Supporting Information for

Highly diastereo- and enantioselective synthesis of trifluoromethyl-substituted cyclopropanes via myoglobin-catalyzed transfer of trifluoromethylcarbene.

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Table of contents:

Table S1. Diastereo- and enantioselectivity of Mb variants in whole-cell cyclopropanation of *p*-methoxystyrene in the presence of EDA or *ex situ* generated DTE. The absolute difference for the % *de* and % *ee* values measured with the two different carbene donors is also indicated. The graph in **Figure 3A** was generated by plotting the % *ee* values with EDA vs % *ee* value with DTE and by fitting the data with a linear regression model.

Mb Variant	*p*-methoxy-styrene + EDA [a]		*p*-methoxy-styrene + DTE [b]		|Δ(%*de*)|	|Δ(%*ee*)|
	% *de* (trans)	% *ee* (1*S*,2*S*)	% *de* (trans)	% *ee* (1*S*,2*S*)		
WT	79	13	70	4	9	9
Mb(H64V)	91	26	>99	65	8	39
Mb(V68A)	97	86	>99	98	2	12
Mb(H64V,V68A)	>99	99	>99	99.5	0	0.5
Mb(H64V,V68S)	98	84	97	83	1	1
Mb(H64V,V68G)	93	99	>99	98	6	1
Mb(H64V,I107W)	93	77	93	30	0	47
Mb(H64V,V68F,L29S) (= RR1)	89	-64	90	-63	1	1
Mb(H64V,V68L,L29T) (= RR2)	96	-57	98	-91	2	34
Mb(H64V,V68F,L29T) (= RR3)	97	-26	92	-39	5	13
Mb(H64V,V68F,L29T,I107L) (= RR4)	96	-73	94	-65	2	8
Mb(H64V,V68F,L29T,F43W) (= RR5)	89	-31	93	-38	4	7

[a] Reaction conditions: 400 µL scale reactions using 10 mM 4-methoxy-styrene (**9a**), 20 mM ethyl diazoacetate (EDA), and 380 µL *E. coli* (C41(DE3)) cells (OD_{600} = 40) expressing the indicated Mb variant in phosphate buffer (pH 7.2), room temp., 16 hours.

[b] Reaction conditions: 10 mL scale using 10 mM 4-methoxy-styrene (**9a**), 4 equiv. trifluoroethylamine (**5**) and 9.5 mL *E. coli* (C41(DE3)) cells (OD_{600} = 40) expressing the indicated Mb variant in phosphate buffer (pH 7.2), room temp., 16 hours.

Table S2. Diastereo- and enantioselectivity of *trans*-(1*R*,2*R*)-selective Mb variant RR2 (and RR4) for cyclopropanation of aryl-substituted olefins in the presence of *ex situ* generated DTE. Reactions were carried out on a 10 mL scale using Mb(H64V,V68L,L29T)-expressing *E. coli* (C41(DE3)) cells (OD_{600} = 40), 7.5 mM olefin, 4 equiv. trifluoroethylamine (**5**) in phosphate buffer (pH 7.2), room temp., 2.5 hours. [a] using OD_{600} = 80. [b] using 15 mM substrate. [c] using 12 equiv. trifluoroethylamine (**5**). [d] 5 hours.

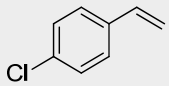
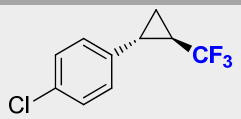
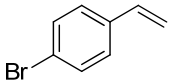
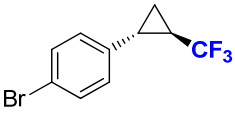
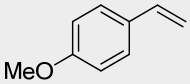
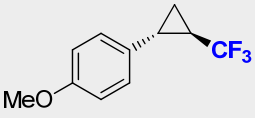
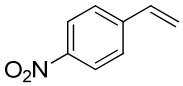
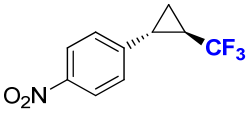
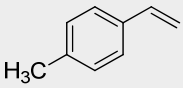
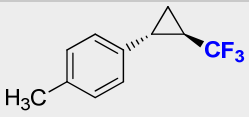
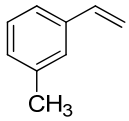
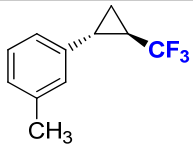
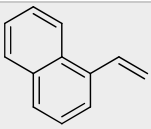
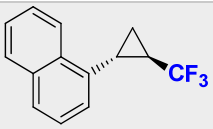
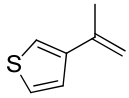
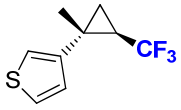
Entry	Substrate	Product	Mb variant	% *de* (trans)	% *ee* (1*R*,2*R*)
1	 **7a**	 **7c**	Mb(H64V,V68L,L29T) = RR2	99.9	83
2	 **8a**	 **8c**	Mb(H64V,V68L,L29T) = RR2	99.9	80
3	 **9a**	 **9c**	Mb(H64V,V68L,L29T) = RR2	98	91
4	 **10a**	 **10c**	Mb(H64V,V68L,L29T) = RR2	99.9	65
5[a,b]	 **11a**	 **11c**	Mb(H64V,V68L,L29T) = RR2	99.9	85
6[a,b]	 **12a**	 **12c**	Mb(H64V,V68L,L29T) = RR2	99.9	88
7[a,c]	 **13a**	 **13c**	Mb(H64V,V68L,L29T) = RR2 Mb(H64V,V68L,L29T,I107L) = RR4	99.9 99.9	21 58
8[a,c]	 **14a**	 **14c**	Mb(H64V,V68L,L29T) = RR2	99.9	92

Figure S1. Impact of Val68 mutations on active site configuration in myoglobin. (a) Ribbon representation of wild-type sperm whale myoglobin (pdb 1A6K) ; (b) close-up view of the heme distal pocket, showing the heme cofactor (tan) and amino acid residues defining the active site (orange) as stick models; (c) top views of the heme pocket in wild-type myoglobin (*left*) and models of this protein after substitution of Val68 with alanine (*middle*) or glycine (*right*). The latter highlight the cavity created by the V68A/G mutations (yellow) in proximity of pyrrole atom N2 (labeled) of the heme group, which is proposed to favor orientation of the heme-bound trifluoromethylcarbene group as depicted in **Figure 2A**.

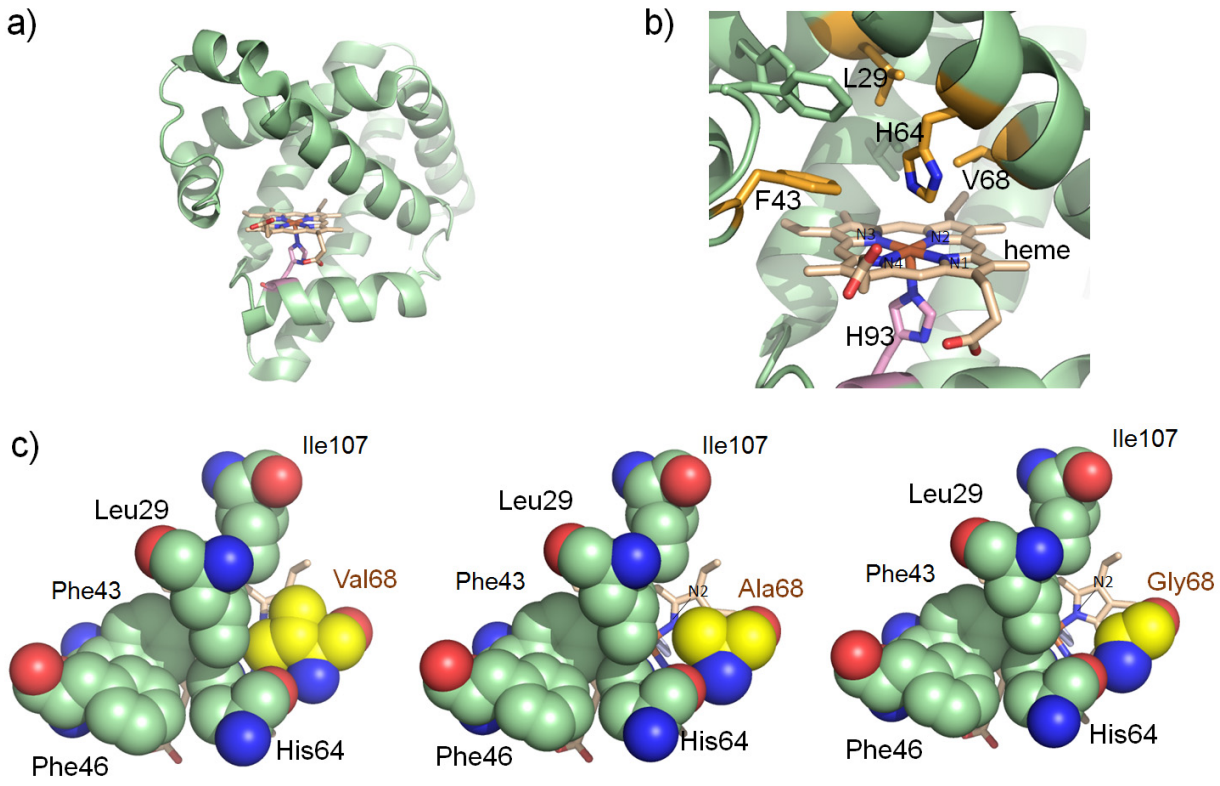
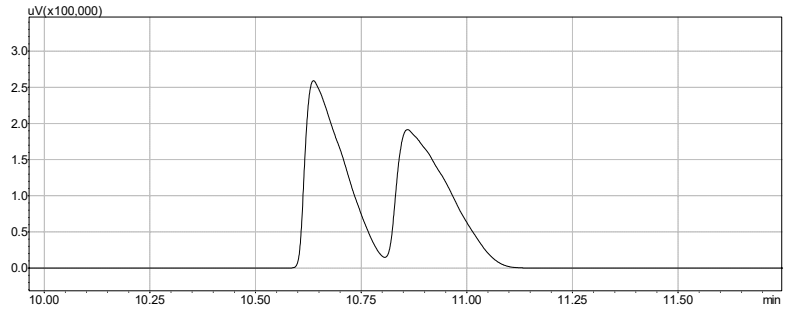


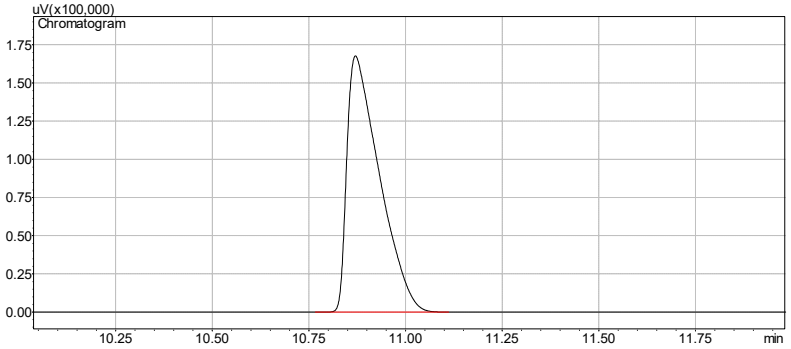
Figure S2. Chiral GC and SFC chromatograms for determination of enantiomeric excess in the cyclopropanation reactions catalyzed by the Mb variants. Reference racemic samples were prepared using Fe(III)(TPP)Cl catalyst as described in the experimental procedures.

(a) Reaction with 4-chloro-styrene (**7a**) and DTE to give **7b-c**:

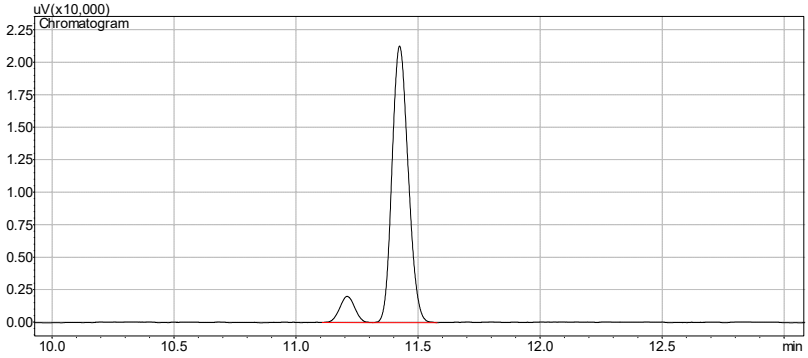
i. Chiral GC analysis of Fe(III)(TPP)Cl-catalyzed reaction:



ii. Chiral GC analysis of Mb(H64V,V68A)-catalyzed reaction:

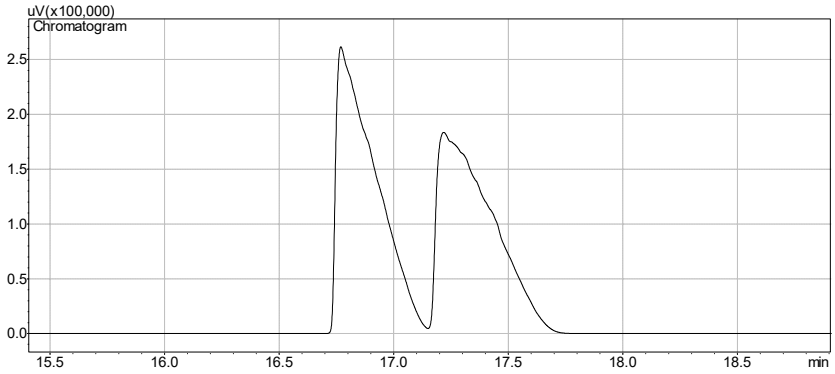


iii. Chiral GC analysis of RR2 (=Mb(H64V,V68L,L29T))-catalyzed reaction:

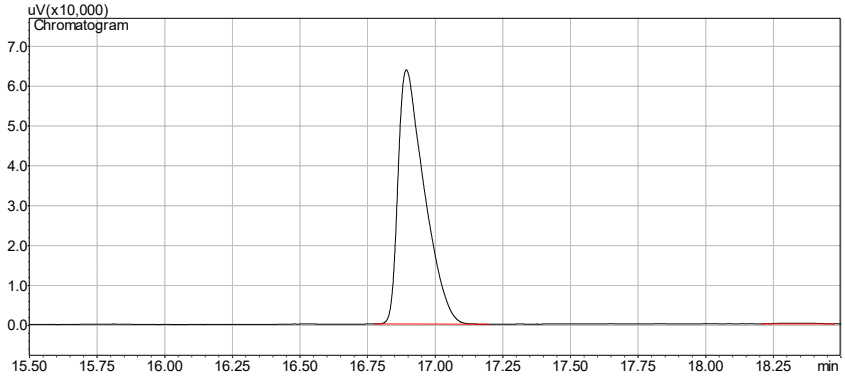


(b) Reaction with 4-bromo-styrene (**8a**) and DTE to give **8b-c**:

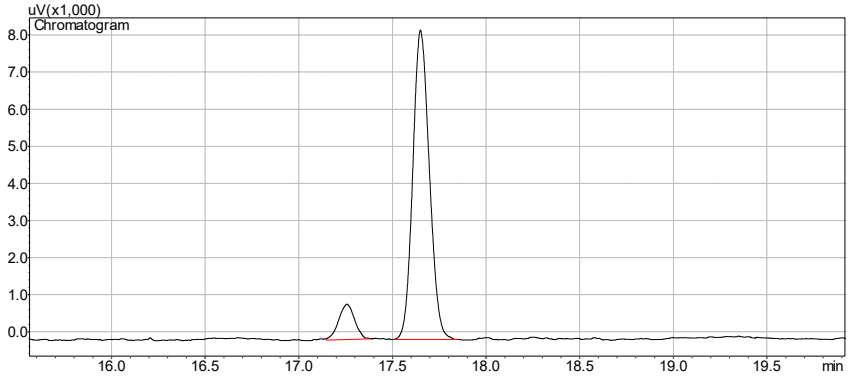
i. Chiral GC analysis of Fe(III)(TPP)Cl-catalyzed reaction:



ii. Chiral GC analysis of Mb(H64V,V68A)-catalyzed reaction:

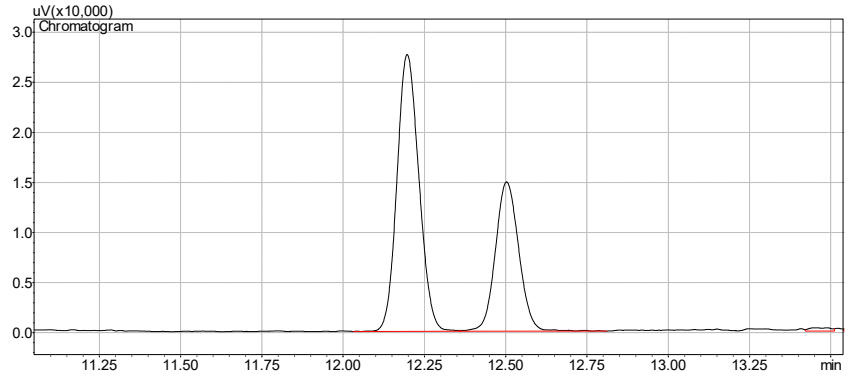


iii. Chiral GC analysis of RR2-catalyzed reaction:

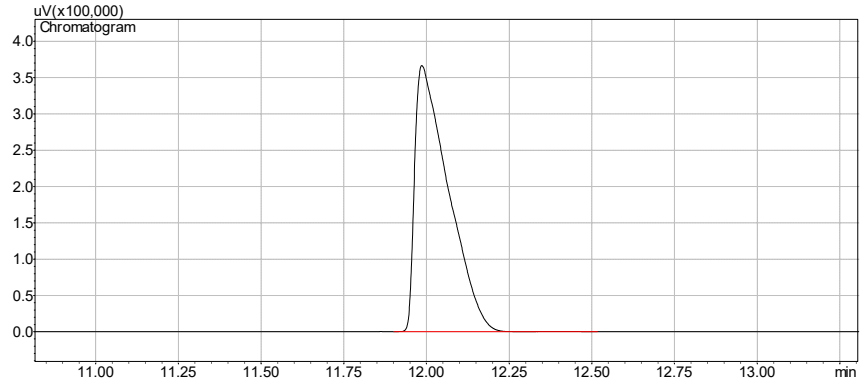


(c) Reaction with 4-methoxy-styrene (**9a**) and DTE to give **9b-c**:

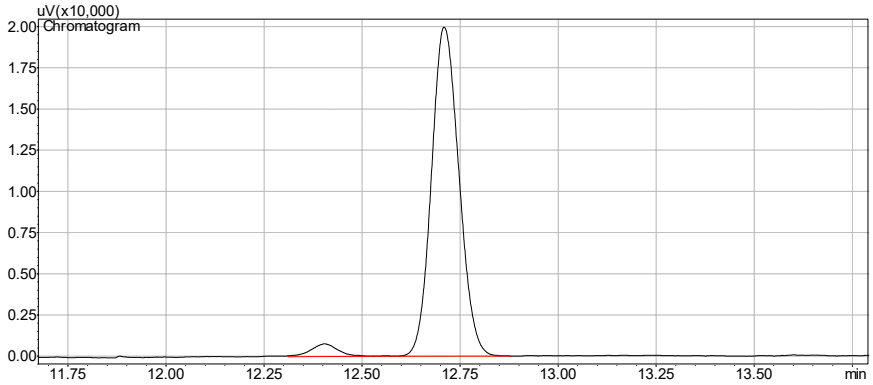
i. Chiral GC analysis of Fe(III)(TPP)Cl-catalyzed reaction:



ii. Chiral GC analysis of Mb(H64V,V68A)-catalyzed reaction:

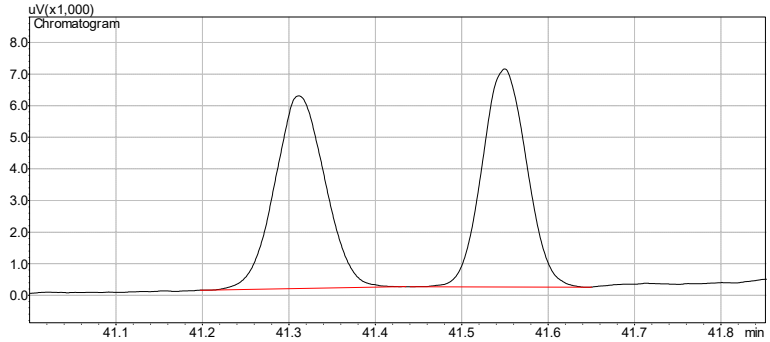


iii. Chiral GC analysis of RR2-catalyzed reaction:

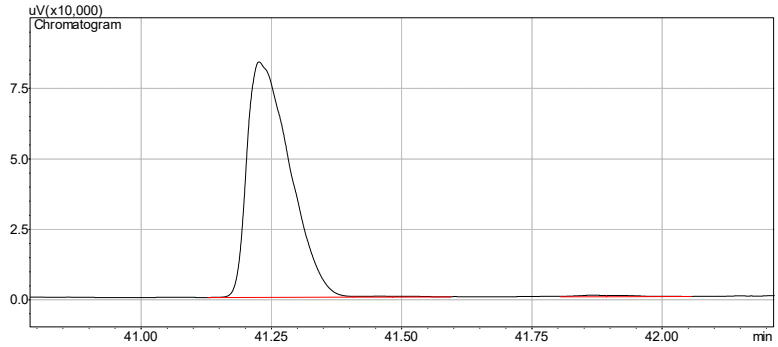


(d) Reaction with 4-nitro-styrene (**10a**) and DTE to give **10b-c**:

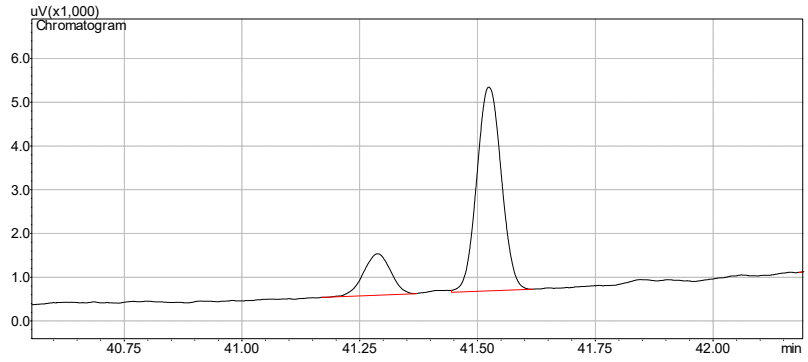
i. Chiral GC analysis of Fe(III)(TPP)Cl-catalyzed reaction:



ii. Chiral GC analysis of Mb(H64V,V68A)-catalyzed reaction:

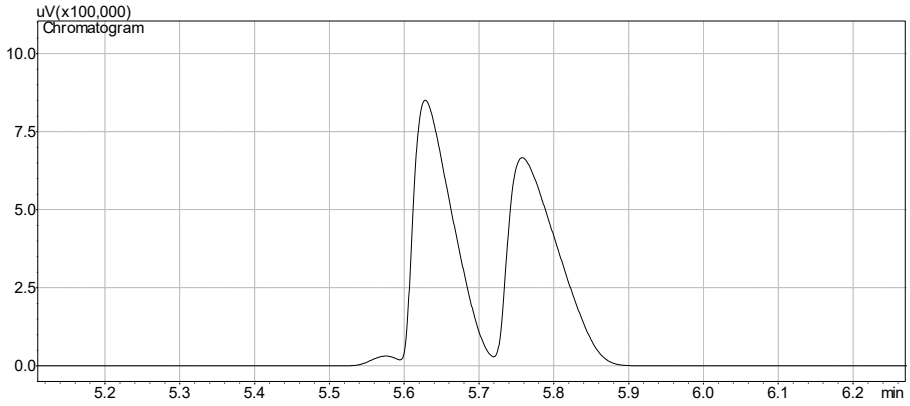


iii. Chiral GC analysis of RR2-catalyzed reaction:

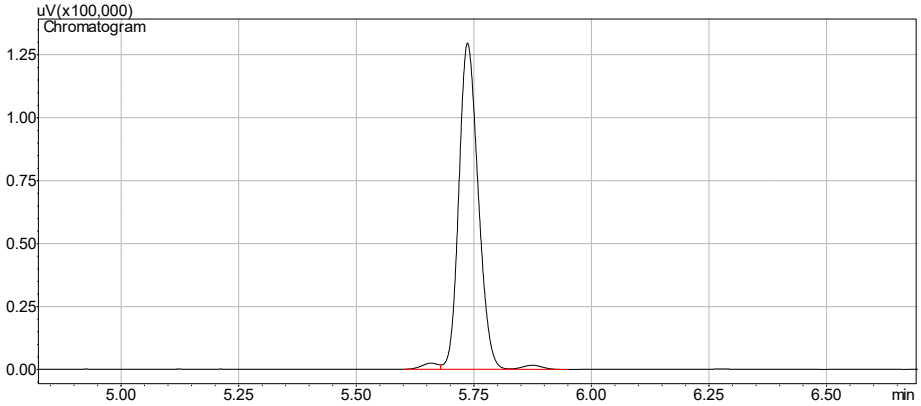


(e) Reaction with 4-methyl-styrene (**11a**) and DTE to give **11b-c**:

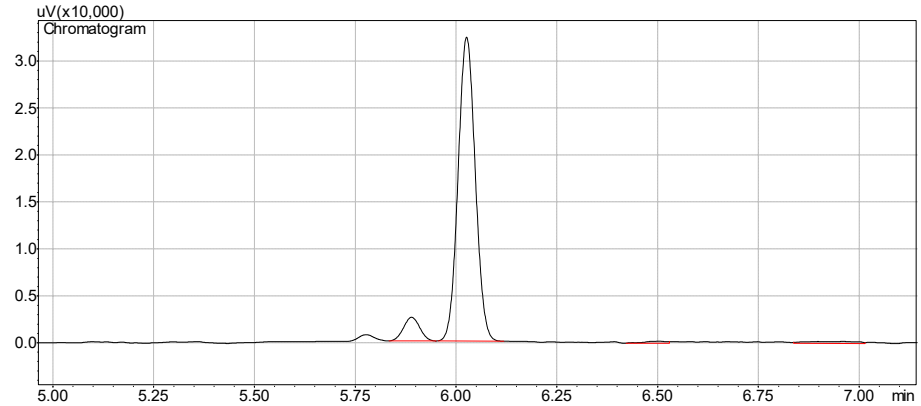
i. Chiral GC analysis of Fe(III)(TPP)Cl-catalyzed reaction:



ii. Chiral GC analysis of Mb(H64V,V68G)-catalyzed reaction:

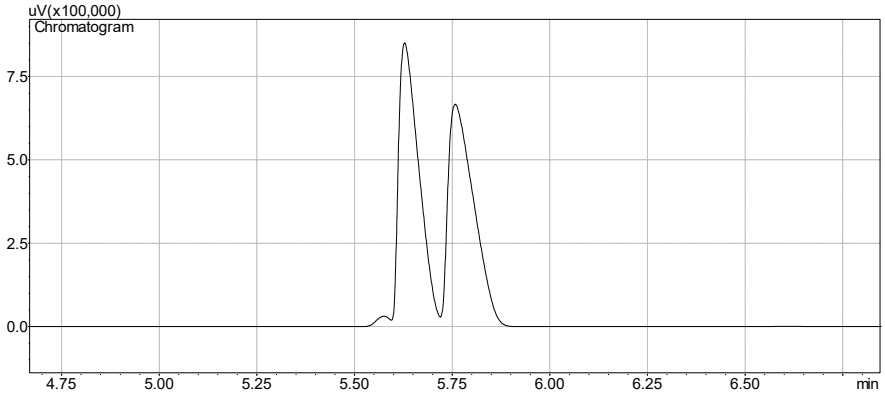


iii. Chiral GC analysis of RR2-catalyzed reaction:

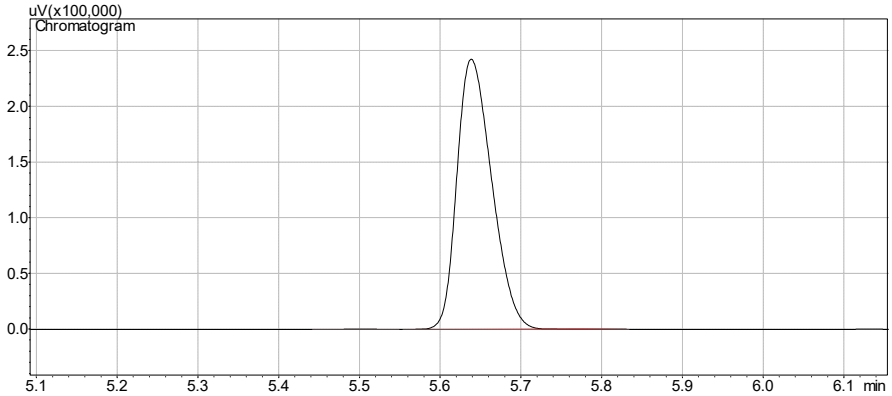


(f) Reaction with 3-methyl-styrene (**12a**) and DTE to give **12b-c**:

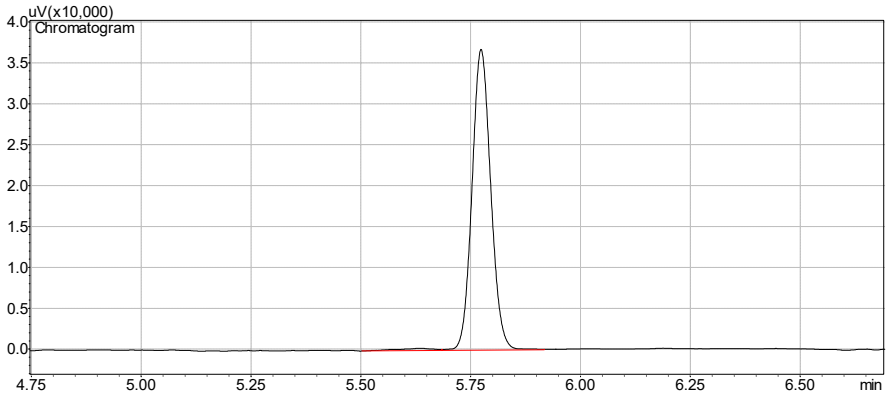
i. Chiral GC analysis of Fe(III)(TPP)Cl-catalyzed reaction:



ii. Chiral GC analysis of Mb(H64V,V68G)-catalyzed reaction:

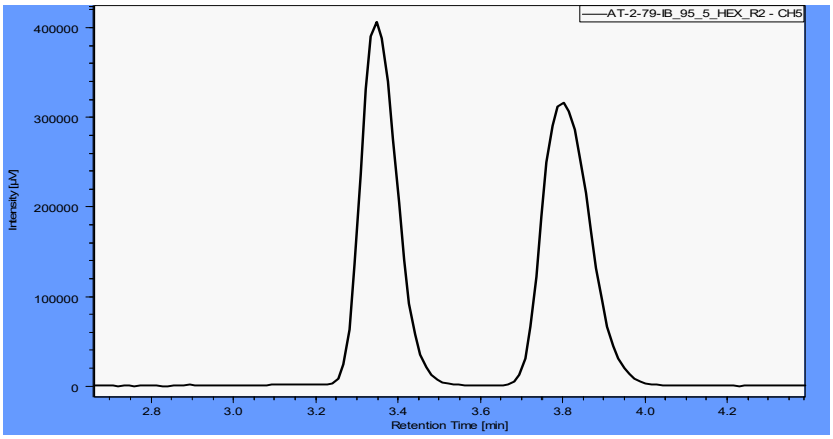


iii. Chiral GC analysis of RR2-catalyzed reaction:

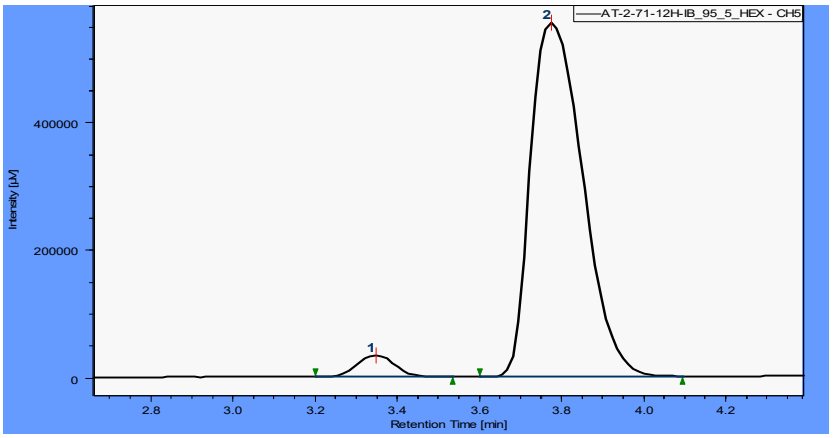


(g) Reaction with 1-vinyl-naphtalene (**13a**) and DTE to give **13b-c**:

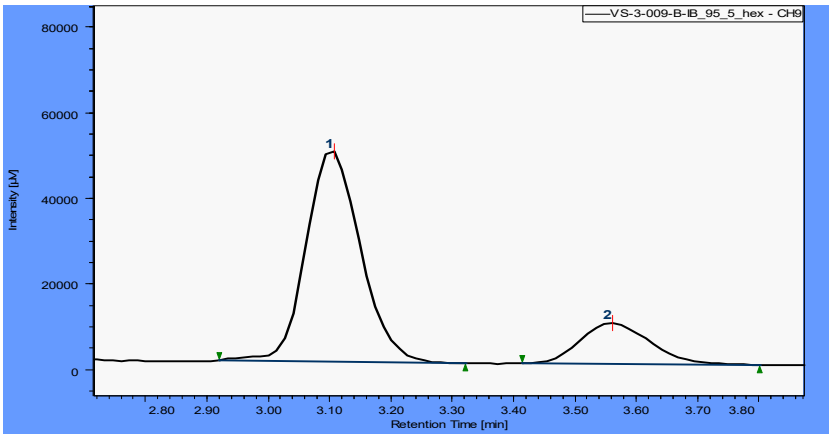
i. Chiral SFC analysis of Fe(III)(TPP)Cl-catalyzed reaction:



ii. Chiral SFC analysis of Mb(H64V,V68A)-catalyzed reaction:

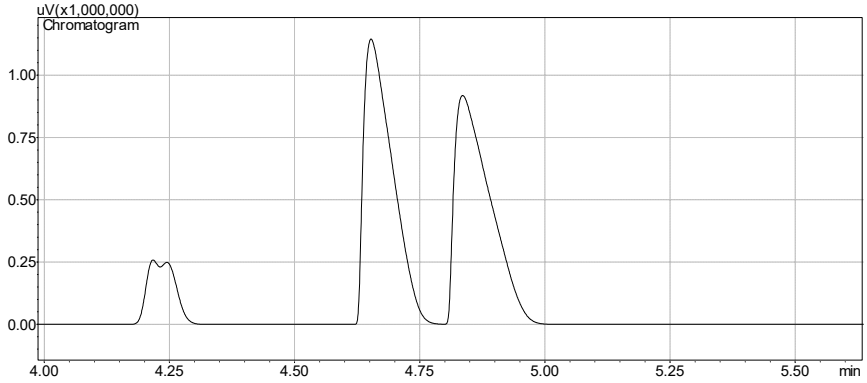


iii. Chiral SFC analysis of RR4-catalyzed reaction:

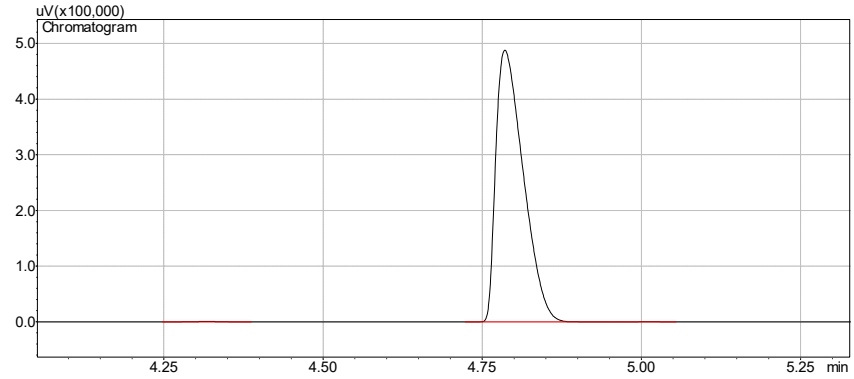


(h) Reaction with 3-(prop-1-en-2-yl)thiophene (**14a**) and DTE to give **14b-c**:

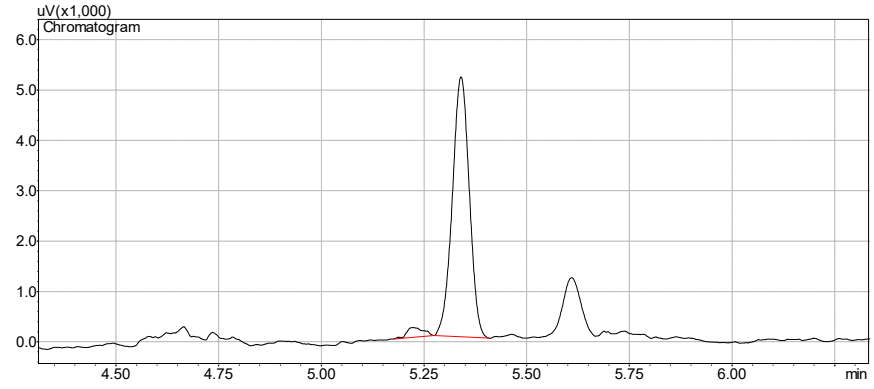
i. Fe(III)(TPP)Cl-catalyzed reaction:



ii. Mb(H64V,V68A)-catalyzed reaction:



iii. RR2 (=Mb(H64V,V68L,L29T))-catalyzed reaction:



Experimental Procedures

General Information

All chemicals and reagents were purchased from commercial suppliers (Sigma-Aldrich, ACS Scientific, Alfa Aeser, J.T. Baker) and used without any further purification, unless otherwise stated. All reactions were carried out under argon pressure in oven-dried glassware with magnetic stirring using standard gas-tight syringes, cannulae, and septa. ^{1}H, ^{13}C, and ^{19}F NMR spectra were measured on a Bruker DPX-400 instrument (operating at 400 MHz for ^{1}H, 100 MHz for ^{13}C, and 375 MHz for ^{19}F) or a Bruker DPX-500 instrument (operating at 500 MHz for ^{1}H and 125 MHz for ^{13}C). Tetramethylsilane (TMS) served as the internal standard (0 ppm) for ^{1}H NMR, $CDCl_3$ was used as the internal standard (77.0 ppm) for ^{13}C NMR, and trifluorotoluene served as the internal standard (0 ppm) for ^{19}F NMR. Column chromatography purification was carried out using AMD Silica Gel 60 Å 230-400 mesh. Thin Layer Chromatography (TLC) was carried out using Merck Millipore TLC silica gel 60 F254 glass plates.

Protein Expression

Cloning of the Mb variants investigated in this work was described previously (Bordeaux *et al.*, *Angew. Chem. Int. Ed.* **2015,** *54*, 1744; Bajaj *et al.*, *Angew. Chem. Int. Ed.* **2016,** *55*, 16110). The Mb variants were expressed in *E. coli* BL21(DE3) or *E. coli* C41(DE3) cells as follows. After transformation, cells were grown in TB medium (ampicillin, 100 mg L^{-1}) at 37 °C (200 rpm) until OD_{600} reached 0.6. Cells were then induced with 0.25 mM isopropyl-β-D-1-thiogalactopyranoside (IPTG) and 0.3 mM δ-aminolevulinic acid (ALA). After induction, cultures were shaken at 180 rpm and 27 °C and harvested after 20 h by centrifugation at 4,000 rpm at 4 °C. Myoglobin concentration was determined after cell lysis by sonication, followed by CO-binding assay using an extinction coefficient ε_{415} = 187 $mM^{-1}cm^{-1}$.

Synthetic Procedures

Alkenes **7a-13b** were purchased from chemical suppliers and used without further purification. Alkene **14a** was synthesized as described previously.[2] Racemic standards for the stereoisomer analyses of the cyclopropane products **7b-14b** were prepared via cyclopropanation with Fe(III)TPPCl catalyst according to the general **Procedure A** provided below, which is based

on a published method by Morandi & Carreira (*Angew. Chem. Int. Ed.* **2010,** *49*, 938). Enantioenriched Mb-catalyzed cyclopropanation products were synthesized following **Procedure B**, and were used as authentic standards for the construction of calibration curves.

Chemical Synthesis of Racemic Standards for Cyclopropanation Products (Procedure A)

To a round bottom flask was added Fe(TPP)Cl (0.0066 mmol), 4-dimethylamino pyridine (DMAP) (0.022 mmol), sodium acetate (0.044 mmol), and trifluoroethylamine hydrochloride (0.33 mmol). Degassed distilled water (1 mL) and H_2SO_4 (1.2 μL, 0.022 mmol) were added, and the solution was degassed for one minute by sparging with argon. The alkene (0.22 mmol) was subsequently added, and a $NaNO_2$ solution (27 mg, 0.399 mmol, in 1 mL of degassed, distilled water) was added via syringe pump over 10 hours. After additional 4 hours, CH_2Cl_2 and water were added, and the aqueous phase was extracted with CH_2Cl_2 three times. The organic layer was collected, dried with $MgSO_4$, and concentrated under reduced pressure. Analysis of the products was performed by filtering the crude reaction mixture through a plug of silica and eluting with pentanes for chiral GC analysis. The cyclopropanation products consist of a racemic mixture of *trans-(S,S)* and *trans-(R,R)* isomers.

Whole-cell Cyclopropanation Reactions with *ex situ* generated DTE (Procedure B)

Whole-cell experiments were carried out at a 20 mL-scale using 19 mL of *E. coli* cells expressing Mb(H64V,V68A), 7.5 mM alkene, and 5 equivalents of EDA or DTE. In a typical procedure, alkene (0.15 mmol alkene in 1 mL of ethanol) was added slowly to a 125 mL Erlenmeyer flask containing a suspension of Mb(H64V,V68A)-expressing cells (OD_{600} = 40 in KPi, pH 7.2) under argon pressure, equipped with a magnetic stir bar and sealed with a rubber septum. The mixture was stirred at room temperature under argon pressure. In a 25 mL round-bottom flask containing a magnetic stir bar, either glycine ethyl ester hydrochloride or 2,2,2-trifluoroethylamine hydrochloride (0.75 mmol), sodium acetate (0.10 mmol), 4-dimethylaminopyridine (DMAP) (0.05 mmol) were added and dissolved in degassed, deionized water (8.00 mL). Then, sulfuric acid (0.05 mmol) was added and the solution was degassed for one minute by sparging with argon. A solution of sodium nitrite (0.90 mmol) in degassed, deionized water (4 mL) was added by syringe pump over 3-4 hours at room temperature. The generated diazo reagent (EDA or TDE) was gradually bubbled into the alkene and whole cell

reaction mixture using a continuous flow of argon. The reaction mixture was stirred for 4-12 hours at room temperature under anaerobic conditions. The TON for the whole-cell reactions were calculated based on Mb concentration in the reaction mixture as measured via UV-vis spectroscopy (ε_{415} = 187 $mM^{-1}cm^{-1}$) after cell lysis. The reaction mixture was extracted using diethyl ether (20 mL x 3) in 50-mL Falcon tubes. The tubes were shaken for 3 min manually, followed by additional vortexing for 3 min, and centrifugation (4,000 rpm, 15 min). The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure in an ice-cold water bath. The crude product was purified via column chromatography using silica gel and 0-5% diethyl ether/pentanes as the eluent, keeping fractions on ice to prevent evaporation of the volatile products. Solvent was then removed by rotary evaporation using an ice-cold water bath to afford the desired product, which was characterized by GC-MS, ^{1}H-NMR, ^{13}C-NMR, and ^{19}F-NMR.

Product Analysis

The reactions were analyzed by adding 20 μL of internal standard (benzodioxole, 100 mM in methanol) to a 400 μL aliquot of the whole-cell reaction mixture, followed by extraction with 400 μL of dichloromethane (DCM) and centrifugation at 14,000 rpm. The organic layer was collected and analyzed by GC-FID (see **Analytical Methods** section for details on GC analyses). Calibration curves for the different cyclopropane products were constructed using pure products isolated from the whole-cell cyclopropanation reactions as references (see **Synthetic Procedures**). All measurements were performed at least in duplicate. For stereoselectivity determination, the samples were analyzed by GC-FID or SFC using a chiral column as described below.

Analytical Methods

Gas chromatography (GC) analyses were carried out using a Shimadzu GC-2010 gas chromatograph equipped with a FID detector, and a Cyclosil-B column (30 m x 0.25 mm x 0.25 μm film). The following GC method was used for TON analysis and stereoisomer separation for **7b-c** through **12b-c** and **14b-c**: 1 μL injection, injector temp.: 200 ºC, detector temp: 300 ºC. Gradient: column temperature set at 120ºC for 3 min, then to 150 ºC at 0.8 ºC/min, then to 245 ºC at 25 ºC/min. Total run time was 46.30 min.

Product	t_R for (*1S,2S*) isomer (min)	t_R for (*1R,2R*) isomer (min)
7b/7c	10.64	10.86
8b/8c	16.77	17.22
9b/9c	12.20	12.50
10b/10c	41.31	41.55
11b/11c	5.63	5.76
12b/12c	5.62	5.76
14b/14c	4.65	4.84

Stereoisomer resolution for compounds **13b-c** was performed by Supercritical Fluid Chromatography (SFC) analysis, using a JASCO Analytical and Semi-Preparative SFC instrument equipped with a column oven (35 °C), photodiode array detector, a backpressure regulator (12.0 MPa), a carbon dioxide pump and a sample injection volume of 3 μL. Daicel Chiralpak IA, IB or IC column (0.46 cm ID × 25 cm L) were used for separation of enantiomers. All samples were eluted using an isocratic solvent system with the indicated modifier (see table below) in liquid CO_2 at an elution rate of 4 mL/min and detected at λ = 220 nm. Total run time was 10.2 min.

Product	Column	Modifier Solvent	t_R for (*1S,2S*) isomer (min)	t_R for (*1R,2R*) isomer (min)
13b/13c	IB	Hexanes	3.77	3.35

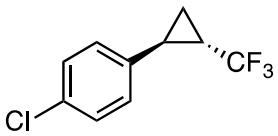
Preparative Scale Cyclopropanation Reaction with *ex situ* Generated DTE (Procedure C)

A preparative scale experiment was carried out using 39 mL of *E. coli* cells expressing Mb(H64V,V68A), 30 mM alkene, and 10 equivalents of DTE. Alkene (0.600 mmol 4-methoxy styrene in 1 mL of ethanol) was added slowly to a 125 mL Erlenmeyer flask containing 39 mL of resuspended Mb(H64V,V68A)-expressing cells (OD_{600} = 80 in KPi, pH 7.2) under argon pressure, equipped with a magnetic stir bar and sealed with a rubber septum. The mixture was stirred at room temperature under argon pressure. A second 125 mL Erlenmeyer flask containing 20 mL of cell suspension and a magnetic stir bar was connected in tandem to the reaction flask. In a 50 mL round-bottom flask containing a magnetic stir bar, 2,2,2-trifluoroethylamine hydrochloride (6.00 mmol), sodium acetate (0.798 mmol), 4-dimethylaminopyridine (DMAP) (0.402 mmol) were

added and dissolved in degassed, deionized water (12.00 mL). Then, sulfuric acid (0.402 mmol) was added and the solution was degassed for one minute by sparging with argon. A solution of (7.20 mmol) sodium nitrite in degassed, deionized water (8 mL) was added by syringe pump over 4 hours at room temperature. The generated DTE was gradually bubbled into the alkene and whole cell reaction mixture using a continuous flow of argon. The reaction mixture was stirred for 5 hours at room temperature under anaerobic conditions. Reaction mixtures from both flasks were combined and extracted with dichloromethane (20 mL x 3). The organic layers were combined and dried over sodium sulfate. Dichloromethane was removed by distillation using a Liebig condenser at 50 °C. The concentrated crude product was transferred to a 250 mL round-bottom flask and a magnetic stir bar was added. Anhydrous dichloromethane (20 mL) was added and the mixture was allowed to stir at 0 °C. Then, *meta*-chloroperoxybenzoic acid (mCPBA) (0.1151 g, 0.667 mmol) was added and the reaction mixture was stirred overnight. After 12 h, residual alkene was consumed, as verified by TLC (1% diethyl ether/pentanes, visualized with CAN stain). The reaction mixture was washed with 5% aqueous KOH (20 mL) and extracted with dicholoromethane (15 mL x 3). Dichloromethane was removed by distillation and the product was purified via flash column chromatography using silica and 5% diethyl ether/pentanes to afford the cyclopropanation product as a clear, colorless oil (98.0 mg, 76% isolated yield, >99.9 $de_{trans,}$ >99.9 $ee_{(1S,2S)}$).

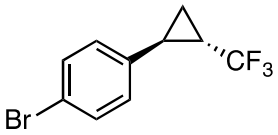
Compound Characterization Data

1-Chloro-4-(2-(trifluoromethyl)cyclopropyl)benzene (7b):



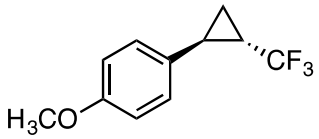
Following standard procedure **B,** except an additional 125 mL Erlenmeyer flask containing 20 mL of cell suspension was connected in tandem to the alkene and whole-cell reaction flask. Enantioenriched *trans* isomer 1-chloro-4-(2-(trifluoromethyl) cyclopropyl) benzene was isolated via column chromatography using silica and 100% pentanes to afford the product as a colorless oil, 67% yield. GC-MS m/z (% relative intensity): 222(13.4), 220(40.3), 185(100), 165(67.8), 151(47.6), 116(64.8), 115(82.9); ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.24 (d, J = 8.5 Hz, 2H), 7.03 (d, J = 8.5 Hz, 2H), 2.32 (dt, J = 10.0, 5.4 Hz, 1H), 1.77-1.70 (m, 1H), 1.37 (dt, 10.9, 5.6 Hz, 1H), 1.12-1.09 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 137.5, 132.6, 128.7, 127.9, 124.6, 23.4 (q, J = 37 Hz), 19.1, 10.8 (d, J = 2 Hz); ^{19}F NMR (375 MHz, $CDCl_3$): δ -4.5 (d, J = 2 Hz).

1-Bromo-4-(2-(trifluoromethyl)cyclopropyl)benzene (8b)



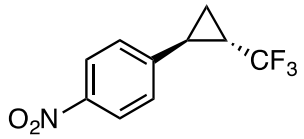
Following standard procedure **B,** except Mb(H64V,V68A)-expressing cells diluted to OD_{600} = 80 (KPi, pH 7.2) were used and an additional 125 mL Erlenmeyer flask containing 20 mL of cell suspension was connected in tandem to the alkene and whole-cell reaction flask. Enantioenriched *trans* isomer 1-bromo-4-(2-(trifluoromethyl)cyclopropyl)benzene was isolated via column chromatography using silica and 100% pentanes to afford the product as a colorless oil, 68% yield. GC-MS m/z (% relative intensity): 266(39.2), 264(41.6), 185(65.8), 165(62.0), 116(100), 115(63.6); ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.39 (d, J = 8.5 Hz, 2H), 6.97 (d, J = 8.4 Hz, 2H), 2.30 (dt, J = 10.1, 5.5 Hz, 1H), 1.77-1.70 (m, 1H), 1.37 (dt, J = 9.8, 5.7 Hz, 1H), 1.13-1.09 (m, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 138.0, 131.7, 128.3, 124.6, 120.5, 23.4 (q, J = 37 Hz), 19.1 (d, J = 2 Hz), 10.8 (d, J = 2 Hz) ; ^{19}F NMR (375 MHz, $CDCl_3$): δ -4.5 (d, J = 2 Hz).

1-Methoxy-4-(2-(trifluoromethyl)cyclopropyl)benzene (9b):



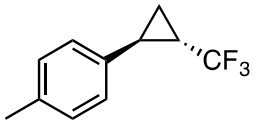
Following standard procedure **C,** enantioenriched *trans* isomer 1-methoxy-4-(2-(trifluoromethyl) cyclopropyl)benzene was isolated via flash column chromatography using silica and 5% diethyl ether in pentanes to afford the product as a colorless oil, 76% yield. GC-MS m/z (% relative intensity): 216(100), 215(45.4), 185(12.6), 147(70.5), 115(20.4); ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.08 (d, *J* = 10.6 Hz, 2H), 6.86 (d, *J* = 10.5 Hz, 2H), 3.80 (s, 3H), 2.35 (dt, *J* = 16.0, 8.5 Hz, 1H), 1.76-1.70 (m, 1H), 1.35 (dt, *J* = 13.0, 6.5 Hz, 1H), 1.14-1.05 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 158.5, 131.0, 127.4 (q, *J* = 338 Hz), 114.0, 53.3, 29.7, 23.0 (q, *J* = 36), 18.9, 10.4; ^{19}F NMR (375 MHz, $CDCl_3$): δ -4.4 (d, *J* = 6.8 Hz).

1-Nitro-4-(2-(trifluoromethyl)cyclopropyl)benzene (10b)



Following procedure **B**, enantioenriched *trans* isomer 1-nitro-4-(2-(trifluoromethyl) cyclopropyl)benzene was isolated via column chromatography using silica gel and 5% diethyl ether in pentanes to afford the product as a white crystalline solid, 43% yield. GC-MS m/z (% relative intensity): 231(80.5), 201(32.5), 165(43.3), 164(43.6), 145(34.4), 116(68.9), 115(100); ^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.14 (d, *J* = 8.5 Hz, 2H), 7.22 (d, *J* = 8.6 Hz, 2H), 2.42 (dt, *J* = 15.0, 5.5 Hz, 1H), 1.92 (m, 1H), 1.50 (dt, *J* = 12.0, 5.9 Hz, 1H), 1.29 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 146.9 (d, *J* = 55 Hz), 127.1, 126.4, 124.2, 123.8, 58.3, 24.3 (q, *J* = 37 Hz), 19.5 (d, *J* = 3 Hz) , 18.4, 11.8 (d, *J* = 2 Hz); ^{19}F NMR (375 MHz, $CDCl_3$): δ -4.4 (d, *J* = 6.8 Hz).

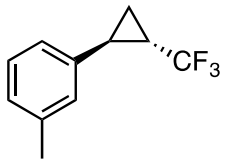
1-Methyl-4-(2-(trifluoromethyl)cyclopropyl)benzene (11b)



Following procedure **B,** except Mb(H64V,V68G)-expressing cells (OD_{600} = 80 in KPi, pH 7.2) were used and an additional 125 mL Erlenmeyer flask containing 20 mL of cell suspension was

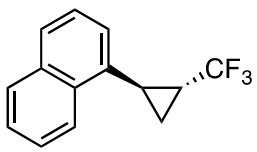
connected in tandem to the alkene and whole-cell reaction flask. Enantioenriched *trans* isomer 1-methyl-4-(2-(trifluoromethyl)cyclopropyl)benzene was isolated via column chromatography using silica gel and 100% pentanes to afford the product as a colorless oil, 78% yield. GC-MS m/z (% relative intensity): 200(77.3), 185(58.2), 165(33.1), 131(100), 116(30.5), 115(38.3), 91(27.1); ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.08 (d, J = 8.0 Hz, 2H), 6.99 (d, J = 7.5, 2H), 2.31 (m, 4H), 1.76 (m, 1H), 1.32 (dt, J = 15.0, 5.5 Hz, 1H), 1.12-1.08 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 136.4, 136.0, 129.3, 126.4, 124.9, 23.2 (q, J = 36 Hz), 21.0, 19.2, 10.7 (d, J = 2.1); ^{19}F NMR (375 MHz, $CDCl_3$): δ -4.3 (d, J = 6.4 Hz).

1-Methyl-3-(2-(trifluoromethyl)cyclopropyl)benzene (12b)



Following procedure **B,** except Mb(H64V,V68G)-expressing cells (OD_{600} = 80 in KPi, pH 7.2) were used and an additional 125 mL Erlenmeyer flask containing 20 mL of cell suspension was connected in tandem to the alkene and whole-cell reaction flask. Enantioenriched *trans* isomer 1-methyl-3-(2-(trifluoromethyl)cyclopropyl)benzene was isolated via column chromatography using silica gel and 100% pentanes to afford the product as a colorless oil, 82% yield. GC-MS m/z (% relative intensity): 200(74.7), 185(47.2), 165(31.8), 131(100), 116(29.9), 115(36.9), 91(26.5); ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.17-7.14 (t, J = 7.5 Hz, 1H), 7.01 (d, J = 7.5 Hz, 1H), 6.91 (s, 1H), 6.90-6.87 (m, 2H), 2.30 (m, 4H), 1.80 (m, 1H), 1.33 (dt, J = 15 Hz, 5 Hz, 1H), 1.14-1.10 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 139.0, 138.3, 128.5, 127.5, 127.3, 127.0 123.4, 23.3 (q, 37 Hz), 21.4, 19.5, 10.8; ^{19}F NMR (375 MHz, $CDCl_3$): δ -4.4 (d, J = 6.4 Hz).

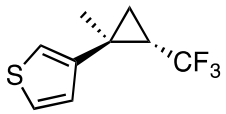
1-(2-(Trifluoromethyl)cyclopropyl)naphthalene (13b)



Following procedure **B**, except Mb(H64V,V68A)-expressing cells (OD_{600} = 80 in KPi, pH 7.2) were used. Enantioenriched *trans* isomer 1-(2-(Trifluoromethyl)cyclopropyl) naphthalene was isolated via column chromatography using silica gel and 100% pentanes to afford the product as a

colorless oil, 58% yield. GC-MS m/z (% relative intensity): 236(86.4), 167(100), 165(57.0), 153(44.3), 152(49.9), 139(20.8); ^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.29 (d, *J* = 8 Hz, 1H), 7.86-7.75 (dd, *J* = 40, 8 Hz, 2H), 7.59-7.49 (dt, *J* = 25, 7 Hz, 2H), 7.40 (t, *J* = 7.2 Hz, 1H), 7.27 (d, *J* = 6.9 Hz, 1H), 2.82-2.77 (m, 1H), 1.86-1.80 (m, 1H), 1.52-1.47 (m, 1H), 1.32 (dt, *J* = 13.0, 6.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 134.6, 133.6, 132.9, 128.6, 127.9, 127.5, 126.4, 126.0, 125.3, 124.5, 123.8, 21.0 (q, *J* = 73, 36 Hz), 17.9 (d, *J* = 2 Hz), 9.1 (d, *J* = 2 Hz); ^{19}F NMR (375 MHz, $CDCl_3$): δ -3.8 (d, *J* = 6.4 Hz).

3-(1-Methyl-2-(trifluoromethyl)cyclopropyl)thiophene (14b)



Following procedure **B**, except Mb(H64V,V68A)-expressing cells (OD_{600} = 80 in KPi, pH 7.2) were used and an additional 125 mL Erlenmeyer flask containing 20 mL of cell suspension was connected in tandem to the alkene and whole-cell reaction flask. Enantioenriched *trans* isomer 3-(1-methyl-2-(trifluoromethyl)cyclopropyl)thiophene was isolated via column chromatography using silica gel and 100% pentanes to afford the product as a colorless oil, 71% yield. GC-MS m/z (% relative intensity): 206(86.8), 191(100), 137(63.1), 97(18.4); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.22 (s, 2H), 6.97 (s, 1H), 6.87 (d, J = 4.9 Hz, 1H), 1.78-1.68 (m, 1H), 1.53 (s, 3H), 1.33-1.31 (m, 1H), 1.22 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 127.4, 126.2, 125.7, 119.8, 29.7, 27.4 (q, *J* = 51, 29 Hz), 18.9, 18.1 (d, *J* = 2 Hz); ^{19}F NMR (375 MHz, $CDCl_3$): δ 2.6 (d, *J* = 7.6 Hz).

X-ray crystallographic analyses

A crystal (0.055 x 0.081 x 0.104 mm^3) was attached to a nylon loop and mounted on a Rigaku Oxford Diffraction XtaLAB Synergy four-circle diffractometer equipped with a HyPix-6000HE area detector for data collection at 100 K (Rigaku Oxford Diffraction. *CrysAlisPro Software system*, version 1.171.39.7f; Rigaku Corporation: Oxford, UK, 2015). A preliminary set of cell constants and an orientation matrix were calculated from reflections harvested from a sampling of reciprocal space. Full data collections were carried out using CuKα radiation (1.54184 Å, PhotonJet-S Cu 50W Microfocus) with frame times ranging from three to seven seconds, frame widths of 0.5 degrees, and a detector distance of approximately four cm. The intensity data were scaled and corrected for absorption, and final cell constants were calculated from the xyz centroids of strong reflections from the actual data collections after integration. Space group $P2_1$ was determined based on systematic absences and intensity statistics. Structures were solved using SHELXT (Sheldrick, G. M. *SHELXT*, version 2014/5; University of Göttingen: Göttingen, Germany) and refined using SHELXL (against F^2) (Sheldrick, G. M. *SHELXL-2016/6*; *Acta Crystallogr.* **2015**, *C71*, 3-8.). All non-hydrogen atoms were refined with anisotropic displacement parameters. All hydrogen atoms were placed in ideal positions and refined as riding atoms with relative isotropic displacement parameters. The final full matrix least squares refinement converged to $R1$ = 0.0294 (F^2, $I > 2\sigma(I)$) and $wR2$ = 0.0796 (F^2, all data). The absolute configuration was determined by anomalous dispersion effects (Parsons, S; Flack, H. D.; Wagner, T. *Acta Crystallogr.* **2013**, *B69*, 249-259).

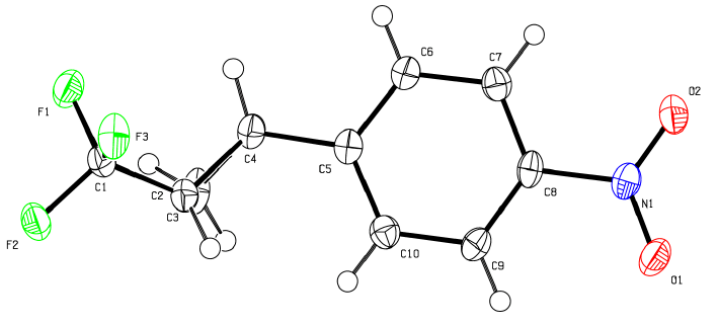


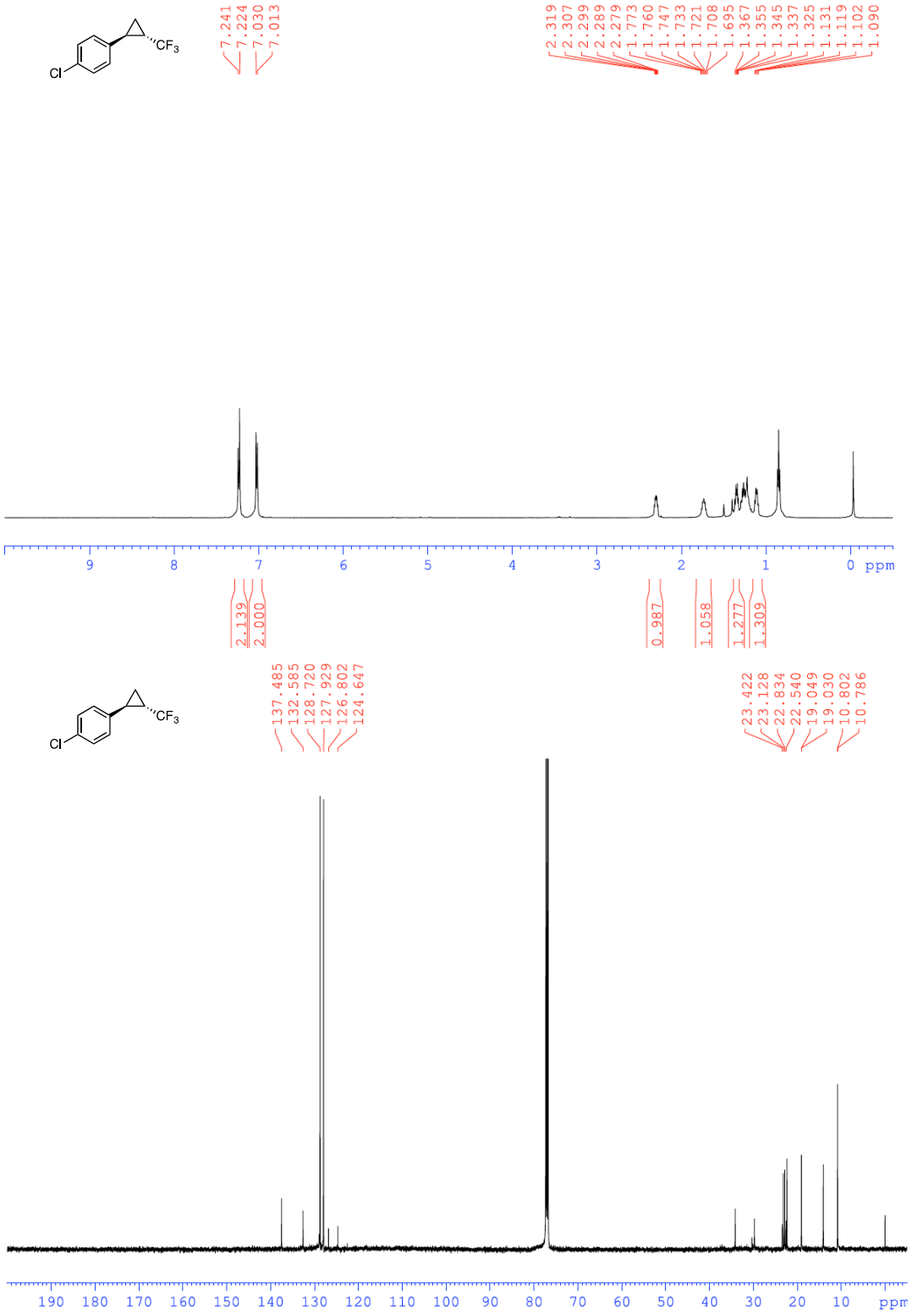
Figure S3. ORTEP of **10b** with ellipsoids drawn at the 50% probability level. Hydrogen atoms were located in the difference Fourier map and refined freely. They are represented here as spheres of arbitrary radius for clarity. Absolute configuration was determined by anomalous dispersion effects produced with CuKα radiation.

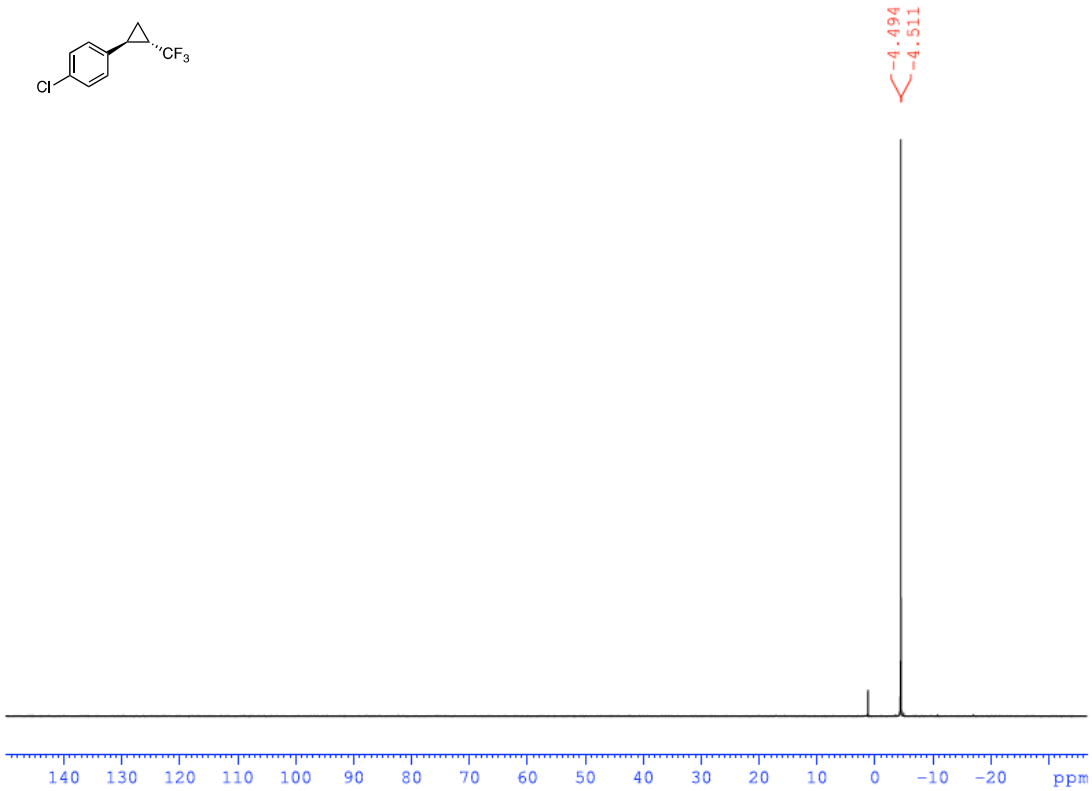
Table S3: Crystal data summary for **10b**.

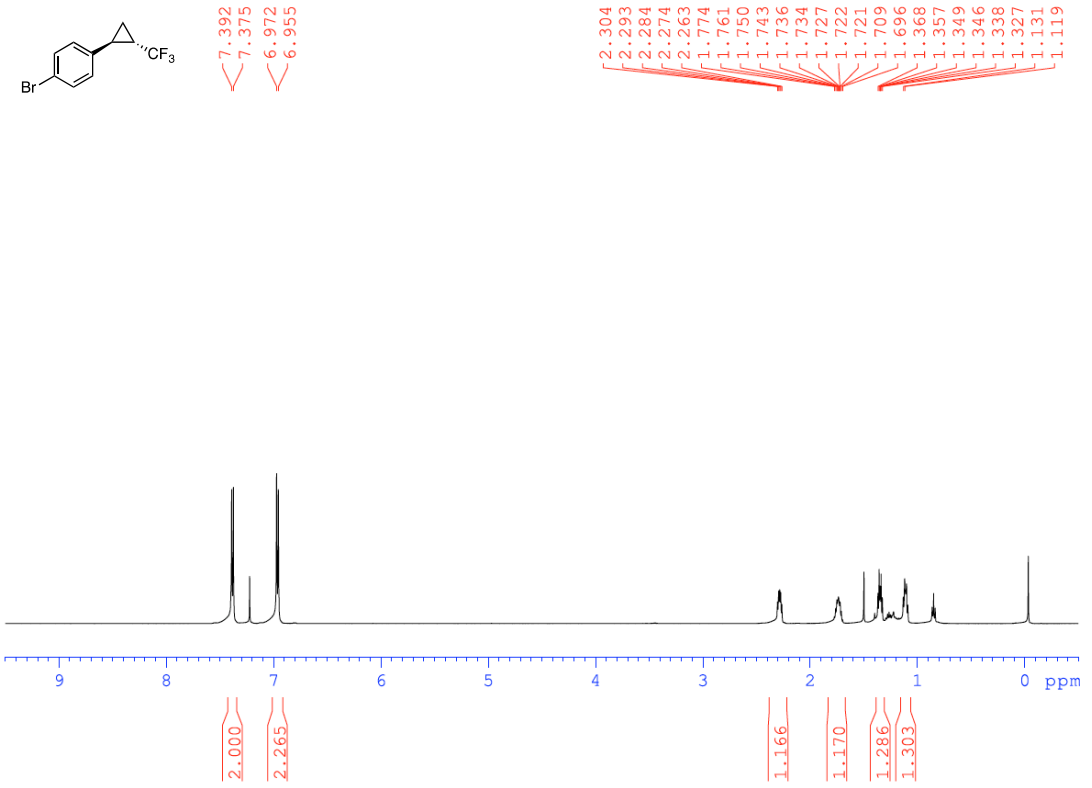
Empirical Formula	$C_{10}H_8F_3NO_2$
FW	231.17
T (K)	100.0(1)
crystal system	monoclinic
space group	$P2_1$
a (Å)	8.0948(3)
b (Å)	6.72581(17)
c (Å)	9.5368(3)
β (deg)	110.999(4)
V (Å^3)	484.74(3)
Z	2
ρ_{calcd} (g cm^{-3})	1.584
μ (mm^{-1})	1.312
color, shape	colorless, plate
reflections collected	16801
reflections independent	1694
R_{int}[a]	0.0722
reflections observed	1645
number of parameters	145
GOF[b] on F^2	1.065
$R1$ [$I > 2\sigma(I)$][c]	0.0294
$wR2$[d]	0.0796

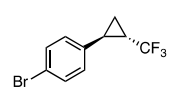
[a] $R_{int} = \Sigma\, |F_o^2 - \langle F_o^2 \rangle| \,/\, \Sigma\, F_o^2$. [b] GOF = $S = [\Sigma\, w(F_o^2 - F_c^2)^2 \,/\, (m - n)]^{1/2}$, where $w = 1 \,/\, [\sigma^2(F_o^2) + (aP)^2 + bP]$, $P = 1/3 \max(0, F_o^2) + 2/3F_c^2$, m = number of independent reflections, and n = number of parameters. [c] $R1 = \Sigma\, ||F_o| - |F_c|| \,/\, \Sigma\, |F_o|$. [d] $wR2 = [\Sigma\, w(F_o^2 - F_c^2)^2 \,/\, \Sigma\, wF_o^2]^{1/2}$.

NMR Spectra

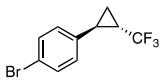

7.241
7.224
7.030
7.013
2.319
2.307
2.299
2.289
2.279
1.773
1.760
1.747
1.733
1.721
1.708
1.695
1.367
1.355
1.345
1.337
1.325
1.131
1.119
1.102
1.090
9
8
7
6
5
4
3
2
1
0 ppm
2.139
2.000
0.987
1.058
1.277
1.309
137.485
132.585
128.720
127.929
126.802
124.647
23.422
23.128
22.834
22.540
19.049
19.030
10.802
10.786
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


Cl
CF3
-4.494
-4.511
140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 ppm

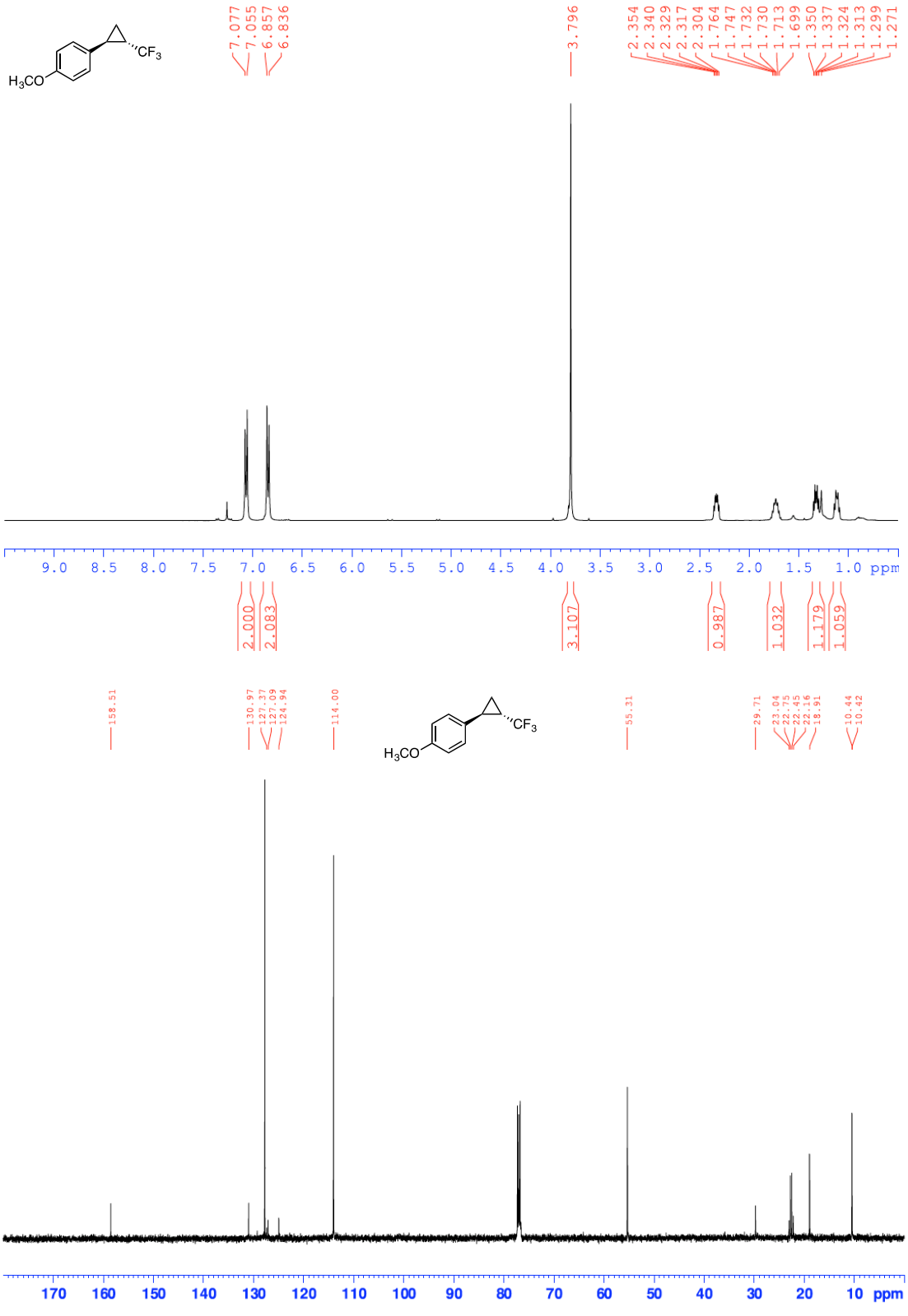

Br
CF3
7.392
7.375
6.972
6.955
2.304
2.293
2.284
2.274
2.263
1.774
1.761
1.750
1.743
1.736
1.734
1.727
1.722
1.721
1.709
1.696
1.368
1.357
1.349
1.346
1.338
1.327
1.131
1.119
9 8 7 6 5 4 3 2 1 0 ppm
2.000
2.265
1.166
1.170
1.286
1.303


Br
CF3

138.033
131.669
128.286
124.629
120.546
23.421
23.124
22.828
19.121
19.102
10.802
10.785
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


Br
CF3

-4.497
90 80 70 60 50 40 30 20 10 0 -10 -20 ppm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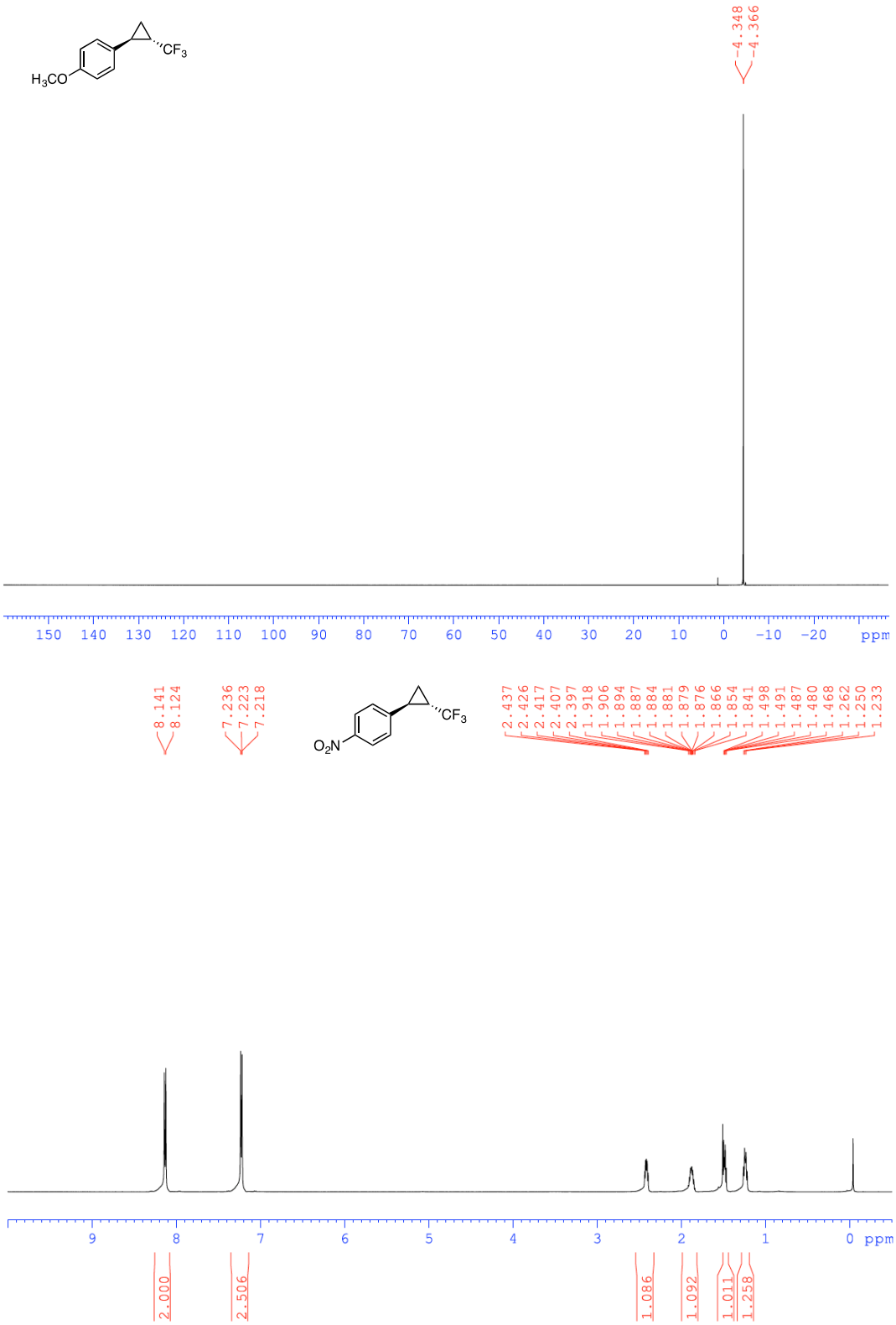
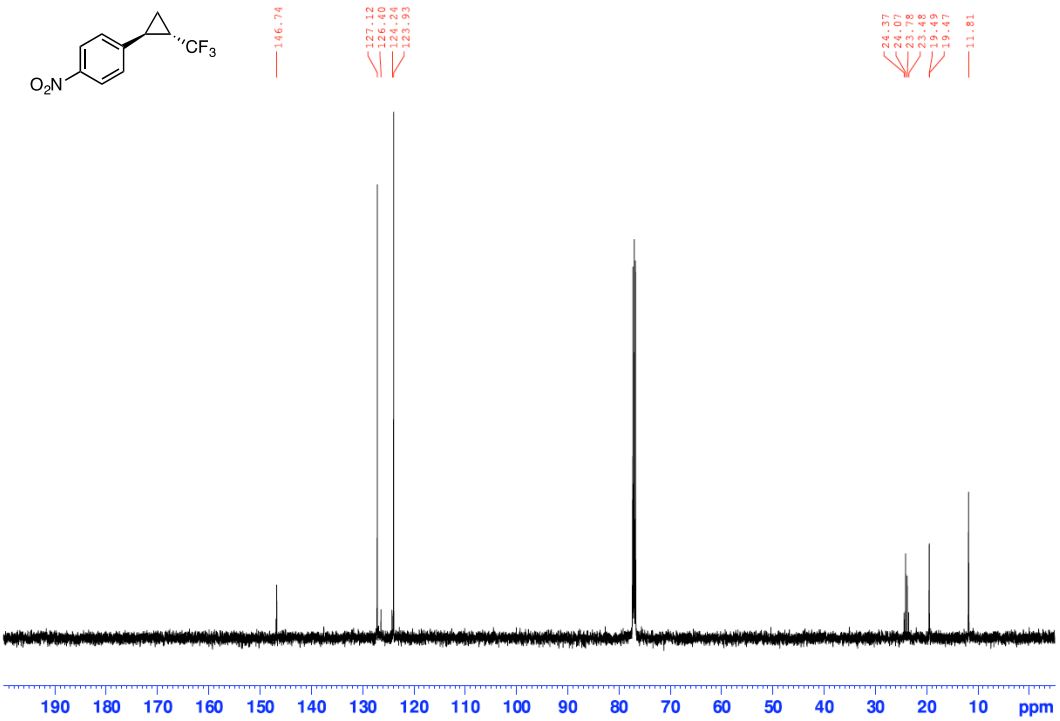
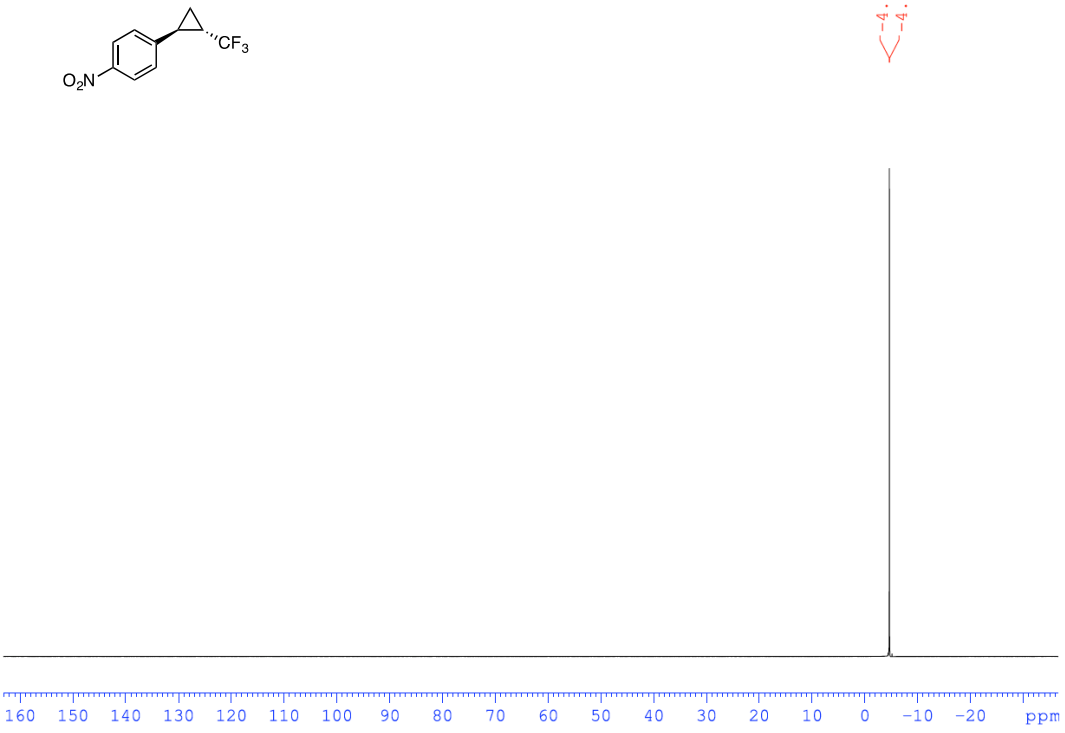
7.055
6.857
6.836
3.796
2.354
2.340
2.329
2.317
2.304
1.764
1.747
1.732
1.730
1.713
1.699
1.350
1.337
1.324
1.313
1.299
1.271
CF3
H3CO
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
2.000
2.083
3.107
0.987
1.032
1.179
1.059
158.51
130.97
127.37
127.09
124.94
114.00
55.31
29.71
23.04
22.75
22.45
22.16
18.91
10.44
10.42
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


H3CO
CF3
4.348
4.366
150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 ppm
8.141
8.124
7.236
7.223
7.218
O2N
CF3
2.437
2.426
2.417
2.407
2.397
1.918
1.906
1.894
1.887
1.884
1.881
1.879
1.876
1.866
1.854
1.841
1.498
1.491
1.487
1.480
1.468
1.262
1.250
1.233
9 8 7 6 5 4 3 2 1 0 ppm
2.000
2.506
1.086
1.092
1.011
1.258


O2N
CF3
146.74
127.12
126.40
124.24
123.93
24.37
24.07
23.78
23.48
19.49
19.47
11.81
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


O2N
CF3
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-4.659
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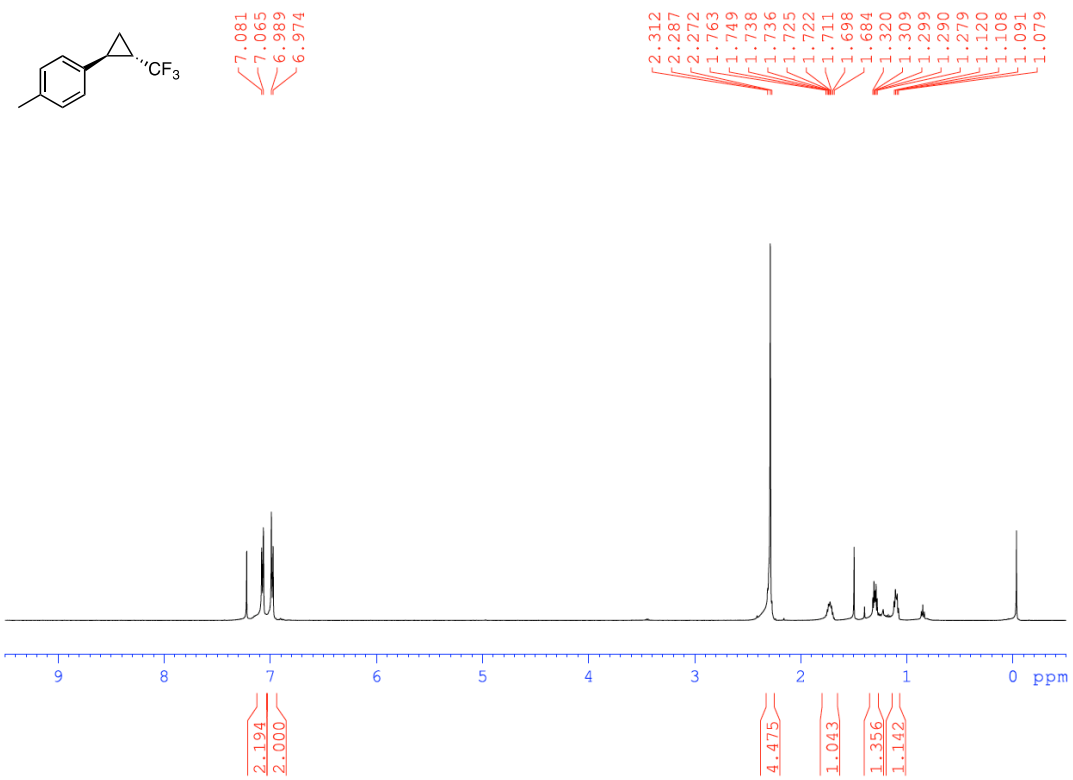
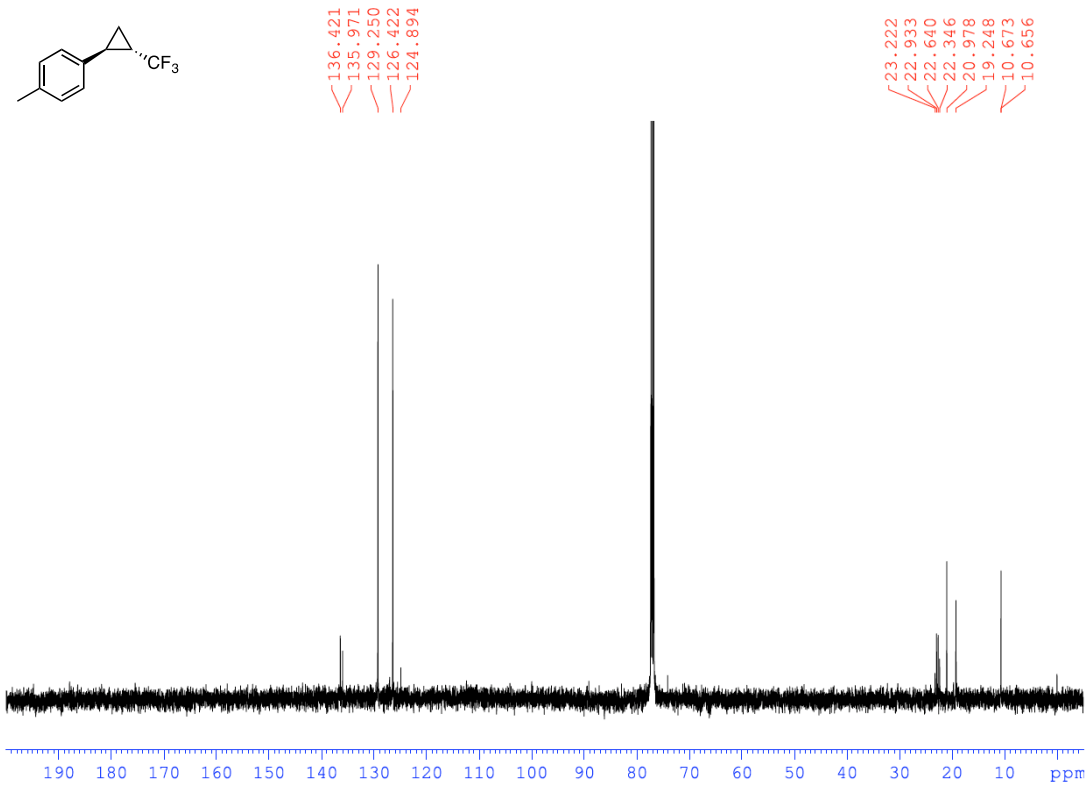

CF3
7.081
7.065
6.989
6.974
2.312
2.287
2.272
1.763
1.749
1.738
1.736
1.725
1.722
1.711
1.698
1.684
1.320
1.309
1.299
1.290
1.279
1.120
1.108
1.091
1.079
9
8
7
6
5
4
3
2
1
0 ppm
2.194
2.000
4.475
1.043
1.356
1.142


CF3
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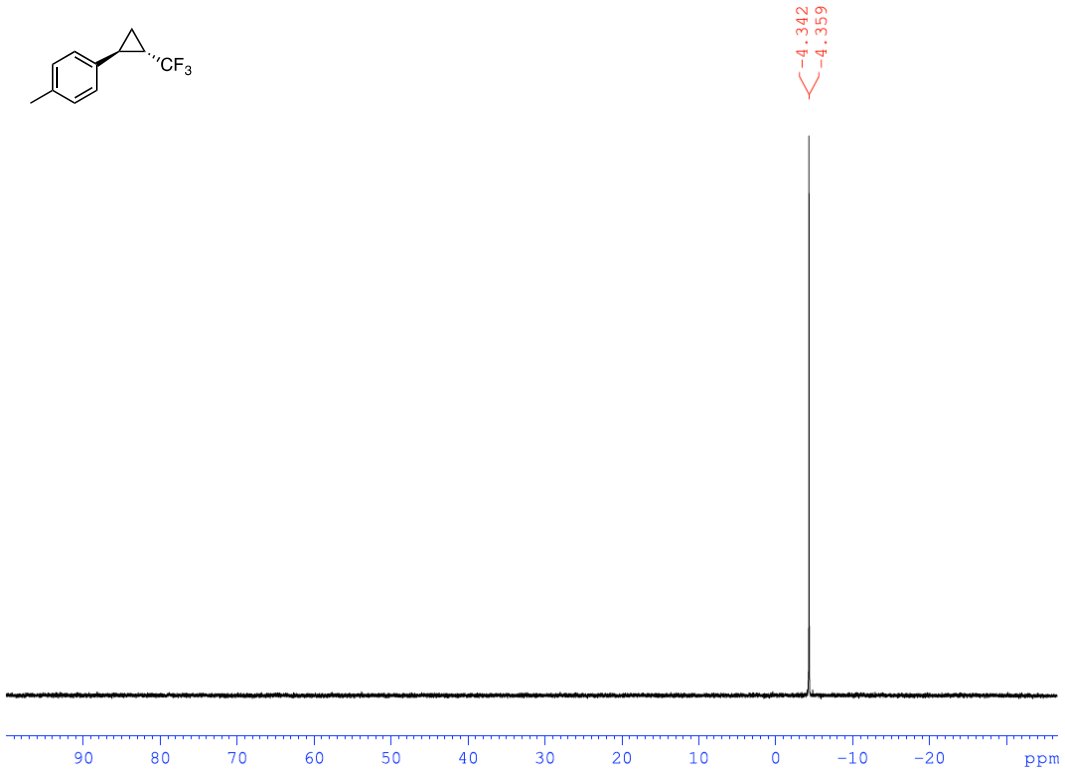
135.971
129.250
126.422
124.894
23.222
22.933
22.640
22.346
20.978
19.248
10.673
10.656
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


CF3
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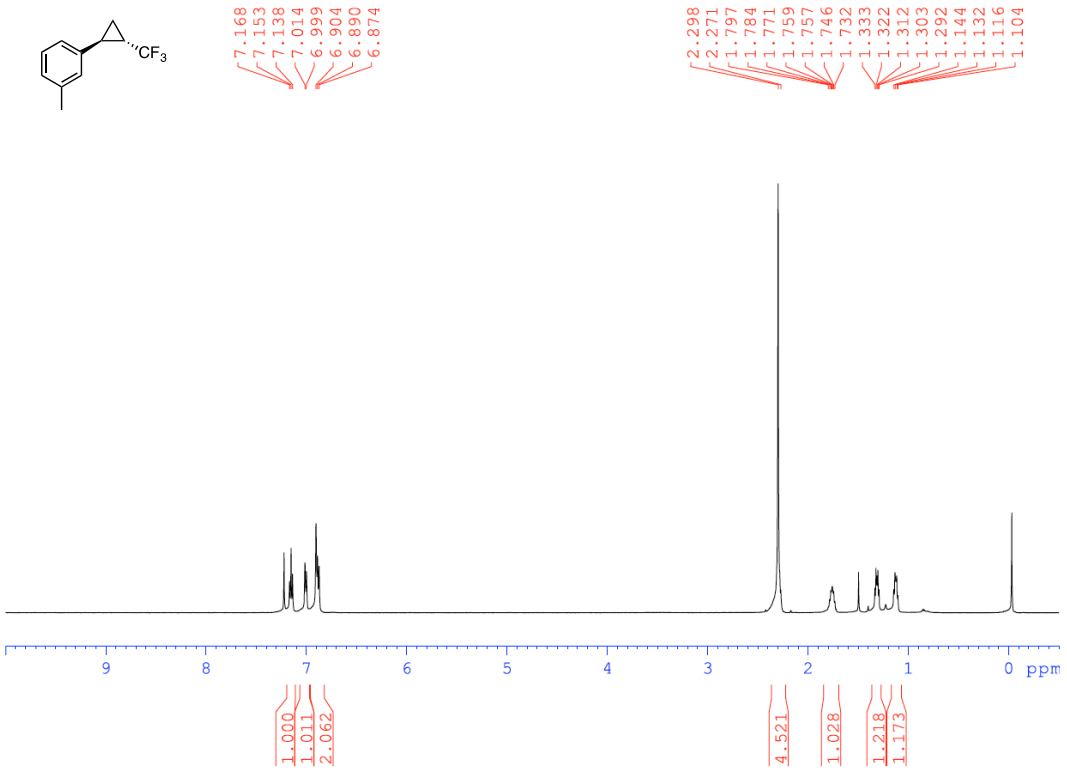
-4.359
90
80
70
60
50
40
30
20
10
0
-10
-20
ppm


CF3
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7.153
7.138
7.014
6.999
6.904
6.890
6.874
2.298
2.271
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1.784
1.771
1.759
1.757
1.746
1.732
1.333
1.322
1.312
1.303
1.292
1.144
1.132
1.116
1.104
9
8
7
6
5
4
3
2
1
0 ppm
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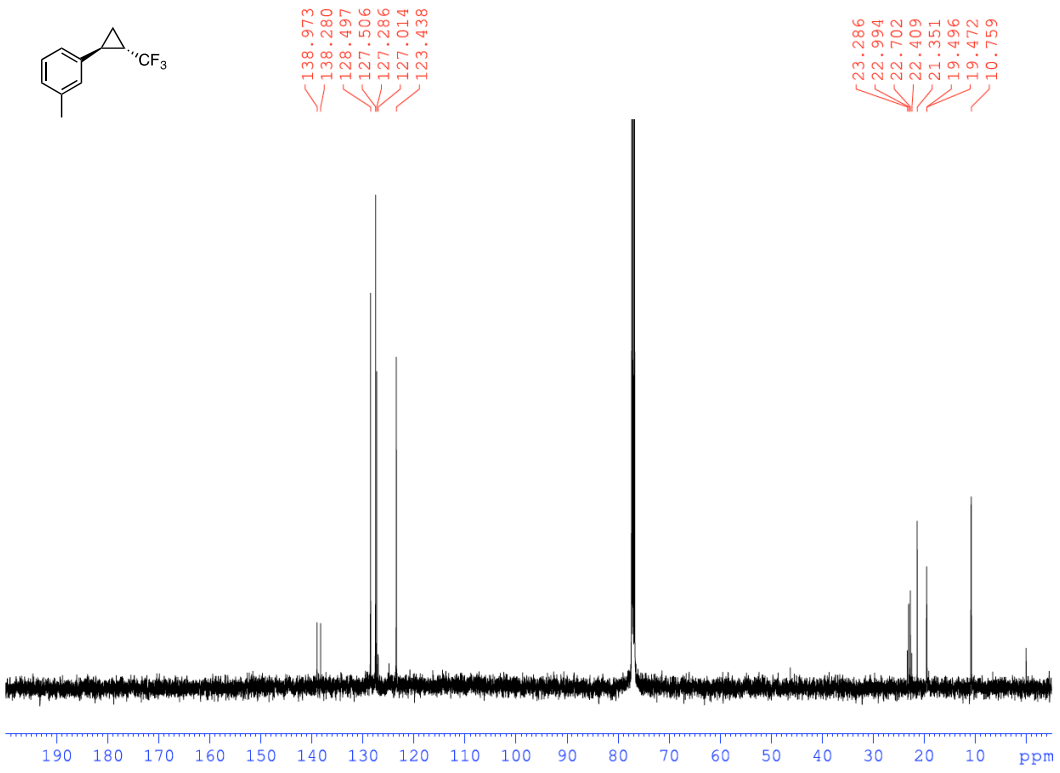
1.011
2.062
4.521
1.028
1.218
1.173


CF3
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138.280
128.497
127.506
127.286
127.014
123.438
23.286
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22.702
22.409
21.351
19.496
19.472
10.759
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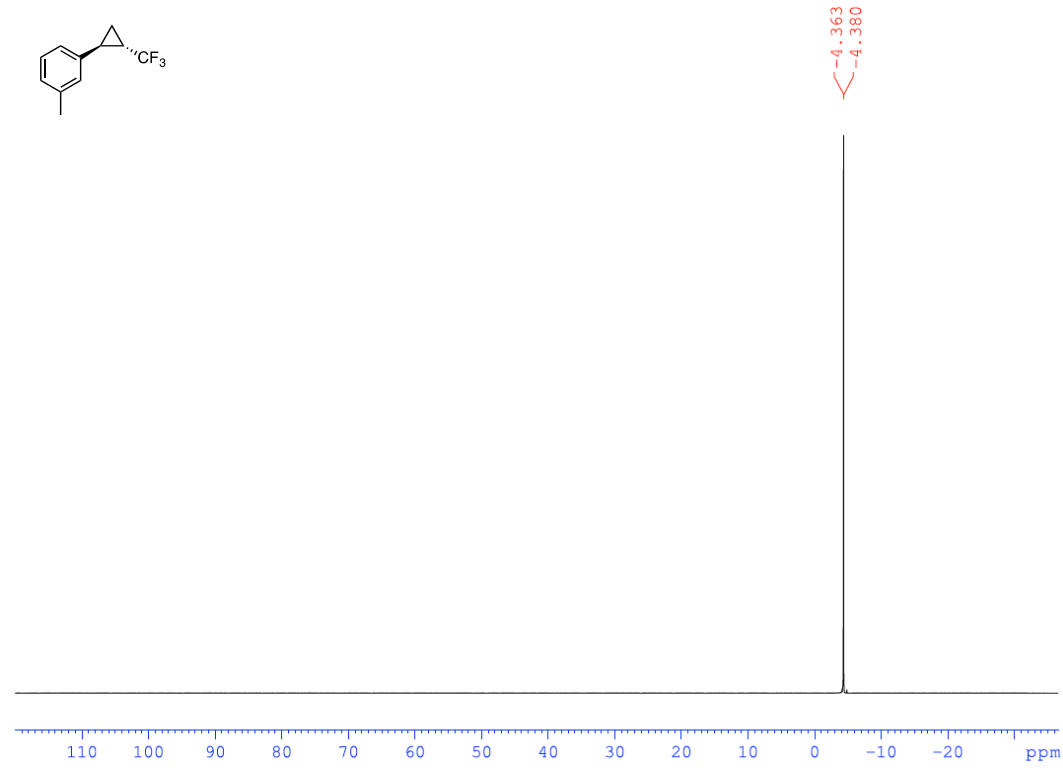
CF3
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-4.380
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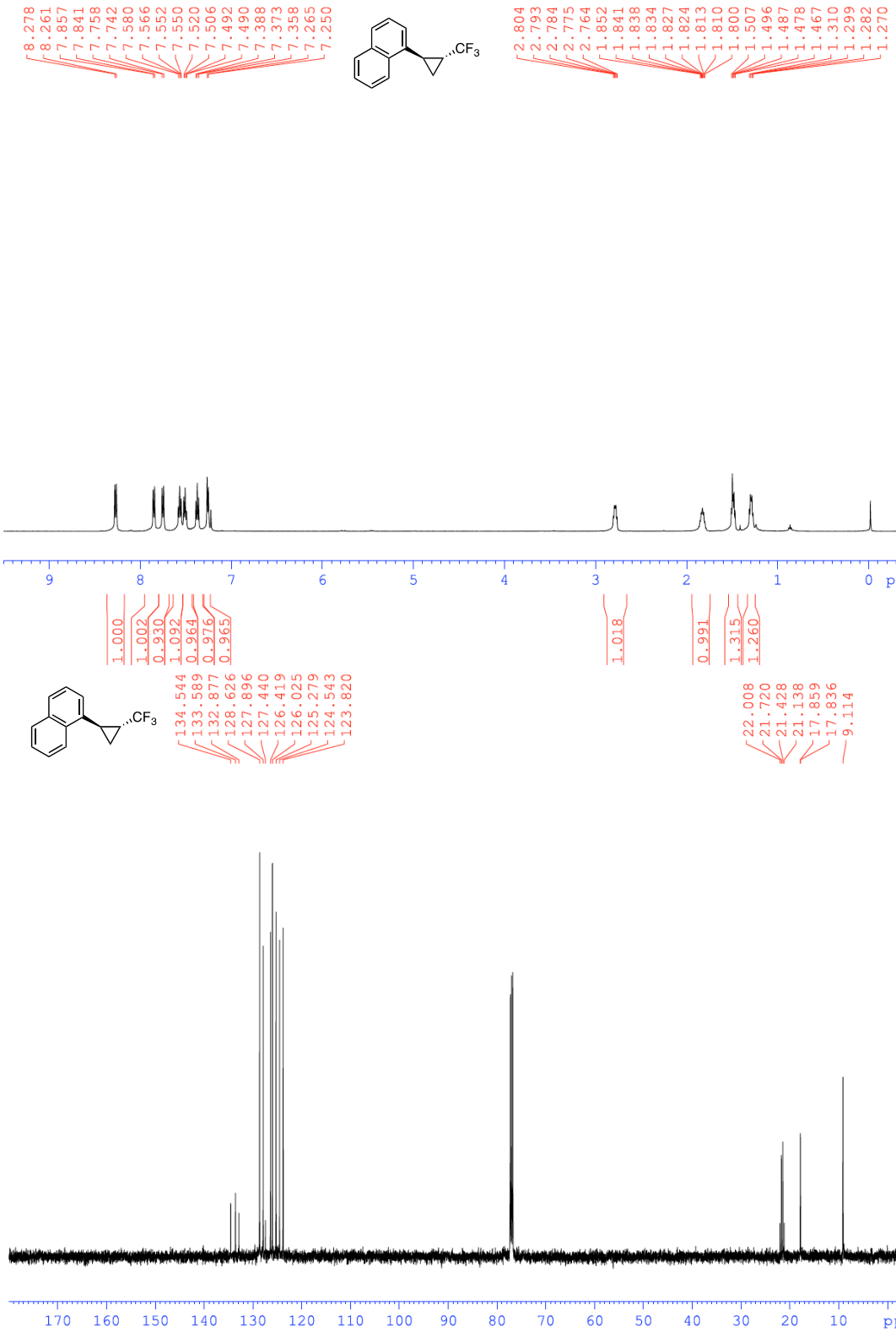
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8.261
7.857
7.841
7.758
7.742
7.580
7.566
7.552
7.550
7.520
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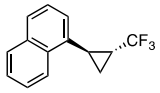
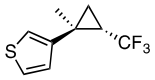
7.492
7.490
7.388
7.373
7.358
7.265
7.250
CF3
2.804
2.793
2.784
2.775
2.764
1.852
1.841
1.838
1.834
1.827
1.824
1.813
1.810
1.800
1.507
1.496
1.487
1.478
1.467
1.310
1.299
1.282
1.270
9 8 7 6 5 4 3 2 1 0 ppm
1.000
1.002
0.930
1.092
0.964
0.976
0.965
1.018
0.991
1.315
1.260
CF3
134.544
133.589
132.877
128.626
127.896
127.440
126.419
126.025
125.279
124.543
123.820
22.008
21.720
21.428
21.138
17.859
17.836
9.114
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


CF3

3.808
3.825
90
80
70
60
50
40
30
20
10
0
-10
-20
ppm


S
CF3


7.224
6.969
6.872
6.859


1.777
1.757
1.736
1.720
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1.678
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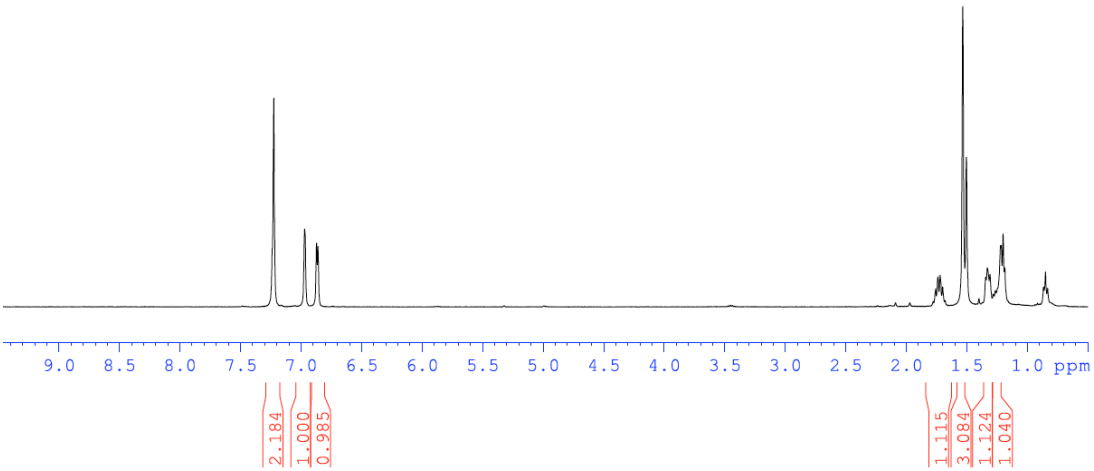
1.308
1.280
1.263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8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0 ppm
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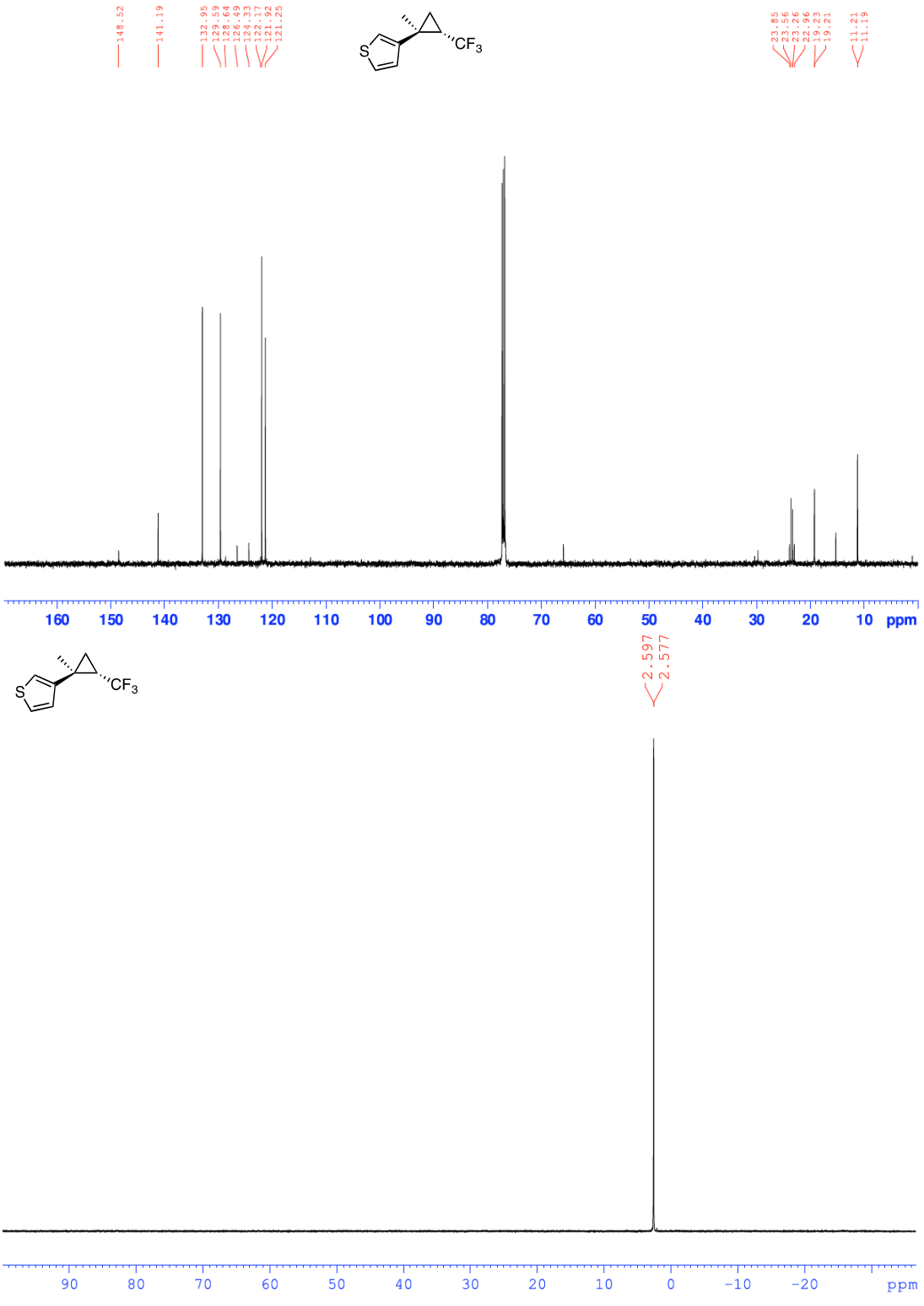
1.000
0.985
1.115
3.084
1.124
1.040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141.19
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129.59
128.64
126.49
124.33
122.17
121.92
121.25
23.85
23.56
23.26
22.96
19.23
19.21
11.21
11.19
S
CF3
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm
2.597
2.577
S
CF3
90
80
70
60
50
40
30
20
10
0
−10
−20
ppm