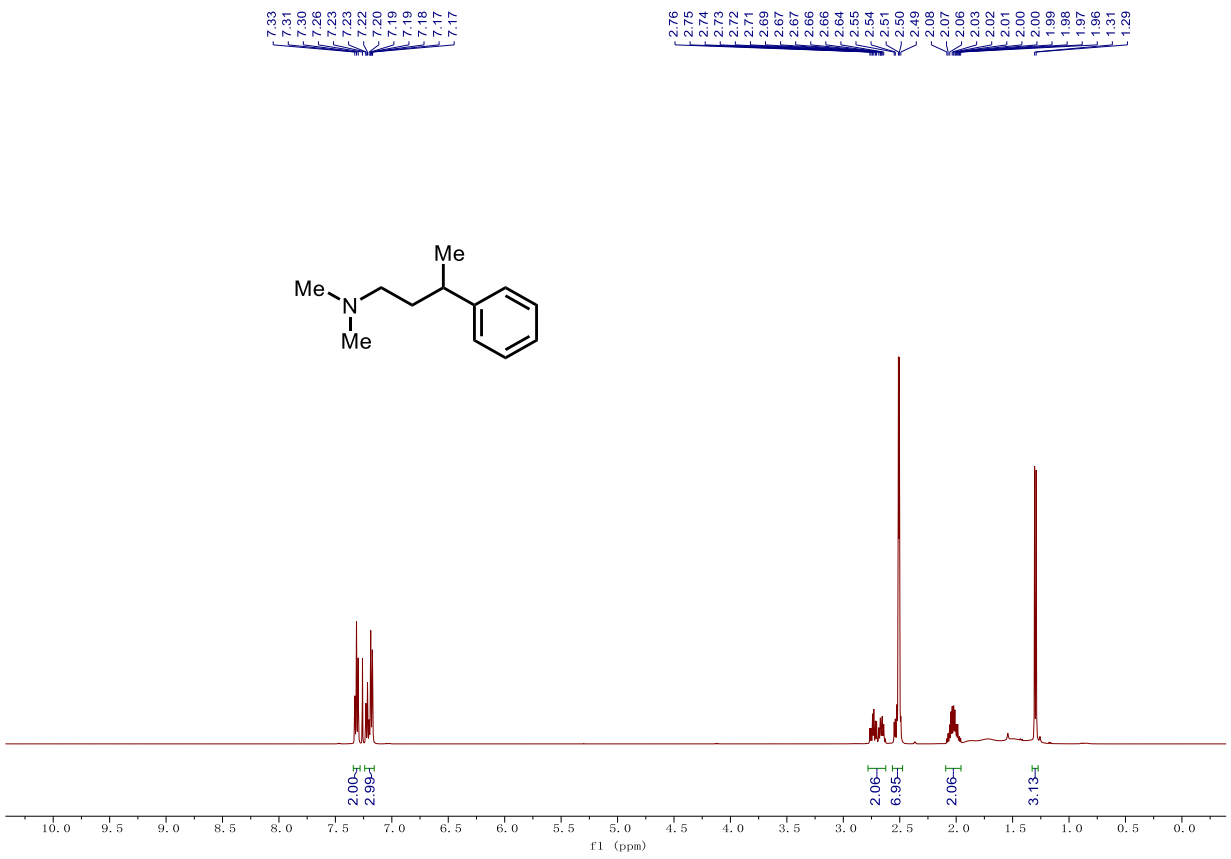
7.40
7.39
7.38
7.26
6.07
6.06
6.05
6.04
3.75
3.73
3.71
3.69
3.05
2.95
2.82
2.82
2.79
2.78
O
NO2
Me
N
Me
5.00
1.00
1.00
3.05
3.04
1.02
f1 (ppm)


168.14
134.66
129.96
129.29
127.46
86.57
37.64
37.10
35.62
O
NO2
Me
N
Me
f1 (ppm)


7.37
7.36
7.35
7.35
7.32
7.30
7.29
7.27
6.30
4.09
4.07
4.06
3.12
3.11
3.09
3.08
2.91
2.84
2.83
2.81
2.80
2.80
2.50
HO
N
Me
O
Me
N
Me
5.06
0.73
1.00
1.00
1.01
2.96
3.95
2.95
f1 (ppm)


171.62
128.63
128.39
127.93
70.74
46.28
38.30
37.55
35.67
129
128
f1 (ppm)
HO
N
Me
O
Me
N
Me
f1 (ppm)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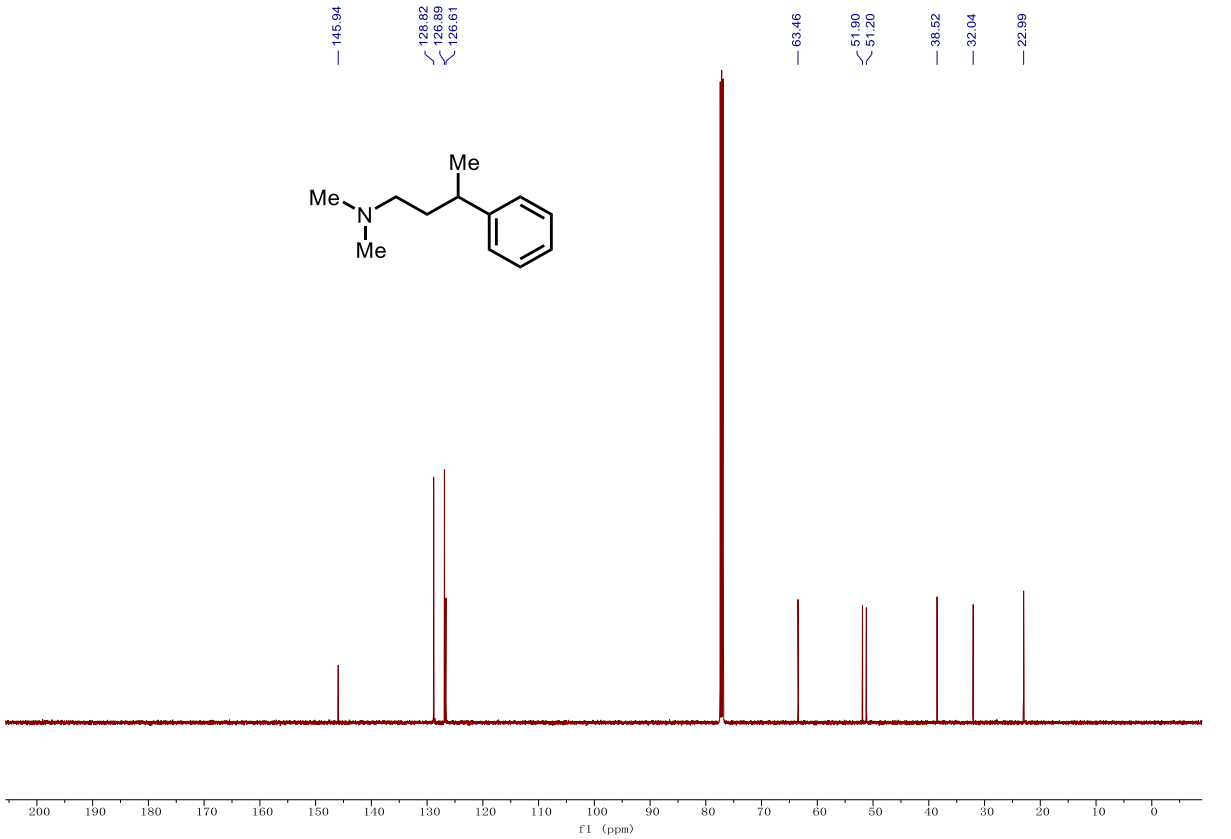
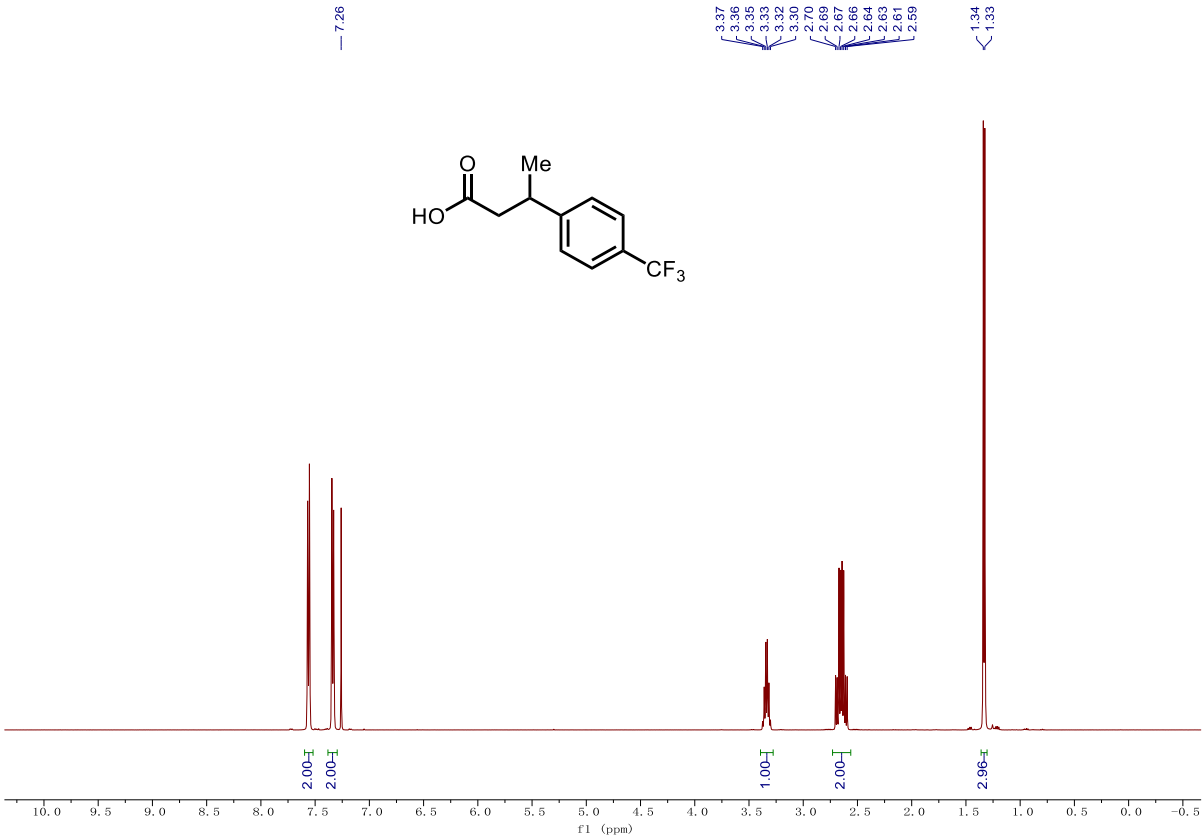
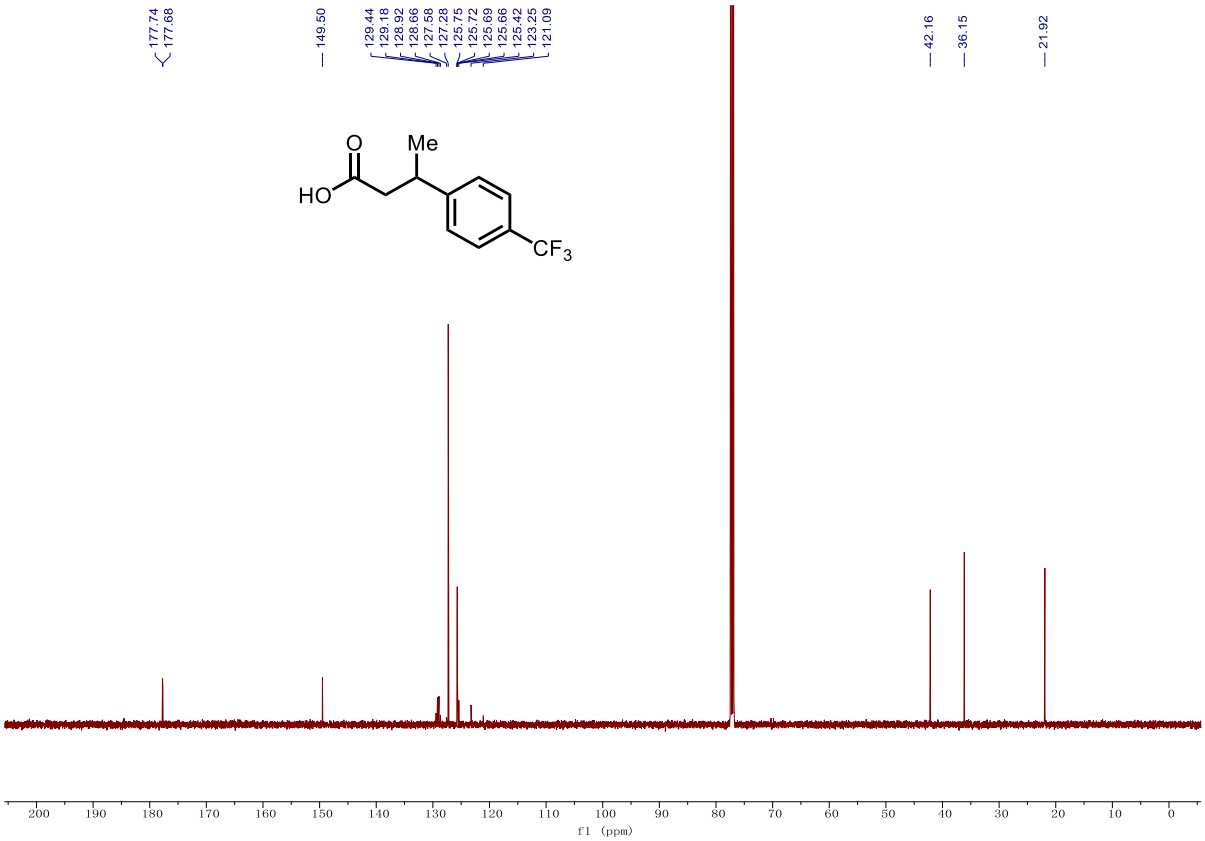
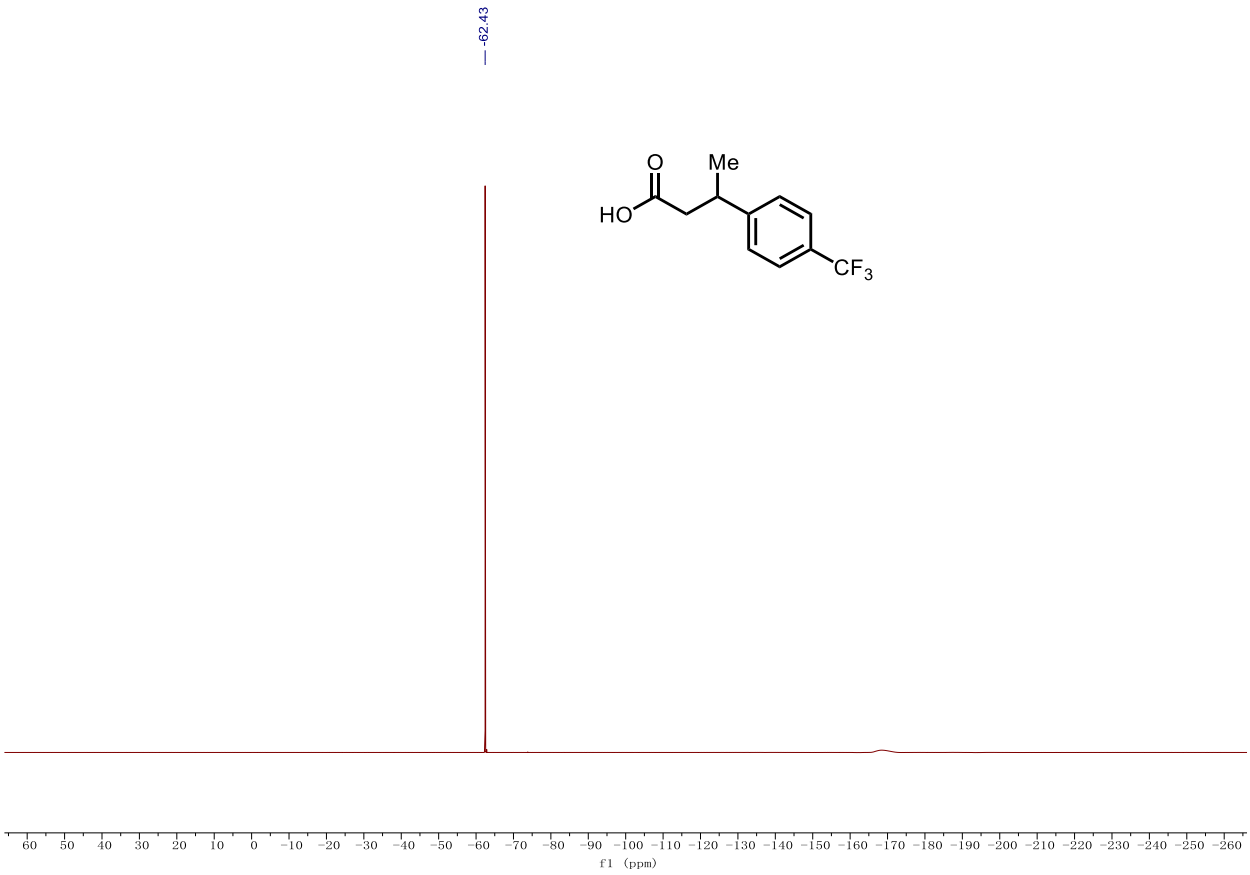
7.18
7.17
7.17
2.76
2.75
2.74
2.73
2.72
2.71
2.69
2.67
2.67
2.66
2.66
2.64
2.55
2.54
2.51
2.50
2.49
2.08
2.07
2.06
2.03
2.02
2.01
2.00
2.00
1.99
1.98
1.97
1.96
1.31
1.29
Me
Me
N
Me
2.00
2.99
2.06
6.95
2.06
3.13
f1 (ppm)


145.94
128.82
126.89
126.61
63.46
51.90
51.20
38.52
32.04
22.99
Me
Me
N
Me
f1 (ppm)


7.26
3.37
3.36
3.35
3.33
3.32
3.30
2.70
2.69
2.67
2.66
2.64
2.63
2.61
2.59
1.34
1.33
O
Me
HO
CF3
2.00
2.00
1.00
2.00
2.96
f1 (ppm)


177.74
177.68
149.50
129.44
129.18
128.92
128.66
127.58
127.28
125.75
125.72
125.69
125.66
125.42
123.25
121.09
42.16
36.15
21.92
O
Me
HO
CF3
f1 (ppm)


-62.43
O
Me
HO
CF3
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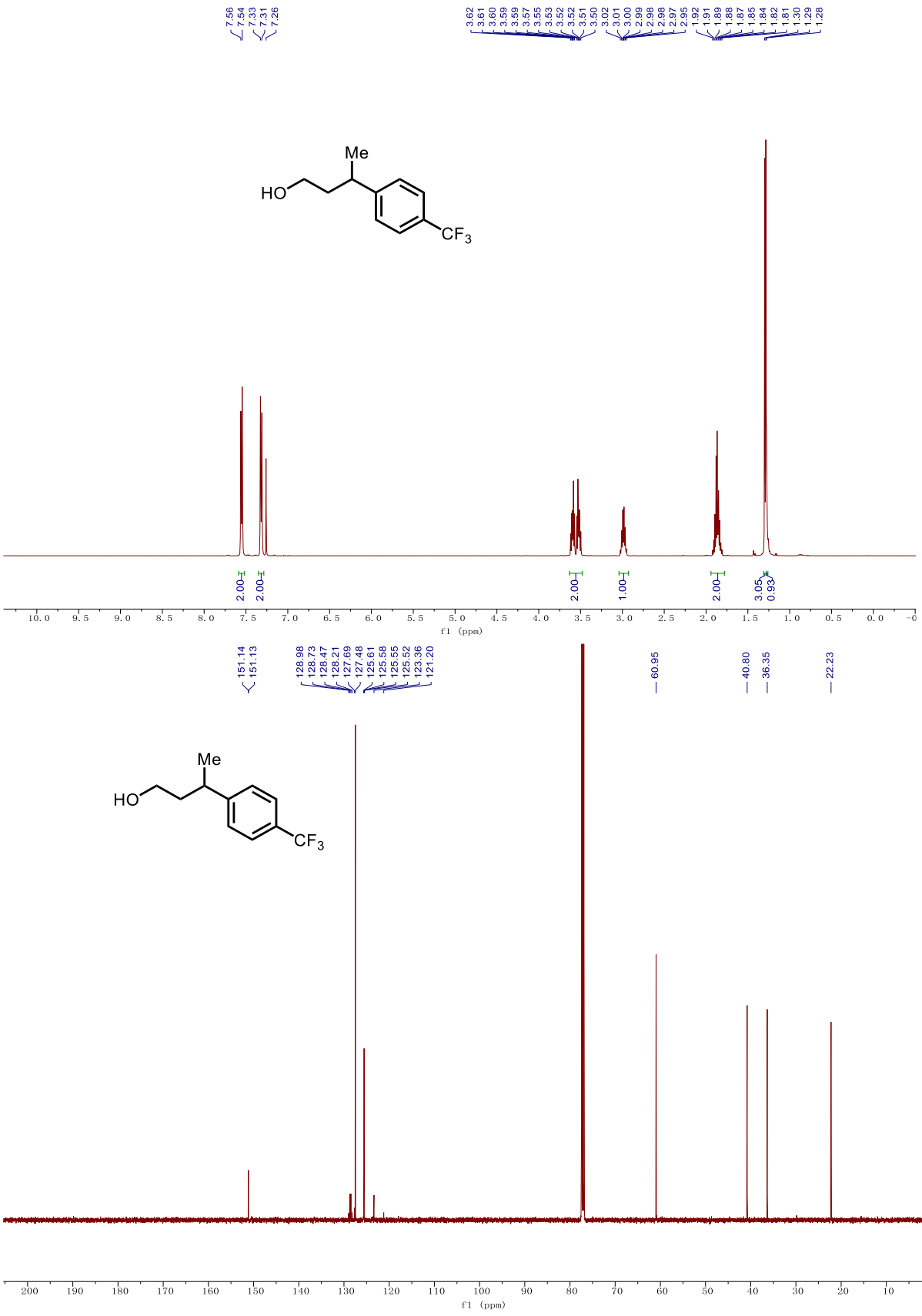
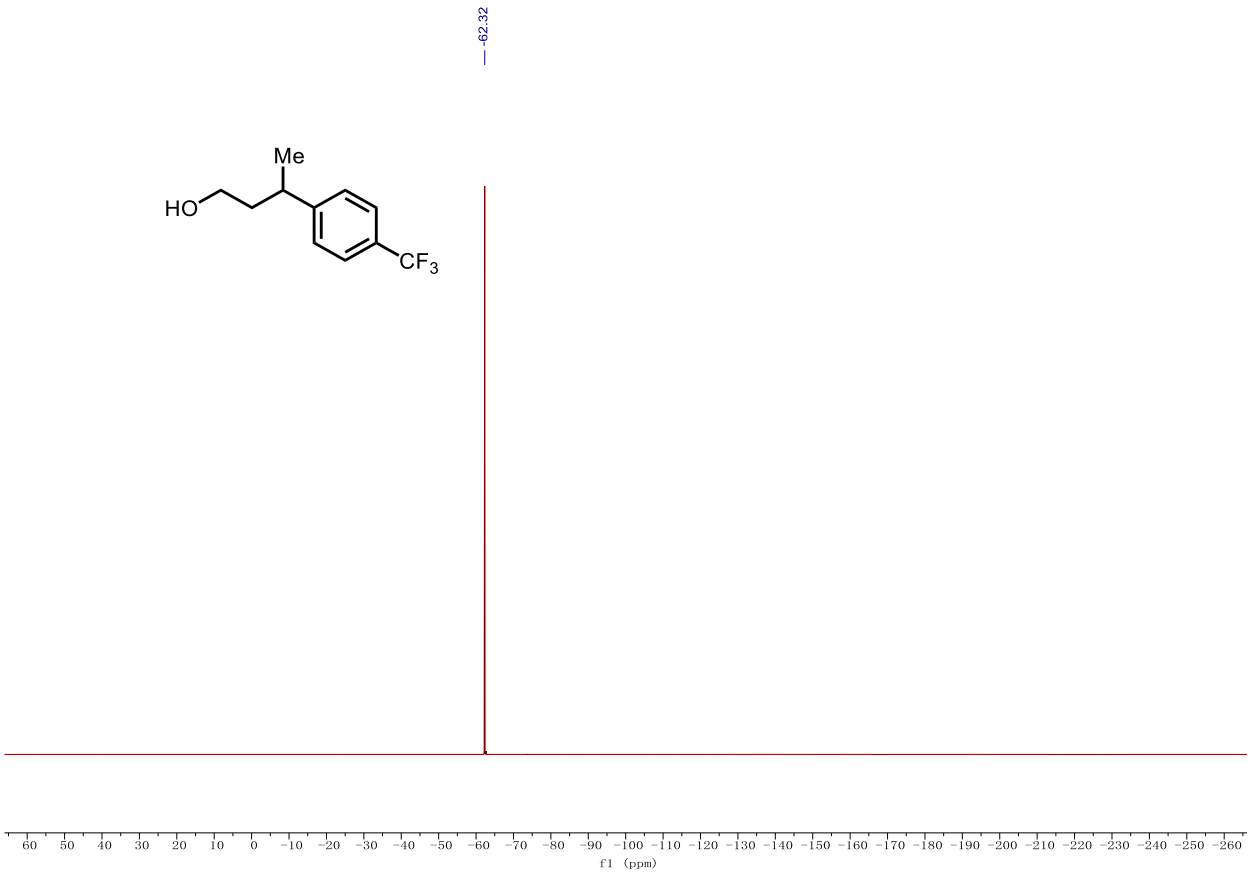
f1 (ppm)


7.56
7.54
7.33
7.31
7.26
3.62
3.61
3.60
3.59
3.59
3.57
3.55
3.53
3.52
3.52
3.51
3.50
3.02
3.01
3.00
2.99
2.98
2.98
2.97
2.95
1.92
1.91
1.89
1.88
1.87
1.85
1.84
1.82
1.81
1.30
1.29
1.28
Me
HO
CF3
2.00
2.00
2.00
1.00
2.00
3.05
0.93
f1 (ppm)
151.14
151.13
128.98
128.73
128.47
128.21
127.69
127.48
125.61
125.58
125.55
125.52
123.36
121.20
60.95
40.80
36.35
22.23
Me
HO
CF3
f1 (ppm)


-62.32
Me
HO
CF3
60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240 -250 -260
f1 (ppm)

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