Supporting Information for

Highly Stereoselective and Enantiodivergent Synthesis of Cyclopropylphosphonates with Engineered Carbene Transferases.

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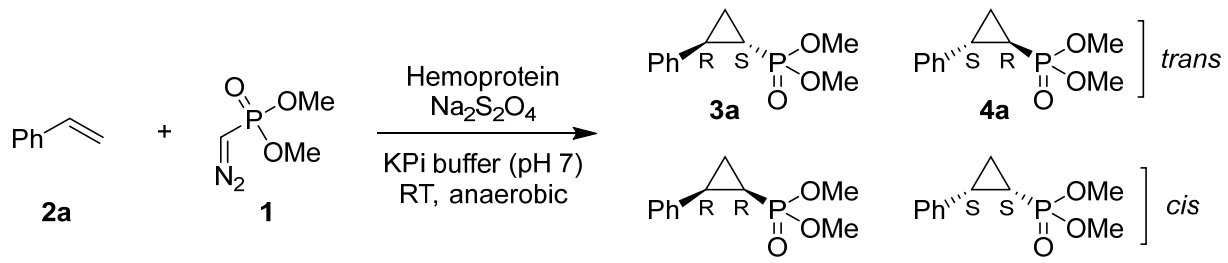
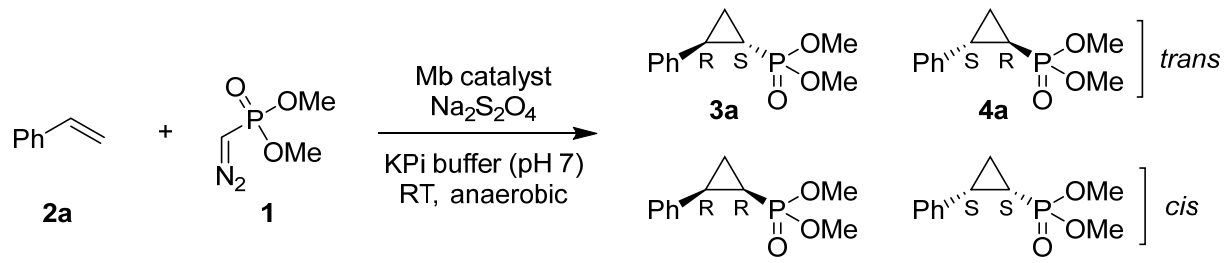
Table S1. Activity of hemin and hemoproteins in the intermolecular cyclopropanation of styrene (**2a**) and dimethyl (diazomethyl)phosphonate (**1**).



Entry	Catalyst	Yield[a]	TON	% de_{trans}[b]	% $ee_{(1S, 2R)}$[c]
1	Hemin	0%	0	n.d.	n.d.
2	Mb	0.4%	1	90	n.d.
3	Mb(H64V,V68A)	1.6%	2	>99	98
4	Catalase	0%	0	n.d.	n.d.
5	Cytochrome *c* (equine heart)	0%	0	n.d.	n.d.
6	Cytochrome *c* (*Hydrogenobacter thermophilus*)	0%	0	n.d.	n.d.
7	$P450_{BM3}$	1%	1	95	n.d.
8	P450 XplA	23%	28	82	-33
9	P450 BezE	3.7%	5	93	15

Reaction conditions: 20 μM catalyst, 2.5 mM dimethyl (diazomethyl)phosphonate (**1**), 5 mM styrene (**2a**), 10 mM $Na_2S_2O_4$, in KPi buffer (50 mM, pH 7), room temperature, 12 hours, in anaerobic chamber. [a] Yield, diastereomeric and enantiomeric excesses determined by chiral GC-FID analysis using 1,3-benzodioxole as internal standard and calibration curve with authentic **3a**/**4a** standards. [b] % *de* values: (*trans* - *cis*)/(*trans* + *cis*). [c] % $ee_{(1S, 2R)}$ values: [(*1S,2R*) - (*1R,2S*)]/[(*1S,2R*) + (*1R,2S*)].

Table S2. Activity and selectivity of representative Mb variants for the intermolecular cyclopropanation of styrene (**2a**) and dimethyl (diazomethyl)phosphonate (**1**) in initial screening.

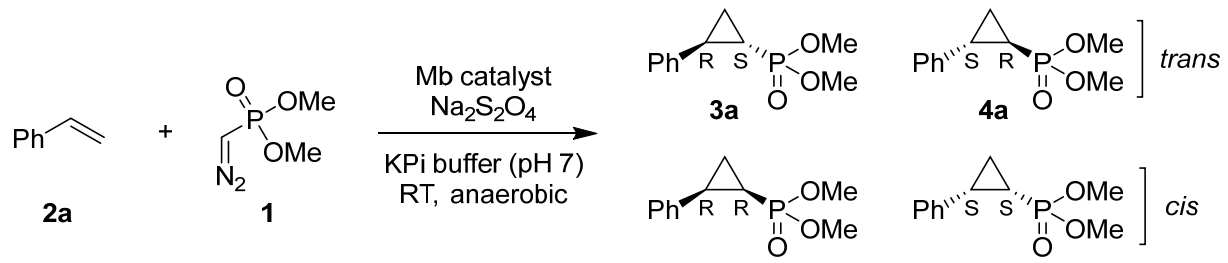


Entry	Mutations	Conversion[a]	TON	% de_{trans}[b]	% $ee_{(1S,2R)}$[c]
1	-	0.4%	1	90	n.d.
2	H64V	3%	4	94	5
3	H64G	0%	0	n.d.	n.d.
4	H64A	>1%	1	97	98
5	V68G	3%	4	99	55
6	V68A	4%	4	99	89
7	V68F	0%	0	n.d.	n.d.
8	F43A	0%	0	n.d.	n.d.
9	H64G/V68A	67%	83	99	99
10	F43C/H64V/V68A	4%	5	93	88
11	F43L/H64V/V68A	7%	9	99	67
12	F43Y/H64V/V68A	8%	10	97	85
13	L29F/H64V/V68A	2%	3	99	57
14	L29T/H64V	0%	0	n.d.	n.d.
15	L29C/H64V	0%	0	n.d.	n.d.
16	L29A/H64V	0%	0	n.d.	n.d.
17	H64V/I107Y	0%	0	n.d.	n.d.
18	H64V/I107S	1%	1	80	85
19	H64V/I107A	>1%	0.3	n.d.	n.d.
20	F43I/H64V	0%	0	n.d.	n.d.

21	H64L/V68G/I107V	24%	30	99	95
22	H64Y/V68G/I107V	13%	16	99	87
23	F43L/H64L/V68G/I107F	13%	17	97	69
24	H64A/V68G/I107A	4%	5	99	72
25	H64A/V68G/I107V	14%	17	99	92
26	H64A/V68G/I107F	16%	20	97	85
27	H64L/V68G/I107F	30%	38	98	91
28	H64V/V68A/I107L	17%	21	99	94
29	F43L/H64A/V68G/I107V	12%	15	99	35
30	F43Y/H64A/V68G/I107F	10%	13	90	81
31	L29W/H64V/V68F	0%	0	n.d.	n.d.
32	F43A/H64W/V68F	0%	0	n.d.	n.d.
33	F43A/H64W/T67S/V68F	0%	0	n.d.	n.d.
34	F43V/H64W	0%	0	n.d.	n.d.
35	L29F/F43V/V68F	0%	0	n.d.	n.d.
36	L29F/F43S/H64W/V68L	0%	0	n.d.	n.d.
37	L29F/F43S/H64F	0.2%	0.2	n.d.	n.d.
38	L29S/H64V/V68F (RR1)	2%	3	99	-90
39	L29T/H64V/V68L (RR2)	2%	2	99	-83
40	L29T/H64V/V68F (RR3)	6%	7	99	-98
41	L29T/H64V/V68F/I107L (RR4)	17%	22	99	-99
42	L29T/F43W/H64V/V68F (RR5)	1%	2	99	-73

Reaction conditions: 20 μM catalyst, 5 mM styrene (**2a**), 2.5 mM dimethyl (diazomethyl)phosphonate (**1**), 10 mM $Na_2S_2O_4$, in KPi buffer (50 mM, pH 7), room temperature, 12 hours, in anaerobic chamber. [a] Yield, diastereomeric and enantiomeric excesses determined by chiral GC-FID analysis using 1,3-benzodioxole as internal standard. [b] % *de* values: (*trans* - *cis*)/(*trans* + *cis*). [c] % $ee_{(1S,\,2R)}$ values: [(*1S,2R*) - (*1R,2S*)]/[(*1S,2R*) + (*1R,2S*)].

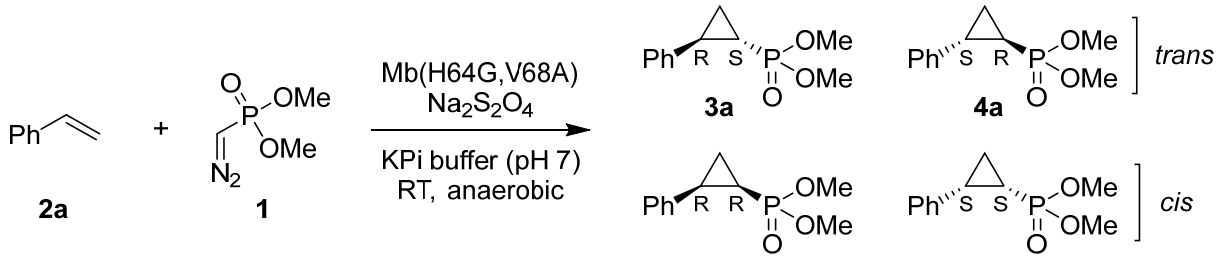
Table S3. Activity and selectivity of evolved Mb variants for the intermolecular cyclopropanation of styrene (**2a**) and dimethyl (diazomethyl)phosphonate (**1**).



Entry	Mutations	Conversion[a]	TON	% de_{trans}[b]	% $ee_{(1S,2R)}$[c]
1	(H64) V68A	4%	4	99	89
2	H64V/V68A	1.6%	2	99	98
3	H64A/V68A	30%	37	99	98
4	H64G/V68A	67%	83	99	>99
5	(H64) V68G	3%	4	99	55
6	H64V/V68G	13%	16	99	97
7	H64A/V68G	18%	23	99	79
8	H64A/V68G/I107L	35%	44	99	97
9	H64V	3%	4	94	5
10	H64V/V68F	0.4%	1	99	-55
11	L29T/H64V/V68F	6%	7	99	-98
12	L29T/H64V/V68F/I107L	17%	22	99	-99

Reaction conditions: 20 μM catalyst, 5 mM styrene (**2a**), 2.5 mM dimethyl (diazomethyl)phosphonate (**1**), 10 mM $Na_2S_2O_4$, in KPi buffer (50 mM, pH 7), room temperature, 12 hours, in anaerobic chamber. [a] Yield, diastereomeric and enantiomeric excesses determined by chiral GC-FID analysis using 1,3-benzodioxole as internal standard. [b] % *de* values: (*trans* - *cis*)/(*trans* + *cis*). [c] % $ee_{(1S, 2R)}$ values: [(*1S,2R*) - (*1R,2S*)]/[(*1S,2R*) + (*1R,2S*)].

Table S4. Optimization studies for Mb(H64G,V68A)-catalyzed intermolecular cyclopropanation of styrene (**2a**) and dimethyl (diazomethyl)phosphonate (**1**) in reactions with purified protein and Mb-expressing *E. coli* cells (C41(DE3)). Reaction conditions: 2.5-20 mM (diazomethyl)phosphonate (**1**), 2.5-40 mM styrene (**2a**), Mb purified protein or Mb-expressing *E. coli* cells (C41(DE3)) at the indicated cell density (OD_{600}) in KPi buffer (50 mM, pH 7), room temperature, 12 hours in sealed crimp vials and in anaerobic chamber. Protein concentration in the whole cell solutions was 65 μM at an OD_{600} of 100.

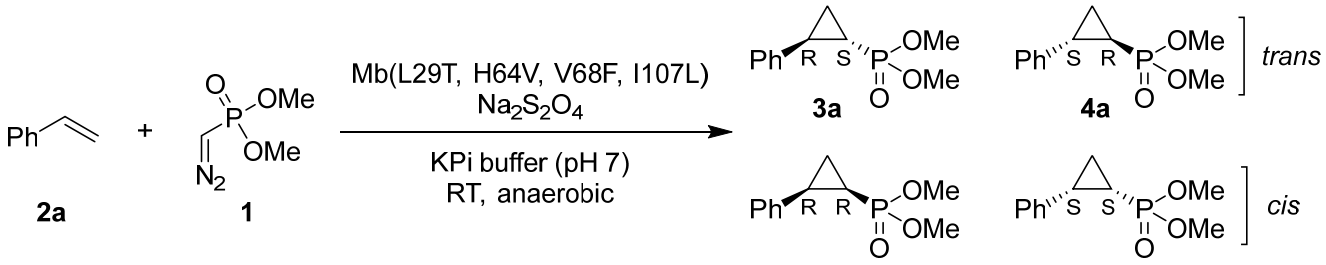


Entry	Catalyst loading	[2a] (mM)	[1] (mM)	Yield (GC)[a]	TON	% de_{trans}[b]	% $ee_{(1S,2R)}$[c]
1	20 μM	10	2.5	67%	83	>99	>99
2	20 μM	5	2.5	67%	83	>99	>99
3	20 μM	2.5	2.5	62%	77	>99	>99
4	20 μM	10	5	47%	118	>99	>99
5	20 μM	5	5	49%	122	>99	>99
6	20 μM	2.5	5	87%	109	>99	>99
7	20 μM	40	10	36%	180	>99	>99
8	20 μM	20	10	45%	225	>99	>99
9	20 μM	10	10	46%	230	>99	>99
10	20 μM	5	10	89%	222	>99	>99
11	20 μM	2.5	10	99%	125	>99	>99
12	10 μM	10	20	47%	470	>99	>99
13	20 μM	10	20	70%	350	>99	>99
14	40 μM	10	20	99%	250	>99	>99
15	60 μM	10	20	99%	167	>99	>99

16	80 µM	10	20	99%	125	>99	>99
17	10 µM	20	40	18%	350	>99	>99
18	20 µM	20	40	33%	330	>99	>99
19	40 µM	20	40	60%	298	>99	>99
20	60 µM	20	40	70%	232	>99	>99
21	80 µM	20	40	86%	215	>99	>99
22	OD=40	10	20	43%	163	>99	>99
23	OD=60	10	20	74%	187	>99	>99
24	OD=80	10	20	99%	187	>99	>99
25	OD=40	20	40	10%	74	>99	>99
26	OD=60	20	40	29%	144	>99	>99
27	OD=80	20	40	30%	114	>99	>99

[a] Yield, diastereomeric and enantiomeric excesses determined by chiral GC-FID analysis using 1,3-benzodioxole as internal standard. [b] % *de* values: (*trans* - *cis*)/(*trans* + *cis*). [c] % $ee_{(1S,\,2R)}$ values: [(*1S,2R*) - (*1R,2S*)]/[(*1S,2R*) + (*1R,2S*)].

Table S5. Optimization studies for Mb(L29T, H64V, V68F, I107L)-catalyzed intermolecular cyclopropanation of styrene (**2a**) and dimethyl (diazomethyl)phosphonate (**1**) in reactions with purified protein and Mb-expressing *E. coli* cells (C41(DE3)). Reaction conditions: 2.5-20 mM (diazomethyl)phosphonate (**1**), 2.5-40 mM styrene (**2a**), Mb purified protein or Mb-expressing *E. coli* cells (C41(DE3)) at the indicated cell density (OD_{600}) in KPi buffer (50 mM, pH 7), room temperature, 12 hours in sealed crimp vials and in anaerobic chamber. Protein concentration in the whole cell solutions was 52 μM at an OD_{600} of 100.



Entry	Catalyst loading	2a (mM)	1 (mM)	Conversion[a]	TON	% de_{trans}[b]	% $ee_{(1S,2R)}$[c]
1	20 μM	4	1	19%	10	>99	-99
2	20 μM	2	1	21%	11	>99	-99
3	20 μM	1	1	13%	6	>99	-99
4	20 μM	0.5	1	23%	6	>99	-99
5	20 μM	0.25	1	26%	3	>99	-99
6	20 μM	10	2.5	17%	21	>99	-99
7	20 μM	5	2.5	14%	17	>99	-99
8	20 μM	2.5	2.5	11%	14	>99	-99
9	20 μM	1.25	2.5	20%	12	>99	-99
10	20 μM	0.62	2.5	29%	9	>99	-99
11	20 μM	20	5	11%	28	>99	-99
12	20 μM	10	5	12%	29	>99	-99
13	20 μM	5	5	10%	25	>99	-99
14	20 μM	2.5	5	18%	22	>99	-99
15	20 μM	1.25	5	22%	14	>99	-99

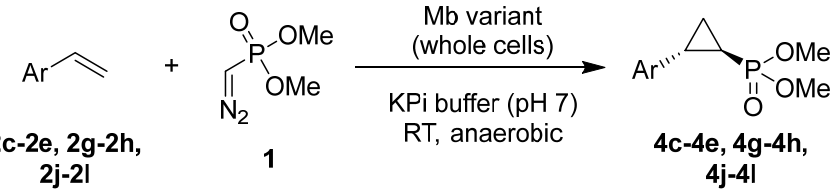
16	20 μM	40	10	9%	45	>99	-99
17	20 μM	20	10	11%	57	>99	-99
18	20 μM	10	10	10%	52	>99	-99
19	20 μM	5	10	15%	37	>99	-99
20	20 μM	2.5	10	20%	25	>99	-99
21	OD=10	0.5	1	9.8%	9	>99	-99
22	OD=20	0.5	1	10%	5	>99	-99
23	OD=40	0.5	1	18%	4	>99	-99
24	OD=60	0.5	1	21%	3	>99	-99
25	OD=80	0.5	1	19%	2	>99	-99
26	OD=100	0.5	1	23%	2	>99	-99
27	OD=10	1	2	6%	12	>99	-99
28	OD=20	1	2	13%	13	>99	-99
29	OD=40	1	2	23%	11	>99	-99
30	OD=60	1	2	24%	8	>99	-99
31	OD=80	1	2	25%	6	>99	-99
32	OD=100	1	2	27%	5	>99	-99
33	OD=10	2.5	5	12%	57	>99	-99
34	OD=20	2.5	5	16%	39	>99	-99
35	OD=40	2.5	5	24%	29	>99	-99
36	OD=60	2.5	5	28%	22	>99	-99
37	OD=80	2.5	5	37%	22	>99	-99
38	OD=100	2.5	5	44%	21	>99	-99
39	OD=10	5	10	11%	107	>99	-99
40	OD=20	5	10	23%	109	>99	-99
41	OD=40	5	10	42%	101	>99	-99
42	OD=60	5	10	57%	91	>99	-99
43	OD=80	5	10	74%	89	>99	-99

44	OD=100	5	10	96%	92	>99	-99
45	OD=10	10	20	7.9%	151	>99	-99
46	OD=20	10	20	15%	144	>99	-99
47	OD=40	10	20	28%	135	>99	-99
48	OD=60	10	20	37%	119	>99	-99
49	OD=80	10	20	44%	107	>99	-99
50	OD=100	10	20	52%	101	>99	-99
51	OD=10	20	40	1.8%	71	>99	-99
52	OD=20	20	40	5.0%	96	>99	-99
53	OD=40	20	40	9.8%	94	>99	-99
54	OD=60	20	40	13%	82	>99	-99
55	OD=80	20	40	17%	82	>99	-99
56	OD=100	20	40	20%	77	>99	-99
57	20 μM	0.5	1	21%	5	>99	-99
58	40 μM	0.5	1	42%	5	>99	-99
59	60 μM	0.5	1	99%	8	>99	-99
60	80 μM	0.5	1	99%	6	>99	-99
61	100 μM	0.5	1	99%	5	>99	-99
62	20 μM	1	2	19%	9	>99	-99
63	40 μM	1	2	23%	6	>99	-99
64	60 μM	1	2	30%	5	>99	-99
65	80 μM	1	2	68%	8	>99	-99
66	100 μM	1	2	91%	9	>99	-99
67	20 μM	2.5	5	14%	17	>99	-99
68	40 μM	2.5	5	31%	20	>99	-99
69	60 μM	2.5	5	47%	20	>99	-99
70	80 μM	2.5	5	50%	16	>99	-99

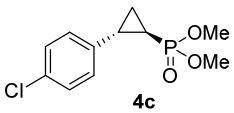
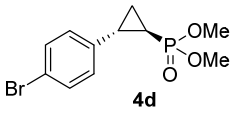
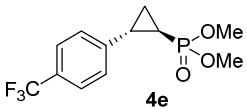
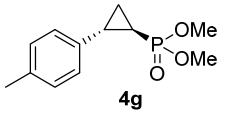
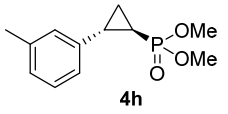
71	100 µM	2.5	5	60%	15	>99	-99
72	20 µM	5	10	12%	31	>99	-99
73	40 µM	5	10	26%	33	>99	-99
74	60 µM	5	10	37%	31	>99	-99
75	80 µM	5	10	48%	30	>99	-99
76	100 µM	5	10	59%	29	>99	-99
77	20 µM	10	20	10%	49	>99	-99
78	40 µM	10	20	24%	60	>99	-99
79	60 µM	10	20	30%	51	>99	-99
80	80 µM	10	20	42%	52	>99	-99
81	100 µM	10	20	51%	51	>99	-99

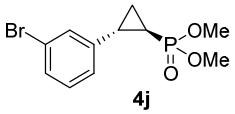
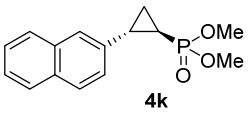
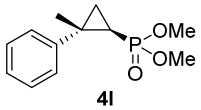
[a] Yield, diastereomeric and enantiomeric excesses determined by chiral GC-FID analysis using 1,3-benzodioxole as internal standard. [b] % *de* values: (*trans* - *cis*)/(*trans* + *cis*). [c] % $ee_{(1S,\,2R)}$ values: [(*1S,2R*) - (*1R,2S*)]/[(*1S,2R*) + (*1R,2S*)].

Table S6. Activity and selectivity of evolved Mb variants for the intermolecular cyclopropanation of olefins (**2c-2e, 2g-2h, 2j-2l**) and dimethyl (diazomethyl)phosphonate (**1**).



2c-2e, 2g-2h, 2j-2l **1** **4c-4e, 4g-4h, 4j-4l**

Entry	Product	Catalyst	Conversion[a]	% de_{trans}[b]	% $ee_{(1R,2S)}$[c]
1	 **4c**	RR4/T29C	67%	99	84
		RR4/T29V	72%	99	57
		RR4/T29C/V64A	64%	99	92
		RR4/T29V/V64A	64%	99	80
2	 **4d**	RR4/T29C	50%	99	71
		RR4/T29V	63%	99	50
		RR4/T29C/V64A	63%	99	84
		RR4/T29V/V64A	56%	99	70
3	 **4e**	RR4/T29C	21%	99	32
		RR4/T29V	26%	99	36
		RR4/T29C/V64A	24%	99	56
		RR4/T29V/V64A	16%	99	50
4	 **4g**	RR4/T29C	28%	99	66
		RR4/T29V	46%	99	53
		RR4/T29C/V64A	41%	99	81
		RR4/T29V/V64A	38%	99	76
5	 **4h**	RR4/T29C	67%	58	86
		RR4/T29V	71%	91	76
		RR4/T29C/V64A	86%	24	99
		RR4/T29V/V64A	75%	44	94

6	 **4j**	RR4/T29C	66%	35	90
		RR4/T29V	99%	94	89
		RR4/T29C/V64A	99%	14	99
		RR4/T29V/V64A	99%	49	99
7	 **4k**	RR4/T29C	11%	99	54
		RR4/T29V	33%	99	33
		RR4/T29C/V64A	7%	99	84
		RR4/T29V/V64A	24%	99	83
8	 **4l**	RR4/T29C	30%	90	73
		RR4/T29V	41%	94	68
		RR4/T29C/V64A	45%	86	94
		RR4/T29V/V64A	32%	89	82

Reaction conditions: 10 mM (diazomethyl)phosphonate (**1**), 5 mM olefin (**2c-2e, 2g-2h, 2j-2l**), Mb-expressing *E. coli* cells (OD_{600}=100) in KPi buffer (50 mM, pH 7), room temperature, 16 hours. [a] Yield, diastereomeric and enantiomeric excesses determined by chiral GC-FID analysis using 1,3-benzodioxole as internal standard. [b] % *de* values: (*trans* - *cis*)/(*trans* + *cis*). [c] % $ee_{(1R,\,2S)}$ values: [(*1R,2S*) - (*1S,2R*)]/[(*1S,2R*) + (*1R, 2S*)].

Table S7. Sequences of the oligonucleotides used for the preparation of myoglobin variants by site saturation mutagenesis.

Entry	Oligonucleotide	Sequence (5'–3')
1	XhoI Rev	GGCTTTGTTAGCAGCCGGAT
2	H64NNK Fwd	GAAGACCTGAAAAAANNKGGTGTTAC
3	L29NNK Fwd	GTCACGGTCAGGACATCNNKATCCGTCTGTTC
4	V68NNK Fwd	CCTGAAAAAACACGGTGTTACCNNKCTGACCGCT
5	F43NNK Fwd	CAC CCG GAAACCCTG GAAAAANNKGACCGTTTC
6	I107NNK Fwd	CCCGATCAAATACCTGGAGTTCNNKTCTGAAGCTATC

Figure S1. Crystal structure of sperm whale myoglobin (Mb). The amino acid residues lining the distal heme pocket are highlighted as stick models in light blue. The heme group (yellow) and the heme-coordinating proximal histidine (green) are shown as stick models.

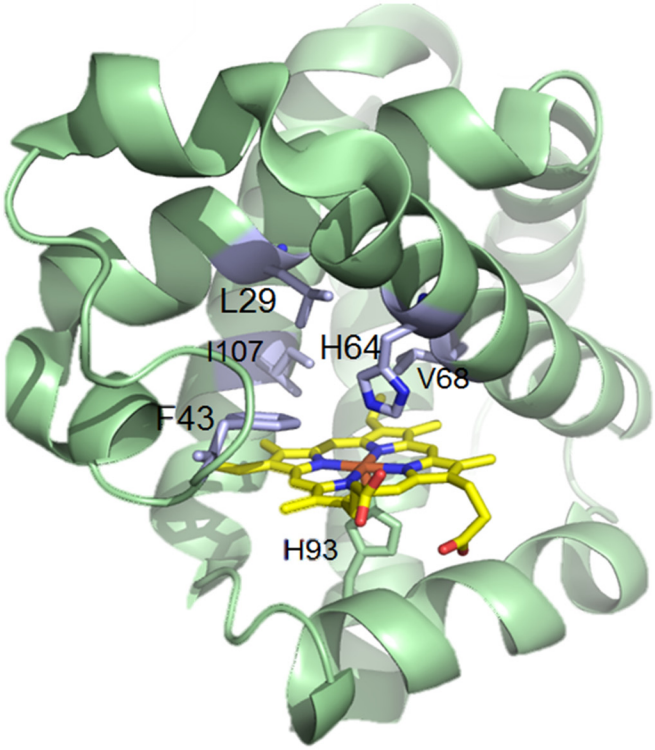


Figure S2. Time-course analysis of Mb(H64G,V68A)-catalyzed intermolecular cyclopropanation of styrene (**2a**) and dimethyl (diazomethyl)phosphonate (**1**).

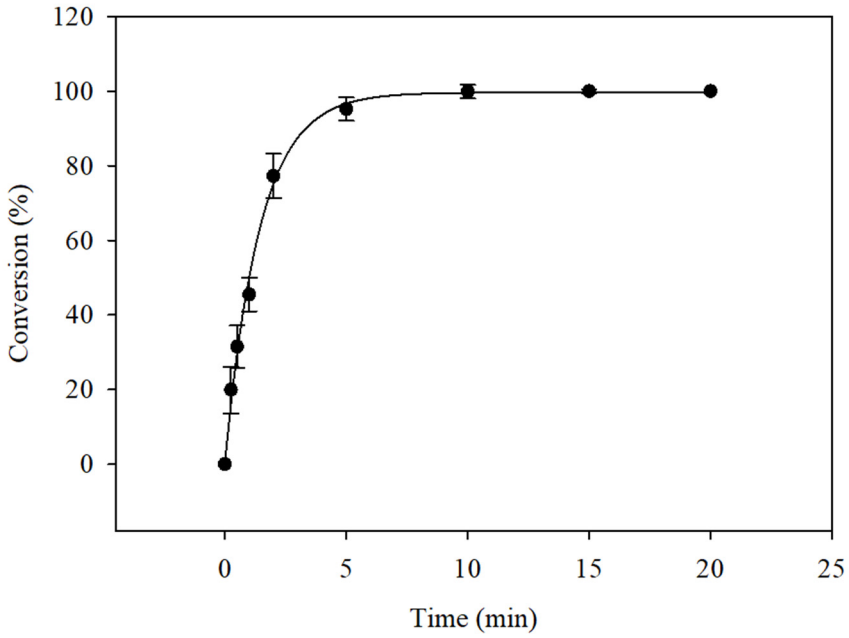


Figure S3. Time-course analysis of Mb(L29T,H64V,V68F,I107L)-catalyzed intermolecular cyclopropanation of styrene (**2a**) and dimethyl (diazomethyl)phosphonate (**1**).

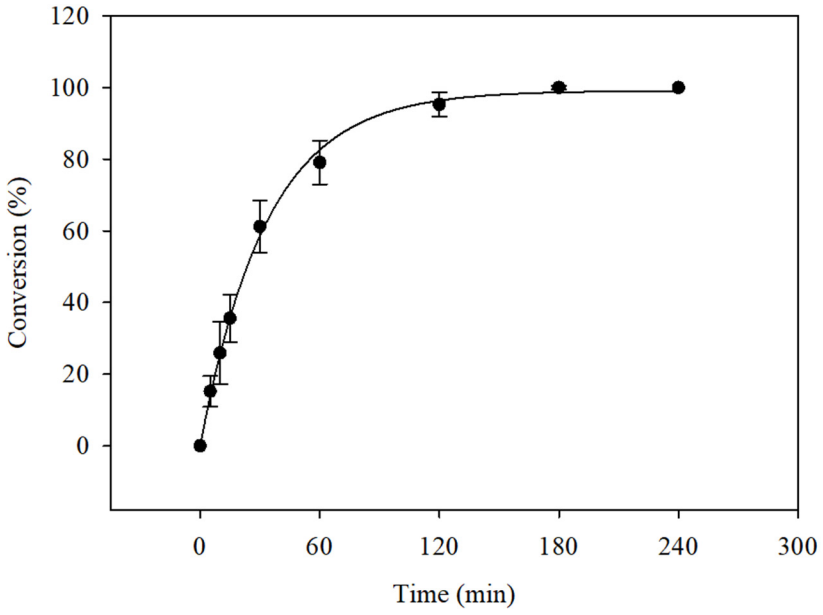
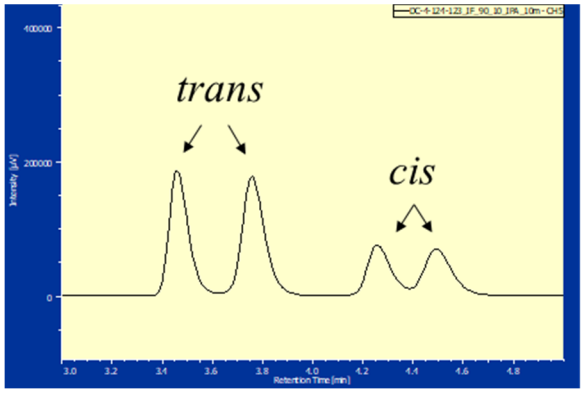
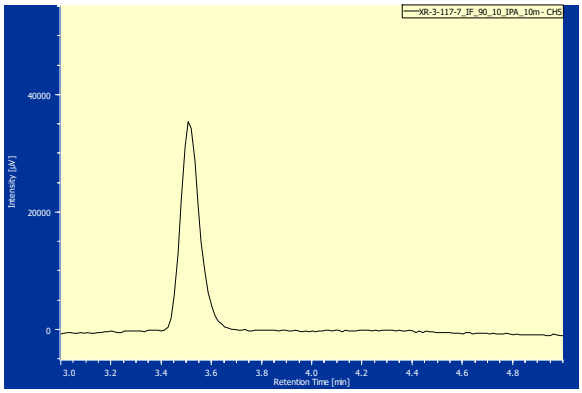


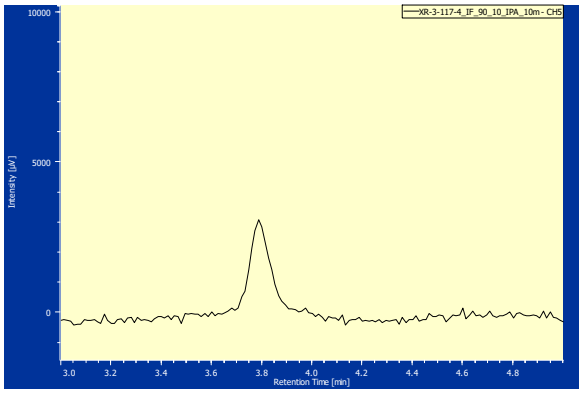
Figure S4. SFC analysis for the determination of an enantiomeric excess in the Mb-catalyzed intermolecular cyclopropanation reactions. The reference racemic samples were prepared as described in the experimental procedures.

➢ Chiral SFC analysis of racemic **3a**/**4a** (*top*) and enzymatically produced **3a** (*middle*) and **4a** product (*bottom*):



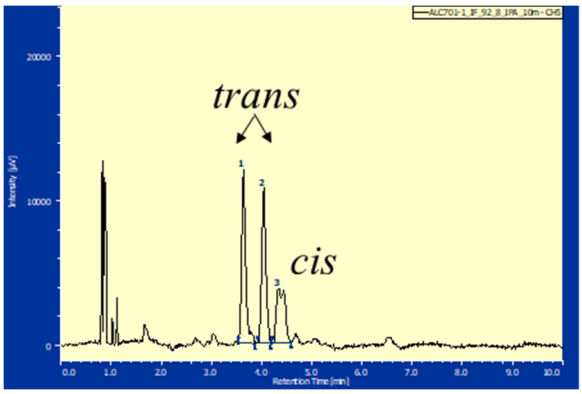


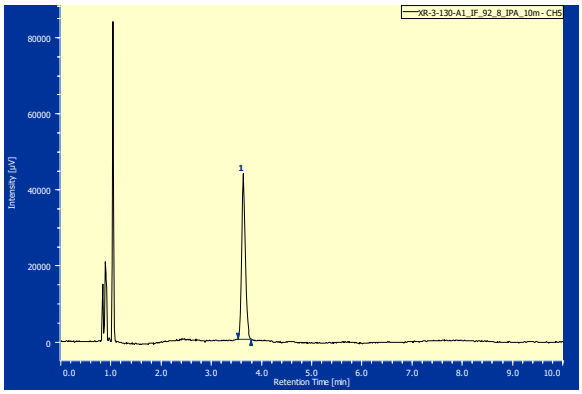
	Retention time/min	Peak area	Percentage
3a	3.45	327645	100%
4a	3.82	0	0%



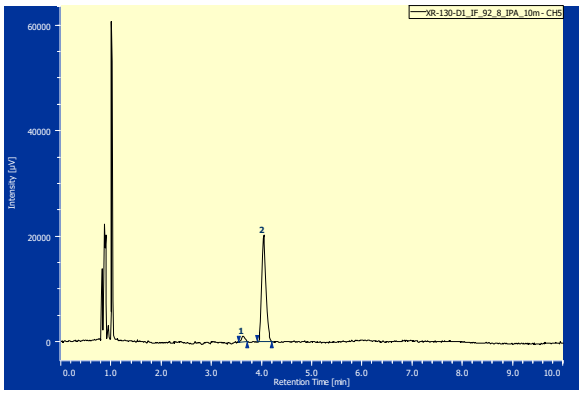
	Retention time/min	Peak area	Percentage
3a	3.45	0	0%
4a	3.82	120635	100%

➢ Chiral SFC analysis of racemic **3b**/**4b** (*top*) and enzymatically produced **3b** (*middle*) and **4b** products (*bottom*):



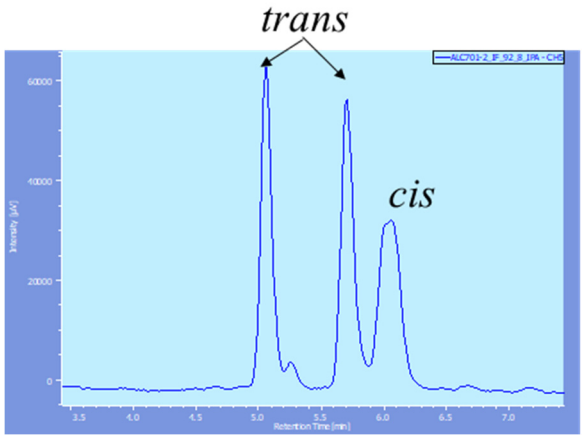


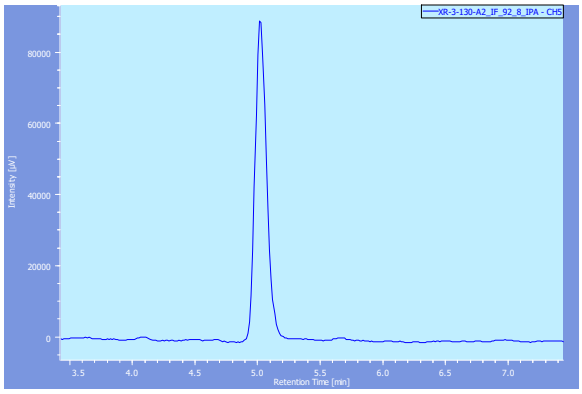
	Retention time/min	Peak area	Percent age
3b	3.63	227823	100%
4b	4.05	0	0%



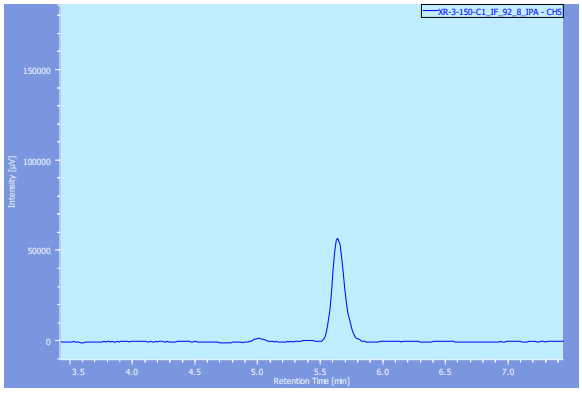
	Retention time/min	Peak area	Percent age
3b	3.63	5863	4.6%
4b	4.05	120696	95.2%

➢ Chiral SFC analysis of racemic **3c**/**4c** (*top*), enzymatically produced **3c** (*middle*) and **4c** products (*bottom*):



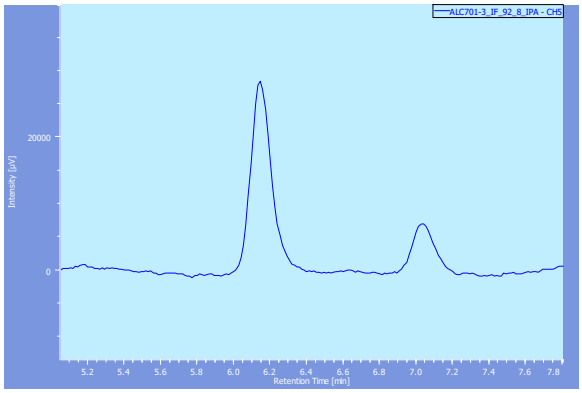


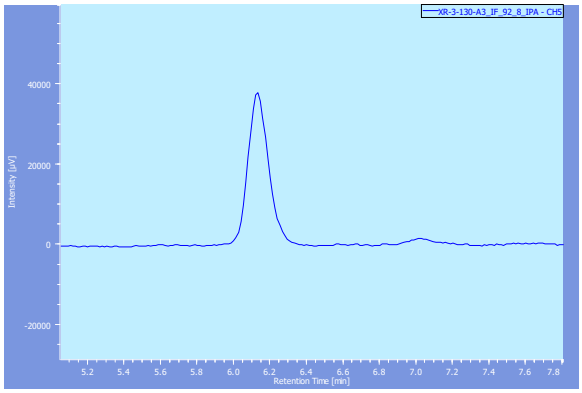
	Retention time/min	Peak area	Percent age
3c	5.04	565787	100%
4c	5.68	0	0%



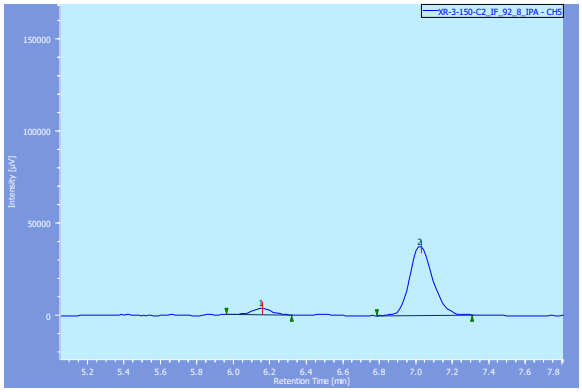
	Retention time/min	Peak area	Percent age
3c	5.04	14088	3.4%
4c	5.68	404425	96.6%

➢ Chiral SFC analysis of enzymatically produced racemic **3d**/**4d** (*top*), enzymatically produced **3d** (*middle*) and **4d** products (*bottom*):



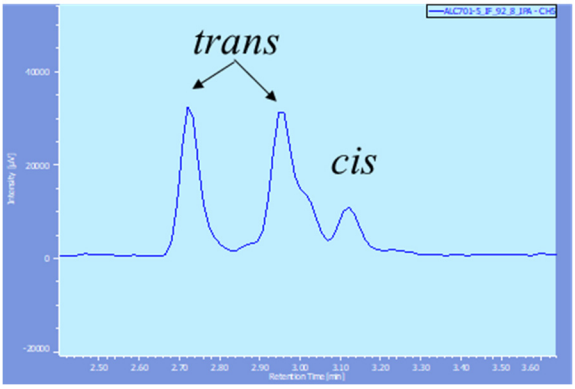


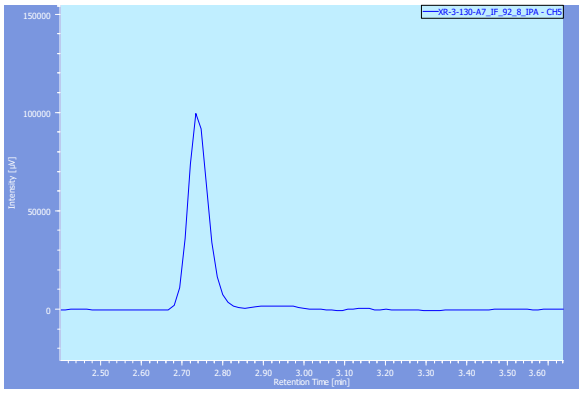
	Retention time/min	Peak area	Percentage
3d	6.16	461079	100%
4d	7.07	0	0%



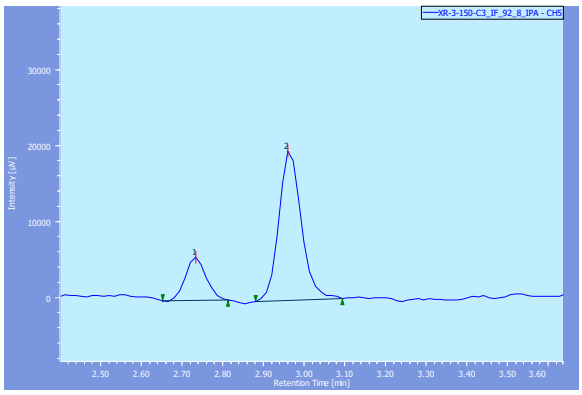
	Retention time/min	Peak area	Percentage
3d	6.16	26728	7.5%
4d	7.07	330632	92.5%

➢ Chiral SFC analysis of racemic **3e/4e** (*top*), enzymatically produced **3e** (*middle*) and **4e** products (*bottom*):



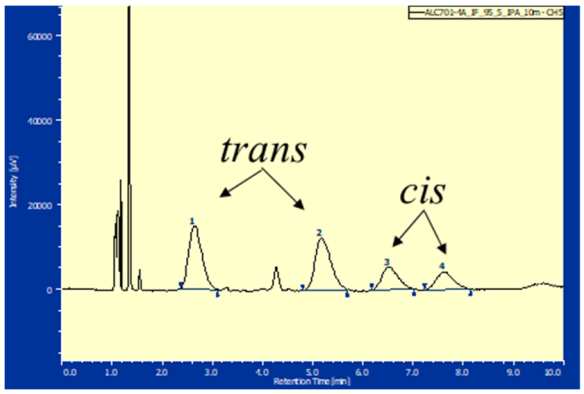


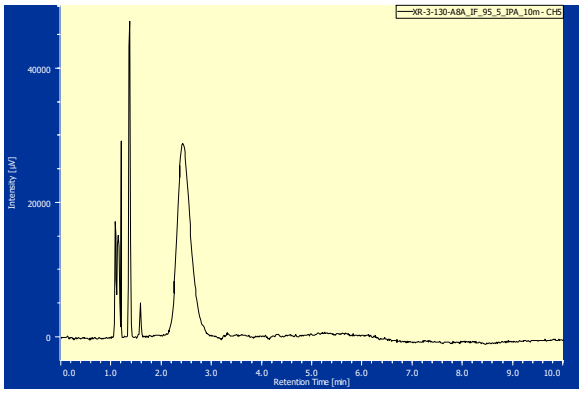
	Retention time/min	Peak area	Percentage
3e	2.74	287613	99%
4e	2.98	3106	1%



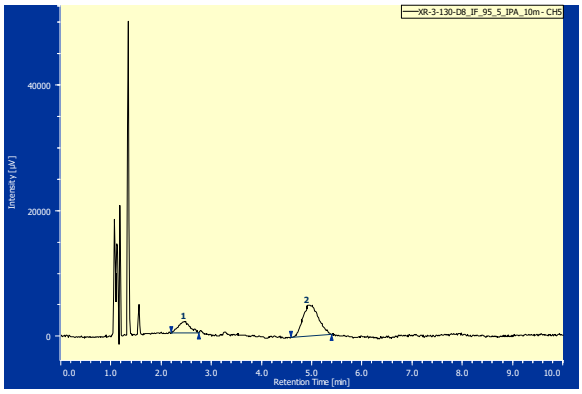
	Retention time/min	Peak area	Percentage
3e	2.74	20301	22.5%
4e	2.98	75758	77.5%

➢ Chiral SFC analysis of racemic **3f/4f** (*top*), enzymatically produced **3f** (*middle*) and **4f** products (*bottom*):



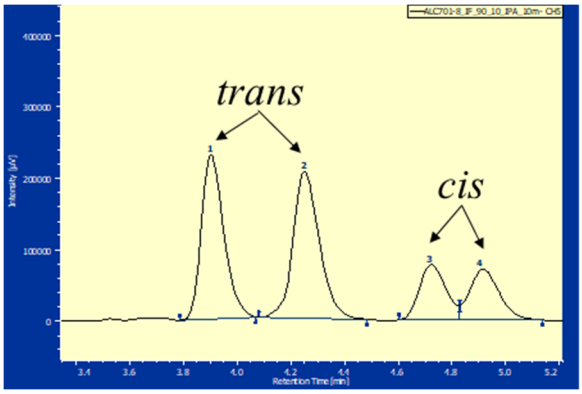


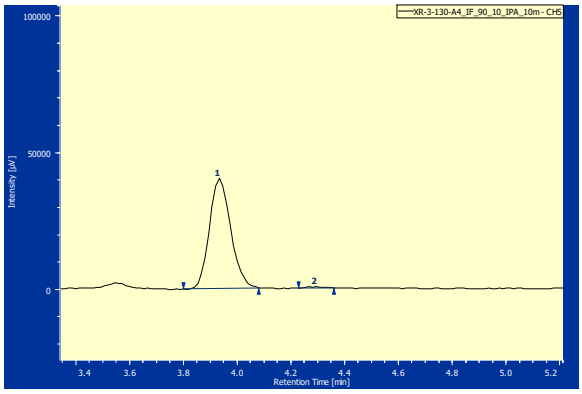
	Retention time/min	Peak area	Percent age
3f	2.64	49906	100%
4f	5.16	0	0%



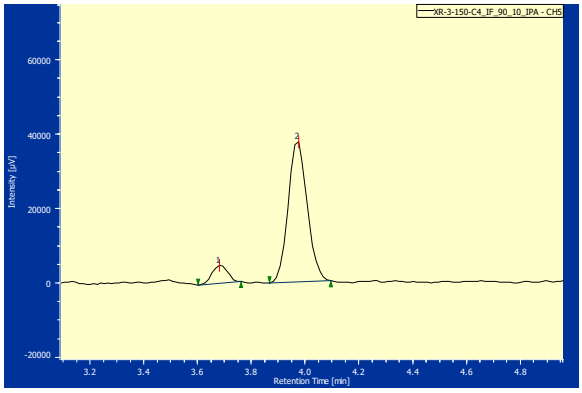
	Retention time/min	Peak area	Percent age
3f	2.64	28113	20.7%
4f	5.16	107715	79.3%

- Chiral SFC analysis of racemic **3g**/**4g** (*top*), enzymatically produced **3g** (*middle*) and **4g** products (*bottom, retention time was slightly shifted*):



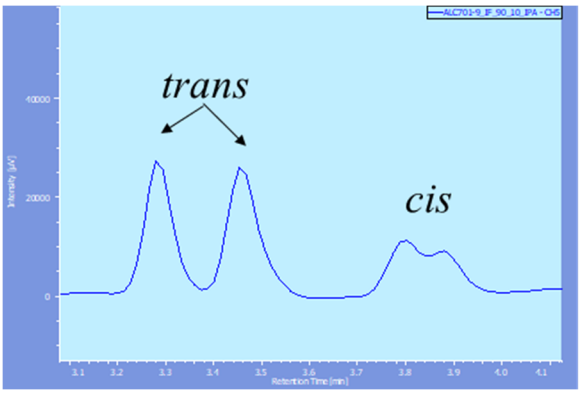


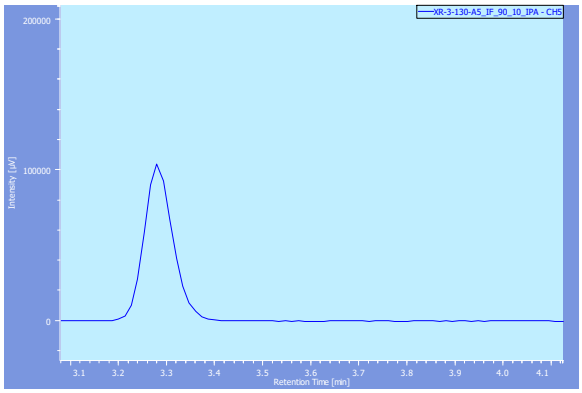
	Retention time/min	Peak area	Percentage
3g	3.91	221391	99.5%
4g	4.25	1092	0.5%



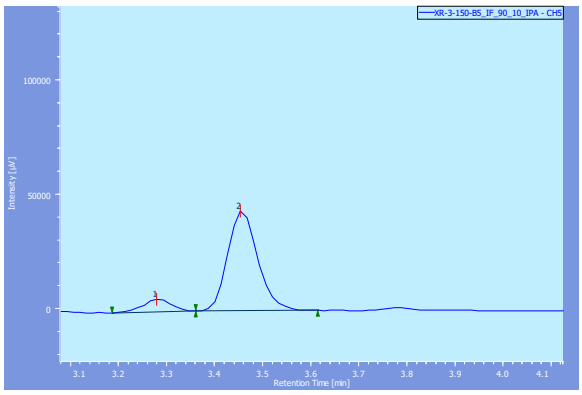
	Retention time/min	Peak area	Percentage
3g	3.68	19398	9.5%
4g	3.97	185430	90.5%

➢ Chiral SFC analysis of racemic **3h**/**4h** (*top*), enzymatically produced **3h** (*middle*) and **4h** products (*bottom*):



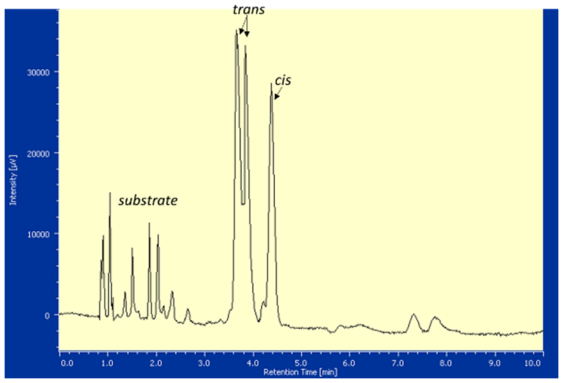


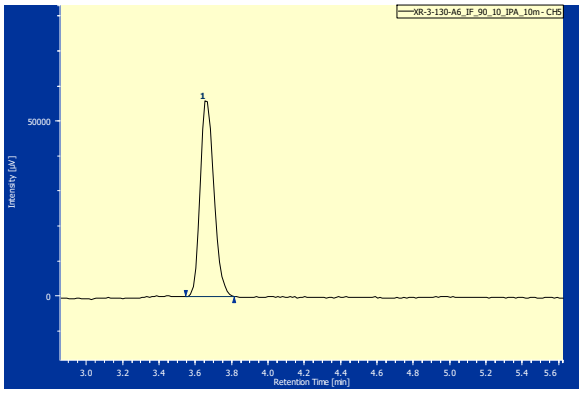
	Retention time/min	Peak area	Percentage
3h	3.30	359904	100%
4h	3.47	0	0%



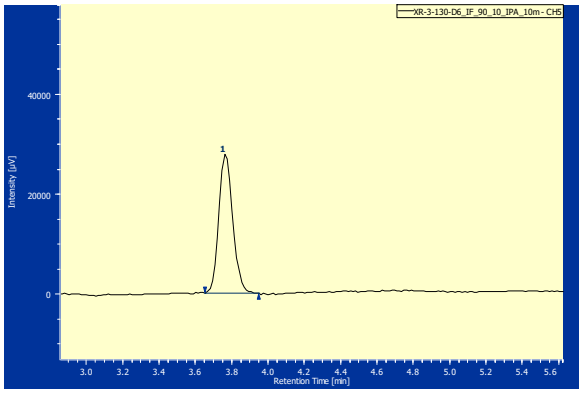
	Retention time/min	Peak area	Percentage
3h	3.30	22703	10.7%
4h	3.47	188556	89.3%

➢ Chiral SFC analysis of racemic **3i/4i** (*top*), enzymatically produced **3i** (*middle*) and **4i** products (*bottom*):



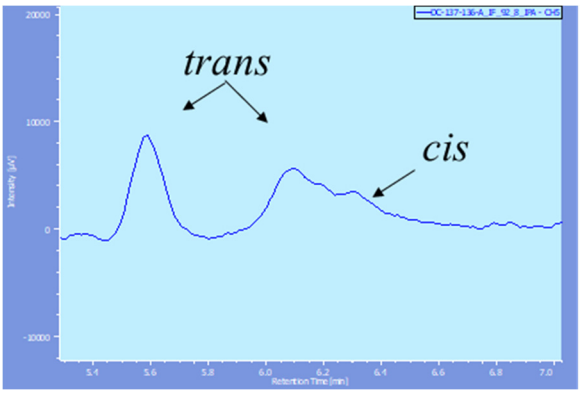


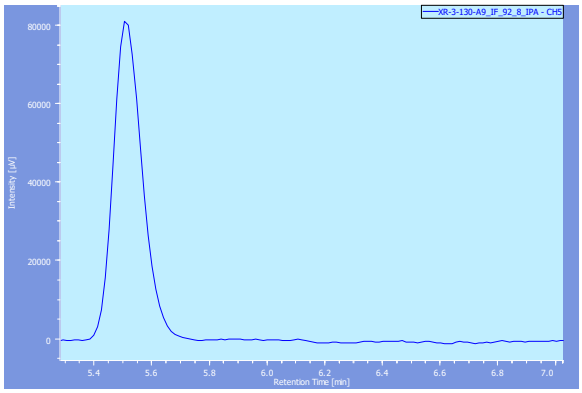
	Retention time/min	Peak area	Percent age
3i	3.65	296943	100%
4i	3.76	0	0%



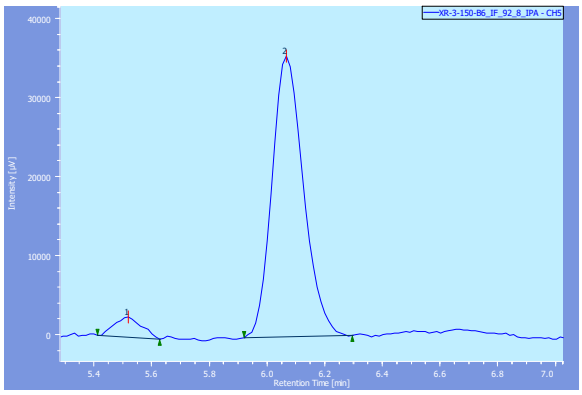
	Retention time/min	Peak area	Percent age
3i	3.65	0	0%
4i	3.76	147195	100%

➢ Chiral SFC analysis of racemic **3j/4j** (*top*), enzymatically produced **3j** (*middle*) and **4j** products (*bottom*):



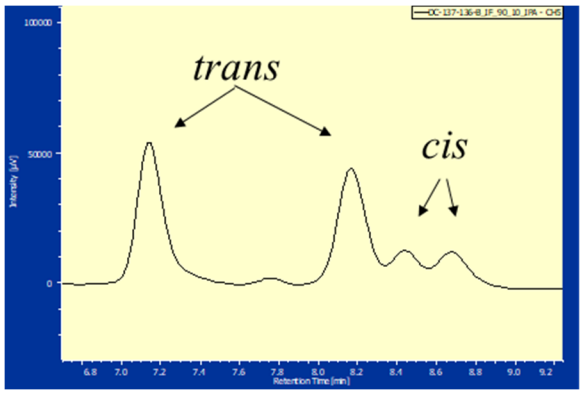


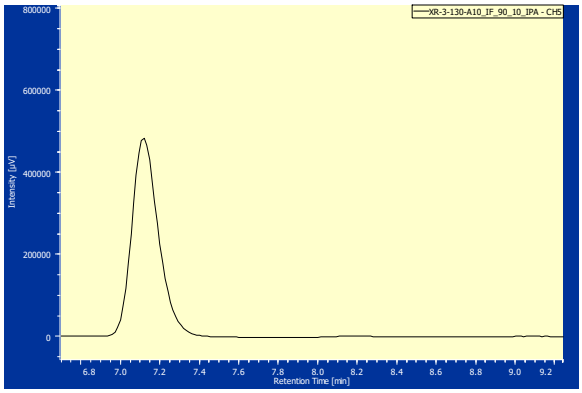
	Retention time/min	Peak area	Percentage
3j	5.50	374838	100%
4j	6.09	0	0%



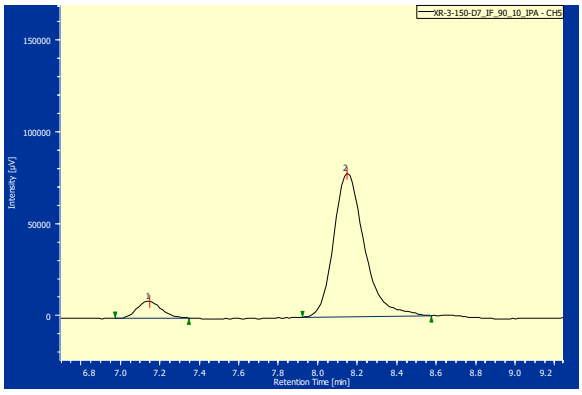
	Retention time/min	Peak area	Percentage
3j	5.50	16480	5.8%
4j	6.09	268847	94.2%

➢ Chiral SFC analysis of racemic **3k**/**4k** (*top*), enzymatically produced **3k** (*middle*) and **4k** products (*bottom*):



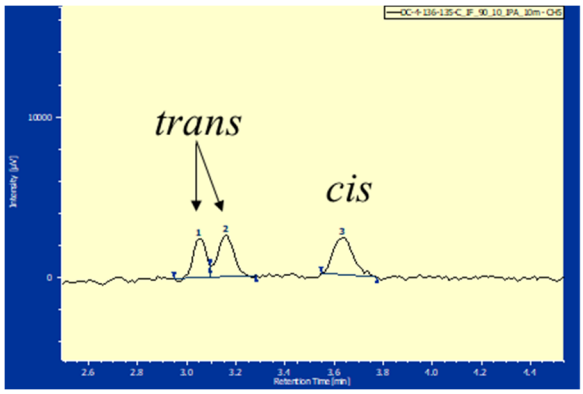


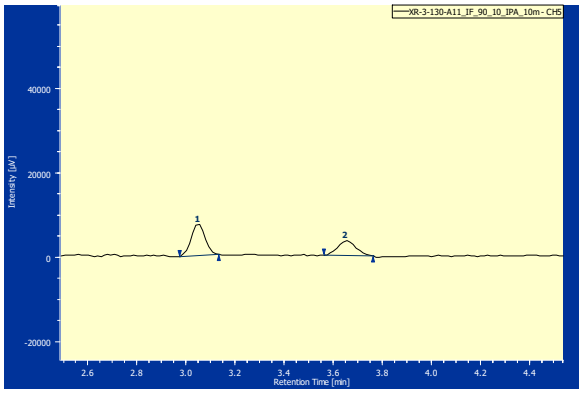
	Retention time/min	Peak area	Percentage
3k	7.16	3958617	99.6%
4k	8.20	16158	0.4%



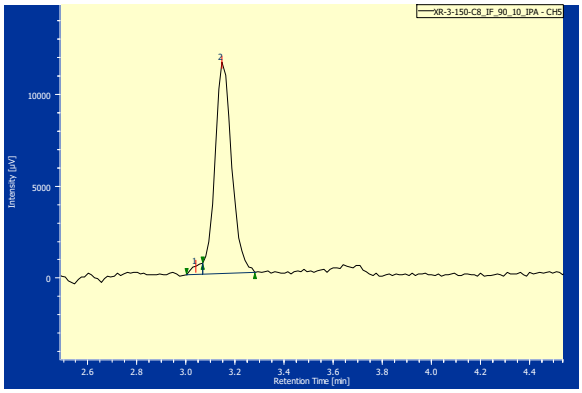
	Retention time/min	Peak area	Percentage
3k	7.16	79136	8.6%
4k	8.20	841944	91.4%

➢ Chiral SFC analysis of racemic **3l/4l** (*top*), enzymatically produced **3l** (*middle*) and **4l** products (*bottom*):





	Retention time/min	Peak area	Percentage
3l	3.05	29661	100%
4l	3.16	0	0%



	Retention time/min	Peak area	Percentage
3l	3.05	1522	2.7%
4l	3.16	54328	97.3%

Figure S5. ORTEP of dimethyl ((*1S,2R*)-2-(4'-methoxy-[1,1'-biphenyl]-4-yl)cyclopropyl)-phosphonate **(3da)** 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.

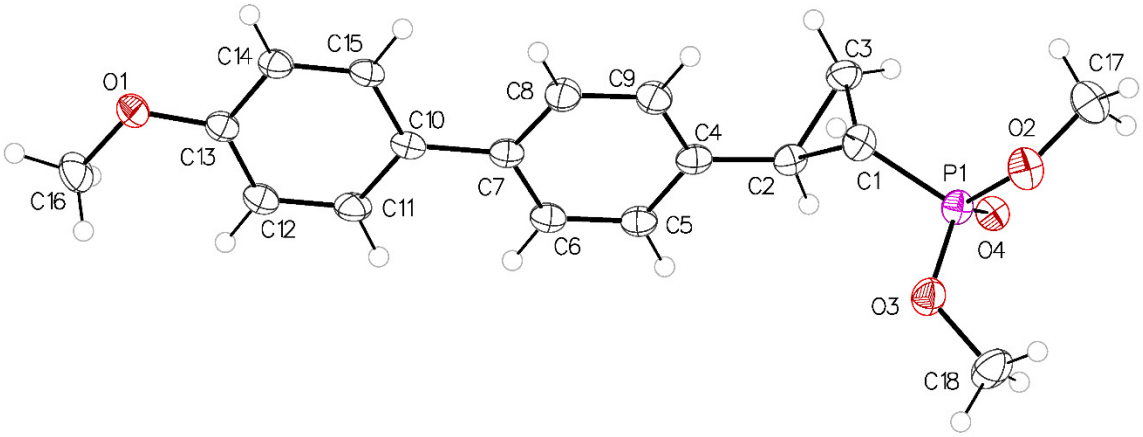


Figure S6. Mechanistic investigations using isotopically labeled substrate *cis*-β-deuterostyrene (**cis-*d*-2a**). (**a-b**) Overlay plot of the ^{2}H and ^{1}H NMR spectrum of the cyclopropanation product from the Mb(H64G,V68A)-catalyzed reaction with **cis-*d*-2a** and dimethyl (diazomethyl)phosphonate (**1**) showing the formation of only **3aa**. The ^{1}H NMR spectrum of the protiated cyclopropanation product **3a** is included as reference (panel **c**). Spectra were recorded using a 400 MHz instrument in $CDCl_3/CD_3OD$ (1:1).

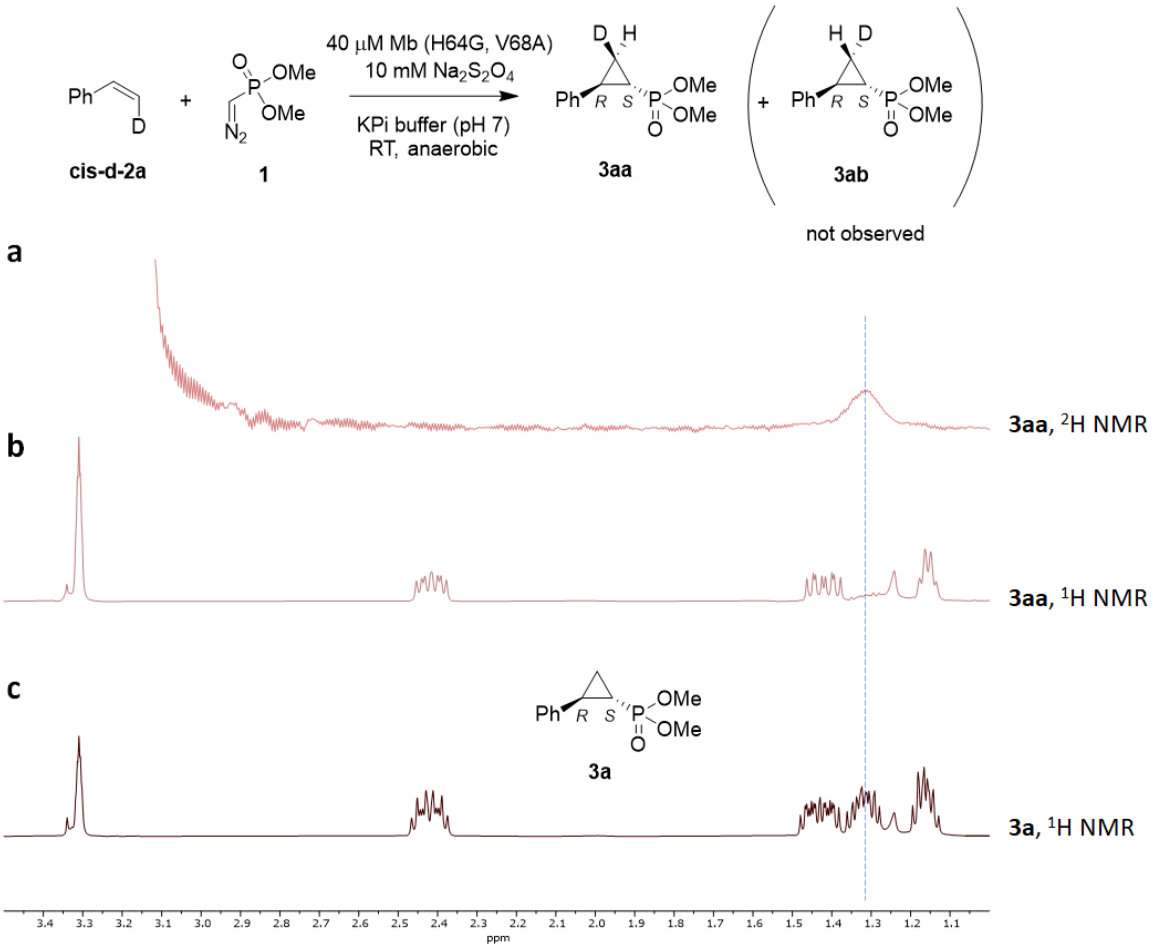


Figure S7. Circular dichroism spectra of compounds **3a** and **3c** (1 mM in methanol)

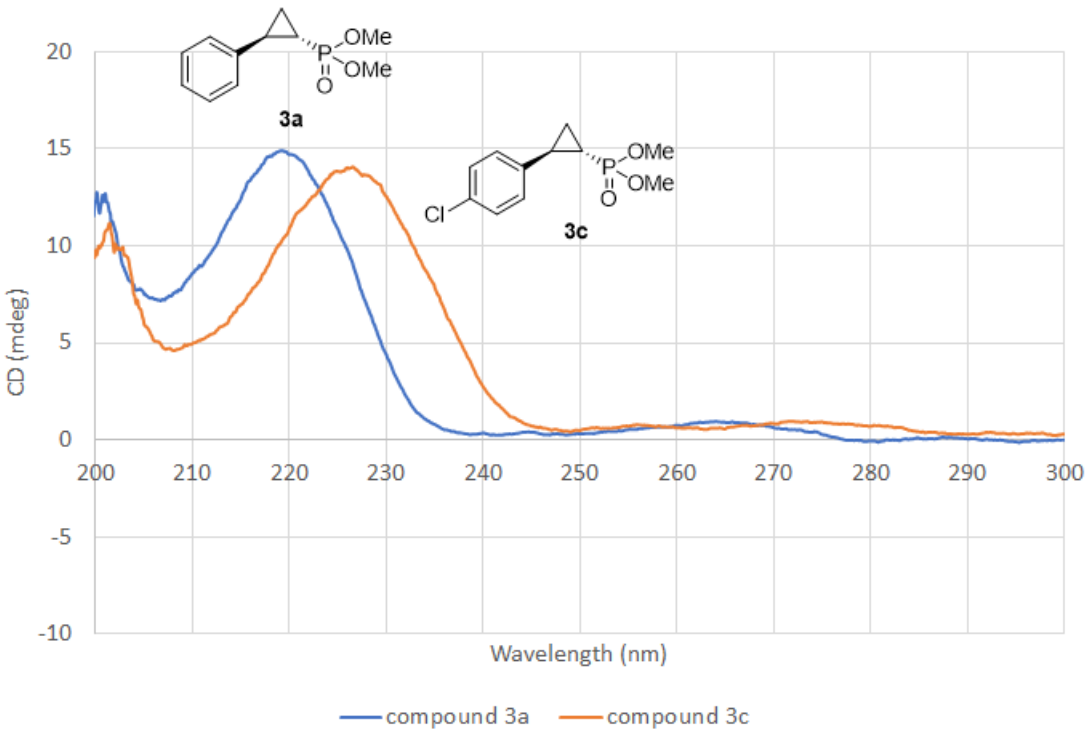
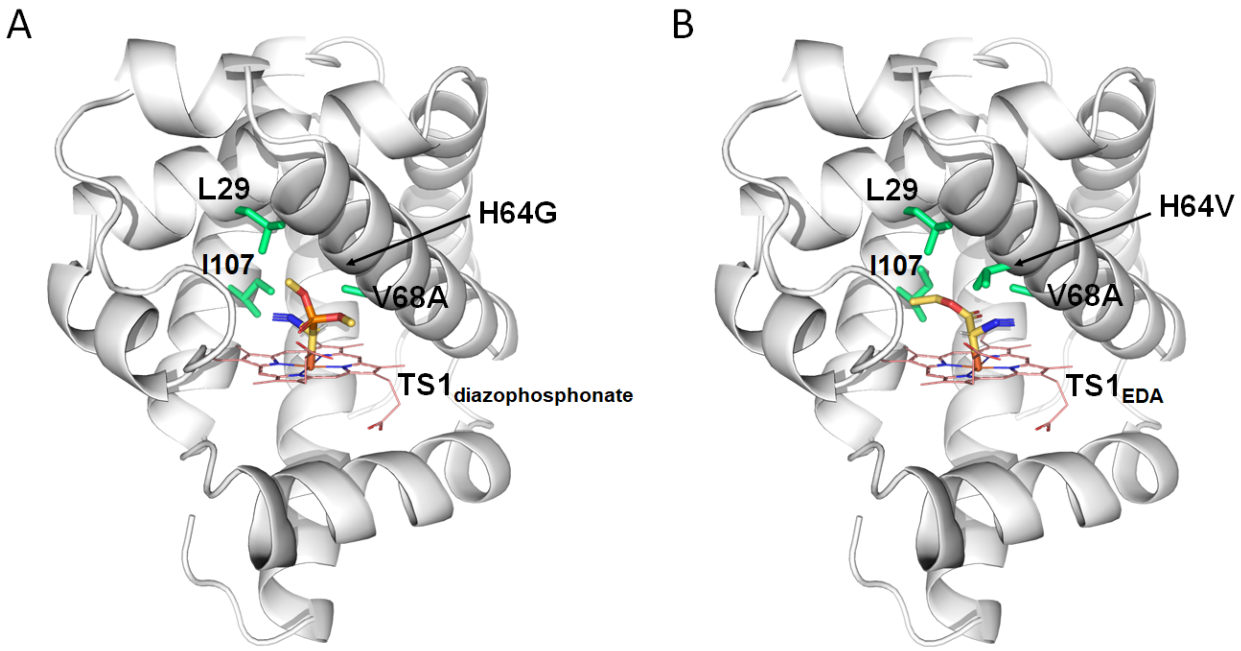


Figure S8. Rosetta model of (A) Mb(H64G,V68A) variant complexed with dimethyl (diazomethyl)phosphonate (**1**) and (B) Mb(H64V,V68A) variant complexed with ethyl diazoacetate (EDA). The table reports Rosetta-calculated energies of the engineered myoglobin biocatalysts complexed with the diazo substrates, the heme-bound diazo substate and the apoenzyme. (Unit: Rosetta Energy Unit (REU))



variant	Diazo substrate	Substrate-bound	Substrate-free	$\Delta E_{binding}$	E_{TS1}
Mb(H64G,V68A)	phosphonate	-461.62	-469.02	7.40	3.87
Mb(H64V,V68A)	diazoacetate	-468.04	-473.85	5.81	1.98

Experimental Procedures

General Information

All chemicals and reagents were purchased from commercial suppliers (Sigma-Aldrich, Alfa Aesar, Frontier Scientific Inc, Chem-Impex Int.) and use without any further purification, unless otherwise stated. All dry reactions were carried out under argon pressure in oven-dried glassware with magnetic stirring using standard gas-tight syringes, cannula, and septa. ^{1}H, ^{19}F, ^{31}P and ^{13}C NMR spectra were measured on a Bruker DPX-400 instrument (operating at 400MHz for ^{1}H, 376 MHz for ^{19}F, 162 MHz for ^{31}P and 100 MHz for ^{13}C) or a Bruker DPX- instrument (operating at 500 MHz for ^{1}H and 125 MHz for ^{13}C). The multiplicity signals were indicated with the common abbreviations: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and br (broad) and the combinations thereof. Column chromatography purification was carried out using AMD silica gel 60 230-400 mesh. Thin Layer Chromatography (TLC) was carried out using Merck Millipore TLC silica gel 60 F254 glass plates. 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 0.25μm film). Supercritical Fluid Chromatography (SFC) analysis were carried out using a JASCO Analytical and Semi-Preparative SFC instrument equipped with a column oven (35°C), photodiode array detector.

Protein Expression

Wild-type and engineered myoglobin variants were expressed in *E.coli* C41(DE3) cells as follows. After transformation, cells were grown in LB medium (ampicillin, 100 mg/L) at 37°C (200 rpm) until OD_{600} reached 1 to 1.2. 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 hours by centrifugation at 4,000 rpm at 4°C. The cells were resuspended in 20 mL of Ni-NTA Lysis Buffer (50 mM KPi, 250 mM NaCl, 10 mM histidine, pH 8.0). Resuspended cells were frozen and stored at -80°C until purification. Cell suspensions were thawed at room temperature, lysed by sonication, and clarified by centrifugation (14,000 rpm, 50 min, 4°C). The clarified lysate was transferred to a Ni-NTA column equilibrated with Ni-NTA Lysis Buffer. The resin was washed with 50 mL of Ni-NTA Lysis Buffer and then 50 mL of Ni-NTA Wash Buffer (50 mM KPi, 250 mM NaCl, 20 mM histidine, pH 8.0). Proteins were eluted with Ni-NTA Elution Buffer (50 mM KPi, 250 mM NaCl, 250 mM histidine,

pH 7.0). After elution from the Ni-NTA column, the protein was buffer exchanged against 50 mM KPi buffer (pH 7.0) using 10 kDa Centricon filters. The concentration of the Mb variants (ferric form) was determined using ε_{410}=156 $mM^{-1}cm^{-1}$ as the extinction coefficients.

Protein evolution

The protein evolution was conducted through iterative rounds of site saturation mutagenesis. In each round, the site saturation library of Mb variants was constructed and transformed into *E.coli.* DH5α cells. The colonies were collected in LB medium (ampicillin, 100 mg L^{-1}) and plasmids were extracted by QIAprep Spin Miniprep Kit (Cat No.27104). The library coverage was assessed by DNA sequencing. The library of Mb variants were then transformed into *E. coli.* C41(DE3) cells and expressed in 96-well plates under the conditions described above. After expression, the cells were pelleted by centrifuge and resuspended in Kpi buffer (50 mM, pH=7). The reactions were initiated by adding substrate into each well of the plate in an anerobic chamber and left shaking for 5 hours. The reactions mixtures were extracted by DCM and analyzed by chiral GC-FID. The Mb variant that showed improved activity and enantioselectivity was sequenced and used as template for next round of mutagenesis and protein evolution.

Enzymatic cyclopropanation reactions

General enzymatic cyclopropanation reactions were carried out at a 500 μL-scale using Mb variant, alkenes, dimethyl (diazomethyl)phosphonate and sodium dithionite ($Na_2S_2O_4$). In a typical procedure, a solution of $Na_2S_2O_4$ in potassium phosphate buffer (50 mM, pH 7.0) was degassed by bubbling argon into the mixture for 3 min in a sealed vial. A buffered solution containing the myoglobin variant was carefully degassed in a similar manner in a separate vial. The two solutions were then mixed via cannula. Reactions were initiated by addition of alkene (from a 0.5 M stock solution in ethanol), followed by the addition of dimethyl (diazomethyl)phosphonate (from a 0.5 M stock solution in ethanol) with a syringe, and the reaction mixture was stirred for 16 hours at room temperature, under positive argon pressure. For whole cell experiments, reactions were carried out at a 500 μL-scale using *E. coli* whole cells expressing myoglobin variant, alkene, and dimethyl (diazomethyl)phosphonate. In a typical procedure, a sealed vial containing whole cells was degassed with argon for 3 min. The reactions were initiated by addition of alkene (from a 0.5 M stock solution in ethanol), followed by the addition of dimethyl (diazomethyl)phosphonate

(from a 0.5 M stock solution in ethanol) with a syringe. The reaction mixture was stirred for 16 hours at room temperature under positive argon pressure. The TON for the whole-cell reactions were calculated based on Mb concentration in the reaction mixture as measured via UV-vis spectroscopy (ε_{410}=156 $mM^{-1}cm^{-1}$) after cell lysis.

Radical spin trap experiments were carried using purified protein as the catalyst and according to the procedure described above with or without 100 mM 5,5-dimethyl-1-pyrroline-N-oxide (DMPO). The deuterium scrambling experiments were carried out using *cis*-β-deutero-styrene (**cis-*d*-2a**) which was prepared as described previously (Wei et al., *J. Am. Chem. Soc.* 2018, 140, 1649−1662).

Kinetic experiments

For the kinetic measurement with Mb(H64G,V68A), reactions were carried out on a 500 µL-scale in oxygen-free KPi buffer (pH 7.0) using 40 µM Mb variant, 10 mM styrene (from a 0.5 M stock solution in ethanol) and 20 mM dimethyl (diazomethyl)phosphonate (from a 0.5 M stock solution in ethanol). At regular intervals 25 µL of solution were collected and quenched with 50 µL of 0.2 M HCl. Aliquots were analysed by adding 25 µL of internal standard (1,3-benzodioxole, 50 mM in ethanol) followed by extraction with 500 µL of dichloromethane and analysis by gas chromatography (GC) using calibration curves with isolated **4a**. For the kinetic measurement with Mb(L29T, H64V, V68F, V68L), reactions were carried out on a 500 µL-scale in oxygen-free KPi buffer (pH 7.0) using Mb(L29T, H64V, V68F, V68L) expressing *E. coli.* C41(DE3) cells with cell density OD_{600}=100, 5 mM styrene (from a 0.5 M stock solution in ethanol) and 10 mM dimethyl (diazomethyl)phosphonate (from a 0.5 M stock solution in ethanol). At regular intervals 25 µL of solution were collected and quenched with 50 µL of 0.2 M HCl. Aliquots were analysed by adding 25 µL of internal standard (1,3-benzodioxole, 50 mM in ethanol) followed by extraction with 500 µL of dichloromethane and analysis by gas chromatography (GC) using calibration curves with isolated **3a**. The experiments were performed in duplicates and rrepresentative kinetic plots corresponding to these experiments are reported in Figure S2 and S3.

Cyclopropanation reactions for preparation of racemic standards

General cyclopropanation reactions were carried out at a 500 µL-scale using $Rh_2(OAc)_4$, alkenes, dimethyl (diazomethyl)phosphonate in CH_2Cl_2. In a typical procedure, a solution of

$Rh_2(OAc)_4$ in CH_2Cl_2 was degassed by bubbling argon into the mixture for 3 min in a sealed vial. Reactions were initiated by addition of alkene (from a 0.5 M stock solution in dichloromethane), followed by the addition of dimethyl (diazomethyl)phosphonate (from a 0.5 M stock solution in dichloromethane) with a syringe, and the reaction mixture was stirred for 16 hours at room temperature, under positive argon pressure.

Product analysis

The reactions were analyzed by adding 25 μL of internal standard (1,3-benzodioxole, 50 mM in ethanol) to the reaction mixture, followed by extraction with 500 μL of dichloromethane (DCM) and analyzed by GC−FID. Calibration curves of the different cyclopropane products were constructed using synthetically produced authentic standards. All measurements were performed at least in duplicate. For stereoselectivity determination, the samples were analyzed by chiral GC. Separation method for cyclopropanation reactions: 1 μL injection, injector temp.: 140ºC, detector temp: 300ºC. Gradient: column temperature set at 70ºC for 3 min, then to 160ºC at 0.45ºC/min, then to 240ºC at 25 ºC/min. Total run time was 206 min. Calibration curves for the different cyclopropane products were constructed using pure product. Stereoisomer resolution was performed by Supercritical Fluid Chromatography (SFC) analysis. Daicel Chiralpak IF column (0.46 cm ID × 25 cm L) was used for separation of enantiomers. All samples were eluted using isocratic solvent system with isopropanol (IPA) as modifier (see table below) in liquid CO_2 at an elution rate of 4 mL/min and detected at λ=220 nm.

Substrate	**Method**	**t_R for *trans* enantiomer 1 (min)**	**t_R for *trans* enantiomer 2 (min)**
styrene	10% IPA	3.45	3.82
4-fluorostyrene	8% IPA	3.63	4.05
4-chlorostyrene	8% IPA	5.04	5.68
4-bromostyrene	8% IPA	6.16	7.07
4-trifluoromethylstyrene	8% IPA	2.74	2.98
4-methoxystyrene	10% IPA	2.64	5.16
4-methylstyrene	10% IPA	3.91	4.25

3-methylstyrene	10% IPA	3.30	3.47
2-methylstyrene	10% IPA	3.65	3.76
3-bromostyrene	8% IPA	5.50	6.09
2-vinyl-naphthalene	10% IPA	7.16	8.20
α-methylstyrene	10% IPA	3.05	3.16

Computational Studies

DFT calculations for styrene cyclopropanation reactions with dimethyl (diazomethyl)phosphonate and EDA. DFT calculations were carried on a truncated heme-bound carbenoid species along the reaction pathway to elucidate the cyclopropanation reaction pathway of styrene with dimethyl (diazomethyl)phosphonate (**1**) and ethyl diazoacetate (EDA) using Gaussian16 (1). All reaction species were geometrically optimized at B3LYP/6-311G**-SDD level of theory (2-4) and using the polarizable continuum model (PCM) (5) to simulate solvent effects. TS1, heme-bound carbenoid intermediate and TS2 were optimized from an unrestricted symmetry-broken initial guess of wavefunction to model the open-shell singlet ground state. Frequency calculations were then carried out to ensure that each reactant or intermediates is the minimum and each transition state is the first-order saddle point on the potential energy surface. Zero-point energy correction (ZPE) and thermal corrections to internal energies, enthalpies, and Gibbs free energies were also obtained. Single-point energy calculations were then conducted at B3LYP-D3BJ/def2-TZVP-SDD level of theory (6-7) to compute the high accuracy electronic energies (E). E and previously obtained corrections were added up to obtain the zero-point energy-corrected electronic energies (namely U/H/G at 0 K), internal energies (U), enthalpies (H), and Gibbs free energies (G), which are reported in **Table S8** and graphically summarized in **Figure 3c**.

Rosetta modeling of engineered myoglobin–TS1 complexes. To further investigate factors influencing the enzyme's cyclopropanation activity in the presence of **1** vs EDA, we modeled the transition state of the rate-determining step as determined via DFT studies —TS1— within the protein environment using the Rosetta software suite.(9) The EDA-derived TS1 ($TS1_{EDA}$) was docked into the active site the myoglobin variant Mb(H64V,V68A) using the available crystal structure of this protein (PDB ID: 6M8F), whereas the dimethyl (diazomethyl)phosphonate-derived TS1 ($TS1_{diazophosphonate}$) was docked into a model of Mb(H64G,V68A) generated by introducing a Val68Gly substitution into the crystal structure of Mb(H64V,V68A). Subsequent structure and energy optimizations provided the energy of each engineered biocatalyst complexed with the corresponding diazo substrate, the heme-bound diazo substate and the apoenzyme (= substrate-free enzyme). The Rosetta models and calculated energies in Rosetta Energy Unit (R.E.U.) are shown in **Figure S8**.

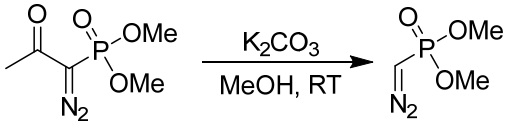
Table S8. Electronic energies (E), zero-point energy-corrected electronic energies (E+ZPE), internal energies (U), enthalpies (H), and Gibbs free energies (G) of optimized species in the cyclopropanation reaction pathway. (Unit: Hartree).

species	E	E+ZPE	U	H	G
heme	-1339.19	-1338.85	-1338.83	-1338.83	-1338.90
styrene	-309.79	-309.66	-309.66	-309.65	-309.69
N_2	-109.57	-109.57	-109.57	-109.57	-109.59
diazophosphonate	-795.33	-795.22	-795.21	-795.21	-795.26
$TS1_{diazophosphonate}$	-2134.52	-2134.06	-2134.03	-2134.02	-2134.13
$Int_{diazophosph}$	-2024.97	-2024.52	-2024.49	-2024.49	-2024.59
$TS2_{diazophosphonate}$	-2334.78	-2334.19	-2334.15	-2334.15	-2334.26
$cyclopropane_P$	-995.64	-995.40	-995.38	-995.38	-995.44
diazoacetate	-416.14	-416.04	-416.03	-416.027	-416.07
$TS1_{EDA}$	-1755.32	-1754.87	-1754.84	-1754.84	-1754.94
Int_{EDA}	-1645.77	-1645.33	-1645.30	-1645.30	-1645.39
$TS2_{EDA}$	-1955.58	-1955.00	-1954.96	-1954.96	-1955.07
cyclopropane	-616.44	-616.21	-616.19	-616.19	-616.25

Synthetic Procedures

Synthesis of dimethyl (diazomethyl)phosphonate (1)

Molecular Weight: 150.07



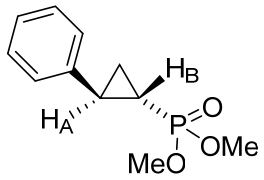
1

A solution of dimethyl (1-diazo-2-oxopropyl)phosphonate (1.92 g, 10 mmol) in 10 mL of MeOH was stirred with potassium carbonate (276 mg, 2 mmol) at room temperature for 15 min (monitored by TLC analysis). The precipitate was filtered off and the solvent was evaporated under reduced pressure. The crude was purified by column chromatography on silica gel (100% dichloromethane) and the product was obtained as a yellow liquid (1.26 g, 84 % yield). The analytical data are in accord with those reported in literature (S. Ohira, *Synth. Commun.* **1989**, 19, 561).

Synthesis of cyclopropanes

Reactions were carried out at a 50 mL-scale using 40 μM Mb(H64G,V68A), 10 mM alkene, 20 mM dimethyl (diazomethyl)phosphonate and 10 mM sodium dithionite ($Na_2S_2O_4$). In a typical procedure, in a 50 mL round-bottom flask, a solution of $Na_2S_2O_4$ in potassium phosphate buffer (50 mM, pH 7.0) was degassed by bubbling argon into the mixture for 15 min. A buffered solution containing the myoglobin variant was carefully degassed in a similar manner in a separate round-bottom flask. The two solutions were then mixed via cannula. Reactions were initiated by addition of 500 μL of alkene (from a 0.5 M stock solution in ethanol), followed by the addition of 1 mL of dimethyl (diazomethyl)phosphonate (from a 0.5 M stock solution in ethanol) with a syringe, and the reaction mixture was stirred for 16 hours at room temperature, under positive argon pressure. The reaction was extracted with CH_2Cl_2 (50 mL) and dried over $MgSO_4$. The solvent was evaporated under reduced pressure, and the crude was purified by flash chromatography (silica gel, from hexane/EtOAc 1:9 to EtOAc). The cyclopropanes were obtained as *trans* isomers. Due to insolubility of final products, mixture of CD_3OD and $CDCl_3$ (1:1) was used for NMR analysis.

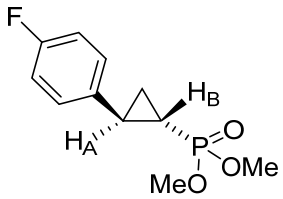
Dimethyl 2-phenylcyclopropyl phosphonate (3a)



Following the general procedure using styrene, *trans* isomer of **3a** was isolated as yellowish oil (106 mg, 94% isolated yield).

GC/MS *m/z* (% relative intensity): 226(40.5), 124(8.2), 118(9.9), 117(100), 116(34.4), 115(75.4), 109(7.0), 94(7.7), 91(15.5), 89(5.8), 79(9.3), 65(5.7), 63(5.2). **^{1}H NMR** ($CDCl_3/CD_3OD$, 500 MHz): δ 7.38 (t, *J*=7.5 Hz, 2H), 7.30 (t, *J*=7.4 Hz, 1H), 7.25 (d, *J*=7.3 Hz, 1H), 3.90 (d, $J_{H\text{-}P}$=10.7 Hz, 3H), 3.88 (d, $J_{H\text{-}P}$=10.4 Hz, 3H), 2.54 (ddt, $^{3}J_{H\text{-}P\ cis}$=14.6, $J_{H\text{-}H}$=8.8, 5.7 Hz, 1H, H_A), 1.52 (dddd, $^{2}J_{H\text{-}P}$=19.4, $J_{H\text{-}H}$=8.8, 6.4, 4.8 Hz,1H, H_B), 1.48-1.41 (m, 1H), 1.33 ppm (m, 1H). **^{31}P NMR** ($CDCl_3/CD_3OD$, 162 MHz): δ 29.84 ppm (s). **^{13}C NMR** ($CDCl_3/CD_3OD$, 126 MHz): δ 129.4, 127.5, 126.9, 21.8, 14.6, 12.9 ppm (d, $J_{C\text{-}P}$=29.0 Hz). The carbon signals for the methoxy groups overlap with the CD_3OD solvent peak.

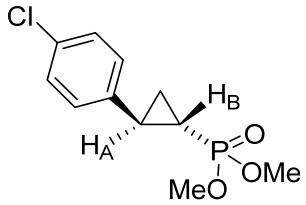
Dimethyl 2-(4-fluoro)phenylcyclopropyl phosphonate (3b)



Following the general procedure using 4-fluoro styrene, *trans* isomer **3b** was isolated as yellowish oil (110 mg, 90% isolated yield).

GC/MS *m/z* (% relative intensity): 244(35.4), 136(10.3), 135(100), 134(17.4), 133(50.0), 124(6.5), 115(19.1), 109(18.6), 94(6.8), 83(5.0), 79(7.9). **^{1}H NMR** ($CDCl_3/CD_3OD$, 500 MHz): δ 7.26 (dd, *J*=8.1 Hz, $J_{H\text{-}F}$=5.5 Hz, 2H), 7.10 (t, *J*=8.6 Hz, 2H), 3.90 (d, $J_{H\text{-}P}$=8.3 Hz, 3H), 3.88 (d, $J_{H\text{-}P}$=8.3 Hz, 3H), 2.54 (ddt, $^{3}J_{H\text{-}P\ cis}$=11.4 Hz, *J*=9.2, 5.7 Hz, 1H, H_A), 1.54 (dddd, $^{2}J_{H\text{-}P}$=11.4 Hz, *J*=8.9, 6.2, 5.6 Hz, 1H, H_B), 1.47-1.39 (m, 1H), 1.30 ppm (m, 1H). **^{19}F NMR** ($CDCl_3/CD_3OD$, 376 MHz): δ -112.67 (ddd, *J*=13.8, 8.6, 5.2 Hz). **^{31}P NMR** ($CDCl_3/CD_3OD$, 162 MHz): δ 29.62 ppm (s). **^{13}C NMR** ($CDCl_3/CD_3OD$, 126 MHz): δ 163.4, 135.9, 128.5 (d, $J_{C\text{-}F}$=8.0 Hz), 115.8 (d, $J_{C\text{-}F}$=21.7 Hz), 20.9, 14.3, 12.5 (d, *J*=5.5 Hz). The carbon signals for the methoxy groups overlap with the CD_3OD solvent peak.

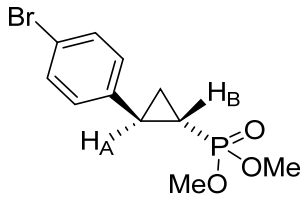
Dimethyl 2-(4-chloro)phenylcyclopropyl phosphonate (3c)



Following the general procedure using 4-chloro, *trans* isomer **3c** was isolated as yellowish oil (77 mg, 59% isolated yield).

GC/MS *m/z* (% relative intensity): 262(17.6), 261(7.5), 260(51.7), 165(5.0), 153(30.3), 152(12.6), 151(100), 150(10.4), 149(22.9), 129(8.4), 125(5.0), 124(11.3), 117(5.5), 116(47.4), 115(75.2), 114(5.3), 109(11.3), 94(9.5), 93(5.5), 89(8.8), 79(11.7), 63(6.4). **^{1}H NMR** ($CDCl_3$/CD_3OD, 500 MHz): δ 7.37 (d, *J*=8.5 Hz, 2H), 7.20 (d, *J*=8.4 Hz, 2H), 3.90 (d, $J_{H\text{-}P}$=9.4 Hz, 3H), 3.88 (d, $J_{H\text{-}P}$=9.5 Hz, 3H), 2.54 (ddt, $^{3}J_{H\text{-}P\ cis}$=14.6 Hz, $J_{H\text{-}H}$=8.9, 5.7 Hz, 1H, H_A), 1.58 (dddd, $^{2}J_{H\text{-}P}$=18.9, $J_{H\text{-}H}$=8.8, 6.4, 4.9 Hz, 1H, H_B), 1.48-1.39 (m, 1H), 1.31-1.24 ppm (m, 1H). **^{31}P NMR** ($CDCl_3$/CD_3OD, 162 MHz): δ 29.35 ppm (s). **^{13}C NMR** ($CDCl_3$/CD_3OD, 126 MHz): δ 138.7, 133.1, 129.3, 128.2, 21.1, 14.7, 12.9 ppm (d, *J*=5.6 Hz). The carbon signals for the methoxy groups overlap with the CD_3OD solvent peak.

Dimethyl 2-(4-bromo)phenylcyclopropyl phosphonate (3d)

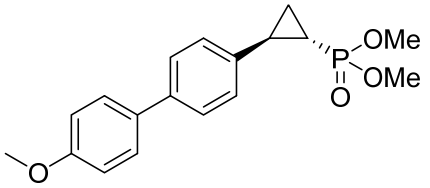


Following the general procedure using 4-bromo styrene (reaction volume 600 mL), *trans* isomer **3d** was isolated as yellowish oil (1.1 g, 61% isolated yield).

GC/MS *m/z* (% relative intensity): 306(25.7), 304(27.0), 197(15.5), 195(22.3), 193(8.8), 130(6.2), 129(5.8), 124(7.7), 117(10.8), 116(100), 115(54.4), 114(5.4), 109(8.1), 94(6.8), 89(7.2), 79(8.4), 63(5.6). **^{1}H NMR** ($CDCl_3$/CD_3OD, 500 MHz): δ 7.52 (d, *J*=8.4 Hz, 2H), 7.14 (d, *J*=8.4 Hz, 2H), 3.90 (d, $J_{H\text{-}P}$=10.7 Hz, 3H), 3.88 (d, $J_{H\text{-}P}$=10.0 Hz, 3H), 2.52 (ddt, $^{3}J_{H\text{-}P\ cis}$=14.6, $J_{H\text{-}H}$=8.8, 5.7, 5.7 Hz, 1H, H_A), 1.60 (dddd, $^{2}J_{H\text{-}P}$=19.4, $J_{H\text{-}H}$=8.8, 6.4, 4.8 Hz, 1H, H_B), 1.47-1.40 (m, 1H), 1.27 ppm (m,1H). **^{31}P NMR** ($CDCl_3$/CD_3OD, 162 MHz): δ 29.27 ppm (s). **^{13}C NMR** ($CDCl_3$/CD_3OD, 126

MHz): δ 141.2, 139.3, 132.2, 128.6, 21.1, 14.6, 12.7 ppm (d, *J*=5.6 Hz). The carbon signals for the methoxy groups overlap with the CD_3OD solvent peak.

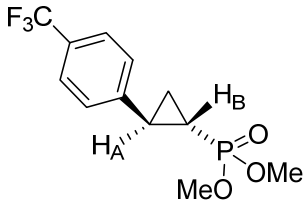
Dimethyl ((*1S*,*2R*)-2-(4'-methoxy-[1,1'-biphenyl]-4-yl)cyclopropyl)phosphonate (3da)



A 50 mL-flask was charged with $Pd(PPh_3)_4$ (0.03 mmol), toluene (10 mL), dimethyl 2-(4-bromo)phenylcyclopropyl phosphonate (**3d,** 1 mmol), and an aqueous solution of Na_2CO_3 (5 mL of a 2M solution) under argon atmosphere, and then (4-methoxyphenyl)boronic acid (1.1 mmol) in ethanol (2.5 mL) was added. The mixture was refluxed overnight. After the reaction was complete, the residual (4-methoxyphenyl)boronic acid was oxidized by 30% H_2O_2 (0.5 mL) at room temperature for 1h. The product was extracted with ether, washed by a saturated NaCl solution, and finally dried over Na_2SO_4. The solvent was evaporated under reduced pressure, and the crude was purified by flash chromatography (silica gel, from hexane/EtOAc 1:9 to EtOAc). Compound **3da** was isolated as white solid (66% isolated yield).

GC/MS *m/z* (% relative intensity): 333(19.5), 332(100), 224(16.5), 223(92.1), 222(39.7), 221(28.8), 209(10.1), 208(52.9), 201(21.6), 206(7.6), 195(26.7), 193(7.8), 192(10.8), 191(19.1), 190(9.0), 189(9.9), 180(6.6), 179(17.6), 166(7.3), 165(24.7), 153(8.0), 152(17.3), 139(6.7), 115(16.8), 109(13.7), 79(10.8). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.49 (d, *J*=8.0 Hz, 2H), 7.47 (d, *J*=8.0 Hz, 2H), 7.16 (d, *J*=8.0 Hz, 2H), 6.97 (d, *J*=8.0 Hz, 2H), 3.85 (s, 3H), 3.80 (d, *J*=6.8 Hz, 3H), 3.77 (d, *J*=6.8 Hz, 3H), 2.60-2.45 (m, 1H), 1.80-1.64 ppm (m, 2H). **^{31}P NMR** ($CDCl_3$, 162 MHz): δ 34.31 ppm (s). **^{13}C NMR** ($CDCl_3$, 101 MHz): δ 159.1, 139.1, 137.9, 134.0, 128.8, 126.9, 126.5, 114.2, 56.2, 53.0, 31.7, 21.9, 15.9, 12.9 ppm (d, *J*=4.0 Hz). The carbon signals for the methoxy groups overlap with the CD_3OD solvent peak. Quaternary carbons were not detected.

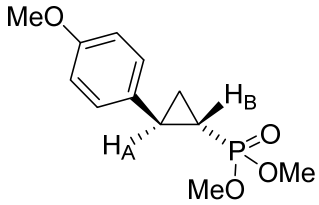
Dimethyl 2-(4-trifluoromethyl)phenylcyclopropyl phosphonate (3e)



Following the general procedure using 4-trifluoromethyl styrene, *trans* isomer **3e** was isolated as yellowish oil (76 mg, 52% isolated yield).

GC/MS *m/z* (% relative intensity): 295(13.4), 294(100), 293(6.7), 275(15.1), 230(5.1), 199(5.8), 186(8.7), 185(75.9), 184(15.1), 183(25.1), 166(15.5), 165(50.6), 164(33.6), 159(5.8), 145(10.6), 133(10.8), 129(11.0), 124(29.9), 120(5.5), 116(23.7), 115(46.0), 110(11.4), 109(49.2), 95(5.4), 94(20.5), 93(11.4), 80(6.1), 79(25.0), 63(5.6). **^{1}H NMR** ($CDCl_3/CD_3OD$, 500 MHz): δ 7.26 (dd, J=8.1 Hz, $J_{H\text{-}F}$=5.5 Hz, 2H), 7.10 (t, J=8.6 Hz, 2H), 3.90 (d, $J_{H\text{-}P}$=8.3 Hz, 3H), 3.88 (d, $J_{H\text{-}P}$=8.3 Hz, 3H), 2.54 (ddt, $^{3}J_{H\text{-}P\ cis}$=11.4 Hz, J=9.2, 5.7 Hz, 1H, H_A), 1.54 (dddd, $^{2}J_{H\text{-}P}$=11.4 Hz, J=8.9, 6.2, 5.6 Hz, 1H, H_B), 1.47-1.39 (m, 1H), 1.30 ppm (m, 1H). **^{19}F NMR** ($CDCl_3/CD_3OD$, 376 MHz): δ -112.67 ppm (ddd, J=13.8, 8.6, 5.2 Hz). **^{31}P NMR** ($CDCl_3/CD_3OD$, 162 MHz): δ 29.62 ppm (s). **^{13}C NMR** ($CDCl_3/CD_3OD$, 126 MHz): δ 163.4, 135.9, 128.5 (d, $J_{C\text{-}F}$=8.0 Hz), 115.8 (d, $J_{C\text{-}F}$=21.7 Hz), 20.9, 14.3, 12.5 ppm (d, J=5.5 Hz). The carbon signals for the methoxy groups overlap with the CD_3OD solvent peak.

Dimethyl 2-(4-methoxy)phenylcyclopropyl phosphonate (3f)

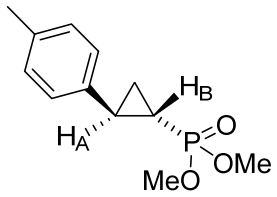


Following the general procedure using 4-methoxy styrene, *trans* isomer **3f** was isolated as yellowish oil (111 mg, 87% isolated yield).

GC/MS *m/z* (% relative intensity): 256(23.0), 148(11.2), 147(100), 146(21.4), 145(16.3), 132(6.4), 131(12.9), 117(5.7), 115(12.4), 103(7.7), 91(15.0), 77(6.4). **^{1}H NMR** ($CDCl_3/CD_3OD$, 500 MHz): δ 7.02 (d, J=8.6 Hz, 2H), 6.79 (d, J=8.7 Hz, 2H), 3.74 (d, $J_{H\text{-}P}$=6.7 Hz, 3H), 3.73 (s, 3H), 3.72 (d, $J_{H\text{-}P}$=7.0 Hz, 3H), 2.36 (ddt, $^{3}J_{H\text{-}P\ cis}$=14.6, $J_{H\text{-}H}$=8.9, 5.7 Hz, 1H), 1.40-1.31 (m, 2H), 1.09-1.02 ppm (m, 1H). **^{31}P NMR** ($CDCl_3/CD_3OD$, 162 MHz): δ 30.16 ppm (s). **^{13}C NMR**

($CDCl_3/CD_3OD$, 126 MHz): δ 127.9, 114.6, 21.0, 14.0, 12.4 ppm (d, *J*=5.2 Hz). The carbon signals for the methoxy groups overlap with the CD_3OD solvent peak. Quaternary carbons were not detected.

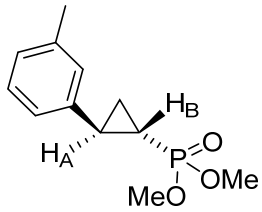
Dimethyl 2-(4-methyl)phenylcyclopropyl phosphonate (3g)



Following the general procedure using 4-methyl styrene, *trans* isomer **3g** was isolated as yellowish oil (49 mg, 41% isolated yield).

GC/MS *m/z* (% relative intensity): 240(28.6), 132(11.0), 131(100), 130(20.2), 129(33.4), 128(13.1), 127(5.1), 116(14.3), 115(20.6), 91(18.0), 79(5.4), 77(5.0). **^{1}H NMR** ($CDCl_3/CD_3OD$, 500 MHz): δ 7.05 (d, *J*=8.0 Hz, 2H), 6.97 (d, *J*=8.1 Hz, 2H), 3.74 (d, $J_{H\text{-}P}$=9.2 Hz, 3H), 3.72 (d, $J_{H\text{-}P}$=9.2 Hz, 3H), 2.36 (ddt, $^3J_{H\text{-}P\ cis}$=11.6, *J*=9.0, 5.7 Hz, 1H, H_A), 2.26 (s, 3H), 1.37 (dddd, $^2J_{H\text{-}P}$=19.0, *J*=8.9, 6.4, 4.8 Hz, 1H, H_B), 1.30-1.24 (m, 1H), 1.13-1.06 ppm (m, 1H). **^{31}P NMR** ($CDCl_3/CD_3OD$, 162 MHz): δ 30.08 ppm (s). **^{13}C NMR** ($CDCl_3/CD_3OD$, 126 MHz): δ 137.0, 136.9, 129.8, 126.6, 21.3 (d, *J*=3.8 Hz), 21.0, 14.2, 12.5 ppm (d, $J_{C\text{-}P}$=5.9 Hz). The carbon signals for the methoxy groups overlap with the CD_3OD solvent peak.

Dimethyl 2-(3-methyl)phenylcyclopropyl phosphonate (3h)

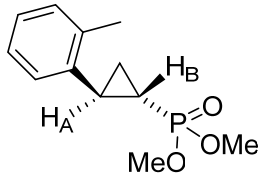


Following the general procedure using 3-methyl styrene, *trans* isomer **3h** was isolated as yellowish oil (102 mg, 85% isolated yield).

GC/MS *m/z* (% relative intensity): 241(5.1), 240(37.5), 132(10.9), 131(100), 130(37.2), 129(41.9), 128(16.0), 127(6.2), 124(6.1), 116(17.7), 115(26.1), 94(6.4), 91(19.8), 79(7.3), 77(5.8). **^{1}H NMR** ($CDCl_3/CD_3OD$, 500 MHz): δ 7.12-7.05 (m, 3H), 6.96-6.93 (m, 1H), 3.77 (d, $J_{H\text{-}P}$=10.8 Hz, 3H), 3.74 (d, $J_{H\text{-}P}$=10.8 Hz, 3H), 2.45-2.39 (m, 1H), 2.38 (s, 3H), 1.44-1.35 (m, 1H), 1.28-1.23

(m, 1H), 1.09 ppm (m, 1H). **^{31}P NMR** ($CDCl_3/CD_3OD$, 162 MHz): δ 35.17 ppm (s). **^{13}C NMR** ($CDCl_3/CD_3OD$, 126 MHz): δ 138.5, 130.5, 127.5, 126.6, 126.2, 20.0 (d, *J*=4.0 Hz), 19.7, 12.8, 11.2 ppm (d, *J*=4.7 Hz). The carbon signals for the methoxy groups overlap with the CD_3OD solvent peak.

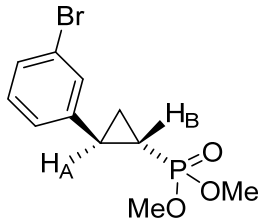
Dimethyl 2-(2-methyl)phenylcyclopropyl phosphonate (3i)



Following the general procedure using 2-methyl styrene, *trans* isomer **3i** was isolated as yellowish oil (61 mg, 51% isolated yield).

GC/MS *m/z* (% relative intensity): 241(5.7), 240(41.6), 225(12.0), 132(6.6), 131(65.2), 130(100), 129(70.0), 128(28.3), 127(10.7), 124(28.1), 116(23.7), 115(43.5), 111(18.6), 110(8.9), 109(5.2), 94(22.1), 91(24.3), 79(12.8), 77(9.1). **^{1}H NMR** ($CDCl_3/CD_3OD$, 500 MHz): δ 7.14-7.03 (m, 1H), 6.99-6.91 (m, 1H), 3.76 (d, *J*=10.8 Hz, 3H), 3.75 (d, *J*=10.8 Hz, 3H), 2.46-2.39 (m, 1H), 2.38 (s, 3H), 1.45-1.34 (m, 1H), 1.31-1.23 (m, 1H), 1.09 ppm (m, 1H). **^{31}P NMR** ($CDCl_3/CD_3OD$, 162 MHz): δ 35.17 ppm (s). **^{13}C NMR** ($CDCl_3/CD_3OD$, 126 MHz): δ 138.5, 130.5, 127.5, 126.6, 126.2, 20.0 (d, *J*=4.0 Hz), 19.7, 12.8, 11.2 ppm (d, *J*=4.7 Hz). The carbon signals for the methoxy groups overlap with the CD_3OD solvent peak.

Dimethyl 2-(3-bromo)phenylcyclopropyl phosphonate (3j)

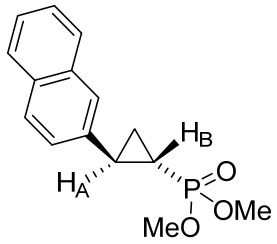


Following the general procedure using 3-bromo styrene, *trans* isomer **3j** was isolated as yellowish oil (54 mg, 36% isolated yield).

GC/MS *m/z* (% relative intensity): 306(15.6), 304(14.0), 225(6.3), 197(5.0), 195(10.2), 194(6.6), 130(6.0), 129(9.7), 124(11.6), 117(11.9), 116(100), 115(92.5), 114(6.7), 111(5.1), 109(24.4), 94(11.7), 93(9.4), 89(13.8), 79(17.6), 77(5.0), 63(12.4). **^{1}H NMR** ($CDCl_3/CD_3OD$, 500 MHz): δ

7.46 (d, J=8.0 Hz, 1H), 7.38 (s, 1H), 7.29 (t, J=7.8 Hz, 1H), 7.19 (d, J=7.7 Hz, 1H), 3.91 (d, $J_{H\text{-}P}$=6.9 Hz, 3H), 3.88 (d, $J_{H\text{-}P}$=6.9 Hz, 2H), 2.53 (ddt, $^{3}J_{H\text{-}P\ cis}$=14.5, J=8.9, 5.7 Hz, 1H, H_A), 1.59 (dddd, $^{2}J_{H\text{-}P}$=19.0, J=8.9, 6.4, 5.0 Hz, 1H, H_B), 1.50-1.40 (m, 1H), 1.34-1.26 ppm (m, 1H). **^{31}P NMR** ($CDCl_3/CD_3OD$, 162 MHz): δ 35.17 ppm (s). **^{13}C NMR** ($CDCl_3/CD_3OD$, 126 MHz): δ 130.4, 130.1, 129.4, 125.2, 122.8, 20.8, 13.7, 12.5 ppm. The carbon signals for the methoxy groups overlap with the CD_3OD solvent peak.

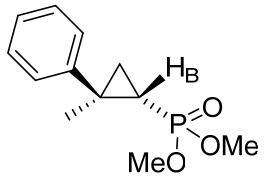
Dimethyl 2-naphthylcyclopropyl phosphonate (3k)



Following the general procedure using naphthyl vinyl, *trans* isomer **3k** was isolated as yellowish oil (57 mg, 41% isolated yield).

GC/MS *m/z* (% relative intensity): 276(34.6), 207(21.2), 168(14.2), 167(100), 166(64.6), 165(60.5), 164(5.8), 152(20.3), 139(5.5), 115(5.6), 73(6.9). **^{1}H NMR** ($CDCl_3/CD_3OD$, 500 MHz): δ 7.95-7.85 (m, 3H), 7.61 (s, 1H), 7.56 (m, 2H), 7.33 (dd, J=8.6, 1.6 Hz, 1H), 3.93 (d, $J_{H\text{-}P}$=8.3 Hz, 3H), 3.90 (d, $J_{H\text{-}P}$=8.3 Hz, 3H), 2.74 (ddt, $^{3}J_{H\text{-}P\ cis}$=14.6, J=8.7, 5.6 Hz, 1H, H_A), 1.65 (dddd, $^{2}J_{H\text{-}P}$=20.0, J=9.1, 6.7, 4.6 Hz, 1H, H_B), 1.61-1.53 (m, 1H), 1.43-1.37 ppm (m,1H). **^{31}P NMR** ($CDCl_3/CD_3OD$, 162 MHz): δ 33.82 ppm (s). **^{13}C NMR** ($CDCl_3/CD_3OD$, 126 MHz): δ 137.0, 133.7, 132.7, 126.6, 125.9, 124.4, 21.5, 12.8, 12.5 ppm (d, J=4.9 Hz). The carbon signals for the methoxy groups overlap with the CD_3OD solvent peak.

Dimethyl 2-methyl-2-phenylcyclopropyl phosphonate (3l)



Following the general procedure using α-methyl styrene, *trans* isomer **3l** was isolated as yellowish oil (18 mg, 15% isolated yield).

GC/MS *m/z* (% relative intensity): 240(5.6), 137(48.6), 131(57.6), 130(100), 129(56), 128(22.5), 116(15.3), 115(37.0), 111(5.3), 110(21.9), 109(5.8), 105(16.9), 103(10.3), 102(7.9), 93(7.7), 91(32.3), 80(6.3), 79(20.8)，78(10.0), 77(18.0), 65(7.2), 63(6.7), 53(5.3), 51(11.7). **^{1}H NMR** ($CDCl_3$/CD_3OD, 400 MHz): δ 7.44-7.39 (m, 4H), 7.36-7.30 (m, 1H), 3.93 (d, $J_{H\text{-}P}$=11.1 Hz, 3H), 3.90 (d, $J_{H\text{-}P}$=10.9 Hz, 3H), 1.73 (s, 3H), 1.64 (td, *J*=9.9, 4.5 Hz, 1H), 1.47 (ddd, $^{2}J_{H\text{-}P}$=18.8, *J*=6.5, 4.6 Hz, 1H, H_B), 1.28 ppm (ddd, *J*=9.5, 6.6, 2.6 Hz, 1H). **^{31}P NMR** ($CDCl_3$/CD_3OD, 162 MHz): δ 29.06 ppm (s). **^{13}C NMR** ($CDCl_3$/CD_3OD, 126 MHz): δ 128.3, 126.4, 125.8, 13.5, 12.0, 11.8 ppm (d, *J*=5.5 Hz). The carbon signals for the methoxy groups overlap with the CD_3OD solvent peak.

X-ray crystallographic analyses

X-ray crystal diffraction data were collected using a XtaLab Synergy-S Dualflex diffractometer equipped with a HyPix-6000HE HPC area detector for data collection at 100.00(10) K. A preliminary set of cell constants and an orientation matrix were calculated from reflections harvested from a sampling of reciprocal space (*CrysAlisPro*, version 171.40.71a; Rigaku Corporation: Oxford, UK, 2020.). The full data collection was carried out using a PhotonJet (Cu) X-ray Source with frame times of 0.07 and 0.26 seconds and a detector distance of 31.2 mm. Series of frames were collected in 0.50º steps in ω at different 2θ, κ, and ϕ settings. 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 groups were determined based on systematic absences and intensity statistics.

Structures were solved using SHELXT(Sheldrick, G. M. *SHELXT*, version 2018/2; *Acta. Crystallogr*. 2015, A71, 3-8.)and refined using SHELXL (against F^2) (Sheldrick, G. M. *SHELXL*, version 2018/3; *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. See **Figure S5** and **Table S9** for additional crystal data and structure refinement information for **3da**.

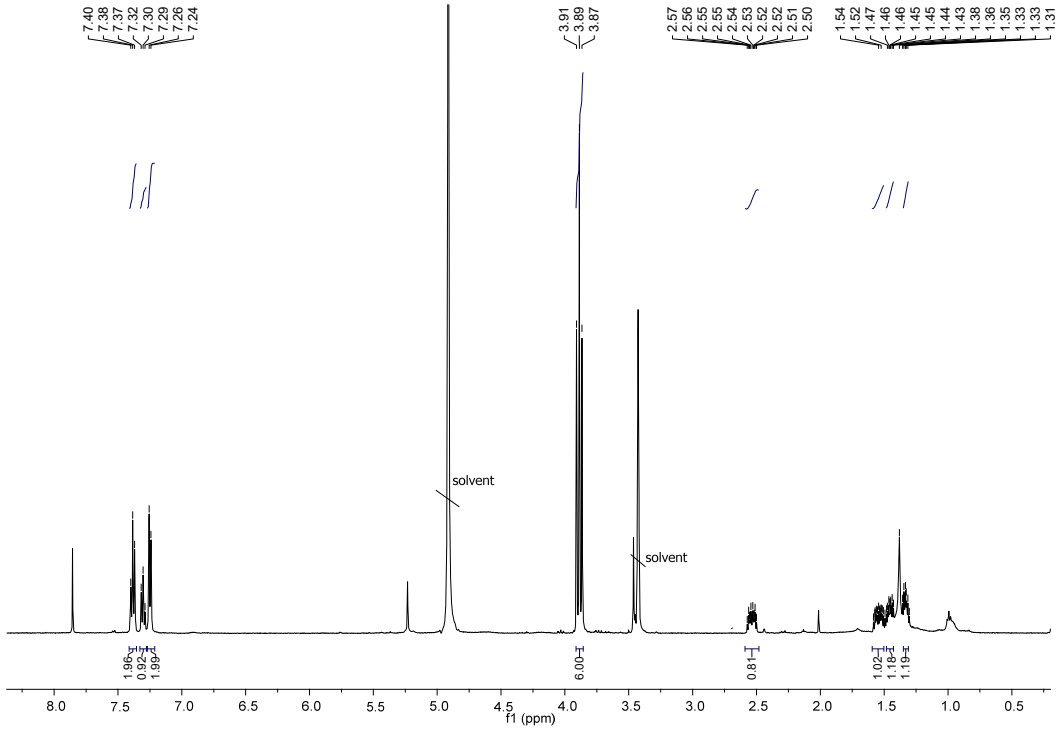
Table S9. Crystal data and structure refinement for dimethyl ((*1S,2R*)-2-(4'-methoxy-[1,1'-biphenyl]-4-yl)cyclopropyl)phosphonate (**3da**). Cambridge Crystallographic Data Centre (CCDC) entry: 2105528.

Identification code	**3da**	
Empirical formula	C18 H27 O7 P	
Formula weight	386.36	
Temperature	100.00(10) K	
Wavelength	1.54184 Å	
Crystal system	orthorhombic	
Space group	$P2_12_12_1$	
Unit cell dimensions	a = 6.38640(10) Å	$\alpha = 90°$
	b = 7.84160(10) Å	$\beta = 90°$
	c = 39.8125(7) Å	$\gamma = 90°$
Volume	1993.79(5) Å^3	
Z	4	
Density (calculated)	1.287 Mg/m^3	
Absorption coefficient	1.534 mm^{-1}	
F(000)	824	
Crystal color, morphology	colourless, plate	
Crystal size	0.153 x 0.122 x 0.015 mm^3	
Theta range for data collection	2.219 to 77.896°	
Index ranges	$-7 \le h \le 8$, $-7 \le k \le 9$, $-50 \le l \le 50$	
Reflections collected	24420	
Independent reflections	4187 [R(int) = 0.0536]	
Observed reflections	3950	
Completeness to theta = 74.504°	100.0%	
Absorption correction	Multi-scan	
Max. and min. transmission	1.00000 and 0.66158	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4187 / 0 / 238	
Goodness-of-fit on F^2	1.098	
Final R indices [I>2sigma(I)]	$R1$ = 0.0432, $wR2$ = 0.1090	
R indices (all data)	$R1$ = 0.0459, $wR2$ = 0.1105	
Absolute structure parameter	0.013(12)	
Largest diff. peak and hole	0.425 and -0.386 e.Å^{-3}	

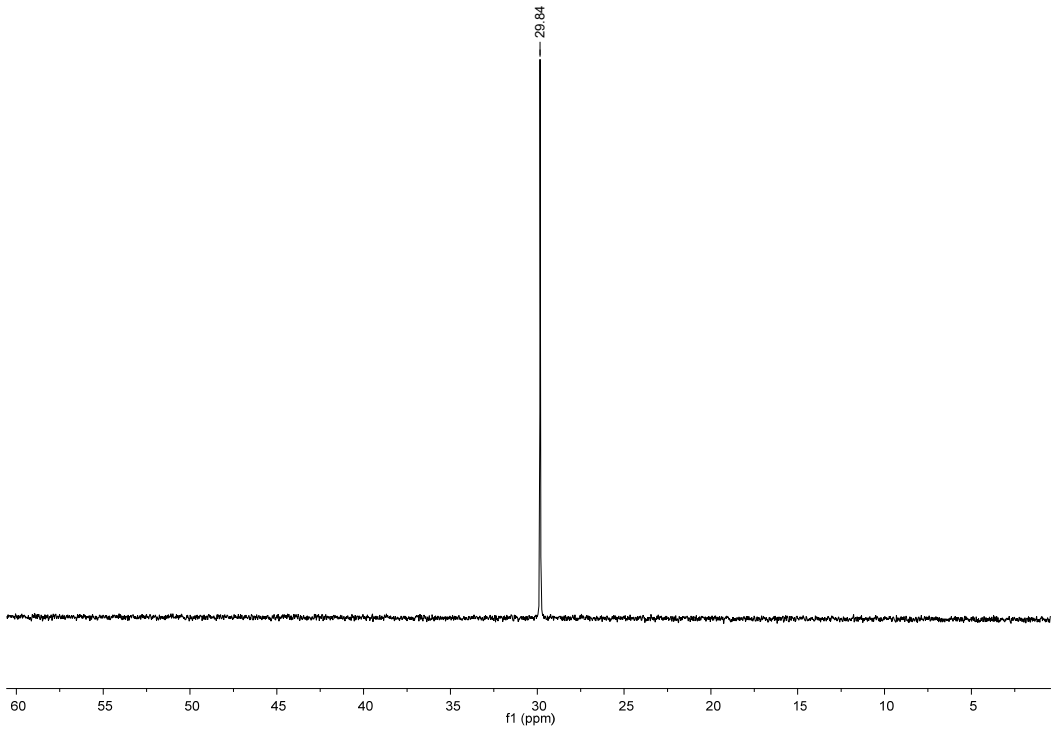
NMR Spectra

Dimethyl 2-phenylcyclopropyl phosphonate (3a)

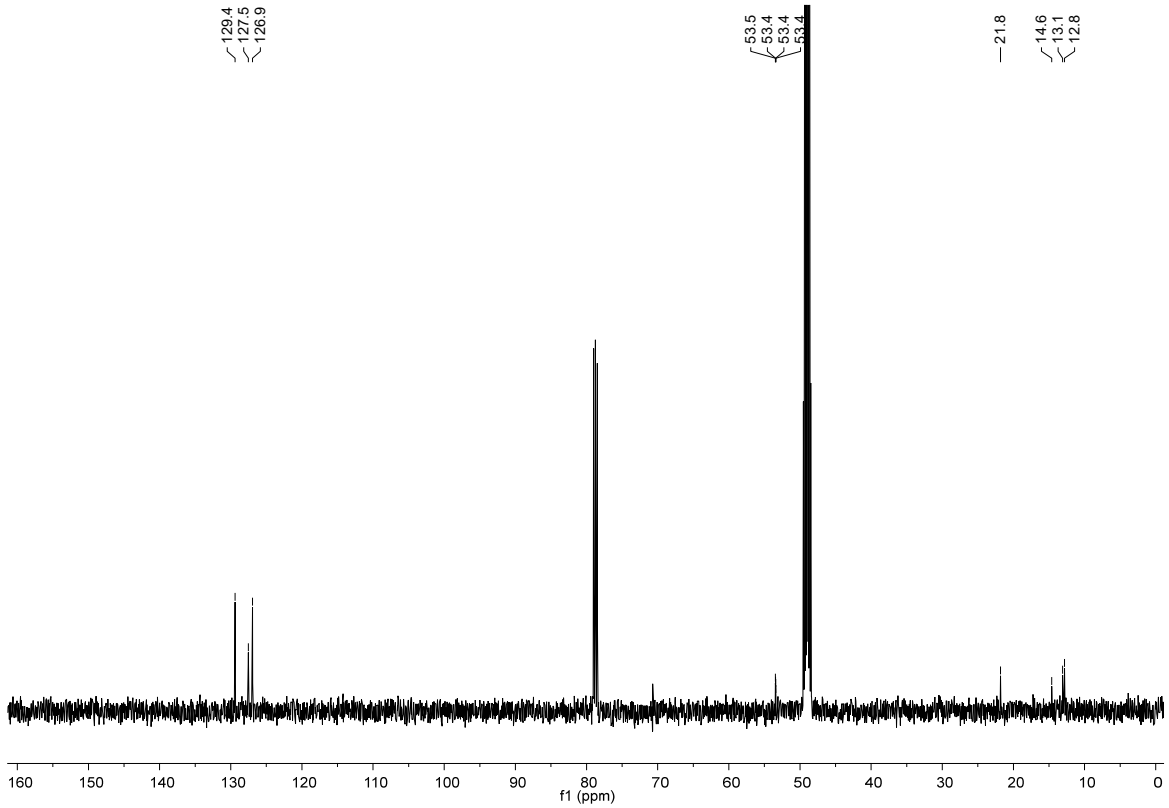
^{1}H NMR ($CDCl_3$/CD_3OD, 500 MHz):



^{31}P NMR ($CDCl_3$/CD_3OD, 162 MHz):

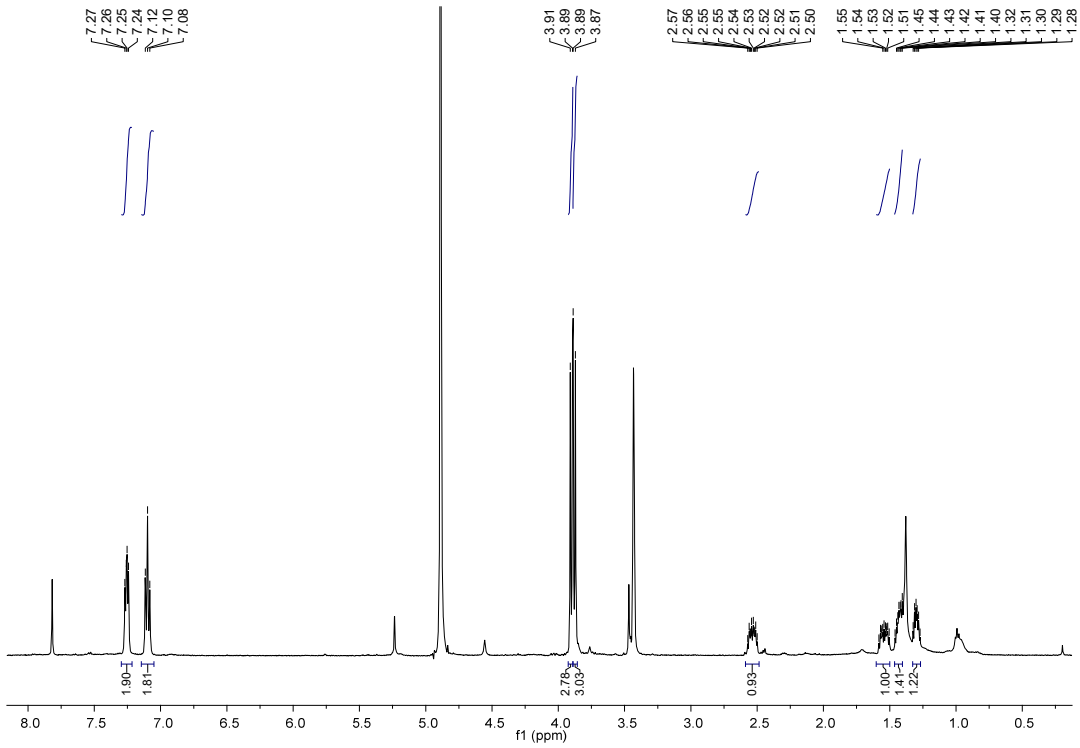


^{13}C NMR ($CDCl_3/CD_3OD$, 126 MHz):

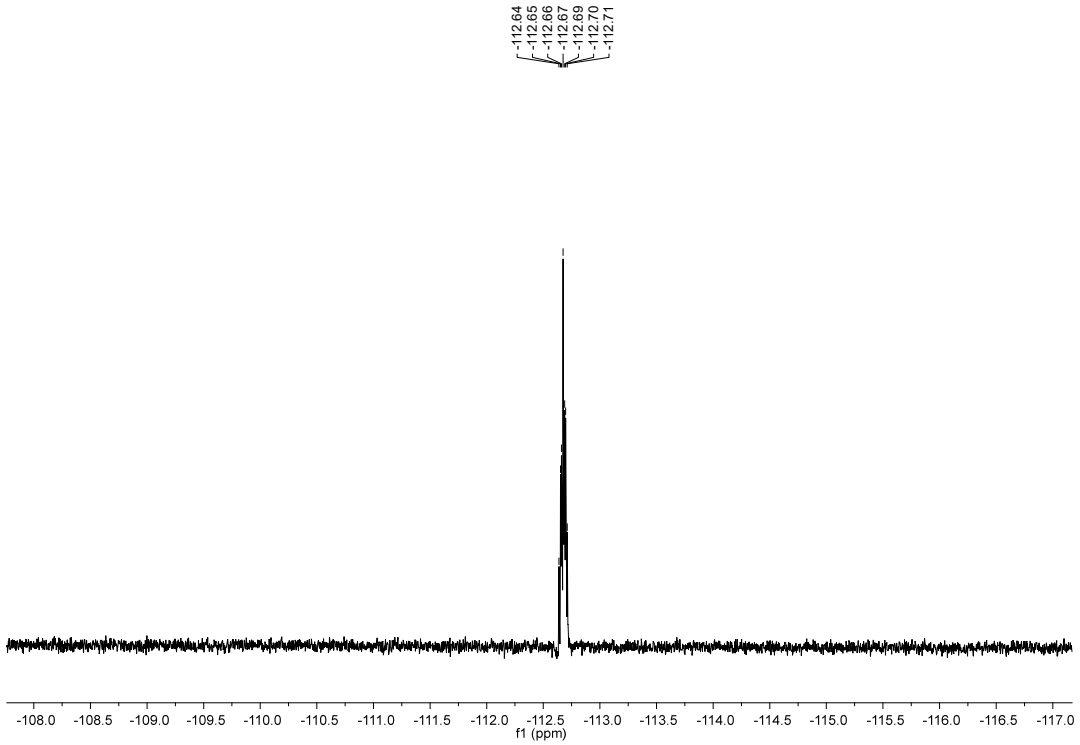


Dimethyl 2-(4-fluoro)phenylcyclopropyl phosphonate (3b)

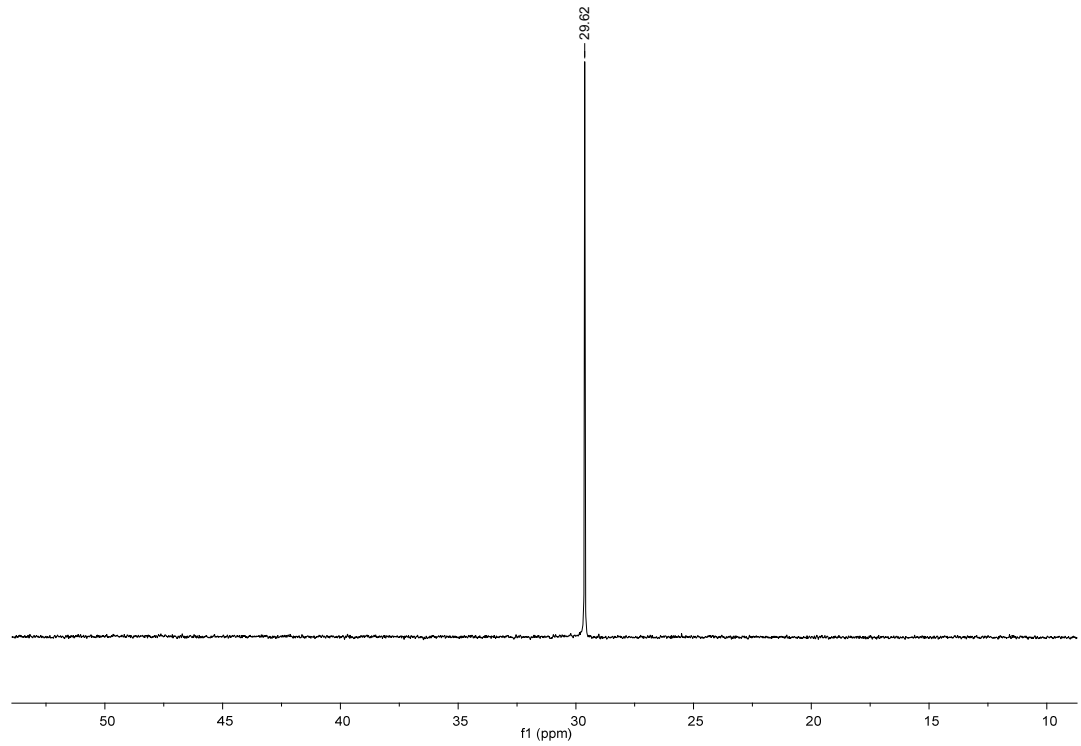
^{1}H NMR ($CDCl_3$/CD_3OD, 500 MHz):



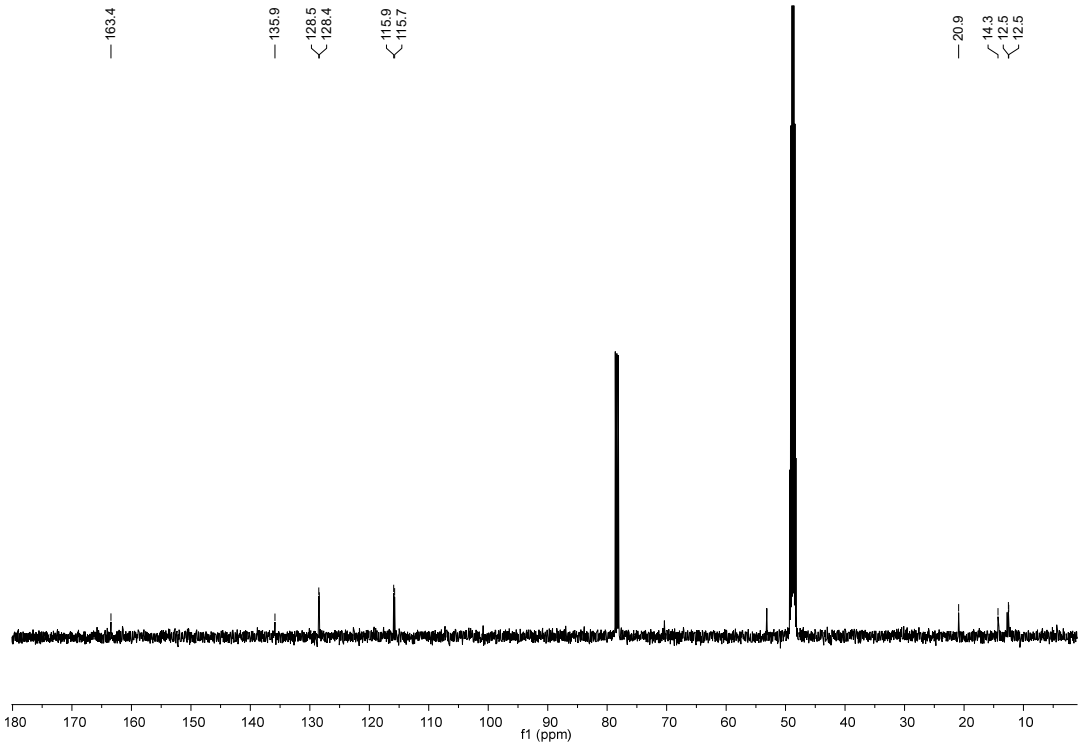
^{19}F NMR ($CDCl_3$/CD_3OD, 376 MHz):



^{31}P NMR ($CDCl_3$/CD_3OD, 162 MHz):

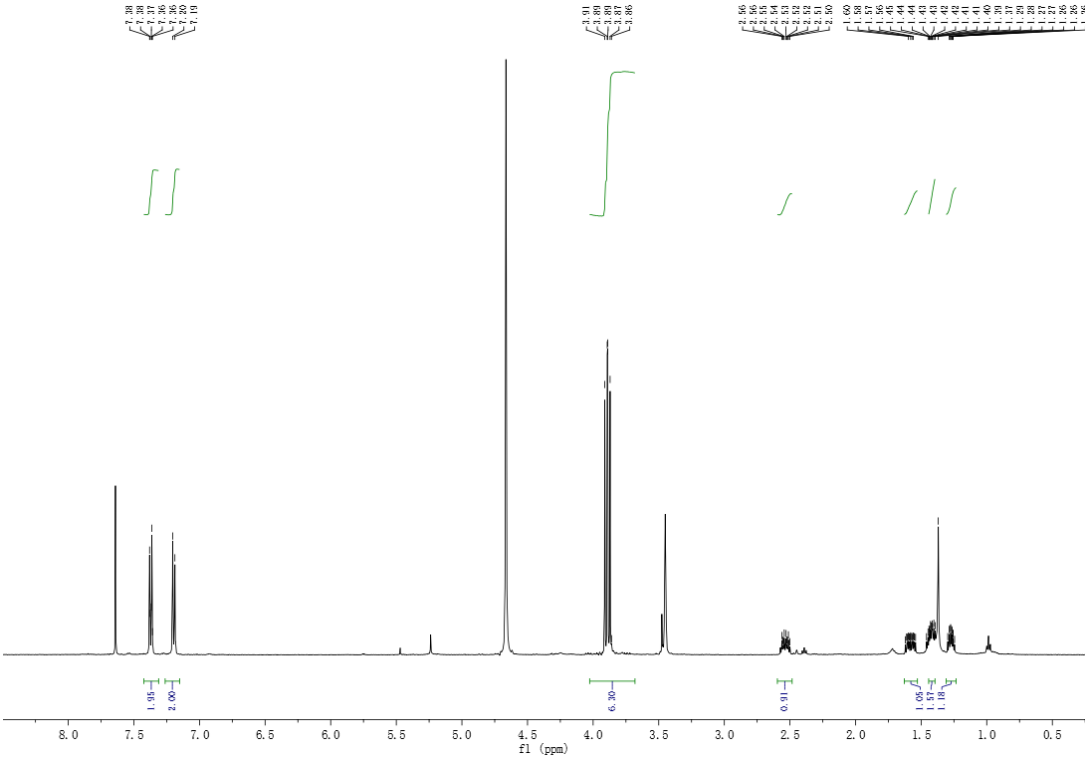


^{13}C NMR ($CDCl_3$/CD_3OD, 126 MHz):

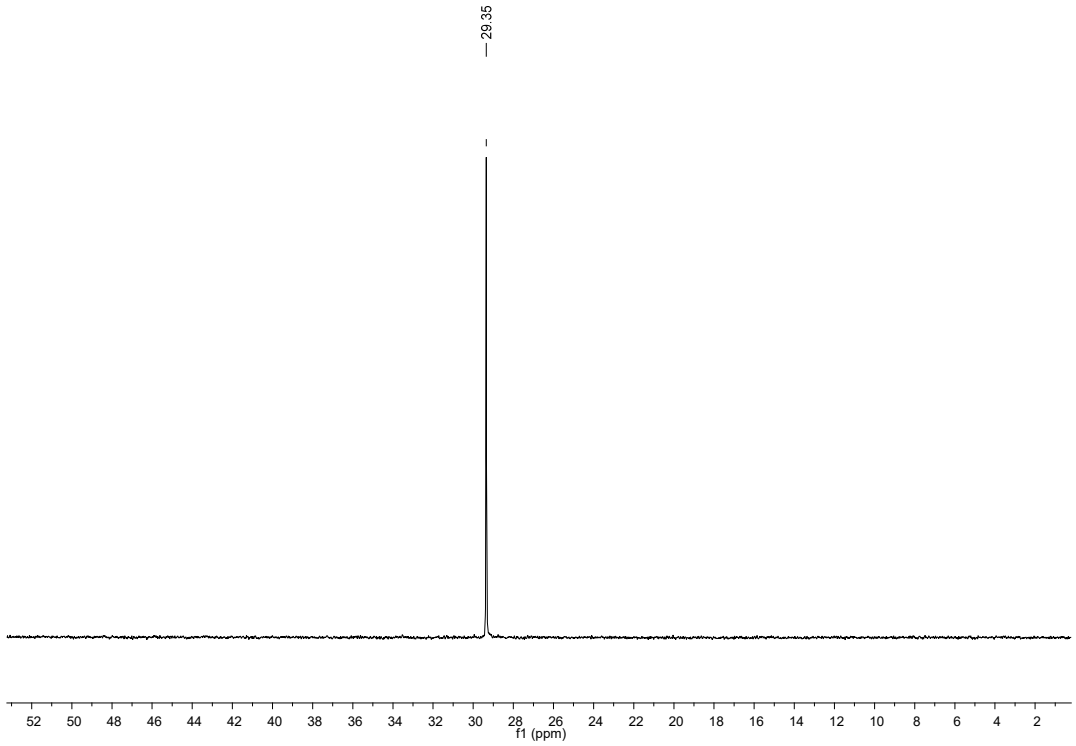


Dimethyl 2-(4-chloro)phenylcyclopropyl phosphonate (3c)

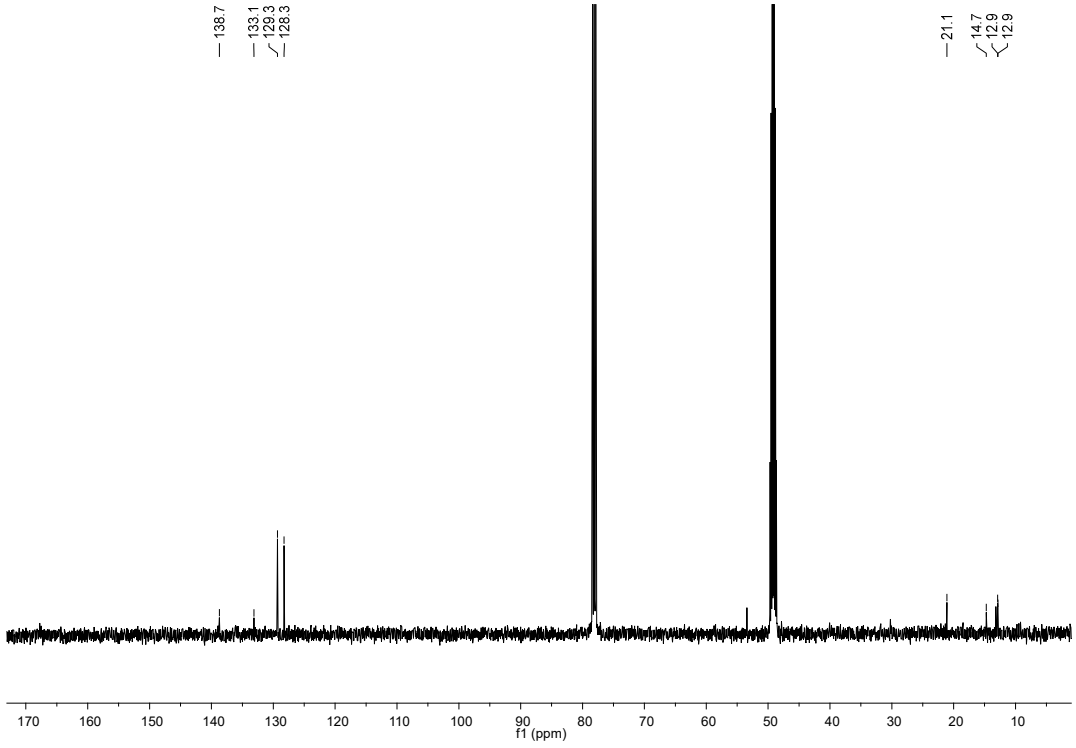
^{1}H NMR ($CDCl_3$/CD_3OD, 500 MHz):



^{31}P NMR ($CDCl_3$/CD_3OD, 162 MHz):

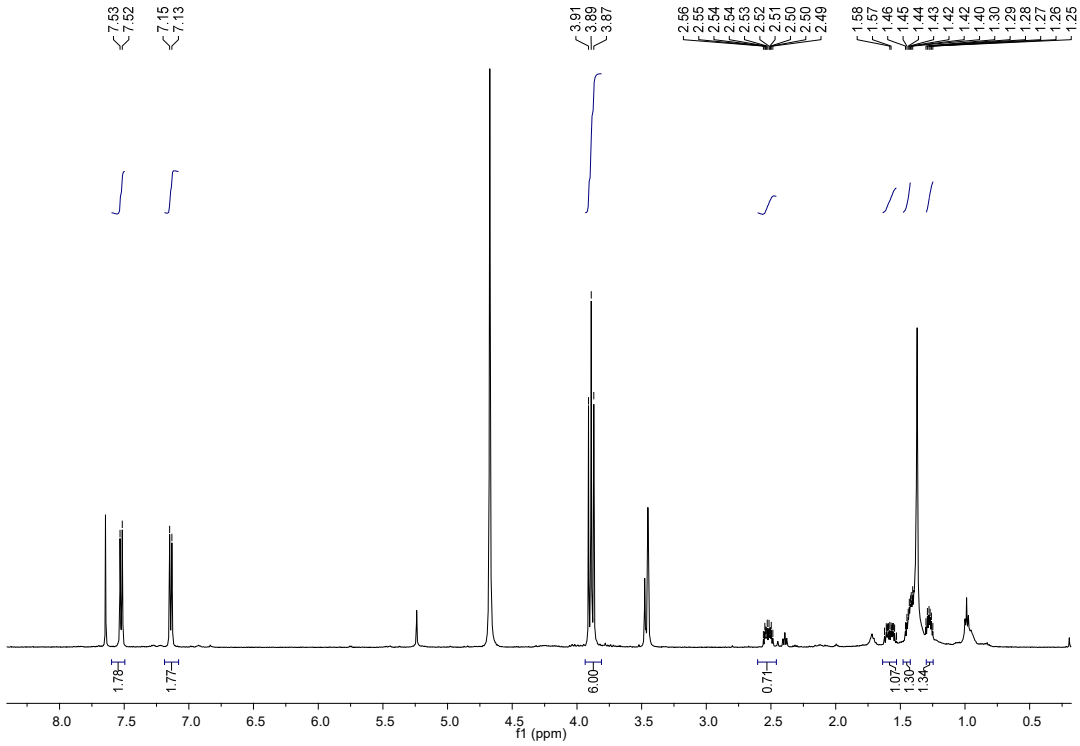


^{13}C NMR ($CDCl_3/CD_3OD$, 126 MHz):

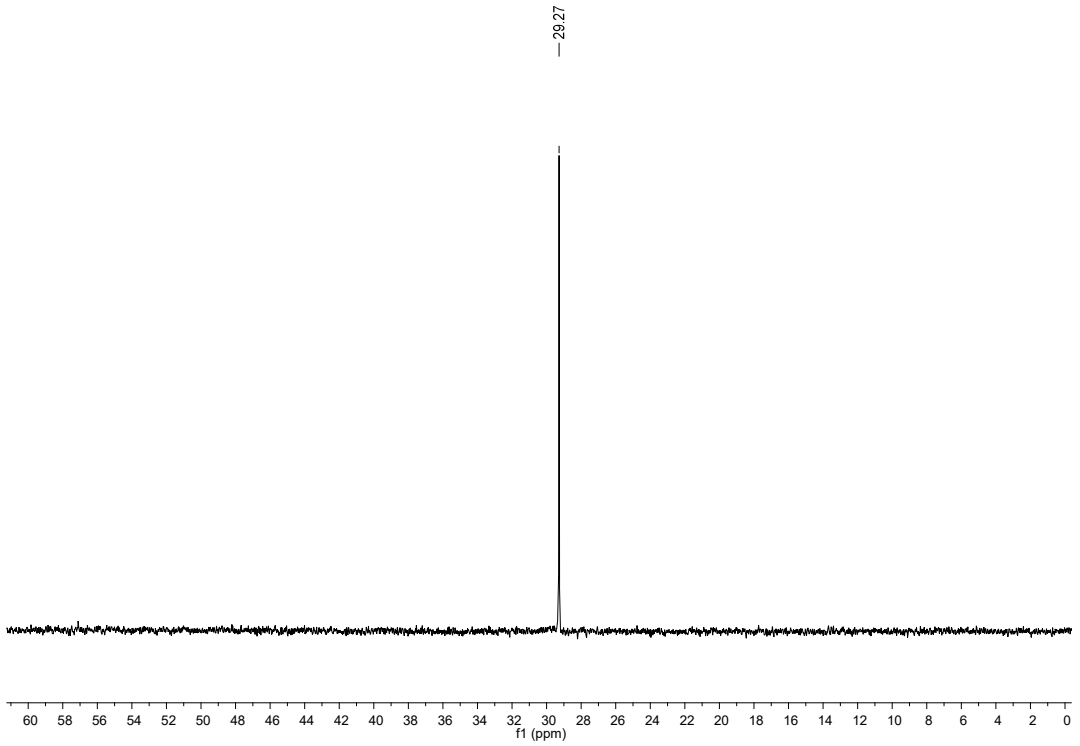


Dimethyl 2-(4-bromo)phenylcyclopropyl phosphonate (3d)

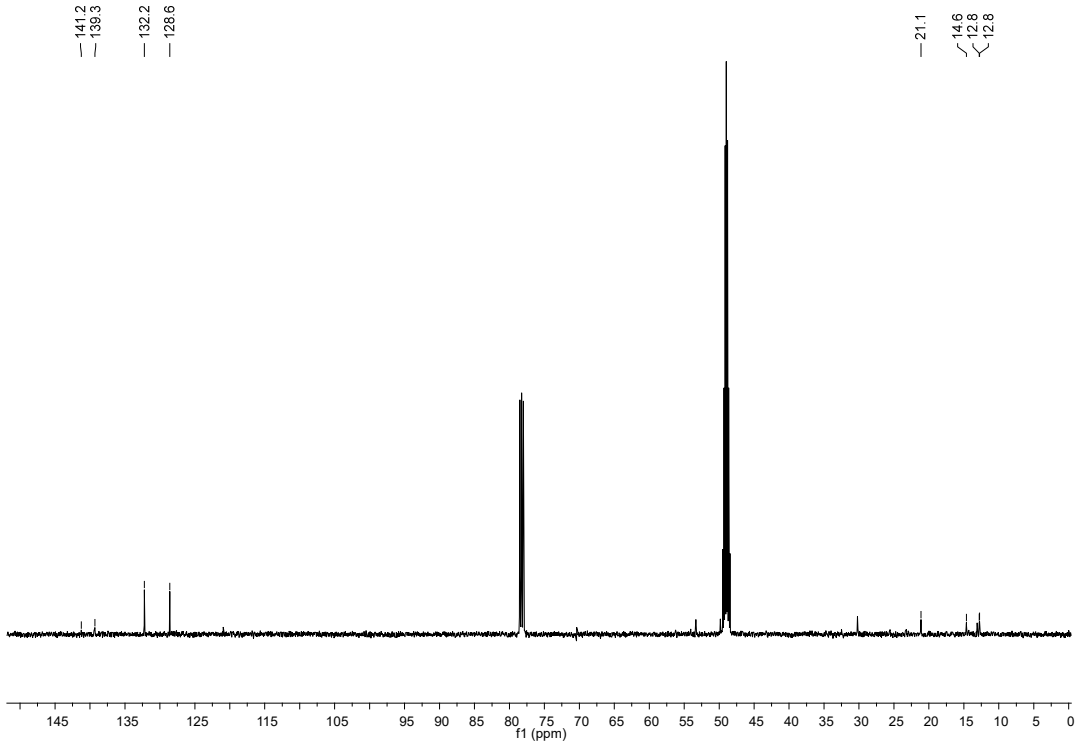
^{1}H NMR ($CDCl_3$/CD_3OD, 500 MHz):



^{31}P NMR ($CDCl_3$/CD_3OD, 162 MHz):

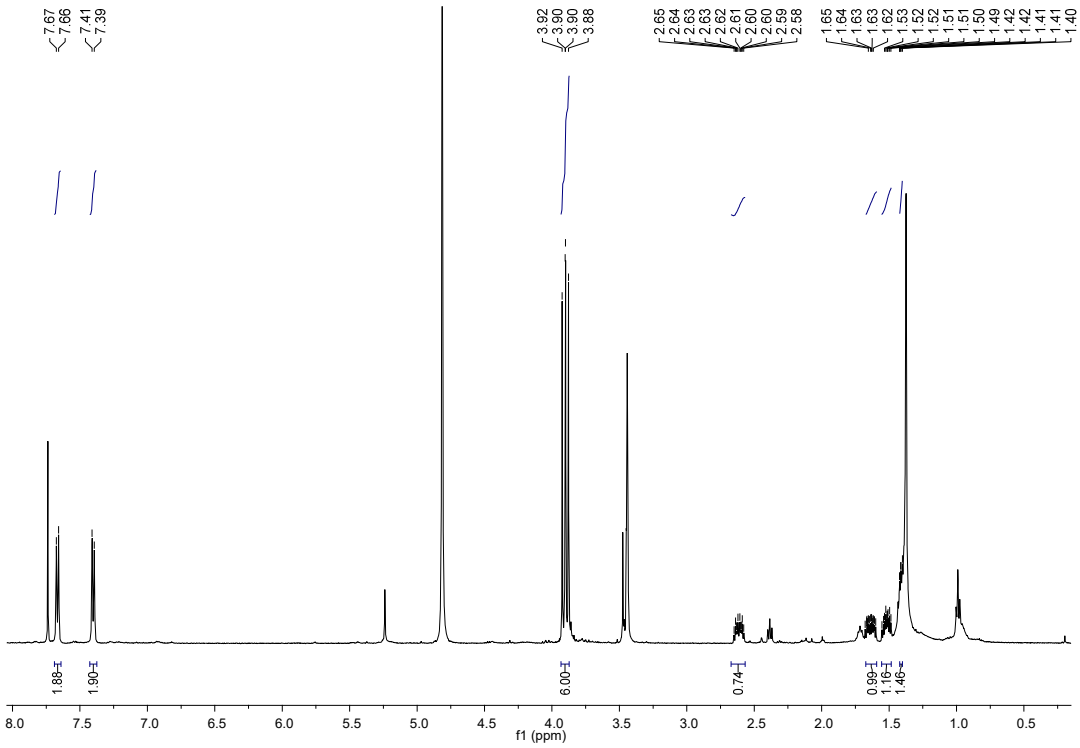


^{13}C NMR ($CDCl_3/CD_3OD$, 126 MHz):

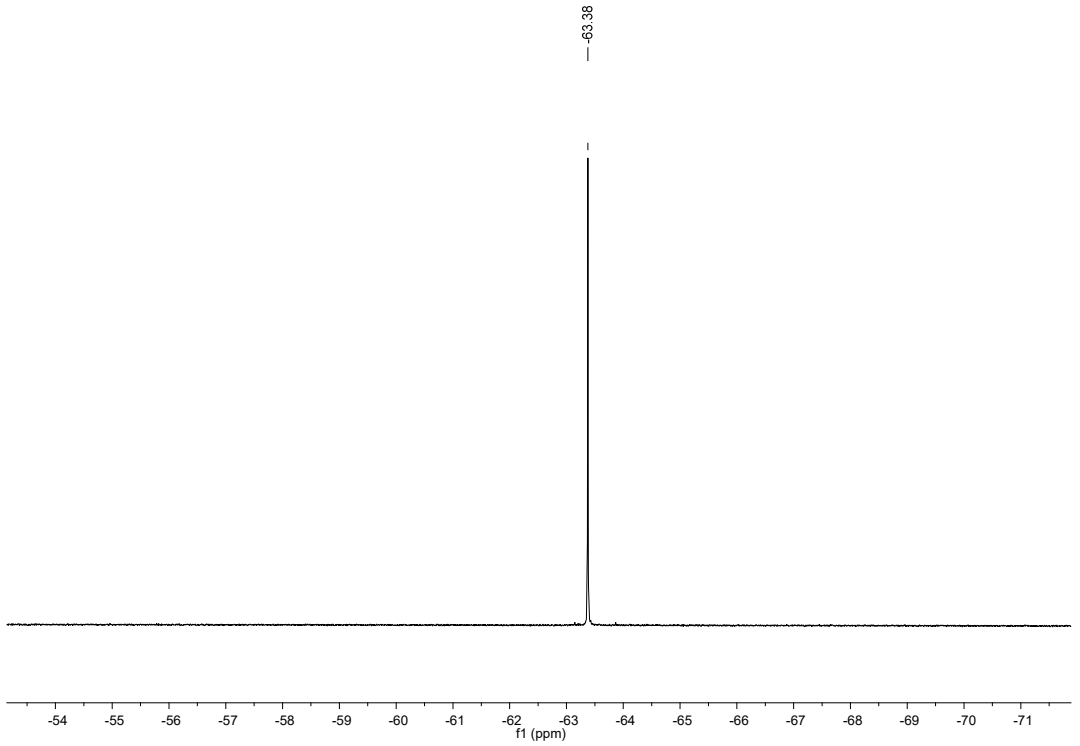


Dimethyl 2-(4-trifluoromethyl)phenylcyclopropyl phosphonate (3e)

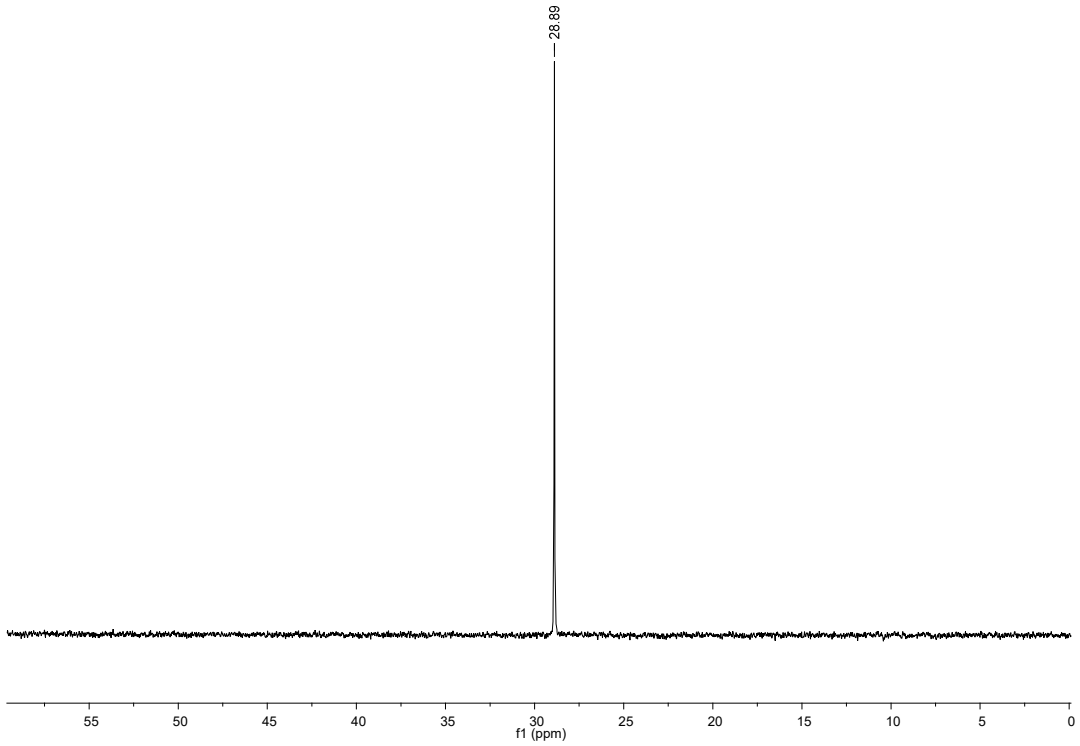
^{1}H NMR ($CDCl_3$/CD_3OD, 500 MHz):



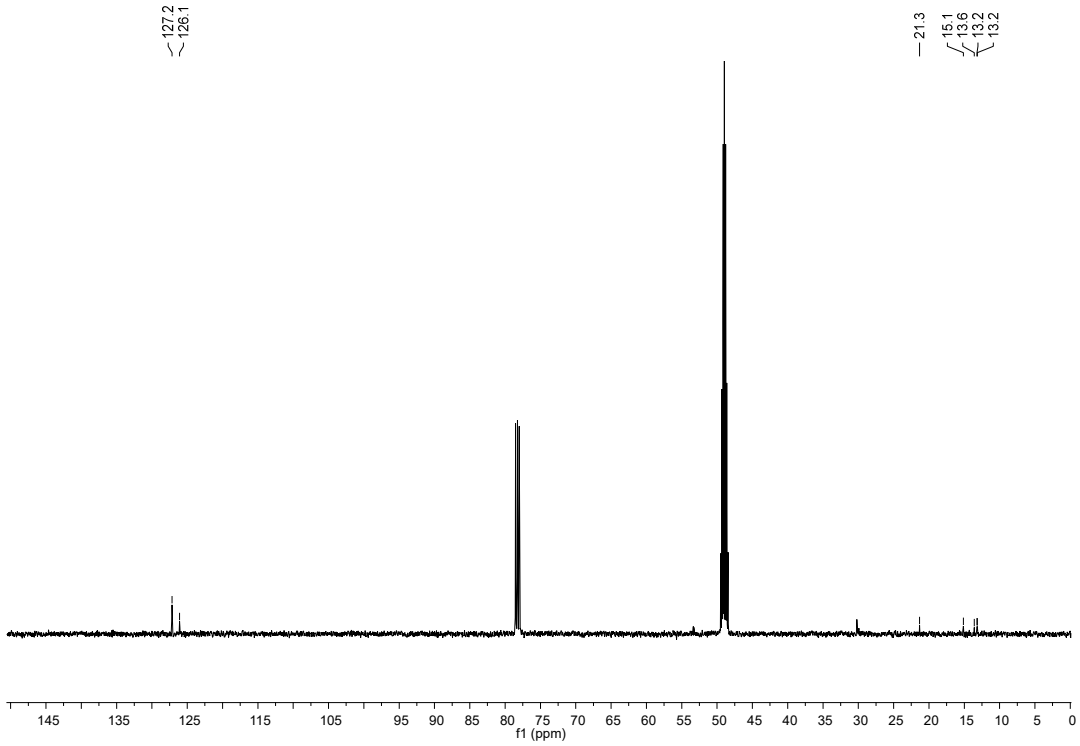
^{19}F NMR ($CDCl_3$/CD_3OD, 376 MHz):



^{31}P NMR ($CDCl_3/CD_3OD$, 162 MHz):

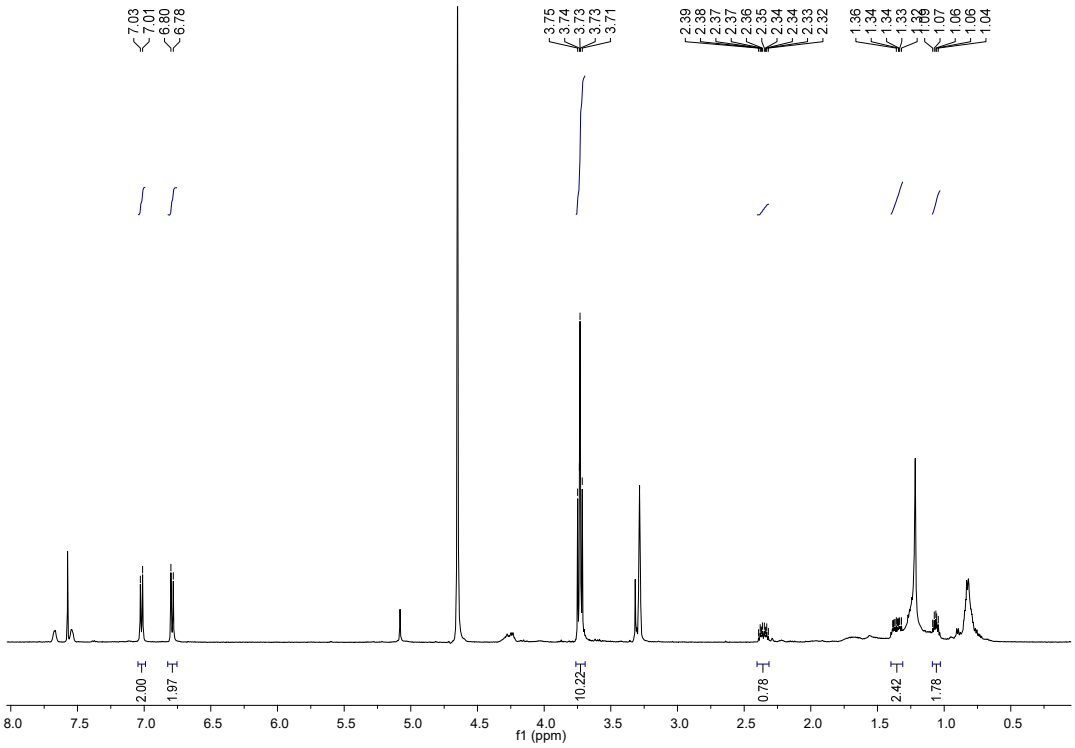


^{13}C NMR ($CDCl_3/CD_3OD$, 126 MHz):

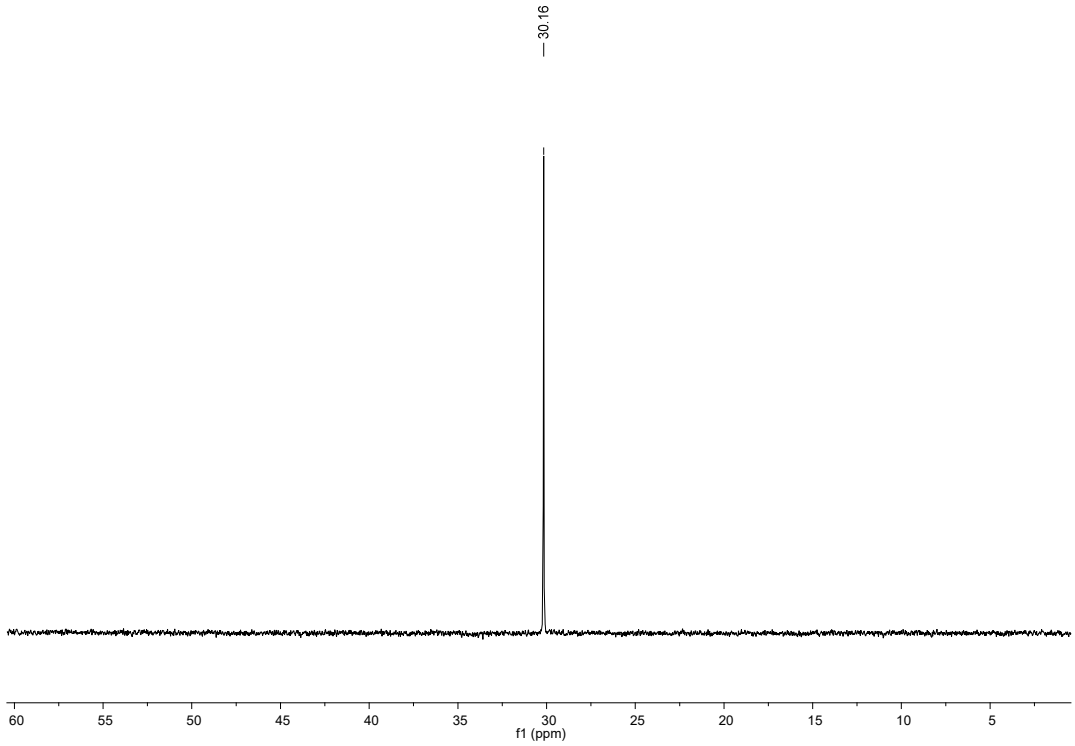


Dimethyl 2-(4-methoxy)phenylcyclopropyl phosphonate (3f)

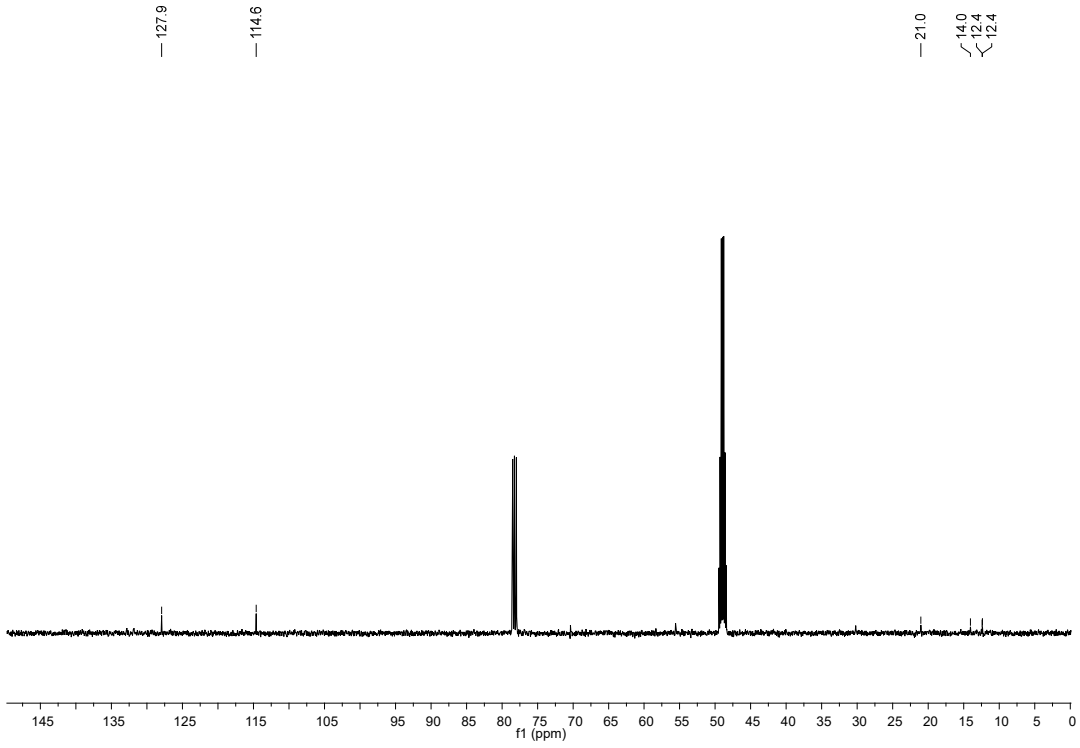
^{1}H NMR ($CDCl_3$/CD_3OD, 500 MHz):



^{31}P NMR ($CDCl_3$/CD_3OD, 162 MHz):

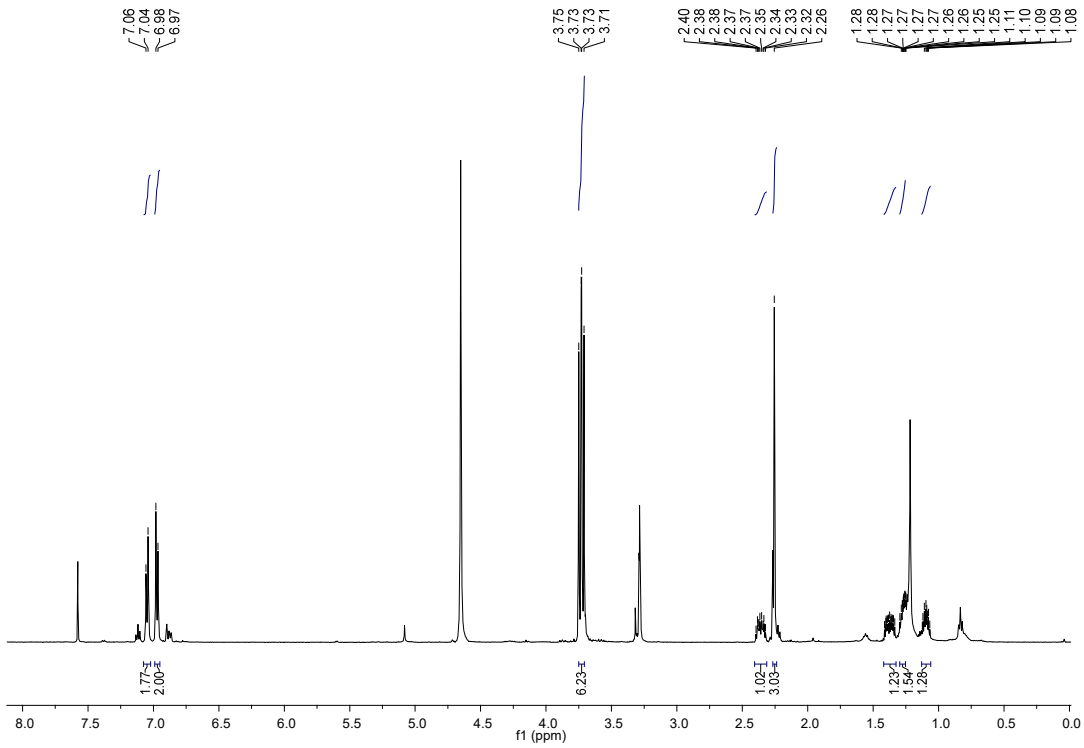


^{13}C NMR ($CDCl_3/CD_3OD$, 126 MHz):

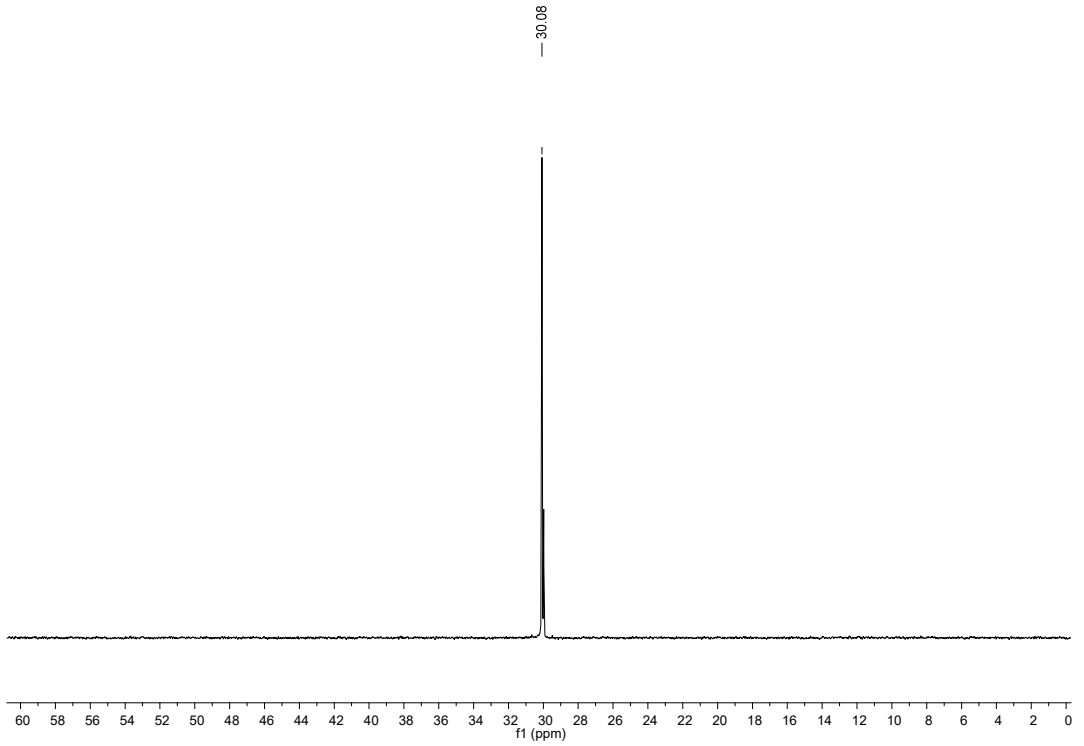


Dimethyl 2-(4-methyl)phenylcyclopropyl phosphonate (3g)

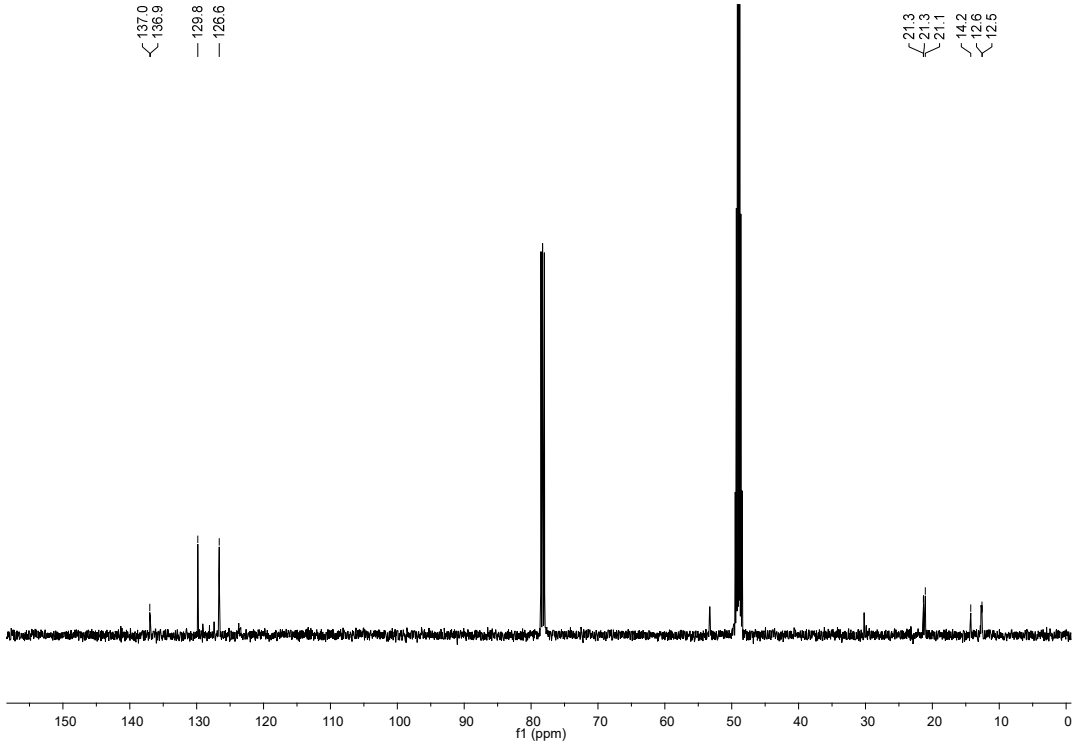
^{1}H NMR ($CDCl_3$/CD_3OD, 500 MHz):



^{31}P NMR ($CDCl_3$/CD_3OD, 162 MHz):

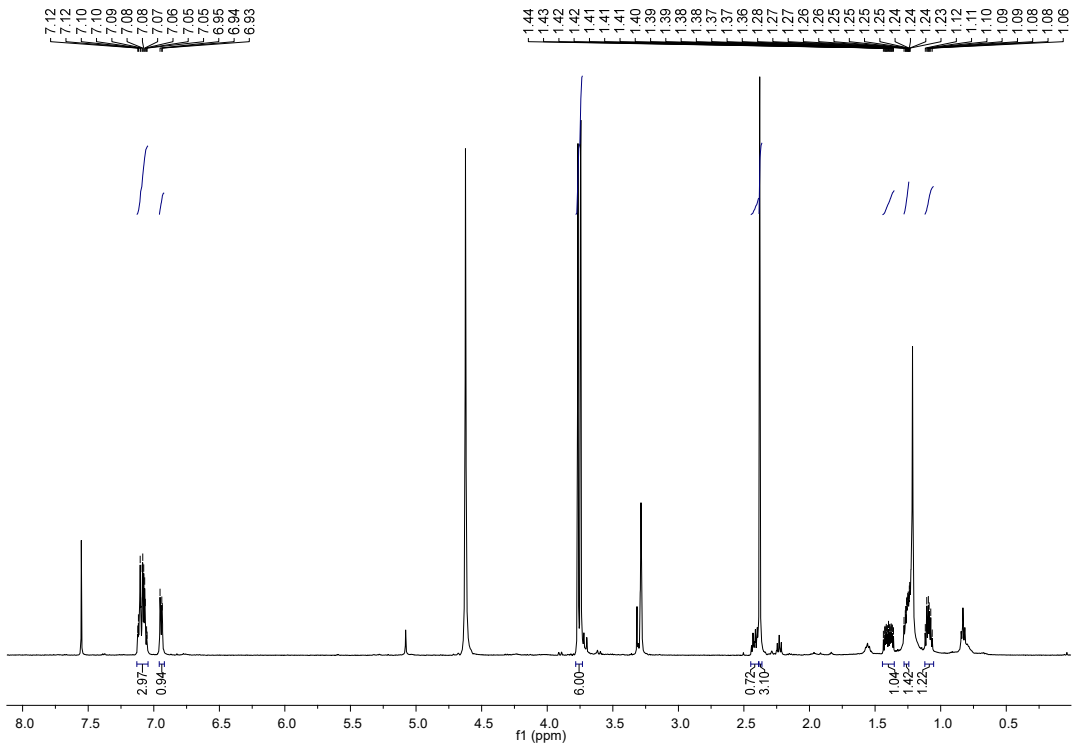


^{13}C NMR ($CDCl_3/CD_3OD$, 126 MHz):

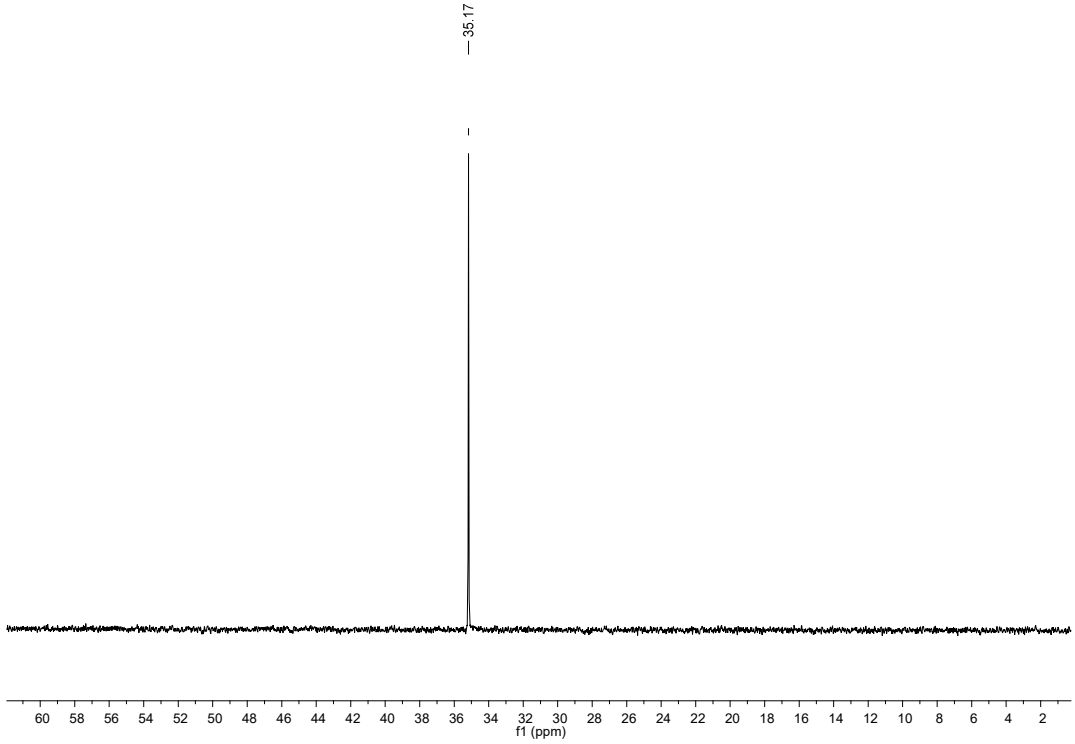


Dimethyl 2-(3-methyl)phenylcyclopropyl phosphonate (3h)

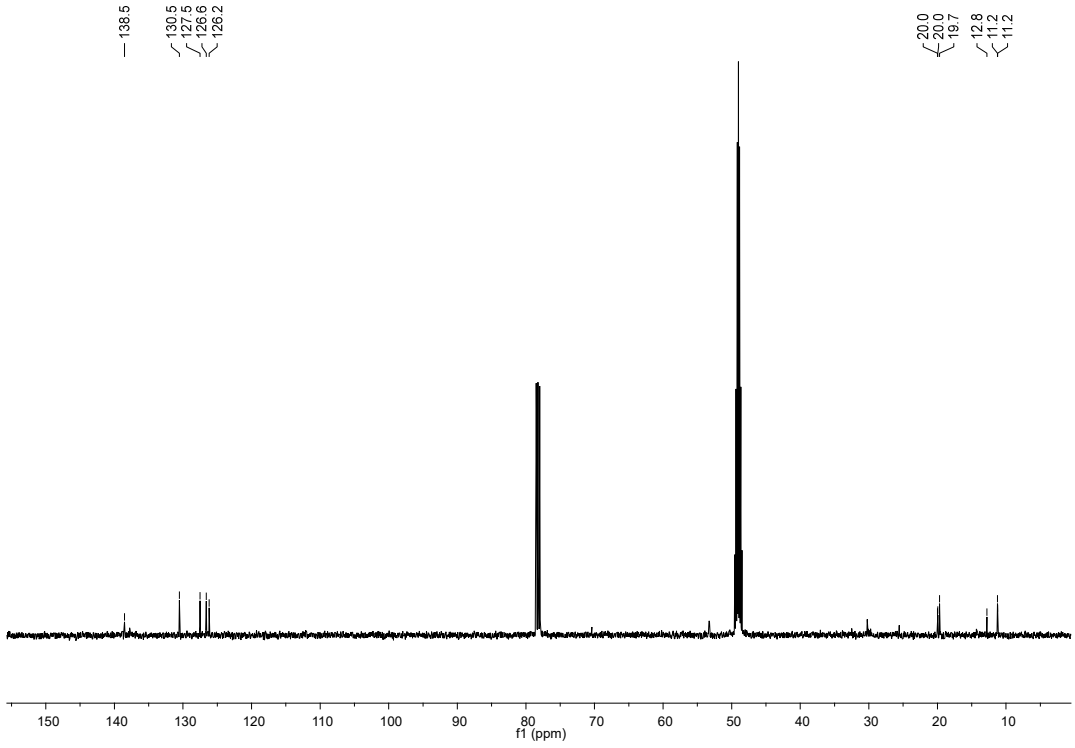
^{1}H NMR ($CDCl_3$/CD_3OD, 500 MHz):



^{31}P NMR ($CDCl_3$/CD_3OD, 162 MHz):

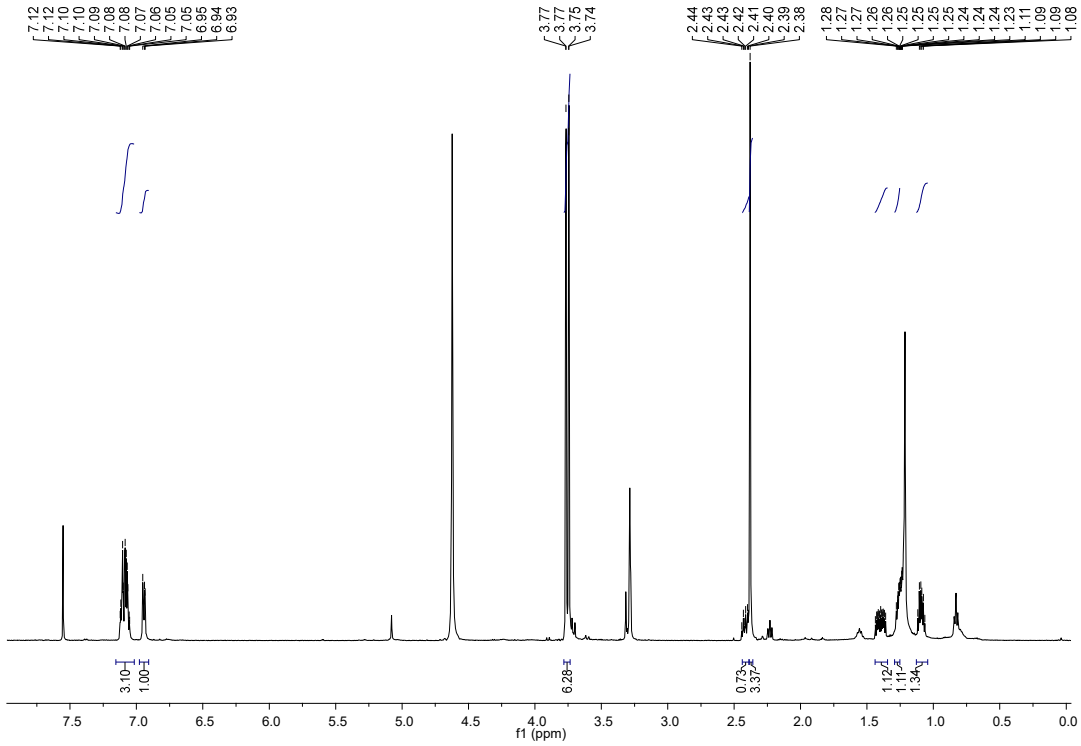


^{13}C NMR ($CDCl_3/CD_3OD$, 126 MHz):

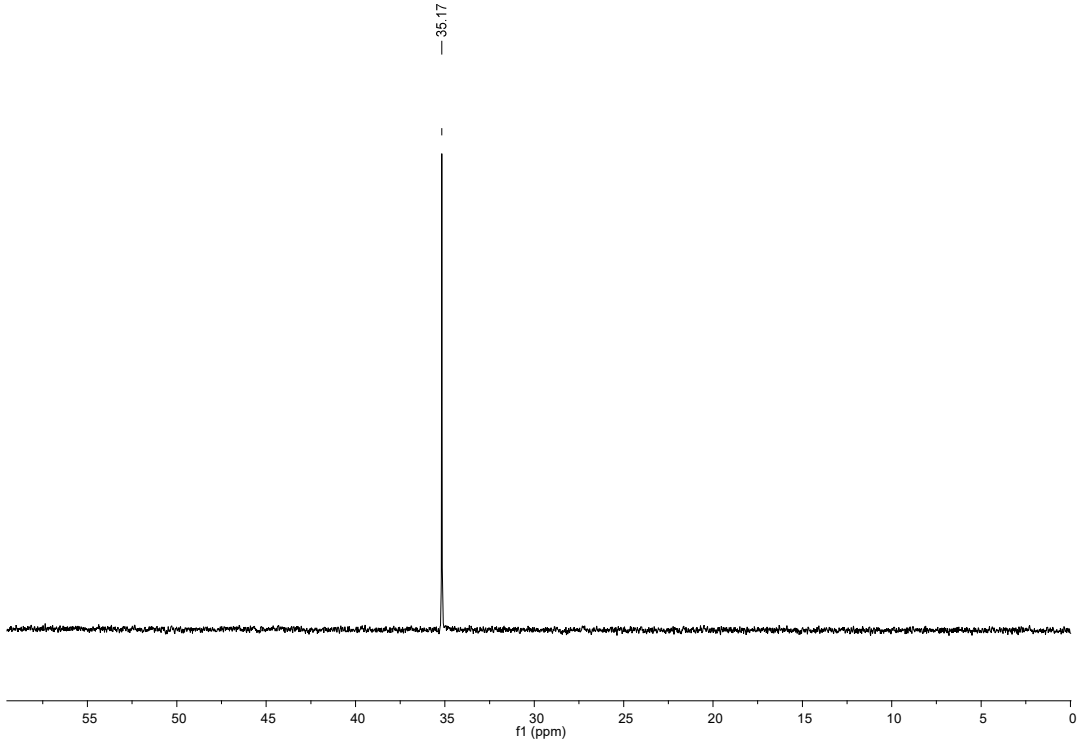


Dimethyl 2-(2-methyl)phenylcyclopropyl phosphonate (3i)

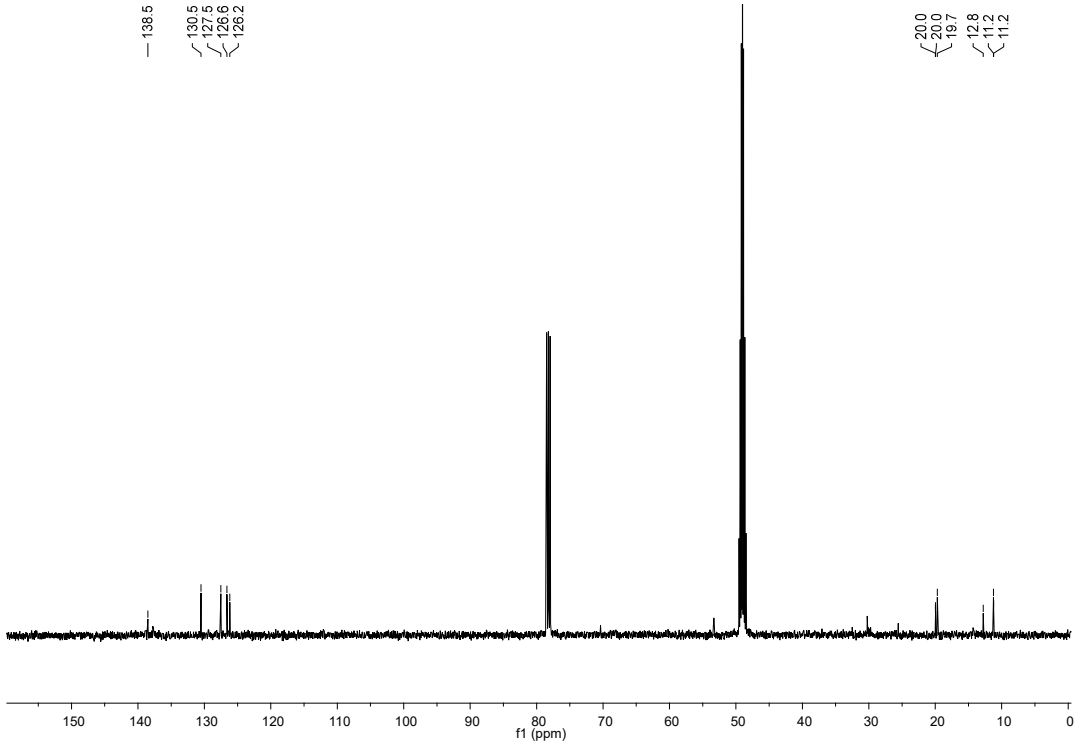
^{1}H NMR ($CDCl_3$/CD_3OD, 500 MHz):



^{31}P NMR ($CDCl_3$/CD_3OD, 162 MHz):

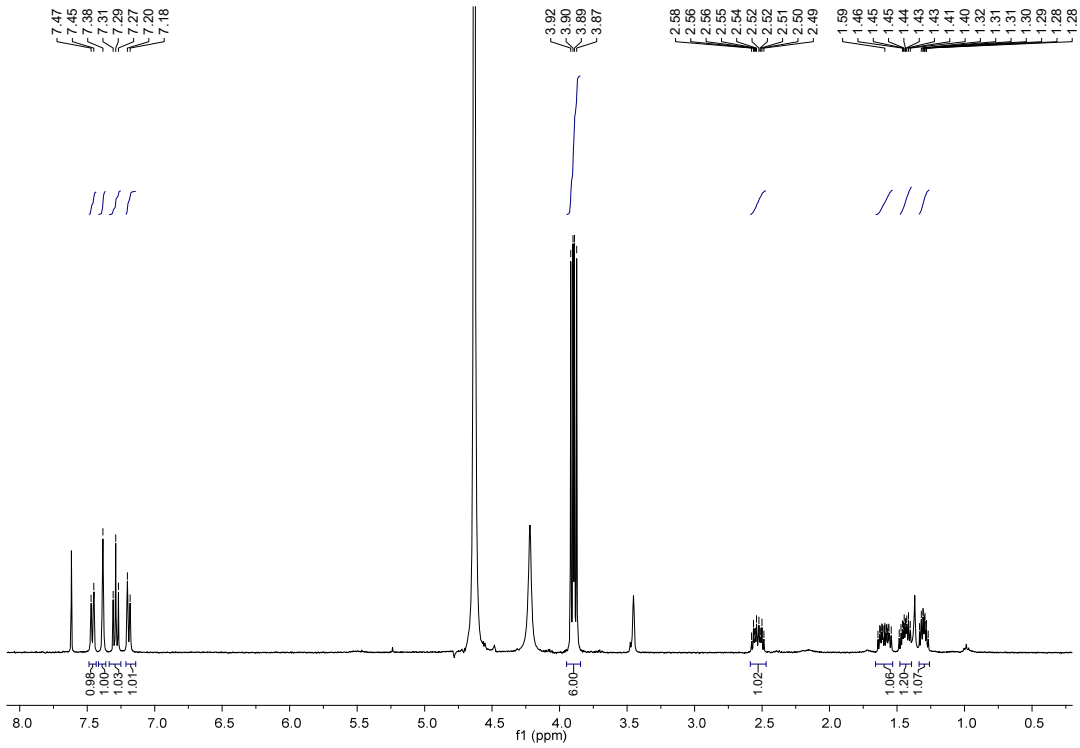


^{13}C NMR ($CDCl_3/CD_3OD$, 126 MHz):

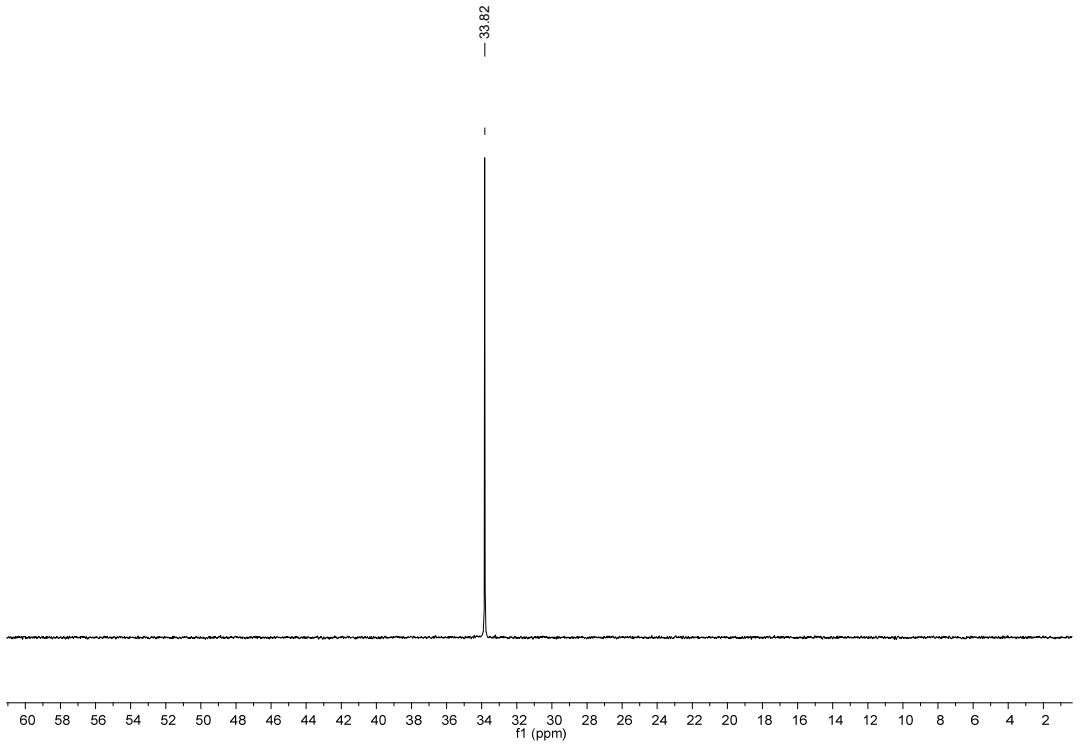


Dimethyl 2-(3-bromo)phenylcyclopropyl phosphonate (3j)

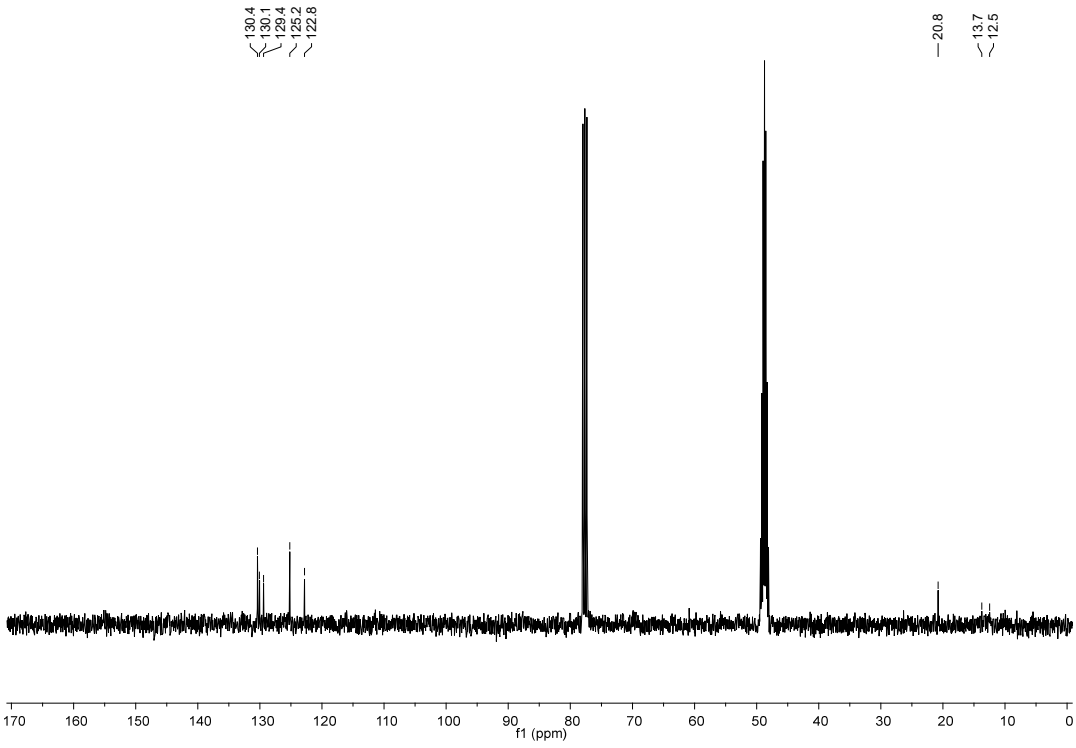
^{1}H NMR ($CDCl_3$/CD_3OD, 500 MHz):



^{31}P NMR ($CDCl_3$/CD_3OD, 162 MHz):

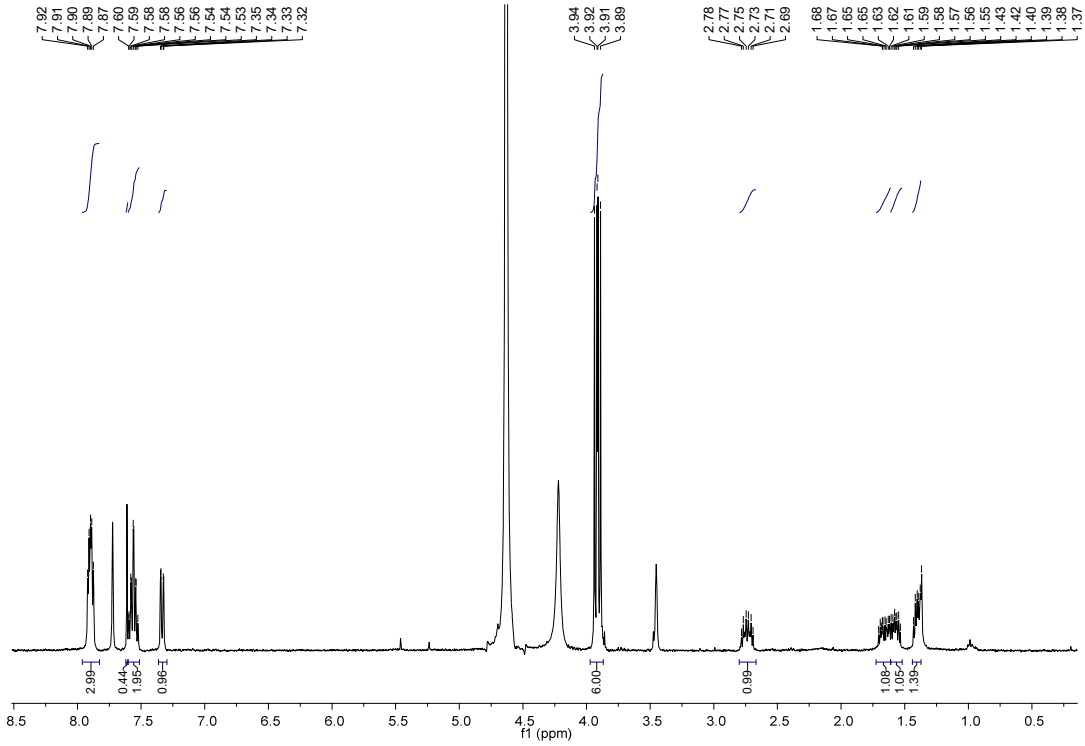


^{13}C NMR ($CDCl_3/CD_3OD$, 126 MHz):

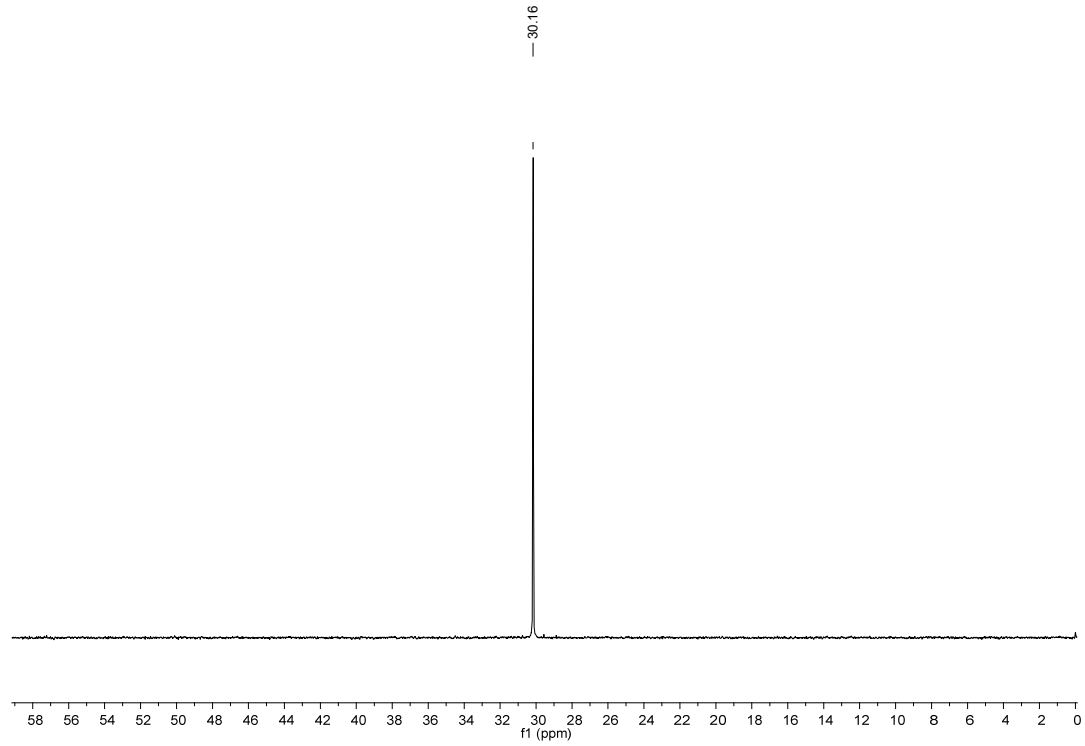


Dimethyl 2-(2-naphthyl)phenylcyclopropyl phosphonate (3k)

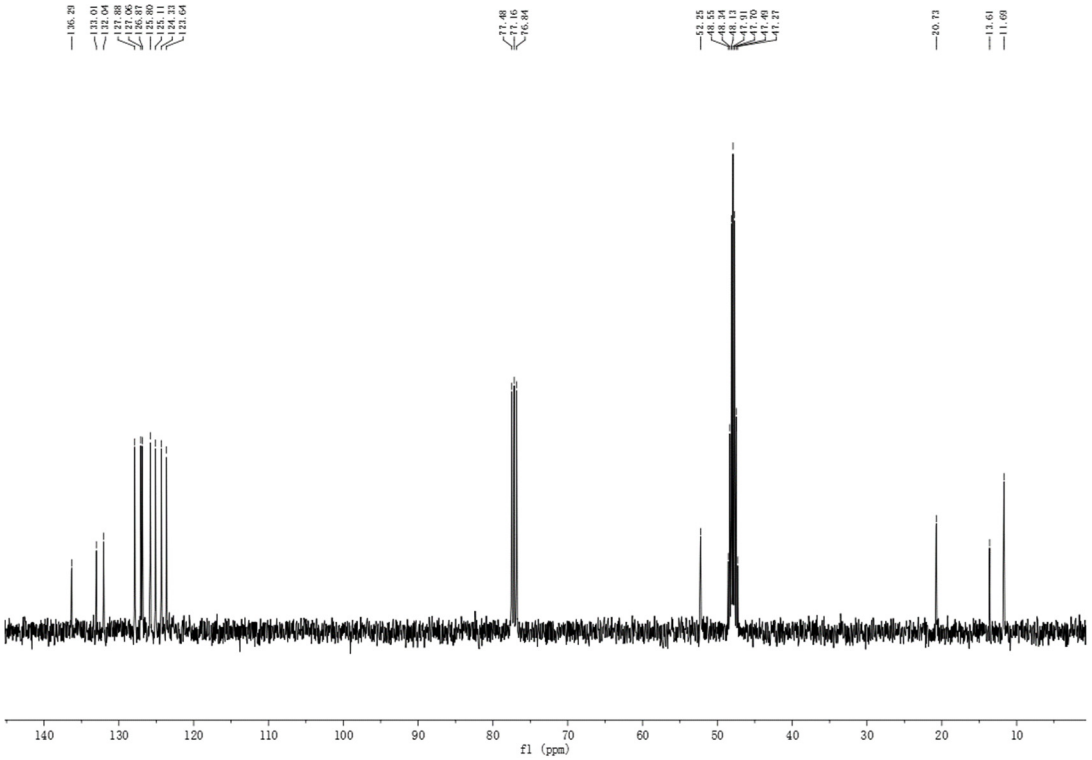
^{1}H NMR ($CDCl_3$/CD_3OD, 500 MHz):



^{31}P NMR ($CDCl_3$/CD_3OD, 162 MHz):

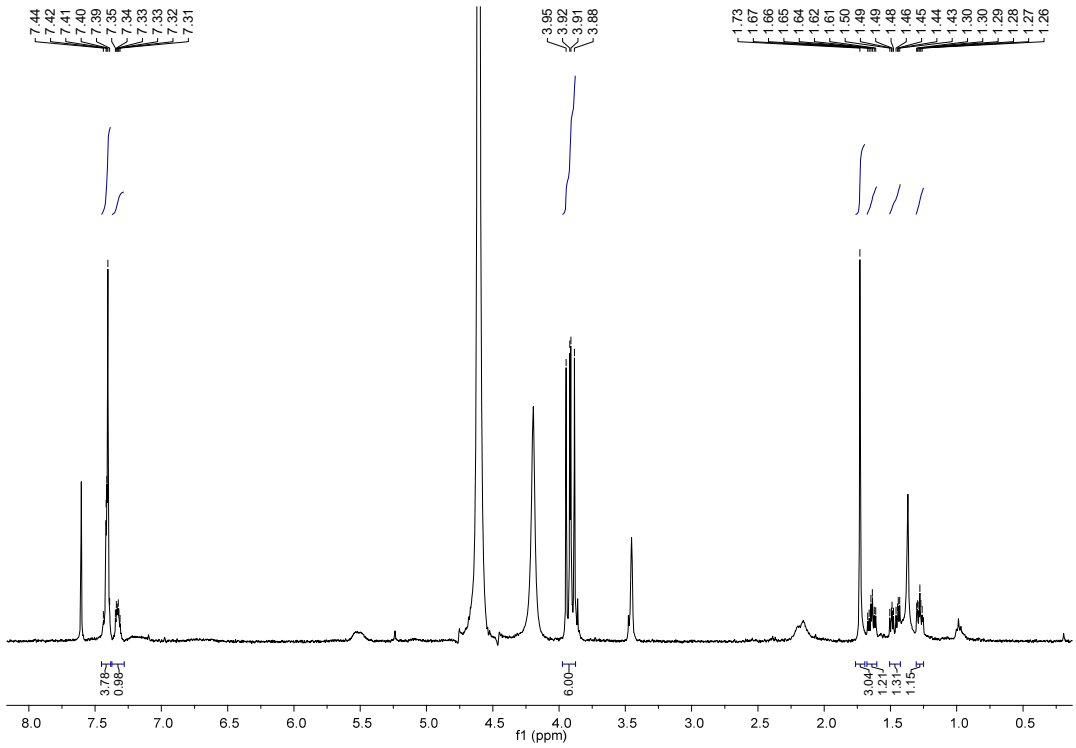


^{13}C NMR ($CDCl_3/CD_3OD$, 126 MHz):

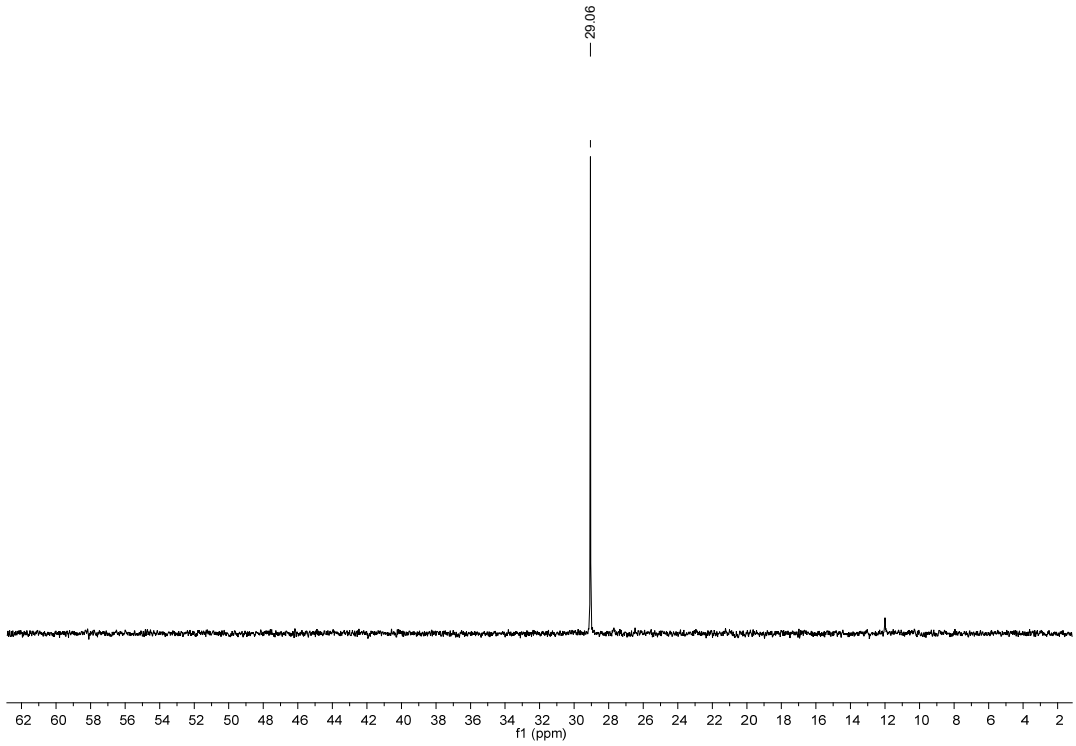


Dimethyl 2-metyl-2-phenylcyclopropyl phosphonate (3l)

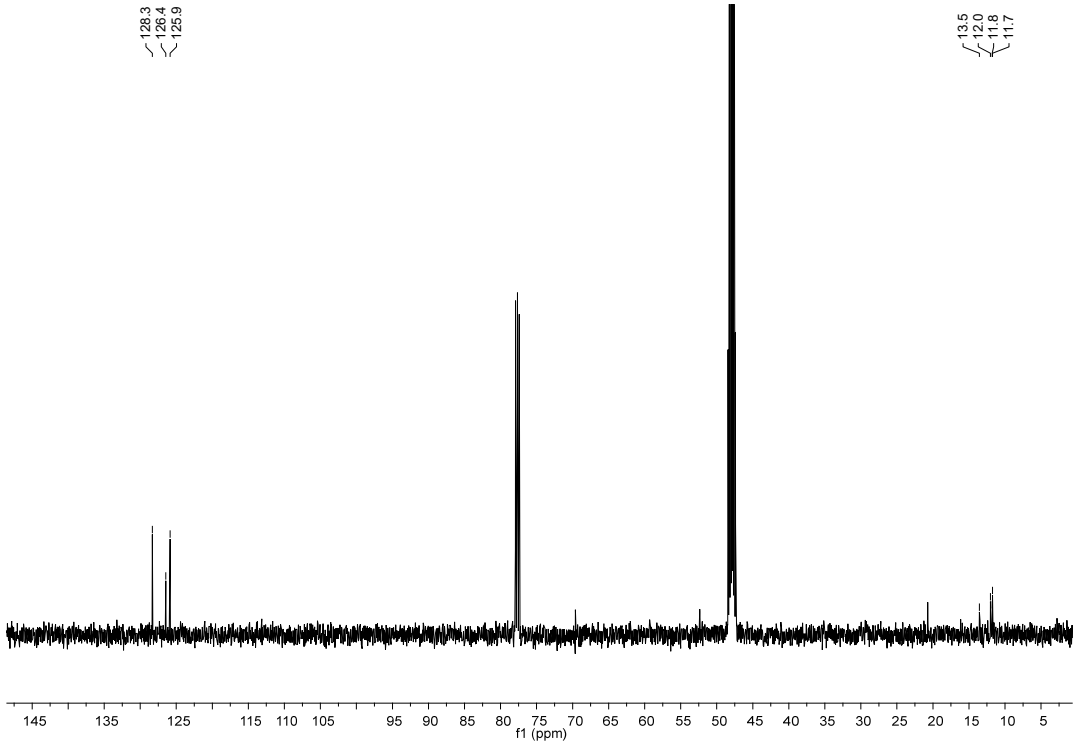
^{1}H NMR ($CDCl_3$/CD_3OD, 500 MHz):



^{31}P NMR ($CDCl_3$/CD_3OD, 162 MHz):



^{13}C NMR ($CDCl_3/CD_3OD$, 126 MHz):



Atom coordinates of optimized molecular geometries

heme

C	2.749805172928	-1.820746915555	2.154295453198
C	3.847666519688	-1.567042278919	0.301228755121
C	4.688951926296	-2.210435453509	1.164146344461
N	2.641779717112	-1.329875997230	0.930984281655
N	3.976048111598	-2.362676229092	2.333437472359
H	5.699658492305	-2.562948540068	1.055233124973
H	4.021431081126	-1.261371325624	-0.715521535242
H	1.984725561730	-1.801346861701	2.910961934290
H	4.304445833764	-2.800883993964	3.179992580722
N	0.731874205721	0.702234410068	1.808052490081
N	2.111873745069	1.070984187369	-0.657952857787
N	-0.242055234300	-1.806207526395	0.887779237964
N	1.137950724395	-1.437210421471	-1.578187844410
C	-0.029188851341	0.382689364117	2.906604207565
C	2.665009331781	1.105106185802	-1.914899529479
C	1.288935585250	1.927273468570	2.082957752800
C	2.484130115600	2.246899362212	-0.053911749356
C	-0.874981160743	-1.795859530189	2.107386711614
C	1.819319581715	-1.072859973132	-2.713967758696
C	-0.616601047789	-2.980855290446	0.282395709667
C	0.578681505218	-2.660812306524	-1.854361315993
C	0.050796189790	1.432304596318	3.896454705819
C	3.403774015726	2.332245505877	-2.106367789651
C	0.869992377971	2.389001691578	3.386372621977

C	3.293645697901	3.039075763144	-0.951337092077
C	-1.667155398887	-2.992904500234	2.273107720187
C	1.685923030472	-2.092217289208	-3.729549285039
C	-1.505051970417	-3.728570623517	1.142159981261
C	0.918677736733	-3.078072116901	-3.195449936628
H	-0.464317862876	1.425991073422	4.846315686310
H	3.925360664696	2.603847767408	-3.012860317985
H	1.163844565080	3.328432882398	3.832111364643
H	3.705521236880	4.010020853584	-0.716489901308
H	-2.268110735183	-3.220446052876	3.141839945069
H	2.121998803731	-2.040879013480	-4.716844739488
H	-1.946401615377	-4.682919003762	0.893176260918
H	0.595366336082	-4.000852892083	-3.655313323393
C	-0.772481040221	-0.782257535791	3.052322497756
C	2.536560409513	0.106388263436	-2.872023265559
C	-0.222809734995	-3.389214049393	-0.985261494662
C	2.118019757229	2.640045535737	1.226597280339
H	-1.328236790561	-0.904967577397	3.974954771005
H	3.027833832178	0.265323681275	-3.825166421301
H	-0.597025062562	-4.343678500841	-1.337541904439
H	2.486230361833	3.597962680155	1.575819711854
Fe	1.054584278143	-0.434715473170	0.171319458885

styrene

C	-1.934906635562	-0.433978391447	-2.043015267929
H	-1.762694136967	-1.350249406847	-1.489108934526
H	-1.140319122703	-0.116328715509	-2.707507575872

C	-3.057189615149	0.281991091762	-1.929571367108
H	-3.146328446629	1.189307582172	-2.523118469822
C	-4.224463775040	-0.006757632312	-1.079463877906
C	-4.304860641482	-1.130709730914	-0.239249816805
H	-3.481826249103	-1.834394577295	-0.196319000685
C	-5.314361843955	0.877299330874	-1.102465652253
H	-5.271769857168	1.751094581919	-1.744626463115
C	-5.430542301772	-1.356451312415	0.543270258244
H	-5.471695022598	-2.229977054434	1.184496875998
C	-6.443456606506	0.652278039511	-0.318558008238
H	-7.272240124341	1.350477289546	-0.354427488886
C	-6.506411674514	-0.466478817105	0.508319942604
H	-7.382933946512	-0.646122277505	1.120344846301

N_2

N	-1.529863402809	-0.861682197493	-1.835525663046
N	-2.016137147191	-1.587398812507	-2.496563676954

dimethyl (diazomethyl)phosphonate

C	-0.327369121442	1.227772625462	-0.676236393212
H	0.159633159955	1.304559029194	0.284827740747
P	-0.327834542167	2.571768973640	-1.831383007186
O	0.335831192425	3.775061284605	-1.271069366754
O	0.293743947737	1.909280556977	-3.151965749394
C	0.300658722474	2.607545127286	-4.420853127480
H	0.818893022145	1.954863267415	-5.119429357077
H	-0.721881271114	2.782497734318	-4.756505871694

H	0.836843574714	3.553495049250	-4.330803042363
O	-1.845331924455	2.805327075617	-2.334840190741
C	-2.773313539165	3.563661275190	-1.529390409851
H	-2.385779164828	4.565761667820	-1.342908305428
H	-3.697235393498	3.619625359397	-2.100775936723
H	-2.958553288441	3.053979041256	-0.580731090509
N	-0.862557188225	0.076971419193	-0.976307033577
N	-1.337879726115	-0.907621796620	-1.258456488756

TS1 dimethyl (diazomethyl)phosphonate

C	-2.751243860584	1.245913802151	1.805265503871
C	-2.449732558110	-0.828078805639	2.334503796339
C	-3.455799454067	-0.370451002323	3.138370575865
N	-2.018246251445	0.188807547258	1.507433075109
N	-3.633893359970	0.951101250329	2.788364143279
H	-4.043437085316	-0.848334510007	3.902852864358
H	-2.011774702608	-1.809962080437	2.294440873851
H	-2.674400263447	2.215921858201	1.345281922329
H	-4.301034182745	1.590947936513	3.190839466070
N	0.377922114255	1.683451660048	0.946738882067
N	0.545619576096	-1.150788288108	1.291216884899
N	-1.603590740621	1.340986374179	-1.075364080832
N	-1.468584845502	-1.505999061486	-0.710806160504
C	0.202341313484	3.004527003374	0.619753552484
C	0.543098911392	-2.521129329579	1.260141245781
C	1.220886133922	1.665292257807	2.030417604465
C	1.390342511292	-0.789207132080	2.306636602147

C	-1.507176399048	2.703074120835	-1.142800045561
C	-1.212265103655	-2.827470121531	-0.462950325421
C	-2.639716563436	0.985311030071	-1.896794465420
C	-2.523235015102	-1.469738191155	-1.581802308142
C	0.971733558003	3.843279875375	1.512281183645
C	1.430986521836	-3.041555394404	2.277222389208
C	1.592375007039	3.014950845370	2.392850908100
C	1.946613414331	-1.968120914239	2.933783625186
C	-2.496181803309	3.228167163236	-2.058688753752
C	-2.129905438424	-3.658012256060	-1.212992068329
C	-3.206621991374	2.163918378043	-2.517324791541
C	-2.950948896508	-2.815941309454	-1.895126247301
H	1.012156673401	4.921954310003	1.463033677858
H	1.610797990590	-4.090840744517	2.463014376978
H	2.250051261194	3.275402327355	3.209664964648
H	2.640179467482	-1.959033138546	3.762418272033
H	-2.623882811800	4.274076487337	-2.297787998531
H	-2.141742585705	-4.738417145736	-1.195040060065
H	-4.036205090973	2.159688481708	-3.209895475027
H	-3.769442988837	-3.066702825705	-2.554695585316
C	-0.646560873323	3.480647832764	-0.373944117218
C	-0.251968144196	-3.304260219228	0.426286043999
C	-3.084244524443	-0.314935050413	-2.116249522039
C	1.686178434027	0.520664904420	2.670801049199
H	-0.678206917062	4.553530214366	-0.525287931037
H	-0.154306756939	-4.380097116129	0.518243115066
H	-3.924271330831	-0.441264894771	-2.790082880437

H	2.361343095471	0.662658002712	3.506933756811
Fe	-0.492741217166	0.097780697499	0.074394439577
C	0.814263846404	-0.247939621128	-1.349479398294
H	1.102773852568	-1.303525882530	-1.348979675043
P	0.907067274335	0.335034325171	-3.098048185602
O	-0.244432592971	-0.580724369297	-3.744443724722
O	0.839668603414	1.790740119238	-3.358295708274
O	2.294205831333	-0.239538969638	-3.723103627685
C	2.590565124956	-1.643222689774	-3.841394289813
H	2.814459359131	-2.076309004342	-2.863064089391
H	1.758101473160	-2.180193844954	-4.299295775813
H	3.471514956206	-1.718799833758	-4.476175993449
C	-0.945244655141	-0.173007834005	-4.941943342156
H	-1.325835671199	0.841642236058	-4.830251060192
H	-0.281049855950	-0.231714194022	-5.806521733850
H	-1.769591812350	-0.872516065729	-5.058425363751
N	2.404124568817	0.352901848871	-0.855280625114
N	3.031306070023	1.052621440432	-0.276049905598

Int$_{\text{dimethyl (diazomethyl)phosphonate}}$

C	2.640839854865	-1.787005052077	2.137116556201
C	3.789956932686	-1.580246428621	0.321132079174
C	4.595632313133	-2.235740547485	1.209634107092
N	2.572515103886	-1.304932013030	0.909855110277
N	3.847302131441	-2.358868626797	2.361248542242
H	5.600157494665	-2.614265261936	1.132239393390
H	4.003335601539	-1.291572418723	-0.693266251897

H	1.859111572435	-1.744983064013	2.876244269169
H	4.141324602798	-2.797839595407	3.220135724427
N	0.628163938983	0.709467199185	1.805380616877
N	2.115540153241	1.125643194741	-0.626184730590
N	-0.296742169511	-1.786378787656	0.803761464893
N	1.163865896170	-1.343116181483	-1.645248923316
C	-0.129190271488	0.342580872450	2.885832368457
C	2.804118543882	1.131264307825	-1.809142955901
C	1.163306588941	1.934081402735	2.105967102723
C	2.449906722472	2.285645009357	0.021286522102
C	-0.931263578334	-1.824474861453	2.016163154736
C	1.979399758633	-1.014634807844	-2.694064618508
C	-0.654337237000	-2.930882206979	0.141526402874
C	0.609654499440	-2.557176773602	-1.953102579409
C	-0.062241768681	1.363286729802	3.906875618041
C	3.598613854224	2.333446082396	-1.914195212882
C	0.738146006246	2.349762756913	3.423277373886
C	3.374809669040	3.051942429471	-0.782914465326
C	-1.700731978396	-3.042513958247	2.132710390741
C	1.930109623737	-2.047594601932	-3.703605727690
C	-1.529299126330	-3.727187455932	0.971694105607
C	1.076588082843	-3.000930007736	-3.246961361687
H	-0.566030486108	1.314241396668	4.861395652482
H	4.239111554043	2.577391149026	-2.749419295948
H	1.025531651554	3.275666986472	3.900166582253
H	3.794434416854	4.005837926840	-0.498025324456
H	-2.289810982086	-3.318804901171	2.995162457322

H	2.484296828218	-2.030279749015	-4.630888683510
H	-1.949746578120	-4.680145602132	0.685349111801
H	0.784842179851	-3.925922567011	-3.722588564115
C	-0.857066785763	-0.837568648842	2.992489702064
C	2.755349569448	0.134051147685	-2.774182145091
C	-0.241804829202	-3.289515788267	-1.135325582535
C	2.002366541050	2.671595170713	1.279228190437
H	-1.417047935268	-0.997290161568	3.906366462583
H	3.362155154659	0.267429487314	-3.662070538274
H	-0.607609162883	-4.232641379031	-1.523898236141
H	2.354757059661	3.624524671905	1.656807726345
Fe	0.819579231591	-0.271098448663	0.037961710406
C	-0.658896398897	0.474306052780	-0.556808221413
H	-1.475477568039	0.572574285602	0.170477109705
P	-1.330017310408	0.979119441689	-2.145742822726
O	-2.221644369384	-0.030969020379	-2.776646359762
O	-2.177364982896	2.335699250869	-1.854829836537
C	-1.553412770917	3.539024317026	-1.363826198915
H	-2.339202946808	4.289863618345	-1.306112521139
H	-1.128757181810	3.380377256493	-0.369520759516
H	-0.769457250308	3.874644964033	-2.045147630184
O	-0.082814556660	1.465977454743	-3.034957372358
C	-0.213400943353	1.652589960118	-4.459266777012
H	-0.921235919524	2.454744756964	-4.680684581639
H	0.776309065663	1.926181621658	-4.818612849382
H	-0.541485779718	0.728321975214	-4.935741320452

TS2dimethyl (diazomethyl)phosphonate

C	2.619412575156	-1.658027538978	2.059808563460
C	3.764701704052	-1.440203042407	0.240962701648
C	4.571707343643	-2.102225366639	1.123447656865
N	2.549951593535	-1.168888141266	0.835904471850
N	3.826657745374	-2.231763753075	2.276613057779
H	5.575537406181	-2.481473374581	1.040966847934
H	3.973775518871	-1.144027153629	-0.772226139600
H	1.838836899525	-1.618061935424	2.800039727651
H	4.122994279623	-2.675629005383	3.132000818982
N	0.855642816499	0.963307995917	1.652358146765
N	2.189960810822	1.084622411817	-0.891939885709
N	-0.324953322306	-1.526317572421	0.916341867123
N	1.050295610901	-1.419425862753	-1.593799935471
C	0.074254888637	0.791690940798	2.763504603566
C	2.702983553725	1.004297391186	-2.155879324985
C	1.647926646279	2.051296332345	1.894045822274
C	2.811939185826	2.143787419742	-0.288975934444
C	-0.952760548963	-1.368030560252	2.123490169172
C	1.702844739357	-1.167576796766	-2.773267725881
C	-0.654918459971	-2.777652362101	0.468940887759
C	0.541040551336	-2.688667560683	-1.698087454464
C	0.365536545821	1.824583782446	3.734380775464
C	3.652310258093	2.073882338573	-2.378442901348
C	1.352470096433	2.593821837416	3.202278644011
C	3.733224547912	2.769363775252	-1.213624029127
C	-1.725129302480	-2.549736291053	2.438558303652

C	1.584988664610	-2.305841385771	-3.657238628268
C	-1.529688081227	-3.429460637390	1.418657982606
C	0.877885920150	-3.252826713150	-2.986018163161
H	-0.114587023890	1.920382981784	4.697748940848
H	4.191499351852	2.240467954657	-3.299785441358
H	1.841089066686	3.453204478852	3.638709784038
H	4.350093008088	3.627027535924	-0.986257368127
H	-2.315478337705	-2.682287901821	3.333952425215
H	2.006322624222	-2.361270446718	-4.650636483447
H	-1.932839197720	-4.425725990332	1.306076086894
H	0.595845272951	-4.241236465806	-3.319265319855
C	-0.800224705371	-0.271530686176	2.970232995302
C	2.441978467724	-0.023947341400	-3.056029005265
C	-0.233243255868	-3.331290391515	-0.737183828738
C	2.583984627575	2.579032326807	1.011414304650
H	-1.356003671793	-0.283176325129	3.900977718243
H	2.910157207036	0.035854307718	-4.031642930253
H	-0.568609608065	-4.336654672398	-0.965130277997
H	3.155769616484	3.434469495419	1.353195834797
Fe	0.861385484639	-0.180269266352	-0.032243287955
C	-0.674460950646	0.819482776271	-0.543065800160
H	-1.491512849470	0.728696775926	0.178133323311
P	-0.830985425721	2.432103133776	-1.378784649090
O	0.027130068373	3.416977859030	-0.429696171203
O	-0.512590814197	2.502637436551	-2.830053788750
O	-2.358986974660	2.989356746997	-1.171882160392
C	-2.912342996887	3.261441013261	0.125078338446

H	-3.106158191544	2.334302324489	0.670476367344
H	-2.244005213383	3.895086491009	0.711689987173
H	-3.856143913123	3.778621648725	-0.042178813405
C	0.385481983295	4.737388955719	-0.880699538977
H	0.944522152673	4.683222536378	-1.815550208052
H	-0.506249338529	5.354161953240	-1.018956182914
H	1.010447851684	5.164939016856	-0.098959916607
C	-1.790543630114	-0.354037488873	-2.042365923213
H	-1.691211476051	-1.245122223322	-1.443582325021
H	-1.029763157701	-0.186959658250	-2.790903563326
C	-2.999843883886	0.270662473887	-2.173412560760
H	-3.077069477241	1.070157040194	-2.902777293047
C	-4.212902998901	0.011413831261	-1.415936963067
C	-4.300789770625	-0.975220699558	-0.412772825734
H	-3.435661385361	-1.578238200096	-0.165427592642
C	-5.361370858660	0.774897659746	-1.701917076815
H	-5.305616648199	1.540335481108	-2.468128209900
C	-5.491085709431	-1.184449629937	0.269659984014
H	-5.540755248250	-1.946254186183	1.039259068185
C	-6.553626180187	0.559009454242	-1.020719235585
H	-7.427547316348	1.154572790763	-1.258505804106
C	-6.622532045505	-0.421387420636	-0.031502018757
H	-7.550394715666	-0.591666657858	0.502546479955

cyclopropane

C	-1.381817563985	0.621683503068	-1.529641278530
H	-1.131566511866	0.028849809229	-0.656967730730

P	-0.253094257273	1.963176067638	-1.885845149927
O	-0.504834338924	2.694125283891	-3.151796981444
O	-0.294505476662	2.993430297074	-0.639708068966
C	-0.040098288759	2.583856315478	0.719184552435
H	0.030053635583	3.497140777822	1.306409519925
H	-0.864360718046	1.974168962753	1.095878260778
H	0.896824078724	2.027787516744	0.789484203712
O	1.174979112356	1.215004583209	-1.770059233050
C	2.383566715021	1.858380293098	-2.236283864545
H	3.186982204587	1.140669734316	-2.085347276145
H	2.296056046977	2.105690272316	-3.294695976740
H	2.584694192927	2.764082266612	-1.660172371970
C	-2.066087152187	-0.095569895808	-2.669227470138
H	-2.217359659870	-1.161856486225	-2.554557032423
H	-1.847039590240	0.233921013264	-3.677024402749
C	-2.870490856766	0.836857731137	-1.802806636926
H	-3.112582883279	1.786011020327	-2.268020647231
C	-3.900717717019	0.359484325732	-0.834443203973
C	-3.804444776029	-0.873590661694	-0.174813006045
H	-2.957728065488	-1.526698207418	-0.357827955085
C	-5.013090677960	1.167571115904	-0.569527262556
H	-5.105279280819	2.125223059917	-1.070990904419
C	-4.788924645101	-1.282577863612	0.720489152014
H	-4.694885150502	-2.240935415121	1.219050535155
C	-6.000045450738	0.759178906033	0.325586138298

H	-6.852958355399	1.401694983534	0.513838908245
C	-5.892118373292	-0.468207385332	0.975212525695
H	-6.658397765972	-0.788459313884	1.671801117336

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