Supplementary Materials for

Beyond Fe: Iridium-Containing P450 Enzymes for Selective Cyclopropanations of Structurally Diverse Alkenes

Hanna M. Key,[†1,2] Paweł Dydio,[†1,2] Zhennan Liu,[1] Jennifer Y-E. Rha,[1] Andrew Nazarenko,[1] Vida Seyedkazemi,[1] Douglas S. Clark,[3,4] John F. Hartwig*[1]

[1] Department of Chemistry, University of California, Berkeley, CA 94720, USA.
[2] Chemical Sciences Division, Lawrence Berkeley National Laboratory, 1 Cyclotron Road, Berkeley, CA 94720, USA.
[3] Department of Chemical and Biomolecular Engineering, University of California, Berkeley, California 94720, USA.
[4] Molecular Biophysics and Integrated Bioimaging Division, Lawrence Berkeley National Laboratory, 1 Cyclotron Road, Berkeley, California 94720, USA.

* Correspondence to: jhartwig@berkeley.edu
† Authors contributed equally

This PDF file includes:

I. Protein Expression, Purification, and Characterization

a. General Methods

Unless otherwise noted, the chemicals, salts, and solvents used were reagent grade and used as received from commercial suppliers without further purification. All expression media and buffers were prepared using ddH_2O (MilliQ A10 Advantage purification system, Millipore). All expression media were sterilized using either an autoclave (45 min, 121ºC) or a sterile syringe filter (0.22 um). To maintain sterile conditions, sterile materials and *E. coli* cells were manipulated near a lit Bunsen burner.

b. Genes and Cloning

The WT CYP119 gene cloned into the vector 2BT (6xHis-TEV-ORF; AddGene #29666) was purchased from GenScript with codon optimization for *E. coli* (Table S1).

c. Media Preparation

Preparation of optimized minimal expression media: Salts (15 g Na_2HPO_4, 7.5 g K_2HPO_4, 0.3 g NaH_2PO_4, 0.3 g KH_2PO_4, 1.5 g NaCl, 5 g NH_4Cl) were dissolved in 2 L ddH_2O and autoclaved to give a media with pH ~8.0 - 8.2. Solutions of glucose (20%), casamino acids (BD Company, low Fe, 20%), and $MgSO_4$ (1 M), were autoclaved separately. Solutions of ampicillin (100 mg/ mL) and $CaCl_2$ (1 M) were sterilized by syringe filter. The following amounts of the listed solutions were added per 2 L of sterile salt solution: 40 mL glucose, 20 mL casamino acids, 4 mL $MgSO_4$, 100 uL $CaCl_2$, 2 mL ampicillin. Stock solutions were stored for several weeks; prepared media was stored for less than 1 day. Minimal media plates were prepared from the same media with the addition of 17 g agar/L media. In this case, agar was autoclaved in 1 L ddH_2O, and salts were autoclaved separately as a 20X solution, after which they were added to the agar solution.

d. Mutagenesis

Site-directed mutagenesis was performed using the QuickChange Lightening mutagenesis kit (Agilent); requisite double stranded DNA primers were designed according to the Agilent Primer Design Program and purchased from Integrated DNA Technology. PCR reactions were performed according to the manufacturer's directions. PCR reactions contained: 5 uL reaction buffer, 34 uL ddH_2O, 1.5 uL QuickSolution, 1 uL plamids (50 ng/uL), 1.25 uL sense primer (100 ng/uL), 1.25 uL antisense primer (100 ng/ uL), 5 uL dNTPs (2 mM/base), and 1 uL polymerase.

PCR Program: Phase 1 (1 cycle): 95 °C, 1.5 min; Phase 2 (18 cycles): 95 °C, 20 sec, 60 °C, 10 sec, 68 °C, 4.5 min; Phase 3 (1 cycle): 68 °C, 3 min; Phase 4 (storage): 4 °C

DNA Isolation and Storage: Following the completion of the above set of PCR procedures, 1.5 uL DPN 1 was added to each reaction, and the reactions were further incubated (3 h, 37°C). The crude PCR mixture was used to transform XL-10 Gold Ultracompetent cells (45 µL cells, 2 µL PCR reactions). The mixture was incubated on ice (30 min), heat shocked (30 s, 42 °C), recovered with SOC media (1 h, 37 °C, 275 rpm), and plated on LB plates. Plates were grown (18 h, 37 °C), and individual colonies were used to inoculate 1 mL rich media cultures, which were grown in 96-well plates (13 h, 37 °C, 300 rpm). DNA was isolated from the 96-well cultures using magnetic bead technology at the UC Berkeley DNA Sequencing Facility. Alternatively, individual colonies were used to inoculate 4 mL rich media cultures and grown overnight (13 h, 37 °C, 300 rpm), and the plasmids were purified using a Qiagen DNA Miniprep kit according to the manufacturer's instructions.

e. Protein Expression

Optimized Expression of Apo CYP119 for production of purified enzyme: BL21 Star chemically competent *E.* coli cells (45 uL, QB3 Macrolab, UC Berkeley) were thawed on ice, transferred to 14 mL falcon tubes , and transformed with the desired plasmid solution (1.5 uL, 50-250 ng/uL). The cells were incubated on ice (30 min), heat shocked (30 sec, 42°C), re-cooled on ice (2 min), and recovered by incubation with SOC media (500 uL, 37 °C, 1 h, 250 rpm). Aliquots of the cultures (50uL) were plated on plates containing minimal media agar (expression media supplemented with 17 g agar/L) and incubated (20 h, 37 °C) to produce approximately 10-100 colonies per plate. Single colonies were used to inoculate starter cultures (3 mL, expression media), which were grown in 14 mL round bottom tubes (4-8 hours, 37°C, 250 rpm) and used to inoculate 100 mL overnight cultures (minimal media, 37° C, 250 rpm). Each overnight culture was used to inoculate 750 mL of expression media, which was cultured further (9 h, 37°C, 275 rpm). Expression was induced with IPTG (800 uL, 1M), and expression was allowed to continue for 15 h (30° C, 250 rpm). Cells were harvested by centrifugation (5000 rpm, 15 min, 4° C), and the pellets were resuspended in 20 mL Ni-NTA lysis buffer (50 mM NaPi, 250 mM NaCl, 10 mM Imidazole, pH = 8.0) and stored at -80° C until purification.

Protein Purification: Cell suspensions were thawed in a room temperature ice bath, decanted to 50 mL glass beakers, and lysed on ice by sonication (4x30 sec on, 2x2 min off, 65% power). Cell debris was removed by centrifugation (10 000 rpm, 30 min, 4° C), and Ni-NTA (5 mL, 50% suspension per 850 mL cell culture) was added. The lysates were briefly incubated with Ni-NTA on an end-over-end mixer (30 min, rt, 20 rpm) and poured into glass frits (coarse, 50 mL). The resin was washed with Ni-NTA lysis buffer (3 x 35 mL), and the wash fractions were monitored using Bradford assay dye. The desired protein was eluded with 18 mL Ni-NTA elusion buffer (50 mM NaPi, 250 mM NaCl, 250 mM Imidazole, pH = 8.0), dialyzed against Tris buffer (10 mM, pH = 8.0, 12 h, 4° C), concentrated to the desired concentration using a spin concentrator, and metallated within several hours as described in section III. Apo protein was not stored for more than 8 hours.

f. Protein Characterization

Gel Electrophoresis: Protein purity was analyzed by sodium dodecyl sulfate-polyacrylamide (SDS-PAGE) gel electrophoresis using precast gels (polyacrylamide, 10-20% linear gradient, Biorad).

Mass Spectrometry: Apo-proteins were analyzed with an Agilent 1200 series liquid chromatograph connected in-line with an Agilent 6224 time-of-flight (TOF) LC/MS system using a Turbospray ion source.

II. Organic Synthesis and Characterization

a. General methods and materials

Unless stated otherwise, all reactions and manipulations were conducted on the laboratory bench in air with reagent grade solvents. Reactions under inert gas atmosphere were carried out in the oven dried glassware in a nitrogen-filled glovebox or by standard Schlenk techniques under nitrogen.

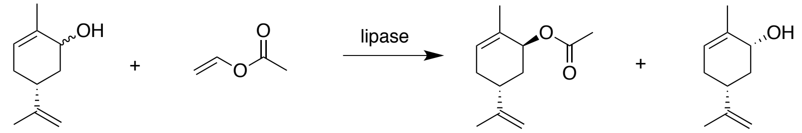
NMR spectra were acquired on 400 MHz, 500 MHz, 600 MHz, or 900 MHz Bruker instruments at the University of California, Berkeley. NMR spectra were processed with MestReNova 9.0 (Mestrelab Research SL). Chemical shifts are reported in ppm and referenced to residual solvent peaks[1]. Coupling constants are reported in hertz. GC analyses were obtained on an Agilent 6890 GC equipped with either, an HP-5 column (25 m x 0.20 mm ID x 0.33 m film) for achiral analysis, Cyclosil-B column (30 m x 0.25 mm ID x 0.25 um film) or CP-Chirasil-Dex CB column (25 m x 0.25 mm ID x 0.25 um film) for chiral analysis, and an FID detector. GC yields were calculated using dodecane as the internal standard and not corrected for response factors of minor isomers. High-resolution mass spectra were obtained via the Micro-Mass/Analytical Facility operated by the College of Chemistry, University of California, Berkeley.

Unless noted otherwise, all reagents and solvents were purchased from commercial suppliers and used without further purification. If required, dichloromethane (DCM) and tetrahydrofuran (THF) were degassed by purging with argon for 15 minutes and dried with a solvent purification system containing a one-meter column of activated alumina; dried and degassed acetonitrile, 1,2-xylene, toluene, N,N-dimethylformamide (DMF), ethanol and methanol were purchased form commercial suppliers and used as received.

b. Substrates

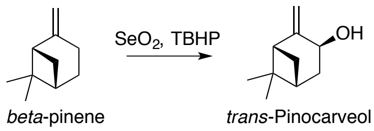
With the exception of the compounds listed below, all substrates were purchased from commercial suppliers and used as received.

A. Synthesis of (1*S*,5*R*)-2-methyl-5-(1-methylethenyl)-2-cyclohexen-1-ol-1-acetate



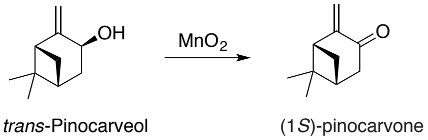
A mixture of *cis*/*trans*-*L*-carveol (2.4 g, 15.8 mmol), lipase (0.25 g, Amano lipase PS), vinyl acetate (0.68 g, 7.88 mmol, 0.5 eq) and *tert*-butyl methyl ether (15 ml) was stirred at room temperature and the formation of the desired acetate was monitored by GC analysis. The reaction was stopped by filtration of the enzyme and subsequent evaporation of the solvent at reduced pressure. Column chromatography of the residue afforded the acetate ester in 26% yield.

B. Allylic oxidation of terpenes



The solution of *tert*-butyl hydroperoxide (6.0 mL, 70% in water) was added dropwise to a stirred mixture of alkene (5.0 mL), distilled water (5.0 mL), and SeO_2 (149 mg), and the reaction mixture was stirred at 40 °C for 4 h. Then water (10 mL) was added and the solution was extracted with diethyl ether (3 × 20 mL). The combined organic fractions were washed with HCl (aq, 0.1 M, 20 mL), saturated Na_2CO_3 solution (aq, 20 mL), brine (20 mL), and water (20 mL). After drying ($MgSO_4$) and filtration, the solvent was evaporated to give an oil. The product was purified by column chromatography using silica gel and hexane/ethyl acetate mixture as an eluent.

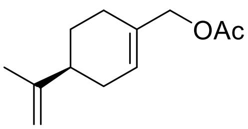
C. Synthesis of pinocarvone



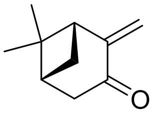
The *trans*-pinocarveol, prepared by procedure B, described above, was oxidized by dropwise addition to a suspension of 15 equiv. of MnO_2 in dichloromethane (25 mL/g starting material). The reaction mixture was stirred for 6 h at room temperatue, then it was filtered through a pad of Celite. The filtrates were concentrated and subjected to a silica column chromatography with hexane/ethyl acetate as eluent to give pinocarvone.

D. Synthesis of acetate derivatives

To a solution of an alcohol (1 equiv.) in 20 mL of methylene chloride was added acetic anhydride (1.5 equiv.) and triethylamine (2 equiv.). With addition of 4-(dimethylamino)pyridine (2 mol%) the reaction mixture was warmed slightly. The reaction was monitored by GC-MS. After completion, the reaction mixture was partitioned between hexane and 10% aqueous hydrochloric acid. The organic layer was further washed with 10% sodium hydroxide, and the solvent was removed in *vacuo*. The product was purified by column chromatography using silica gel and hexane/ethyl acetate as eluent.



S1



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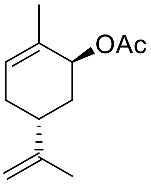
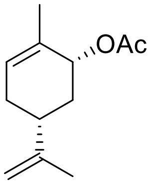


S3



S4

The NMR data of isolated products matched those for reported molecules. (*S*)-(4-(Prop-1-en-2-yl)cyclohex-1-enyl)methyl acetate **S1**[2] was obtained from commercially available (-)-perillyl alcohol following procedure D. (1*R*)-(+)-Pinocarvone **S2**[3] was synthesized from (1*S*)-(-)-pinene via (+)-*trans*-pinocarveol following procedure B and C. (1*S*,5*R*)-2-Methyl-5-(prop-1-en-2-yl)cyclohex-2-en-1-yl acetate **S3**[4] was obtained from procedure A. (1*R*,5*R*)-2-Methyl-5-(prop-1-en-2-yl)cyclohex-2-en-1-yl acetate **S4**[5] was obtained from procedure A and D.

c. Authentic Products

General procedures for synthesis of cyclopropanes:

Procedure A:

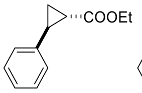
To a vial charged with the alkene (5-10 mmol, 5-10 equiv.) in toluene (10 ml), was added 100 ul of an 8 mM solution of Ir(Me)-PIX (0.0008 equiv.) in DMF. A solution of ethyl diazoacetate (1 mmol, 1 equiv.) in toluene (1 ml) was then added slowly while the reaction mixture was vigorously stirred. After complete addition of EDA, the reaction was stirred for 30-60 min, after which time the evolution of nitrogen stopped, indicating full consumption of EDA. Then, the volatile materials were removed, and the residue was purified by column chromatography on silica gel, with a mixture of hexanes and ethyl acetate (100:0 → 85:15 gradient) as the eluent. Fractions of the pure product(s) were combined, and the solvent evaporated, yielding cyclopropanation products.

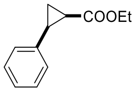
Procedure B:

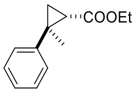
To a solution of alkene (~0.2 M) and $Rh_2(OAc)_4$ (~0.1-1 mol% in respect to EDA) in dry DCM, a solution of ethyl diazoacetate (~1 M) in dry DCM was added slowly while the reaction mixture was vigorously stirred. After complete addition of EDA, the reaction was stirred for 30-60 min, after which time the evolution of nitrogen stopped, indicating full consumption of EDA. Then, the volatile materials were removed, and the residue was purified by column chromatography on silica gel, with a mixture of hexanes and ethyl acetate (100:0 → 85:15 gradient) as the eluent. Fractions of the pure product(s) were combined, and the solvent evaporated, yielding cyclopropanation products.

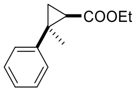
The NMR data of isolated products matched those for reported molecules (below): Cis- and trans- ethyl 2-phenylcyclopropane-1-carboxylates, prepared following Procedure A for the trans-isomer and Procedure B for cis-isomer, both with styrene as alkene)[6], cis- and trans- ethyl 2-methyl-2-phenylcyclopropane-1-carboxylates, both prepared following Procedure A, with alpha-methylstyrene as alkene[7], ethyl syn-2-methyl-syn-3-phenylcyclopropane-1-carboxylate (prepared following Procedure A, with cis-beta-methylstyrene as alkene),[6] ethyl syn-2-methyl-anti-3-phenylcyclopropane-1-carboxylate, prepared following Procedure B, with trans-beta-methylstyrene as alkene),[8,9] ethyl syn-2-methyl-syn-3-phenylcyclopropane-1-carboxylate, prepared following Procedure B, with trans-beta-methylstyrene as alkene),[8] and cis- and trans-ethyl 2-hexylcyclopropane-1-carboxylates, prepared following Procedure B for the cis-isomer and Procedure A for trans-isomer, with 1-octene as alkene).

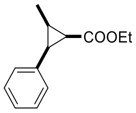
The absolute configurations of cis- and trans- ethyl 2-phenylcyclopropane-1-carboxylates,[10,11] cis- and trans- ethyl 2-methyl-2-phenylcyclopropane-1-carboxylates[11] and cis- ethyl 2-hexylcyclopropane-1-carboxylate[11] were assigned on the basis of reported retention times, conducting analysis according to literature methods (Table S4).

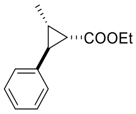


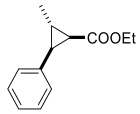


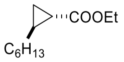


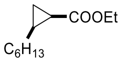






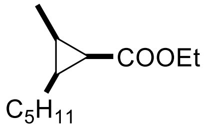






Ethyl syn-2-methyl-syn-3-pentylcyclopropane-1-carboxylate

The relative configuration was assigned based on the cis-coupling between protons of the cyclopropane ring.



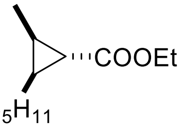
The product was isolated from a reaction of cis-2-octene (1 ml) with EDA (0.25 ml) conducted following Procedure B.

^{1}H NMR (900 MHz, $CDCl_3$): d = 4.09–4.05 (m, 2H), 1.60–1.57 (m, 3H), 1.38–1.36 (dq, J =6.5 Hz, J = 2.2 Hz, 1H), 1.31-1.22 (m, 11H), 1.18 (d, J = 6.2 Hz, 3H), 0.85 (m, J = 6.7 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): d = 172.34, 59.76, 31.84, 29.57, 25.36, 22.82, 22.10, 20.76, 19.04, 14.55, 14.20, 7.53;

HR MS (EI): calcd. for $C_{12}H_{21}O_2$ $[M]^+$: 198.1620, found: 198.1622.**Ethyl anti-2-methyl-anti-3-pentylcyclopropane-1-carboxylate**

The relative configuration was assigned based on the cis and trans-coupling between protons of the cyclopropane ring.



The product was isolated from a reaction of cis-2-octene (1 ml) with EDA (0.25 ml) conducted following Procedure B.

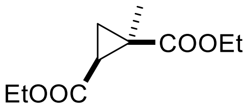
^{1}H NMR (900 MHz, $CDCl_3$): d = 4.08 (q, J= 7.2 Hz, 2H), 1.46 (m, 1H), 1.39-1.30 (m, 5H), 1.28-1.24 (m, 4H), 1.23 (t, J = 7.2 Hz, 3H), 1.08 (d, J = 6.3 Hz, 3H), 0.99 (t, J = 4.8 Hz, 1H), 0.87 (t, J = 7.4 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): d = 174.85, 60.33, 31.77, 29.31, 28.15, 27.99, 27.23, 22.76, 21.92, 14.47, 14.19, 12.16;

HR MS (EI): calcd. for $C_{12}H_{21}O_2$ $[M]^+$: 198.1620, found: 198.1619.

Syn-2-ethyl 1-ethyl 1-methylcyclopropane-1,2-dicarboxylate

Stereochemistry assigned based on comparison of NMR data to analogous compound [12]



The product was isolated from a reaction of ethyl methacrylate (3 ml) with EDA (1 ml) conducted following Procedure B. The isolated product contains 5% impurity by GC.

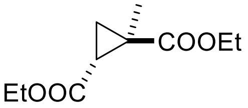
^{1}H NMR (500 MHz, $CDCl_3$): d = 4.10–4.20 (m, 4H), 1.78–1.84 (m, 2H), 1.41 (s, 3H), 1.24-1.28 (m, 6H), 1.04-1.10 (m, 1H);

^{13}C NMR (151 MHz, $CDCl_3$): d = 171.73, 170.55, 61.12, 60.93, 29.06, 28.97, 21.33, 19.64, 14.33, 14.24;

HR MS (EI): calcd. for $C_{10}H_{16}O_4$ $[M]^+$: 200.1049, found: 200.1051.

Anti-2-ethyl 1-ethyl 1-methylcyclopropane-1,2-dicarboxylate[12]

Relative stereochemistry was assigned based on comparison with the NMR data for the methyl ester analogue: anti-2-ethyl 1-methyl 1-methylcyclopropane-1,2-dicarboxylate



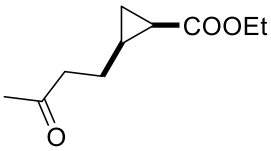
The product was isolated from a reaction of ethyl methacrylate (3 ml) with EDA (1 ml) conducted following Procedure B. The isolated product contains 5% impurity by GC.

^{1}H NMR (600 MHz, $CDCl_3$): d = 4.07-4.16 (m, 4H), 2.29 (dd, J = 8.7, 6.5 Hz, 1H), 1.53 (dd, J = 8.7, 4.2 Hz, 1H), 1.36 (s, 3H), 1.31 – 1.26 (m, 1H), 1.23 (dt, J = 10.7, 7.1 Hz, 6H);

^{13}C NMR (151 MHz, $CDCl_3$): d = 173.64, 170.63, 61.37, 61.04, 27.98, 27.10, 21.12, 14.45, 14.28, 13.21;

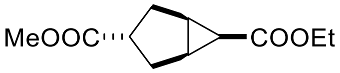
HR MS (EI): calcd. for $C_{10}H_{16}O_4$ $[M]^+$: 200.1049, found: 200.1051.

Cis-ethyl 2-(3-oxobutyl)cyclopropane-1-carboxylate



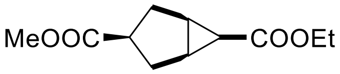
The product was isolated from a reaction of hex-5-en-2-one (2 ml) with EDA (1 ml) conducted following Procedure B.
^{1}H NMR (600 MHz, CDCl$_3$): d = 4.13 – 4.04 (m, 2H), 2.41 (td, J = 7.3, 4.9 Hz, 2H), 2.08 (s, 2H), 1.83 (ddt, J = 14.4, 7.2, 7.2 Hz, 1H), 1.72 (ddt, J = 14.6, 7.4, 7.4 Hz, 1H), 1.63 (ddd, J = 8.3, 5.5 Hz, 1H), 1.17-1.26 (m, 3+1H), 0.96 (ddd, J = 8.2, 8.2, 4.5 Hz, 1H), 0.88 (ddd, J = 6.9, 5.0, 5.0 Hz, 1H);
^{13}C NMR (151 MHz, CDCl$_3$): d = 208.44, 172.89, 60.46, 43.50, 29.92, 21.67, 21.65, 21.09, 21.08, 18.37, 14.46, 13.52, 13.51;
HR MS (EI): calcd. for $C_{10}H_{16}O_3$ [M]$^+$: 184.1099, found: 184.1199.

6-ethyl 3-methyl (1R,3s,5S,6s)-bicyclo[3.1.0]hexane-3,6-dicarboxylate
Relative stereochemistry was assigned based on comparison with the NMR data for the analogue: methyl syn-3-carbomethoxybicyclo[3.1.0]hexane-6-acetate[13]



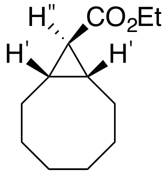
The product was isolated from a reaction of methyl cyclopent-3-ene-1-carboxylate (0.3 ml) with EDA (0.5 ml) conducted following Procedure B.
^{1}H NMR (900 MHz, CDCl$_3$): d = 4.11 (q, J = 7.1 Hz, 2H), 3.63 (s, 3H), 2.93 (p, J = 8.7 Hz, 1H), 2.22 (m, 4H), 1.82 (m, 2H), 1.67 (t, J = 8.3 Hz, 1H), 1.25 (t, J = 7.4 Hz, 3H).
^{13}C NMR (226 MHz, CDCl$_3$): d = 176.50, 171.61, 61.24, 51.75, 43.08, 29.80, 25.71, 23.60, 14.26.
HR MS (EI): calcd. for $C_{11}H_{16}O_4$ [M]$^+$: 212.1049, found: 212.1048.

6-ethyl 3-methyl (1R,3r,5S,6s)-bicyclo[3.1.0]hexane-3,6-dicarboxylate - Relative stereochemistry was assigned based on comparison with the NMR data for the analogue: methyl syn-3-carbomethoxybicyclo[3.1.0]hexane-6-acetate.[13]



The product was isolated from a reaction of methyl cyclopent-3-ene-1-carboxylate (0.3 ml) with EDA (0.5 ml) conducted following Procedure B.
^{1}H NMR (900 MHz, CDCl$_3$): d = 4.09 (q, J= 7.1 Hz, 2H), 3.65 (s, 3H), 3.34 (p, J = 9.5 Hz, 1H), 2.26 (m, 4H), 1.88 (m, 3H), 1.66 (t, J = 8.5 Hz, 1H), 1.22 (t, J= 7.2 Hz, 3H);
^{13}C NMR (226 MHz, CDCl$_3$): d = 175.18, 171.25, 59.90, 51.87, 49.45, 27.67, 26.29, 14.33.
HR MS (EI): calcd. for $C_{11}H_{16}O_4$ [M]$^+$: 212.1049, found: 212.1050.

Ethyl (1*R*,8*S*,9*R*)-bicyclo[6.1.0]nonane-9-carboxylate



The product was isolated from a reaction of cyclooctene (1 ml) with EDA (0.25 ml) conducted following Procedure B.

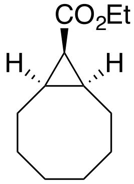
^{1}H NMR (600 MHz, CDCl$_3$): d = 4.10 (q, *J* = 7.1 Hz, 2H), 2.05 (dd, *J* = 14.2, 3.7 Hz, 2H), 1.71 – 1.62 (m, 2H), 1.60 – 1.53 (m, 2H), 1.46 – 1.32 (m, 6H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.09 (t, *J* = 4.3 Hz, 1H), 1.07 – 0.98 (m, 2H).

^{13}C NMR (151 MHz, CDCl$_3$): d = 174.4, 60.2, 29.0, 27.3, 26.4, 25.9, 25.8, 14.3.

HRMS (EI) Calculated for $C_{12}H_{21}O_2$ [M+H]$^+$: 197.1542, Found: 197.1534. IR (neat, cm^{-1}): 2980, 2923, 2851, 1369, 787.

The relative configuration was assigned according to the *trans*-coupling between H' and H''.

Ethyl (1*R*,8*S*,9*S*)-bicyclo[6.1.0]nonane-9-carboxylate



The product was isolated from a reaction of cyclooctene (1 ml) with EDA (0.25 ml) conducted following Procedure B.

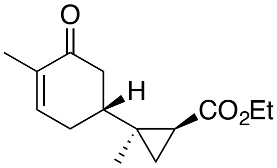
^{1}H NMR (600 MHz, CDCl$_3$): d = 4.10 (q, *J* = 7.1 Hz, 2H), 1.90 – 1.78 (m, 2H), 1.74 – 1.54 (m, 7H), 1.46 – 1.32 (m, 4H), 1.25 (t, *J* = 7.2 Hz, 3H), 1.23 – 1.19 (m, 2H).

^{13}C NMR (151 MHz, CDCl$_3$): d = 172.4, 59.7, 29.2, 26.4, 24.6, 20.9, 20.8, 14.4.

HRMS (EI) calculated for $C_{12}H_{21}O_2$ [M+H]$^+$: 197.1542, Found: 197.1531. IR (neat, cm^{-1}): 2983, 2924, 2851, 1725, 1380, 789.

The relative configuration was assigned with reference to its *trans* diastereomer.

Ethyl 2-methyl-2-((*R*)-4-methyl-5-oxocyclohex-3-en-1-yl)cyclopropane-1-carboxylate



The product was isolated from a reaction of (*R*)-(-)-carvone (1 ml) with EDA (0.25 ml) conducted following Procedure B.

^{1}H NMR (600 MHz, CDCl$_3$): d = 6.77 (ddd, *J* = 6.0, 2.5, 1.4 Hz, 1H), 4.20 – 4.04 (m, 2H), 2.46 – 2.31 (m, 2H), 2.31 – 2.16 (m, 2H), 1.79 – 1.71 (m, 3H), 1.61 – 1.52 (m, 4H), 1.26 (t, *J* = 7.1 Hz, 3H), 1.15 – 1.10 (m, 1H), 0.91 (dd, *J* = 7.9, 4.5 Hz, 1H).

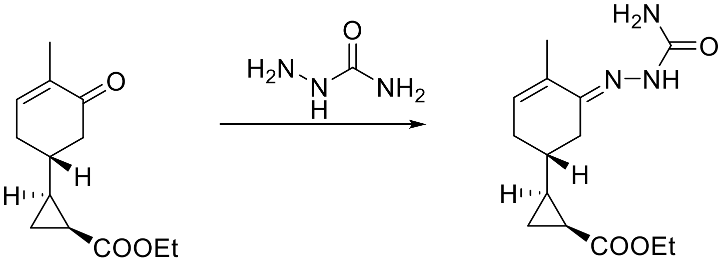
^{13}C NMR (151 MHz, CDCl$_3$): d = 172.0, 144.9, 135.4, 60.6, 41.8, 36.5, 29.4, 29.1, 27.0, 21.1, 19.7, 15.7, 14.3.

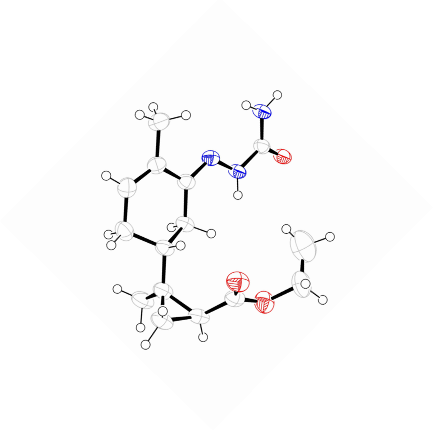
HRMS (EI) Calculated for $C_{14}H_{21}O_3$ [M+H]$^+$: 237.1491, Found: 237.1469. IR (neat, cm^{-1}): 2979, 2926, 1720, 1689, 1190, 837.

The absolute configuration was assigned according to the structure of its semicarbazone derivative.

X-ray structural determination of absolute configuration:

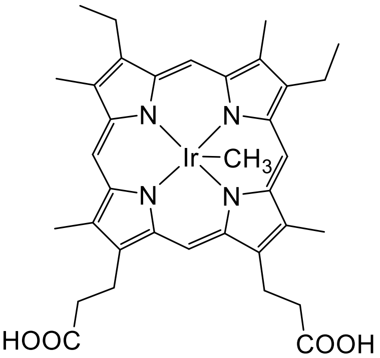
The major isomer of the cyclopropanation of carvone was isolated following procedure B in Section IIc.
Product derivatization:





The cyclopropane product (32 mg, 0.14 mmol), (23 mg, 0.21 mmol), and NaOAc (23 mg, 0.28 mmol) were dissolved in a mixture of EtOH (0.7 mL) and H_2O (0.4 mL) and heated at 85 ºC for 1 h. Excess water (6 mL) was added, the resulting precipitate was filtered, washed with water and dried under vacuum. A white powder was obtained and dissolved in 0.8 mL DCM and 0.8 mL hexane. Clear needle-like crystals were observed from the solution after 18 h at 4 ºC. These crystals were used for analysis by single-crystal X-ray diffraction. Details on the structure determination are included in the .cif file.

d. Ir(Me)-Mesoporphyrin IX (Ir(Me)-PIX) cofactor used in the studies:



The synthetic procedures and characterization of Ir(Me)-PIX were reported previously. [14]

III. Catalytic Experiments

a. *General Methods*:

Unless otherwise noted, catalytic reactions were performed in 4 mL individually-capped vials or in 1.2 mL glass vials arranged in a 96-well metal block covered by lid attached by screws. Reactions on 96 well plates were assembled in a nitrogen atmosphere glove box. Reactions in individual vials were conducted under air after determining that comparable results are obtained under atmospheres of either nitrogen or air. Solutions of Ir(Me)-CYP119 variants were gently degassed on a Schlenk line (3 cycles vacuum/refill) before being brought into a glove box in sealed vials. Organic reagents were added as stock solutions in DMF, such that the final amount of DMF in the reaction was approximately 2% by volume (unless noted otherwise). If necessary, purified, degassed protein catalysts were diluted to the suitable reaction concentration using sodium phosphate buffer (100 mM, pH = 6.0, containing 100 mM NaCl) before being added to reaction vials. Unless otherwise noted, all reactions with purified enzymes were performed with catalysts generated from a 1:2 ratio of Ir(Me)-cofactor : apo protein, with 0.17 mol% catalyst loading with respect to metal-cofactor and limiting reagent. Unless otherwise noted, all reactions were conducted in a shaking incubator (20 °C, 16 h, 275 rpm).

b. *Procedure for enzymatic reactions conducted in a 96 well plate format.*

The catalyst stock solution: To apo-CYP119 (0.14 mM protein in 10 mM tris buffer) was added Ir(Me)PIX as a 3.5 mM stock solution in DMF. The apo protein and Ir(Me)-PIX cofactor were combined in a 50 : 1 (v:v) ratio, producing a solution with a 2 : 1 mol ratio of protein : [Ir]. The buffer of the protein solution was subsequently exchanged to 100 mM NaPi, 100 mM NaCl, pH = 6.0 using a NAP column. The protein solution was degassed and introduced to a nitrogen atmosphere glove box as described in the general methods.

General reaction set up: In a glove box, the appropriate catalyst stock solution (250 uL, 0.01 mM) was added to each well of a 96-well array of glass vials. To each catalyst solution, the appropriate alkene was added (~3-5 uL, depending on the alkene) to give a final alkene concentration of 100 mM. After the addition of the alkene, ethyl diazoacetate (EDA) was added as a stock solution in DMF (5 uL of an 0.5 M solution of EDA in DMF) to give a final EDA concentration of 10 mM in the reaction. The plate was sealed and removed from the glovebox, and the reactions were incubated overnight at rt in an orbital shaker (150 rpm). The reactions were analyzed as described in section IV.

Reaction set up to form products ***14, 18, 22, 24****:* In a glove box, the appropriate catalyst stock solution (250 uL, 0.02 mM) was added to each well of 96 well array of glass vials. To each catalyst solution, the appropriate alkene was added (5 uL). After the addition of the alkene, ethyl diazoacetate (EDA) was added as a stock solution in DMF (5 uL of a 500 mM solution of EDA in DMF) to give a final EDA concentration of 10 mM in the reaction. The plate was sealed and removed from the glovebox, and the reactions were incubated overnight at rt in an orbital shaker (250 rpm). The reactions were analyzed as described in section IV.

Reaction set up to form products ***17, 19, 20, 21****:* The appropriate catalyst stock solution (250 uL, 0.02 mM) was added to each well of 96 well array of glass vials under air. To each catalyst solution, the appropriate alkene was added (5 uL in DMF) to give a final concentration of 17 mM. After the addition of the alkene, ethyl diazoacetate (EDA) was added slowly over 30 min (5 uL in DMF) to give a final EDA concentration of 32 mM in the reaction. The reactions were incubated overnight at rt in an orbital shaker (250 rpm). The reactions were analyzed as described in section IV.

c. *Procedure for enzymatic reactions conducted in 4 mL vials using a syringe pump. The optimized parameters for the reaction of each substrate can be found in Fig 2-5 (the main text) and Table S2.*

The catalyst stock solution: The catalyst solution was prepared as described in section IIIb, except that the protein solution was not degassed and the reaction wasset up on a bench instead of inside of a glove box.

General reaction set up: Under air, 1 mL of catalyst stock solution (catalyst loadings as listed in Fig 2-5 and Table S2) was added to a 4 mL glass vial equipped with a micro stirring bar. The vial was sealed using a cap containing a Teflon-septum. To the reaction vial under air, 10-30 umol of alkene were added as a stock solution in 10 uL DMF via a syringe. The syringe of a multichannel syringe pump was loaded with a stock solution of EDA in DMF (20 uL of 0.5-5 M solution of EDA in DMF), and the EDA was added to the reaction over 1-6 hours, as specified in the tabulated results.The reaction was quenched upon the conclusion of the addition of EDA as described in section IV. Using a moderate rate of stirring was essential to obtain a high yield for this reaction.

d. Procedure for the cycloparopanation of carvone in the presence of Rh(II) catalysts

To a solution of (*R*)-(-)-carvone (5 equiv.) and Rh(II) catalysts (0.5 mol%) in anhydrous CH_2Cl_2 (1 M) at room temperature and under nitrogen was added the diazo ester (1 equiv.) in 5 mL of CH_2Cl_2 (0.4 M) through a syringe pump at a rate of 1.0 mL/h. After addition was complete, the reaction mixture was stirred for another 12 h. The dichloromethane solution was then evaporated under reduced pressure and the internal standard (0.1% dodecane in EA by volume) was added for GC analysis.

IV. Analysis of Yield and Enantiomeric Ratio (er)

Yields were determined by achiral or chiral GC using dodecane as an internal standard (Figures S2-S3). Enantiomeric ratios were determined either by chiral or achiral GC (Figures S2-S3). Representative traces can be found in Figure S3. Samples for analysis were prepared as follows, depending on the analysis method:

Analysis of Reaction from 96 well plates by chiral GC: The reaction was quenched by the addition of HBr (60 uL, 50% in water) to each reaction vial, followed with the addition of saturated NaCl (200 uL) and a solution of dodecane (500 ul, 1 ul/ml) in EtOAc. The contents of the vial were mixed by pipet, and the phases were allowed to separate. After separation of the layers, approximately 400 uL of the aqueous phase was removed from the bottom of the vial by pipet. The remaining contents of the vial were neutralized by the addition of sat. $NaHCO_3$ (200 uL), and the organic layer was further diluted with EtOAc (500 uL). The organic layer was then transferred to a separate vial for GC analysis. In the case of experiments performed in a 96-well array, all manipulations were performed using a multichannel pipet.

Analysis of Reaction from 4 mL vials by chiral GC (general method): Saturated NaCl (500 uL) was added to each reaction vial, followed by a solution of dodecane (500 ul, 1 ul/ml) in EtOAc. The reaction was quenched by the addition of HBr (100 uL, 50% in water). The reaction mixture was mixed by pipet, and the layer were separated by centrifugation of the reaction vial (2 min, 2500 rpm). The aqueous phase was removed from the bottom of the vial by pipet, after which the remaining contents of the vial were neutralized by the addition of sat. $NaHCO_3$ (500 uL). The organic layer was then transferred to a separate vial for GC analysis.

Analysis of Reaction from 4 mL vials by chiral GC for Products 13-18, 20: Saturated NaCl (800 uL) was added to each reaction vial, followed by a solution of dodecane (2 mL, 1 uL/mL) in EtOAc. The reaction was quenched by the addition of HBr (240 uL, 50% in water). The contents of the vial were mixed by pipet, and the phases were allowed to separate. After separation of the layers, approximately 800 uL of the aqueous phase was removed from the bottom of the vial by pipet. The remaining contents of the vial were neutralized by the addition of sat. $NaHCO_3$ (800 uL). The organic layer was then transferred to a separate vial for GC analysis.

V. Strategy for Directed evolution

To identify selective mutants for cyclopropanation, a multi-phase, directed evolution approach was followed. All variants were expressed in 1 L cell culture, purified by NiNTA affinity chromatography, metallated with Ir(Me)-PIX cofactor, and exchanged to the reaction buffer using a P10 or NAP25 desalting column as described in section **V**.

Phase 1: Double mutants of CYP119 carrying the mutation C317G (a mutation to the axial ligand residue of the protein to introduce a non-coordinating residue at this position) and one additional mutation (to L, V, A, G, Y, W, F, or T) at one site close to the substrate binding site (V254, T213, A209, and L69) were evaluated as catalysts for the reaction of styrenes **1** - **4**, 1-octene, cis-2-octene, beta-pinene, limonine, and carvone. The plasmids were obtained by site directed mutagenesis using a mixture of primers in each PCR reaction that collectively encoded the desired set of substitutions. The primers were designed by the Agilent Primer Design Program (http://www.genomics.agilent.com/primerDesignProgram.jsp), purchased as complementary pairs from IDT, combined to create the aforementioned mixtures, and used in PCR reactions performed using the Agilent Quick Change lightening kit as described in section **I**. Twenty-four mutants were evaluated in Phase 1.

Phase 2. A library of triple mutants of CYP119 carrying the mutation C317G (a mutation to the axial ligand residue of the protein to introduce a non-coordinating residue at this position) and two additional mutations (to L, V, A, G, Y, W, F, or T) at two sites close to the substrate binding site (V254, T213, A209, and L69) was prepared using site directed mutagenesis. Each PCR reaction contained the plasmid encoding CYP119-C317G and a mixture of primers that collectively encoded the desired set of substitutions at two sites. Separate reactions were conducted to create mutants containing a pair of substitutions at positions 69/213, 213/254, 209/254, and 69/209. The PCR reactions were conducted according to section **V**. From this library, those members containing mutations that were present in the most selective mutants in Phase 1 were evaluated as catalysts for the reaction of styrenes **1** - **4**, 1-octene, cis-2-octene, beta-pinene, limonine, and carvone. Fifty-six mutants were evaluated in Phase 2. From the first two phases of the evolution, the mutants CYP-119(+) and (-) were identified as catalysts leading to high, complementary selectivity for most of the substrates, as shown in Table 1 of the main text.

In a few cases, mutants other than CYP119(+) and (-) that were identified in Phase 2 provided the highest selectivities, such as for reactions that generate the 2-*t, 3*-c "trans" cyclopropane from trans-β-Me-styrene. In contrast, CYP119(+) and (-) led to the formation of opposite enantiomers of the 2-*c*, 3-*c* "cis" cyclopropane from trans-β-Me-styrene. However, only CYP119 (+) and (-) were used for Phase 3.

Phase 3. A library of additional mutants was created from CYP119(+) and (-). These mutants contained one or two additional mutations at either the original positions that were targeted (V254, T213, A209, and L69) or at positions that are located more distally from the substrate binding site (A152, L155, F310, L318). In all cases, the native amino acids were changed to L, V, A, G, Y, W, F, or T. The plasmids were prepared as in the previous phases. Approximately 100 mutants were evaluated for the reactions of styrenes **1-4**, 1-octene, cis-2-octene, beta-pinene, limonine, and carvone in Phase 3."

VI. Supporting Figures

Figure S1. Native Nanospray Ionization Mass Spectrum of Ir(Me)-CYP119 C317G (12+ to 14+) charge states shown. Initial shoulder of each charge state corresponds to the apo-protein, while the most intense signal corresponds to the metallated protein (addition of Ir(Me)-PIX cofactor). For +13 charge state, expected M/Z = 3532.7; Found = 3532.2

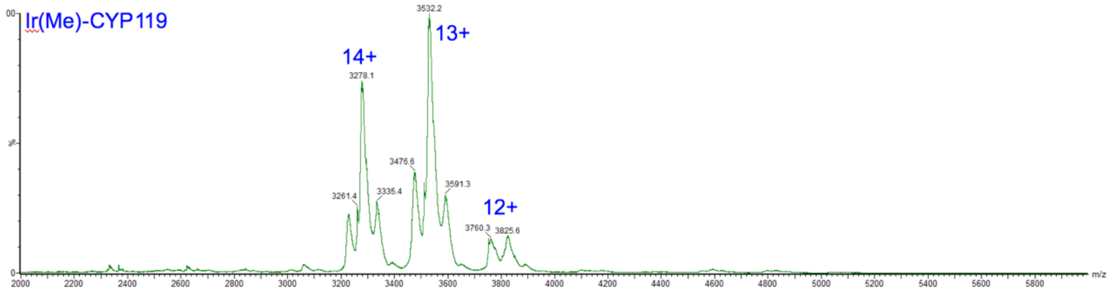
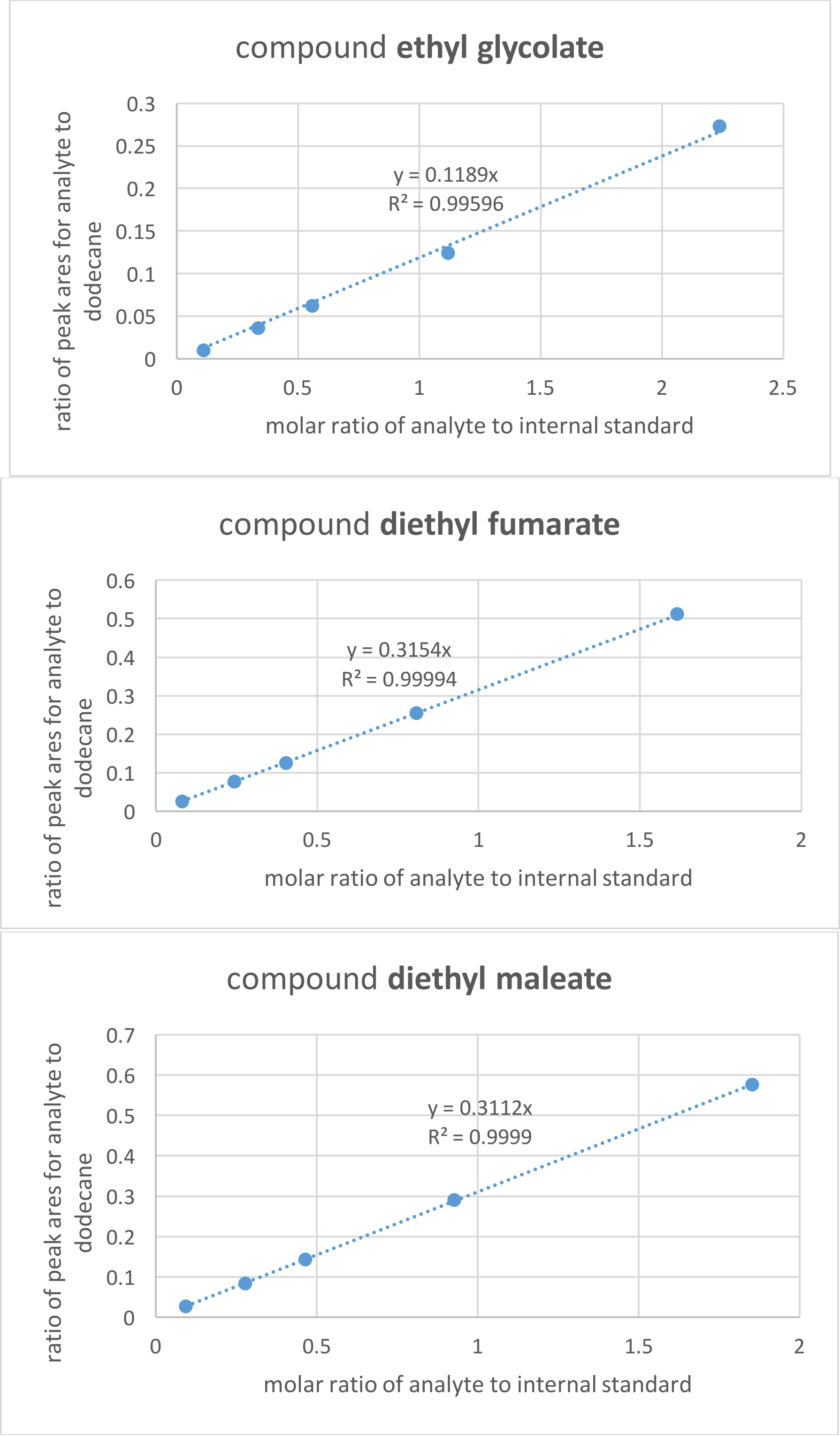
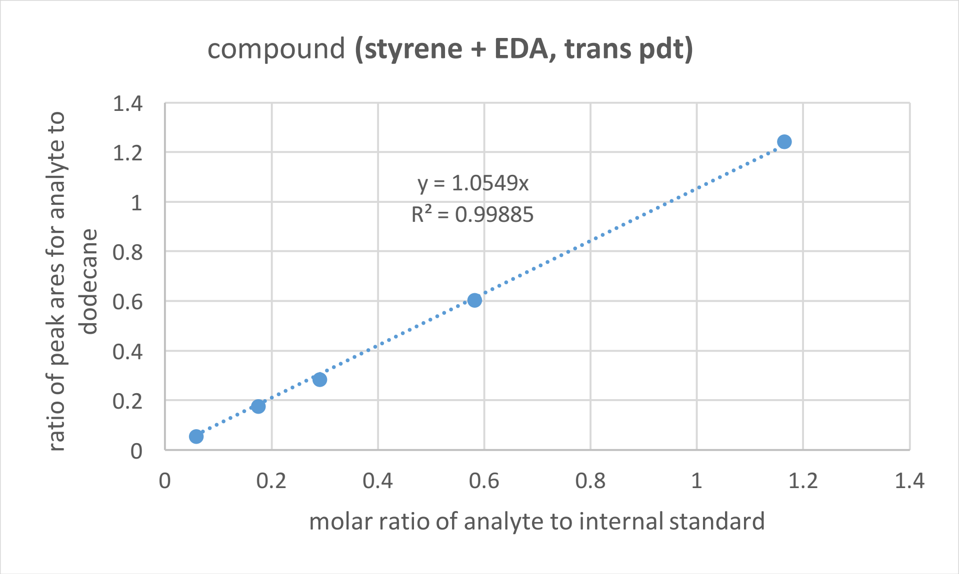


Figure S2. Calibration curves used to determine GC yields of cyclopropanation reactions




compound **(styrene + EDA, trans pdt)**
y = 1.0549x
R² = 0.99885
ratio of peak ares for analyte to dodecane
molar ratio of analyte to internal standard
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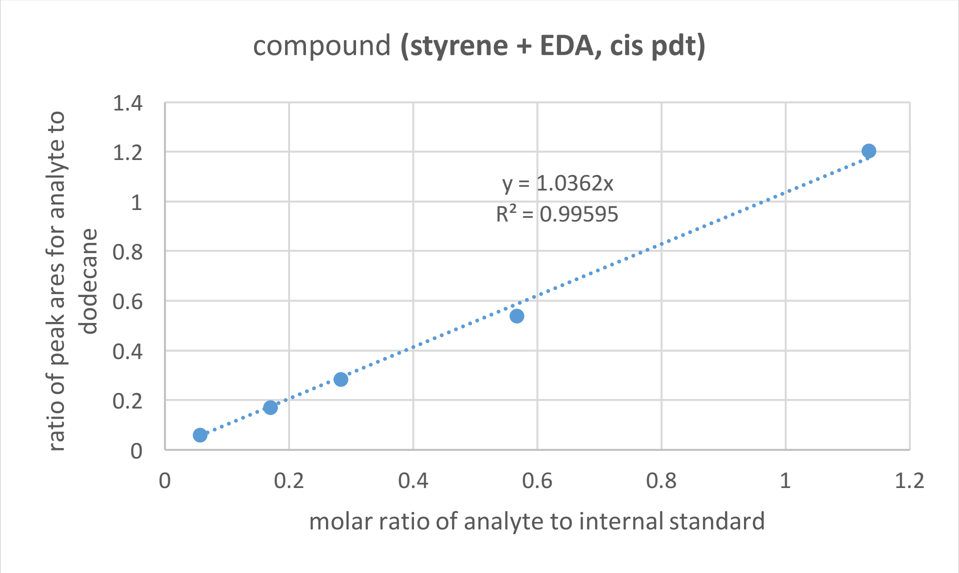
0.2
0.4
0.6
0.8
1
1.2
1.4


compound **(styrene + EDA, cis pdt)**
y = 1.0362x
R² = 0.99595
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molar ratio of analyte to internal standard
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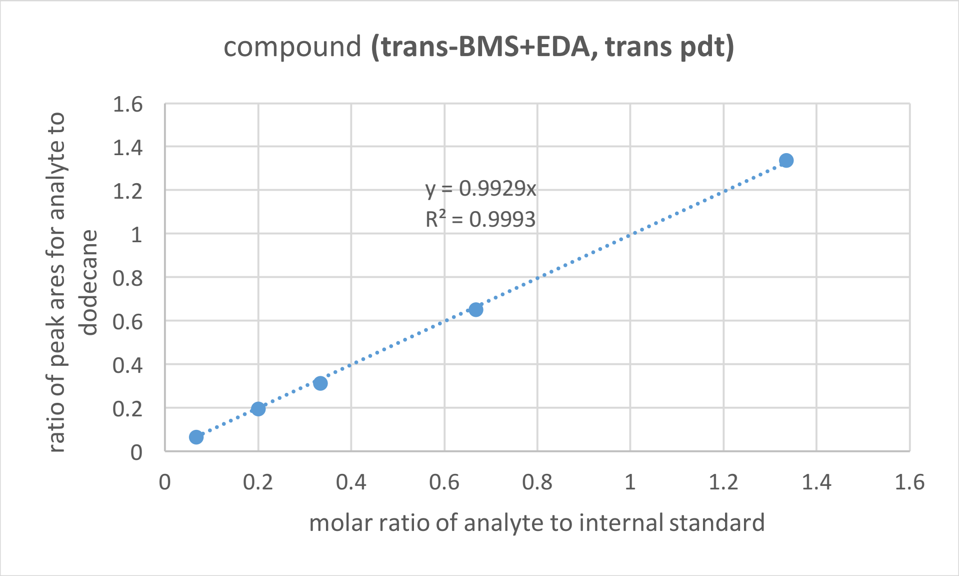
0.6
0.8
1
1.2
1.4


compound **(trans-BMS+EDA, trans pdt)**
y = 0.9929x
R² = 0.9993
ratio of peak ares for analyte to dodecane
molar ratio of analyte to internal standard
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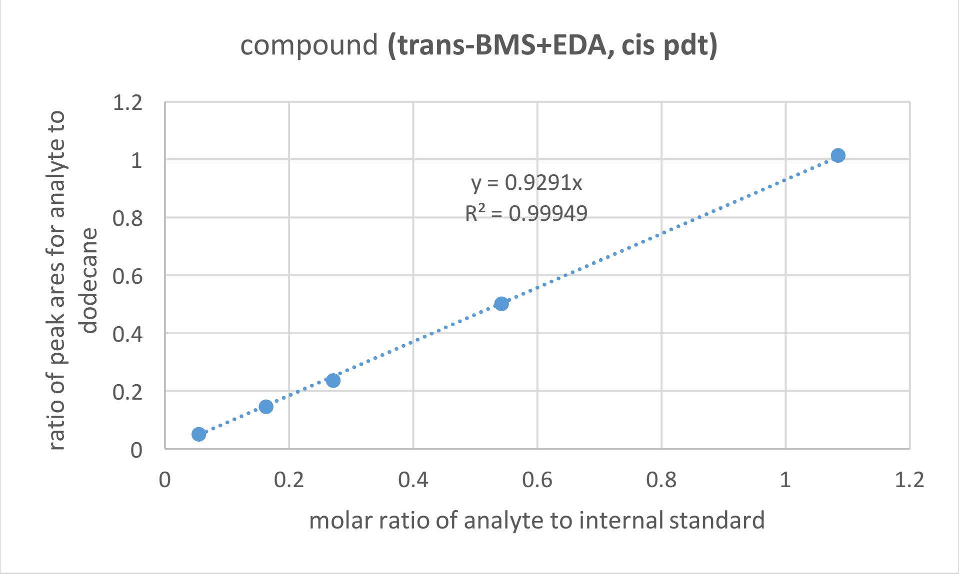
0.4
0.6
0.8
1
1.2
1.4
1.6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R² = 0.99949
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molar ratio of analyte to internal standard
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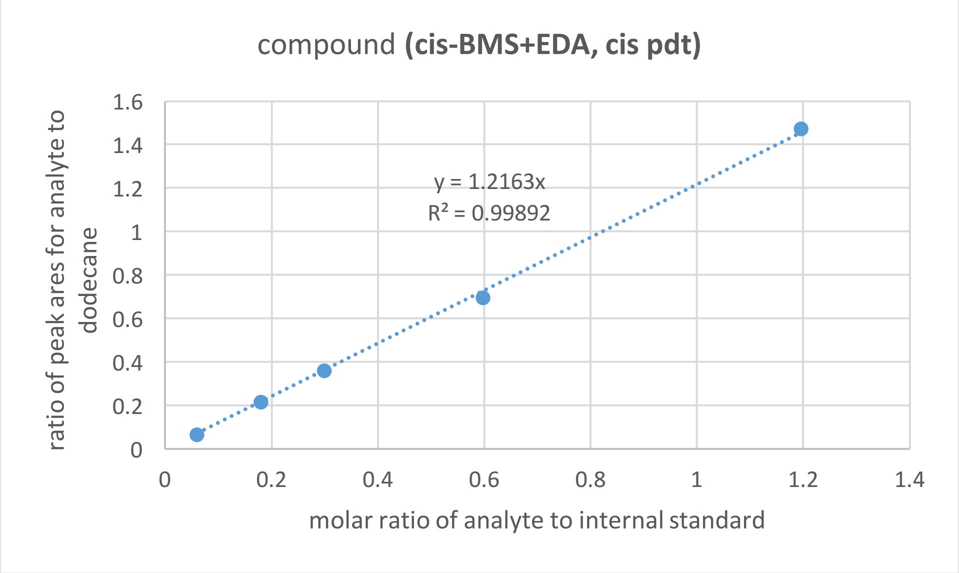
0.4
0.6
0.8
1
1.2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y = 1.2163x
R² = 0.99892
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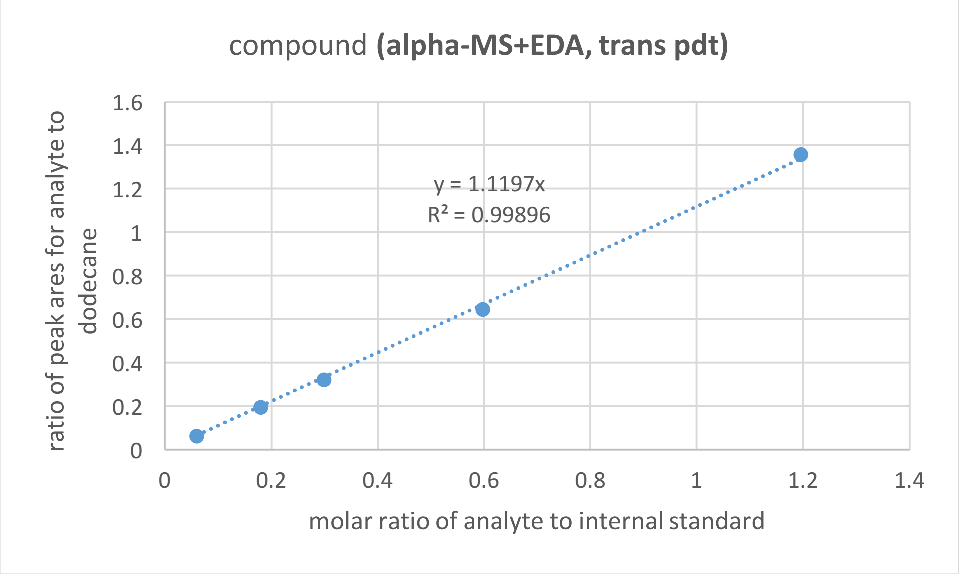
0.4
0.6
0.8
1
1.2
1.4
1.6


compound **(alpha-MS+EDA, trans pdt)**
y = 1.1197x
R² = 0.99896
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molar ratio of analyte to internal standard
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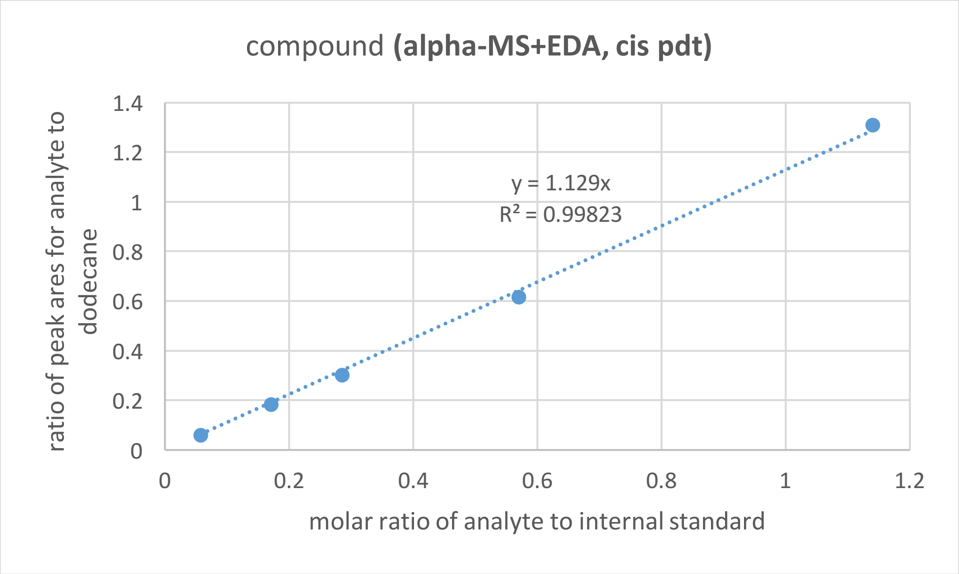
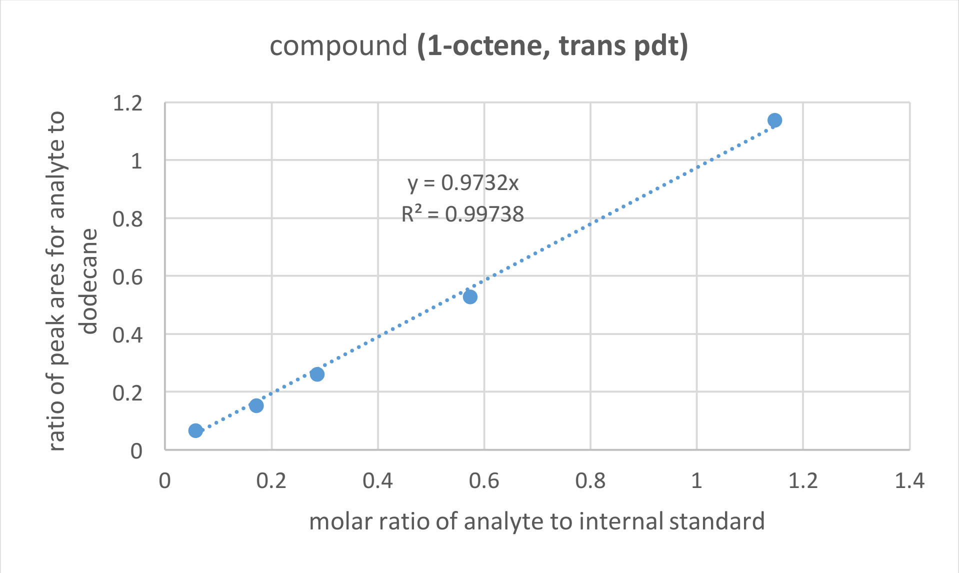
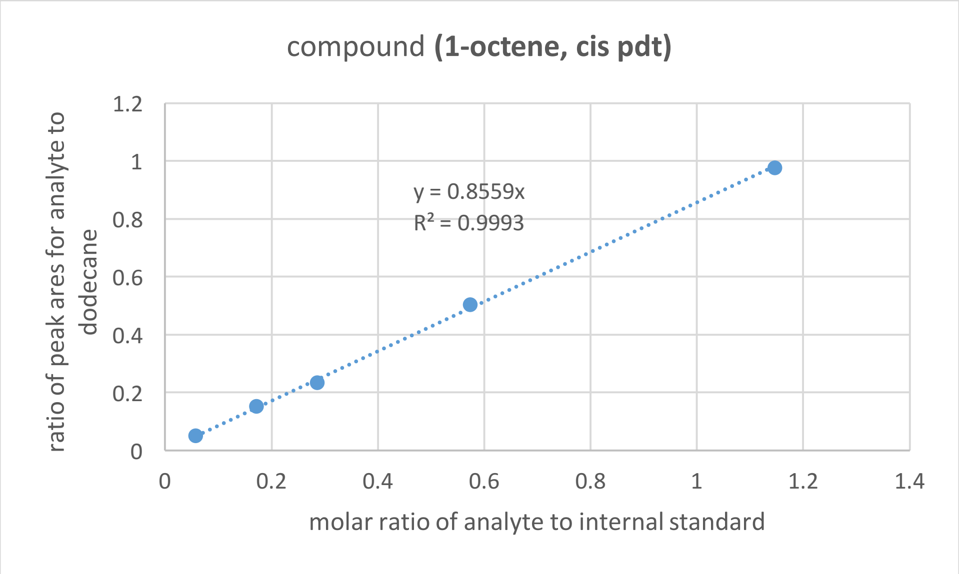
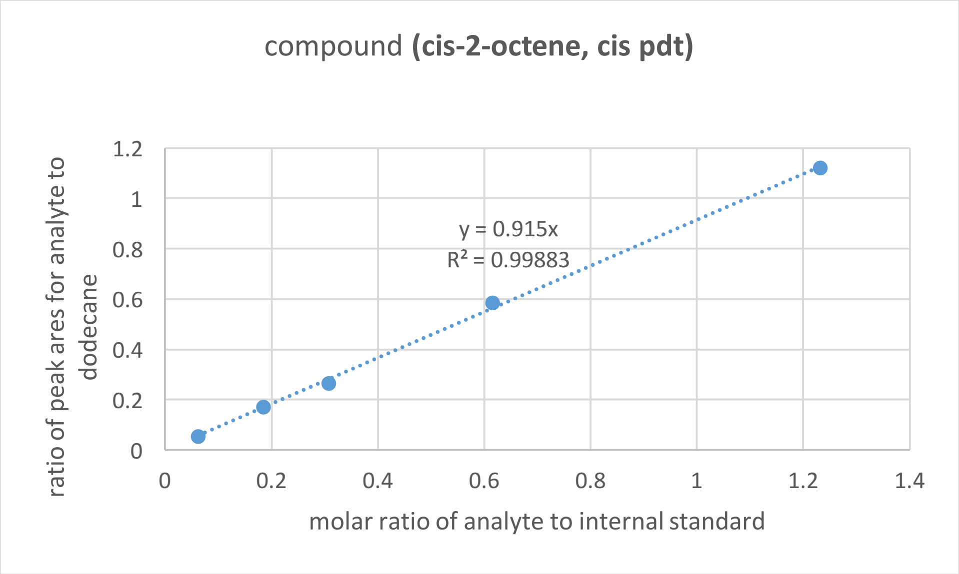
0.6
0.8
1
1.2
1.4
1.6


compound **(alpha-MS+EDA, cis pdt)**


compound **(1-octene, trans pdt)**


compound **(1-octene, cis pdt)**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molar ratio of analyte to internal standard
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0.2
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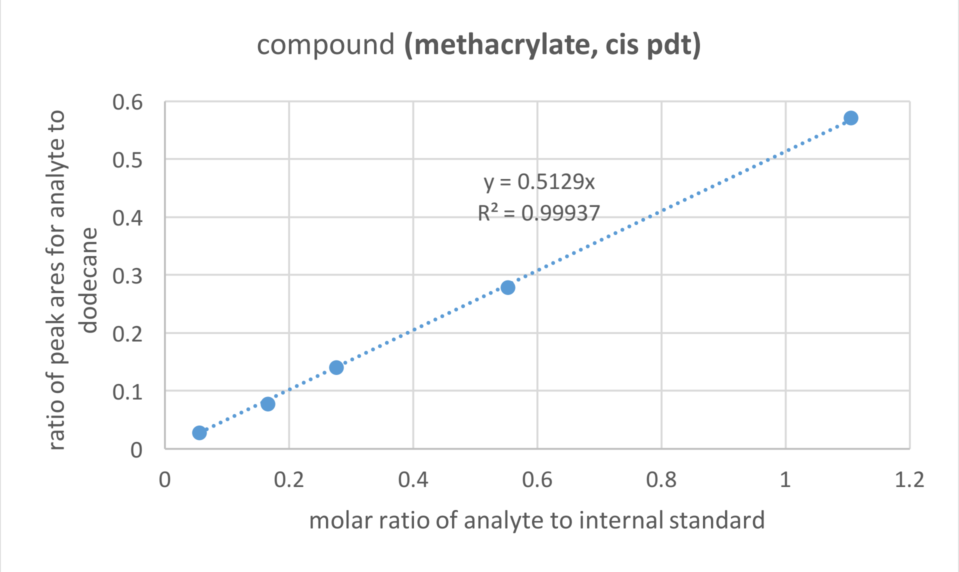
0.6
0.8
1
1.2
0
0.2
0.4
0.6
0.8
1
1.2
1.4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R² = 0.99937
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molar ratio of analyte to internal standard
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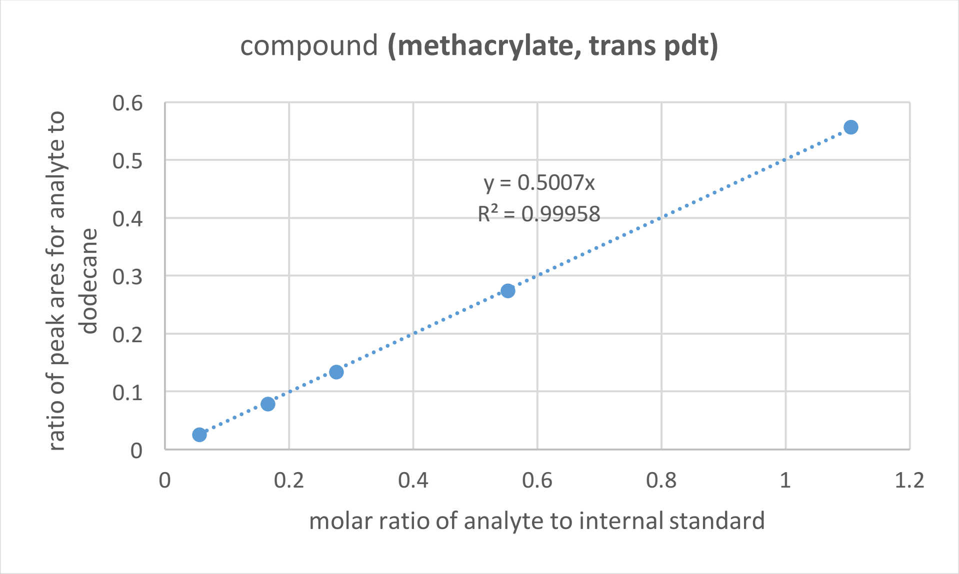
0.2
0.3
0.4
0.5
0.6
0
0.2
0.4
0.6
0.8
1
1.2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R² = 0.99958
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molar ratio of analyte to internal standard
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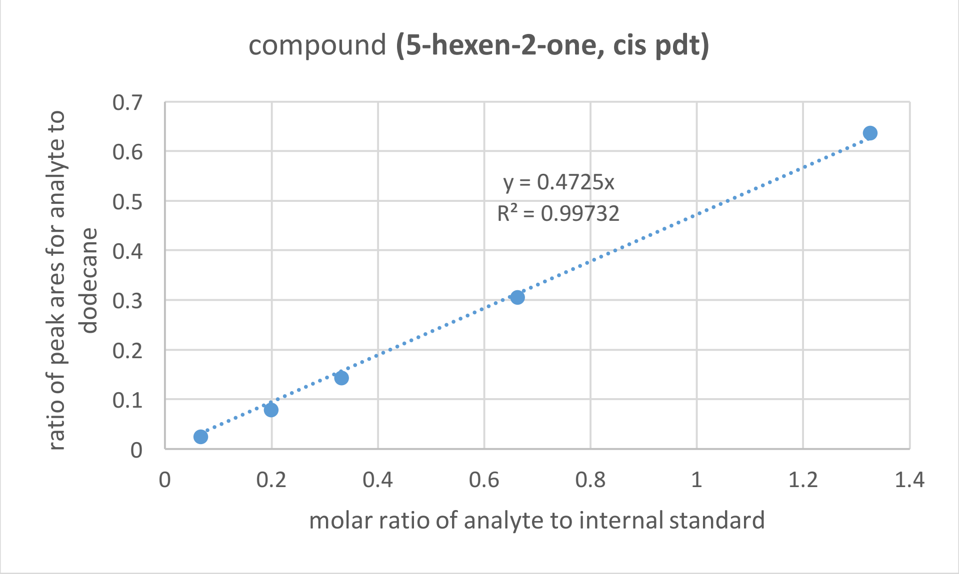
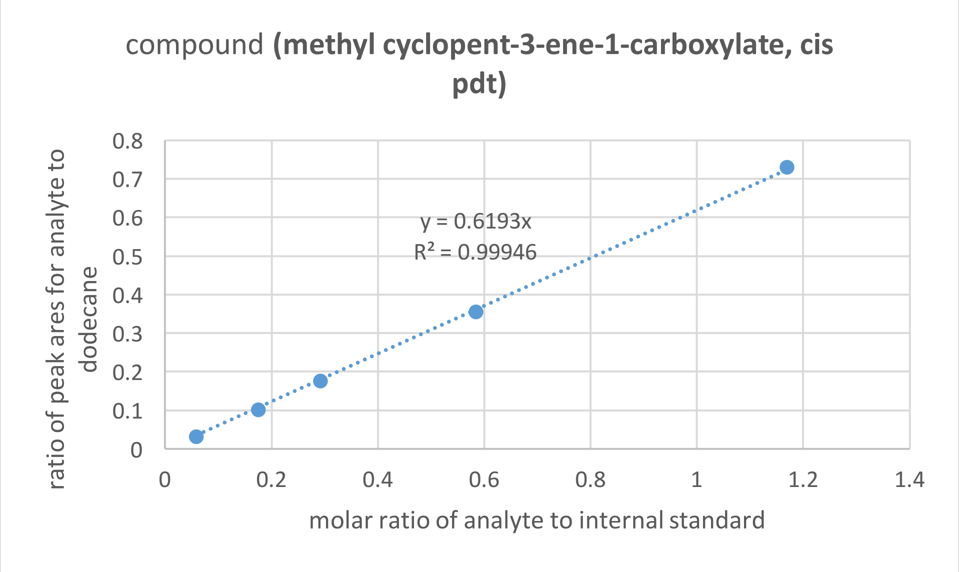
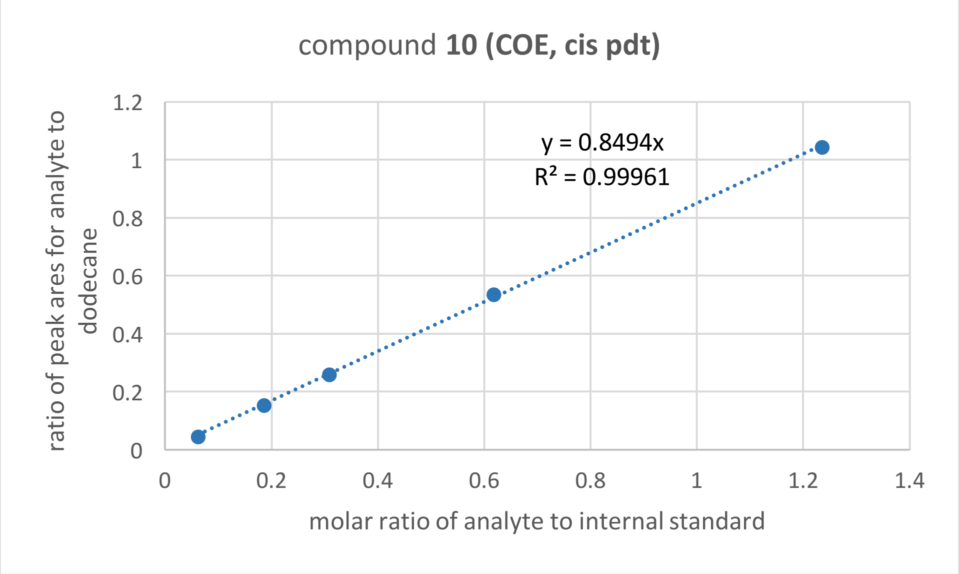
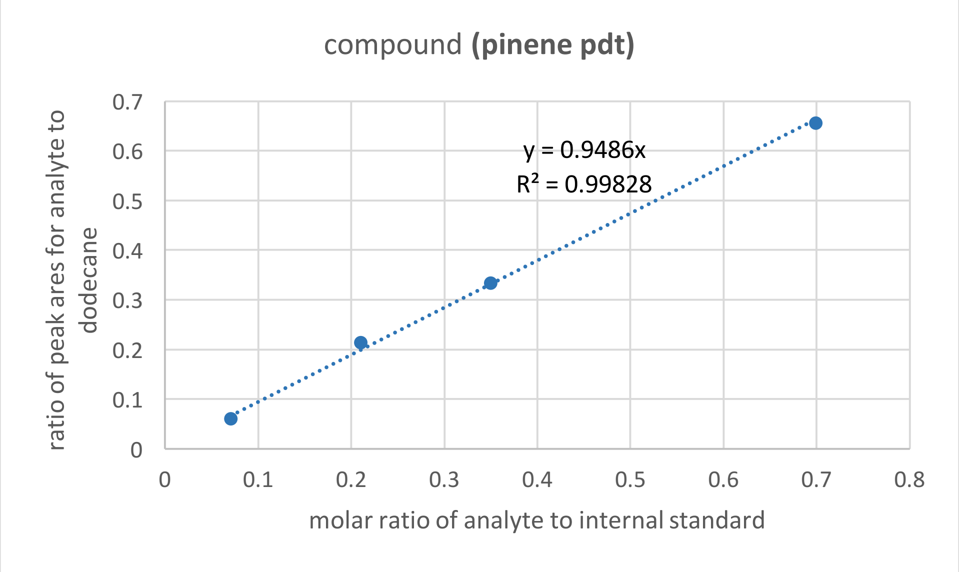
0.1
0.2
0.3
0.4
0.5
0.6
0
0.2
0.4
0.6
0.8
1
1.2


compound (5-hexen-2-one, cis pdt)
y = 0.4725x
R² = 0.99732
ratio of peak ares for analyte to dodecane
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0
0.2
0.4
0.6
0.8
1
1.2
1.4
molar ratio of analyte to internal standard


compound (methyl cyclopent-3-ene-1-carboxylate, cis pdt)
y = 0.6193x
R² = 0.99946
ratio of peak ares for analyte to dodecane
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0
0.2
0.4
0.6
0.8
1
1.2
1.4
molar ratio of analyte to internal standard


compound **10 (COE, cis pdt)**
y = 0.8494x
R² = 0.99961
ratio of peak ares for analyte to dodecane
molar ratio of analyte to internal standard
0
0.2
0.4
0.6
0.8
1
1.2
1.4


compound **(pinene pdt)**
y = 0.9486x
R² = 0.99828
ratio of peak ares for analyte to dodecane
molar ratio of analyte to internal standard
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8

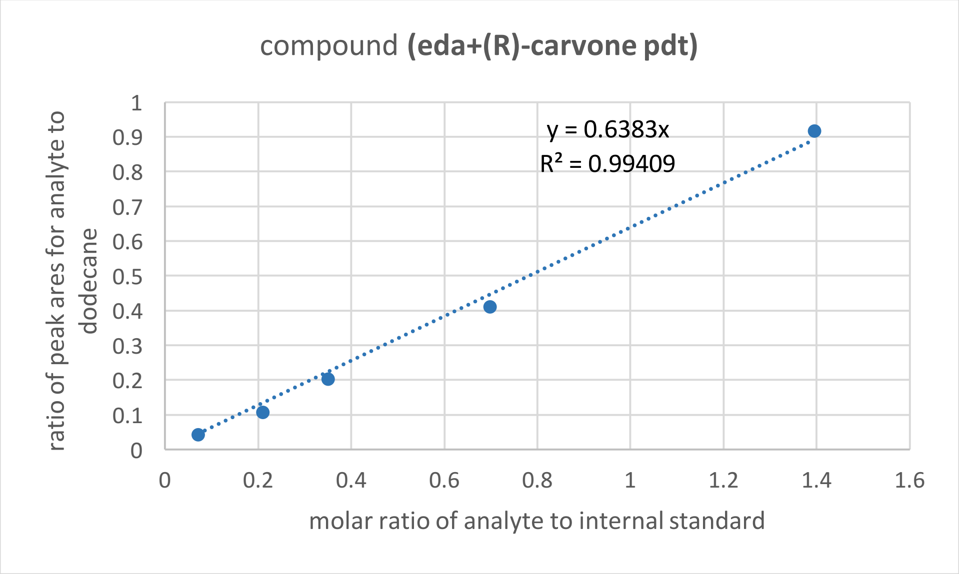
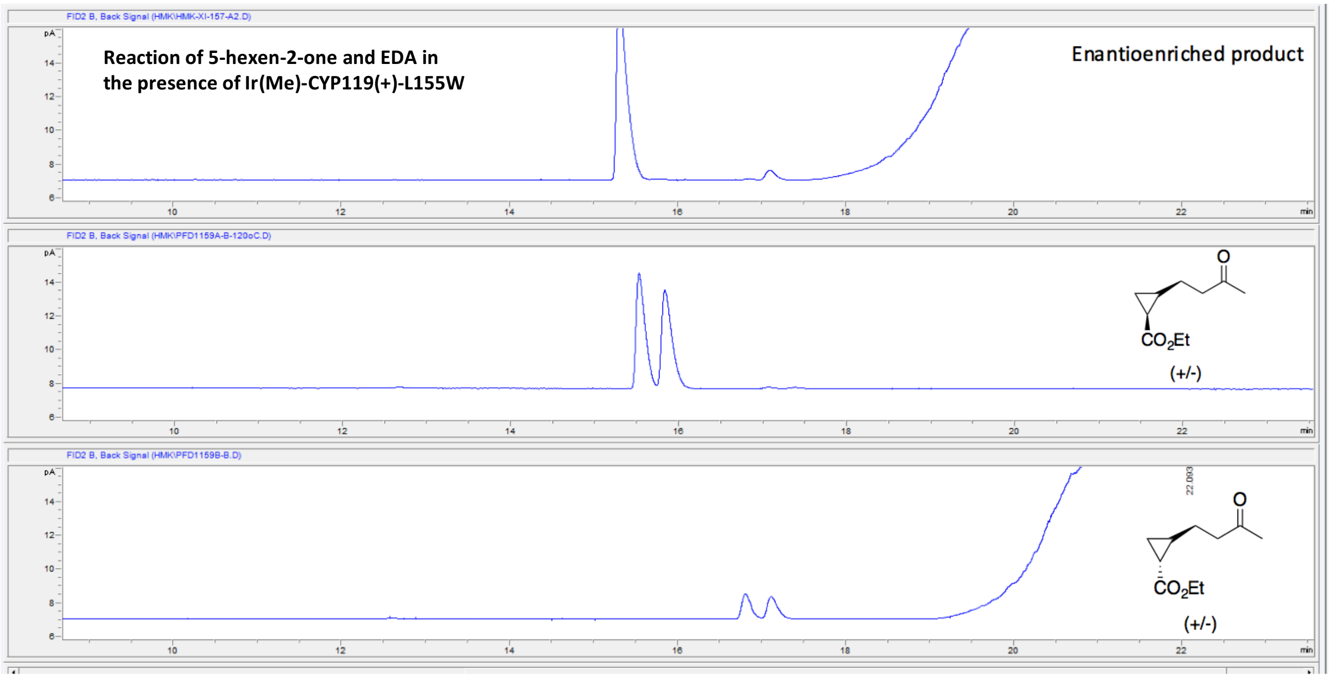
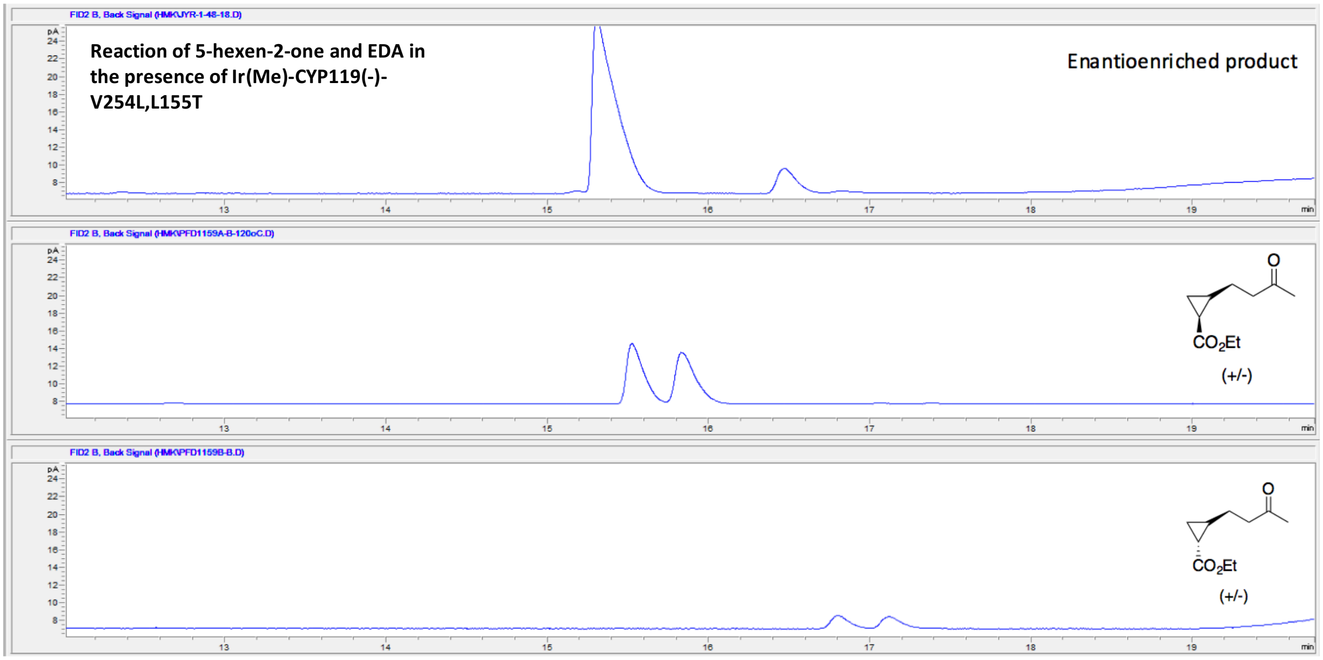
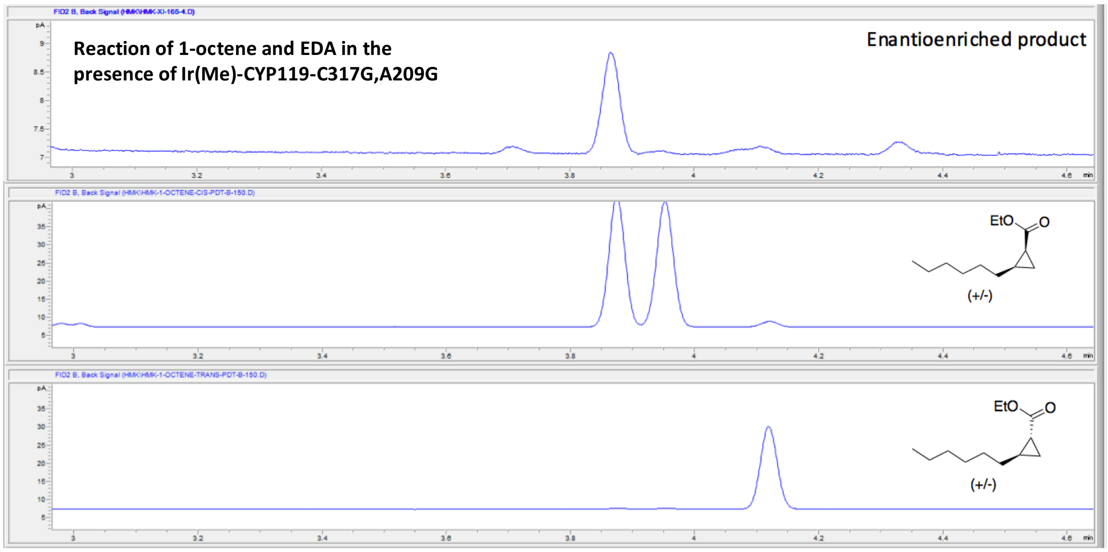

compound **(eda+(R)-carvone pdt)**
y = 0.6383x
R² = 0.99409
ratio of peak ares for analyte to dodecane
molar ratio of analyte to internal standard
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
1.2
1.4
1.6

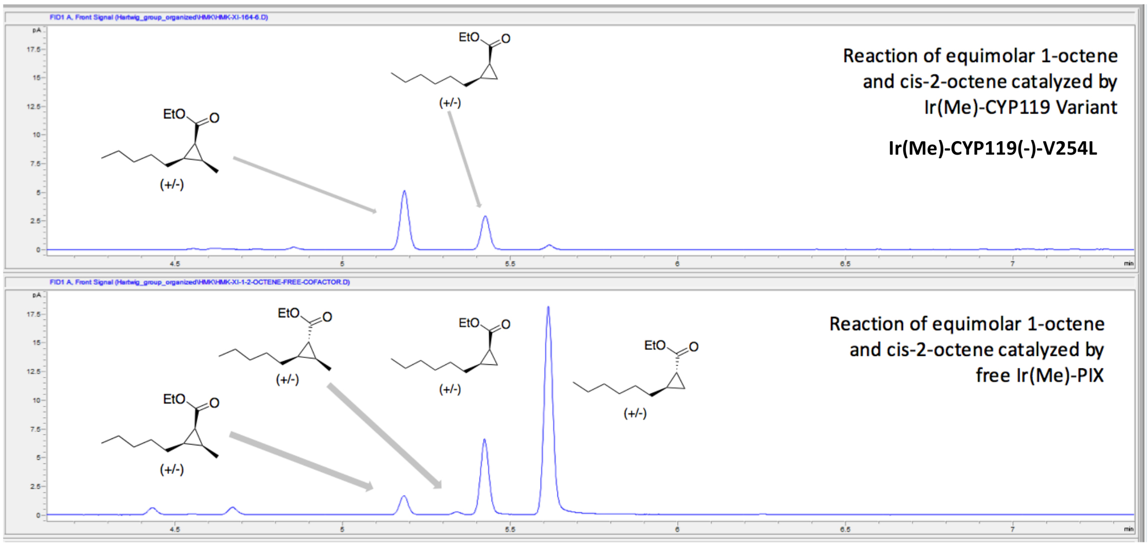
Figure S3. Representative traces showing the formation of stereo-enriched products.

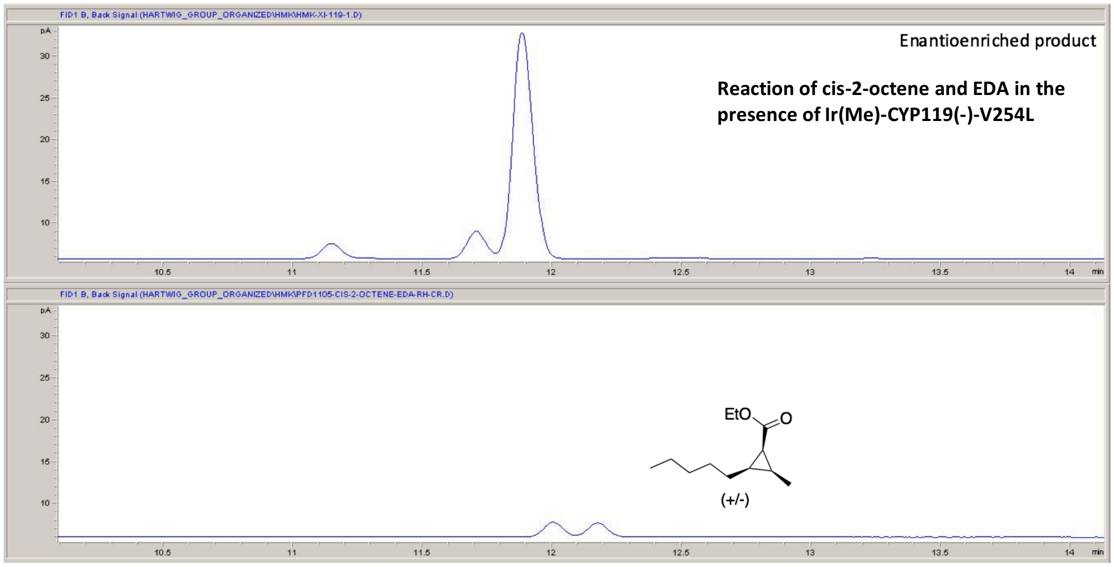
A. GC Traces of stereoselective cyclopropanation reactions in comparison to racemic products or unselective reactions catalyzed by free Ir(Me)-PIX cofactor





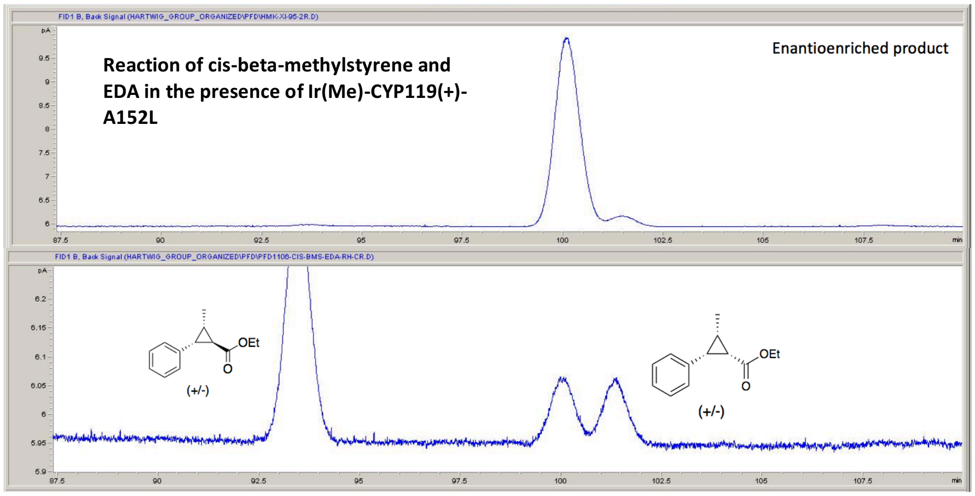

FID2 B, Back Signal (HMK\HMK-XI-165-4.D)
Reaction of 1-octene and EDA in the presence of Ir(Me)-CYP119-C317G,A209G
Enantioenriched product
pA
9
8.5
8
7.5
7
3
3.2
3.4
3.6
3.8
4
4.2
4.4
4.6
min
FID2 B, Back Signal (HMK\HMK-1-OCTENE-CIS-PDT-B-150.D)
pA
35
30
25
20
15
10
5
EtO
O
(+/-)
FID2 B, Back Signal (HMK\HMK-1-OCTENE-TRANS-PDT-B-150.D)
pA
35
30
25
20
15
10
5
EtO
O
(+/-)
3
3.2
3.4
3.6
3.8
4
4.2
4.4
4.6
min


FID1 A, Front Signal (Hartwig_group_organized\HMK\HMK-XI-164-6.D)
pA
17.5
15
12.5
10
7.5
5
2.5
0
EtO
O
(+/-)
EtO
O
(+/-)
Reaction of equimolar 1-octene and cis-2-octene catalyzed by Ir(Me)-CYP119 Variant
Ir(Me)-CYP119(-)-V254L
4.5
5
5.5
6
6.5
7
min
FID1 A, Front Signal (Hartwig_group_organized\HMK\HMK-XI-1-2-OCTENE-FREE-COFACTOR.D)
pA
17.5
15
12.5
10
7.5
5
2.5
0
EtO
O
(+/-)
EtO
O
(+/-)
EtO
O
(+/-)
EtO
O
(+/-)
Reaction of equimolar 1-octene and cis-2-octene catalyzed by free Ir(Me)-PIX
4.5
5
5.5
6
6.5
7
min



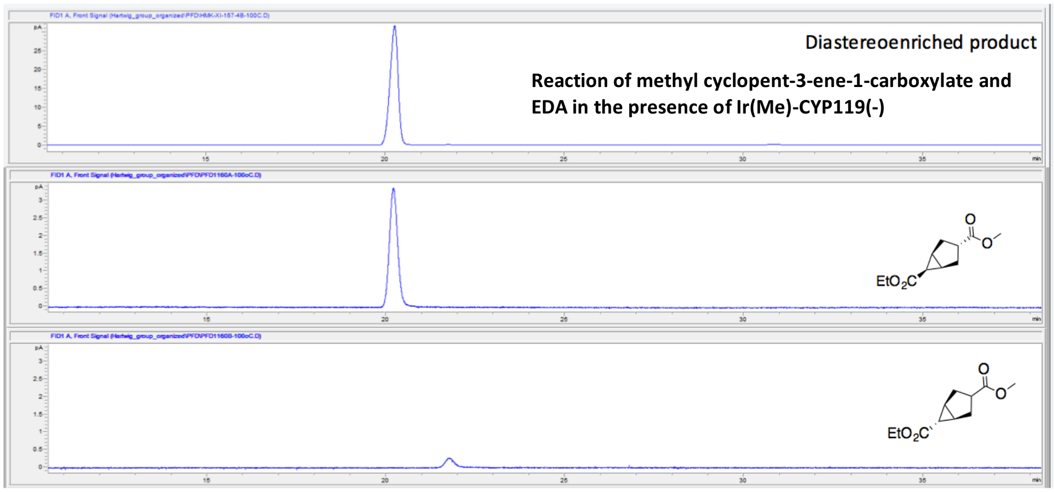
Enantioenriched product

Reaction of cis-2-octene and EDA in the presence of Ir(Me)-CYP119(-)-V254L



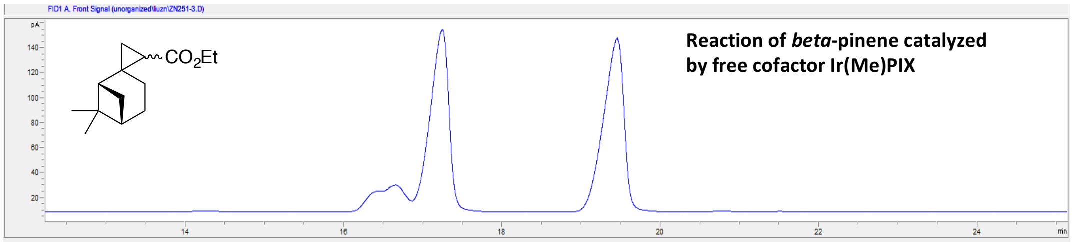
Reaction of cis-beta-methylstyrene and EDA in the presence of Ir(Me)-CYP119(+)-A152L

Enantioenriched product

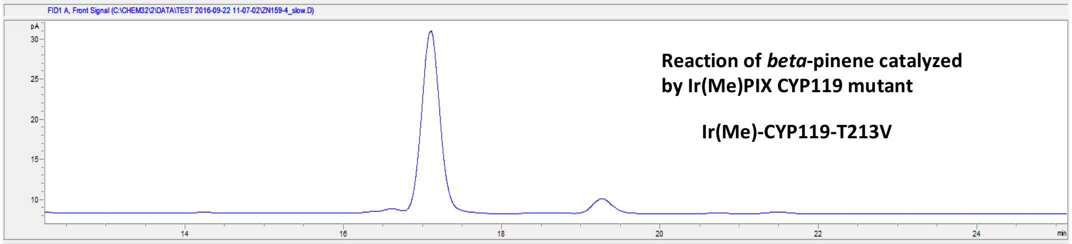


Diastereoenriched product

Reaction of methyl cyclopent-3-ene-1-carboxylate and EDA in the presence of Ir(Me)-CYP119(-)

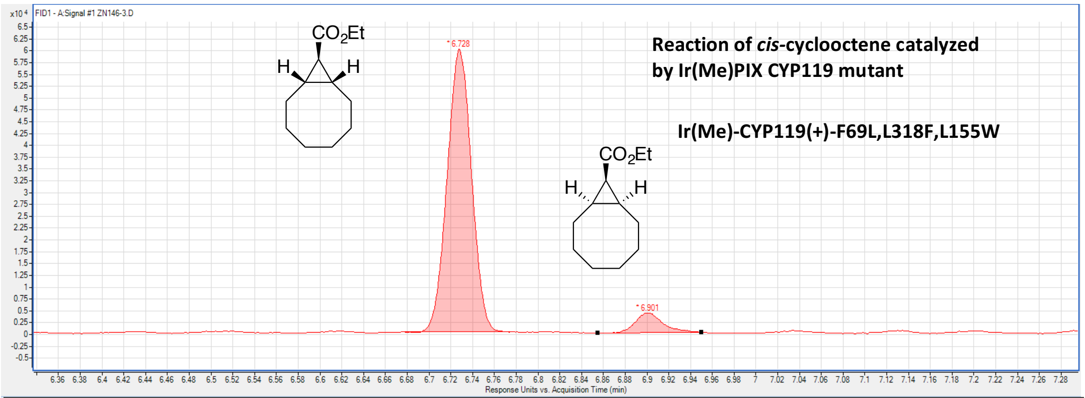


Reaction of *beta*-pinene catalyzed by free cofactor Ir(Me)PIX



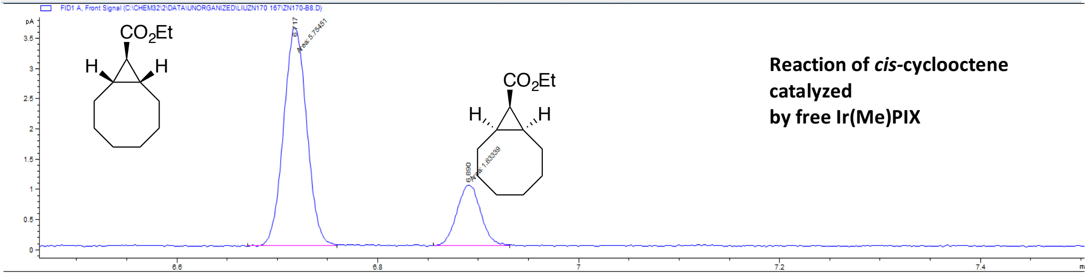
Reaction of *beta*-pinene catalyzed by Ir(Me)PIX CYP119 mutant

Ir(Me)-CYP119-T213V

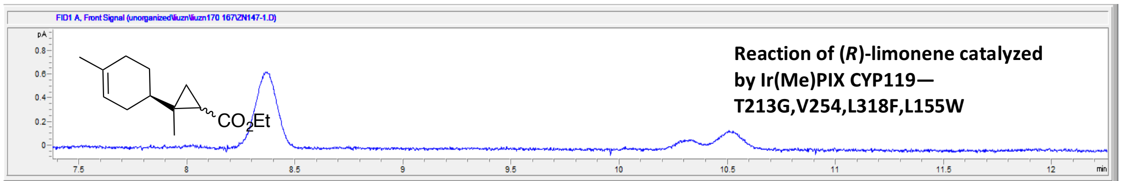


Reaction of *cis*-cyclooctene catalyzed by Ir(Me)PIX CYP119 mutant

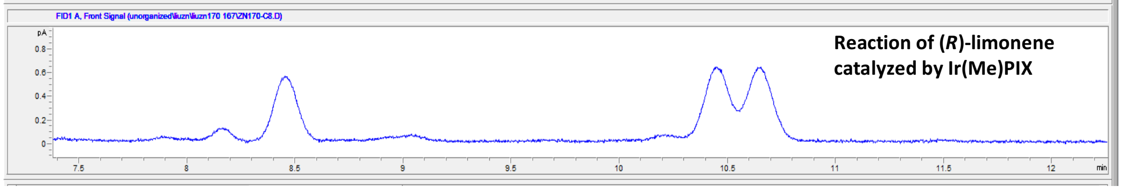
Ir(Me)-CYP119(+)-F69L,L318F,L155W



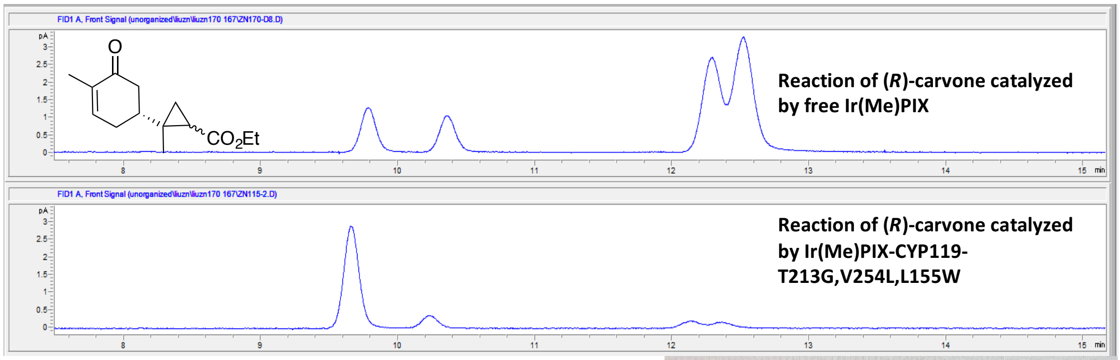
Reaction of *cis*-cyclooctene catalyzed by free Ir(Me)PIX

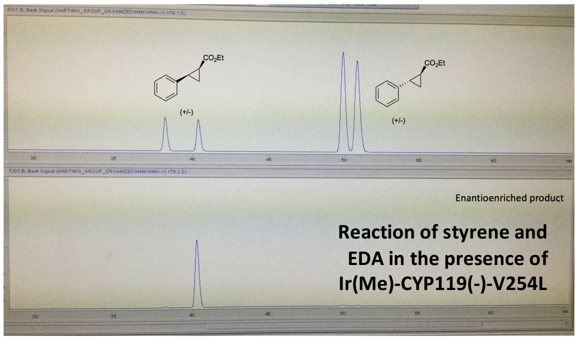


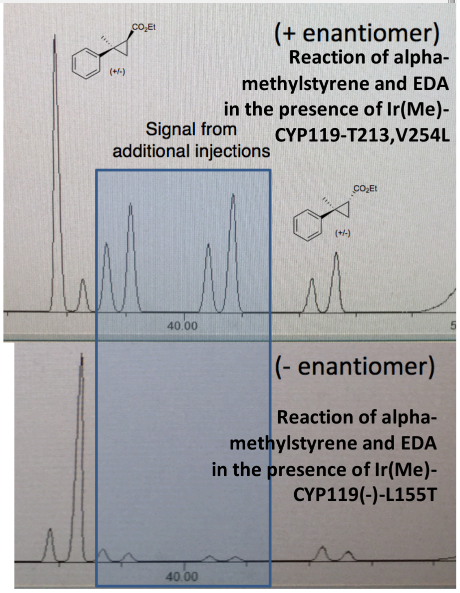
Reaction of (*R*)-limonene catalyzed by Ir(Me)PIX CYP119—T213G,V254,L318F,L155W



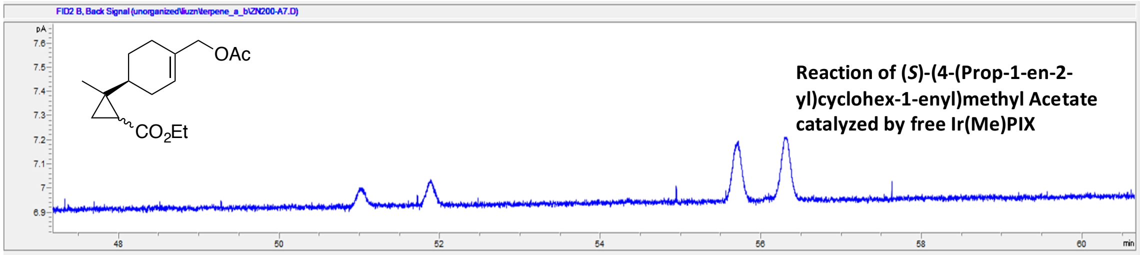
Reaction of (*R*)-limonene catalyzed by Ir(Me)PIX



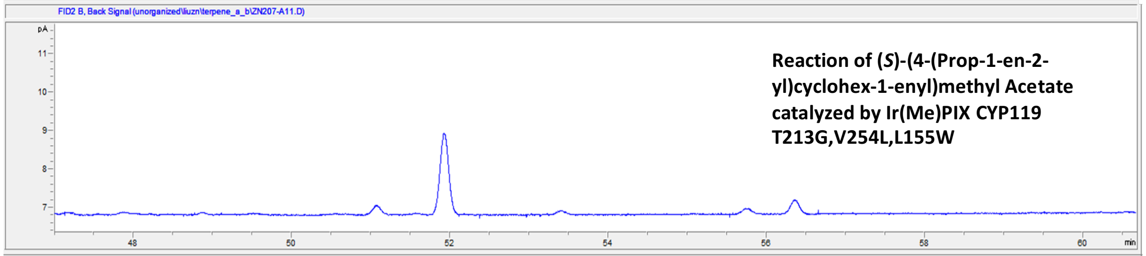




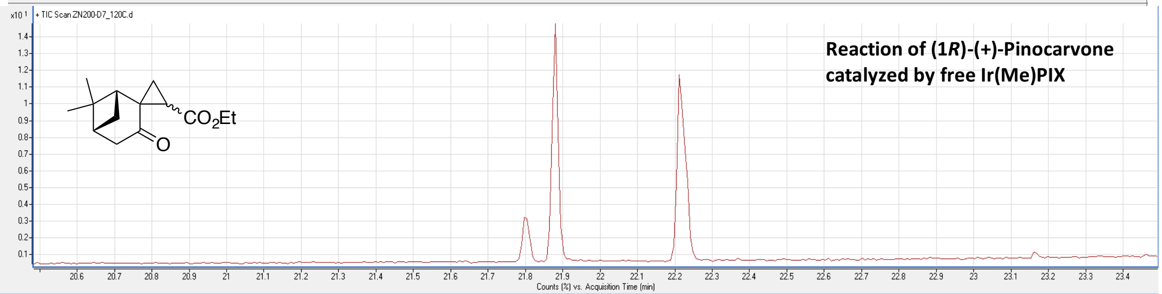
Signals firm additional injections: The GC analysis was performed in the MISER (multiple injections in a single experimental run) fashion, with multiple samples analyzed in parallel. [15] The additional signals in the blue box correspond to samples of other reactions.



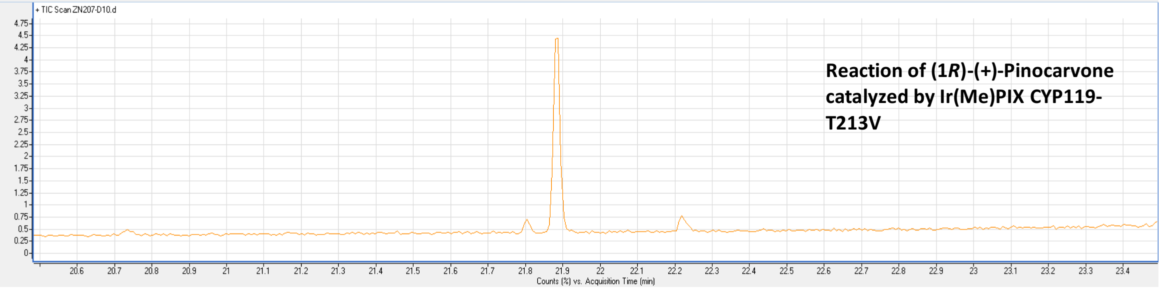
Reaction of (*S*)-(4-(Prop-1-en-2-yl)cyclohex-1-enyl)methyl Acetate catalyzed by free Ir(Me)PIX



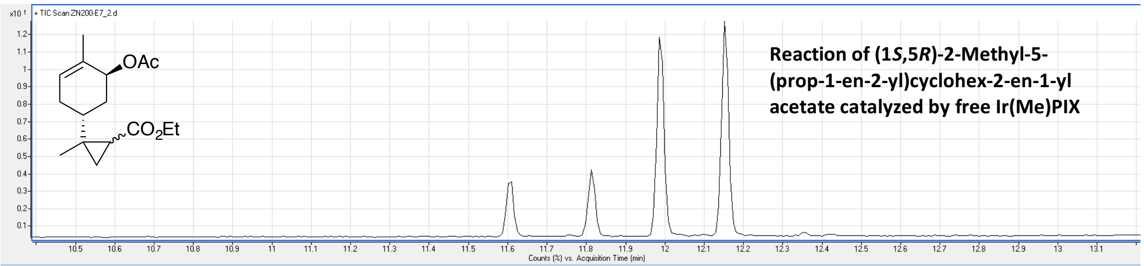
Reaction of (*S*)-(4-(Prop-1-en-2-yl)cyclohex-1-enyl)methyl Acetate catalyzed by Ir(Me)PIX CYP119 T213G,V254L,L155W



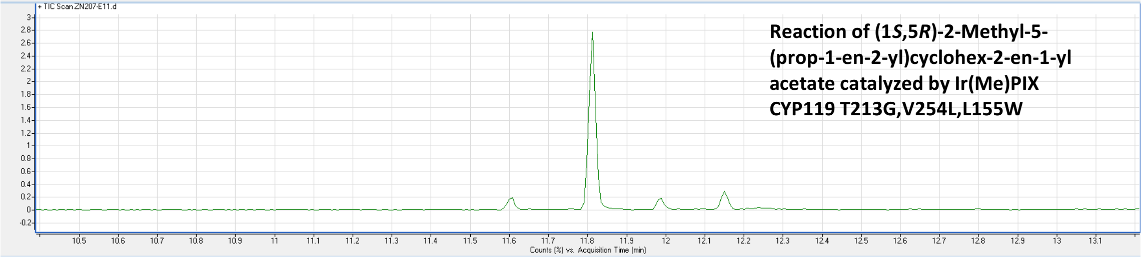
Reaction of (1*R*)-(+)-Pinocarvone catalyzed by free Ir(Me)PIX



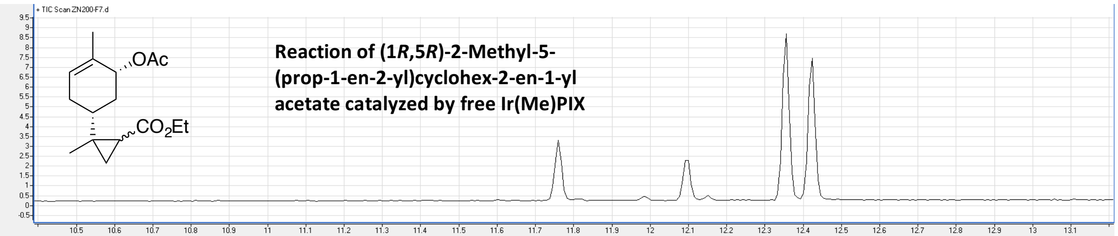
Reaction of (1*R*)-(+)-Pinocarvone catalyzed by Ir(Me)PIX CYP119-T213V

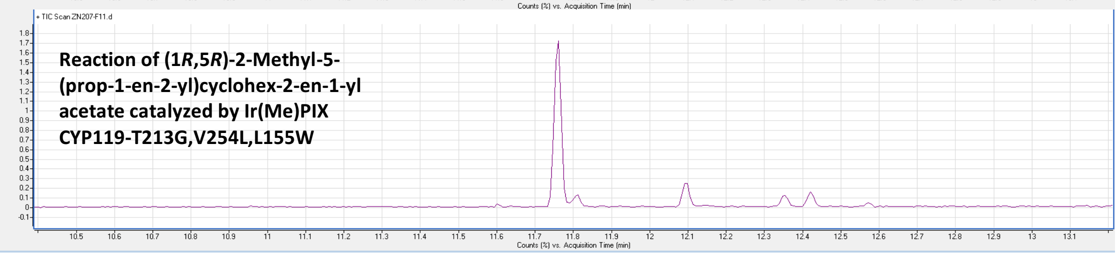


Reaction of (1*S*,5*R*)-2-Methyl-5-(prop-1-en-2-yl)cyclohex-2-en-1-yl acetate catalyzed by free Ir(Me)PIX

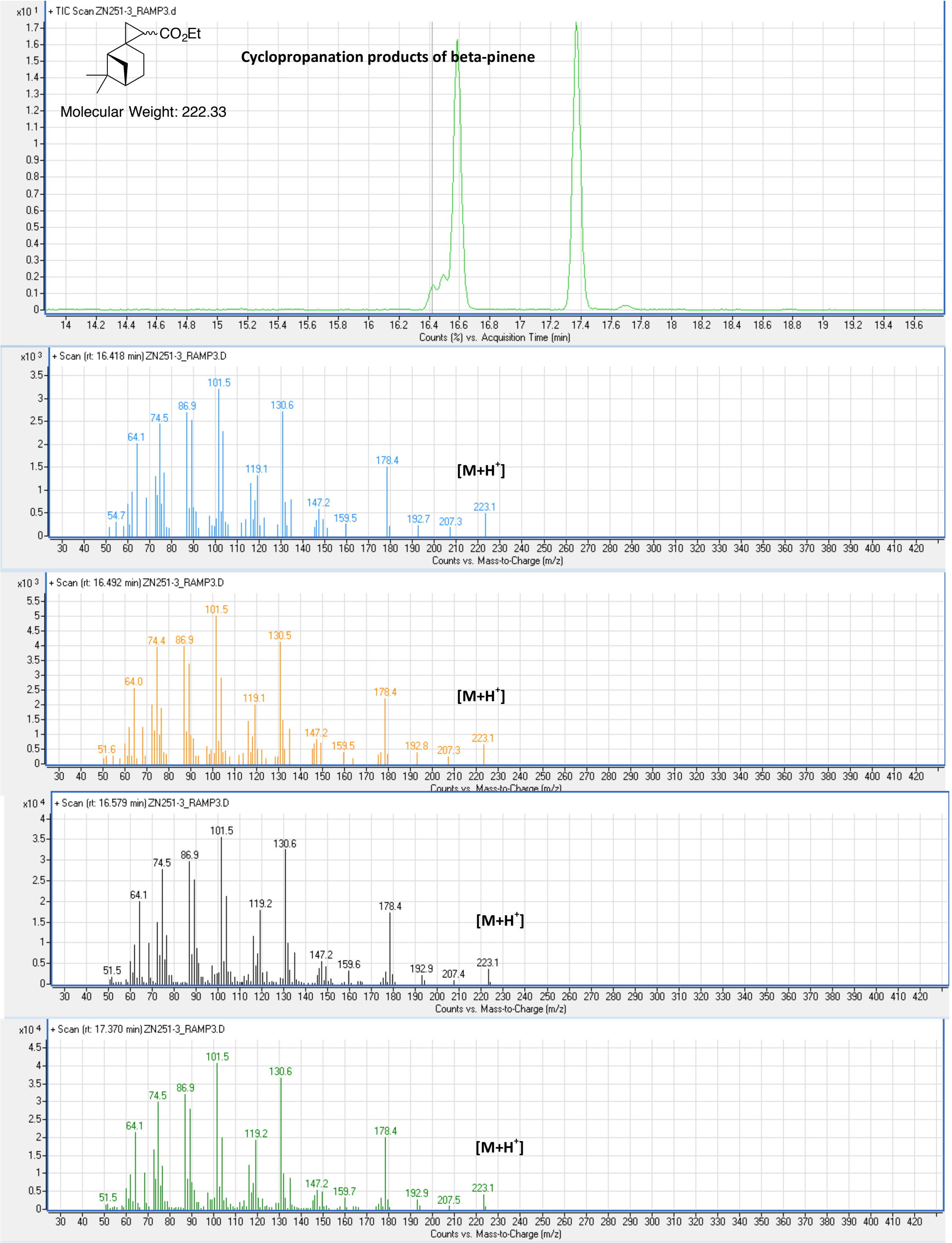


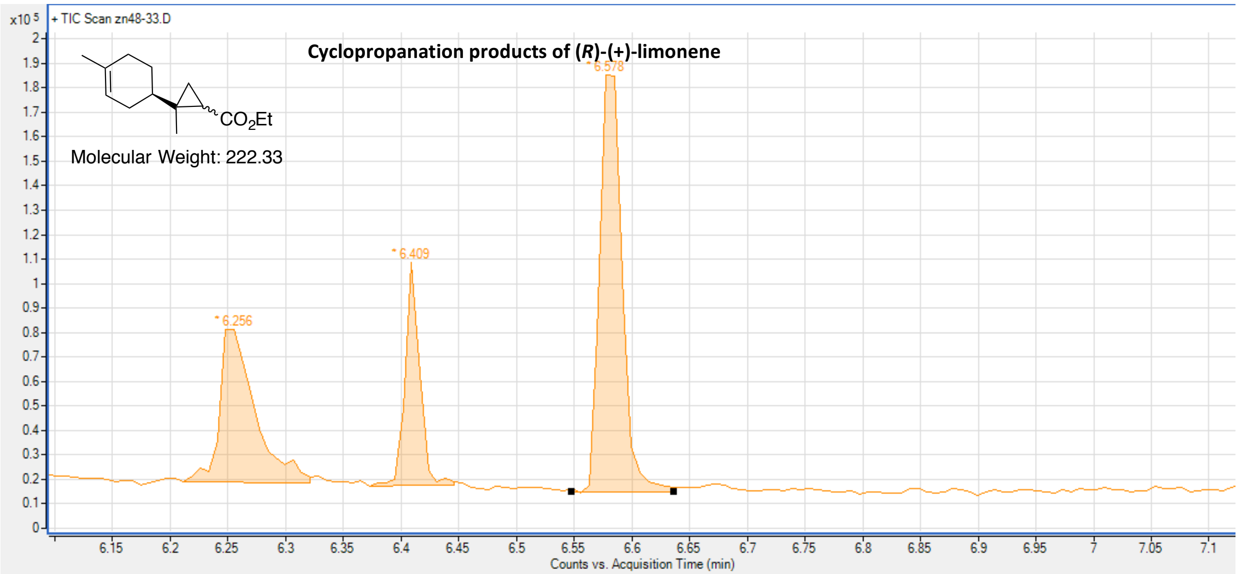
Reaction of (1*S*,5*R*)-2-Methyl-5-(prop-1-en-2-yl)cyclohex-2-en-1-yl acetate catalyzed by Ir(Me)PIX CYP119 T213G,V254L,L155W


Reaction of (1*R*,5*R*)-2-Methyl-5-(prop-1-en-2-yl)cyclohex-2-en-1-yl acetate catalyzed by free Ir(Me)PIX


Reaction of (1*R*,5*R*)-2-Methyl-5-(prop-1-en-2-yl)cyclohex-2-en-1-yl acetate catalyzed by Ir(Me)PIX CYP119-T213G,V254L,L155W

B. GC trace showing the ratio of cyclopropane diastereomers formed in reactions catalyzed by Ir(Me)-PIX cofactor and GC-MS traces used to identify the products.

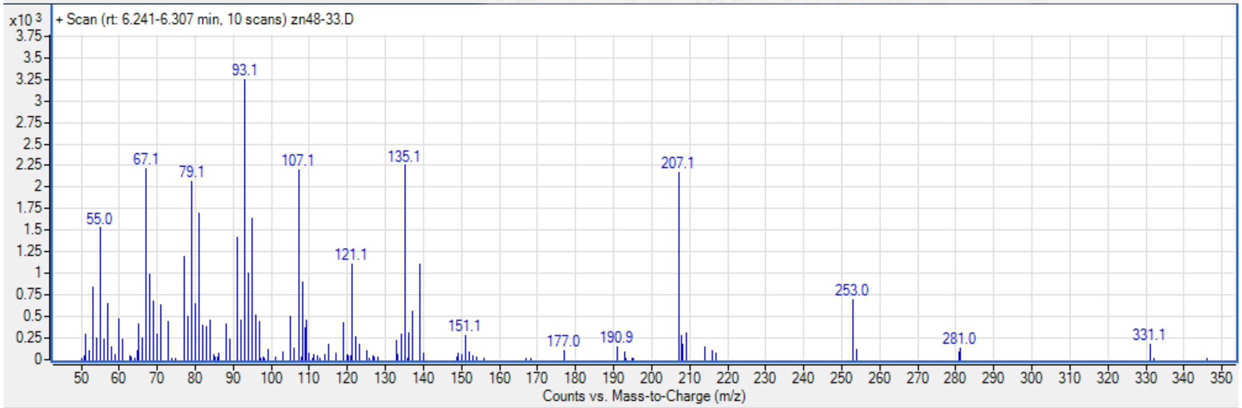




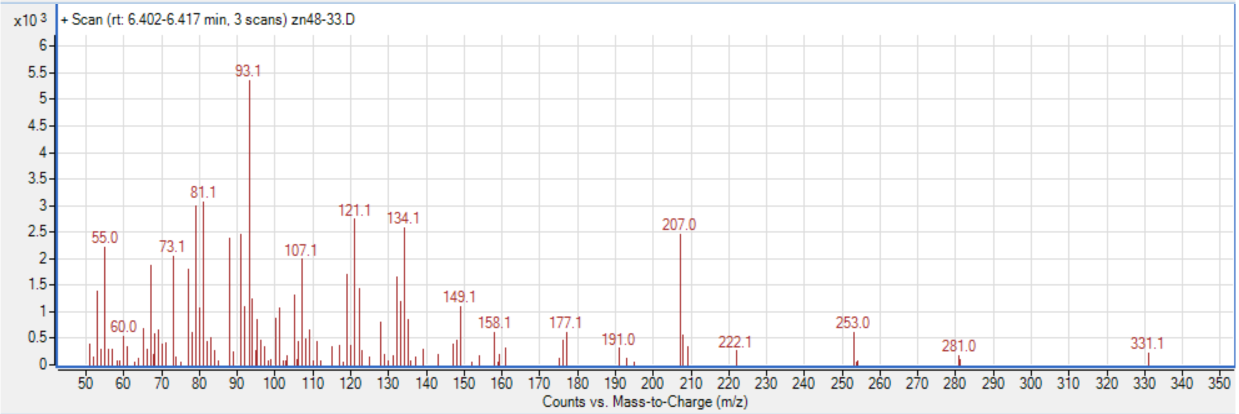
+ TIC Scan zn48-33.D

Cyclopropanation products of (*R*)-(+)-limonene

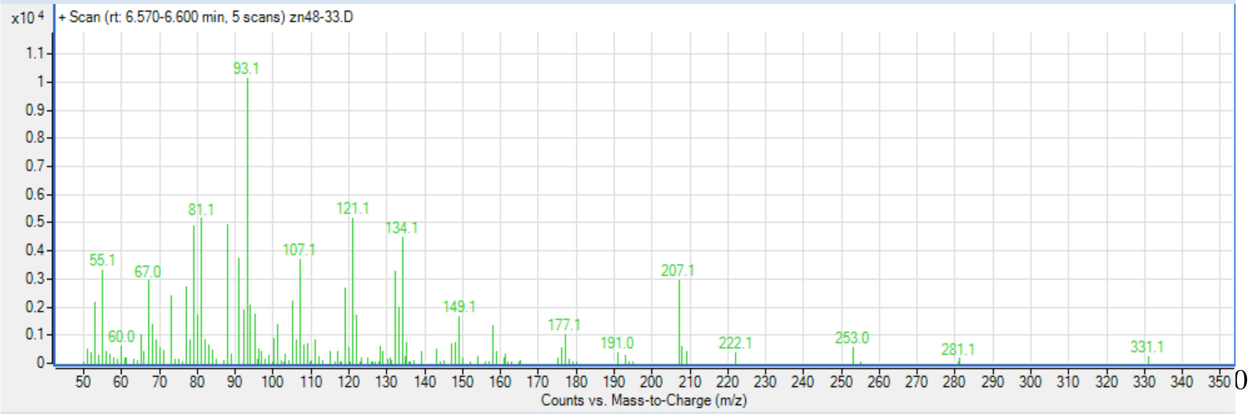
Molecular Weight: 222.33



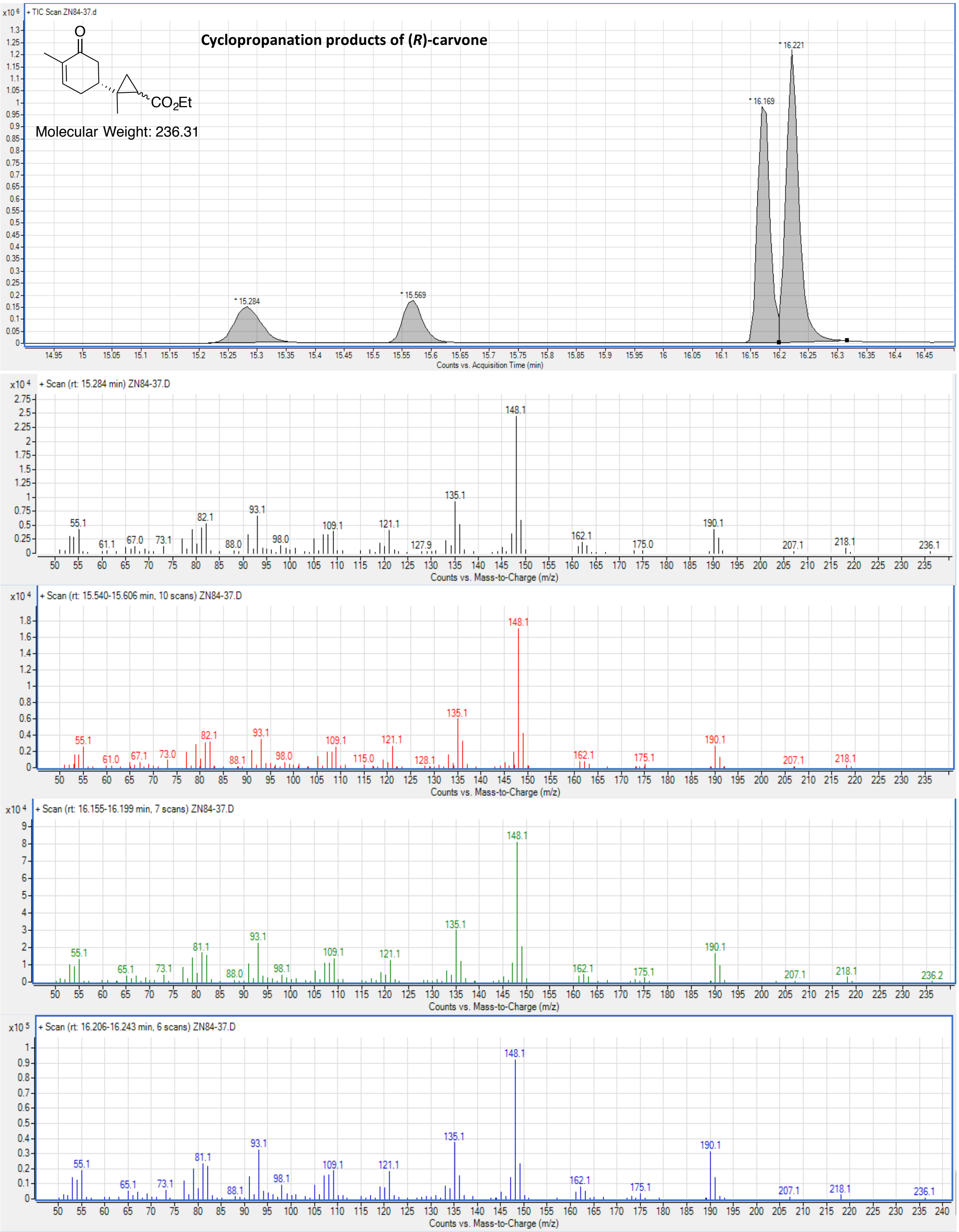
+ Scan (rt: 6.241-6.307 min, 10 scans) zn48-33.D

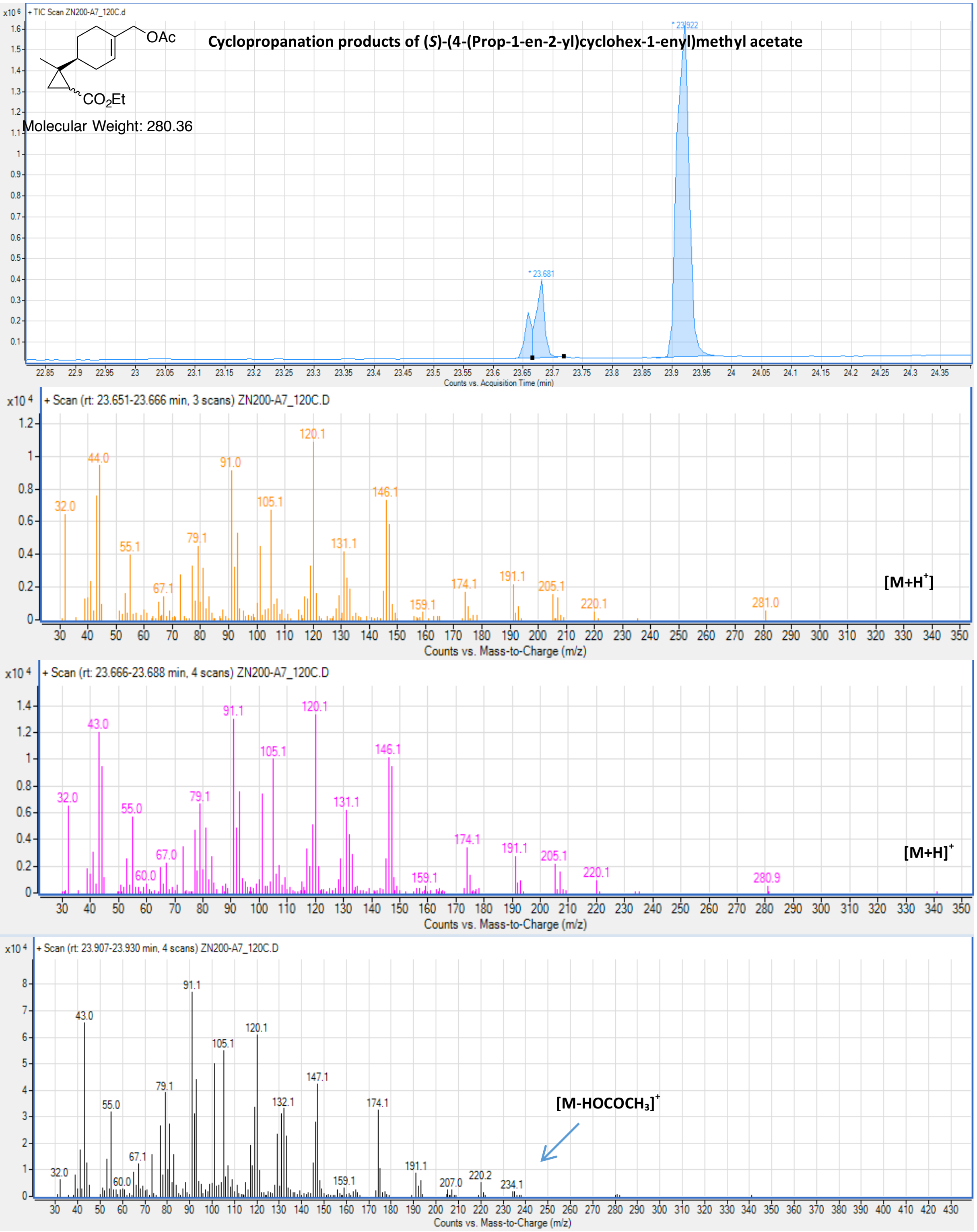


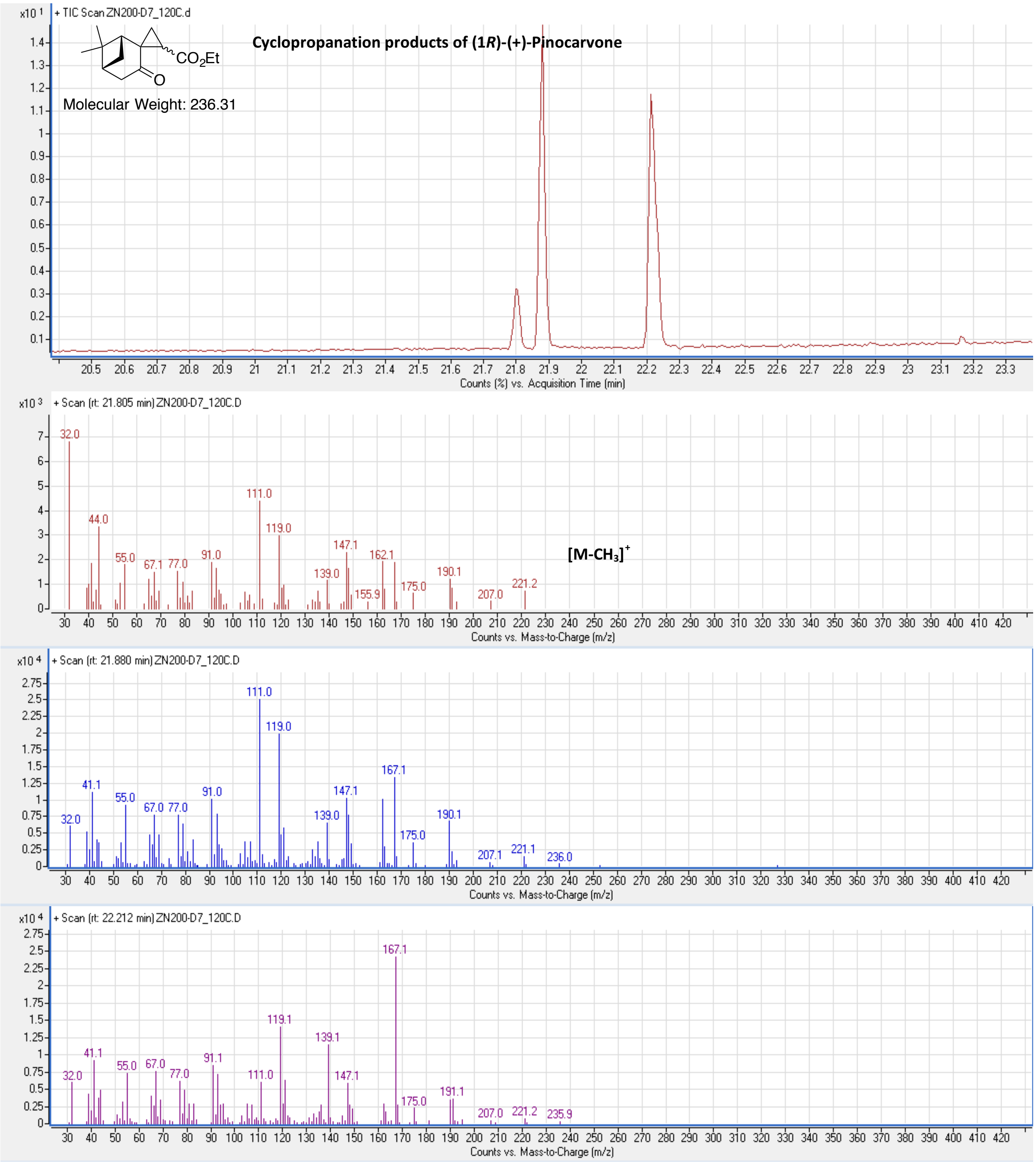
+ Scan (rt: 6.402-6.417 min, 3 scans) zn48-33.D

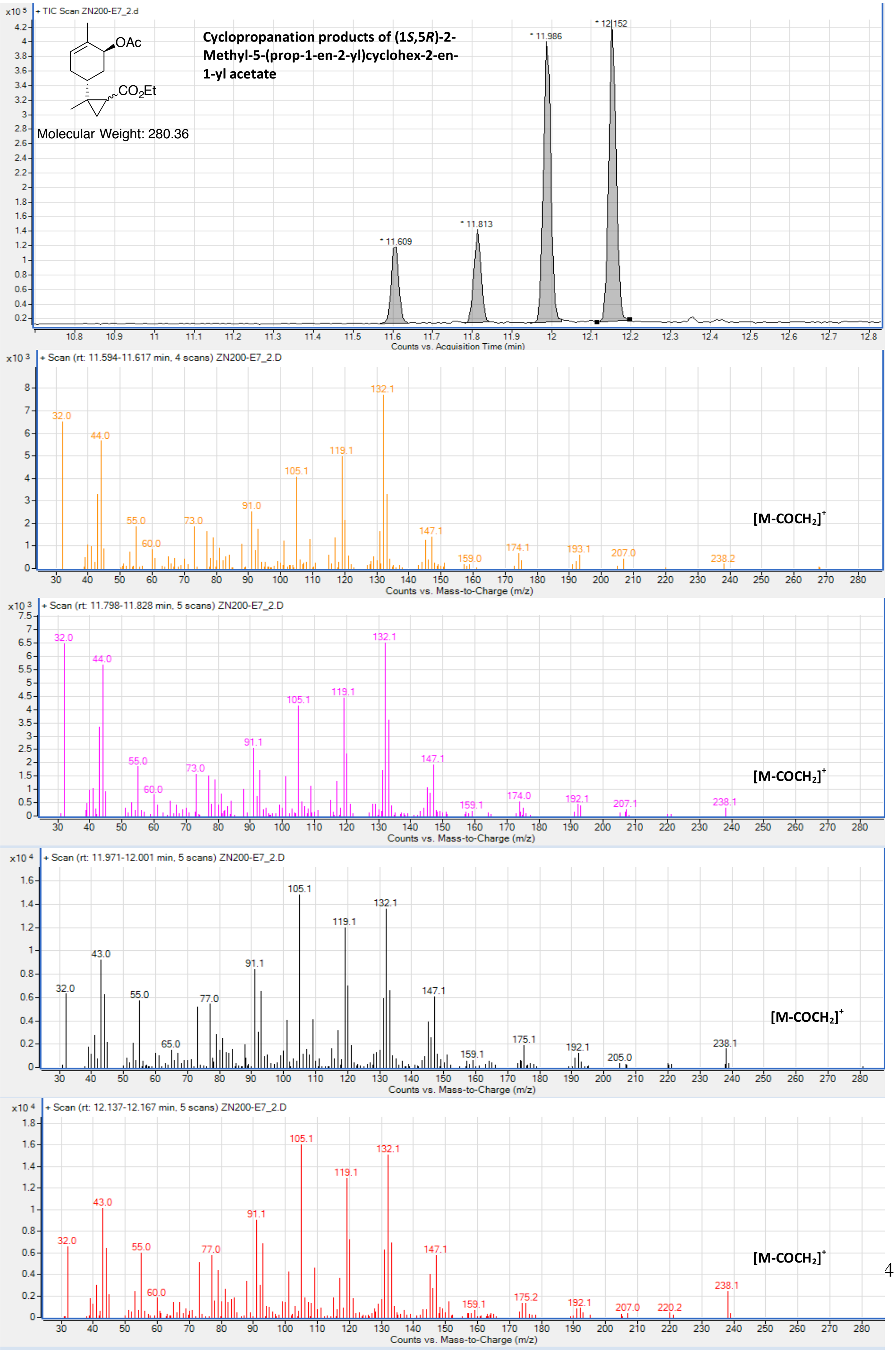


+ Scan (rt: 6.570-6.600 min, 5 scans) zn48-33.D

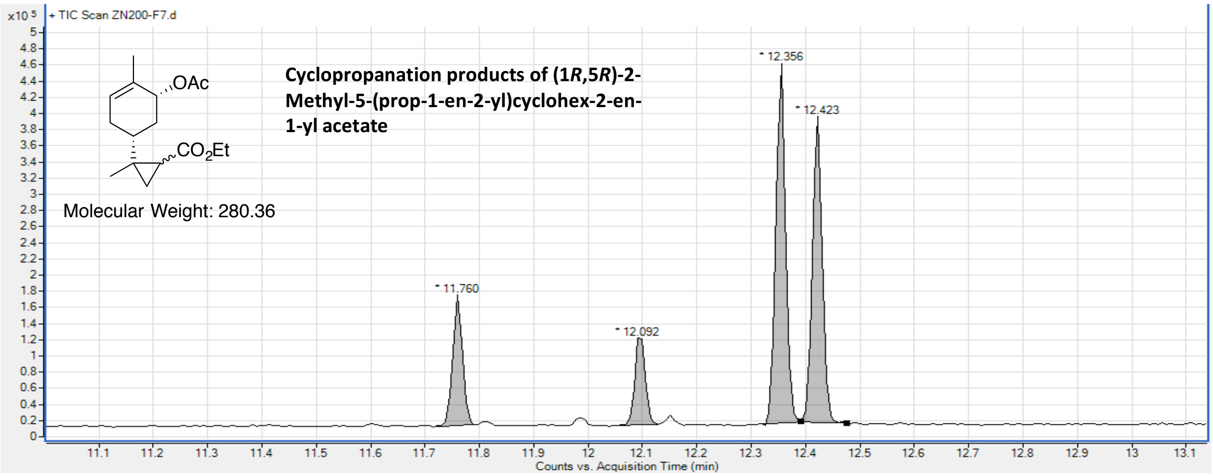

+ TIC Scan ZN84-37.d
x10 6
Cyclopropanation products of (R)-carvone
O
CO2Et
Molecular Weight: 236.31
15.284
15.569
16.169
16.221
Counts vs. Acquisition Time (min)
x10 4
+ Scan (rt: 15.284 min) ZN84-37.D
55.1
61.1
67.0
73.1
82.1
88.0
93.1
98.0
109.1
121.1
127.9
135.1
148.1
162.1
175.0
190.1
207.1
218.1
236.1
Counts vs. Mass-to-Charge (m/z)
x10 4
+ Scan (rt: 15.540-15.606 min, 10 scans) ZN84-37.D
55.1
61.0
67.1
73.0
82.1
88.1
93.1
98.0
109.1
115.0
121.1
128.1
135.1
148.1
162.1
175.1
190.1
207.1
218.1
Counts vs. Mass-to-Charge (m/z)
x10 4
+ Scan (rt: 16.155-16.199 min, 7 scans) ZN84-37.D
55.1
65.1
73.1
81.1
88.0
93.1
98.1
109.1
121.1
135.1
148.1
162.1
175.1
190.1
207.1
218.1
236.2
Counts vs. Mass-to-Charge (m/z)
x10 5
+ Scan (rt: 16.206-16.243 min, 6 scans) ZN84-37.D
55.1
65.1
73.1
81.1
88.1
93.1
98.1
109.1
121.1
135.1
148.1
162.1
175.1
190.1
207.1
218.1
236.1
Counts vs. Mass-to-Charge (m/z)

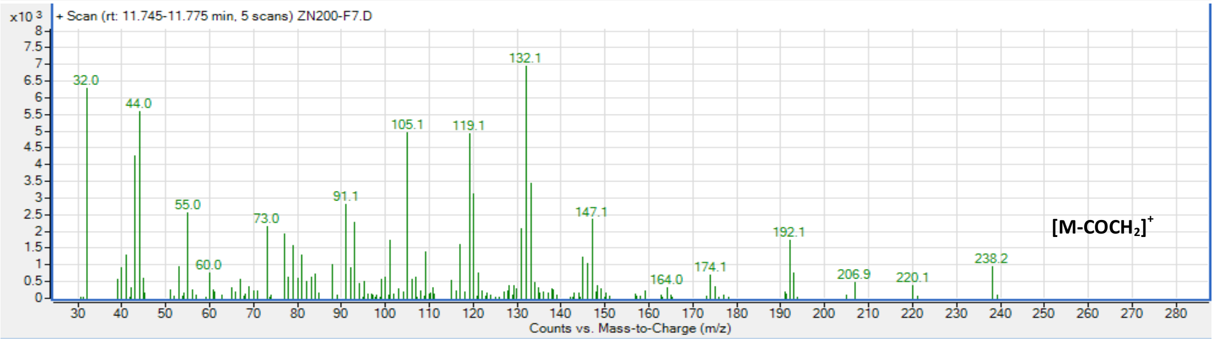

x10 6
+ TIC Scan ZN200-A7_120C.d
OAc
CO_2Et
Cyclopropanation products of (*S*)-(4-(Prop-1-en-2-yl)cyclohex-1-enyl)methyl acetate
Molecular Weight: 280.36
* 23.922
* 23.681
1.6 1.5 1.4 1.3 1.2 1.1 1 0.9 0.8 0.7 0.6 0.5 0.4 0.3 0.2 0.1
22.85 22.9 22.95 23 23.05 23.1 23.15 23.2 23.25 23.3 23.35 23.4 23.45 23.5 23.55 23.6 23.65 23.7 23.75 23.8 23.85 23.9 23.95 24 24.05 24.1 24.15 24.2 24.25 24.3 24.35
Counts vs. Acquisition Time (min)
x10 4
+ Scan (rt: 23.651-23.666 min, 3 scans) ZN200-A7_120C.D
1.2 1 0.8 0.6 0.4 0.2 0
32.0
44.0
55.1
67.1
79.1
91.0
105.1
120.1
131.1
146.1
159.1
174.1
191.1
205.1
220.1
281.0
[M+H⁺]
30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180 190 200 210 220 230 240 250 260 270 280 290 300 310 320 330 340 350
Counts vs. Mass-to-Charge (m/z)
x10 4
+ Scan (rt: 23.666-23.688 min, 4 scans) ZN200-A7_120C.D
1.4 1.2 1 0.8 0.6 0.4 0.2 0
32.0
43.0
55.0
60.0
67.0
79.1
91.1
105.1
120.1
131.1
146.1
159.1
174.1
191.1
205.1
220.1
280.9
$[M+H]^+$
30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180 190 200 210 220 230 240 250 260 270 280 290 300 310 320 330 340 350
Counts vs. Mass-to-Charge (m/z)
x10 4
+ Scan (rt: 23.907-23.930 min, 4 scans) ZN200-A7_120C.D
8 7 6 5 4 3 2 1 0
32.0
43.0
55.0
60.0
67.1
79.1
91.1
105.1
120.1
132.1
147.1
159.1
174.1
191.1
207.0
220.2
234.1
$[M-HOCOCH_3]^+$
30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180 190 200 210 220 230 240 250 260 270 280 290 300 310 320 330 340 350 360 370 380 390 400 410 420 430
Counts vs. Mass-to-Charge (m/z)

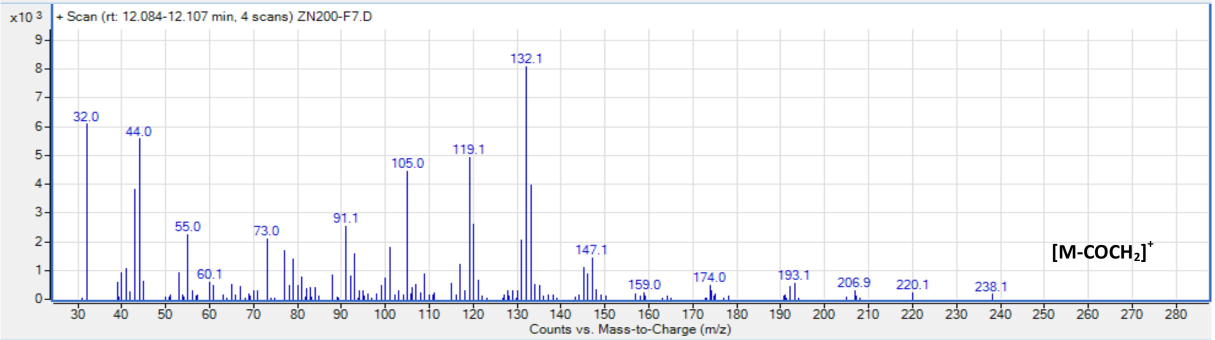

x10 1 + TIC Scan ZN200-D7_120C.d
CO2Et
O
Molecular Weight: 236.31
Cyclopropanation products of (1R)-(+)-Pinocarvone
Counts (%) vs. Acquisition Time (min)
x10 3 + Scan (rt: 21.805 min) ZN200-D7_120C.D
32.0
44.0
55.0
67.1
77.0
91.0
111.0
119.0
139.0
147.1
155.9
162.1
175.0
190.1
207.0
221.2
[M-CH3]+
Counts vs. Mass-to-Charge (m/z)
x10 4 + Scan (rt: 21.880 min) ZN200-D7_120C.D
32.0
41.1
55.0
67.0
77.0
91.0
111.0
119.0
139.0
147.1
167.1
175.0
190.1
207.1
221.1
236.0
Counts vs. Mass-to-Charge (m/z)
x10 4 + Scan (rt: 22.212 min) ZN200-D7_120C.D
32.0
41.1
55.0
67.0
77.0
91.1
111.0
119.1
139.1
147.1
167.1
175.0
191.1
207.0
221.2
235.9
Counts vs. Mass-to-Charge (m/z)

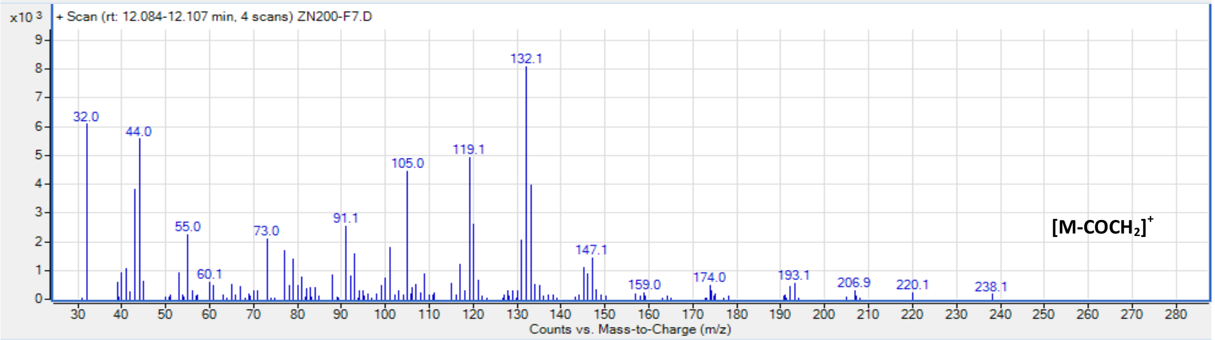


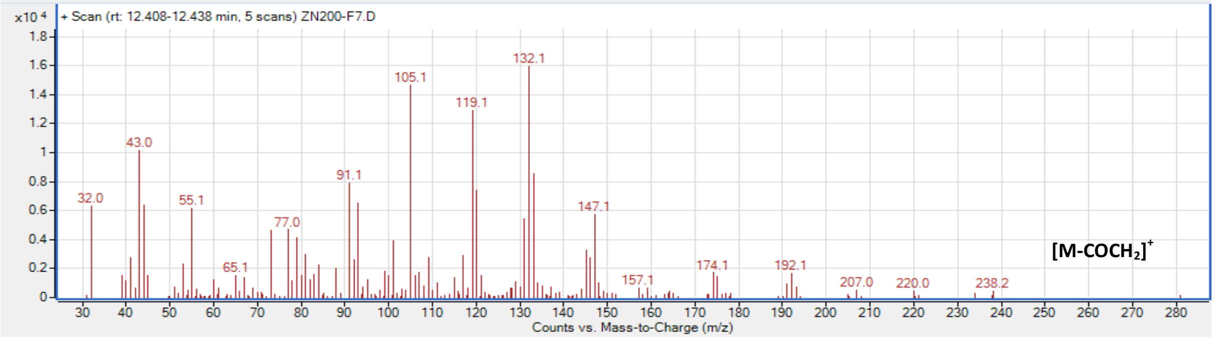
x10 5
+ TIC Scan ZN200-E7_2.d
OAc
CO2Et
Molecular Weight: 280.36
Cyclopropanation products of (1S,5R)-2-Methyl-5-(prop-1-en-2-yl)cyclohex-2-en-1-yl acetate
11.609
11.813
11.986
12.152
Counts vs. Acquisition Time (min)
x10 3
+ Scan (rt: 11.594-11.617 min, 4 scans) ZN200-E7_2.D
32.0
44.0
55.0
60.0
73.0
91.0
105.1
119.1
132.1
147.1
159.0
174.1
193.1
207.0
238.2
[M-COCH2]+
Counts vs. Mass-to-Charge (m/z)
x10 3
+ Scan (rt: 11.798-11.828 min, 5 scans) ZN200-E7_2.D
32.0
44.0
55.0
60.0
73.0
91.1
105.1
119.1
132.1
147.1
159.1
174.0
192.1
207.1
238.1
[M-COCH2]+
Counts vs. Mass-to-Charge (m/z)
x10 4
+ Scan (rt: 11.971-12.001 min, 5 scans) ZN200-E7_2.D
32.0
43.0
55.0
65.0
77.0
91.1
105.1
119.1
132.1
147.1
159.1
175.1
192.1
205.0
238.1
[M-COCH2]+
Counts vs. Mass-to-Charge (m/z)
x10 4
+ Scan (rt: 12.137-12.167 min, 5 scans) ZN200-E7_2.D
32.0
43.0
55.0
60.0
77.0
91.1
105.1
119.1
132.1
147.1
159.1
175.2
192.1
207.0
220.2
238.1
[M-COCH2]+
Counts vs. Mass-to-Charge (m/z)


x10 5
+ TIC Scan ZN200-F7.d
OAc
CO_2Et
Molecular Weight: 280.36
Cyclopropanation products of (1*R*,5*R*)-2-Methyl-5-(prop-1-en-2-yl)cyclohex-2-en-1-yl acetate
11.760
12.092
12.356
12.423
Counts vs. Acquisition Time (min)

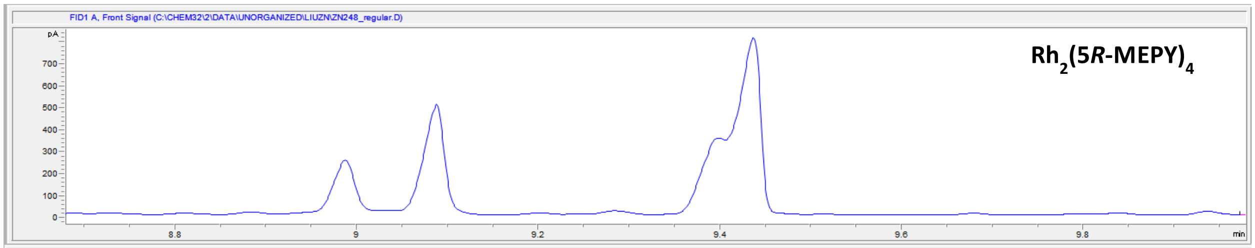

x10 3
+ Scan (rt: 11.745-11.775 min, 5 scans) ZN200-F7.D
32.0
44.0
55.0
60.0
73.0
91.1
105.1
119.1
132.1
147.1
164.0
174.1
192.1
206.9
220.1
238.2
[M-COCH$_2$]$^+$
Counts vs. Mass-to-Charge (m/z)

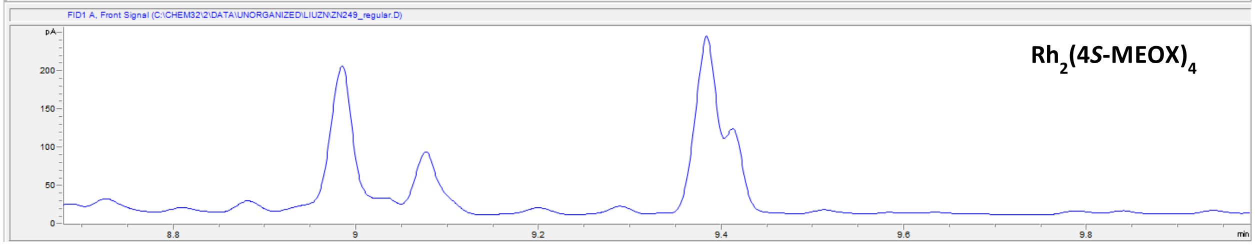

x10 3
+ Scan (rt: 12.084-12.107 min, 4 scans) ZN200-F7.D
32.0
44.0
55.0
60.1
73.0
91.1
105.0
119.1
132.1
147.1
159.0
174.0
193.1
206.9
220.1
238.1
[M-COCH$_2$]$^+$
Counts vs. Mass-to-Charge (m/z)


x10 3
+ Scan (rt: 12.084-12.107 min, 4 scans) ZN200-F7.D
32.0
44.0
55.0
60.1
73.0
91.1
105.0
119.1
132.1
147.1
159.0
174.0
193.1
206.9
220.1
238.1
[M-COCH$_2$]$^+$
Counts vs. Mass-to-Charge (m/z)


x10 4
+ Scan (rt: 12.408-12.438 min, 5 scans) ZN200-F7.D
32.0
43.0
55.1
65.1
77.0
91.1
105.1
119.1
132.1
147.1
157.1
174.1
192.1
207.0
220.0
238.2
[M-COCH$_2$]$^+$
Counts vs. Mass-to-Charge (m/z)

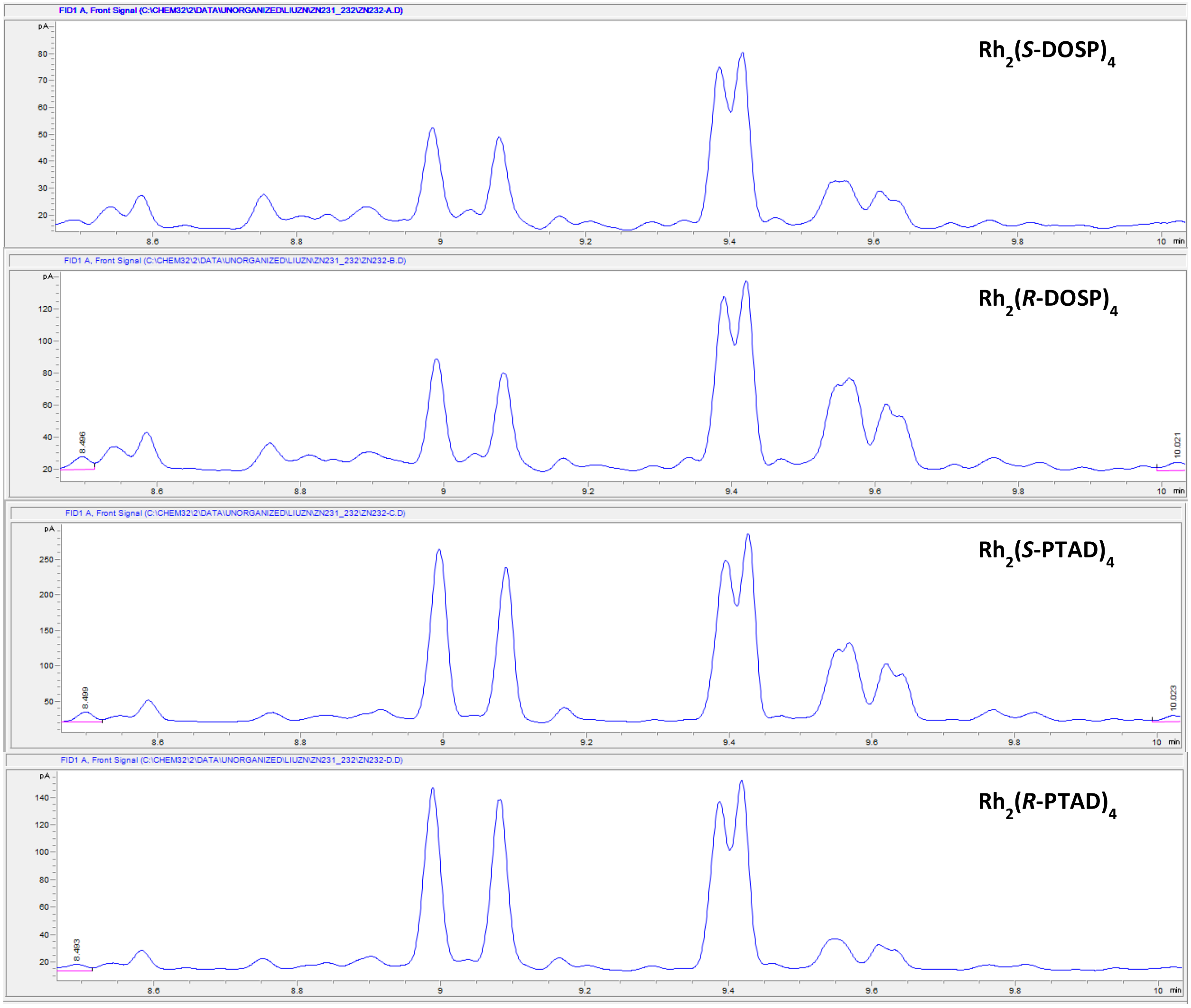
C. GC traces showing the outcome of cyclopropanation of (-)-carvone catalyzed by chiral rhodium catalysts at preparative scales (procedure see section IIId).





D. Cyclopropanation of (-)-carvone catalyzed by chiral rhodium catalysts at analytical scales.

Reaction conditions: Under nitrogen, a solution of alkene (10 mM, 1 equiv.) in dry DCM (1 mL) and Rh(II) catalyst (1 mol%, in 5 μL dry DMF) were mixed in a 4 mL vial. A solution of ethyl diazoacetate (3 equiv.) in DMF (20 μL) was added slowly to the vial through syringe pump while the reaction mixture was vigorously stirred. After complete addition of EDA, the reaction was stirred for 15 h. The volatile materials were then removed, and the residue was dissolved in EA and subjected to GC analysis.



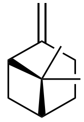
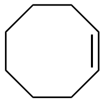
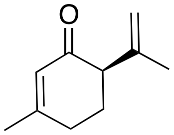
Supporting Tables

Table S1. Sequence information for heme proteins used in this study

Amino acid sequences of proteins evaluated in this study

Protein	Organism	Construction	Vector	Sequence
CYP 119	*Sulfolobus solfataricus*	6xHis-TEV-CYP119	2BT	EGDIHMKSSHHHHHHENLYFQSNAMYDWFSEMRKKDPVYYDGNIWQVFSYRYTKEVLNNFSKFSSDLTGYHERLEDLRNGKIRFDIPTRYTMLTSDPPLHDELRSMSADIFSPQKLQTLETFIRETTRSLLDSIDPREDDIVKKLAVPLPIIVISKILGLPIEDKEKFKEWSDLVAFRLGKPGEIFELGKKYLELIGYVKDHLNSGTEVVSRVVNSNLSDIEKLGYIILLLIAGNETTTNLISNSVIDFTRFNLWQRIREENLYLKAIEEALRYSPPVMRTVRKTKERVKLGDQTIEEGEYVRVWIASANRDEEVFHDGEKFIPDRNPNPHLSFGSGIHLCLGAPLARLEARIAIEEFSKRFRHIEILDTEKVPNEVLNGYKRLVVRLKSNE

Table S2. Summary of reaction conditions for specific substrates.

Substrate	equiv. of EDA	Time for slow addition of EDA (h)	Mutant	Yield[a]	TON	Selectivity
	6	5	T213V	9%	46	6.6:1[c]
	6	5	T213G, V254L, L318F, L155W	7%	35	14:1[d]
	10	5	T213G, V254L, L155W	76%	380	8:1:1:1

Reaction condition: 10 mM alkene, EDA (X equiv., slow addition over 5 h), 0.2 mol% Ir(Me)PIX CYP119 mutant,1 mL NaPi buffer (100 mM, 100 mM NaCl, pH=6).

[a] The yields of the major products were measured with dodecane as internal standard. [b]The diastereoselectivity was analyzed by GC. [c]Only two major diastereomers were observed. [d]*cis*/*trans*.

Table S3. Cyclopropanation of carvone catalyzed by different catalysts.

Entry	Catalyst	Cat. loading	Carvone (mmol)	EDA (mmol)	Solvent volume	Slow addition time (h)	dr	GC yield with internal standard (isolated yield)
1	$Rh_2(OAc)_4$	0.2 mol%	5	5	11 mL DCM	5	-	(60%)
2	$Rh_2(OAc)_4$	0.5 mol%	10	2	15 mL DCM	5	1 : 1.1 : 1.7 : 1.1	50%
3	Rh_2(5*R*-MEPY)$_4$	0.5 mol%	10	2	9 mL DCM	5	1 : 2 : 1.7 : 3.4	13%
4	Rh_2(4*S*-MEOX)$_4$	0.5 mol%	10	2	9 mL DCM	5	2.6 : 1 : 3.4 : 1.2	24%
5	T213G, V254L, L155W	0.2 mol%	0.01	0.1	1 mL NaPi	2	80% de (major pdt)	76%
7	T213G, V254L, L155W	0.037 mol%	1	10 (+750 uL DMF)	66 mL NaPi	2	79% de (major pdt)	(52%)

Table S4. Methods used to separate enantiomers and/or diastereomers of the reaction products.

Products from EDA + Alkene	Instrument	Column	Method	Retention Times
Styrene	GC	CYCLOSIL-B (30m x 0.25mm x 0.25u)	Isothermal: 120 °C	Cis: isomer (1S,2R): t1= 36.9 min isomer (1R, 2S): t2= 40 min Trans: isomer (1R,2R): t1 =49.5 min isomer (1S,2S): t2 =50.2 min
alpha-methylstyrene	GC	CYCLOSIL-B (30m x 0.25mm x 0.25u)	Isothermal: 130 °C	Trans: isomer (1R, 2S): t1=29.0 min isomer (1S,2R): t2=29.5 min Cis: isomer (1S,2S): t1=37.2 min isomer (1R,2R): t2=39 min
trans-beta- methylstyrene	GC	CYCLOSIL-B (30m x 0.25mm x 0.25u)	Isothermal: 120 °C	Trans: 128 min Cis: t1=137 min t2=142 min
cis-beta-methylstyrene	GC	CYCLOSIL-B (30m x 0.25mm x 0.25u)	Isothermal: 110 °C	Trans: 92.5 min Cis: t1=99.2 min t2=100.8 min
1-octene	GC	CP-Chirocel Dex-CB (30m x 0.25mm x 0.25u)	Isothermal: 150 °C	Trans: 4.1 min Cis: isomer (1R,2R): t1=3.8 min isomer (1S,2S): t2= 3.9 min
cis-2-octene	GC	CP-Chirocel Dex-CB (30m x 0.25mm x 0.25u)	Isothermal: 120 °C	Trans: t1=20.1 min t2=20.4 min Cis: t1=11.7 min t2=11.9 min
1-Hexen-5-one	GC	CP-Chirocel Dex-CB (30m x 0.25mm x 0.25u)	Isothermal: 120 °C	Trans: t1=16.9 min t2=17.1 min Cis: t1=15.6 min t2=15.8 min
Methyl 3-cyclopentenecarboxylate	GC (achiral)	HP-5	Isothermal: 100 °C	t1=20.1 min t2=21.9 min t3=23.2 min t4=24.2 min
***cis*-cyclooctene**	GC (achiral)	HP-5	100 °C to 300 °C; Ramp: 14 °C/min	Cis: t1=6.7 min Trans: t2=6.9 min
***beta*-pinene**	GC (achiral)	HP-5	100 °C, 20 min; 100 °C - 120 °C, 1 °C/min; 120 °C -140 °C, 2 °C/min; 140 °C -200 °C, 5 °C/min;	t1=16.5min t2=16.7 min t3=17.3 min t4=19.5 min

			200 °C -250 °C, 10 °C/min; 250 °C -300 °C, 50 °C/min;	
(*R*)-(+)-Limonene	GC (achiral)	HP-5	Isothermal: 120 °C	t1=8.2 min t2=8.4 min t3=10.4 min t4=10.6 min
(*R*)-(−)-Carvone	GC (achiral)	HP-5	Isothermal: 140 °C	major isomer (1S,2R): t1=9.8 min minor isomers t2=10.4 min t3=12.3 min t4=12.5 min
(*S*)-(4-(Prop-1-en-2-yl)cyclohex-1-enyl)methyl acetate	GC (chiral)	CP-Chirocel Dex-CB (30m x 0.25mm x 0.25u)	100 °C, 5 min; 100 °C -150 °C, 2 °C/min; 150 °C -180 °C, 1 °C/min; 180 °C -200 °C, 75 °C/min	t1=51.1 min t2=51.9 min t3=55.7 min t4=56.4 min
(1*R*)-(+)-Pinocarvone	GC (achiral)	HP-5	Isothermal: 120 °C	t1=21.8 min t2=21.9 min t3=22.2 min* * - 2 diastereomers
(1*S*,5*R*)-2-Methyl-5-(prop-1-en-2-yl)cyclohex-2-en-1-yl acetate	GC (achiral)	HP-5	100 °C to 300 °C; Ramp: 14 °C/min	t1=11.6 min t2=11.8 min t3=12.0 min t4=12.12 min
(1*R*,5*R*)-2-Methyl-5-(prop-1-en-2-yl)cyclohex-2-en-1-yl acetate	GC (achiral)	HP-5	100 °C to 300 °C; Ramp: 14 °C/min	t1=11.8 min t2=12.1 min t3=12.3 min t4=12.4 min

Table S5. Complete data of reactions catalyzed by CYP119(+) and CYP119(-)

Alkene	CYP119 (+)			CYP119 (-)			Free Ir(Me)-PIX	
	ee	dr (cis : trans)	Yield (GC)	ee	dr (cis : trans)	Yield (GC)	ee	dr (cis : trans)
Styrene	73%	2: 1	40%	-74%	5 : 1	49%	0%	1 : 4
a-Me Styrene	82%	11 : 1	11%	-86%	3 : 1	15%	0%	1 : 2
cis b-Me Styrene	75%	27 : 1*	5%	-18%	40 : 1*	7%	0%	10 : 1*
trans b-Me Styrene	86%	13 : 1**	2%	-32%	4 : 1**	2%	0%	1 : >25**
Hexen-5-one	79%	4 : 1	37%	-88%	8 : 1	50%	0%	1 : 4
Cyclopentene **8**	---	2 : 1 : t : t***	2%	---	228 : 1 : t : 1 ***	79%	---	3 : 1 : 1 : 3***
1-Octene	66%	4 : 1	2%	-78%	6 : 1	5%	0%	1 : 4
Cis-2-octene	39%	8 : 1**	1%	-60%	1 : 1**	1%	0%	5 : 1**

CYP119 (+): Ir(Me)-PIX CYP119 with the mutations C317G, V254A

CYP119 (-): Ir(Me)-PIX CYP119 with the mutations C317G, L69F, T213V

*2-c,3-c : 2-t, 3-t, Ref = COOEt ; **2-c,3-c : 2-t, 3-t, Ref = COOEt

***minor pdts not determined, major product shown as compound **9**, t = trace

Table S6. Crystal data and structure refinement

X-ray ID		
Sample/notebook ID	ZNII19-1	
Empirical formula	C15 H23 N3 O3	
Formula weight	293.36	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	Orthorhombic	
Space group	P 21 21 21	
Unit cell dimensions	a = 16.7445(6) Å	a= 90°.
	b = 18.3357(7) Å	b= 90°.
	c = 27.3157(10) Å	c = 90°.
Volume	8386.5(5) Å^3	
Z	16	
Density (calculated)	0.929 Mg/m^3	
Absorption coefficient	0.533 mm^{-1}	
F(000)	2528	
Crystal size	0.120 x 0.050 x 0.050 mm^3	
Theta range for data collection	2.903 to 68.372°.	
Index ranges	-19<=h<=20, -22<=k<=22, -32<=l<=28	
Reflections collected	107730	
Independent reflections	15368 [R(int) = 0.0402]	
Completeness to theta = 67.000°	100.0 %	

Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.929 and 0.817
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	15368 / 0 / 769
Goodness-of-fit on F^2	1.085
Final R indices [I>2sigma(I)]	R1 = 0.0487, wR2 = 0.1453
R indices (all data)	R1 = 0.0529, wR2 = 0.1504
Absolute structure parameter	0.06(4)
Extinction coefficient	n/a
Largest diff. peak and hole	0.533 and -0.277 e.Å^{-3}

Table S7. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^{2}x 10^3) for hartwig152. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	7458(2)	7463(2)	540(1)	36(1)
C(2)	7653(2)	8227(2)	637(1)	39(1)
C(3)	7841(2)	8673(2)	265(1)	44(1)
C(4)	7816(2)	8444(2)	-260(1)	47(1)
C(5)	7228(2)	7824(2)	-336(1)	38(1)
C(6)	7420(2)	7200(2)	18(1)	38(1)
C(7)	7052(2)	5917(2)	1272(1)	36(1)
C(8)	7653(2)	8492(2)	1159(1)	49(1)
C(9)	7185(2)	7579(2)	-866(1)	44(1)
C(10)	7936(2)	7243(2)	-1076(1)	57(1)
C(11)	6653(2)	7989(2)	-1201(1)	50(1)
C(12)	6410(2)	7230(2)	-1050(1)	42(1)
C(13)	5731(2)	7131(2)	-704(1)	41(1)
C(14)	4907(2)	6238(2)	-320(2)	65(1)
C(15)	5227(4)	6080(4)	144(3)	102(2)
C(16)	9238(2)	4826(2)	2813(1)	40(1)
C(17)	10030(2)	4485(2)	2766(1)	51(1)
C(18)	10500(2)	4653(2)	2378(1)	62(1)
C(19)	10285(2)	5183(2)	1995(1)	60(1)
C(20)	9662(2)	5736(2)	2174(1)	41(1)
C(21)	8959(2)	5325(2)	2411(1)	38(1)
C(22)	7714(2)	4850(2)	3695(1)	35(1)
C(23)	10278(2)	3934(3)	3145(2)	68(1)
C(24)	9393(2)	6241(2)	1765(1)	43(1)
C(25)	9118(2)	5884(2)	1293(1)	54(1)
C(26)	9806(2)	6965(2)	1723(1)	62(1)
C(27)	8941(2)	6942(2)	1892(1)	46(1)
C(28)	8752(2)	7132(2)	2401(1)	52(1)
C(29)	7704(5)	7554(7)	2911(3)	148(4)
C(30)	7443(8)	7025(6)	3165(4)	181(6)
C(31)	5246(2)	3759(2)	3263(1)	44(1)

C(32)	4766(2)	3087(2)	3217(1)	61(1)
C(33)	4496(2)	2754(2)	3619(1)	59(1)
C(34)	4625(2)	3027(2)	4128(1)	49(1)
C(35)	4710(2)	3855(2)	4131(1)	42(1)
C(36)	5350(2)	4093(2)	3762(1)	37(1)
C(37)	6393(2)	4892(2)	2496(1)	41(1)
C(38)	4620(4)	2789(3)	2709(2)	94(2)
C(39)	4876(2)	4142(2)	4644(1)	45(1)
C(40)	5609(2)	3850(2)	4896(1)	50(1)
C(41)	4174(2)	4345(2)	4955(1)	59(1)
C(42)	4694(2)	4944(2)	4753(1)	55(1)
C(43)	4402(2)	5409(2)	4361(2)	65(1)
C(44)	4773(5)	6366(4)	3819(4)	147(4)
C(45)	5365(10)	6688(9)	3642(5)	248(10)
C(46)	6190(2)	6180(2)	6031(1)	44(1)
C(47)	5427(3)	6562(2)	6105(1)	61(1)
C(48)	5306(3)	6943(2)	6520(1)	67(1)
C(49)	5925(3)	7058(2)	6901(1)	68(1)
C(50)	6764(2)	6953(2)	6698(1)	54(1)
C(51)	6809(2)	6224(2)	6424(1)	45(1)
C(52)	7078(2)	5149(1)	5090(1)	35(1)
C(53)	4795(3)	6484(3)	5722(2)	81(1)
C(54)	7405(3)	7034(2)	7085(1)	62(1)
C(55)	7310(3)	6583(2)	7540(1)	68(1)
C(56)	7782(4)	7767(2)	7142(2)	97(2)
C(57)	8266(3)	7150(2)	6924(2)	77(1)
C(58)	8463(4)	7135(3)	6396(2)	85(2)
C(59)	9209(5)	6488(5)	5796(2)	121(3)
C(60)	9696(8)	5853(5)	5758(3)	167(5)
N(1)	7347(1)	7057(1)	923(1)	36(1)
N(2)	7177(1)	6328(1)	860(1)	37(1)
N(3)	7012(2)	6274(1)	1697(1)	39(1)
N(4)	8845(1)	4660(1)	3202(1)	40(1)
N(5)	8082(1)	4935(1)	3253(1)	37(1)
N(6)	8148(2)	4575(2)	4057(1)	44(1)
N(7)	5570(2)	4006(2)	2870(1)	49(1)

N(8)	6057(2)	4611(2)	2910(1)	42(1)
N(9)	6120(2)	4651(2)	2063(1)	51(1)
N(10)	6264(2)	5837(1)	5621(1)	42(1)
N(11)	6941(2)	5425(1)	5548(1)	38(1)
N(12)	6660(1)	5444(1)	4723(1)	39(1)
O(1)	6975(1)	5244(1)	1235(1)	41(1)
O(2)	5401(1)	7605(1)	-483(1)	50(1)
O(3)	5537(1)	6426(1)	-666(1)	52(1)
O(4)	6998(1)	5031(1)	3743(1)	37(1)
O(5)	9209(2)	7126(2)	2743(1)	64(1)
O(6)	7986(2)	7323(2)	2437(1)	91(1)
O(7)	6925(1)	5363(1)	2533(1)	40(1)
O(8)	3792(2)	5333(2)	4127(2)	93(1)
O(9)	4935(2)	5945(2)	4264(2)	83(1)
O(10)	7587(1)	4662(1)	5032(1)	38(1)
O(11)	8169(3)	7496(2)	6079(1)	107(1)
O(12)	9023(3)	6622(2)	6301(1)	95(1)

Table S8. Bond lengths [Å] and angles [°] for hartwig152.

C(1)-N(1)	1.297(4)	C(14)-C(15)	1.405(8)
C(1)-C(2)	1.463(4)	C(14)-O(3)	1.459(4)
C(1)-C(6)	1.507(4)	C(14)-H(14A)	0.9900
C(2)-C(3)	1.341(4)	C(14)-H(14B)	0.9900
C(2)-C(8)	1.507(4)	C(15)-H(15A)	0.9800
C(3)-C(4)	1.496(5)	C(15)-H(15B)	0.9800
C(3)-H(3)	0.9500	C(15)-H(15C)	0.9800
C(4)-C(5)	1.518(4)	C(16)-N(4)	1.287(4)
C(4)-H(4A)	0.9900	C(16)-C(17)	1.471(4)
C(4)-H(4B)	0.9900	C(16)-C(21)	1.502(4)
C(5)-C(9)	1.518(4)	C(17)-C(18)	1.356(5)
C(5)-C(6)	1.532(4)	C(17)-C(23)	1.504(5)
C(5)-H(5)	1.0000	C(18)-C(19)	1.473(5)
C(6)-H(6A)	0.9900	C(18)-H(18)	0.9500
C(6)-H(6B)	0.9900	C(19)-C(20)	1.534(5)
C(7)-O(1)	1.246(4)	C(19)-H(19A)	0.9900
C(7)-N(3)	1.335(4)	C(19)-H(19B)	0.9900
C(7)-N(2)	1.369(3)	C(20)-C(24)	1.518(4)
C(8)-H(8A)	0.9800	C(20)-C(21)	1.541(4)
C(8)-H(8B)	0.9800	C(20)-H(20)	1.0000
C(8)-H(8C)	0.9800	C(21)-H(21A)	0.9900
C(9)-C(11)	1.480(4)	C(21)-H(21B)	0.9900
C(9)-C(10)	1.514(4)	C(22)-O(4)	1.251(3)
C(9)-C(12)	1.532(4)	C(22)-N(6)	1.326(4)
C(10)-H(10A)	0.9800	C(22)-N(5)	1.364(3)
C(10)-H(10B)	0.9800	C(23)-H(23A)	0.9800
C(10)-H(10C)	0.9800	C(23)-H(23B)	0.9800
C(11)-C(12)	1.507(5)	C(23)-H(23C)	0.9800
C(11)-H(11A)	0.9900	C(24)-C(26)	1.500(5)
C(11)-H(11B)	0.9900	C(24)-C(25)	1.519(4)
C(12)-C(13)	1.490(4)	C(24)-C(27)	1.531(5)
C(12)-H(12)	1.0000	C(25)-H(25A)	0.9800
C(13)-O(2)	1.194(4)	C(25)-H(25B)	0.9800
C(13)-O(3)	1.337(4)	C(25)-H(25C)	0.9800

C(26)-C(27)	1.519(5)	C(39)-C(40)	1.507(5)
C(26)-H(26A)	0.9900	C(39)-C(42)	1.530(5)
C(26)-H(26B)	0.9900	C(40)-H(40A)	0.9800
C(27)-C(28)	1.469(5)	C(40)-H(40B)	0.9800
C(27)-H(27)	1.0000	C(40)-H(40C)	0.9800
C(28)-O(5)	1.206(4)	C(41)-C(42)	1.505(5)
C(28)-O(6)	1.334(5)	C(41)-H(41A)	0.9900
C(29)-C(30)	1.270(14)	C(41)-H(41B)	0.9900
C(29)-O(6)	1.443(6)	C(42)-C(43)	1.453(6)
C(29)-H(29A)	0.9900	C(42)-H(42)	1.0000
C(29)-H(29B)	0.9900	C(43)-O(8)	1.213(5)
C(30)-H(30A)	0.9800	C(43)-O(9)	1.354(5)
C(30)-H(30B)	0.9800	C(44)-C(45)	1.252(15)
C(30)-H(30C)	0.9800	C(44)-O(9)	1.466(9)
C(31)-N(7)	1.286(4)	C(44)-H(44A)	0.9900
C(31)-C(32)	1.477(4)	C(44)-H(44B)	0.9900
C(31)-C(36)	1.506(4)	C(45)-H(45A)	0.9800
C(32)-C(33)	1.335(5)	C(45)-H(45B)	0.9800
C(32)-C(38)	1.509(5)	C(45)-H(45C)	0.9800
C(33)-C(34)	1.493(5)	C(46)-N(10)	1.290(4)
C(33)-H(33)	0.9500	C(46)-C(47)	1.471(5)
C(34)-C(35)	1.525(4)	C(46)-C(51)	1.494(5)
C(34)-H(34A)	0.9900	C(47)-C(48)	1.347(5)
C(34)-H(34B)	0.9900	C(47)-C(53)	1.495(6)
C(35)-C(39)	1.522(4)	C(48)-C(49)	1.483(6)
C(35)-C(36)	1.534(4)	C(48)-H(48)	0.9500
C(35)-H(35)	1.0000	C(49)-C(50)	1.522(6)
C(36)-H(36A)	0.9900	C(49)-H(49A)	0.9900
C(36)-H(36B)	0.9900	C(49)-H(49B)	0.9900
C(37)-O(7)	1.246(4)	C(50)-C(54)	1.514(5)
C(37)-N(9)	1.344(4)	C(50)-C(51)	1.534(4)
C(37)-N(8)	1.362(4)	C(50)-H(50)	1.0000
C(38)-H(38A)	0.9800	C(51)-H(51A)	0.9900
C(38)-H(38B)	0.9800	C(51)-H(51B)	0.9900
C(38)-H(38C)	0.9800	C(52)-O(10)	1.244(3)
C(39)-C(41)	1.497(4)	C(52)-N(12)	1.336(4)

C(52)-N(11)	1.368(3)	C(59)-H(59B)	0.9900
C(53)-H(53A)	0.9800	C(60)-H(60A)	0.9800
C(53)-H(53B)	0.9800	C(60)-H(60B)	0.9800
C(53)-H(53C)	0.9800	C(60)-H(60C)	0.9800
C(54)-C(56)	1.493(6)	N(1)-N(2)	1.377(3)
C(54)-C(55)	1.502(6)	N(2)-H(2)	0.8800
C(54)-C(57)	1.521(7)	N(3)-H(3A)	0.8800
C(55)-H(55A)	0.9800	N(3)-H(3B)	0.8800
C(55)-H(55B)	0.9800	N(4)-N(5)	1.381(3)
C(55)-H(55C)	0.9800	N(5)-H(5A)	0.8800
C(56)-C(57)	1.513(8)	N(6)-H(6C)	0.8800
C(56)-H(56A)	0.9900	N(6)-H(6D)	0.8800
C(56)-H(56B)	0.9900	N(7)-N(8)	1.381(4)
C(57)-C(58)	1.479(7)	N(8)-H(8)	0.8800
C(57)-H(57)	1.0000	N(9)-H(9A)	0.8800
C(58)-O(11)	1.197(7)	N(9)-H(9B)	0.8800
C(58)-O(12)	1.353(8)	N(10)-N(11)	1.376(3)
C(59)-C(60)	1.425(13)	N(11)-H(11)	0.8800
C(59)-O(12)	1.435(7)	N(12)-H(12A)	0.8800
C(59)-H(59A)	0.9900	N(12)-H(12B)	0.8800

N(1)-C(1)-C(2)	115.9(2)	C(9)-C(5)-C(4)	112.5(2)
N(1)-C(1)-C(6)	125.0(2)	C(9)-C(5)-C(6)	113.1(2)
C(2)-C(1)-C(6)	119.1(2)	C(4)-C(5)-C(6)	109.7(2)
C(3)-C(2)-C(1)	120.1(3)	C(9)-C(5)-H(5)	107.1
C(3)-C(2)-C(8)	121.3(3)	C(4)-C(5)-H(5)	107.1
C(1)-C(2)-C(8)	118.6(3)	C(6)-C(5)-H(5)	107.1
C(2)-C(3)-C(4)	123.2(3)	C(1)-C(6)-C(5)	111.6(2)
C(2)-C(3)-H(3)	118.4	C(1)-C(6)-H(6A)	109.3
C(4)-C(3)-H(3)	118.4	C(5)-C(6)-H(6A)	109.3
C(3)-C(4)-C(5)	111.1(2)	C(1)-C(6)-H(6B)	109.3
C(3)-C(4)-H(4A)	109.4	C(5)-C(6)-H(6B)	109.3
C(5)-C(4)-H(4A)	109.4	H(6A)-C(6)-H(6B)	108.0
C(3)-C(4)-H(4B)	109.4	O(1)-C(7)-N(3)	123.4(2)
C(5)-C(4)-H(4B)	109.4	O(1)-C(7)-N(2)	119.6(2)
H(4A)-C(4)-H(4B)	108.0	N(3)-C(7)-N(2)	117.0(2)

C(2)-C(8)-H(8A)	109.5	C(15)-C(14)-H(14B)	109.4
C(2)-C(8)-H(8B)	109.5	O(3)-C(14)-H(14B)	109.4
H(8A)-C(8)-H(8B)	109.5	H(14A)-C(14)-H(14B)	108.0
C(2)-C(8)-H(8C)	109.5	C(14)-C(15)-H(15A)	109.5
H(8A)-C(8)-H(8C)	109.5	C(14)-C(15)-H(15B)	109.5
H(8B)-C(8)-H(8C)	109.5	H(15A)-C(15)-H(15B)	109.5
C(11)-C(9)-C(10)	118.2(3)	C(14)-C(15)-H(15C)	109.5
C(11)-C(9)-C(5)	117.9(3)	H(15A)-C(15)-H(15C)	109.5
C(10)-C(9)-C(5)	116.3(3)	H(15B)-C(15)-H(15C)	109.5
C(11)-C(9)-C(12)	60.0(2)	N(4)-C(16)-C(17)	115.6(3)
C(10)-C(9)-C(12)	114.2(3)	N(4)-C(16)-C(21)	126.0(3)
C(5)-C(9)-C(12)	118.5(2)	C(17)-C(16)-C(21)	118.4(2)
C(9)-C(10)-H(10A)	109.5	C(18)-C(17)-C(16)	119.6(3)
C(9)-C(10)-H(10B)	109.5	C(18)-C(17)-C(23)	122.0(3)
H(10A)-C(10)-H(10B)	109.5	C(16)-C(17)-C(23)	118.4(3)
C(9)-C(10)-H(10C)	109.5	C(17)-C(18)-C(19)	124.3(3)
H(10A)-C(10)-H(10C)	109.5	C(17)-C(18)-H(18)	117.9
H(10B)-C(10)-H(10C)	109.5	C(19)-C(18)-H(18)	117.9
C(9)-C(11)-C(12)	61.7(2)	C(18)-C(19)-C(20)	112.1(3)
C(9)-C(11)-H(11A)	117.6	C(18)-C(19)-H(19A)	109.2
C(12)-C(11)-H(11A)	117.6	C(20)-C(19)-H(19A)	109.2
C(9)-C(11)-H(11B)	117.6	C(18)-C(19)-H(19B)	109.2
C(12)-C(11)-H(11B)	117.6	C(20)-C(19)-H(19B)	109.2
H(11A)-C(11)-H(11B)	114.7	H(19A)-C(19)-H(19B)	107.9
C(13)-C(12)-C(11)	119.5(3)	C(24)-C(20)-C(19)	111.8(2)
C(13)-C(12)-C(9)	119.3(2)	C(24)-C(20)-C(21)	112.4(2)
C(11)-C(12)-C(9)	58.3(2)	C(19)-C(20)-C(21)	109.3(3)
C(13)-C(12)-H(12)	115.9	C(24)-C(20)-H(20)	107.7
C(11)-C(12)-H(12)	115.9	C(19)-C(20)-H(20)	107.7
C(9)-C(12)-H(12)	115.9	C(21)-C(20)-H(20)	107.7
O(2)-C(13)-O(3)	123.5(3)	C(16)-C(21)-C(20)	111.6(2)
O(2)-C(13)-C(12)	125.8(3)	C(16)-C(21)-H(21A)	109.3
O(3)-C(13)-C(12)	110.7(2)	C(20)-C(21)-H(21A)	109.3
C(15)-C(14)-O(3)	111.0(4)	C(16)-C(21)-H(21B)	109.3
C(15)-C(14)-H(14A)	109.4	C(20)-C(21)-H(21B)	109.3
O(3)-C(14)-H(14A)	109.4	H(21A)-C(21)-H(21B)	108.0

O(4)-C(22)-N(6)	123.3(2)
O(4)-C(22)-N(5)	119.7(2)
N(6)-C(22)-N(5)	117.0(2)
C(17)-C(23)-H(23A)	109.5
C(17)-C(23)-H(23B)	109.5
H(23A)-C(23)-H(23B)	109.5
C(17)-C(23)-H(23C)	109.5
H(23A)-C(23)-H(23C)	109.5
H(23B)-C(23)-H(23C)	109.5
C(26)-C(24)-C(20)	117.4(3)
C(26)-C(24)-C(25)	117.2(3)
C(20)-C(24)-C(25)	116.8(3)
C(26)-C(24)-C(27)	60.1(2)
C(20)-C(24)-C(27)	119.5(3)
C(25)-C(24)-C(27)	113.8(3)
C(24)-C(25)-H(25A)	109.5
C(24)-C(25)-H(25B)	109.5
H(25A)-C(25)-H(25B)	109.5
C(24)-C(25)-H(25C)	109.5
H(25A)-C(25)-H(25C)	109.5
H(25B)-C(25)-H(25C)	109.5
C(24)-C(26)-C(27)	60.9(2)
C(24)-C(26)-H(26A)	117.7
C(27)-C(26)-H(26A)	117.7
C(24)-C(26)-H(26B)	117.7
C(27)-C(26)-H(26B)	117.7
H(26A)-C(26)-H(26B)	114.8
C(28)-C(27)-C(26)	119.1(3)
C(28)-C(27)-C(24)	121.3(3)
C(26)-C(27)-C(24)	58.9(2)
C(28)-C(27)-H(27)	115.3
C(26)-C(27)-H(27)	115.3
C(24)-C(27)-H(27)	115.3
O(5)-C(28)-O(6)	123.8(3)
O(5)-C(28)-C(27)	126.4(3)
O(6)-C(28)-C(27)	109.8(3)
C(30)-C(29)-O(6)	112.2(10)
C(30)-C(29)-H(29A)	109.2
O(6)-C(29)-H(29A)	109.2
C(30)-C(29)-H(29B)	109.2
O(6)-C(29)-H(29B)	109.2
H(29A)-C(29)-H(29B)	107.9
C(29)-C(30)-H(30A)	109.5
C(29)-C(30)-H(30B)	109.5
H(30A)-C(30)-H(30B)	109.5
C(29)-C(30)-H(30C)	109.5
H(30A)-C(30)-H(30C)	109.5
H(30B)-C(30)-H(30C)	109.5
N(7)-C(31)-C(32)	116.9(3)
N(7)-C(31)-C(36)	124.3(3)
C(32)-C(31)-C(36)	118.7(3)
C(33)-C(32)-C(31)	119.7(3)
C(33)-C(32)-C(38)	122.4(3)
C(31)-C(32)-C(38)	117.9(3)
C(32)-C(33)-C(34)	124.4(3)
C(32)-C(33)-H(33)	117.8
C(34)-C(33)-H(33)	117.8
C(33)-C(34)-C(35)	110.7(3)
C(33)-C(34)-H(34A)	109.5
C(35)-C(34)-H(34A)	109.5
C(33)-C(34)-H(34B)	109.5
C(35)-C(34)-H(34B)	109.5
H(34A)-C(34)-H(34B)	108.1
C(39)-C(35)-C(34)	111.5(3)
C(39)-C(35)-C(36)	112.3(2)
C(34)-C(35)-C(36)	110.2(2)
C(39)-C(35)-H(35)	107.5
C(34)-C(35)-H(35)	107.5
C(36)-C(35)-H(35)	107.5
C(31)-C(36)-C(35)	113.5(2)
C(31)-C(36)-H(36A)	108.9
C(35)-C(36)-H(36A)	108.9

C(31)-C(36)-H(36B)	108.9
C(35)-C(36)-H(36B)	108.9
H(36A)-C(36)-H(36B)	107.7
O(7)-C(37)-N(9)	122.9(3)
O(7)-C(37)-N(8)	119.4(3)
N(9)-C(37)-N(8)	117.7(3)
C(32)-C(38)-H(38A)	109.5
C(32)-C(38)-H(38B)	109.5
H(38A)-C(38)-H(38B)	109.5
C(32)-C(38)-H(38C)	109.5
H(38A)-C(38)-H(38C)	109.5
H(38B)-C(38)-H(38C)	109.5
C(41)-C(39)-C(40)	118.0(3)
C(41)-C(39)-C(35)	117.7(3)
C(40)-C(39)-C(35)	116.5(3)
C(41)-C(39)-C(42)	59.6(2)
C(40)-C(39)-C(42)	114.5(3)
C(35)-C(39)-C(42)	118.4(3)
C(39)-C(40)-H(40A)	109.5
C(39)-C(40)-H(40B)	109.5
H(40A)-C(40)-H(40B)	109.5
C(39)-C(40)-H(40C)	109.5
H(40A)-C(40)-H(40C)	109.5
H(40B)-C(40)-H(40C)	109.5
C(39)-C(41)-C(42)	61.3(2)
C(39)-C(41)-H(41A)	117.6
C(42)-C(41)-H(41A)	117.6
C(39)-C(41)-H(41B)	117.6
C(42)-C(41)-H(41B)	117.6
H(41A)-C(41)-H(41B)	114.7
C(43)-C(42)-C(41)	120.2(3)
C(43)-C(42)-C(39)	119.2(3)
C(41)-C(42)-C(39)	59.1(2)
C(43)-C(42)-H(42)	115.6
C(41)-C(42)-H(42)	115.6
C(39)-C(42)-H(42)	115.6
O(8)-C(43)-O(9)	122.3(4)
O(8)-C(43)-C(42)	127.2(4)
O(9)-C(43)-C(42)	110.4(3)
C(45)-C(44)-O(9)	114.9(8)
C(45)-C(44)-H(44A)	108.5
O(9)-C(44)-H(44A)	108.5
C(45)-C(44)-H(44B)	108.5
O(9)-C(44)-H(44B)	108.5
H(44A)-C(44)-H(44B)	107.5
C(44)-C(45)-H(45A)	109.5
C(44)-C(45)-H(45B)	109.5
H(45A)-C(45)-H(45B)	109.5
C(44)-C(45)-H(45C)	109.5
H(45A)-C(45)-H(45C)	109.5
H(45B)-C(45)-H(45C)	109.5
N(10)-C(46)-C(47)	115.8(3)
N(10)-C(46)-C(51)	125.6(3)
C(47)-C(46)-C(51)	118.5(3)
C(48)-C(47)-C(46)	119.6(4)
C(48)-C(47)-C(53)	122.2(4)
C(46)-C(47)-C(53)	118.2(3)
C(47)-C(48)-C(49)	124.0(4)
C(47)-C(48)-H(48)	118.0
C(49)-C(48)-H(48)	118.0
C(48)-C(49)-C(50)	111.8(3)
C(48)-C(49)-H(49A)	109.3
C(50)-C(49)-H(49A)	109.3
C(48)-C(49)-H(49B)	109.3
C(50)-C(49)-H(49B)	109.3
H(49A)-C(49)-H(49B)	107.9
C(54)-C(50)-C(49)	112.8(3)
C(54)-C(50)-C(51)	113.0(3)
C(49)-C(50)-C(51)	109.5(3)
C(54)-C(50)-H(50)	107.0
C(49)-C(50)-H(50)	107.0
C(51)-C(50)-H(50)	107.0

C(46)-C(51)-C(50)	111.3(3)
C(46)-C(51)-H(51A)	109.4
C(50)-C(51)-H(51A)	109.4
C(46)-C(51)-H(51B)	109.4
C(50)-C(51)-H(51B)	109.4
H(51A)-C(51)-H(51B)	108.0
O(10)-C(52)-N(12)	123.6(2)
O(10)-C(52)-N(11)	119.8(2)
N(12)-C(52)-N(11)	116.6(2)
C(47)-C(53)-H(53A)	109.5
C(47)-C(53)-H(53B)	109.5
H(53A)-C(53)-H(53B)	109.5
C(47)-C(53)-H(53C)	109.5
H(53A)-C(53)-H(53C)	109.5
H(53B)-C(53)-H(53C)	109.5
C(56)-C(54)-C(55)	117.0(3)
C(56)-C(54)-C(50)	117.5(3)
C(55)-C(54)-C(50)	116.7(4)
C(56)-C(54)-C(57)	60.2(4)
C(55)-C(54)-C(57)	114.6(4)
C(50)-C(54)-C(57)	118.9(3)
C(54)-C(55)-H(55A)	109.5
C(54)-C(55)-H(55B)	109.5
H(55A)-C(55)-H(55B)	109.5
C(54)-C(55)-H(55C)	109.5
H(55A)-C(55)-H(55C)	109.5
H(55B)-C(55)-H(55C)	109.5
C(54)-C(56)-C(57)	60.8(3)
C(54)-C(56)-H(56A)	117.7
C(57)-C(56)-H(56A)	117.7
C(54)-C(56)-H(56B)	117.7
C(57)-C(56)-H(56B)	117.7
H(56A)-C(56)-H(56B)	114.8
C(58)-C(57)-C(56)	121.2(5)
C(58)-C(57)-C(54)	119.4(4)
C(56)-C(57)-C(54)	58.9(3)
C(58)-C(57)-H(57)	115.2
C(56)-C(57)-H(57)	115.2
C(54)-C(57)-H(57)	115.2
O(11)-C(58)-O(12)	122.0(6)
O(11)-C(58)-C(57)	127.1(7)
O(12)-C(58)-C(57)	110.9(5)
C(60)-C(59)-O(12)	109.6(7)
C(60)-C(59)-H(59A)	109.8
O(12)-C(59)-H(59A)	109.8
C(60)-C(59)-H(59B)	109.8
O(12)-C(59)-H(59B)	109.8
H(59A)-C(59)-H(59B)	108.2
C(59)-C(60)-H(60A)	109.5
C(59)-C(60)-H(60B)	109.5
H(60A)-C(60)-H(60B)	109.5
C(59)-C(60)-H(60C)	109.5
H(60A)-C(60)-H(60C)	109.5
H(60B)-C(60)-H(60C)	109.5
C(1)-N(1)-N(2)	119.1(2)
C(7)-N(2)-N(1)	117.5(2)
C(7)-N(2)-H(2)	121.2
N(1)-N(2)-H(2)	121.2
C(7)-N(3)-H(3A)	120.0
C(7)-N(3)-H(3B)	120.0
H(3A)-N(3)-H(3B)	120.0
C(16)-N(4)-N(5)	118.1(2)
C(22)-N(5)-N(4)	117.8(2)
C(22)-N(5)-H(5A)	121.1
N(4)-N(5)-H(5A)	121.1
C(22)-N(6)-H(6C)	120.0
C(22)-N(6)-H(6D)	120.0
H(6C)-N(6)-H(6D)	120.0
C(31)-N(7)-N(8)	117.8(3)
C(37)-N(8)-N(7)	118.8(2)
C(37)-N(8)-H(8)	120.6
N(7)-N(8)-H(8)	120.6

C(37)-N(9)-H(9A)	120.0	C(52)-N(12)-H(12A)	120.0
C(37)-N(9)-H(9B)	120.0	C(52)-N(12)-H(12B)	120.0
H(9A)-N(9)-H(9B)	120.0	H(12A)-N(12)-H(12B)	120.0
C(46)-N(10)-N(11)	118.2(3)	C(13)-O(3)-C(14)	117.0(3)
C(52)-N(11)-N(10)	118.3(2)	C(28)-O(6)-C(29)	117.2(4)
C(52)-N(11)-H(11)	120.8	C(43)-O(9)-C(44)	115.0(5)
N(10)-N(11)-H(11)	120.8	C(58)-O(12)-C(59)	117.0(6)

Symmetry transformations used to generate equivalent atoms:

Table S9. Anisotropic displacement parameters ($Å^2$x 10^3)for hartwig152. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	33(1)	44(1)	31(1)	3(1)	-3(1)	5(1)
C(2)	36(1)	43(1)	39(1)	2(1)	-7(1)	4(1)
C(3)	38(1)	45(2)	50(2)	6(1)	-6(1)	2(1)
C(4)	48(2)	50(2)	44(2)	12(1)	1(1)	-1(1)
C(5)	35(1)	50(2)	29(1)	5(1)	-1(1)	7(1)
C(6)	42(1)	43(1)	29(1)	4(1)	1(1)	5(1)
C(7)	35(1)	45(1)	29(1)	4(1)	-2(1)	1(1)
C(8)	59(2)	44(2)	43(2)	-4(1)	-10(1)	-2(1)
C(9)	43(2)	57(2)	32(1)	6(1)	1(1)	6(1)
C(10)	47(2)	91(3)	33(2)	4(2)	7(1)	10(2)
C(11)	56(2)	61(2)	33(1)	12(1)	-1(1)	8(2)
C(12)	45(2)	53(2)	27(1)	1(1)	-1(1)	11(1)
C(13)	34(1)	54(2)	35(1)	2(1)	-6(1)	10(1)
C(14)	48(2)	70(2)	77(3)	2(2)	23(2)	1(2)
C(15)	87(3)	107(4)	113(4)	18(3)	26(3)	10(3)
C(16)	38(1)	51(2)	31(1)	1(1)	3(1)	5(1)
C(17)	45(2)	69(2)	39(2)	7(1)	7(1)	19(2)
C(18)	47(2)	92(3)	47(2)	10(2)	12(1)	26(2)
C(19)	46(2)	94(3)	39(2)	13(2)	14(1)	17(2)
C(20)	33(1)	60(2)	30(1)	6(1)	1(1)	-2(1)
C(21)	33(1)	52(2)	29(1)	2(1)	1(1)	0(1)
C(22)	39(1)	41(1)	25(1)	-1(1)	1(1)	-1(1)
C(23)	58(2)	88(3)	57(2)	22(2)	7(2)	33(2)
C(24)	35(1)	61(2)	32(1)	7(1)	4(1)	-3(1)
C(25)	59(2)	77(2)	26(1)	4(1)	2(1)	15(2)
C(26)	51(2)	79(2)	55(2)	20(2)	4(2)	-23(2)
C(27)	45(2)	51(2)	42(2)	8(1)	-2(1)	-9(1)
C(28)	60(2)	49(2)	48(2)	-6(1)	-8(2)	-7(1)
C(29)	96(4)	266(12)	82(4)	-65(6)	5(3)	54(6)
C(30)	228(12)	195(10)	119(6)	-72(7)	67(7)	-96(9)
C(31)	42(2)	53(2)	37(1)	1(1)	2(1)	-12(1)

C(32)	60(2)	72(2)	49(2)	-13(2)	11(2)	-26(2)
C(33)	58(2)	61(2)	58(2)	-10(2)	21(2)	-27(2)
C(34)	45(2)	55(2)	48(2)	-2(1)	13(1)	-17(1)
C(35)	34(1)	52(2)	40(2)	-1(1)	6(1)	-7(1)
C(36)	31(1)	46(1)	33(1)	1(1)	1(1)	-4(1)
C(37)	41(1)	52(2)	30(1)	6(1)	-4(1)	-3(1)
C(38)	113(4)	114(4)	55(2)	-25(2)	21(2)	-73(3)
C(39)	41(2)	51(2)	43(2)	-1(1)	7(1)	-7(1)
C(40)	48(2)	65(2)	38(2)	9(1)	4(1)	-8(1)
C(41)	44(2)	77(2)	56(2)	-19(2)	17(2)	-17(2)
C(42)	42(2)	60(2)	62(2)	-19(2)	8(2)	-5(1)
C(43)	43(2)	54(2)	99(3)	-11(2)	5(2)	7(2)
C(44)	94(4)	103(5)	243(11)	87(6)	-25(6)	6(4)
C(45)	249(15)	292(17)	204(11)	168(12)	102(11)	146(15)
C(46)	54(2)	43(1)	34(1)	-4(1)	5(1)	3(1)
C(47)	67(2)	67(2)	47(2)	-11(2)	1(2)	18(2)
C(48)	76(3)	70(2)	56(2)	-16(2)	5(2)	28(2)
C(49)	98(3)	65(2)	41(2)	-18(2)	0(2)	26(2)
C(50)	86(2)	39(2)	37(2)	-6(1)	-4(2)	4(2)
C(51)	62(2)	42(1)	31(1)	-2(1)	3(1)	2(1)
C(52)	37(1)	41(1)	27(1)	-1(1)	3(1)	-4(1)
C(53)	69(2)	102(3)	74(3)	-36(2)	-11(2)	38(2)
C(54)	90(3)	49(2)	46(2)	-9(1)	-11(2)	2(2)
C(55)	92(3)	76(2)	36(2)	-10(2)	-7(2)	13(2)
C(56)	153(5)	53(2)	85(3)	-12(2)	-49(3)	-13(3)
C(57)	99(3)	67(2)	64(2)	-2(2)	-21(2)	-26(2)
C(58)	104(4)	78(3)	71(3)	11(2)	-12(3)	-45(3)
C(59)	144(6)	155(7)	66(3)	12(4)	19(3)	-52(5)
C(60)	250(12)	128(6)	124(6)	-18(5)	94(8)	-49(8)
N(1)	38(1)	40(1)	30(1)	1(1)	-3(1)	3(1)
N(2)	45(1)	41(1)	24(1)	2(1)	0(1)	1(1)
N(3)	50(1)	43(1)	24(1)	3(1)	1(1)	2(1)
N(4)	39(1)	53(1)	29(1)	3(1)	2(1)	7(1)
N(5)	34(1)	52(1)	25(1)	5(1)	1(1)	5(1)
N(6)	41(1)	62(1)	28(1)	10(1)	3(1)	10(1)
N(7)	50(1)	63(2)	34(1)	-2(1)	0(1)	-16(1)

N(8)	43(1)	57(1)	26(1)	1(1)	-1(1)	-12(1)
N(9)	56(2)	68(2)	28(1)	4(1)	-3(1)	-22(1)
N(10)	47(1)	44(1)	36(1)	-3(1)	2(1)	5(1)
N(11)	43(1)	45(1)	26(1)	-4(1)	1(1)	6(1)
N(12)	40(1)	47(1)	29(1)	-1(1)	1(1)	5(1)
O(1)	52(1)	43(1)	29(1)	1(1)	2(1)	-1(1)
O(2)	46(1)	58(1)	46(1)	-6(1)	5(1)	12(1)
O(3)	44(1)	56(1)	57(1)	-6(1)	12(1)	4(1)
O(4)	32(1)	52(1)	27(1)	1(1)	0(1)	1(1)
O(5)	72(2)	66(2)	55(1)	-15(1)	-13(1)	-13(1)
O(6)	72(2)	137(3)	64(2)	-40(2)	-8(2)	34(2)
O(7)	39(1)	52(1)	29(1)	5(1)	-6(1)	-7(1)
O(8)	56(2)	78(2)	145(3)	-1(2)	-24(2)	16(1)
O(9)	57(2)	60(2)	131(3)	18(2)	5(2)	12(1)
O(10)	42(1)	45(1)	26(1)	-1(1)	3(1)	3(1)
O(11)	134(3)	109(3)	78(2)	31(2)	-18(2)	-60(3)
O(12)	118(3)	105(3)	63(2)	4(2)	11(2)	-46(2)

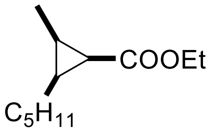
Table S10. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for hartwig152.

	x	y	z	U(eq)
H(3)	7997	9159	339	53
H(4A)	8355	8285	-364	56
H(4B)	7658	8864	-466	56
H(5)	6687	8013	-246	46
H(6A)	7005	6818	-11	46
H(6B)	7939	6980	-73	46
H(8A)	7697	9025	1163	73
H(8B)	8107	8279	1334	73
H(8C)	7154	8345	1319	73
H(10A)	7866	7162	-1428	85
H(10B)	8042	6777	-914	85
H(10C)	8388	7574	-1023	85
H(11A)	6836	8061	-1542	60
H(11B)	6348	8403	-1062	60
H(12)	6473	6844	-1306	50
H(14A)	4528	6650	-292	78
H(14B)	4610	5808	-442	78
H(15A)	5675	5740	109	153
H(15B)	4813	5858	350	153
H(15C)	5414	6532	297	153
H(18)	11001	4412	2351	75
H(19A)	10070	4919	1707	72
H(19B)	10771	5447	1889	72
H(20)	9918	6042	2432	49
H(21A)	8576	5682	2548	46
H(21B)	8678	5036	2158	46
H(23A)	10812	3749	3066	102
H(23B)	9897	3529	3147	102
H(23C)	10287	4165	3468	102
H(25A)	8929	6259	1066	81

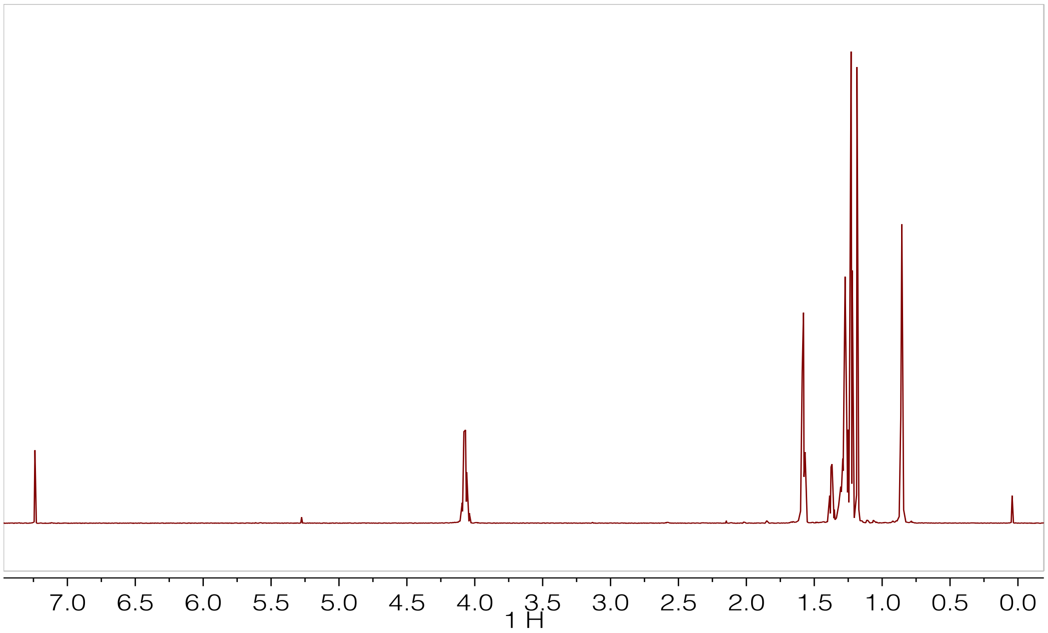
H(25B)	8682	5543	1364	81
H(25C)	9565	5618	1145	81
H(26A)	9915	7153	1390	74
H(26B)	10218	7084	1970	74
H(27)	8539	7103	1643	55
H(29A)	8146	7794	3090	177
H(29B)	7272	7917	2867	177
H(30A)	7077	6731	2966	271
H(30B)	7158	7214	3451	271
H(30C)	7892	6722	3272	271
H(33)	4204	2314	3579	71
H(34A)	5113	2803	4266	59
H(34B)	4167	2884	4336	59
H(35)	4189	4066	4021	51
H(36A)	5335	4631	3730	44
H(36B)	5882	3957	3891	44
H(38A)	4236	2386	2727	141
H(38B)	5124	2612	2572	141
H(38C)	4405	3176	2500	141
H(40A)	5665	4081	5218	75
H(40B)	6082	3957	4697	75
H(40C)	5558	3321	4937	75
H(41A)	4208	4243	5310	71
H(41B)	3635	4286	4812	71
H(42)	5057	5184	4995	66
H(44A)	4553	6033	3568	176
H(44B)	4356	6733	3894	176
H(45A)	5767	6761	3898	372
H(45B)	5199	7162	3511	372
H(45C)	5594	6393	3378	372
H(48)	4794	7151	6572	81
H(49A)	5837	6711	7173	81
H(49B)	5875	7559	7034	81
H(50)	6854	7347	6451	65
H(51A)	7346	6169	6276	54
H(51B)	6730	5818	6658	54

H(53A)	4312	6742	5827	122
H(53B)	4672	5967	5675	122
H(53C)	4987	6693	5413	122
H(55A)	7781	6645	7749	102
H(55B)	7255	6068	7450	102
H(55C)	6832	6742	7718	102
H(56A)	7919	7928	7477	117
H(56B)	7604	8160	6919	117
H(57)	8679	6936	7145	92
H(59A)	8709	6417	5608	146
H(59B)	9495	6913	5657	146
H(60A)	10190	5927	5943	251
H(60B)	9825	5764	5413	251
H(60C)	9407	5433	5891	251
H(2)	7151	6133	566	44
H(3A)	6927	6032	1971	47
H(3B)	7071	6751	1704	47
H(5A)	7842	5159	3009	45
H(6C)	7935	4512	4348	52
H(6D)	8650	4455	4005	52
H(8)	6150	4811	3197	51
H(9A)	6318	4828	1789	61
H(9B)	5742	4317	2053	61
H(11)	7276	5341	5789	46
H(12A)	6739	5295	4421	46
H(12B)	6307	5788	4784	46

NMR spectra:



^{1}H NMR



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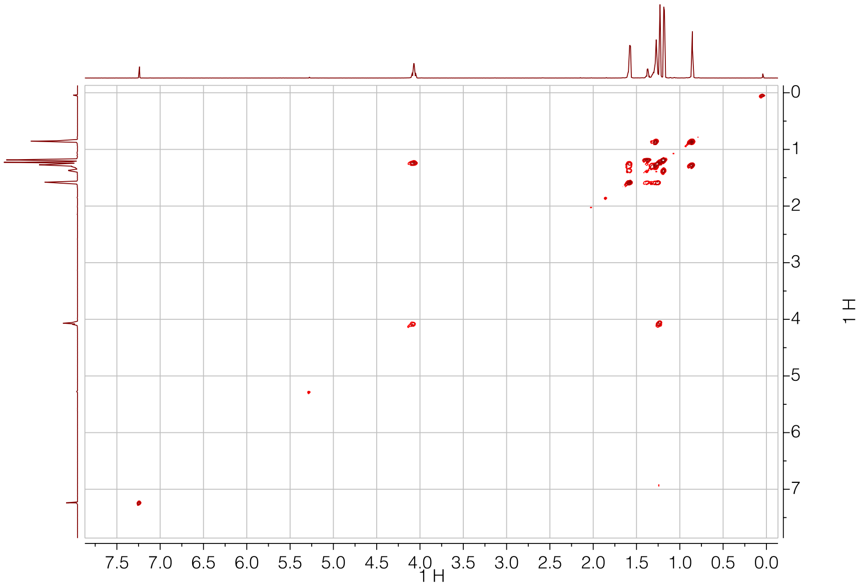
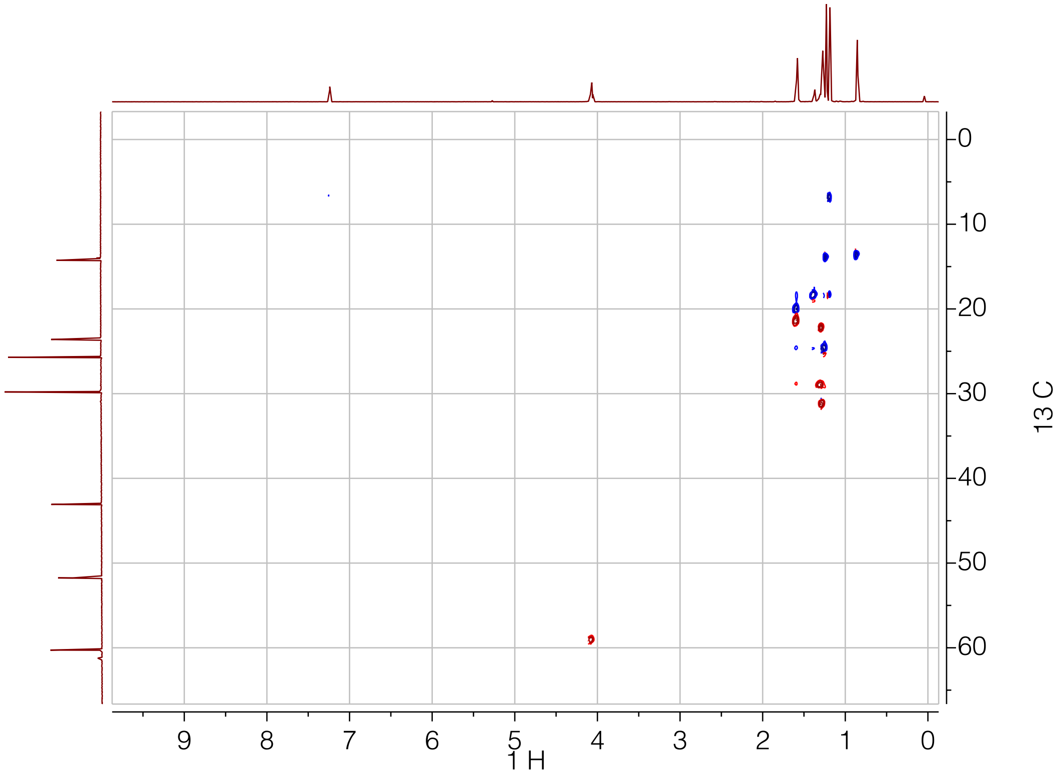
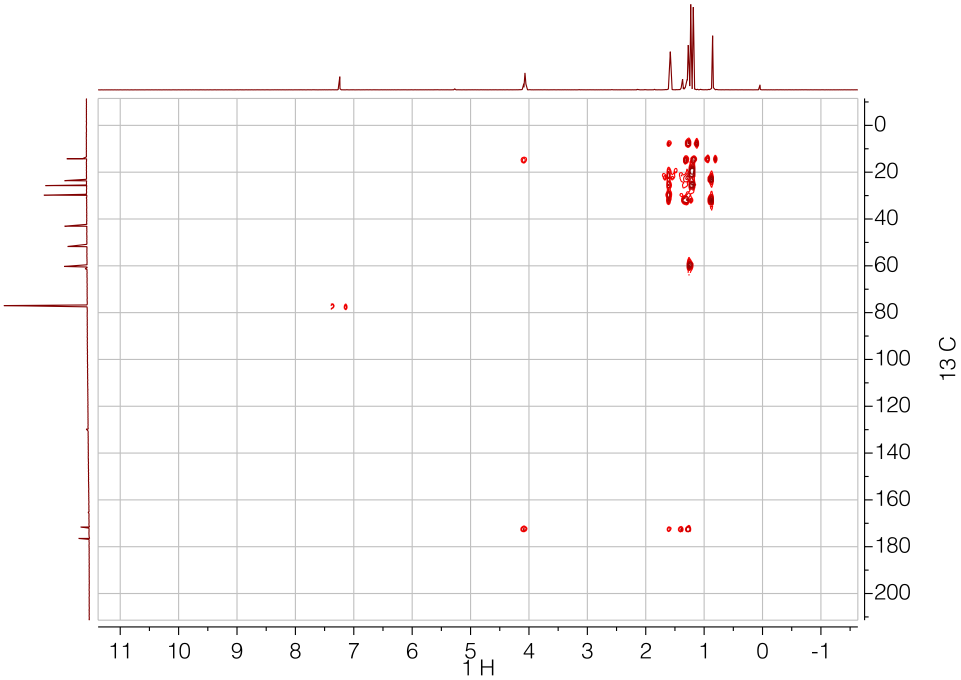


HSQC



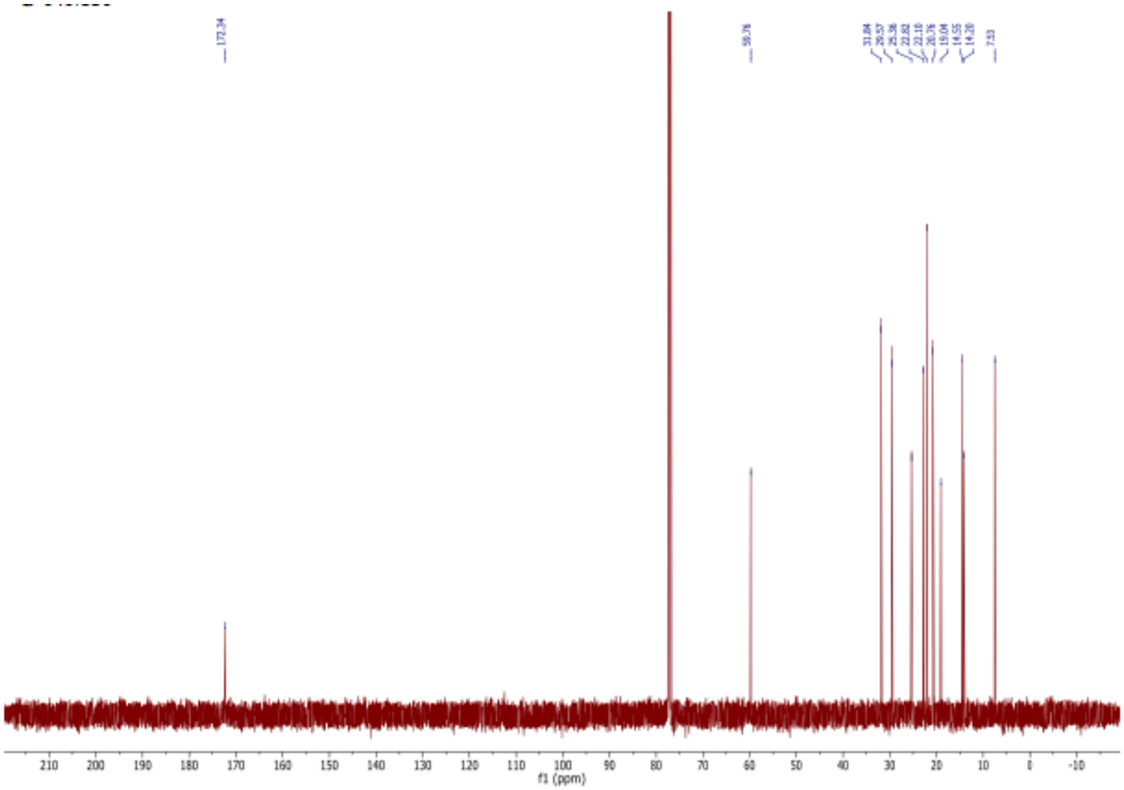
0
10
20
30
40
50
60
13 C
9
8
7
6
5
4
3
2
1
0
1 H

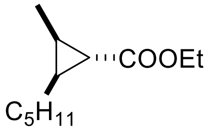
HMBC



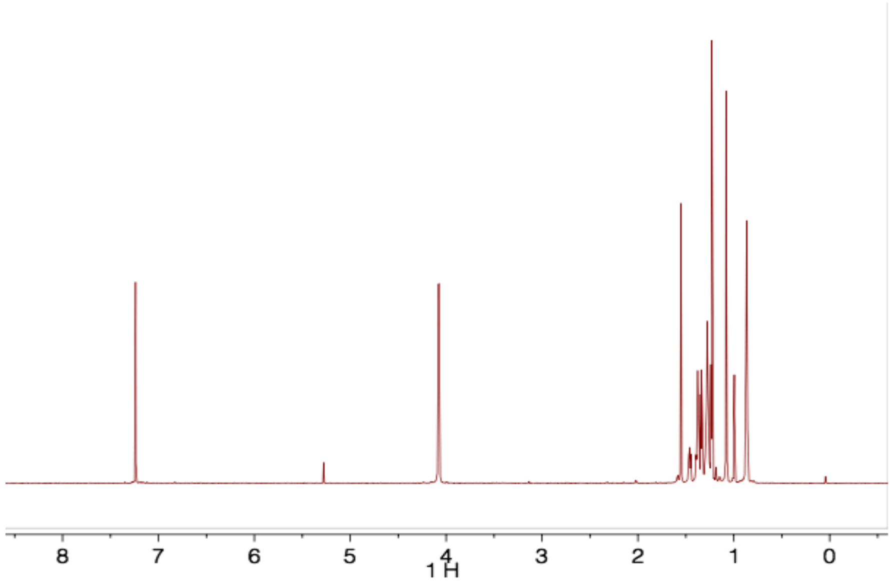
0
20
40
60
80
100
120
140
160
180
200
13 C
11
10
9
8
7
6
5
4
3
2
1
0
-1
1 H

^{13}C NMR


172.34
59.76
31.84
29.57
25.36
22.82
22.10
20.76
19.04
14.55
14.29
7.53
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)



^{1}H NMR



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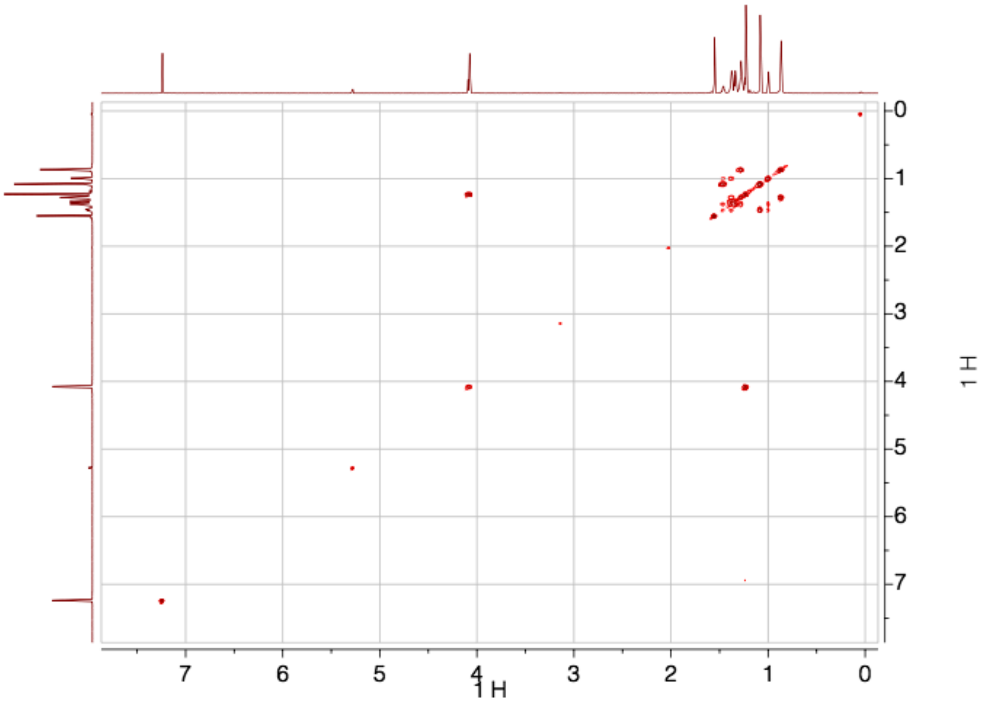
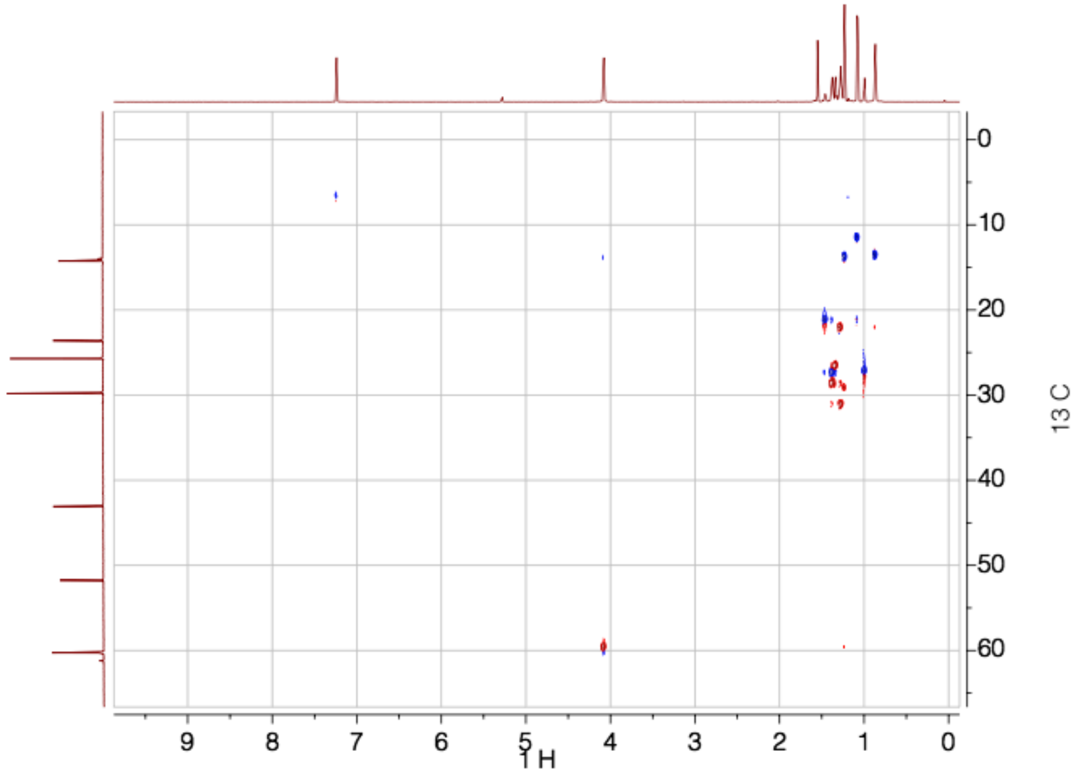
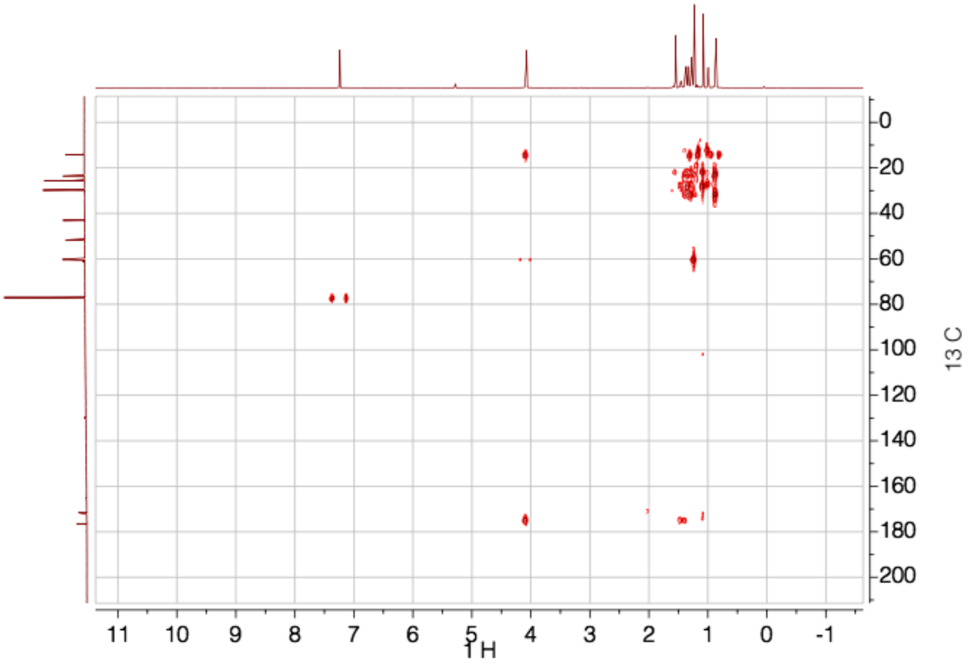


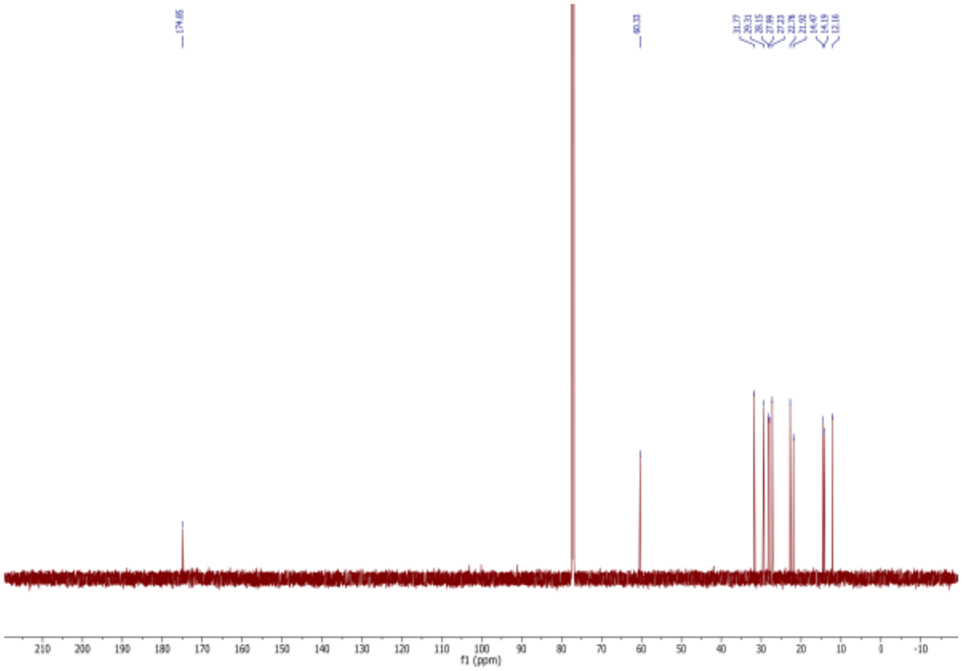
HSQC

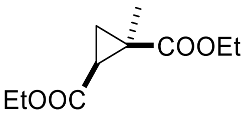

0
10
20
30
40
50
60
13 C
9
8
7
6
5
4
3
2
1
0
1 H

HMBC

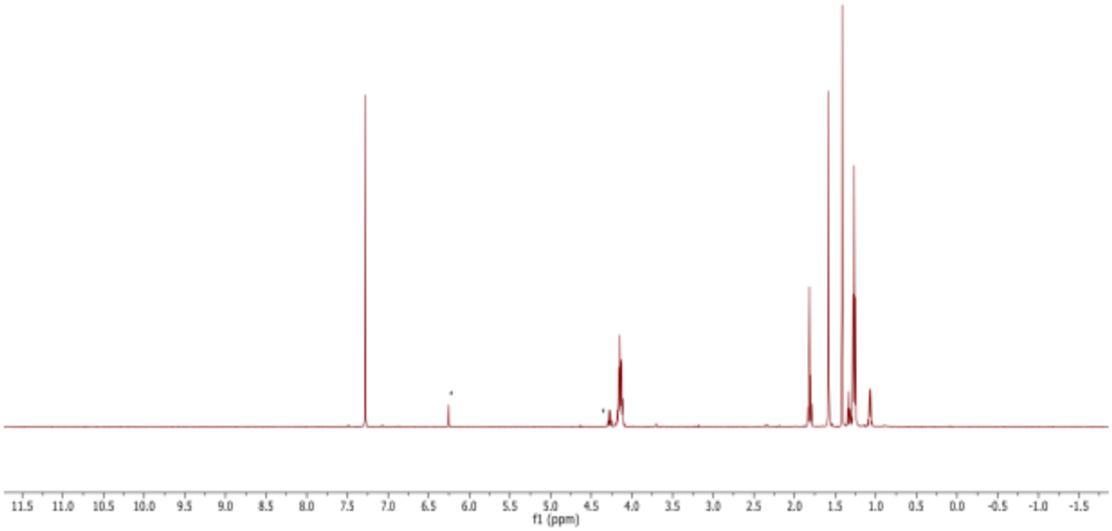

0
20
40
60
80
100
120
140
160
180
200
13 C
11
10
9
8
7
6
5
4
3
2
1
0
-1
1 H

^{13}C NMR

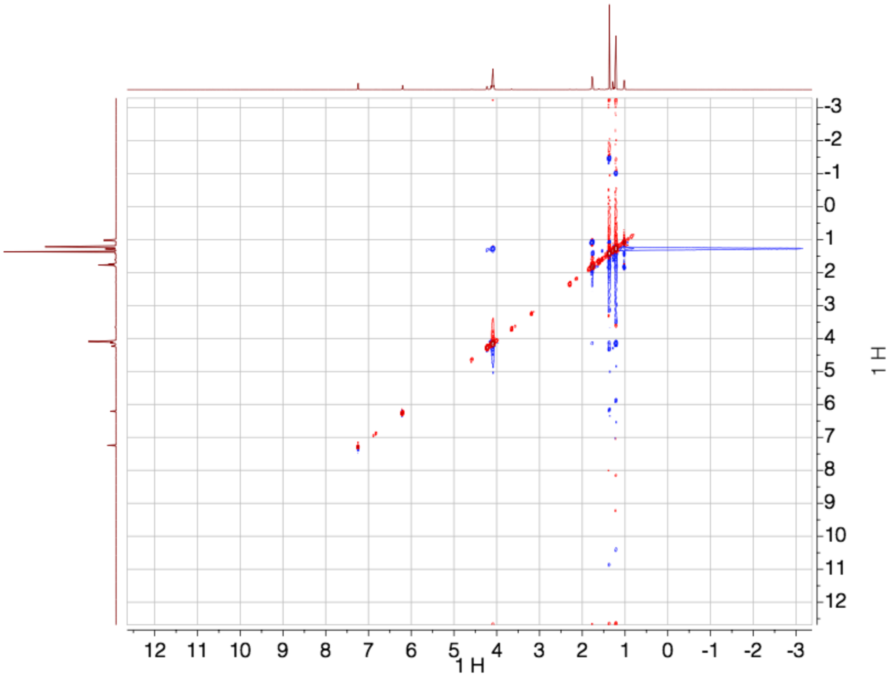

174.85
60.33
31.77
29.31
28.15
27.89
27.23
22.76
21.92
14.47
14.19
12.16
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


COOEt
EtOOC

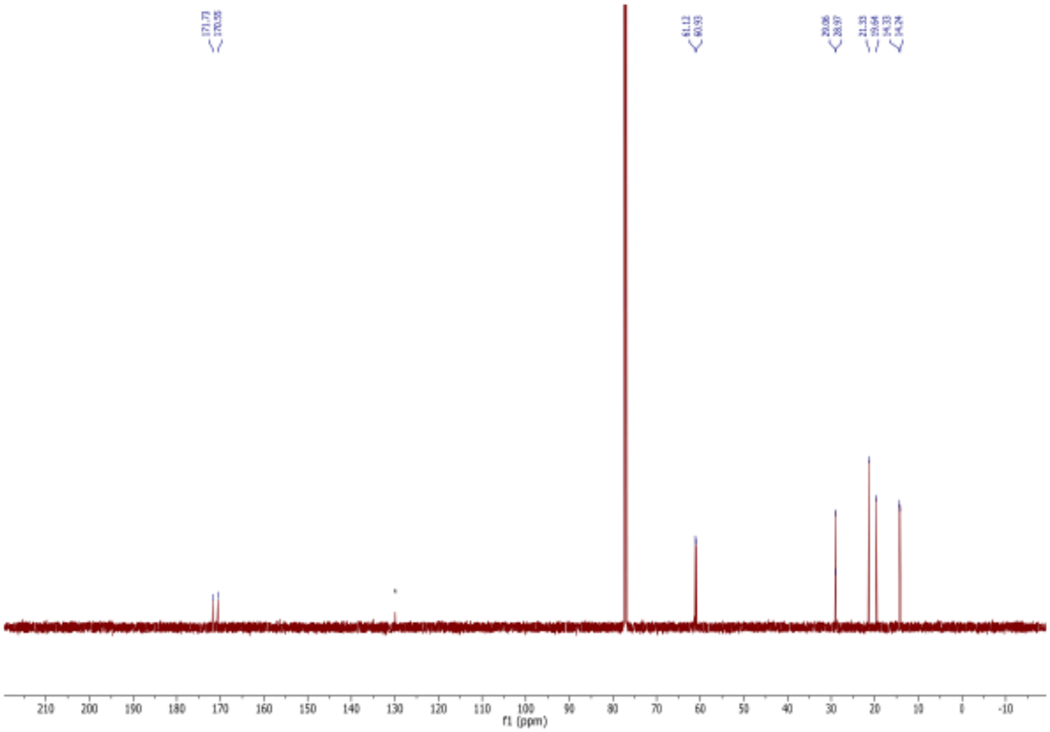
^{1}H NMR

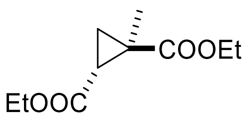

11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0 -1.5
f1 (ppm)

NOESY

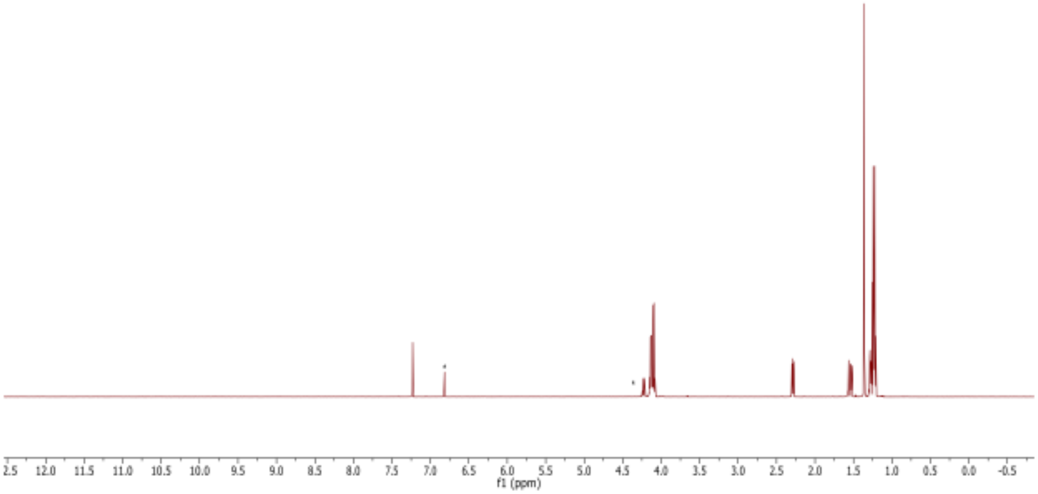

12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2 -3
1 H
-3 -2 -1 0 1 2 3 4 5 6 7 8 9 10 11 12
1 H

^{13}C NMR

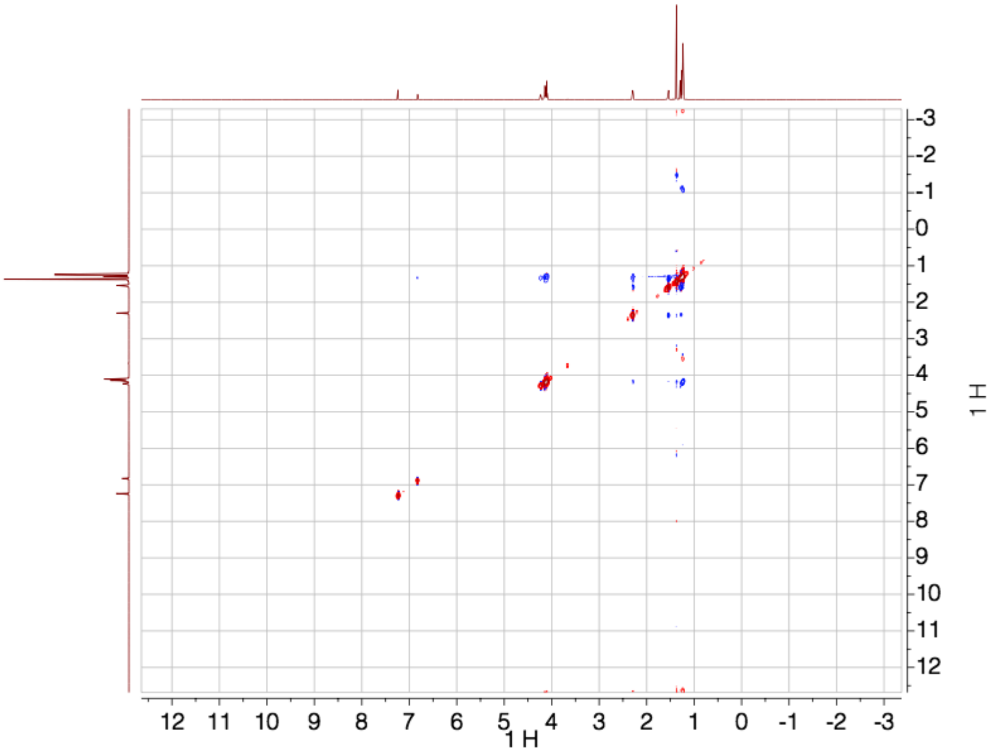

171.73
170.55
61.12
60.93
29.06
28.97
21.33
19.64
14.33
14.24
*
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


COOEt
EtOOC

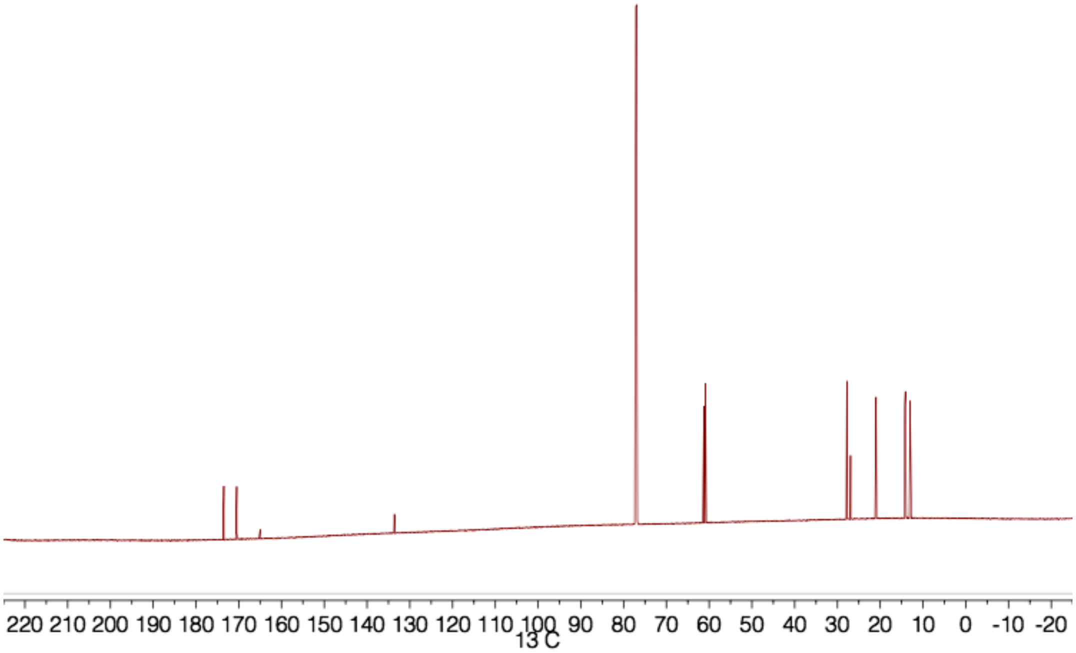
^{1}H NMR

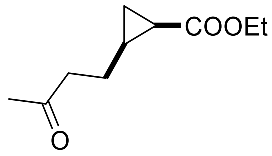

12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

NOESY

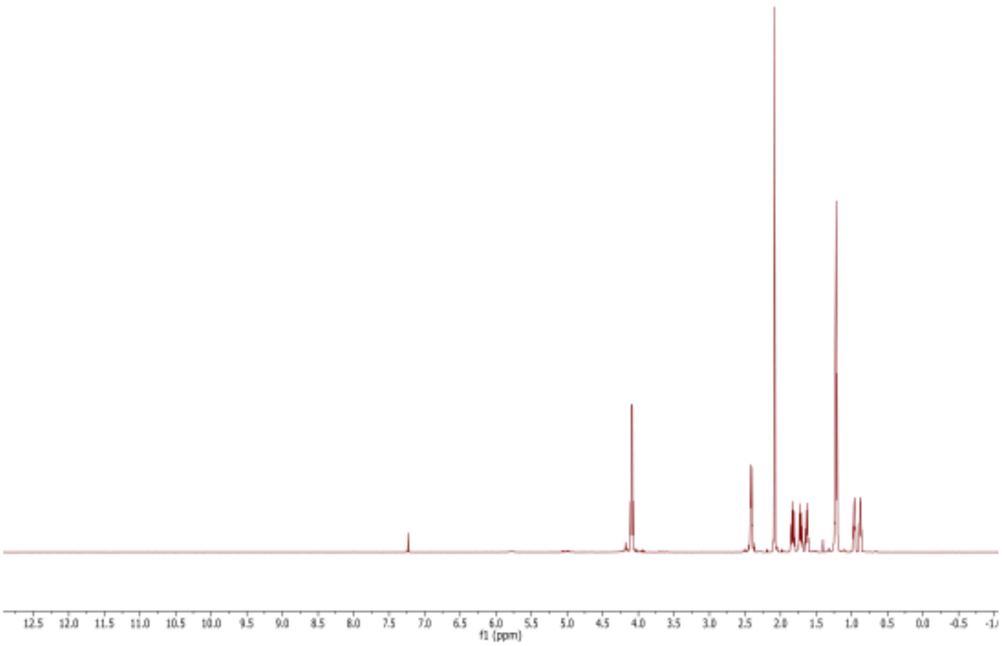

12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2 -3
1 H
-3 -2 -1 0 1 2 3 4 5 6 7 8 9 10 11 12
1 H

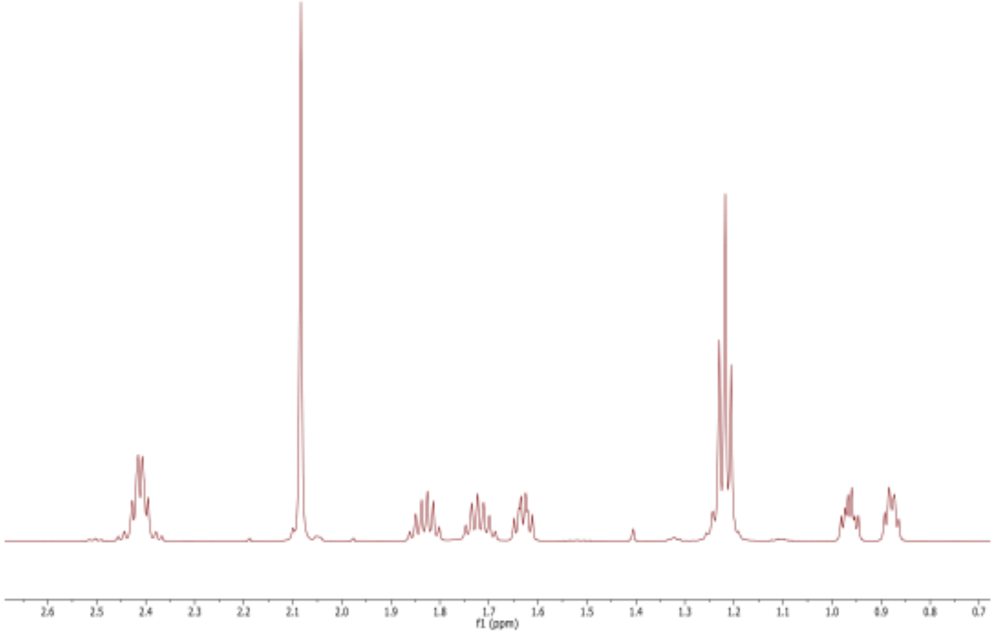
^{13}C NMR


220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
13 C

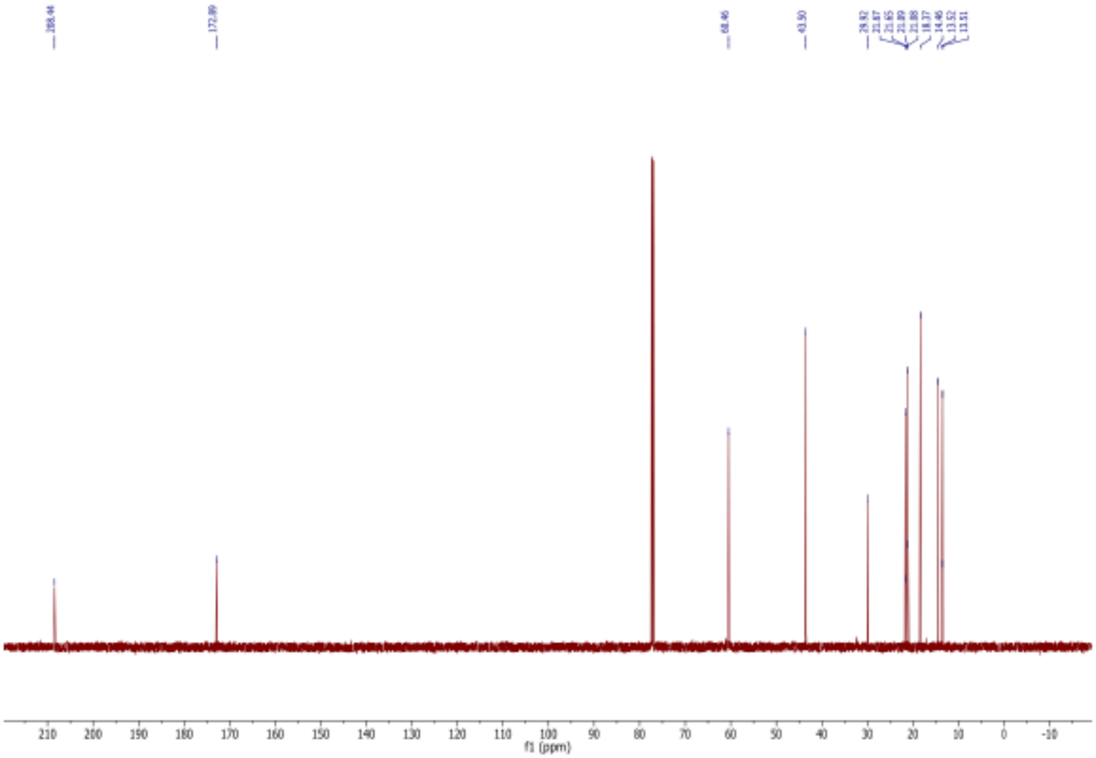

COOEt
O

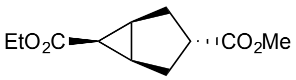
^{1}H NMR


12.5
12.0
11.5
11.0
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)

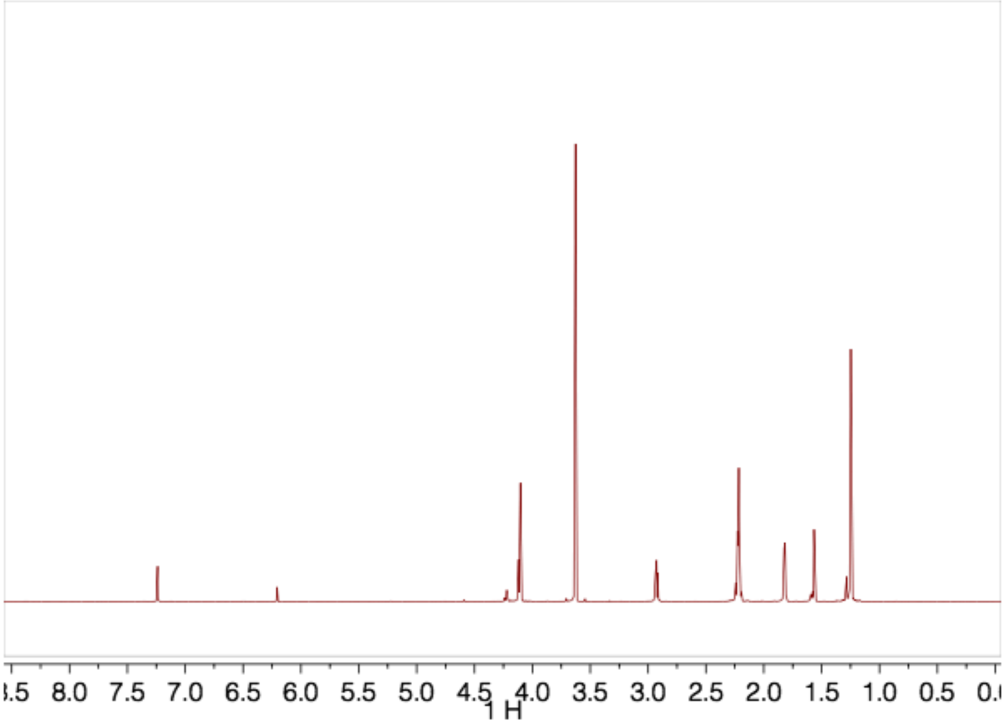

2.6
2.5
2.4
2.3
2.2
2.1
2.0
1.9
1.8
1.7
1.6
1.5
1.4
1.3
1.2
1.1
1.0
0.9
0.8
0.7
f1 (ppm)

^{13}C NMR

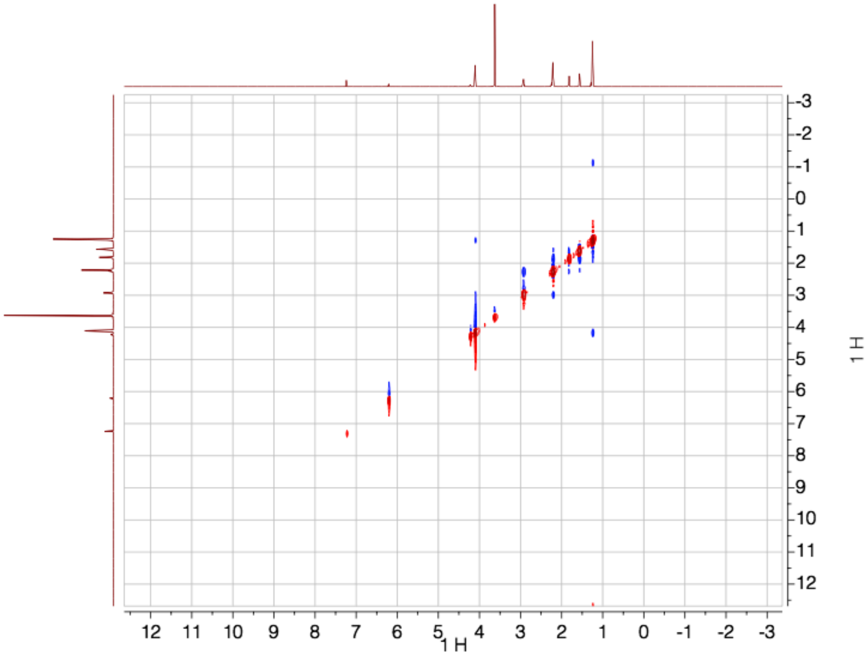




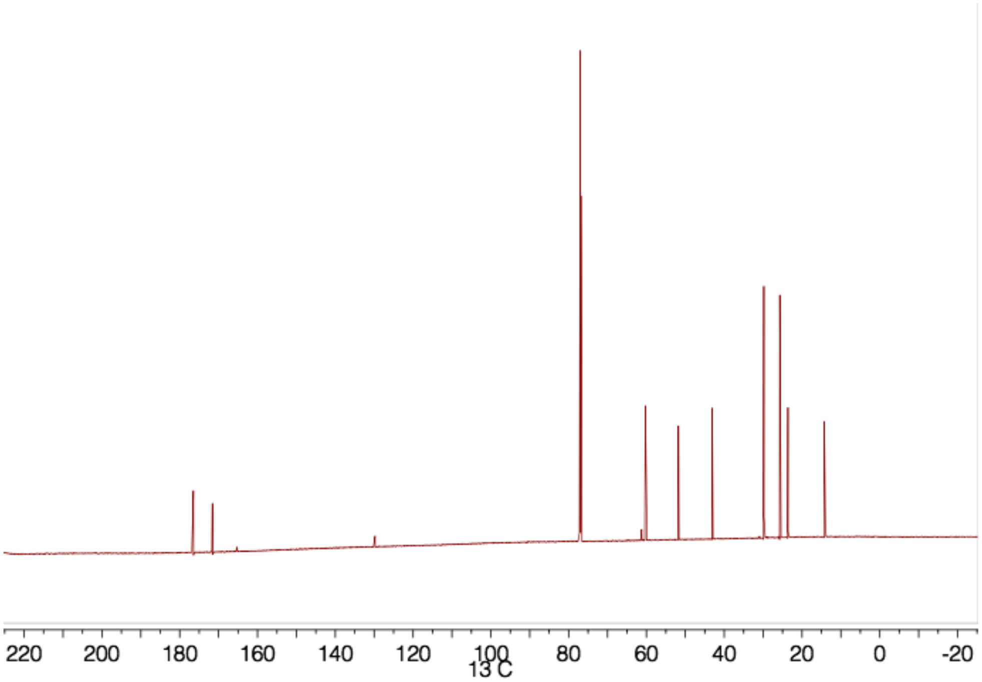
^{1}H NMR

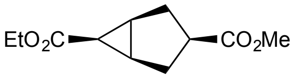

8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
1 H

NOESY

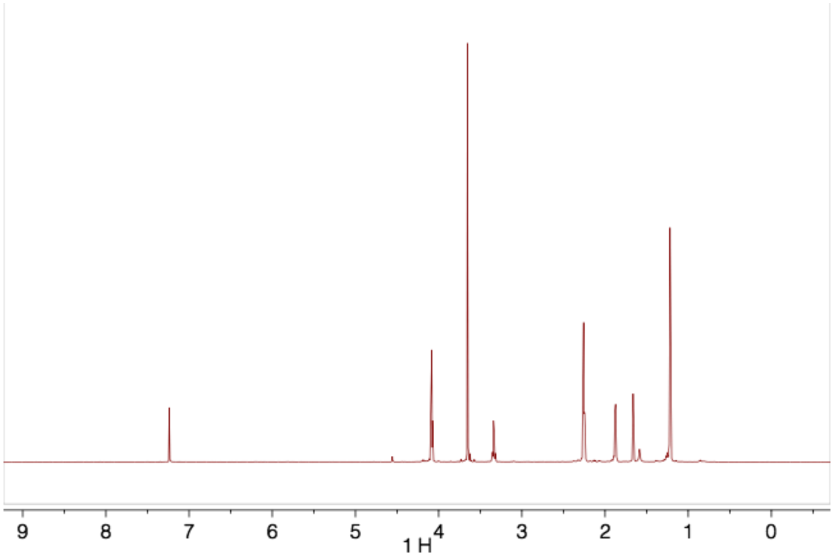

12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
-3
1 H
1 H

^{13}C NMR



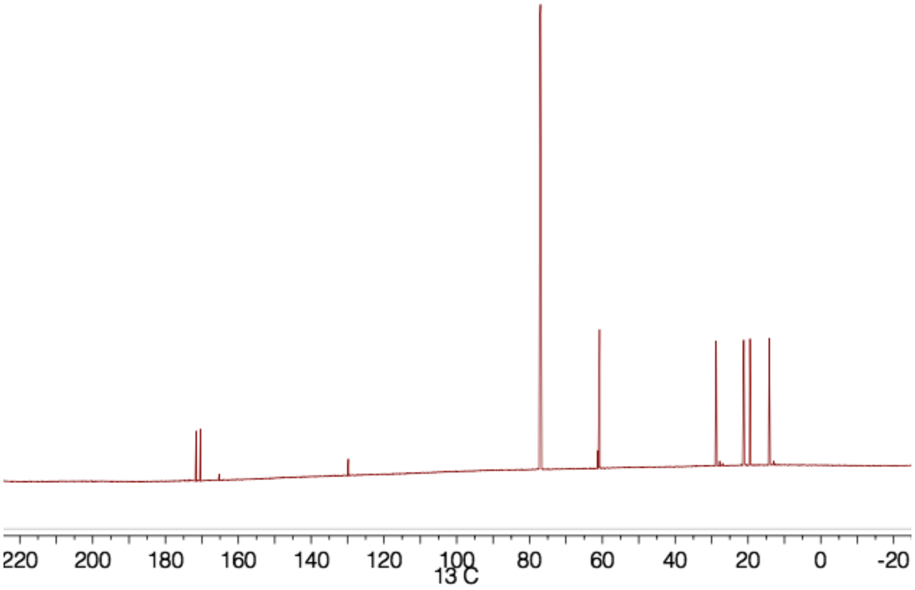


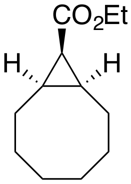
^{1}H NMR



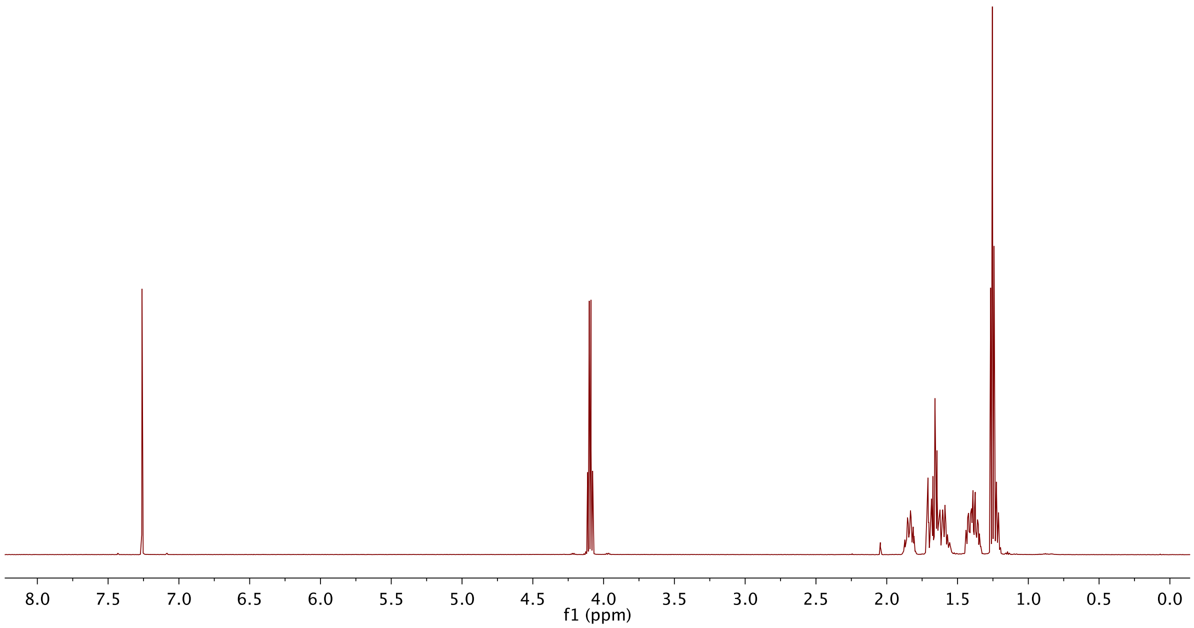
NOESY

^{13}C NMR

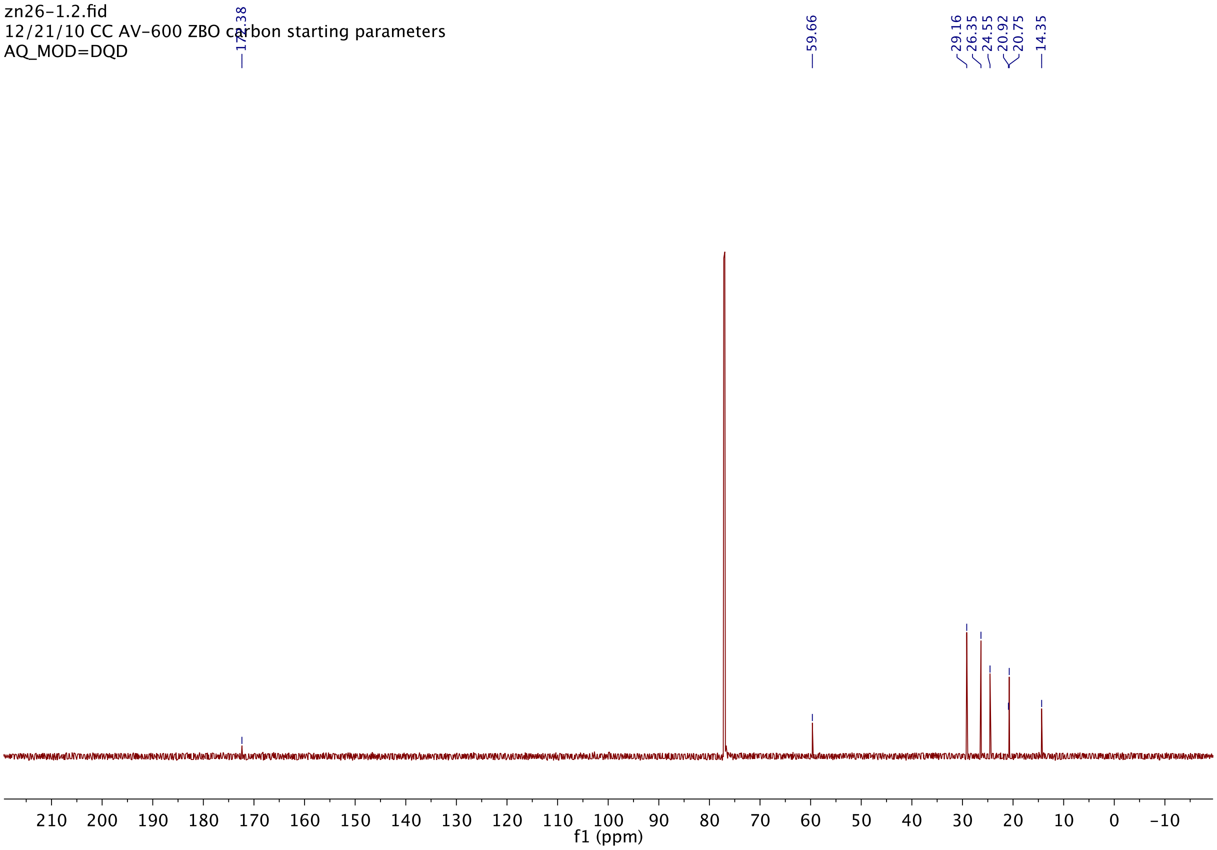


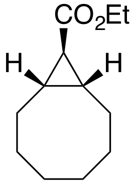


zn26-1.1.fid
AV-600 ZBO proton starting parameters 11/16/08 RN

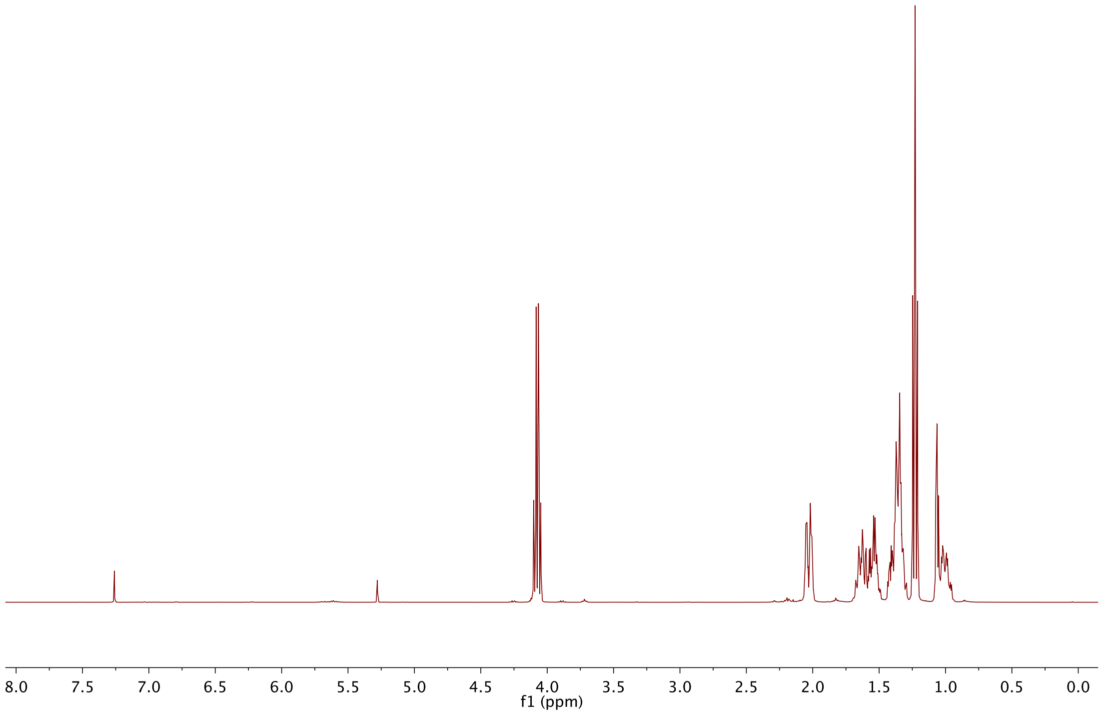


zn26-1.2.fid
12/21/10 CC AV-600 ZBO carbon starting parameters
AQ_MOD=DQD

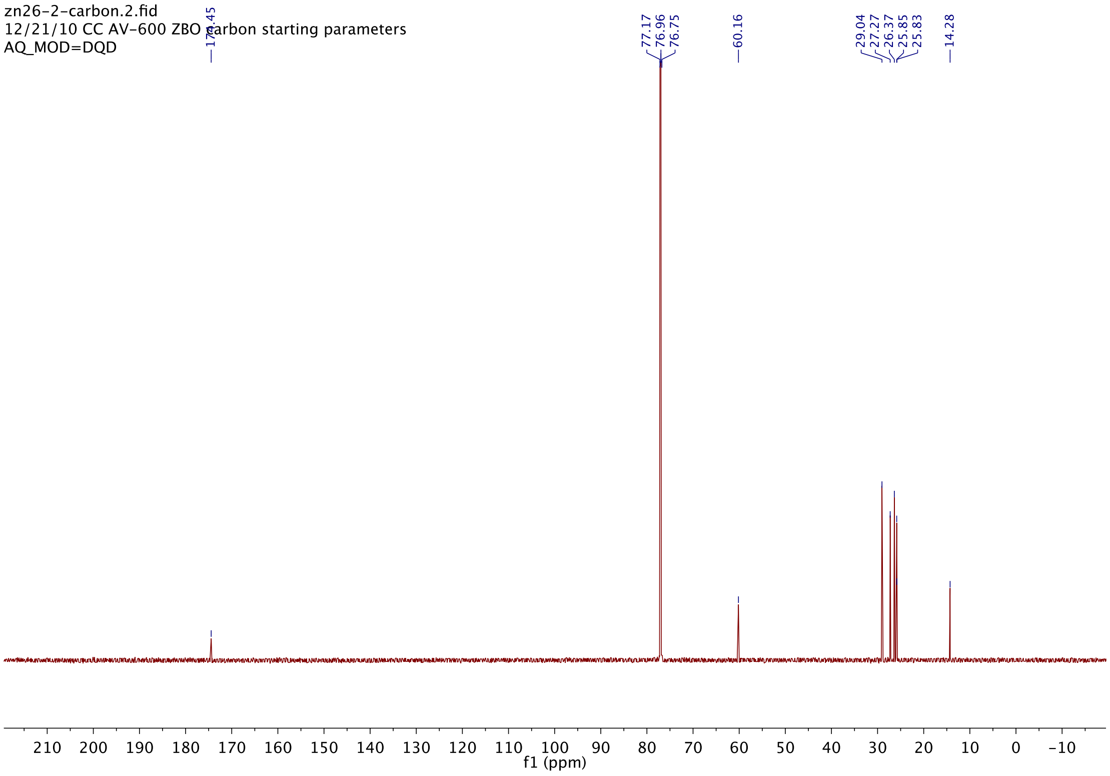


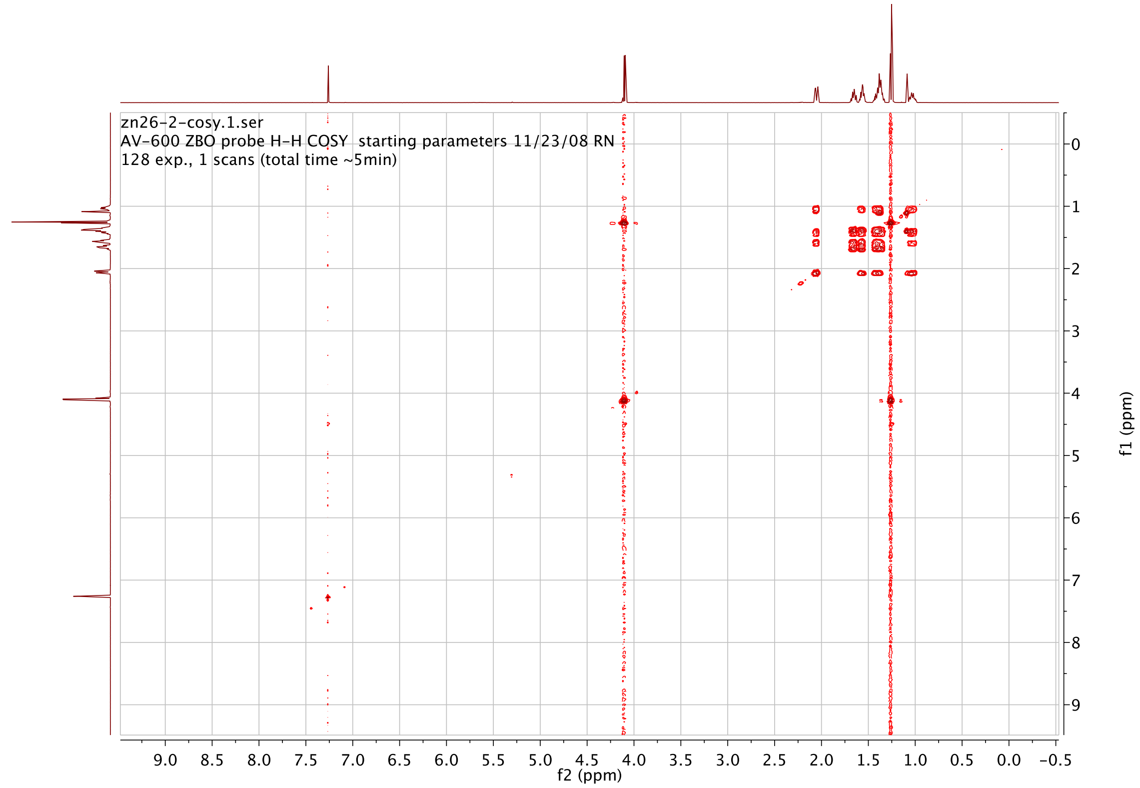


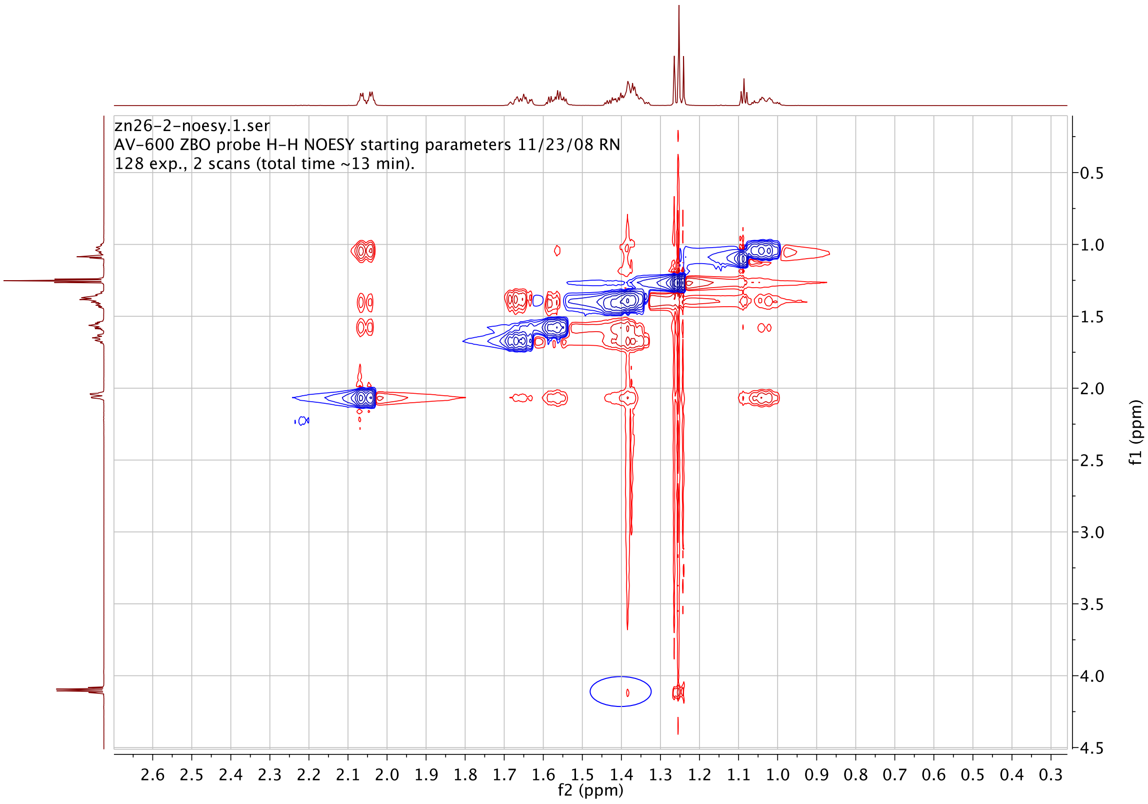
zn26_2.1.fid
AVQ-400 QNP Proton starting parameters. 7/16/03. Revised 7/22/03 RN

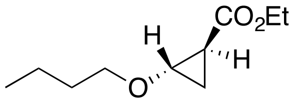


zn26-2-carbon.2.fid
12/21/10 CC AV-600 ZBO carbon starting parameters
AQ_MOD=DQD

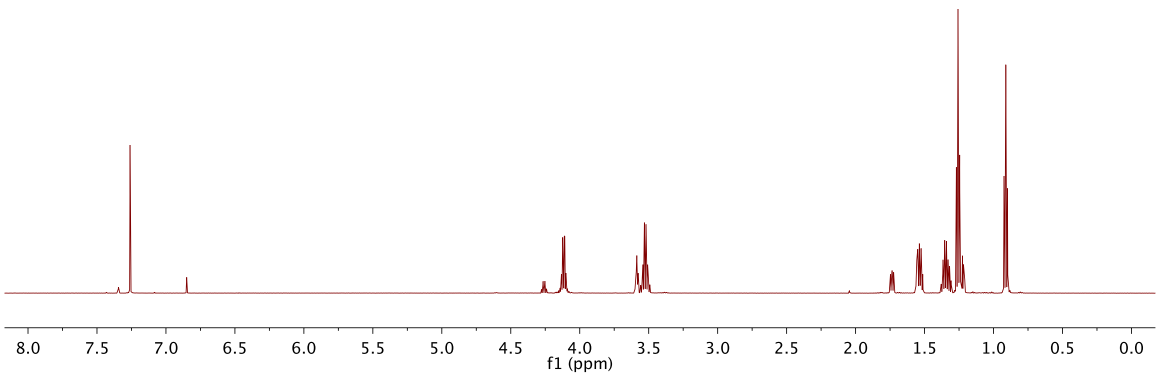



zn26-2-cosy.1.ser
AV-600 ZBO probe H-H COSY starting parameters 11/23/08 RN
128 exp., 1 scans (total time ~5min)
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f2 (ppm)
0 1 2 3 4 5 6 7 8 9
f1 (ppm)

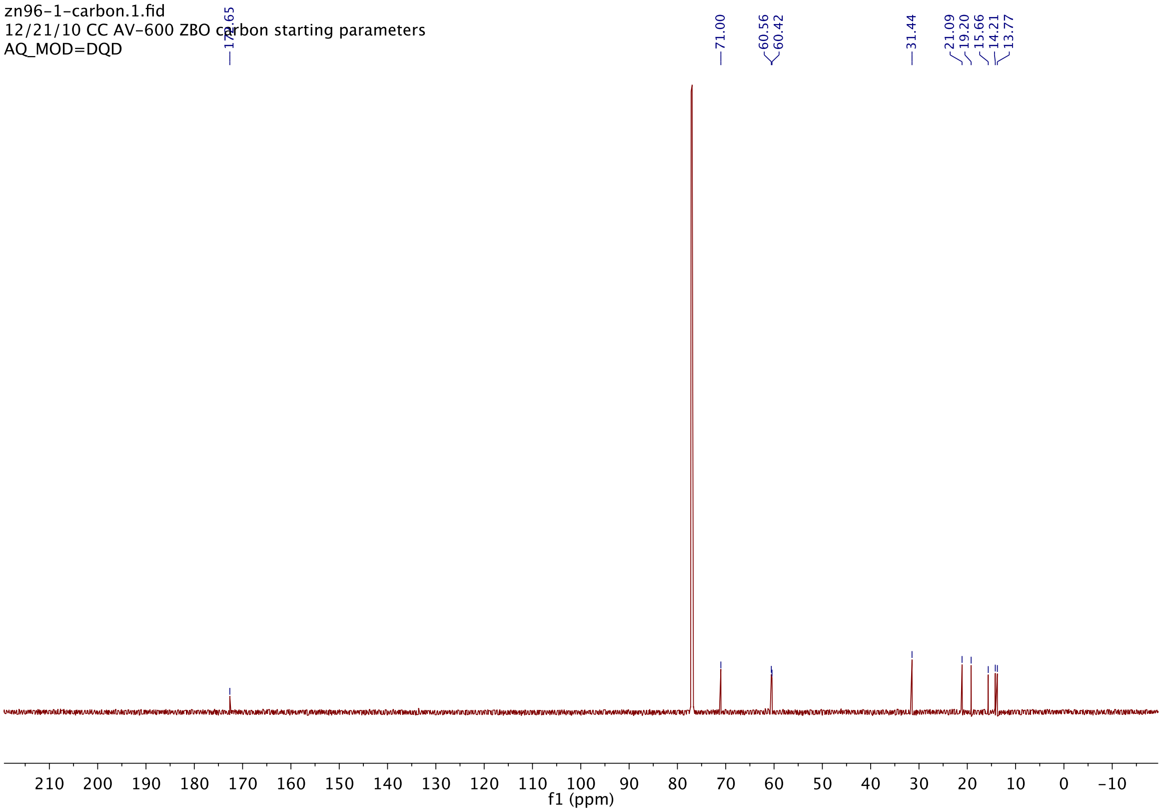

zn26-2-noesy.1.ser
AV-600 ZBO probe H-H NOESY starting parameters 11/23/08 RN
128 exp., 2 scans (total time ~13 min).
2.6 2.5 2.4 2.3 2.2 2.1 2.0 1.9 1.8 1.7 1.6 1.5 1.4 1.3 1.2 1.1 1.0 0.9 0.8 0.7 0.6 0.5 0.4 0.3
f2 (ppm)
0.5 1.0 1.5 2.0 2.5 3.0 3.5 4.0 4.5
f1 (ppm)

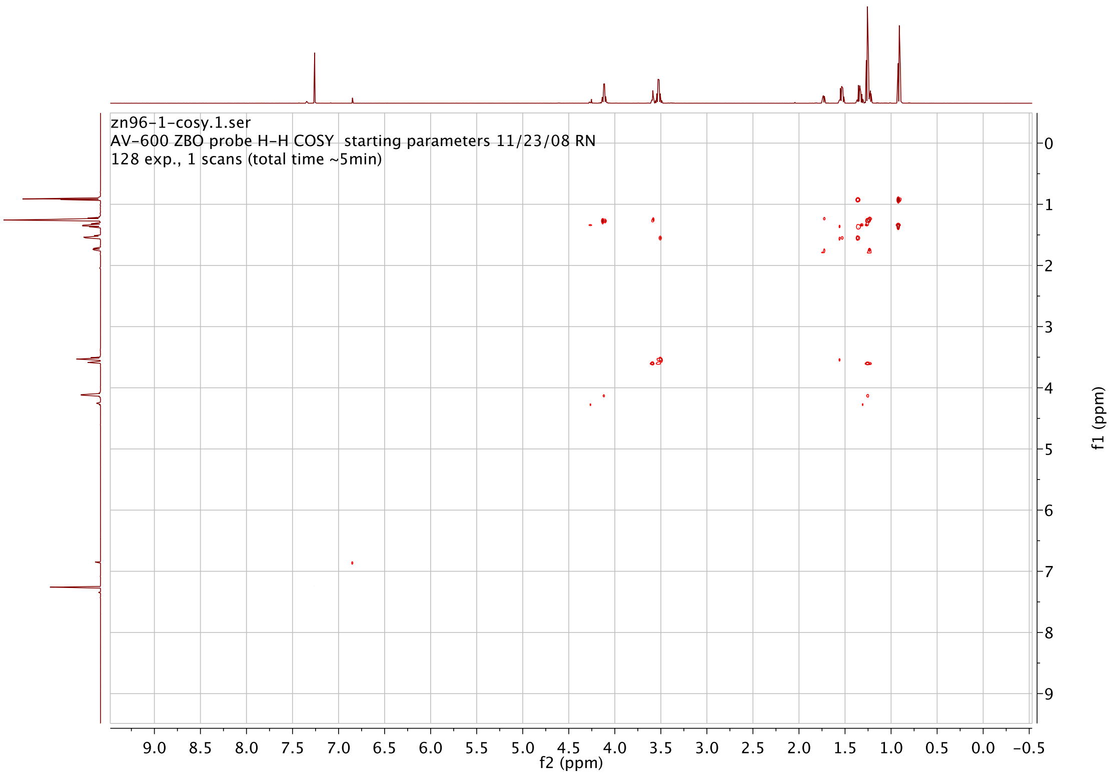


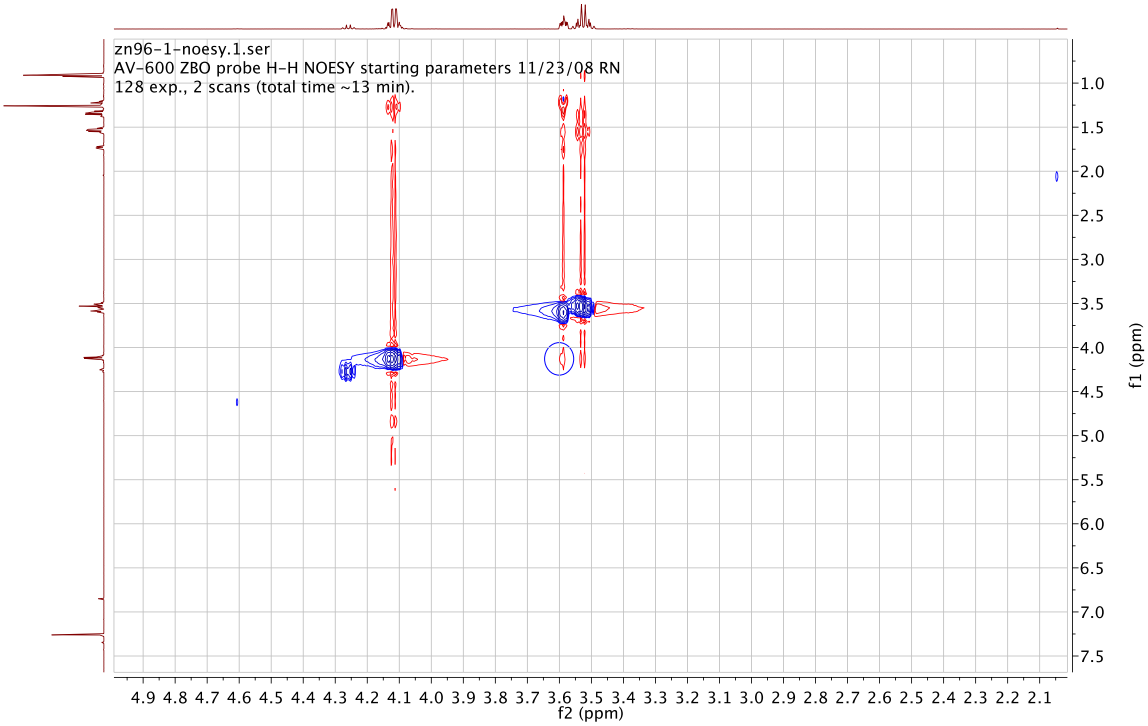
zn96-1.2.fid
AV-600 ZBO proton starting parameters 11/16/08 RN

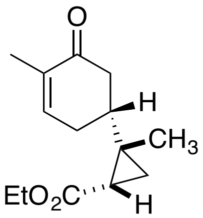


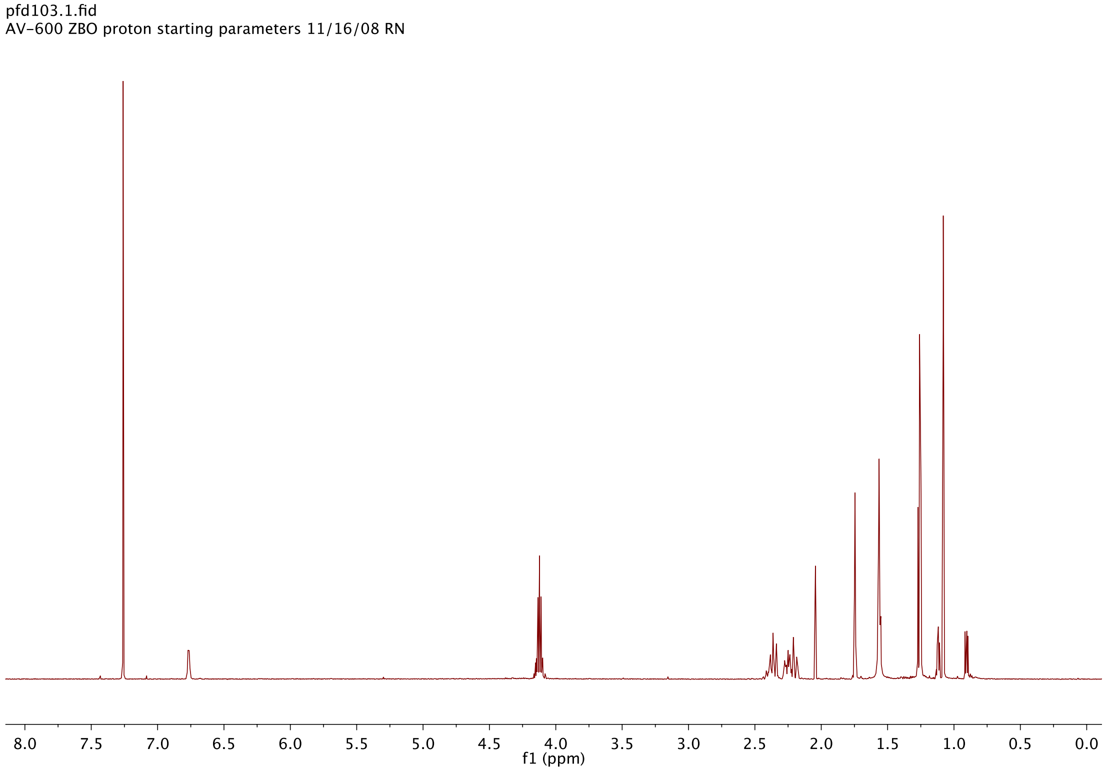
zn96-1-carbon.1.fid
12/21/10 CC AV-600 ZBO carbon starting parameters
AQ_MOD=DQD

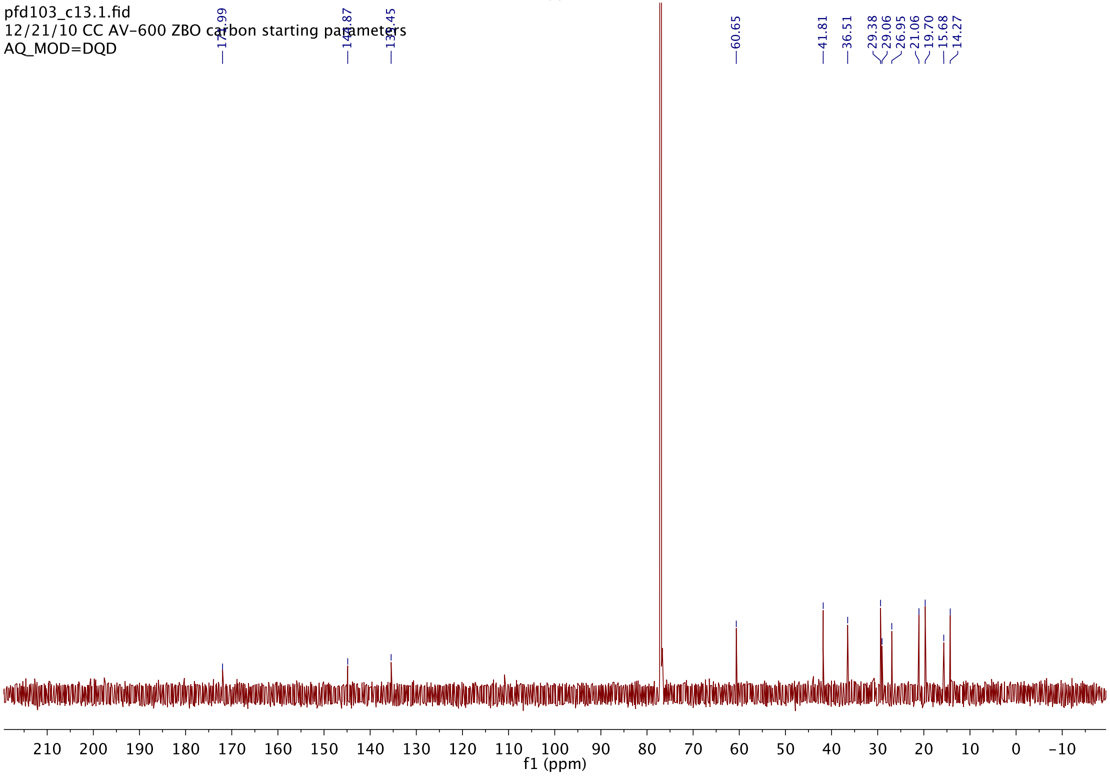



zn96-1-cosy.1.ser
AV-600 ZBO probe H-H COSY starting parameters 11/23/08 RN
128 exp., 1 scans (total time ~5min)
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 −0.5
f2 (ppm)
0 1 2 3 4 5 6 7 8 9
f1 (ppm)

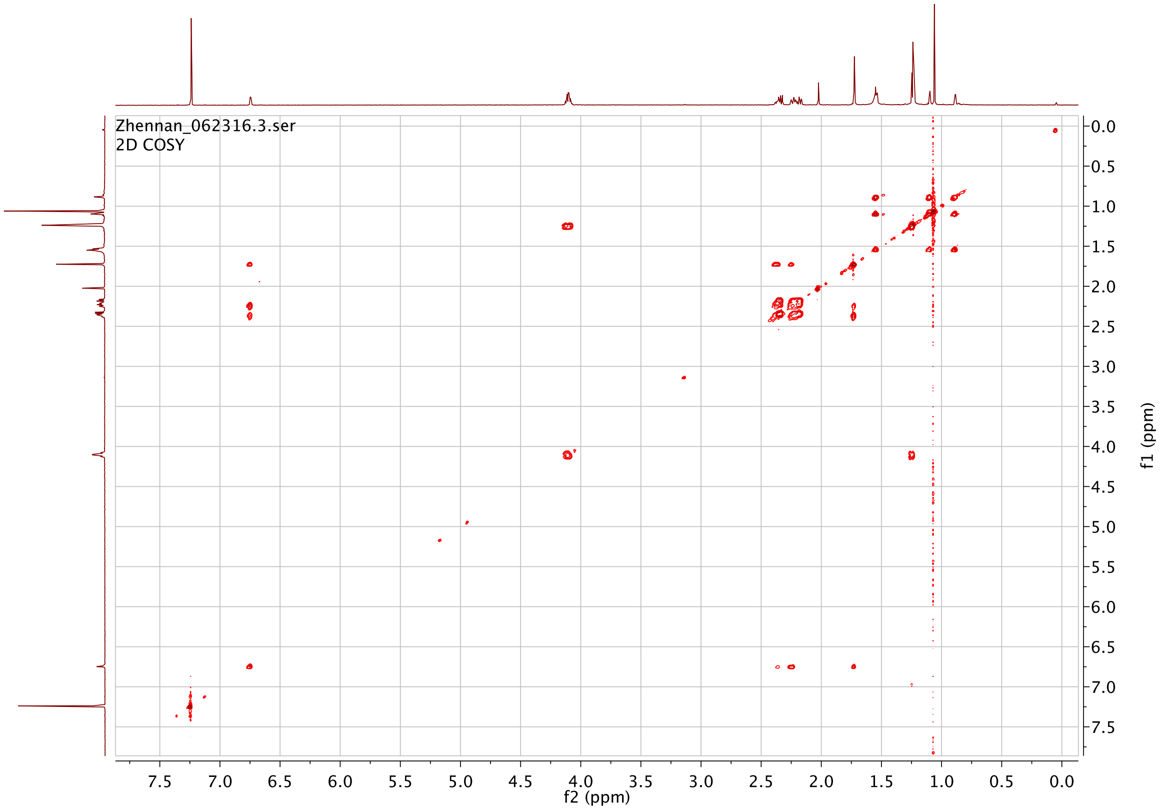

zn96-1-noesy.1.ser
AV-600 ZBO probe H-H NOESY starting parameters 11/23/08 RN
128 exp., 2 scans (total time ~13 min).
4.9 4.8 4.7 4.6 4.5 4.4 4.3 4.2 4.1 4.0 3.9 3.8 3.7 3.6 3.5 3.4 3.3 3.2 3.1 3.0 2.9 2.8 2.7 2.6 2.5 2.4 2.3 2.2 2.1
f2 (ppm)
1.0 1.5 2.0 2.5 3.0 3.5 4.0 4.5 5.0 5.5 6.0 6.5 7.0 7.5
f1 (ppm)


O
H
CH3
EtO2C
H

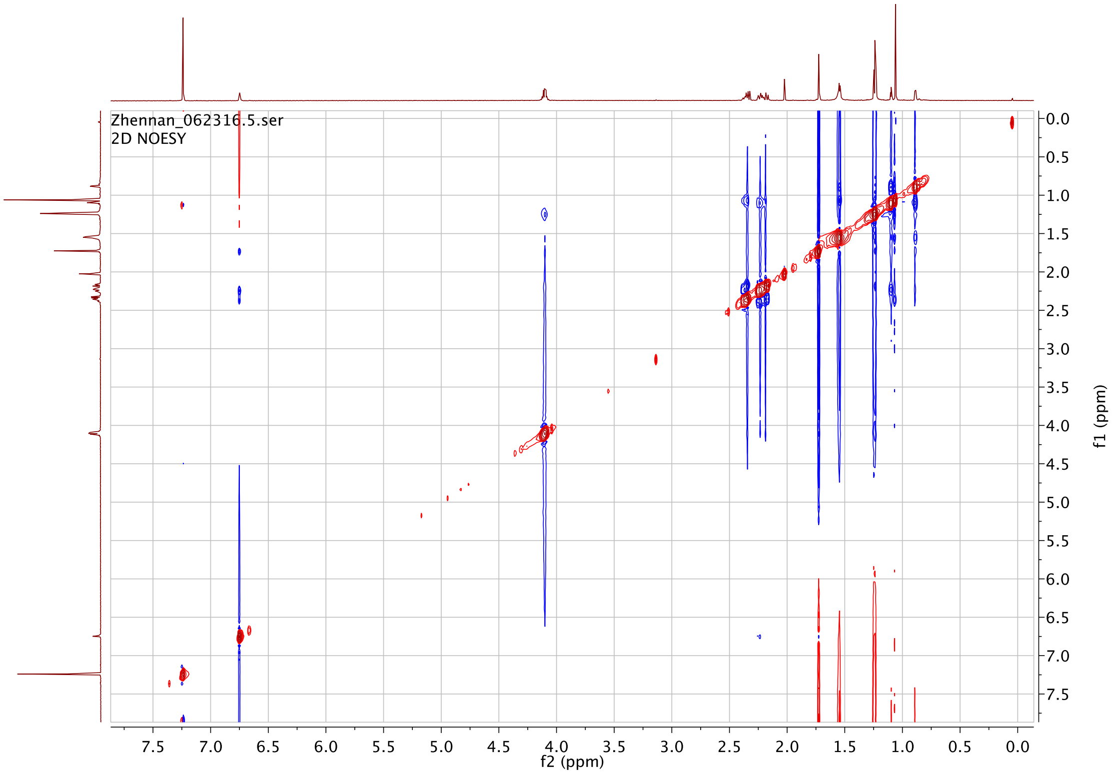

pfd103.1.fid
AV-600 ZBO proton starting parameters 11/16/08 RN
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


pfd103_c13.1.fid
12/21/10 CC AV-600 ZBO carbon starting parameters
AQ_MOD=DQD
171.99
144.87
135.45
60.65
41.81
36.51
29.38
29.06
26.95
21.06
19.70
15.68
14.27
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

Zhennan_062316.2.ser
2D HSQC
f1 (ppm)
f2 (ppm)



Zhennan_062316.3.ser
2D COSY
f1 (ppm)
f2 (ppm)


Zhennan_062316.5.ser
2D NOESY
f2 (ppm)
f1 (ppm)
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

References:

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