Preparation of Optically Pure Tertiary Phosphine Oxides via Addition of P-Stereogenic Secondary Phosphine Oxide to Activated Alkenes

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Table of Contents

General Chemistry:

^{1}H NMR spectra were recorded on a 400-MHz spectrometer. Chemical shift for ^{1}H NMR spectra (in parts per million) relative to internal tetramethylsilane (Me_4Si, δ= 0.00 ppm) with Chloroform-d. ^{13}C NMR spectra were recorded at 101 mHz Chemical shifts for ^{13}C NMR spectra are reported (in parts per million) relative to Chloroform-d (δ= 77.0 ppm). ^{31}P NMR spectra were recorded at 162 MHz, and chemical shifts reported (in parts per million) relative to external 85% phosphoric acid (δ= 0.0 ppm). TLC plates were visualized by UV..

Reagent and solvents:

All starting material were purchased from commercial sources and used as received. The solvents were distilled under N_2 and dried according to standard procedures.

^{31}P NMR Yield measurements:

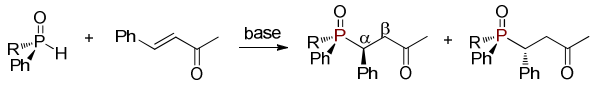
^{31}P NMR spectra were referenced to phosphoric acid. The NMR yields of the article are determined by integration of all the resonances in the ^{31}P spectra. The yields obtained by the approach are generally accurate and reproducible

Part 1. Investigation of the reaction under alkali condition

General procedure, in DMSO or DMF:

To the solution of **1** (50 mg, 0.189 mmol), **2a** (33 mg, 0.227 mmol) in some solvent (0.5 ml), the base was added and the mixture was stirred at the temperature for the time as indicated in Table S-1. The suspension (0.1 ml) was added to saturated aqueous ammonium chloride, extracted with dichloromethane, washed with water and dried over anhydrous magnesium sulfate. After removing solvent, the residue was analyzed with proton and ^{31}P-NMR spectra, and the results were summarized in Table S-1. The ^{31}P and proton NMR spectroscopy of **3a**/**3a'** were shown in Figure S-1 and S-2.

Table S-1. Base-catalyzed addition of **1** to benzaacetone **2a**.



entry	solvent	Catalyst (mol %)	temp. /time	Peak of **3a** on ^{31}P-NMR (45.07 ppm) % [a]	Peak of **3a'** (46.68 ppm) % [a]	Peak of unconsumed **1** on ^{31}P-NMR (33.26 ppm) % [a]
1	DMSO	KOH (25)	34°C/25h	53	45	2
2	DMSO	KOH (25)	80°C/21h	--	--	97
3	DMSO	LiOH (25)	80°C/70h	47	53	--
4	DMF	$Ca(OH)_2$ (25)	15°C/21 h	87	13	--
5	DMF	$Ca(OH)_2$ (25)	-5°C/21 h	87	10	3
6	iPrOH	KOH (25)	60°C/19h	30	70	--
7	iPrOH	KOH (25)	40°C/0.5h	79	21	--
			40°C/5h	62	38	--
			40°C/11h	54	46	--
8	iPrOH	KOH (25)	40°C/48h	38	62	--
9	THF	*n*BuLi (20)	-78°C/3h	64	4	15[b]
10	THF	*n*BuLi (50)	-78°C/3h	74	6	7[b]
11	THF	*n*BuLi (100)	-78°C/3h	74	9	7[b]

[a] The photocopy of NMR spectroscopy of **3a** and **3a'** were presented in Figure S-1 and S-2. [b] By-products other than **3a**/**3a'** were detected.

General procedure, in isopropanol:

The KOH (0.047 mmol) was dissolved previously in isopropanol (0.5 ml) with stirring. If necessary, the mixture can be heated to accelerate the dissolving, and the resulting solution was cooled to room temperature before using. To the clear solution of KOH, **1** (0.05 g，0.189 mmol) and **2a** (0.033 g, 0.227 mmol) were added. The mixture was stirred at the temperature for the time as indicated in Table S-1. The suspension (0.1 ml) was added to saturated aqueous ammonium chloride, extracted with dichloromethane, washed with water and dried over anhydrous magnesium sulfate. After removing solvent, the residue was analyzed with proton and ^{31}P-NMR spectra, and the results were summarized in Table S-1.

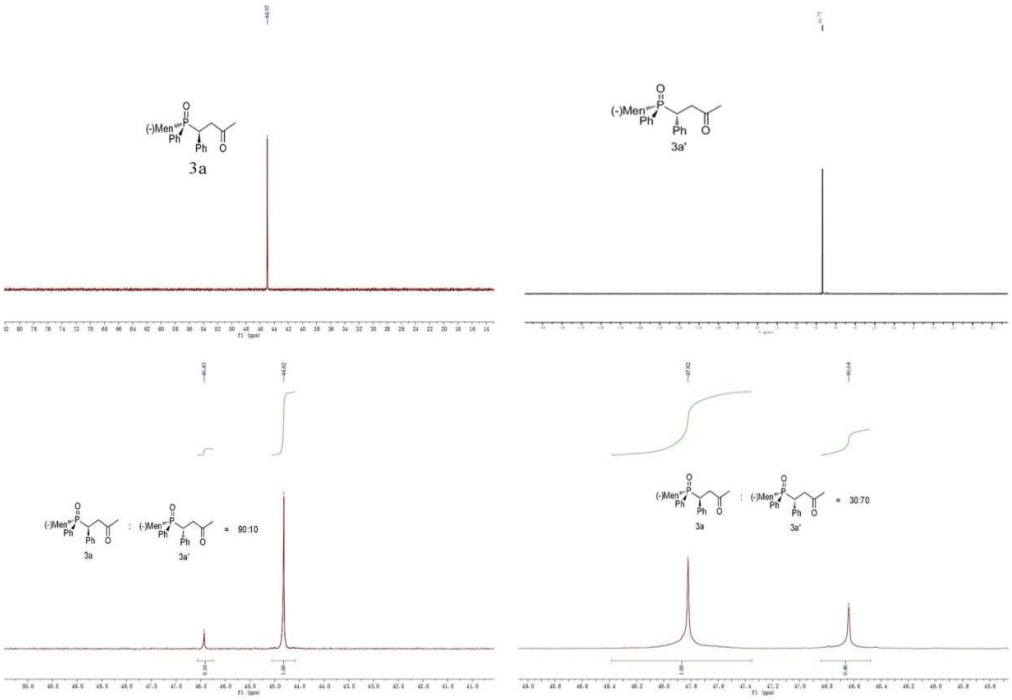


Figure S-1. ^{31}P NMR spectroscopy of **3a** and **3a'**.

General procedure, for *n*BuLi in THF:

To the solution of **1** (0.053 g, 0.2 mmol) in THF (1 ml), the solution of *n*BuLi (2.2 M solution in hexane, 0,091 ml, 0.2 mmol) was added at -78°C. The resulting solution was stirred for 10 min at the same temperature, then **2a** (0.032 g, 0.22 mmol) was added in one portion. After the mixture was stirred for 3 h, the mixed solvent of acetic acid/THF (2:1, 0.2 ml) was added dropwise at the same temperature to stop the reaction. The mixture was added to saturated aqueous ammonium chloride, extracted with dichloromethane, washed with water and dried over anhydrous magnesium sulfate. After removing solvent, the residue was analyzed with proton and ^{31}P-NMR spectra, and the results were summarized in Table S-1.

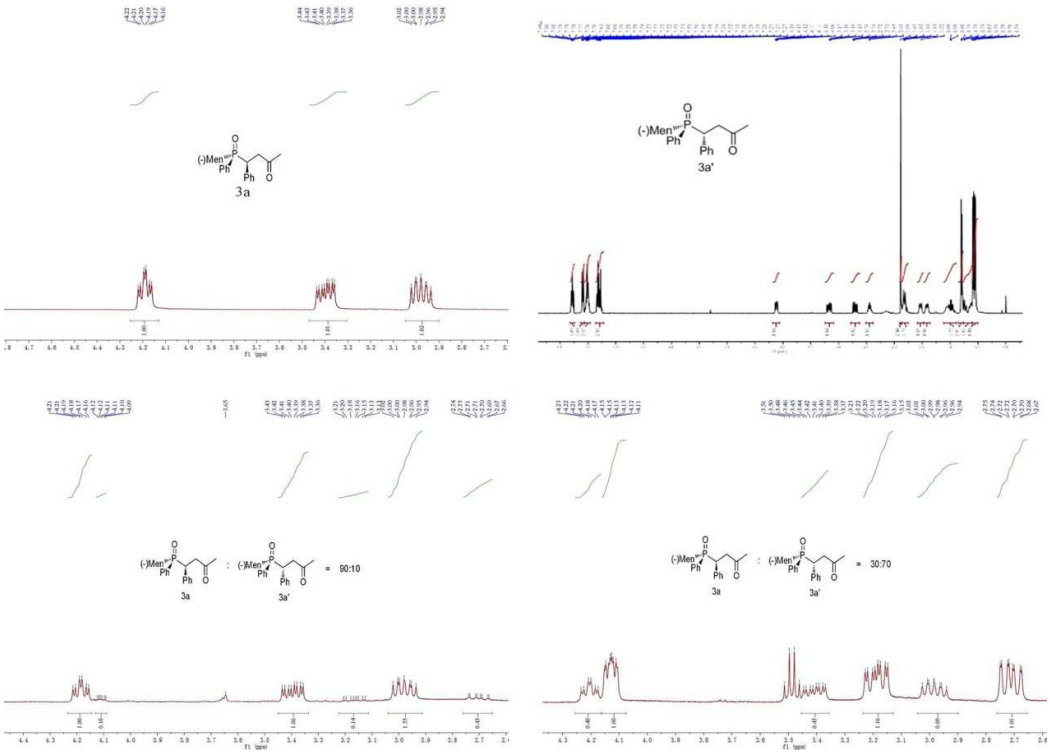


Figure S-2. Proton NMR spectroscopy of **3a** and **3a'**.

Table S-2. Optimization of the thermal addition of **1** to **2a**.

entry	solvent	Catalyst or additive (mol %)	temp. /time [a]	**3a** (45.07 ppm) % [a]	**3a'** (46.68 ppm) % [a]	Unconsumed **1** (33.26 ppm) % [a]
1	no	no	80 °C /22 h	88	12	--
2	toluene	no	80 °C /17 h	91	9	--
3	toluene	no	80 °C /24 h	89	11	--
4	toluene	no	60 °C /24 h	74	9	17
5	DMSO	no	80 °C /46 h	92	8	--
6	nC_8H_{18}	no	80 °C /46 h	59	7	--[b]
7	pyridine	no	80 °C /24 h	83	10	7
8	MeOH	no	60 °C /19 h	24	4	--[b]
9	toluene	AIBN (20)	60 °C /25 h	85	9	6
10	toluene	AIBN (20)	80 °C /52 h	92	8	--
11	toluene	Ph3P (20)	Rt/40h	Nr		
12	toluene	Et3N (20)	Rt/40h	Nr		
13	toluene	TEMPO (20)	80 °C /24 h	76	1	2[b]
14	toluene	TEMPO (20)	100°C/41 h	Complicated[c]		

[a] The photocopy of NMR spectroscopy of **3a** and **3a'** were presented in Figure S-1 and S-2. [b] By-products other than **3a/3a'** were detected. [c] The epimerization of **1** and formation of the stereomers other than **3a**/**3a'** were detected.

Part 2. Investigation of the reaction under thermal condition

General procedure, neat condition:

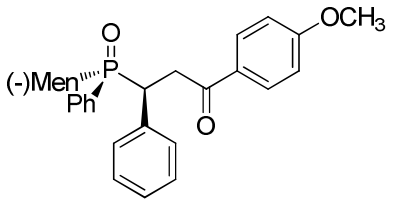
The mixture of **1** (0.050 g, 0.189 mmol) and **2a** (0.033 g, 0.227 mmol) was heated at 80 ^{o}C with stirring. The oily substance (ca. 0.02 ml) was dissolved in *d*-chloroform, analyzed with proton and ^{31}P-NMR spectra, and the results were summarized in Table S-2.

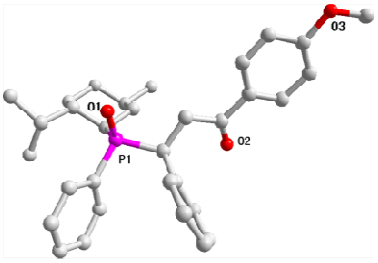
General procedure, thermal addition in a solution:

The solution of **1** (0.050 g, 0.189 mmol), **2a** (0.033 g, 0.227 mmol) and additive (AIBN or TEMPO) in solvent (0.1 ml) was heated at 80 ^{o}C with stirring. The solution (ca. 0.020 ml) was dissolved in *d*-chloroform, analyzed with proton and ^{31}P-NMR spectra, and the results were summarized in Table S-2.

Part 3. Crystallographic Information

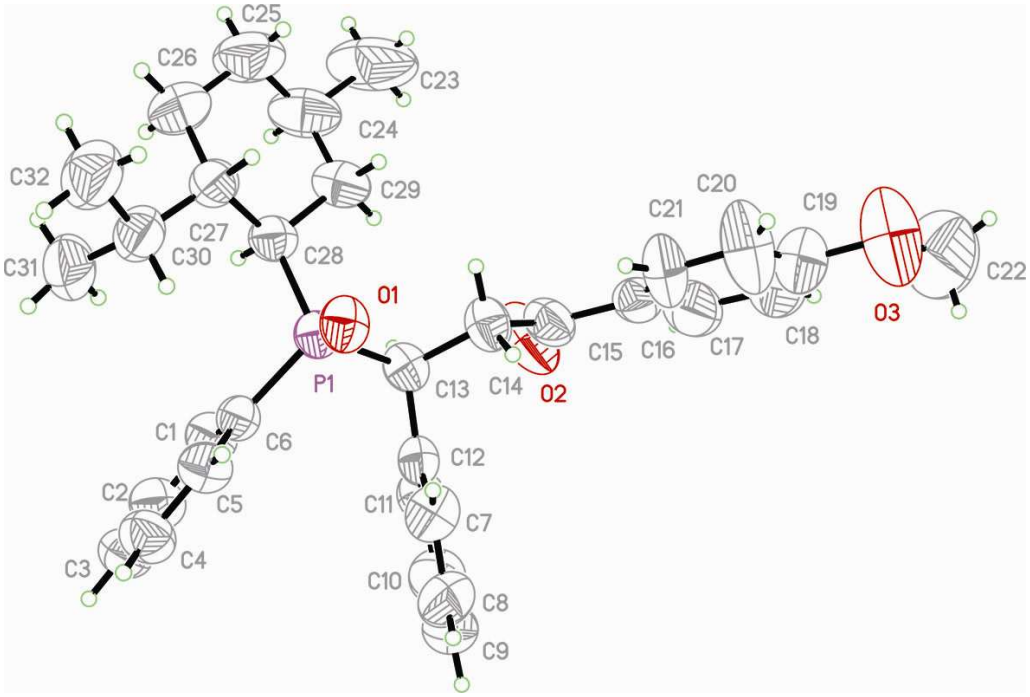
(S_P,*S*)-4-[(–)-Menthylphenylphosphoryl]-1-(*p*-methoxyphenyl)-4-phenylpropan-2-one, 3e





Empirical formula	C32 H39 O3 P
Crystal system	Orthorhombic
Space group	P212121
Formula weight	502.60
a, Å	5.9316(3)
b, Å	16.4646(10)
c, Å	29.5614(18)
α, deg	90
β, deg	90
γ, deg	90
V, Å3	2887.0(3)
Z	4
T, K	293(2)
λ, Å	1.54184
ρ, g cm−3	1.156
Rint	0.0732
R1 [I N 2σ(I)]	0.0628
R1 (all data)	0.1244
wR2 [I N 2σ(I)]	0.1208
wR2 (all data)	0.1419
Flack	-0.01(3)
CCDC	1449993

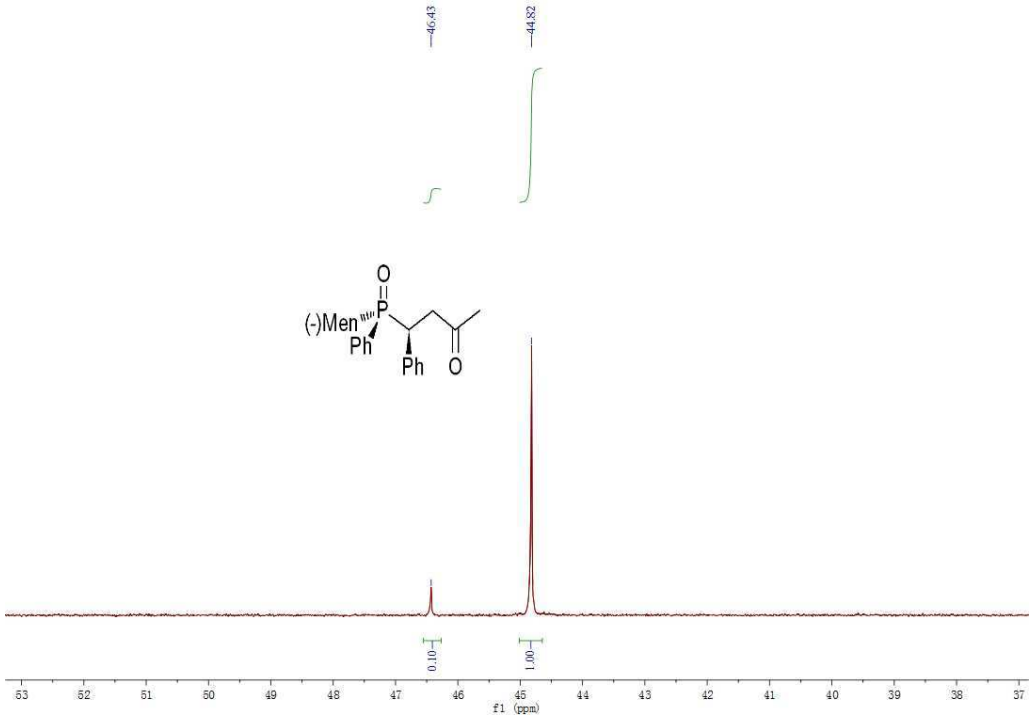
Fig S-1. ORTEP drawing of **3e** with thermal ellipsoids at the 50% probability.



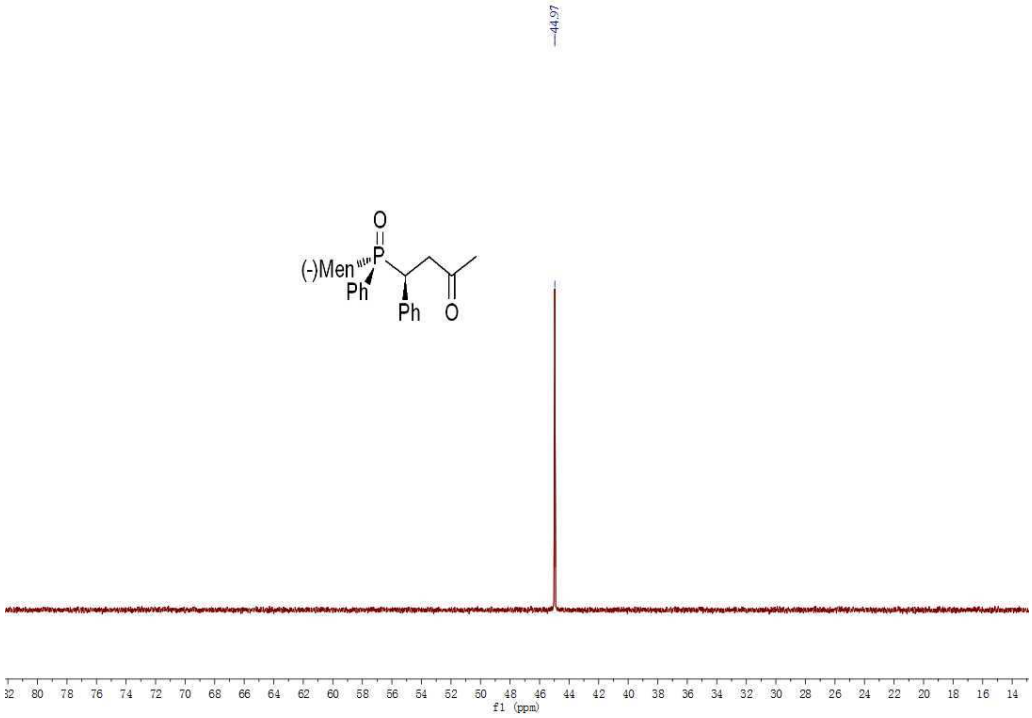
Part 4. Selected 1H, 31P and 13C NMR spectroscopy of 3 and 5

(S_P,*S*)-4-[(–)-Menthylphenylphosphoryl]-4-phenylbutan-2-one, 3a

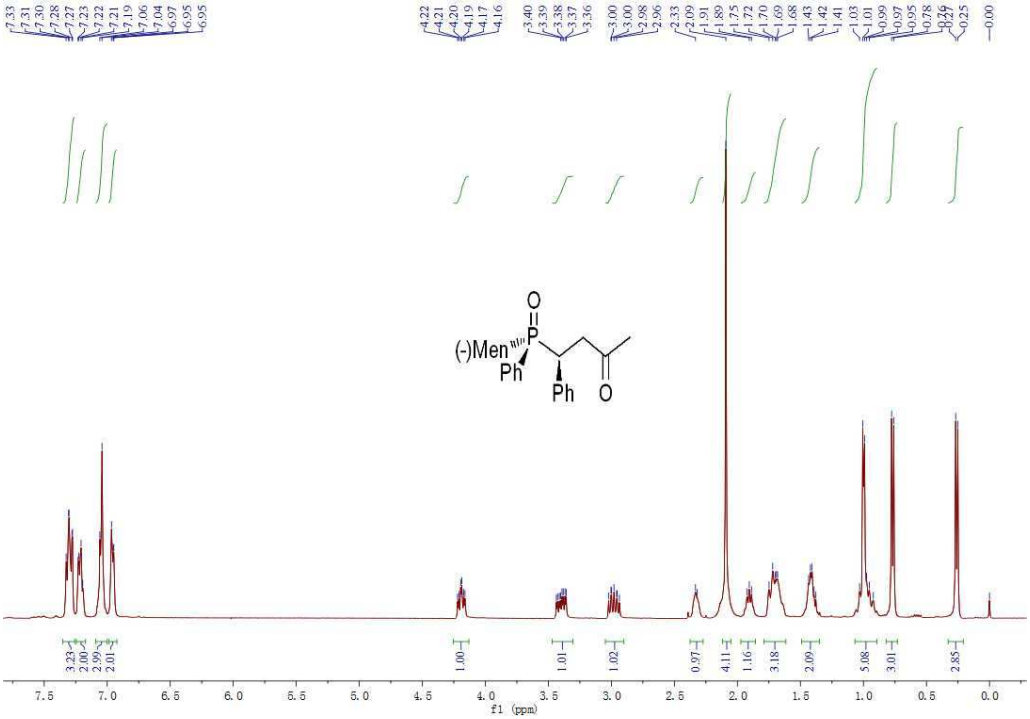
^{31}P-NMR spectroscopy of crude 3a/3a'=91:9



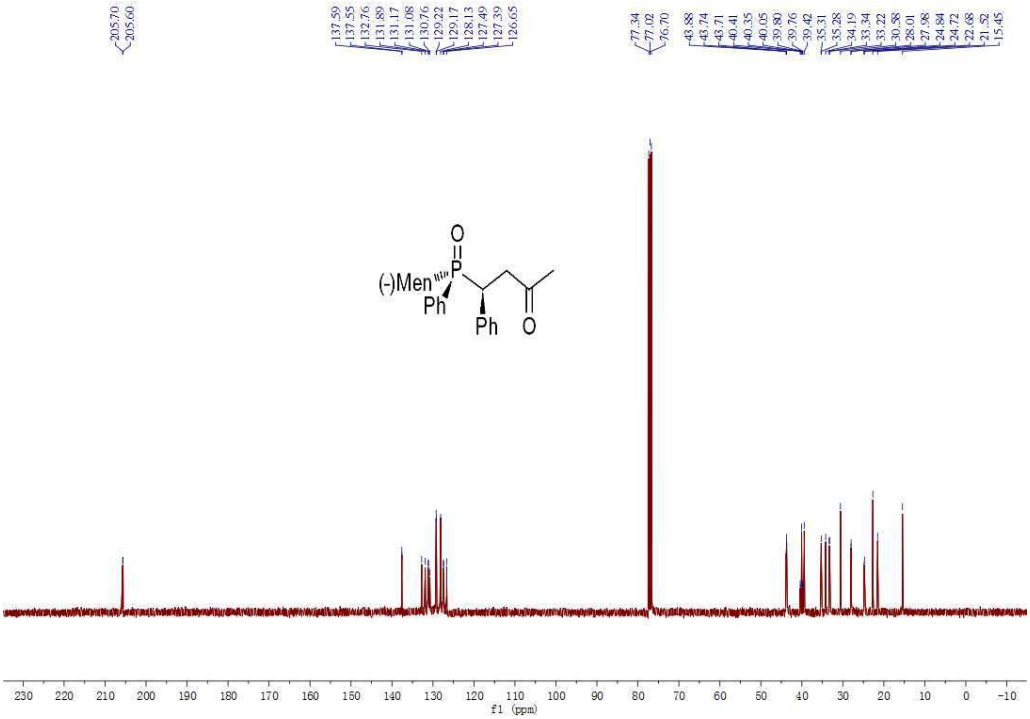
^{31}P-NMR spectroscopy of isolated 3a



^{1}H-NMR spectroscopy of isolated 3a

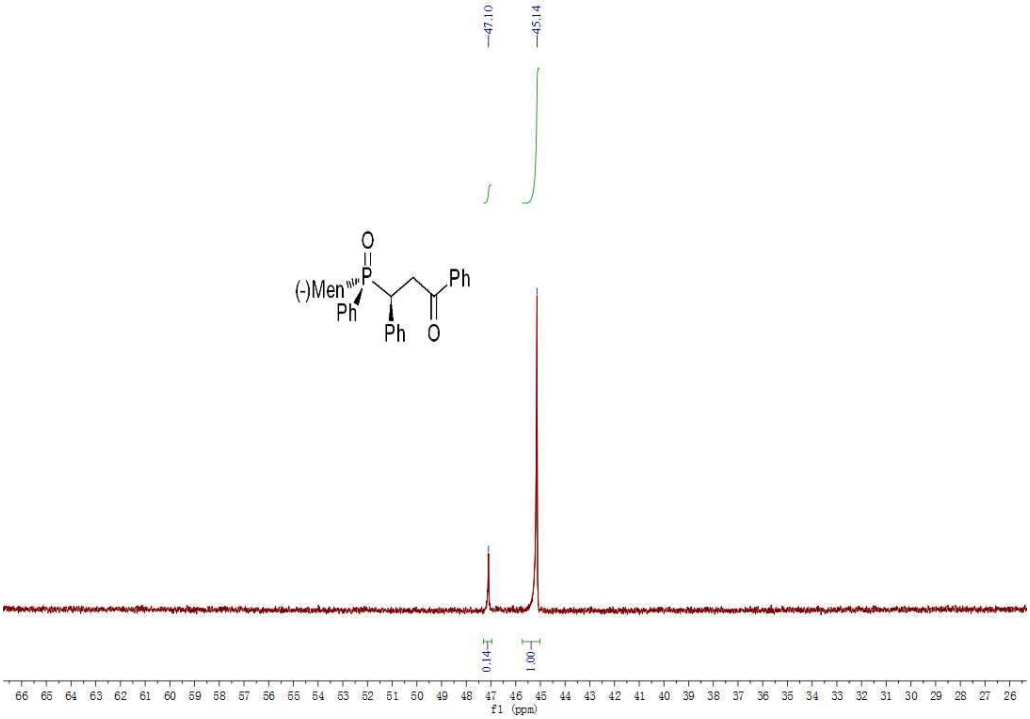


^{13}C-NMR spectroscopy of isolated 3a

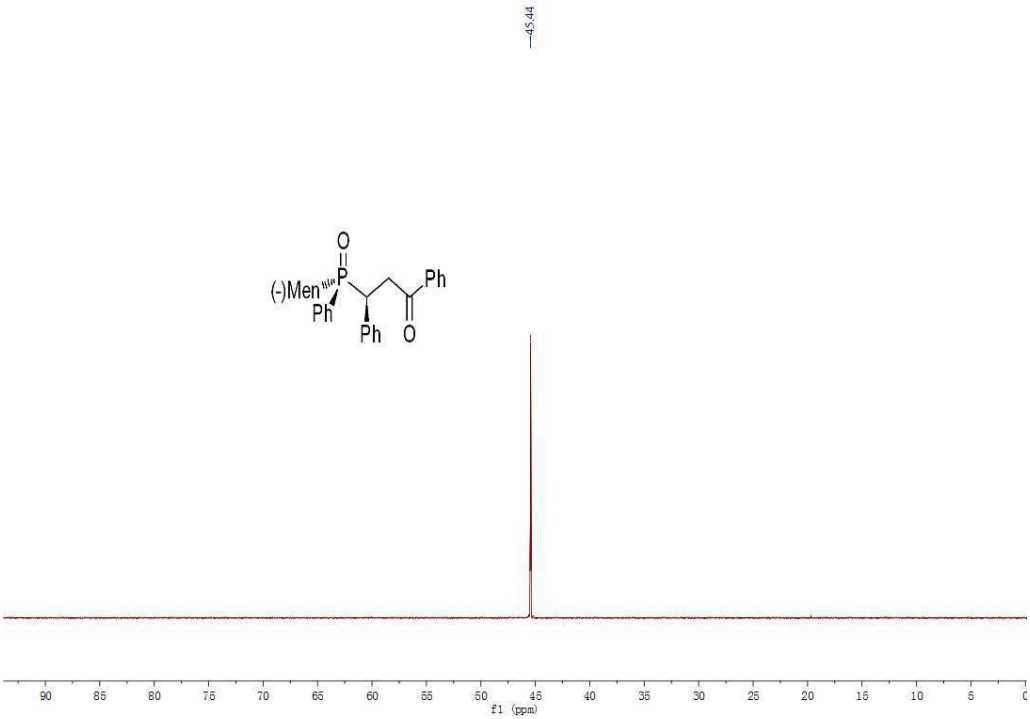


(S_P,S)-4-[(–)-Menthylphenylphosphoryl]-1-phenyl-4-phenylpropan-2-one, 3b

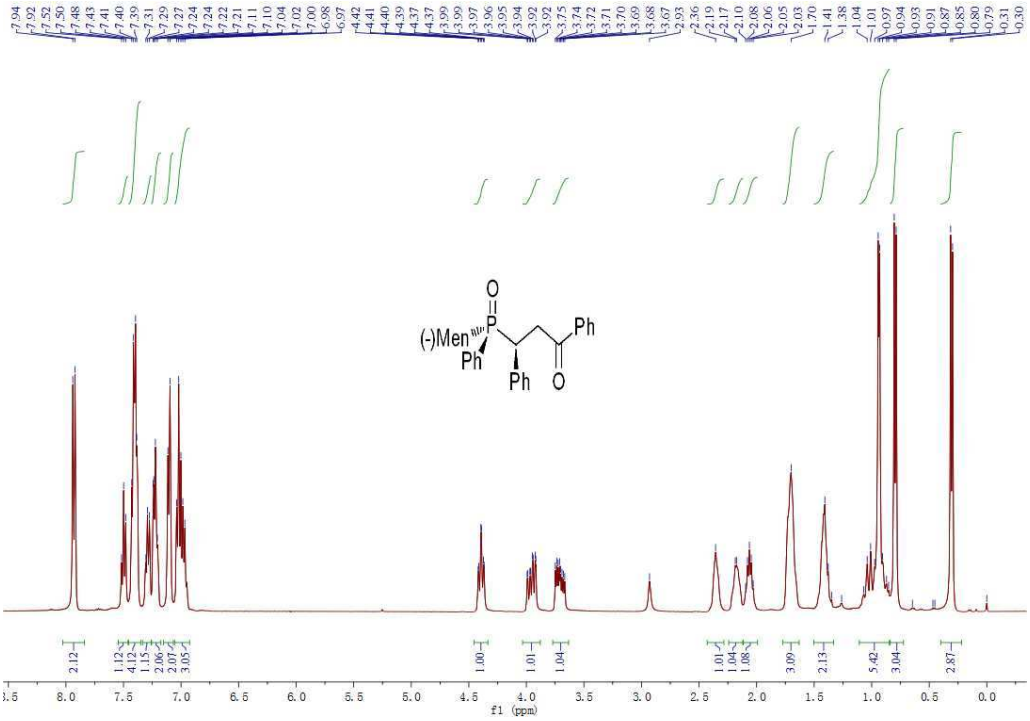
^{31}P-NMR spectroscopy of crude 3b/3b'=88:12



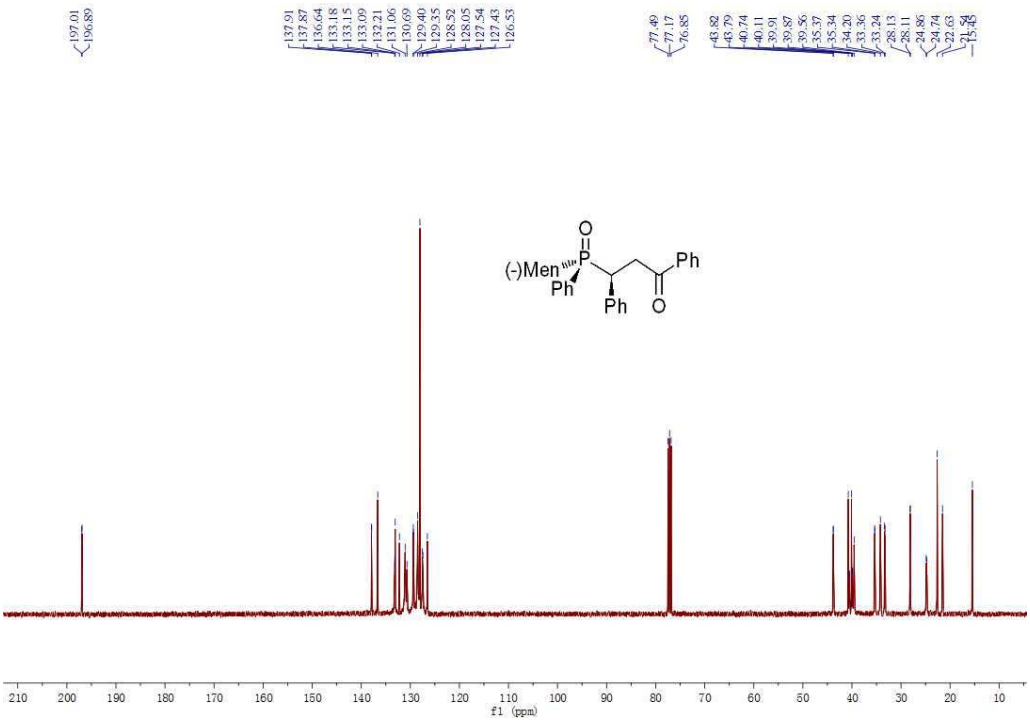
^{31}P-NMR spectroscopy of isolated 3b



^{1}H-NMR spectroscopy of isolated 3b

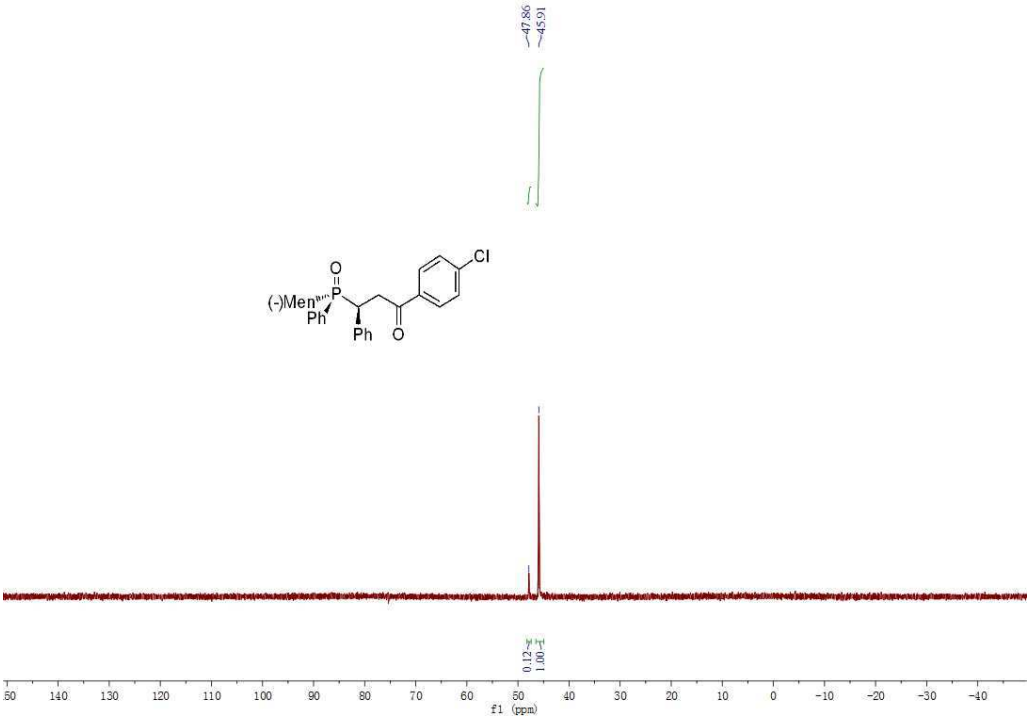


^{13}C-NMR spectroscopy of isolated 3b

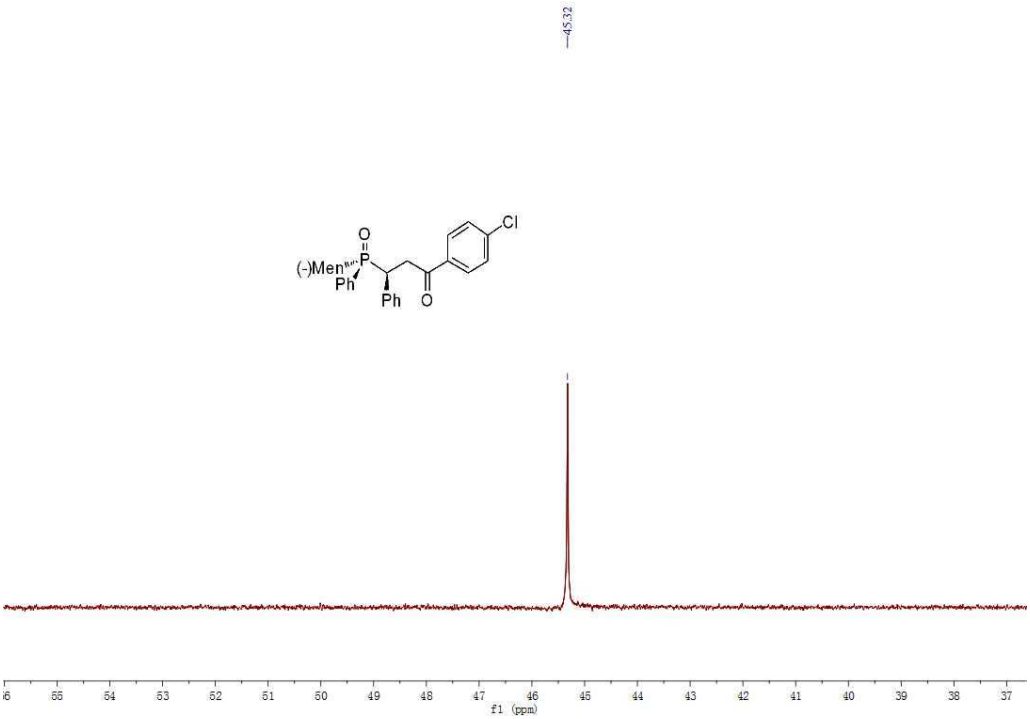


(S_P,S)-4-[(–)-Menthylphenylphosphoryl]-1-(*p*-chlorophenyl)-4-phenylpropan-2-one, 3c

^{31}P-NMR spectroscopy of crude 3c/3c'=89:11



^{31}P-NMR spectroscopy of isolated 3c



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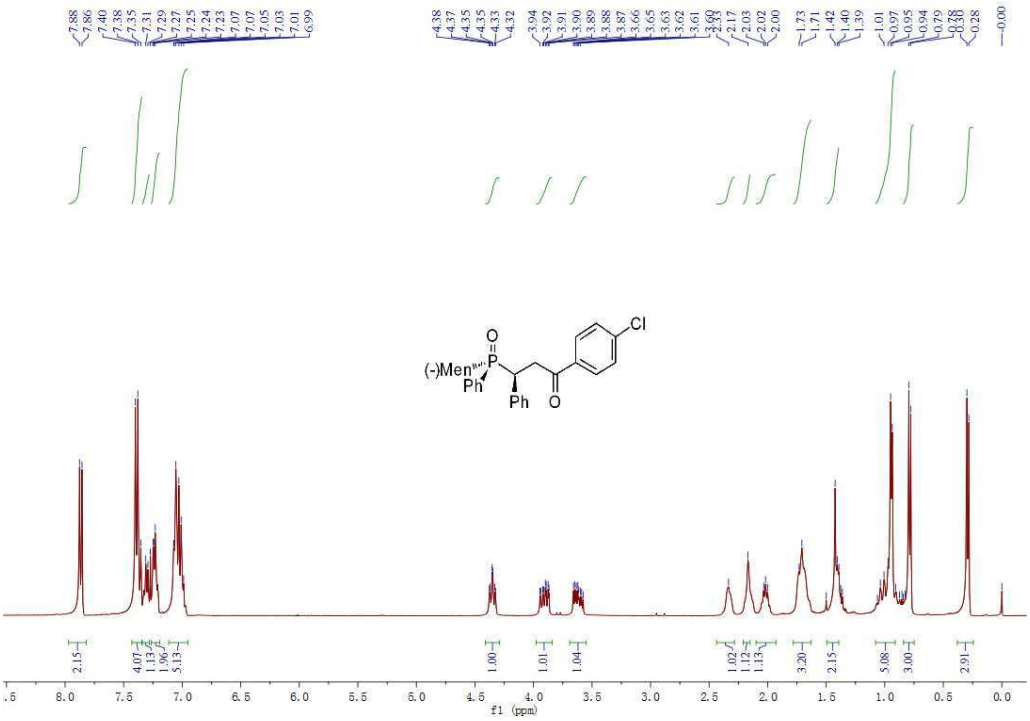
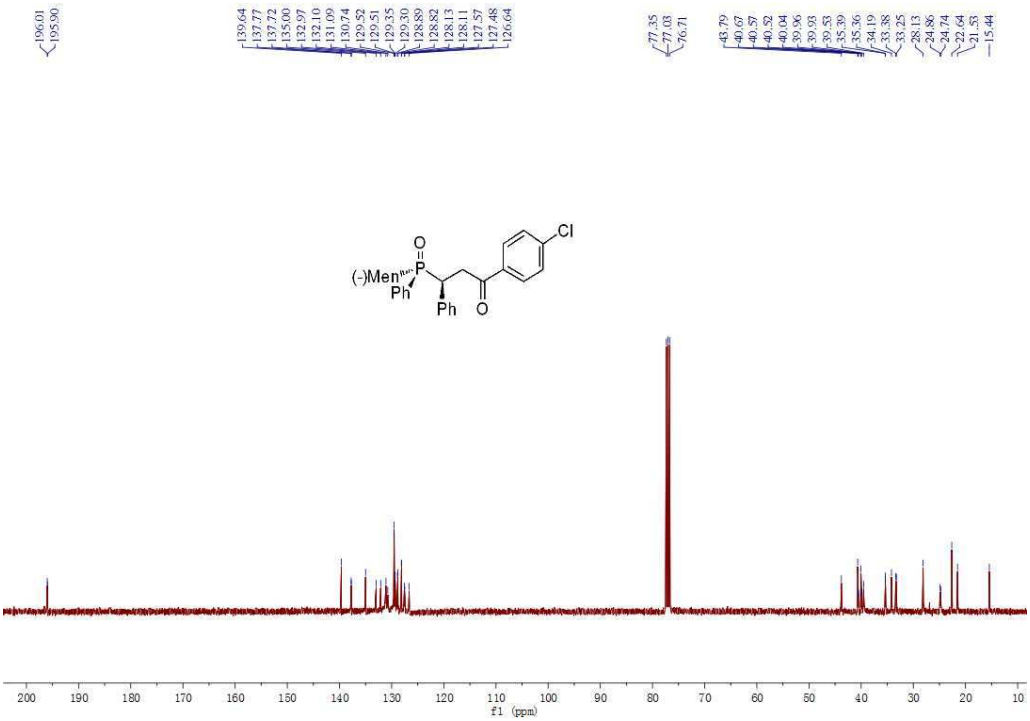
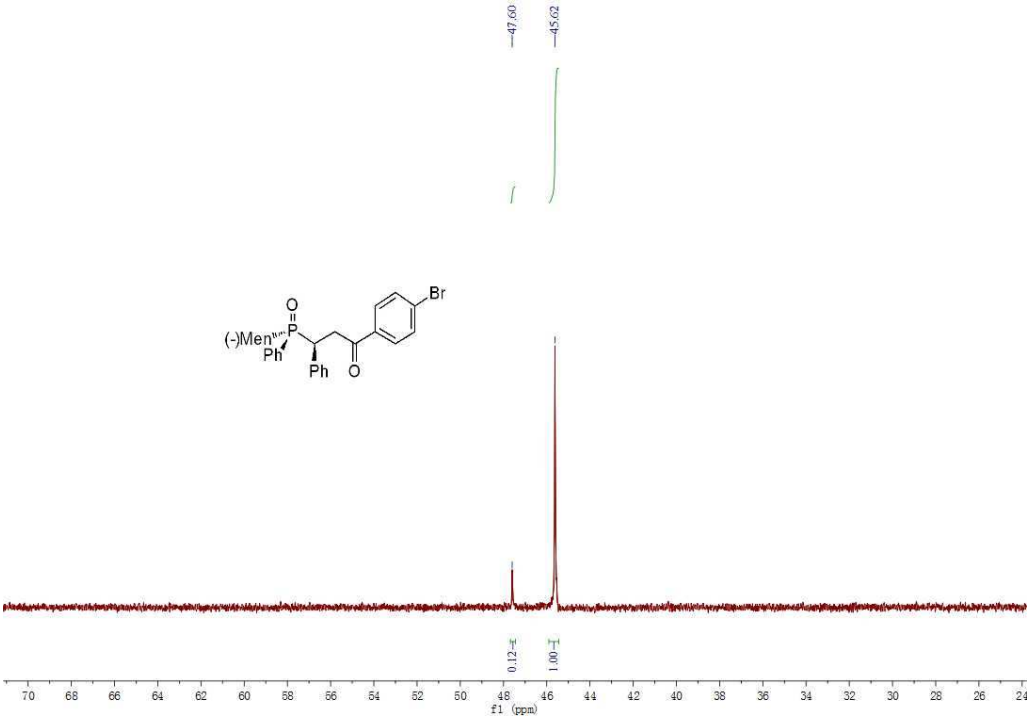


^{13}C-NMR spectroscopy of isolated 3c



(S_P,S)-4-[(–)-Menthylphenylphosphoryl]-1-(*p*-bromophenyl)-4-phenylpropan-2-one, 3d

^{31}P-NMR spectroscopy of crude 3d/3d'=89:11



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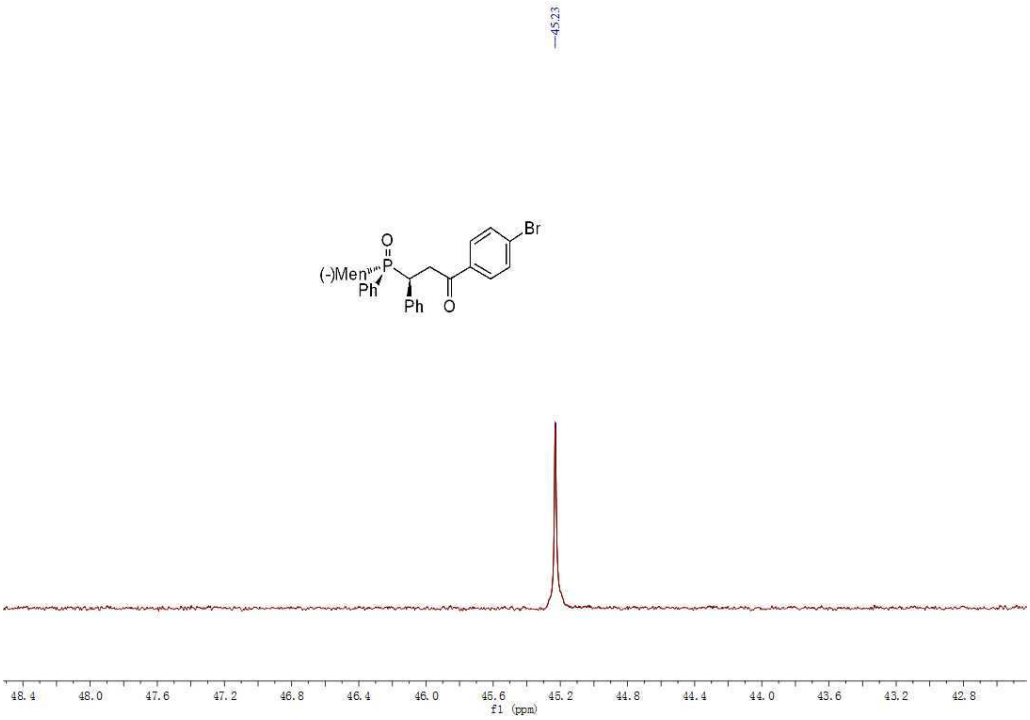

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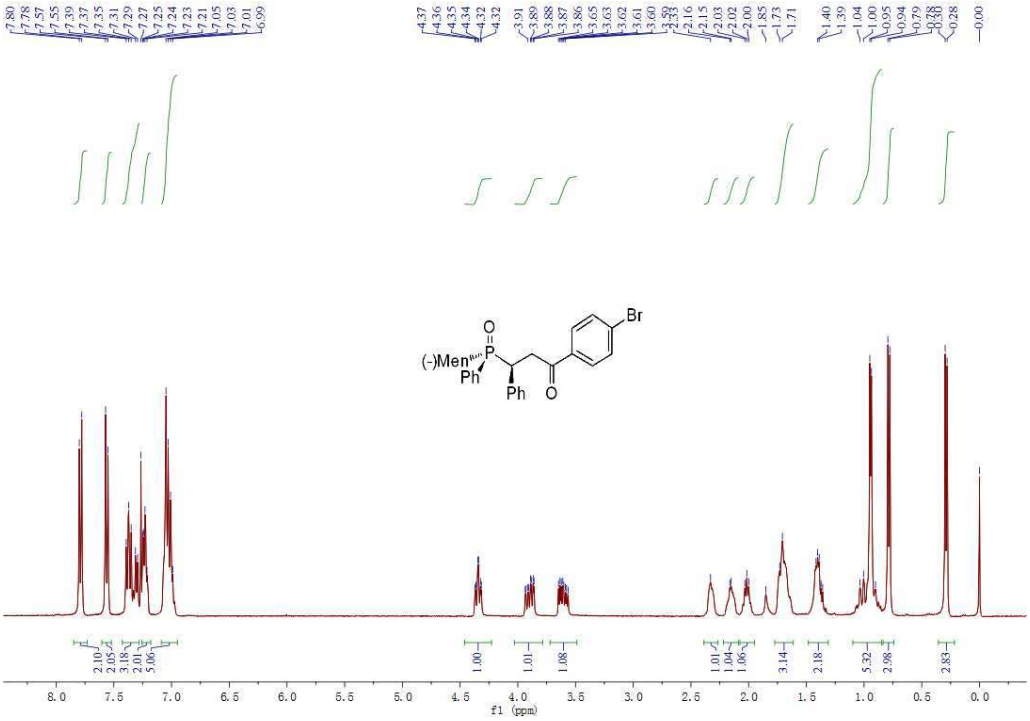

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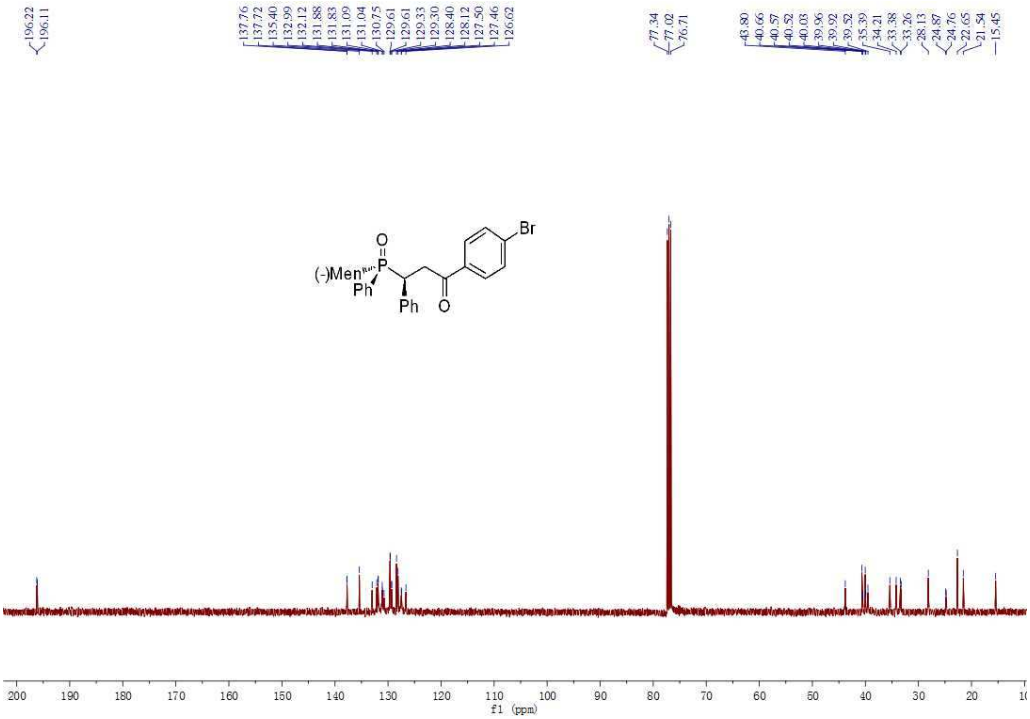
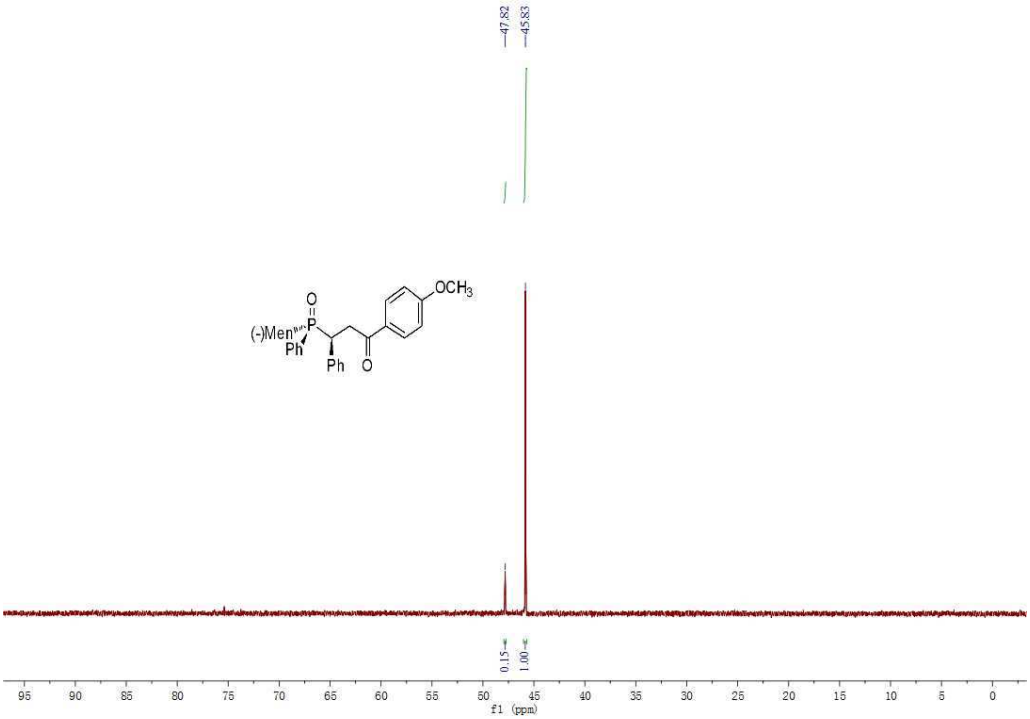


(S_P,S)-4-[(–)-Menthylphenylphosphoryl]-1-(*p*-methoxyphenyl)-4-phenylpropan-2-one, 3e

^{31}P-NMR spectroscopy of crude 3e/3e'=87:13



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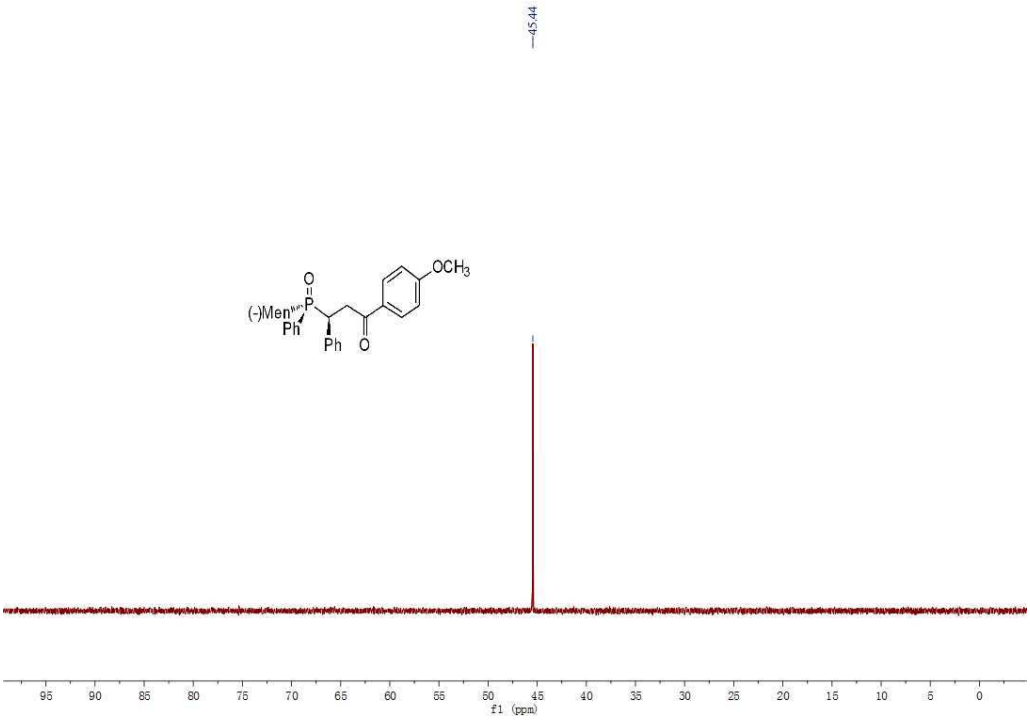
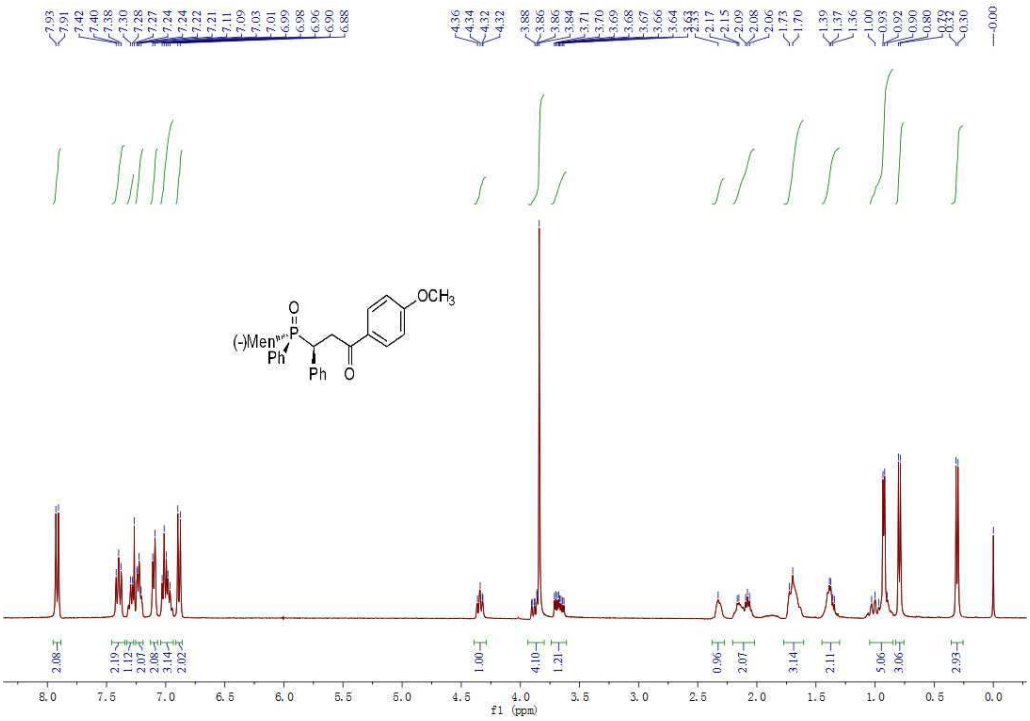
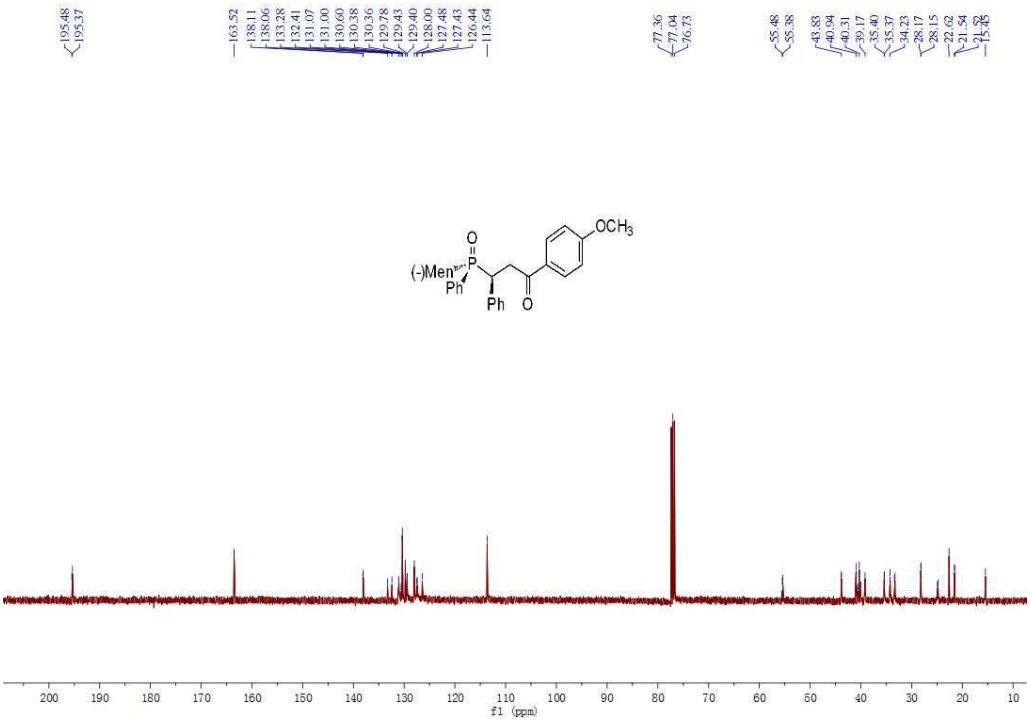


^{1}H-NMR spectroscopy of isolated 3e

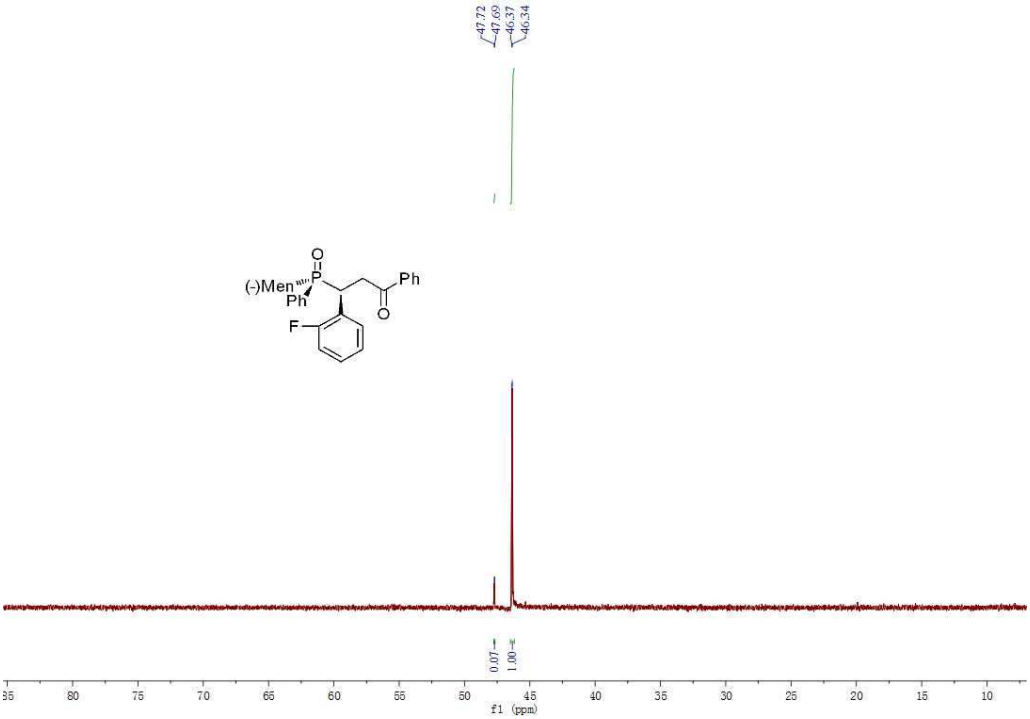


^{13}C-NMR spectroscopy of isolated 3e



(S_P,S)-4-[(–)-Menthylphenylphosphoryl]-1-phenyl-4-(*o*-fluorophenyl)propan-2-one, 3f

^{31}P-NMR spectroscopy of crude 3f/3f'=93:7



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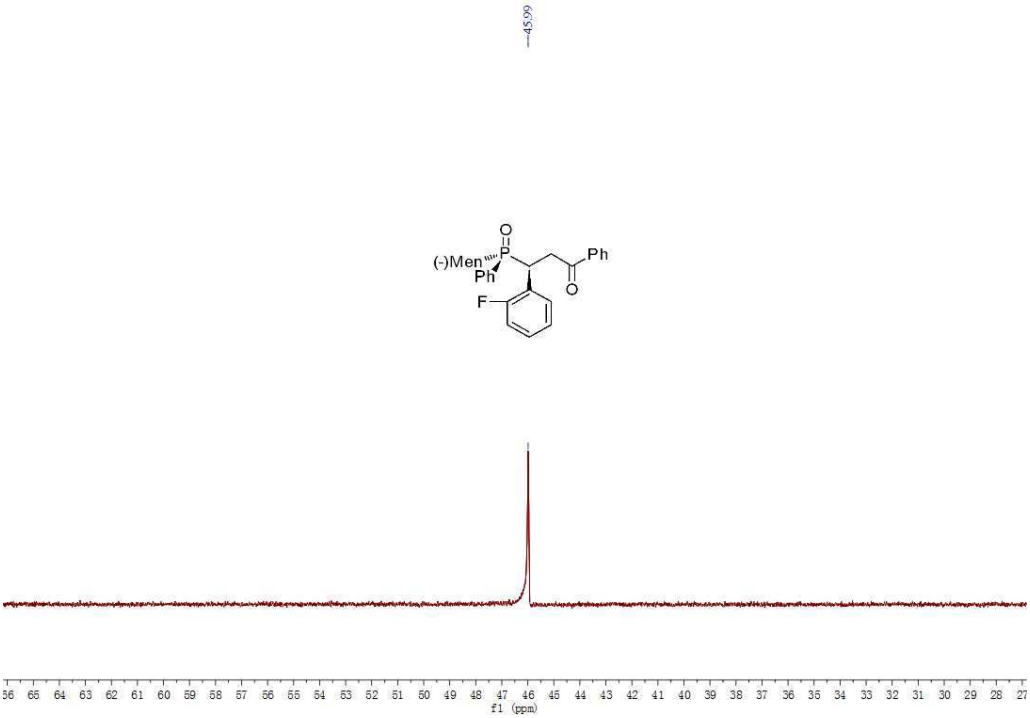

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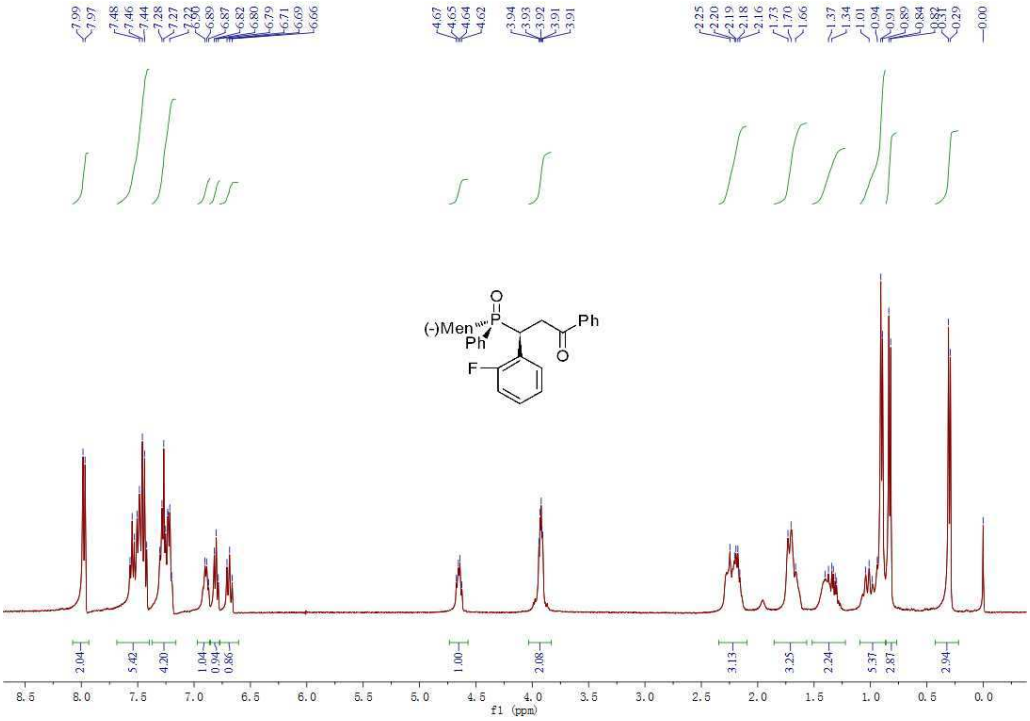

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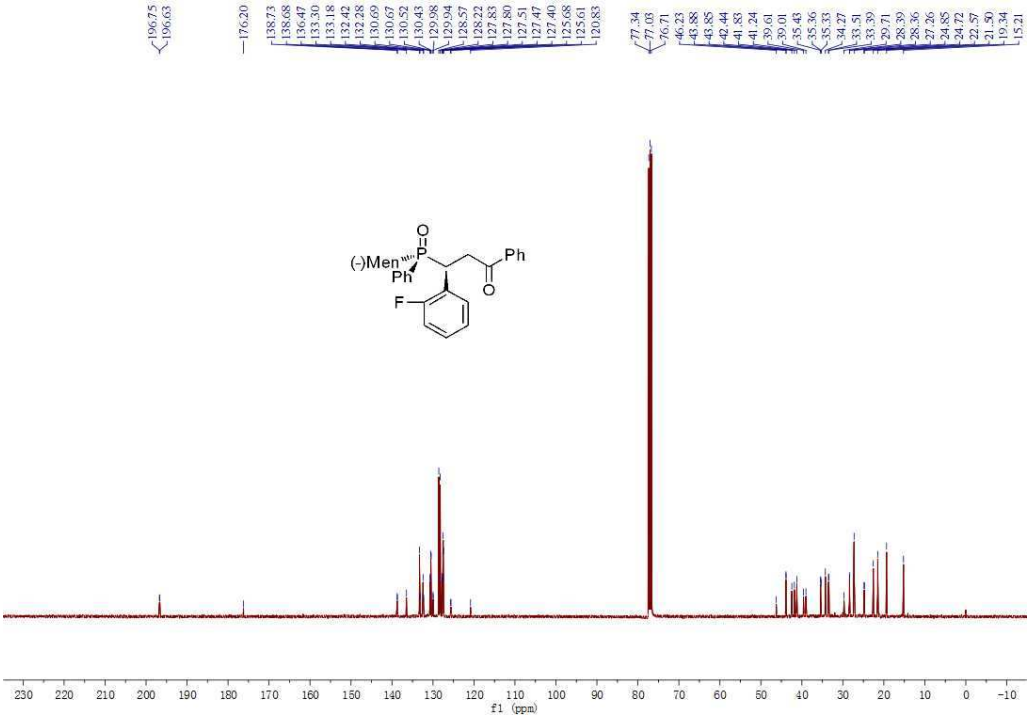
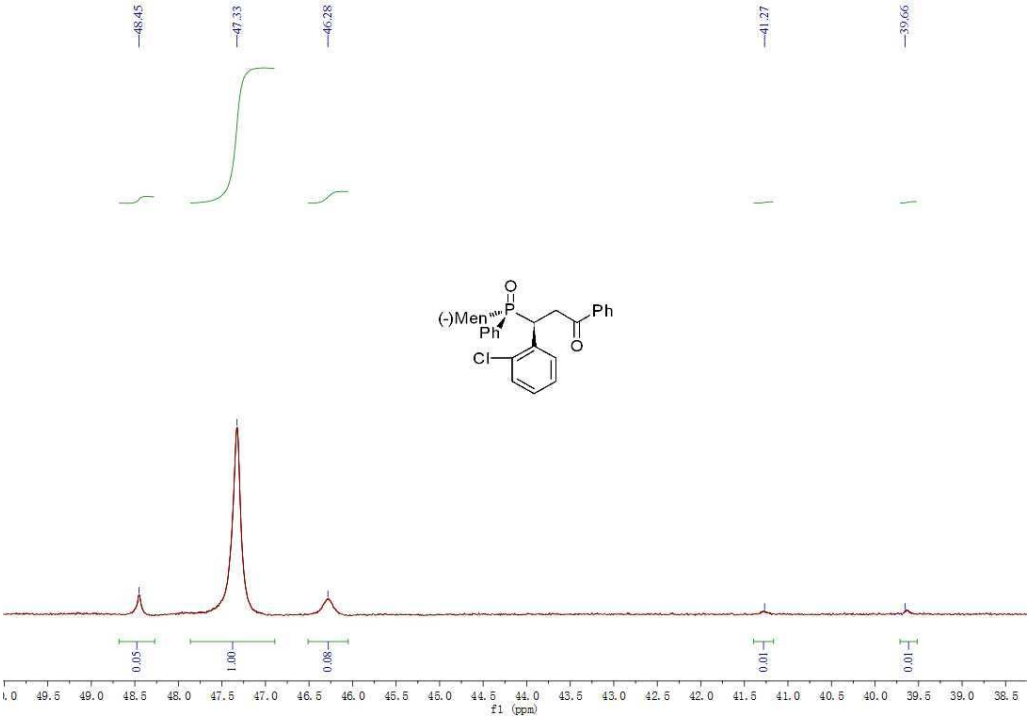


(S_P,*S*)-4-[(–)-Menthylphenylphosphoryl]-1-phenyl-4-(*o*-chlorophenyl)propan-2-one, 3g

^{31}P-NMR spectroscopy of crude 3g/3g'=95:5



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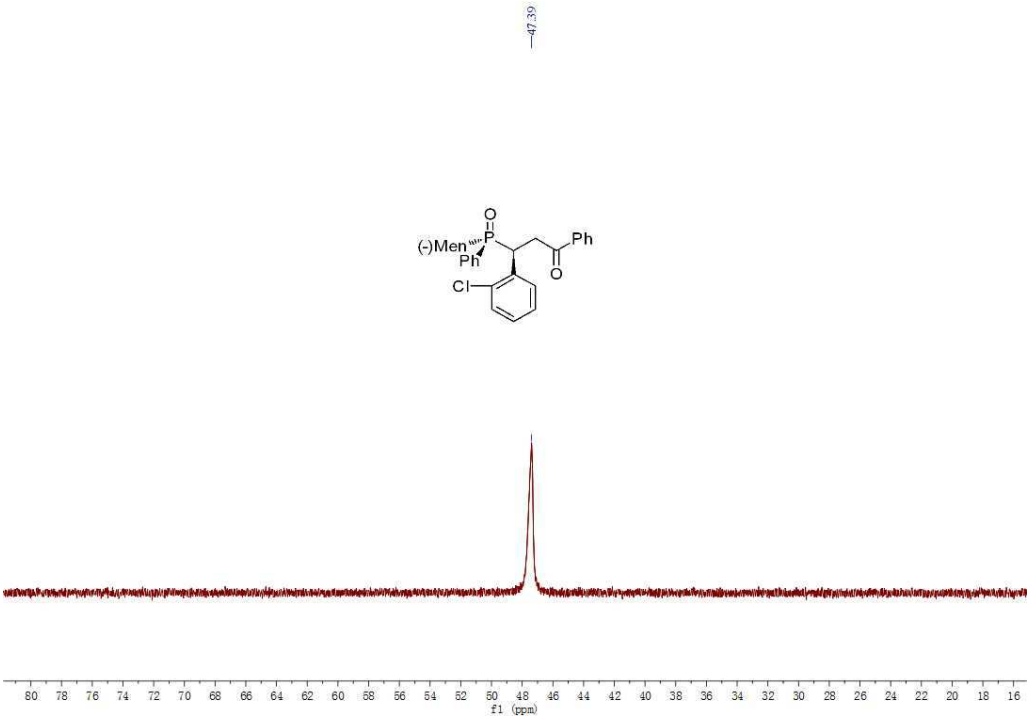
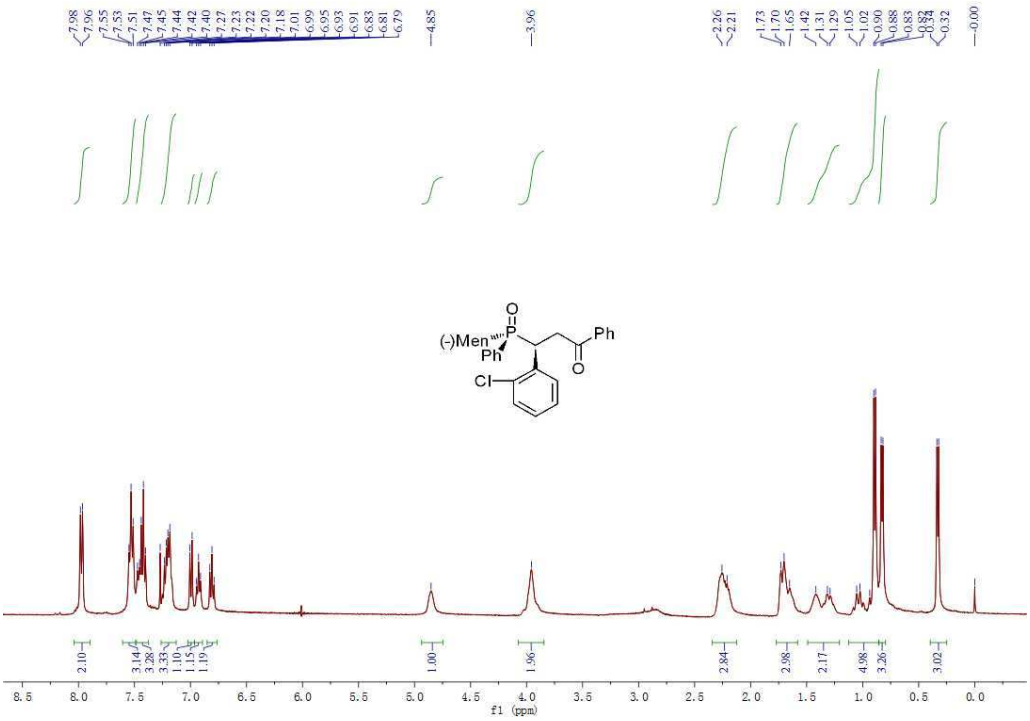
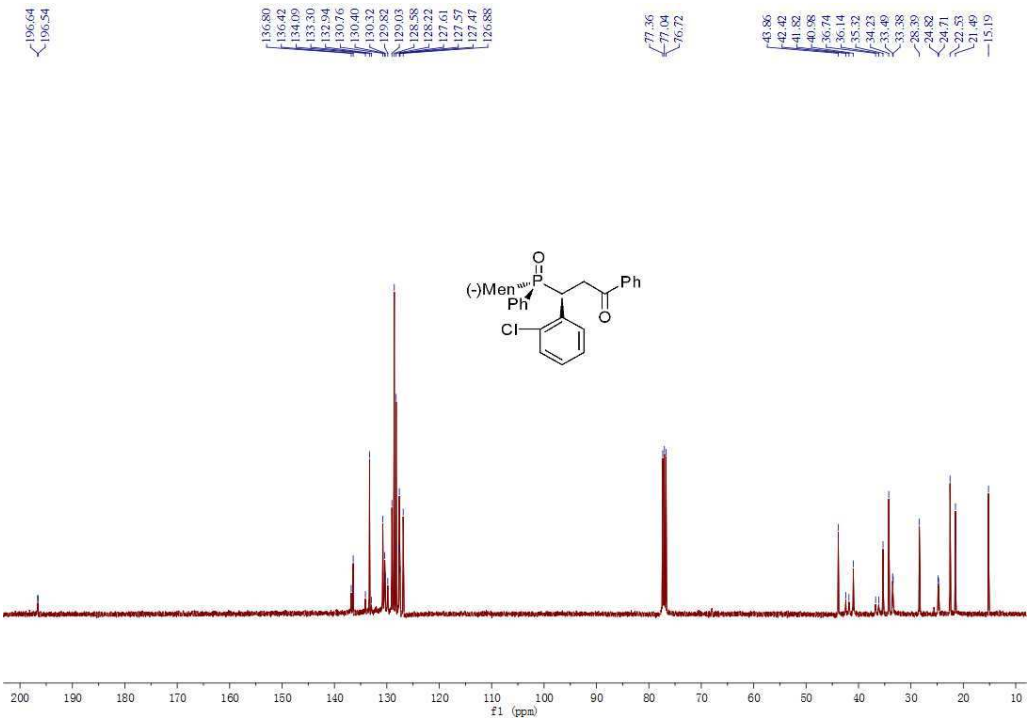


^{1}H-NMR spectroscopy of isolated 3g

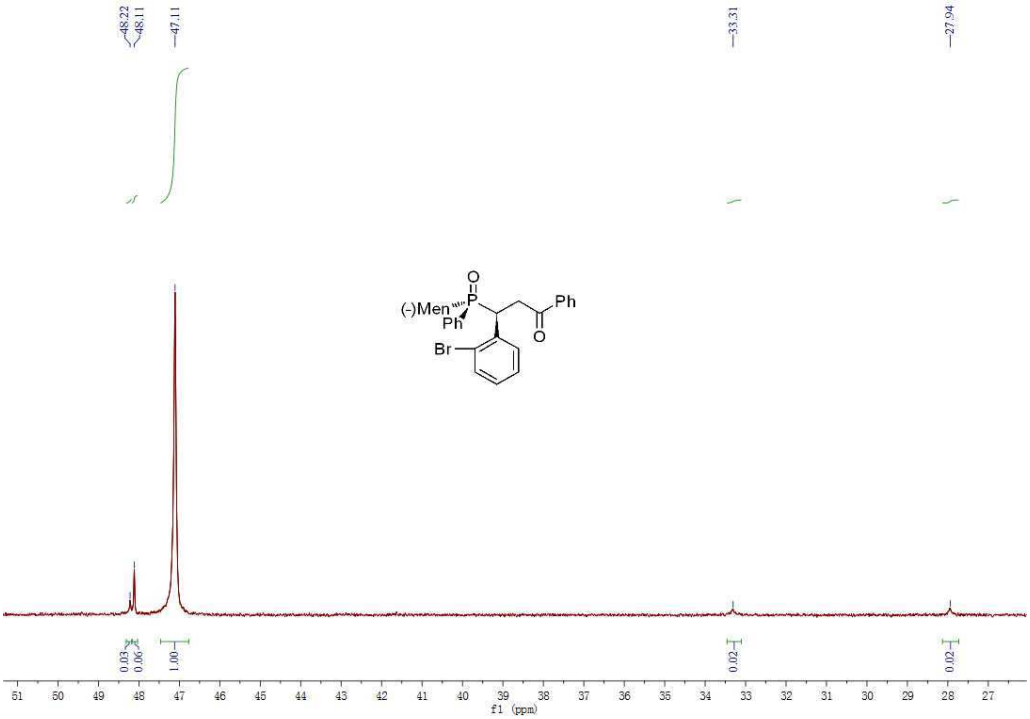


^{13}C-NMR spectroscopy of isolated 3g

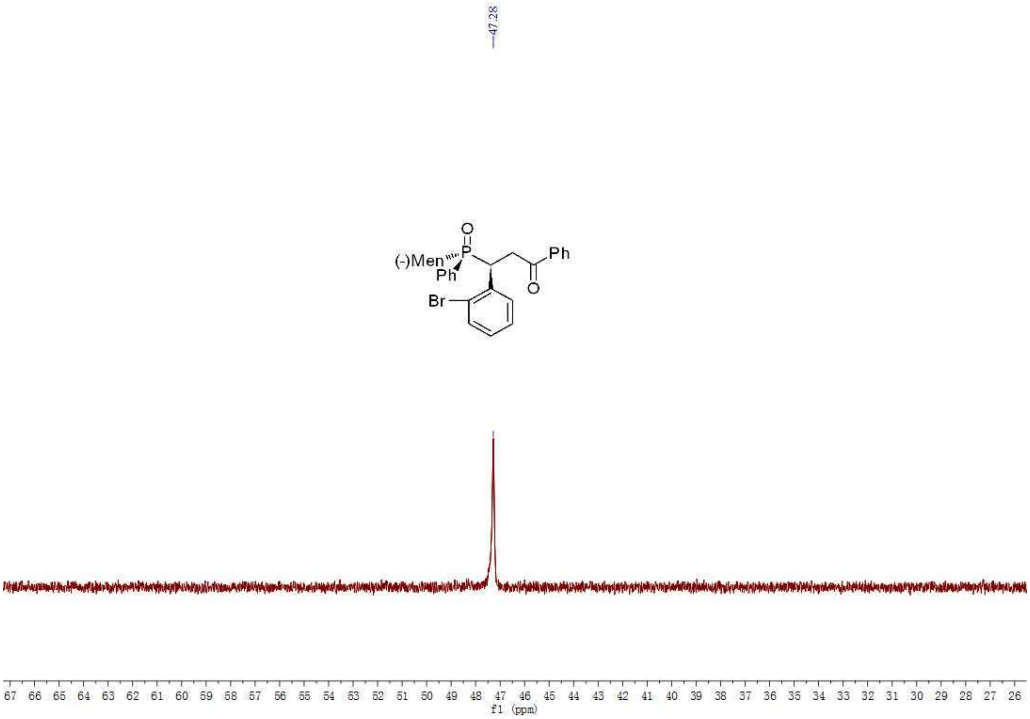


(S_P,S)-4-[(–)-Menthylphenylphosphoryl]-1-phenyl-4-(*o*-bromophenyl)propan-2-one, 3h

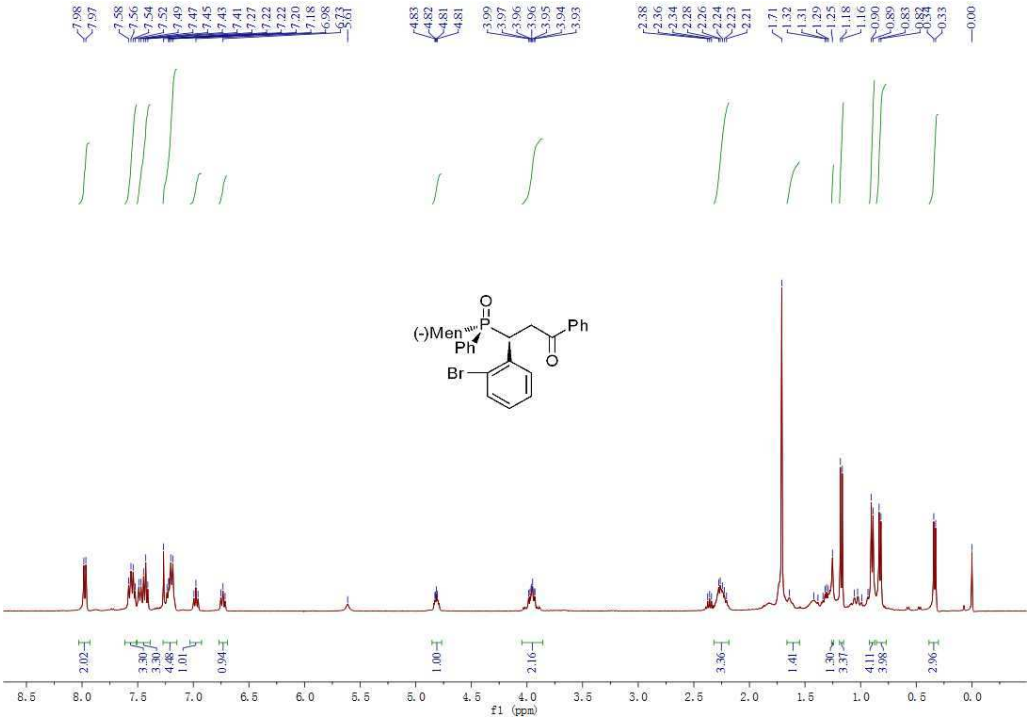
^{31}P-NMR spectroscopy of crude 3h/3h'=94:6



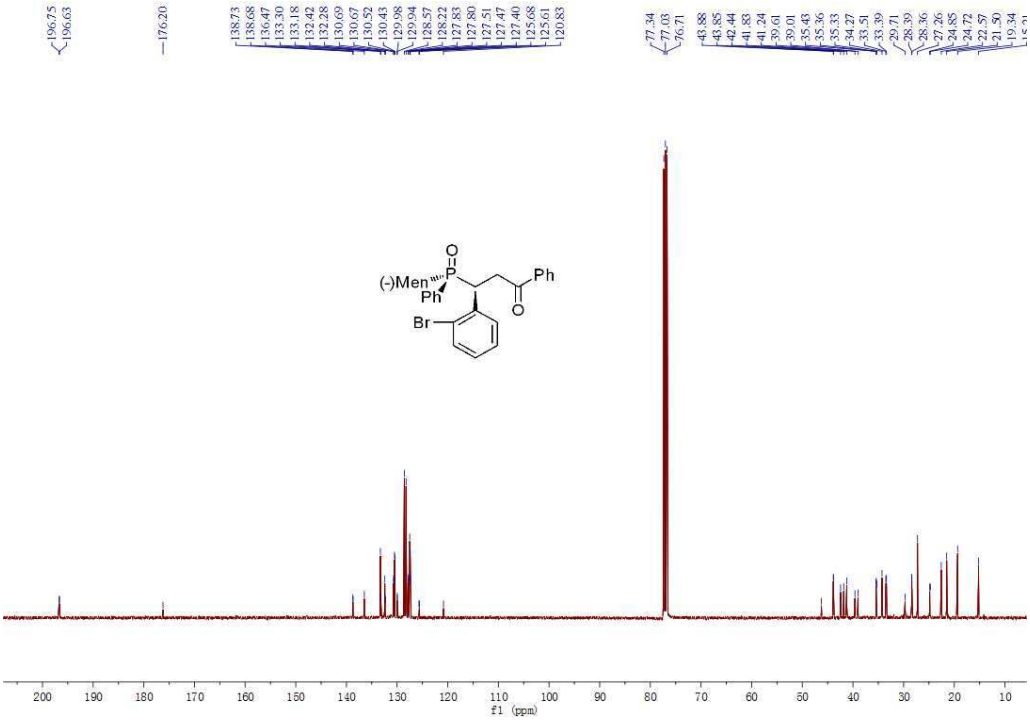
^{31}P-NMR spectroscopy of isolated 3h



^{1}H-NMR spectroscopy of isolated 3h

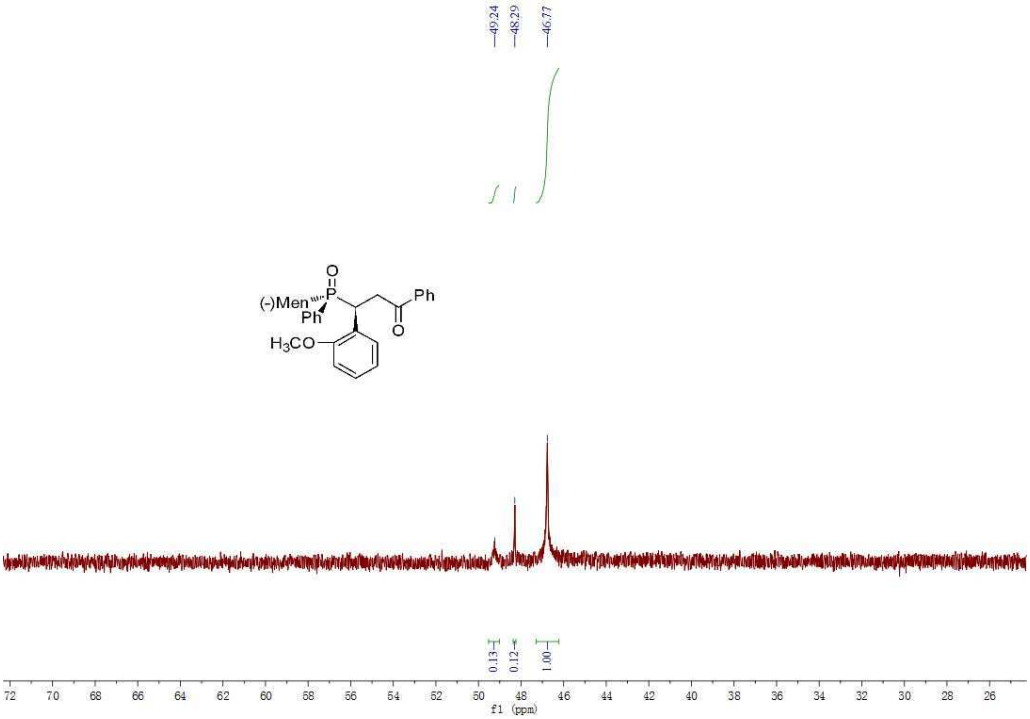


^{13}C-NMR spectroscopy of isolated 3h

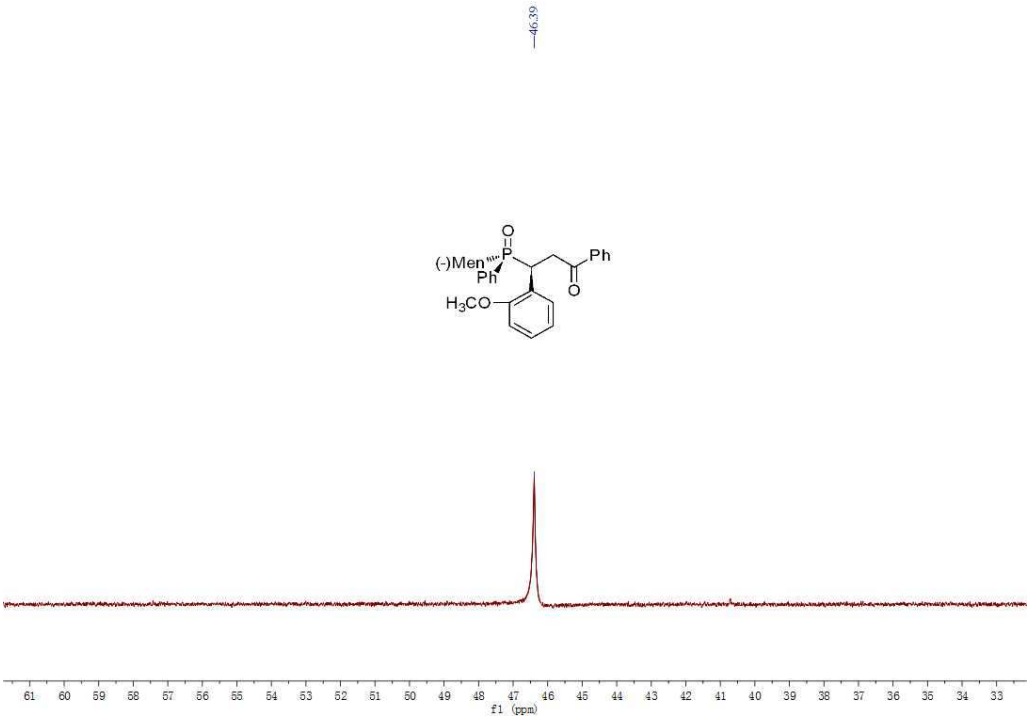


(S_P,S)-4-[(–)-Menthylphenylphosphoryl]-1-phenyl-4-(*o*-methoxyphenyl)propan-2-one, 3i

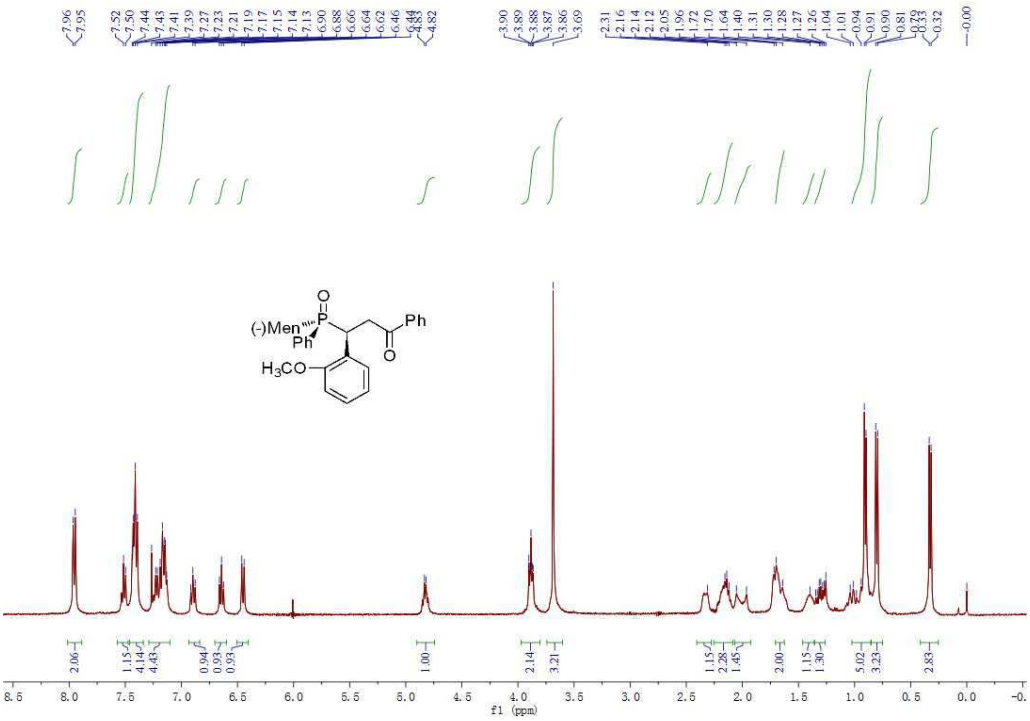
^{31}P-NMR spectroscopy of crude 3i/3i'=89:11



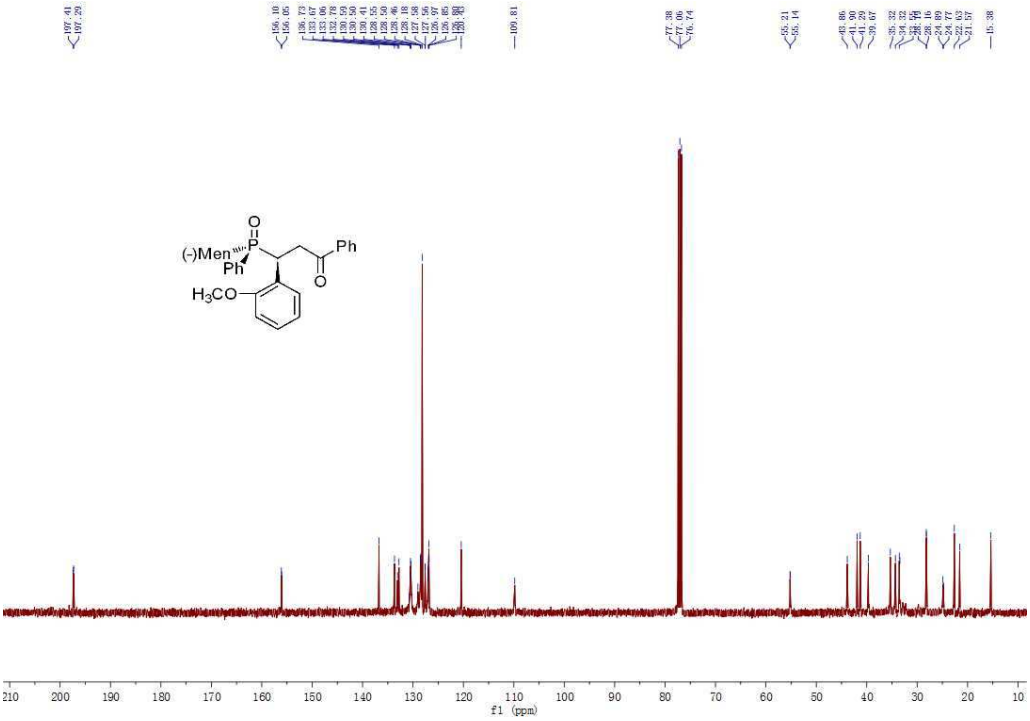
^{31}P-NMR spectroscopy of isolated 3i



^{1}H-NMR spectroscopy of isolated 3i

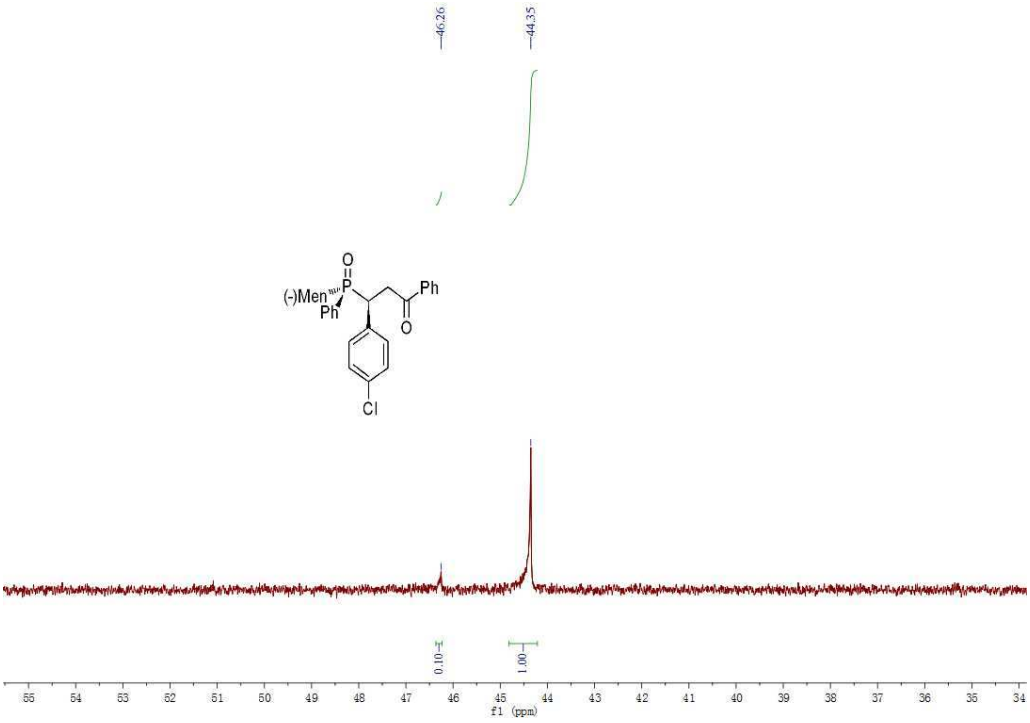


^{13}C-NMR spectroscopy of isolated 3i

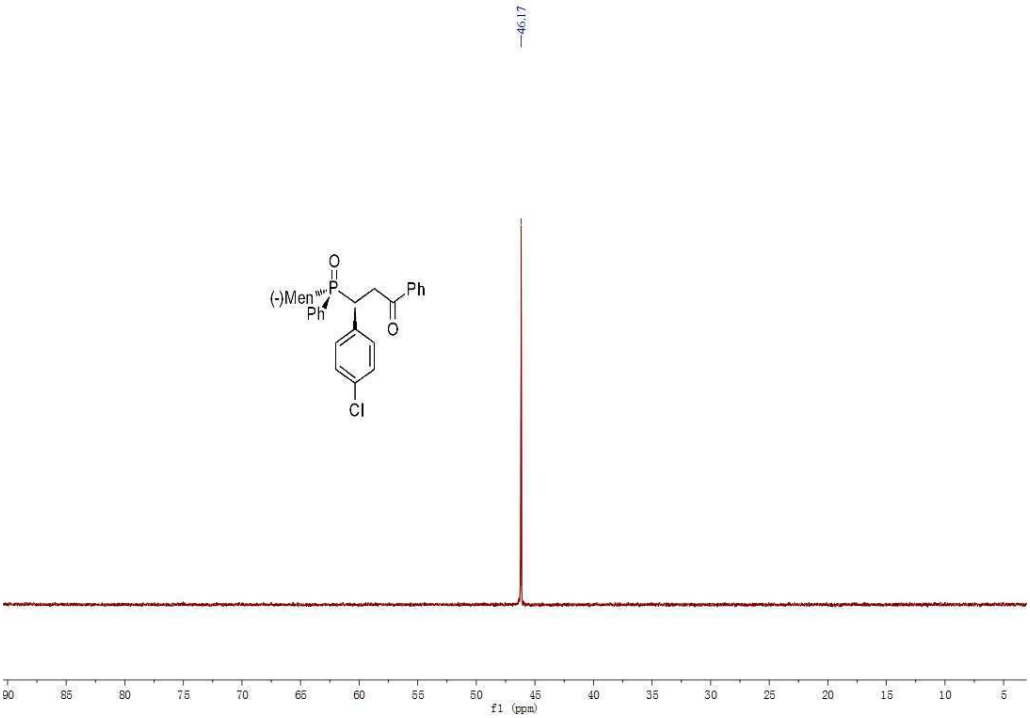


(S_P,S)-4-[(–)-Menthylphenylphosphoryl]-1-phenyl-4-(*p*-chlorophenyl)propan-2-one, 3j

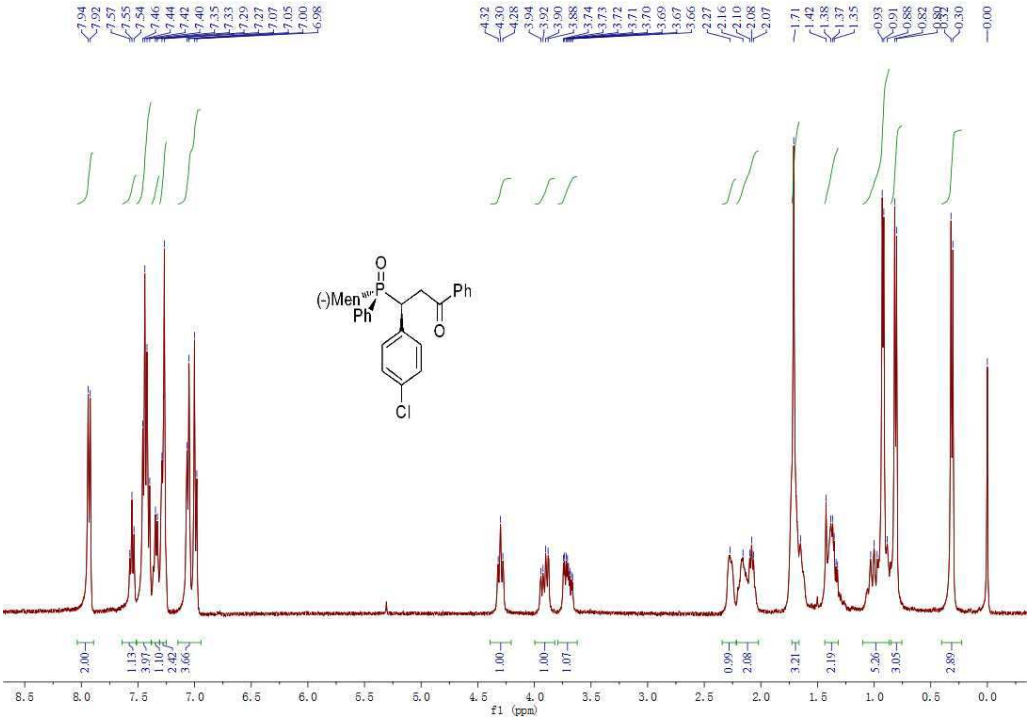
^{31}P-NMR spectroscopy of crude 3j/3j'=91:9



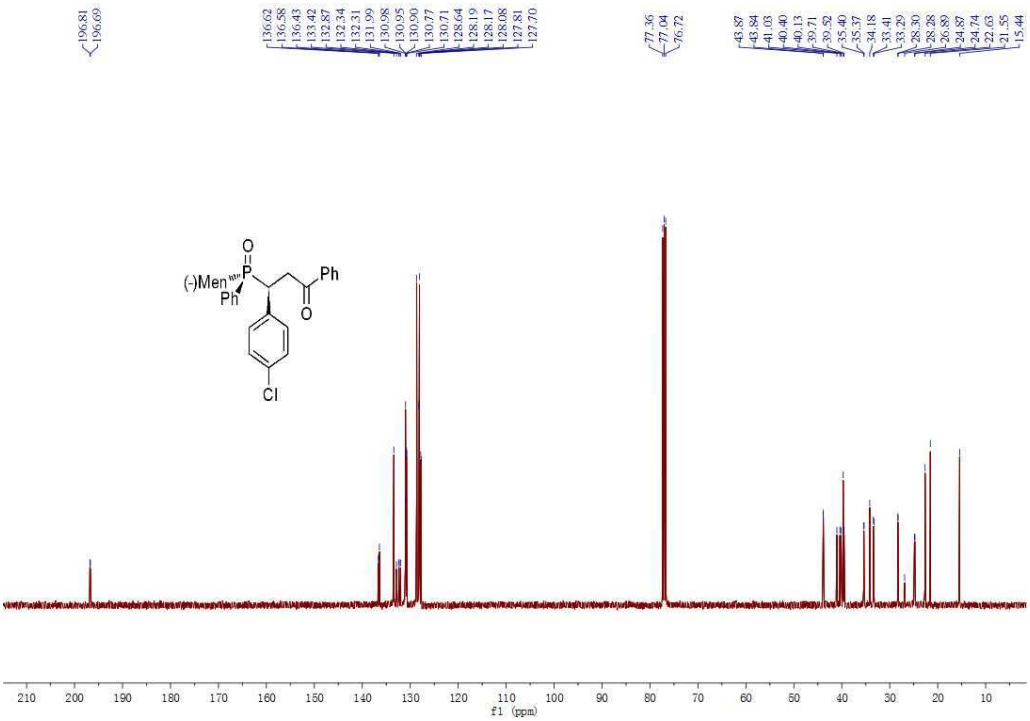
^{31}P-NMR spectroscopy of isolated 3j



^{1}H-NMR spectroscopy of isolated 3j

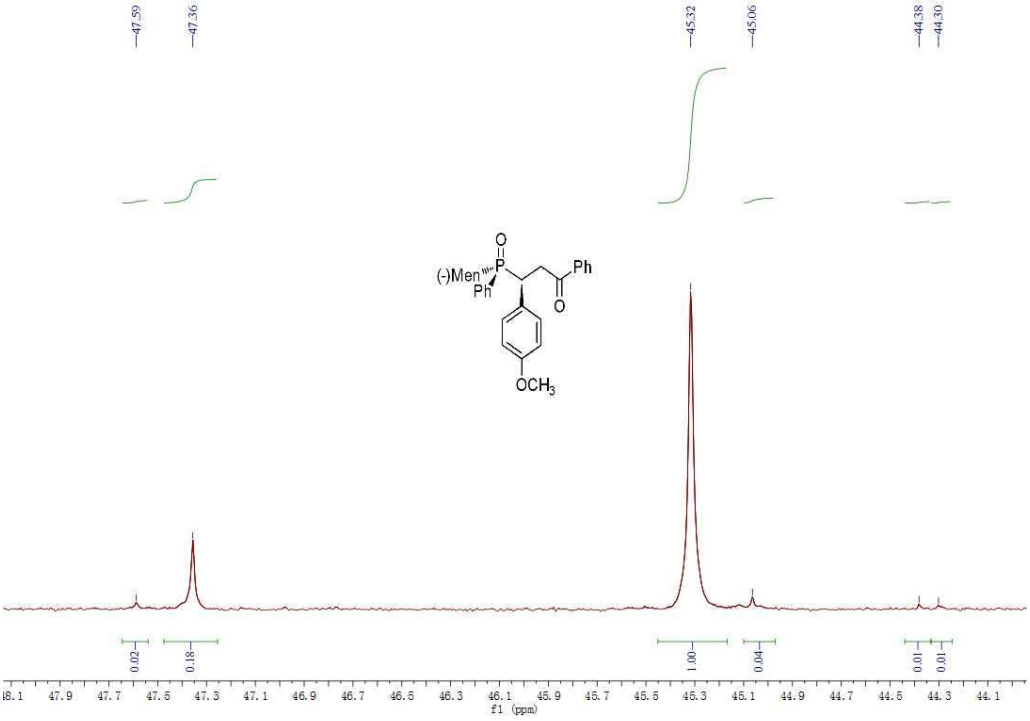


^{13}C-NMR spectroscopy of isolated 3j

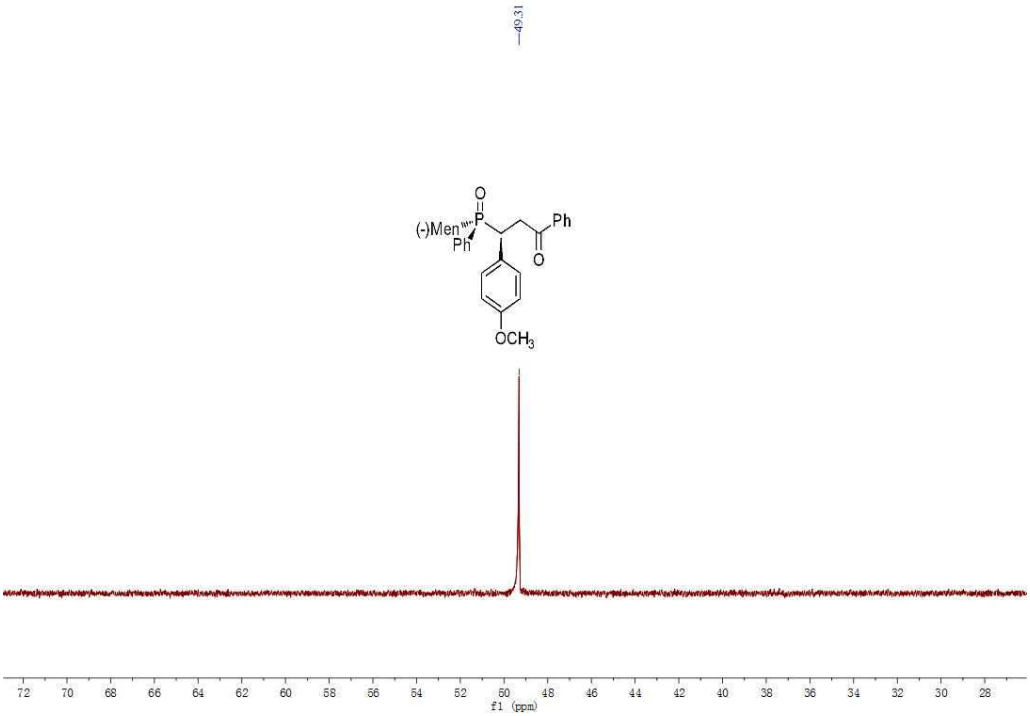


(S_P,S)-4-[(–)-Menthylphenylphosphoryl]-1-phenyl-4-(*p*-methoxyphenyl)propan-2-one, 3k

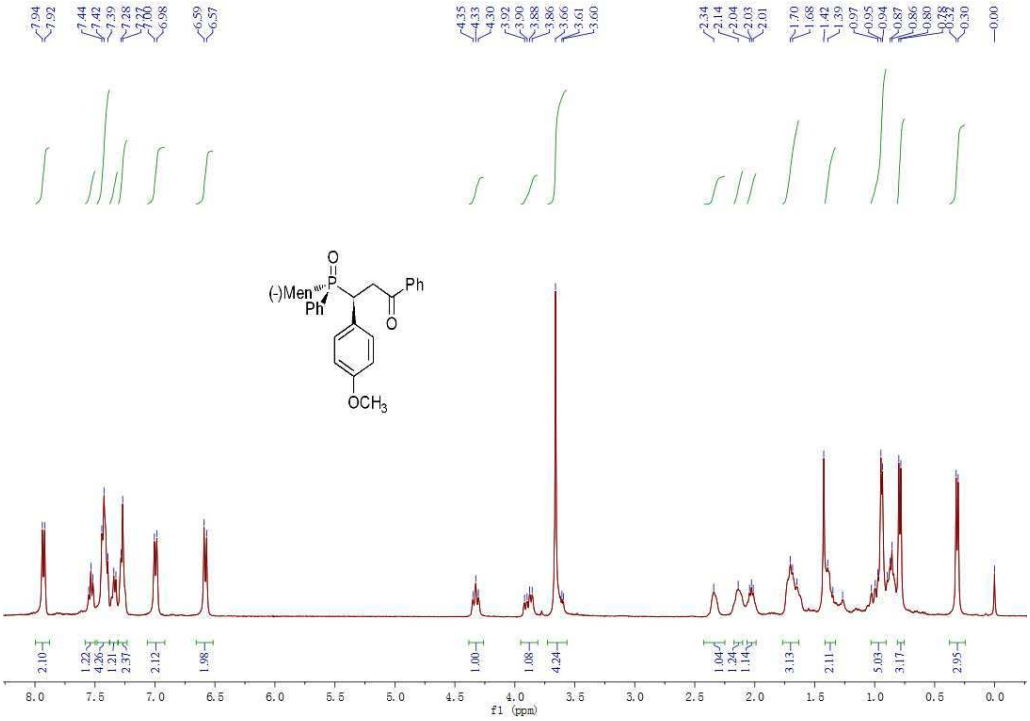
^{31}P-NMR spectroscopy of crude 3k/3k'=85:15



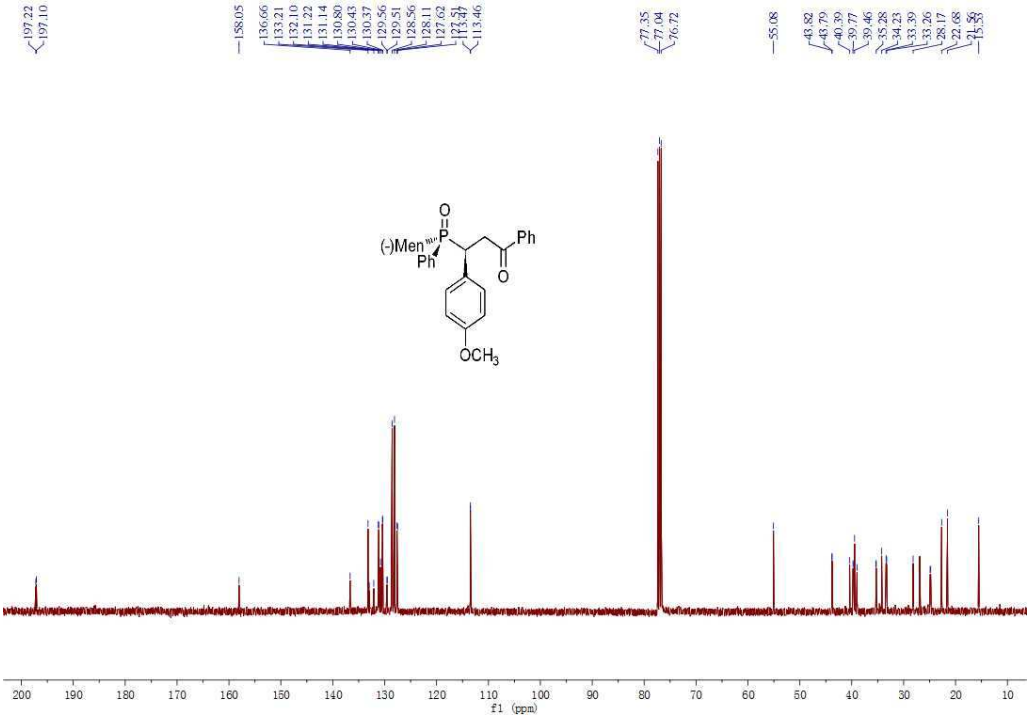
^{31}P-NMR spectroscopy of isolated 3k



^{1}H-NMR spectroscopy of isolated 3k

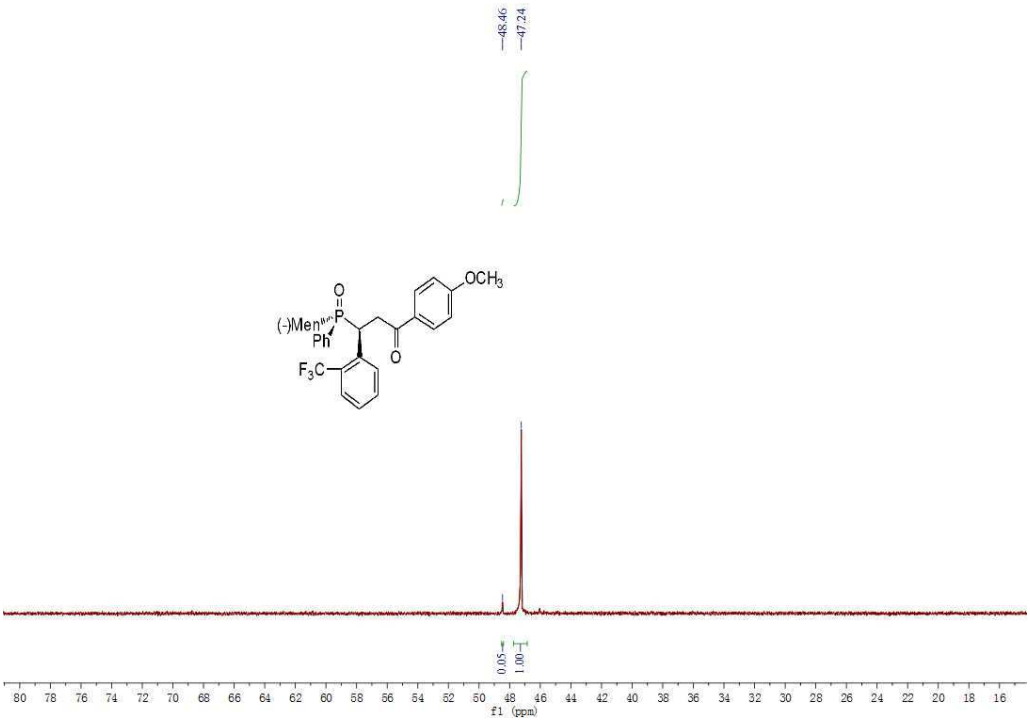


^{13}C-NMR spectroscopy of isolated 3k

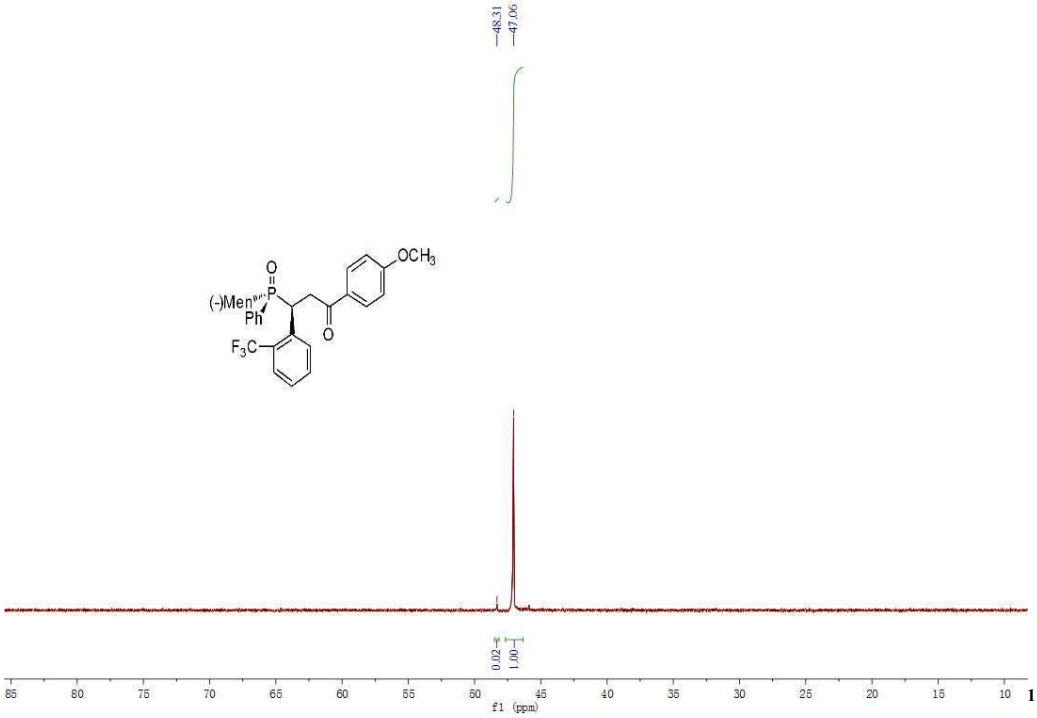


(S_P,S)-4-[(–)-Menthylphenylphosphoryl]-1-(*p*-methoxyphenyl)-4-(*o*-trifluoromethylphenyl)propan-2-one, 3l

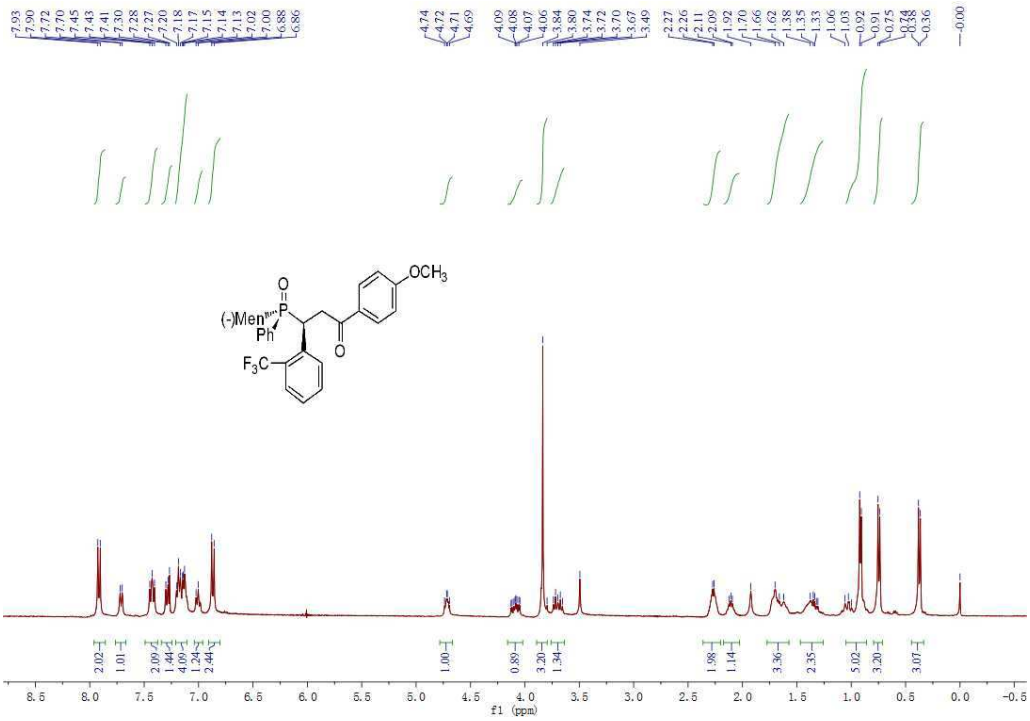
^{31}P-NMR spectroscopy of crude 3l/3l'=95:5



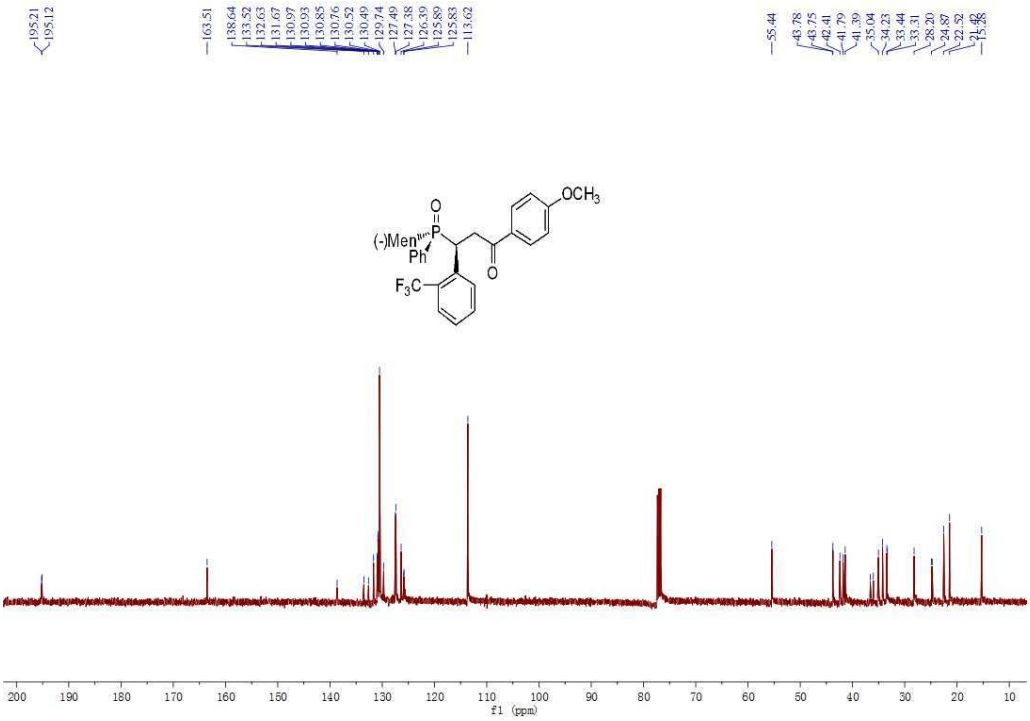
^{31}P-NMR spectroscopy of isolated 3l/3l'=98:2



H-NMR spectroscopy of isolated 3l/3l'=98:2

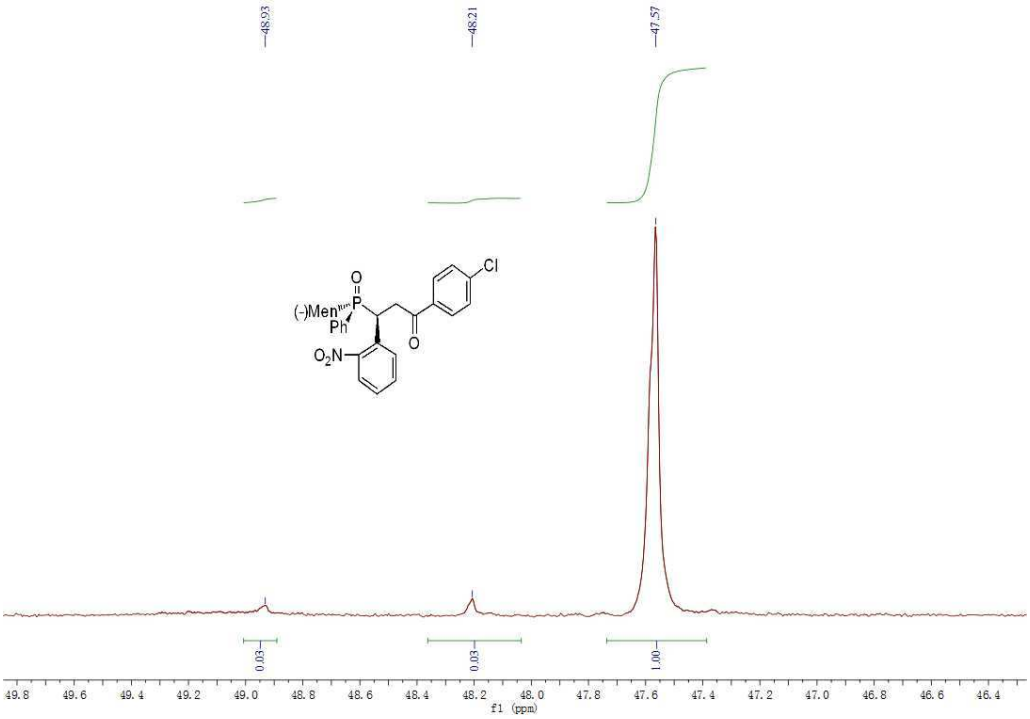


^{13}C-NMR spectroscopy of isolated 3l/3l'=98:2

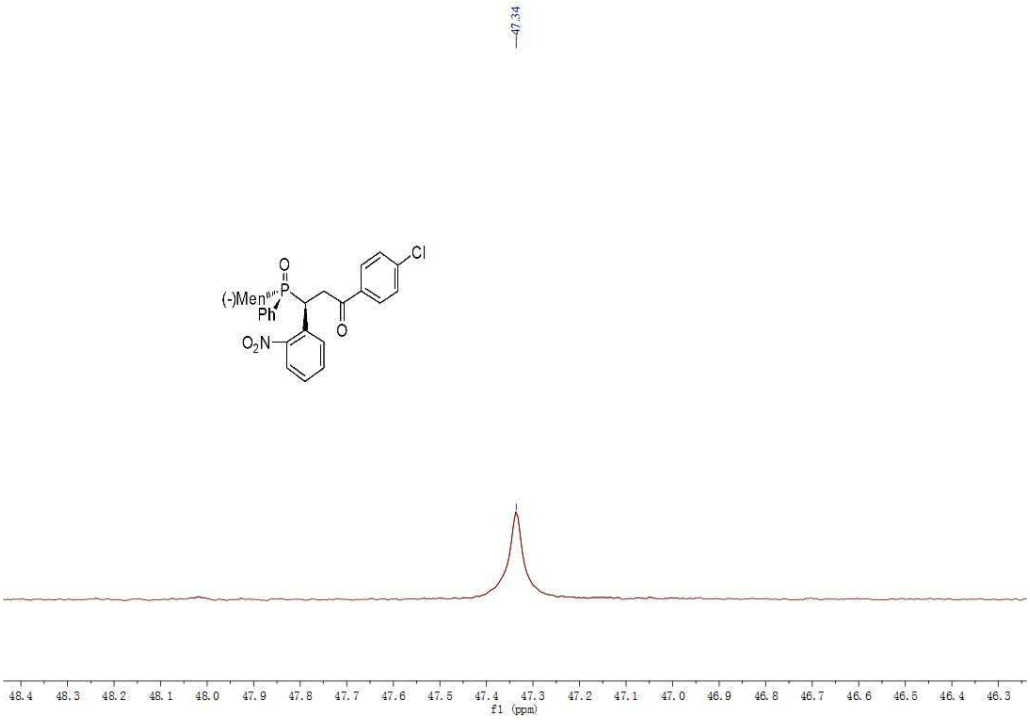


(S_P,S)-4-[(–)-Menthylphenylphosphoryl]-1-(*p*-chlorophenyl)-4-(*o*-nitrophenyl)propan-2-one, 3m

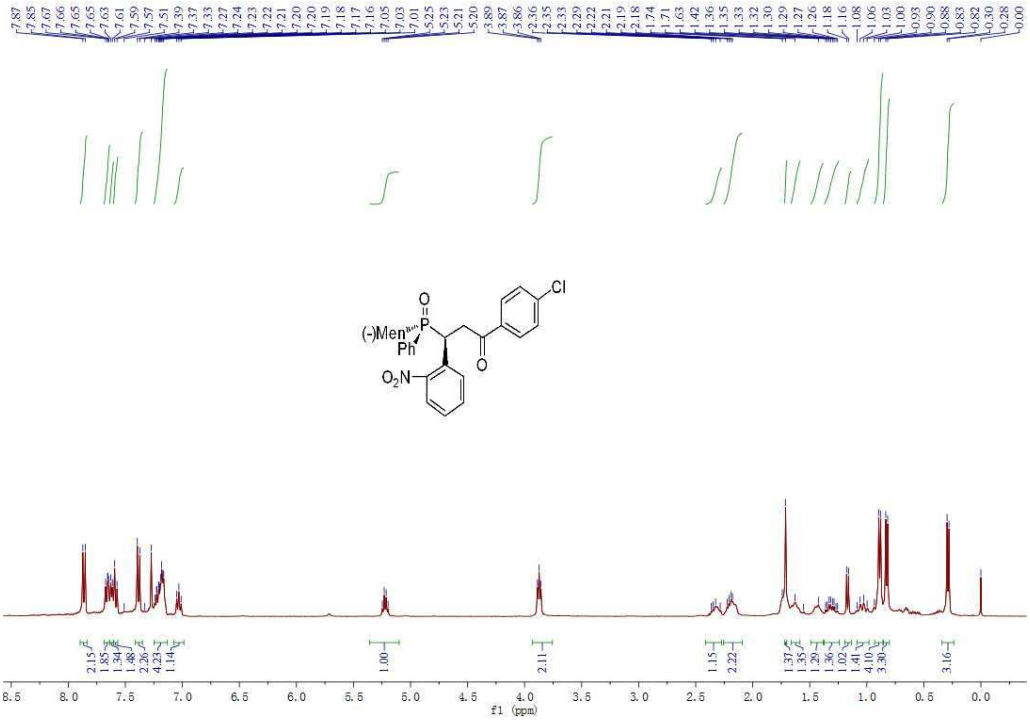
^{31}P-NMR spectroscopy of crude 3m/3m'=97:3



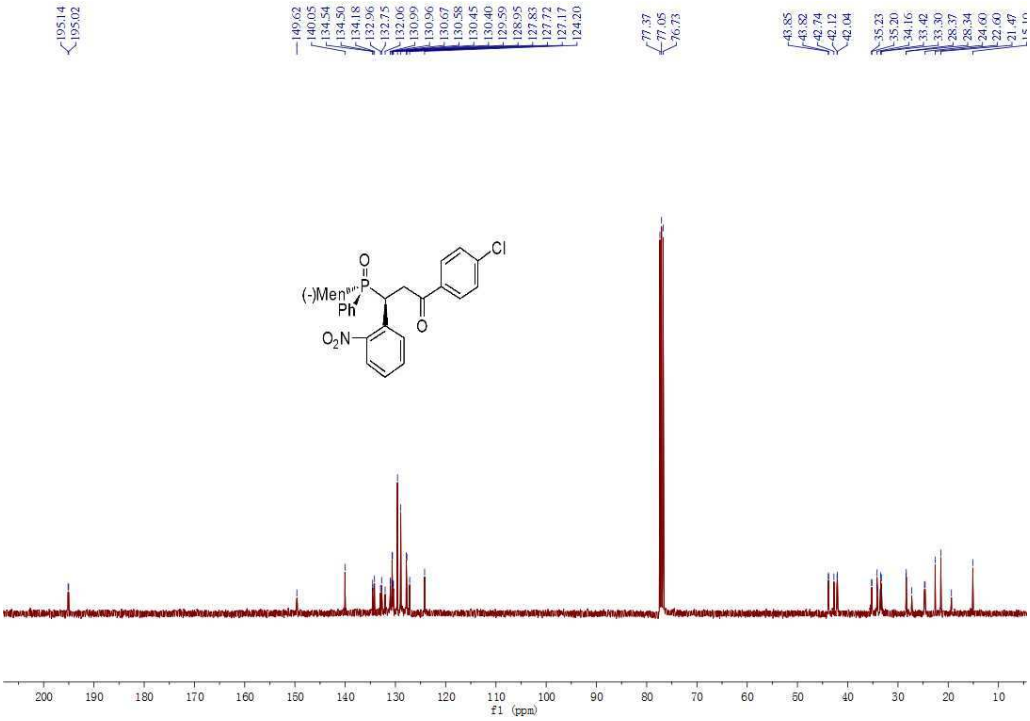
^{31}P-NMR spectroscopy of isolated 3m



^{1}H-NMR spectroscopy of isolated 3m

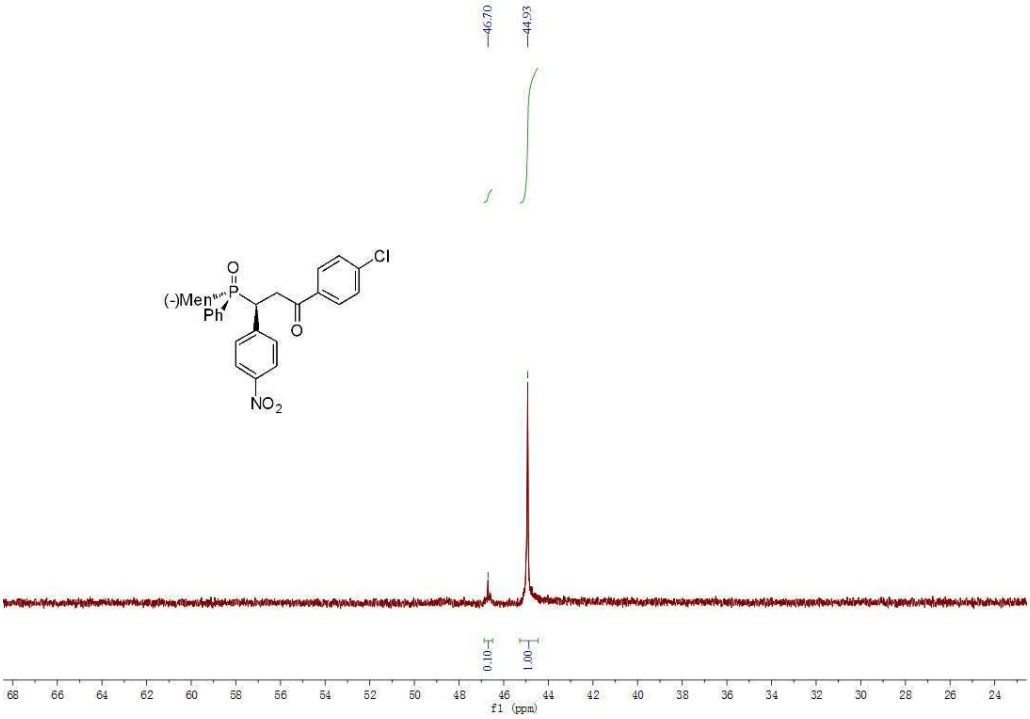


^{13}C-NMR spectroscopy of isolated 3m

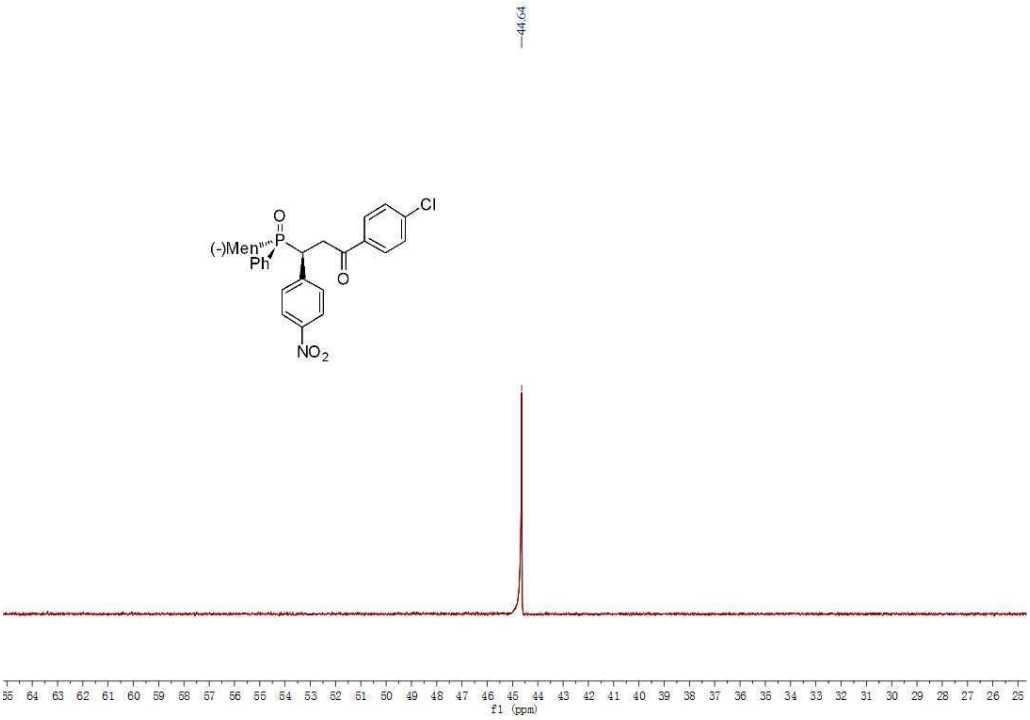


(S_P,S)-4-[(–)-Menthylphenylphosphoryl]-1-(*p*-chlorophenyl)-4-(*p*-nitrophenyl)propan-2-one, 3n

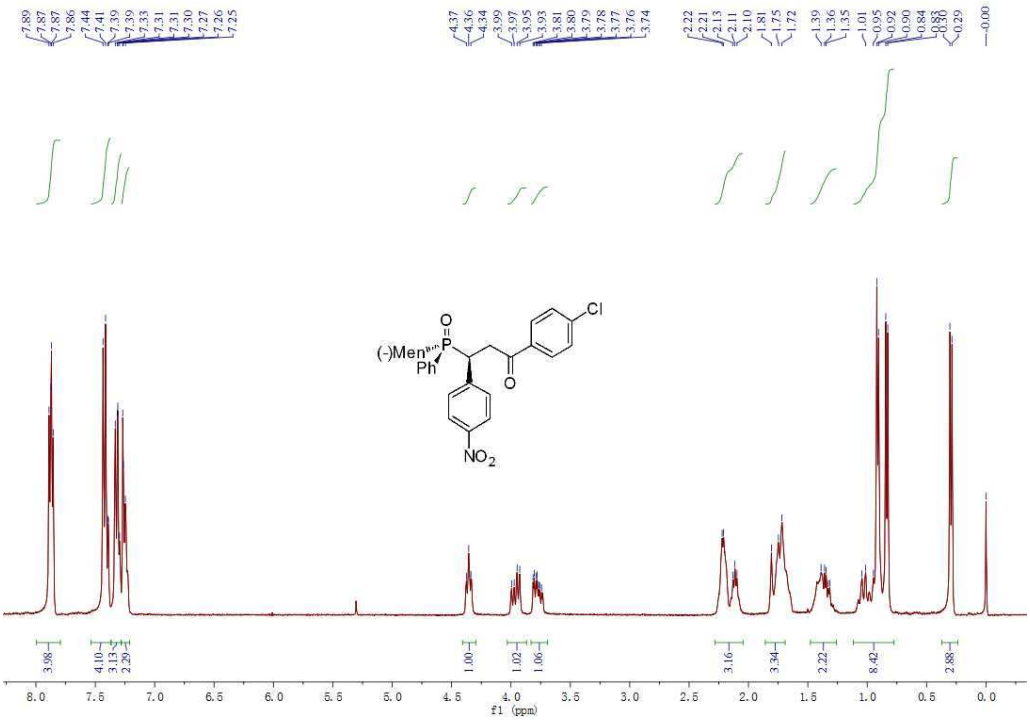
^{31}P-NMR spectroscopy of crude 3n/3n'=91:9



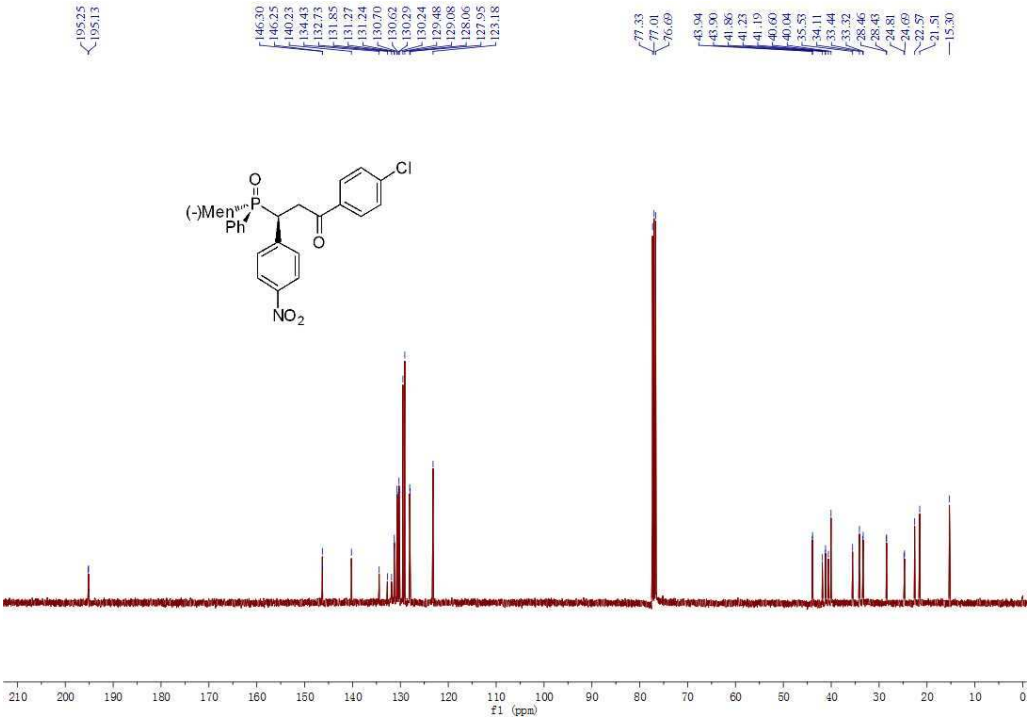
^{31}P-NMR spectroscopy of isolated 3n



^{1}H-NMR spectroscopy of isolated 3n

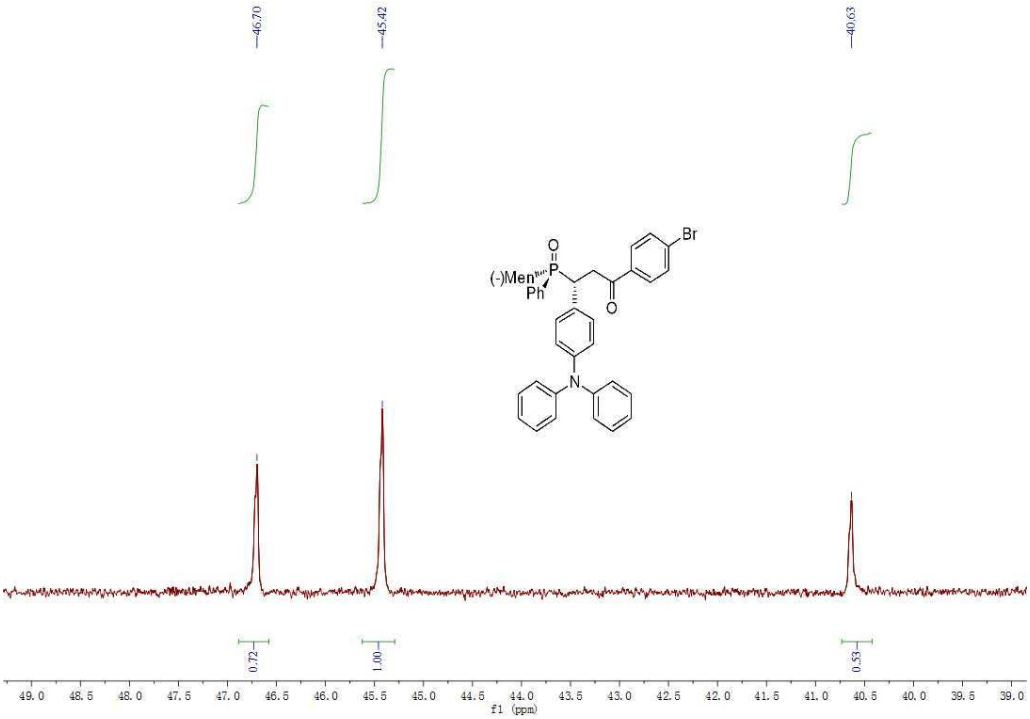


^{13}C-NMR spectroscopy of isolated 3n

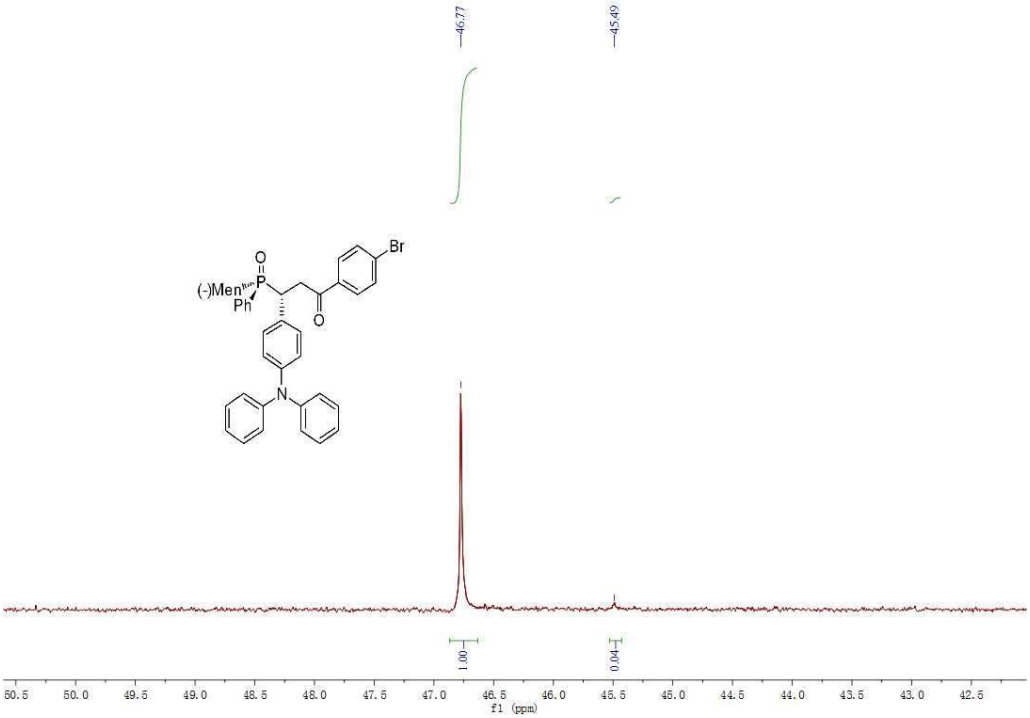


(S_P,*R*)-4-[(–)-Menthylphenylphosphoryl]-1-(*p*-bromophenyl)-4-(*p*-diphenylaminephenyl)propan-2-one, 3o'

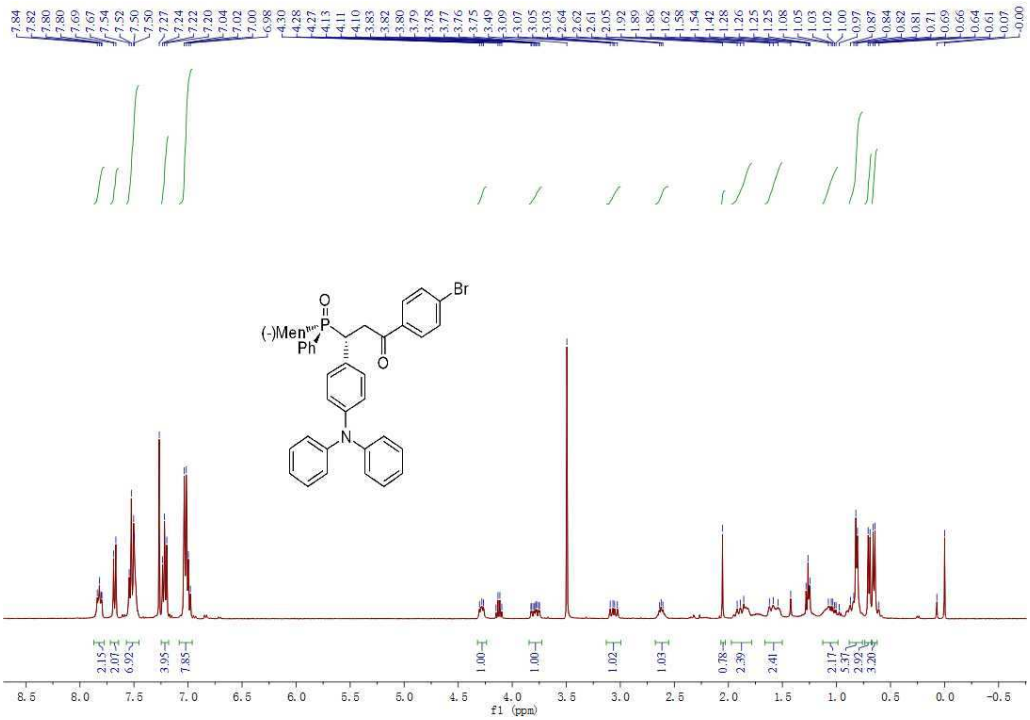
^{31}P-NMR spectroscopy of crude 3o/3o'=58:42



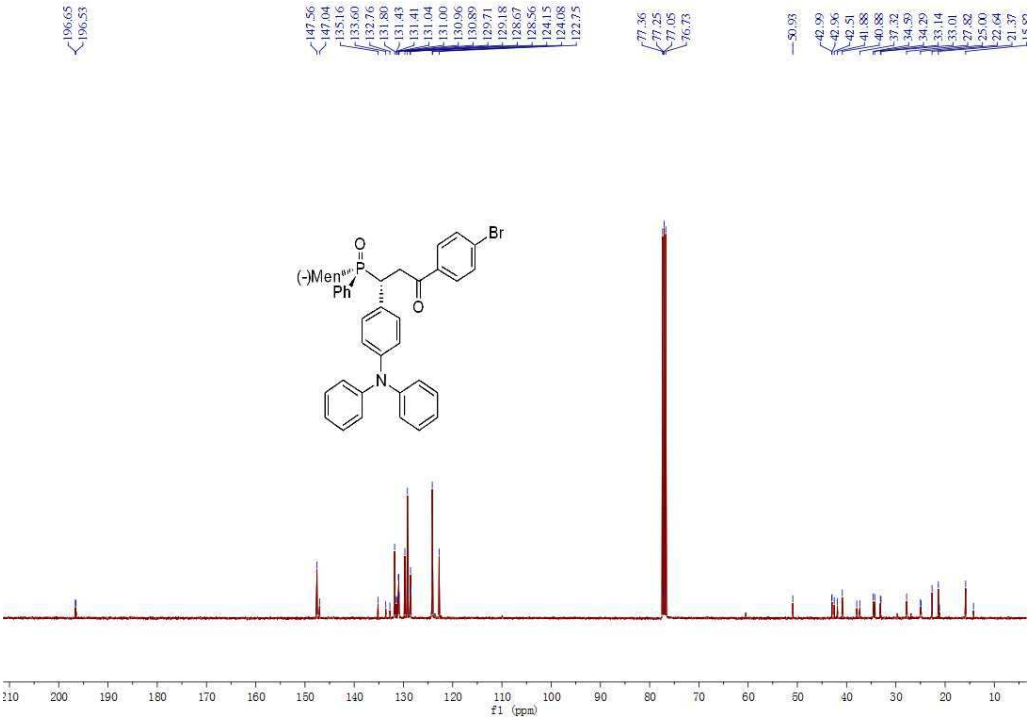
^{31}P-NMR spectroscopy of isolated 3o/3o'=4:96



^{1}H-NMR spectroscopy of isolated 3o/3o'=4:96

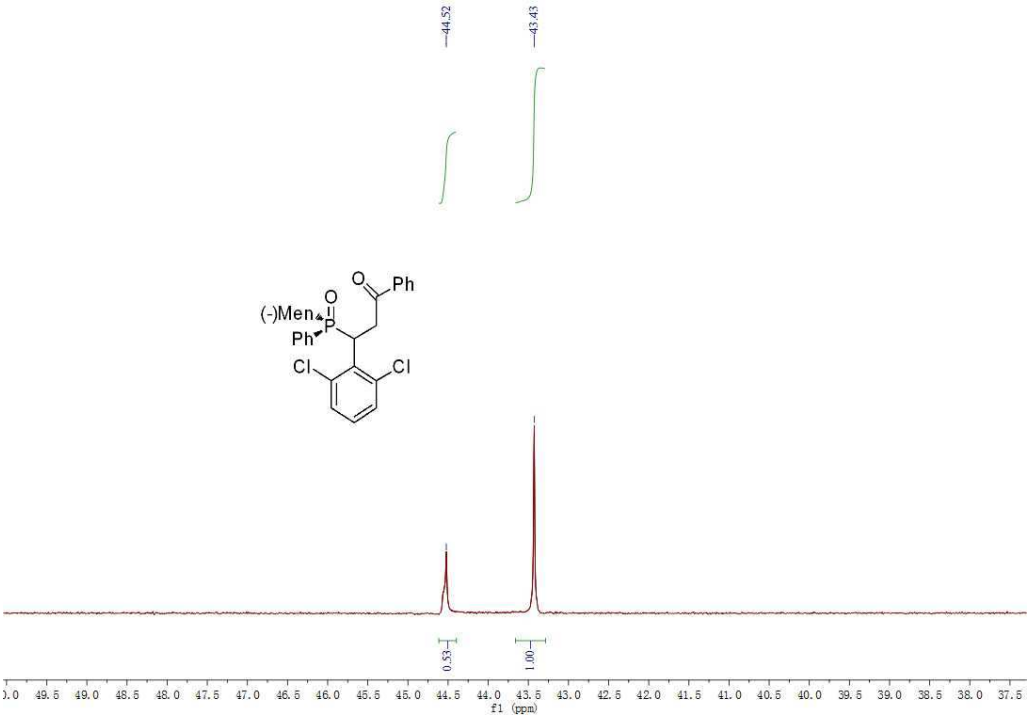


^{13}C-NMR spectroscopy of isolated 3o/3o'=4:96

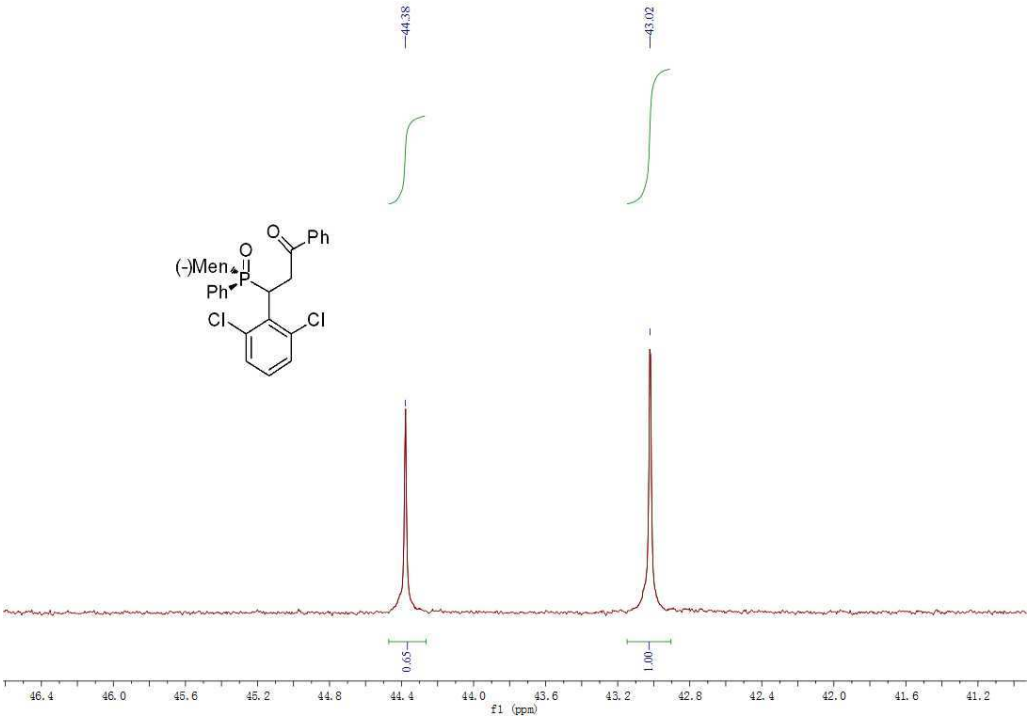


(S_P)-4-[(–)-Menthylphenylphosphoryl]-1-phenyl-4-(2,6-dichlorophenyl)propan-2-one, 3p/3p'

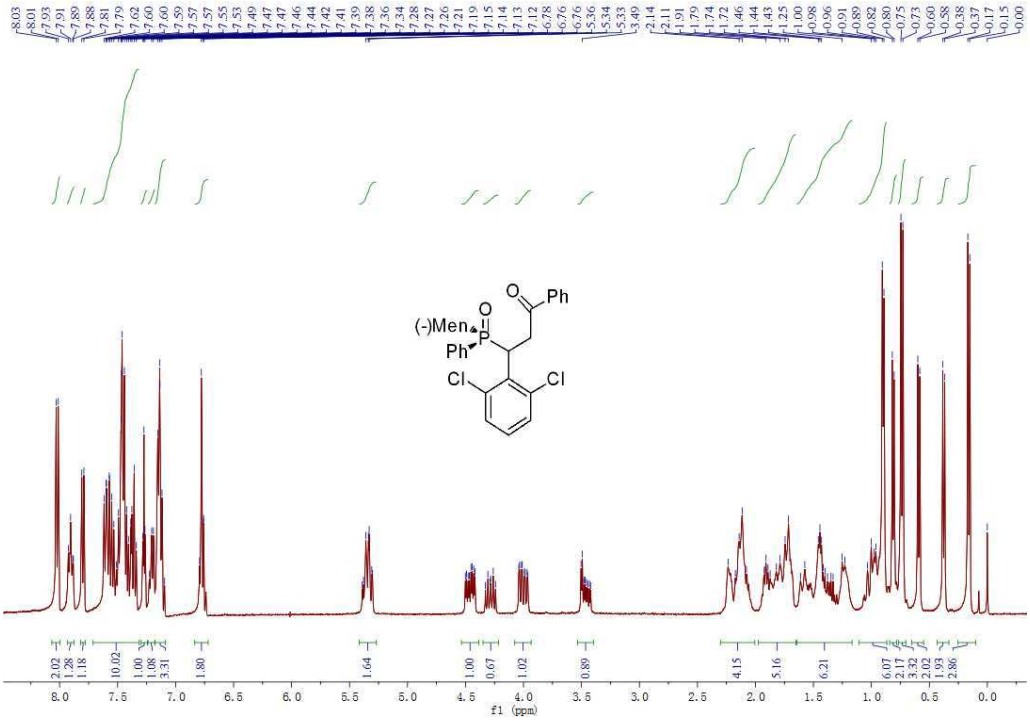
^{31}P-NMR spectroscopy of crude 3p/3p'=65:35



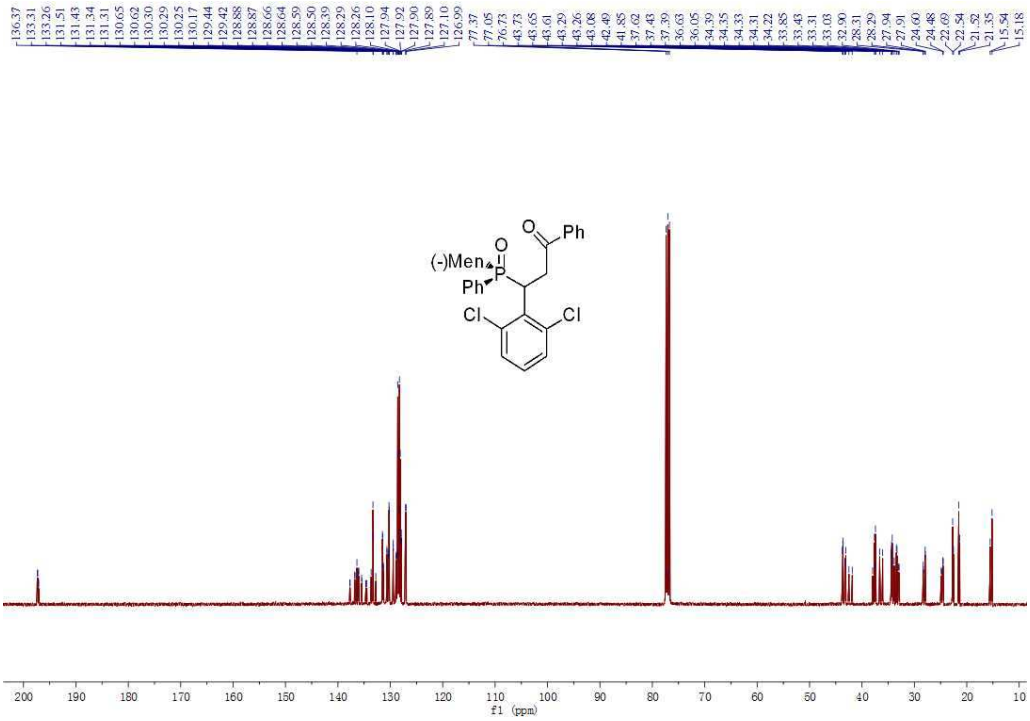
^{31}P-NMR spectroscopy of isolated 3p/3p'=60:40



^{1}H-NMR spectroscopy of isolated 3p/3p'=60:40

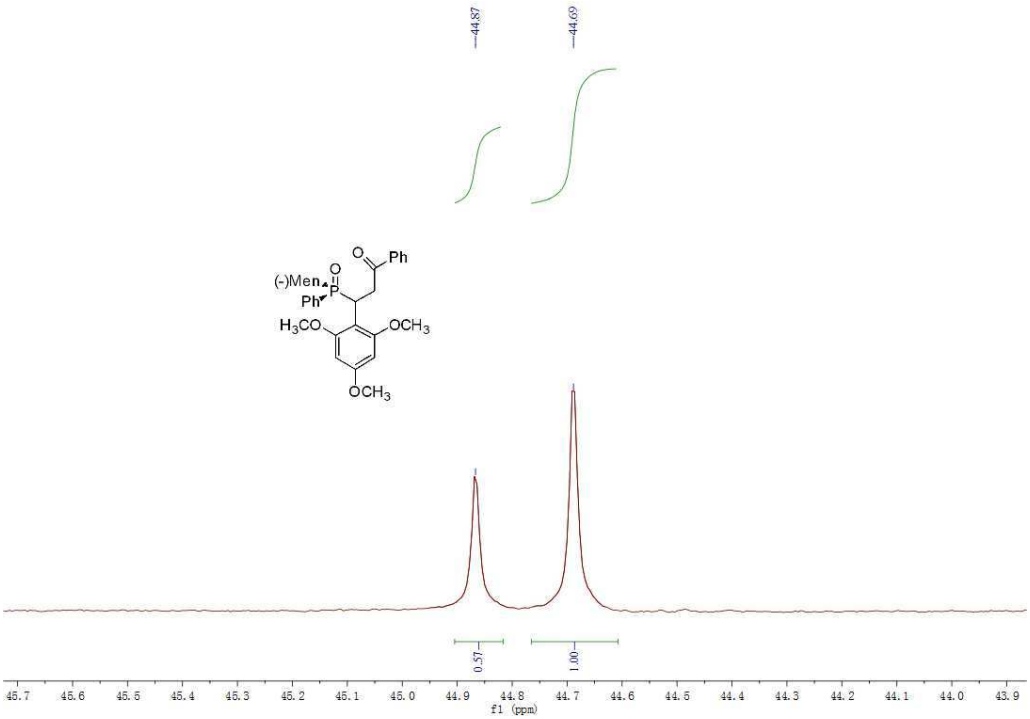


^{13}C-NMR spectroscopy of isolated 3p/3p'=60:40

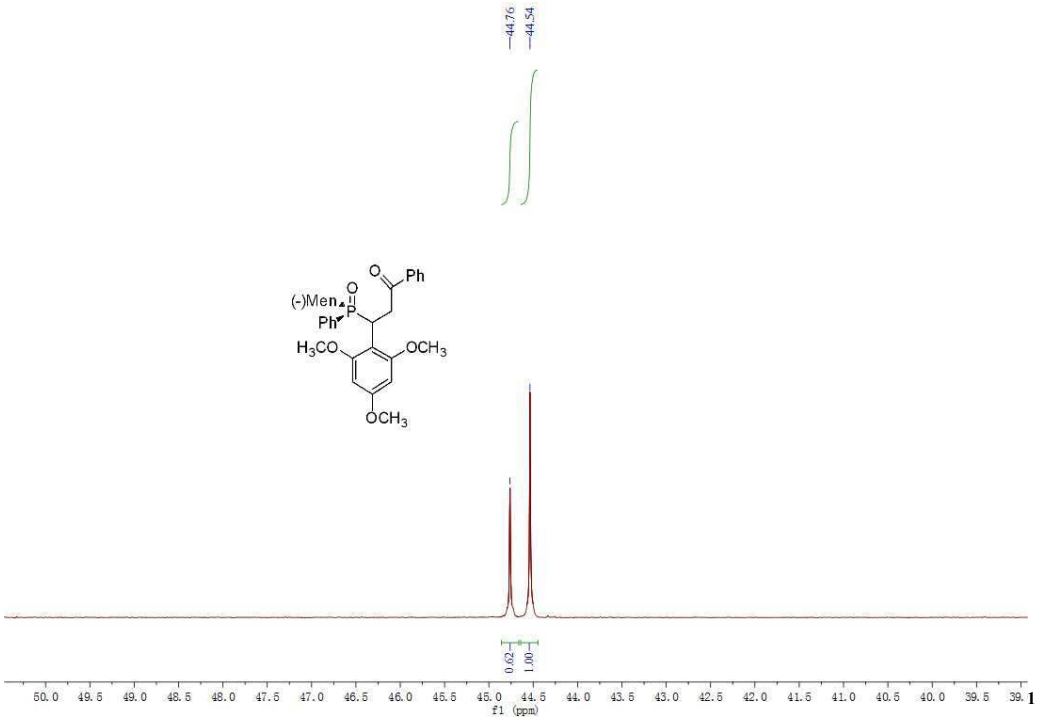


(S_P)-4-[(–)-Menthylphenylphosphoryl]-1-phenyl-4-(2,4,6-trimethoxyphenyl)propan-2-one, 3q/3q'

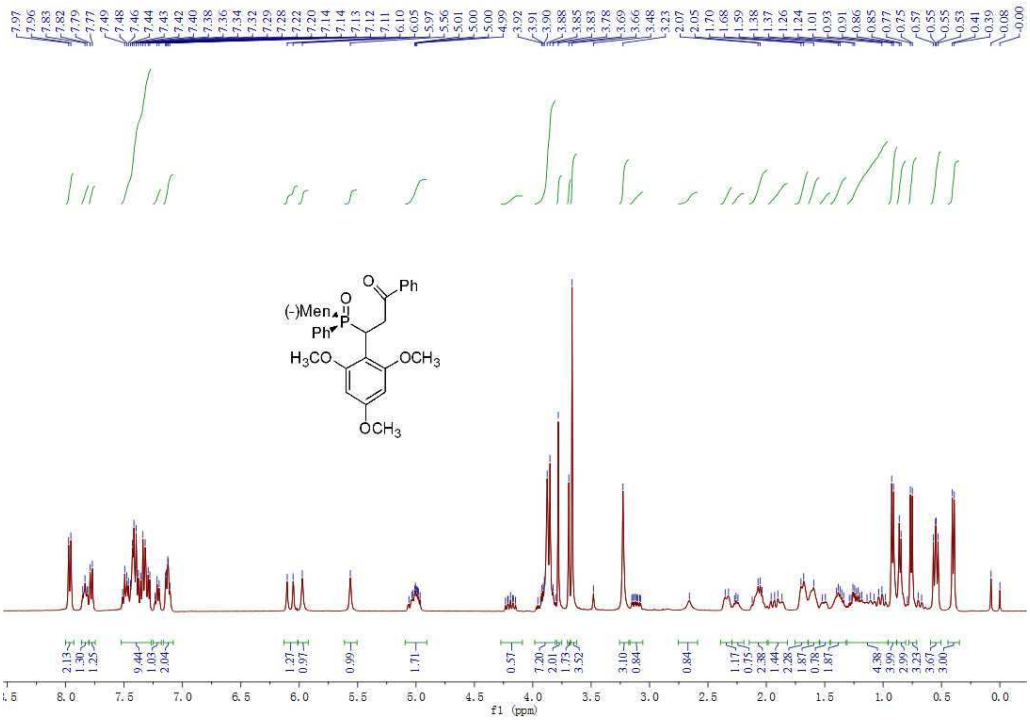
^{31}P-NMR spectroscopy of crude 3q/3q'=64:36



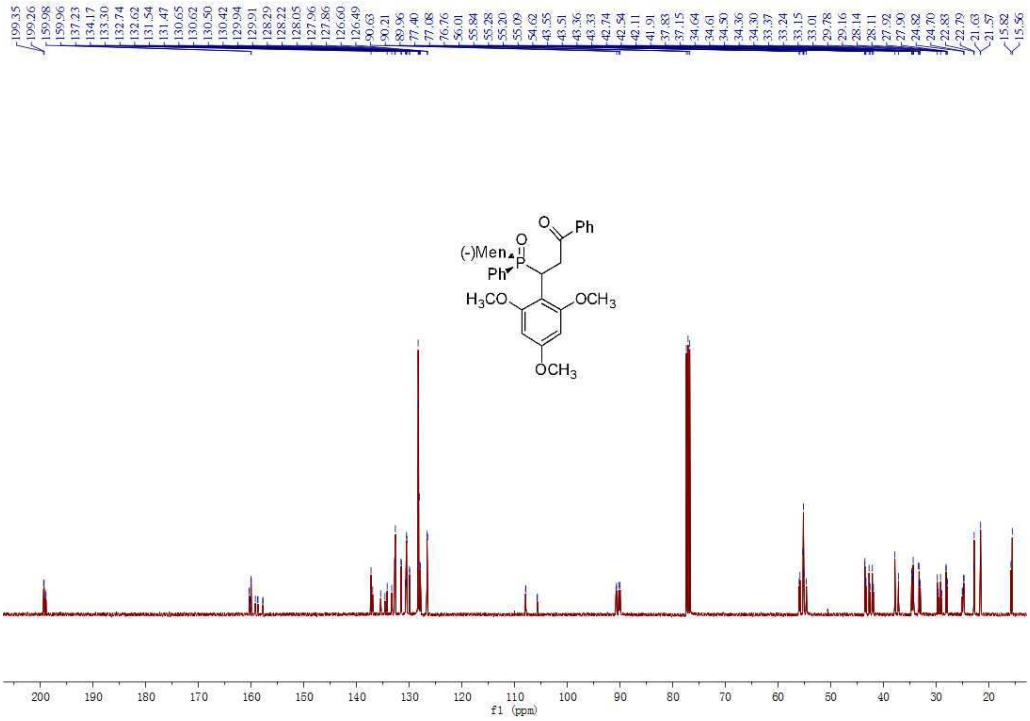
^{31}P-NMR spectroscopy of isolated 3q/3q'=62:38



H-NMR spectroscopy of isolated 3q/3q'=62:38

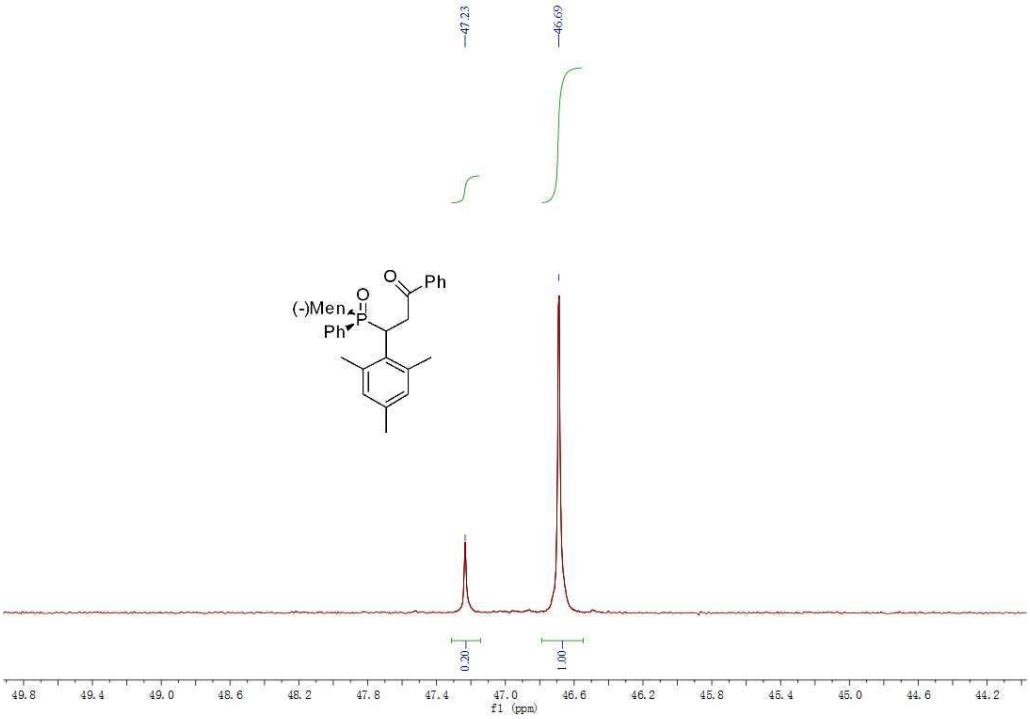


^{13}C-NMR spectroscopy of isolated 3q/3q'=62:38

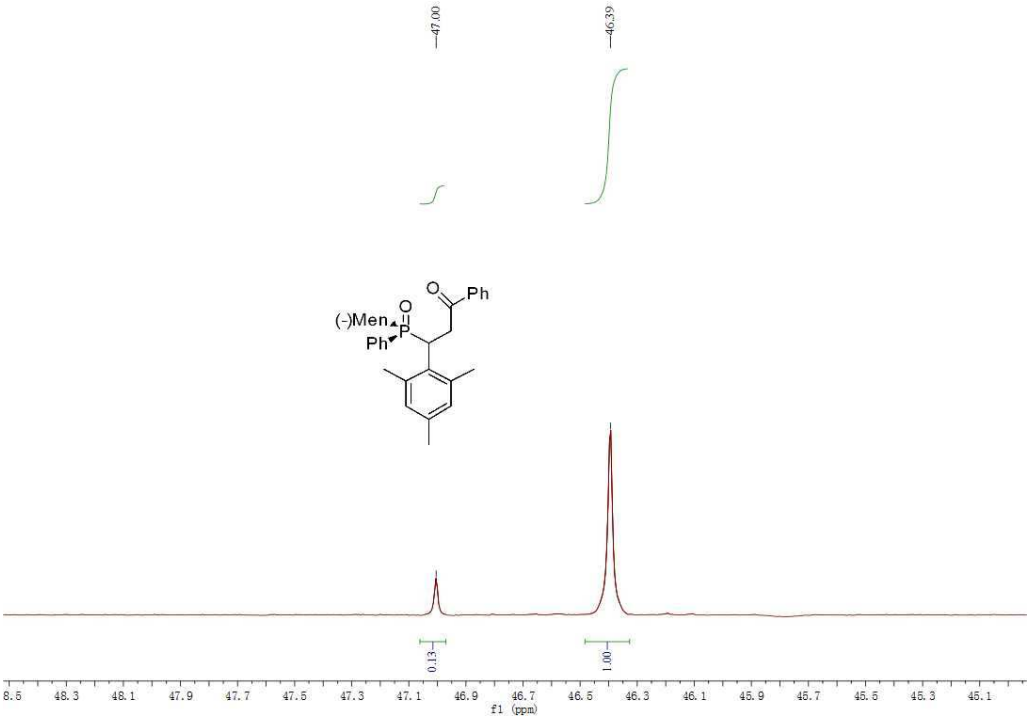


(S_P)-4-[(–)-Menthylphenylphosphoryl]-1-phenyl-4-(2,4,6-trimethylphenyl)propan-2-one, 3r/3r'

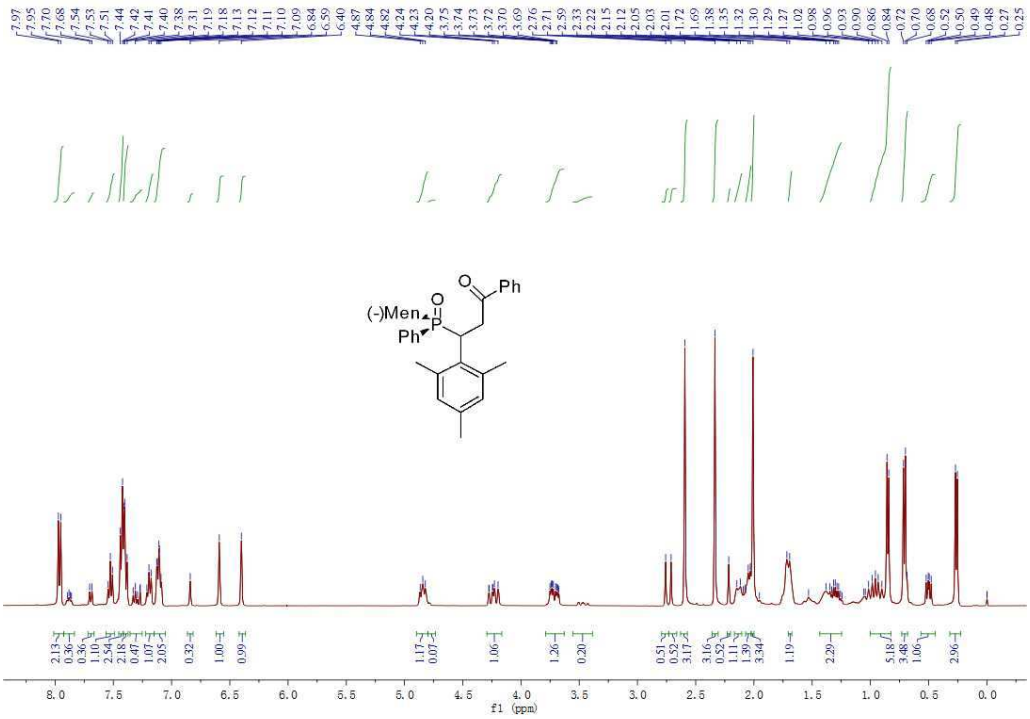
^{31}P-NMR spectroscopy of crude 3r/3r'=83:17



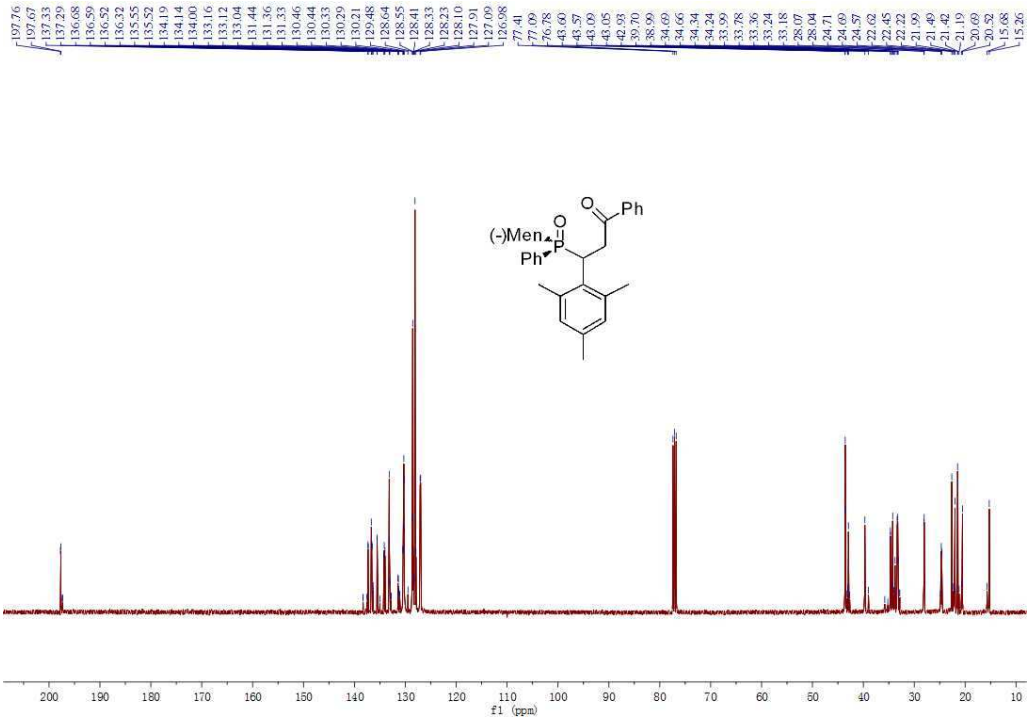
^{31}P-NMR spectroscopy of isolated 3r/3r'=88:12



^{1}H-NMR spectroscopy of isolated 3r/3r'=88:12

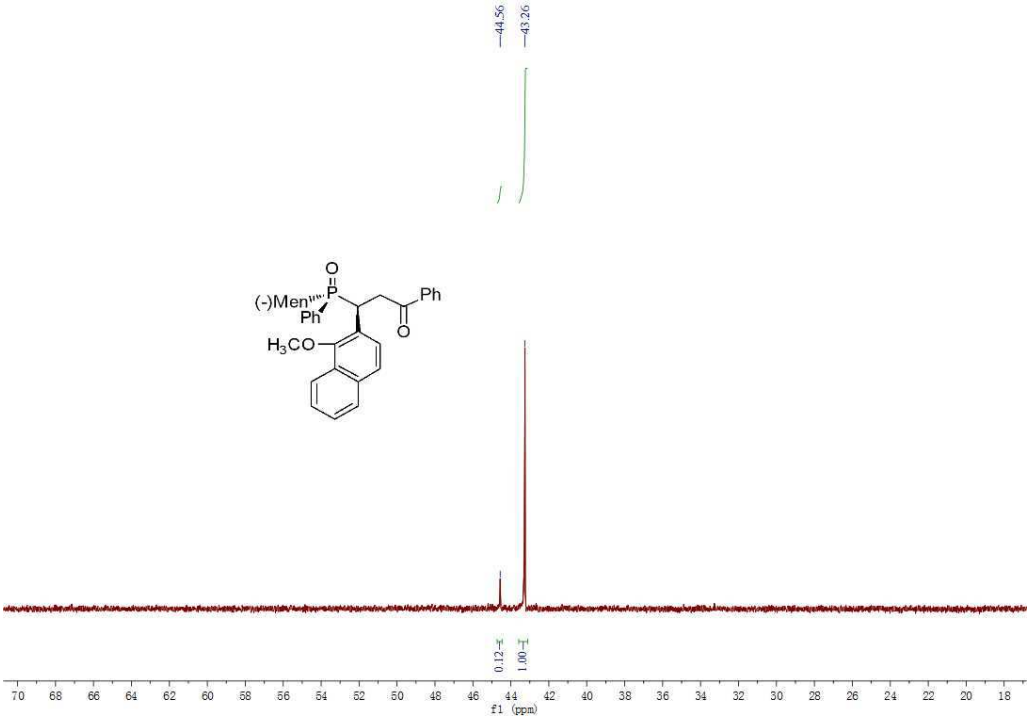


^{13}C-NMR spectroscopy of isolated 3r/3r'=88:12

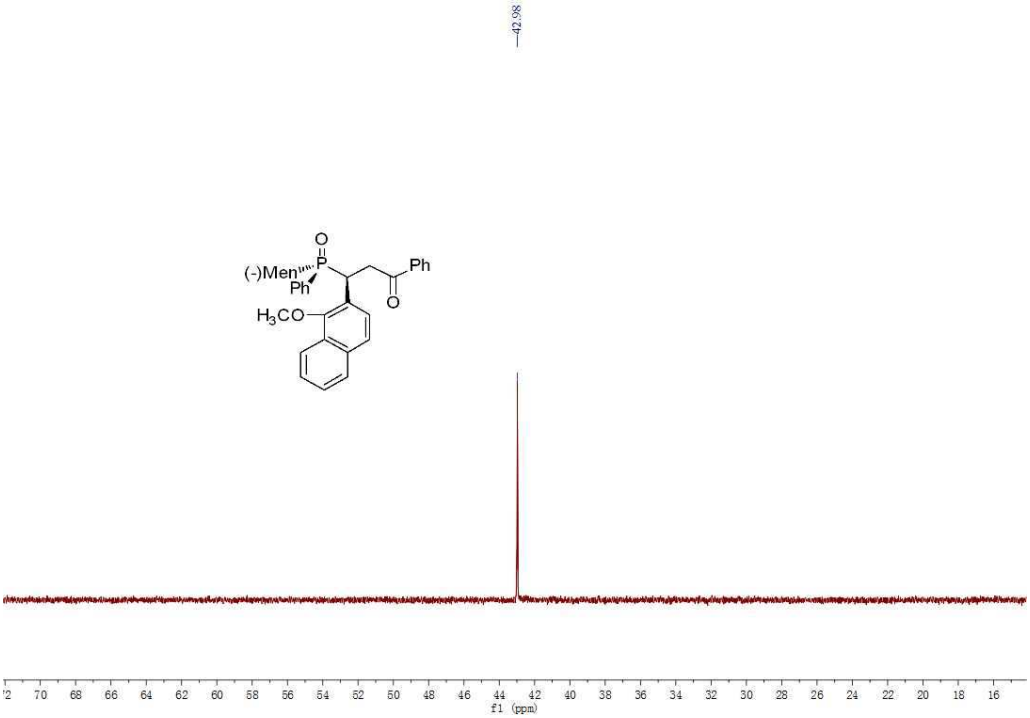


(S_P,S)-4-[(–)-Menthylphenylphosphoryl]-1-phenyl-4-(*o*-methoxynaphthyl)propan-2-one, 3s

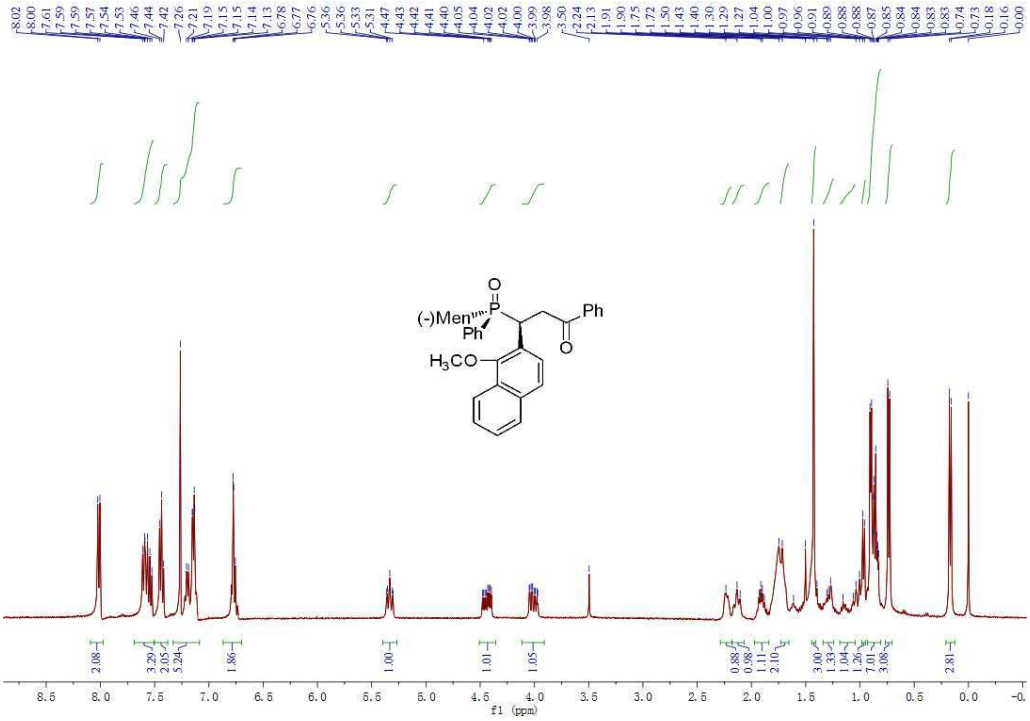
^{31}P-NMR spectroscopy of crude 3s/3s'=89:11



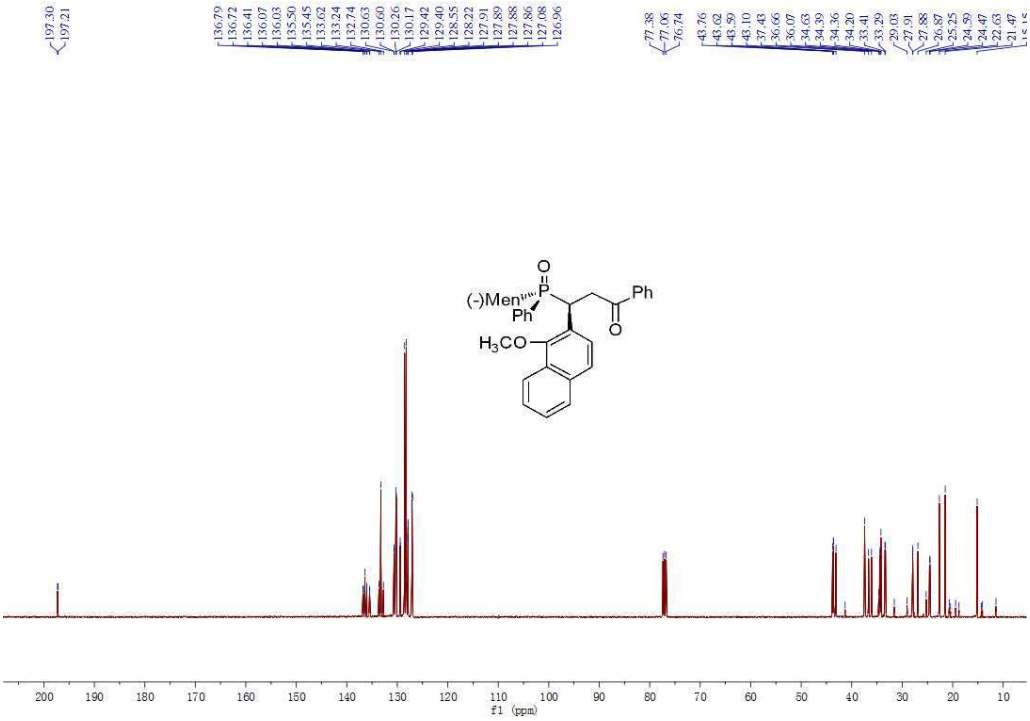
^{31}P-NMR spectroscopy of isolated 3s



^{1}H-NMR spectroscopy of isolated 3s

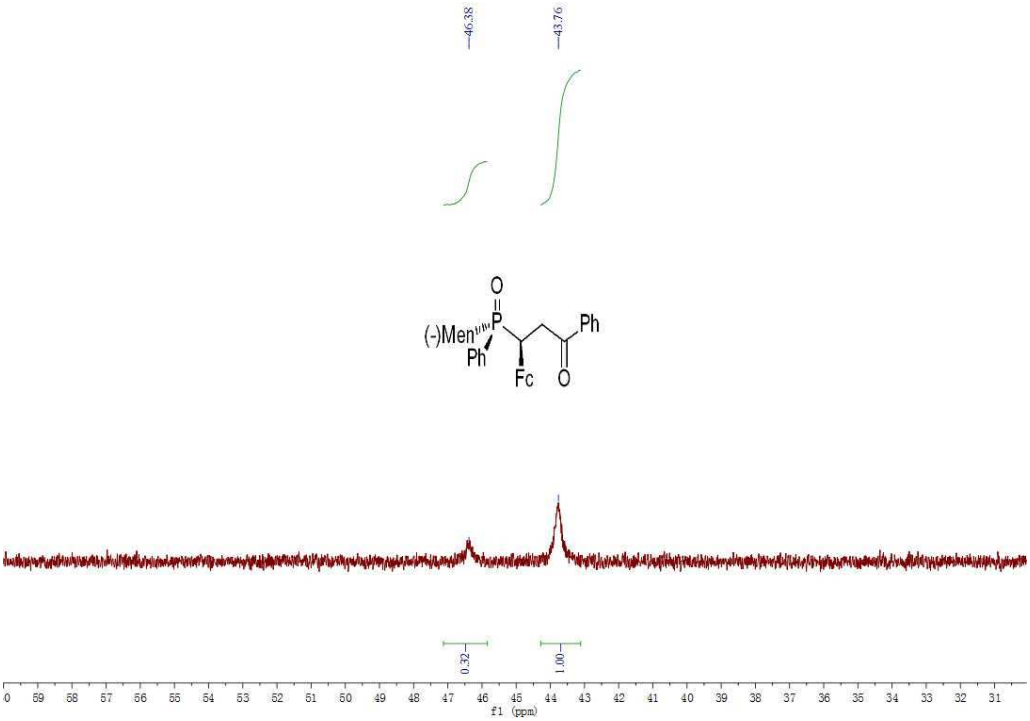


^{13}C-NMR spectroscopy of isolated 3s

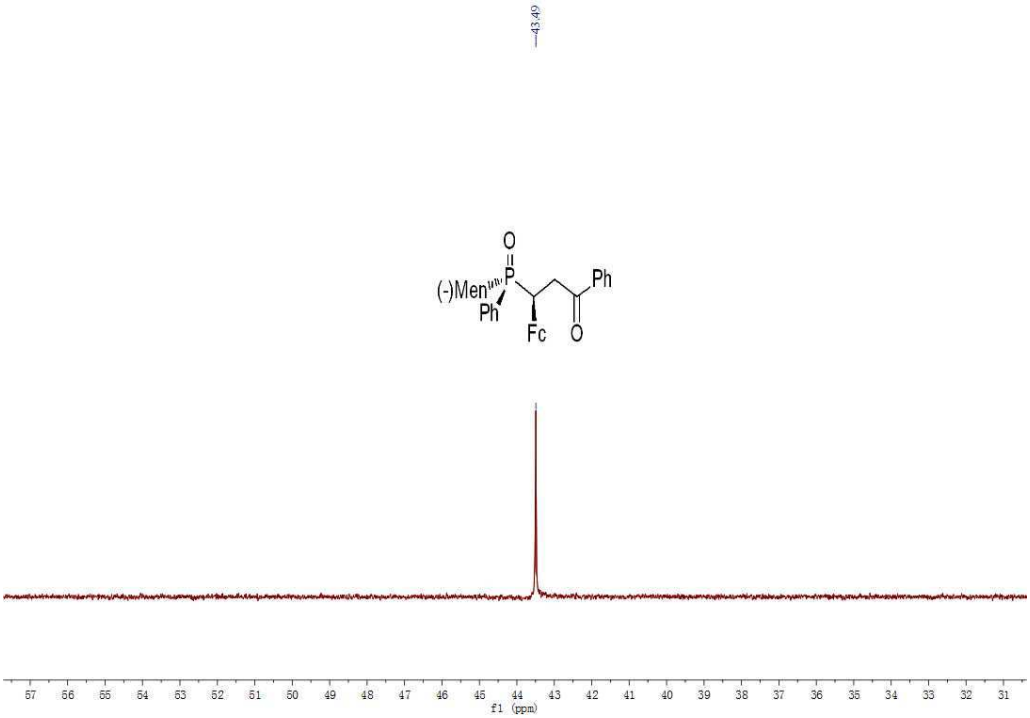


(S_P,S)-4-[(–)-Menthylphenylphosphoryl]-1-phenyl-4-ferrocenecarboxpropan-2-one, 3t

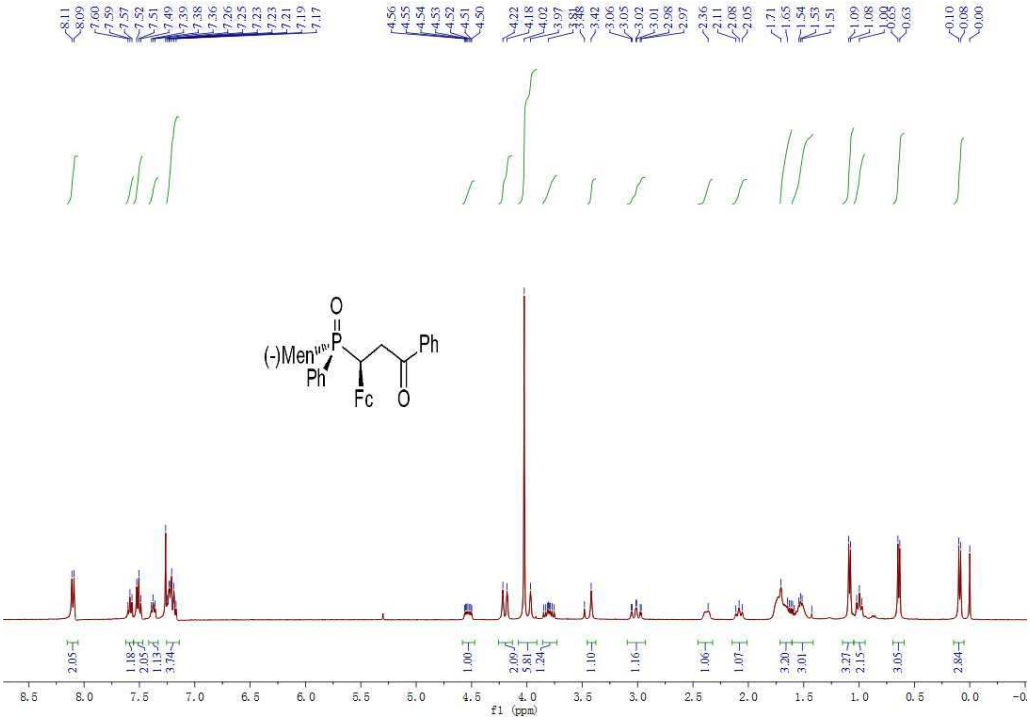
^{31}P-NMR spectroscopy of crude 3t/3t'=76:24



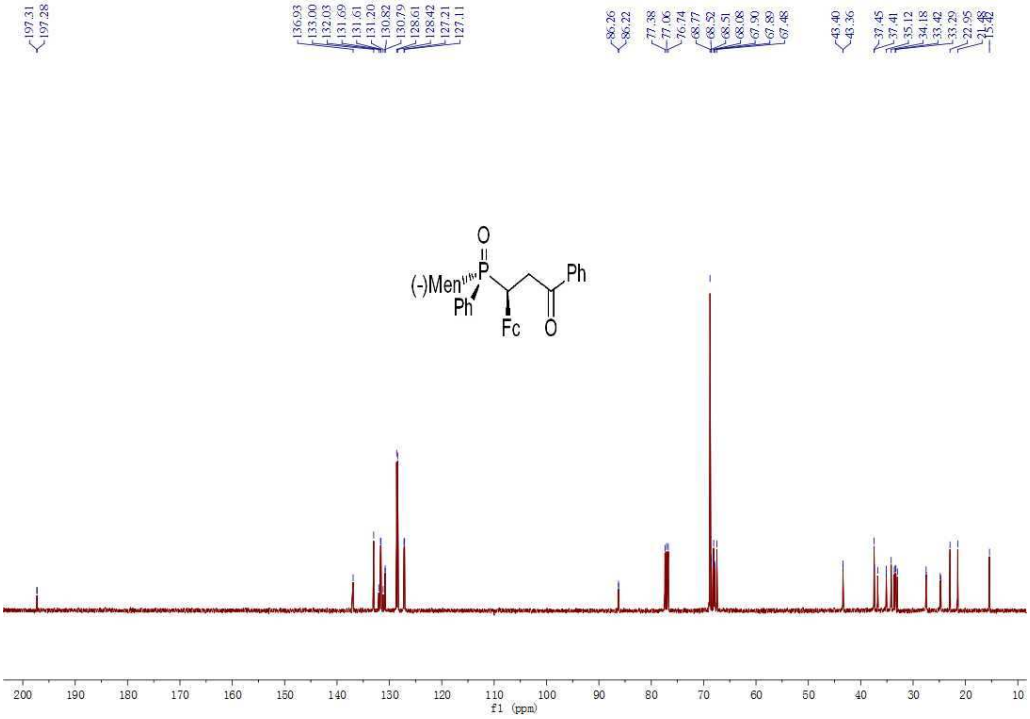
^{31}P-NMR spectroscopy of isolated 3t



^{1}H-NMR spectroscopy of isolated 3t

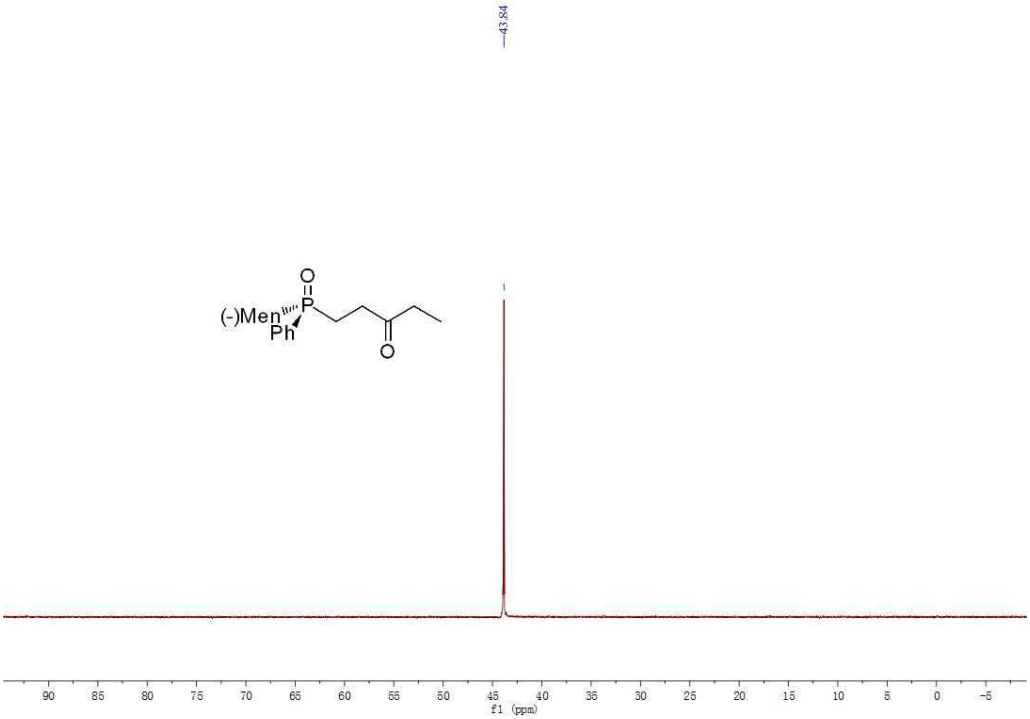


^{13}C-NMR spectroscopy of isolated 3t

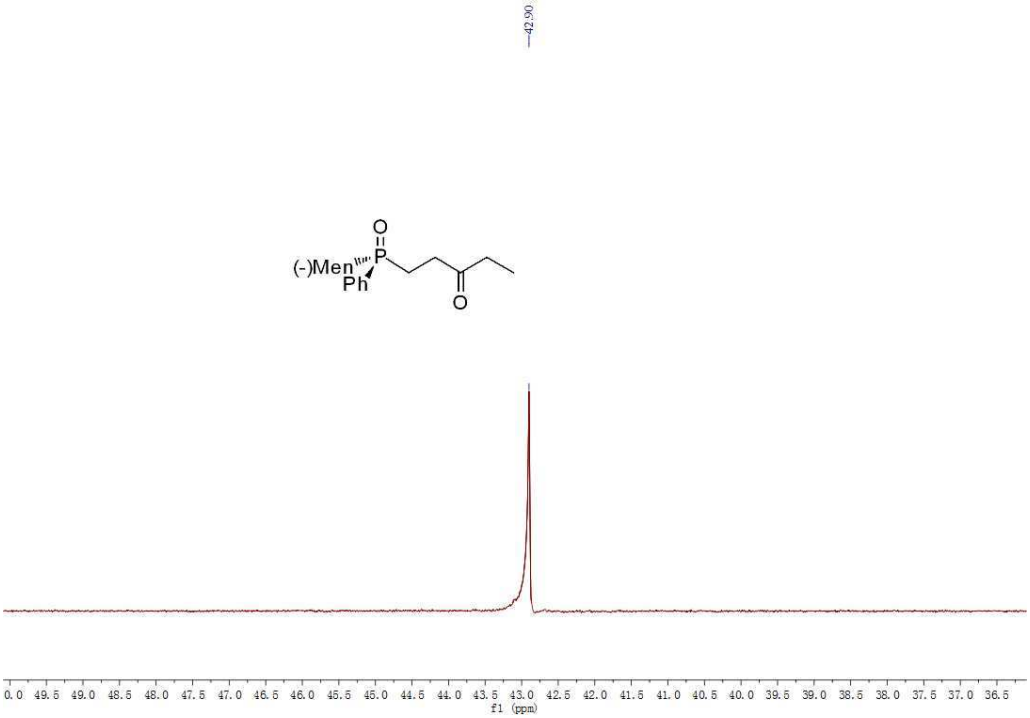


(S_P)-4-[(–)-Menthylphenylphosphoryl]-pentan-3-one, 3u

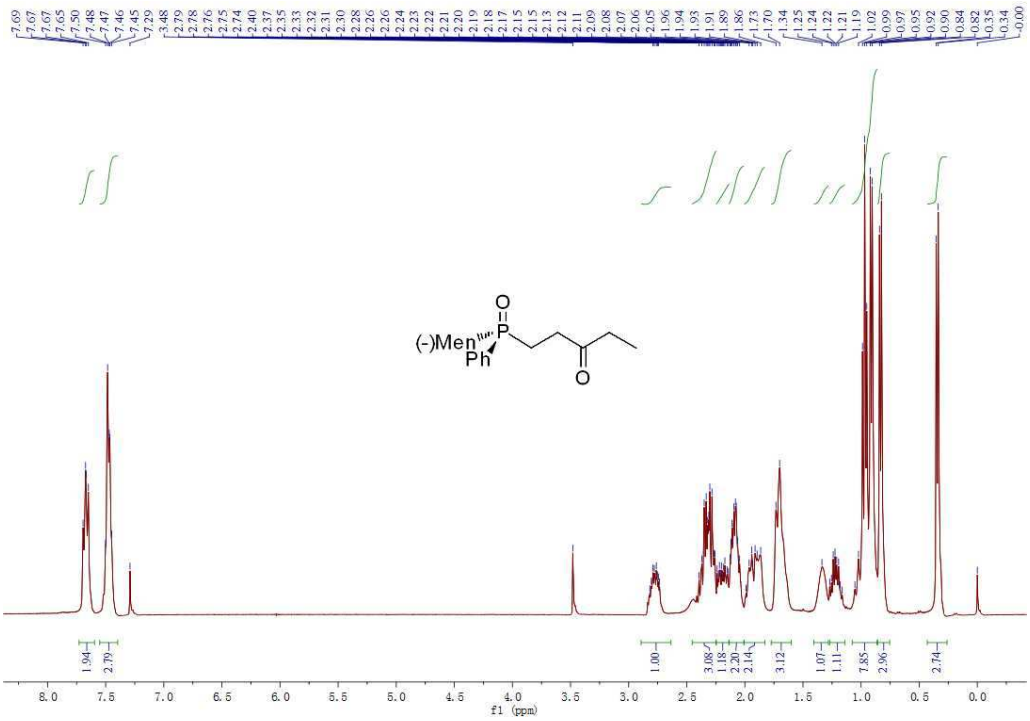
^{31}P-NMR spectroscopy of crude 3u



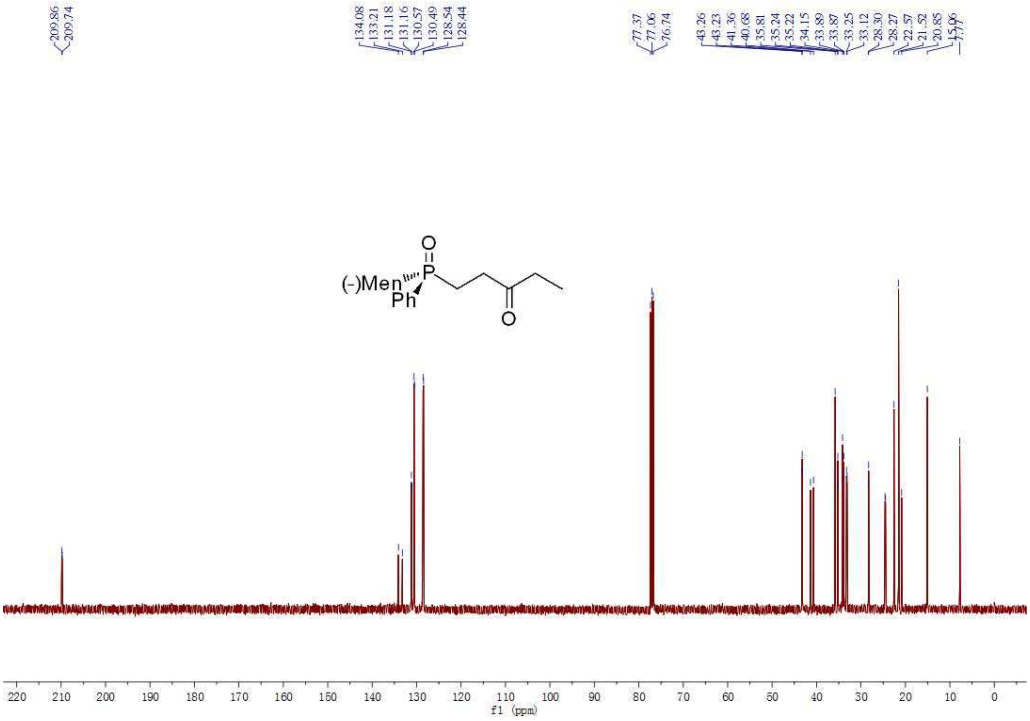
^{31}P-NMR spectroscopy of isolated 3u



^{1}H-NMR spectroscopy of isolated 3u

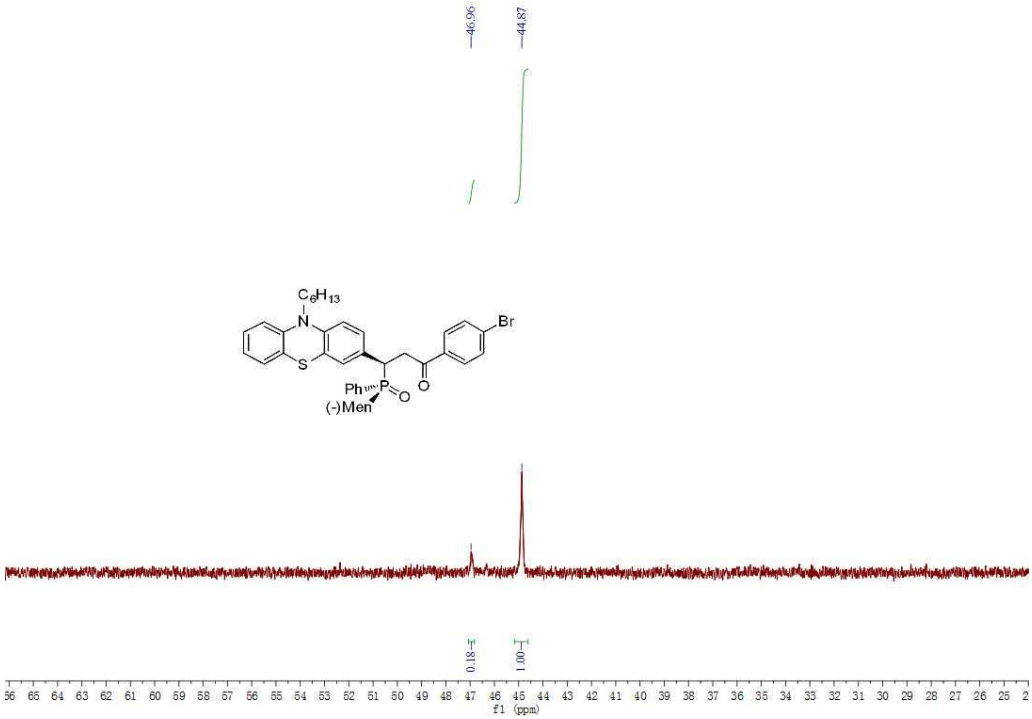


^{13}C-NMR spectroscopy of isolated 3u

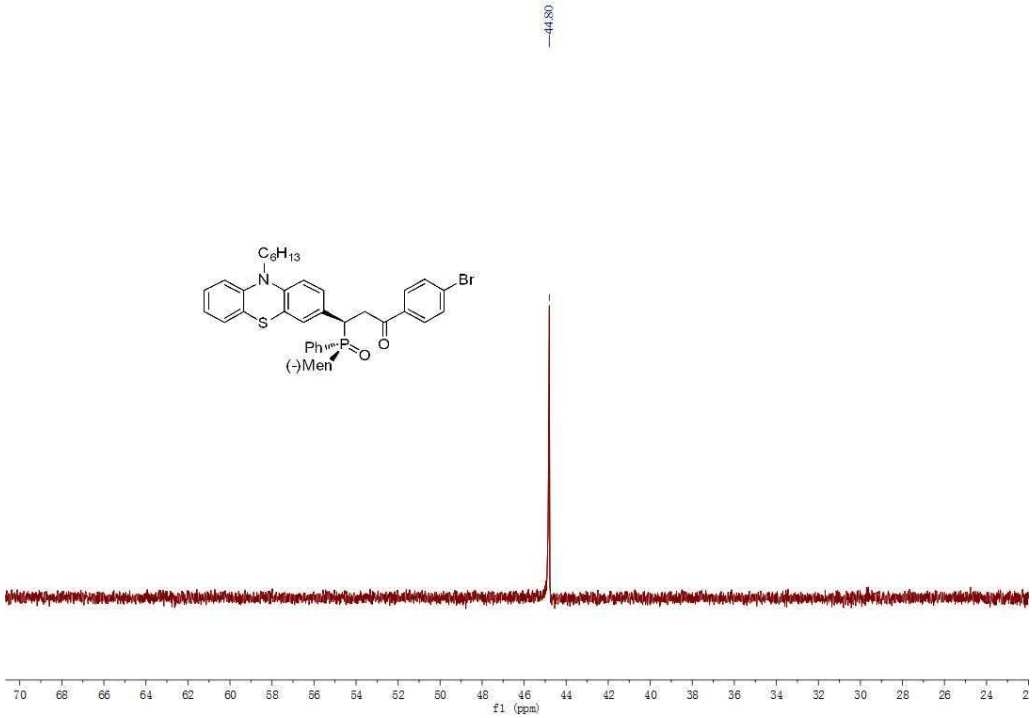


(S_P,*S*)-4-[(–)-Menthylphenylphosphoryl]-1-(*p*-bromophenyl)-4-(*N*-hexylphenothiazin)propan-2-one, 3v

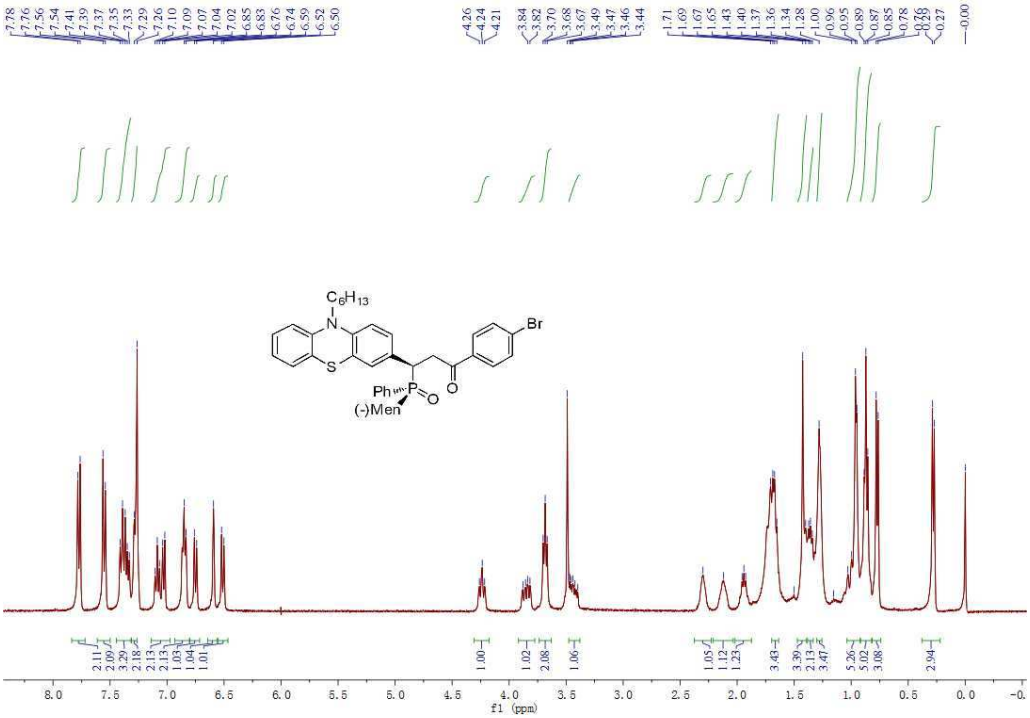
^{31}P-NMR spectroscopy of crude 3v/3v'=85:15



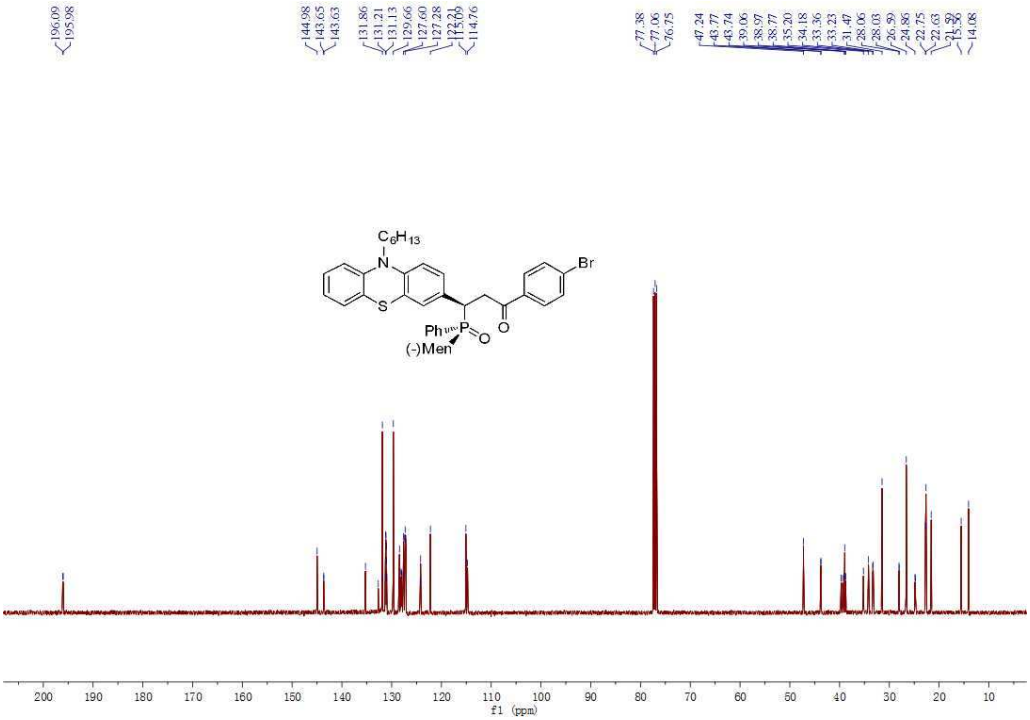
^{31}P-NMR spectroscopy of isolated 3v



^{1}H-NMR spectroscopy of isolated 3v

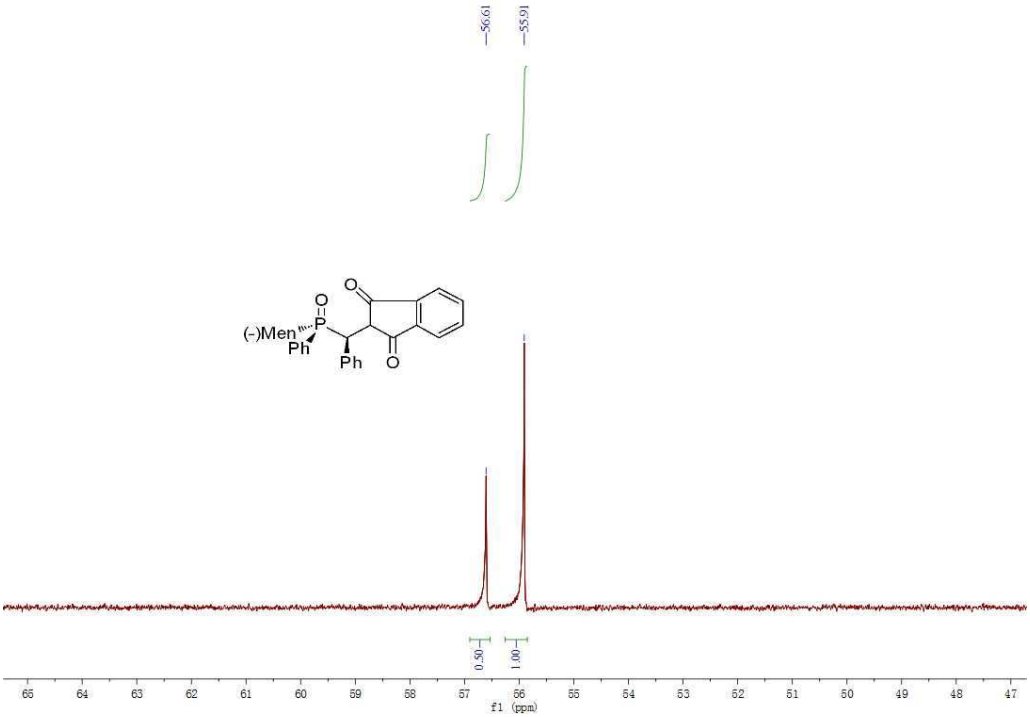


^{13}C-NMR spectroscopy of isolated 3v

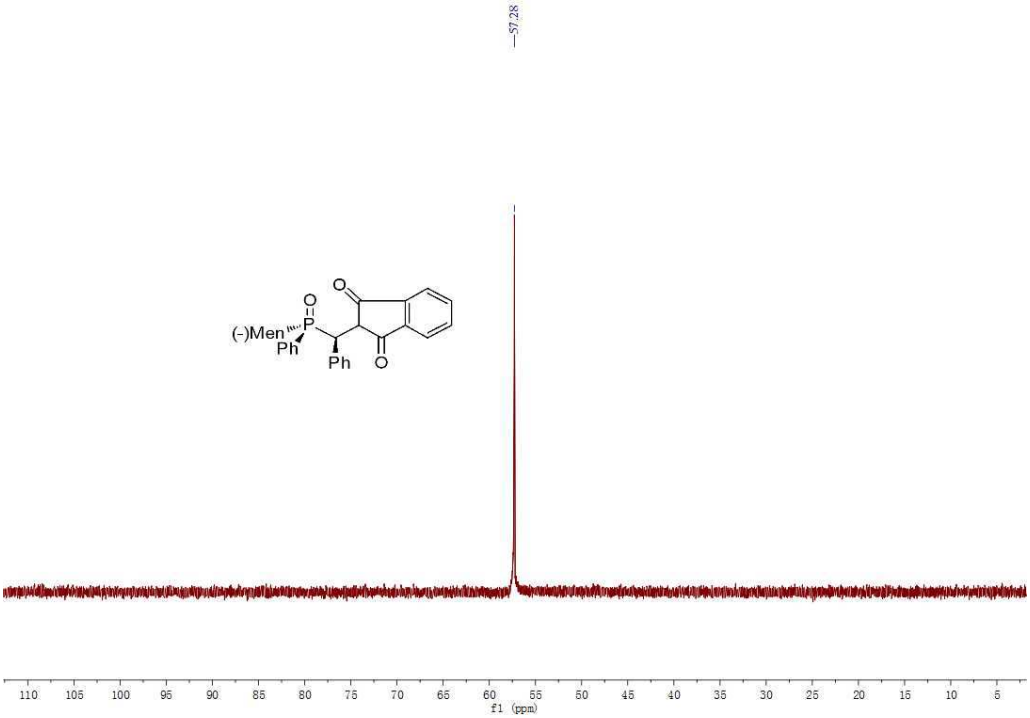


(S_P,S)-2-[(–)-Menthylphenylphosphoryl]-2-phenyl-1*H*-indene-1,3(2H)-dione, 3w

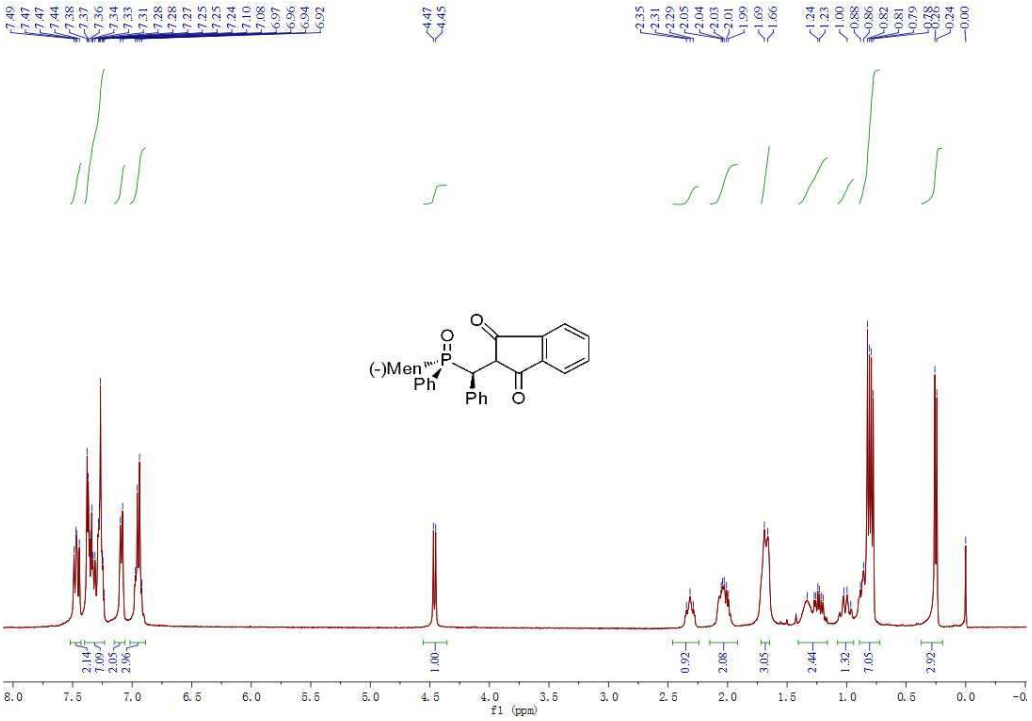
^{31}P-NMR spectroscopy of crude 3w/3w'=67:33



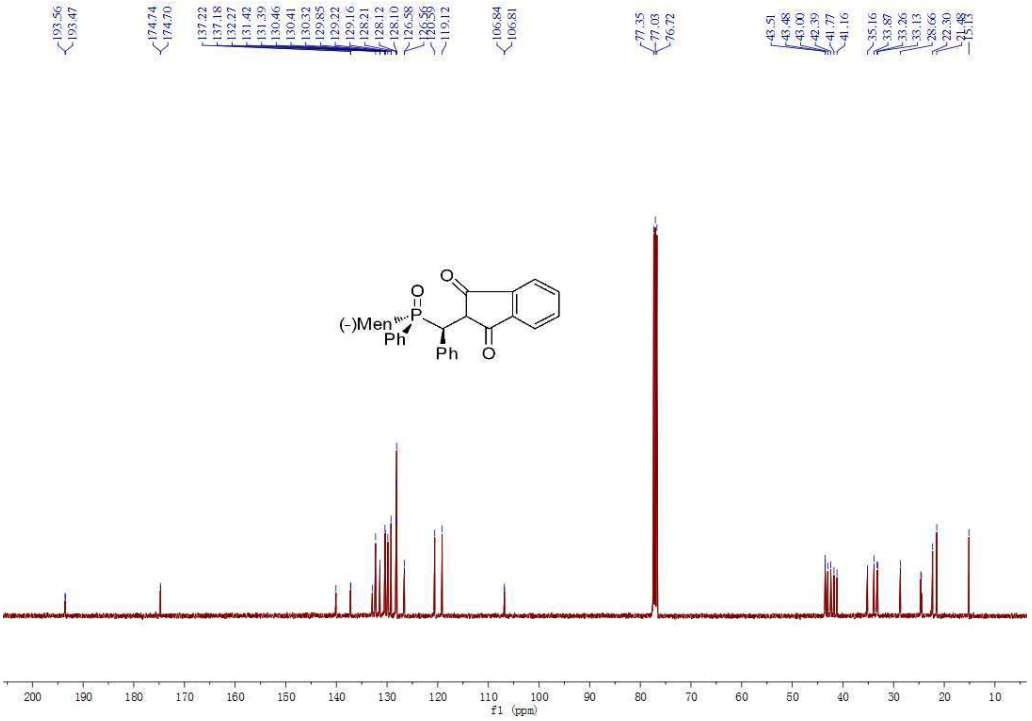
^{31}P-NMR spectroscopy of isolated 3w



^{1}H-NMR spectroscopy of isolated 3w

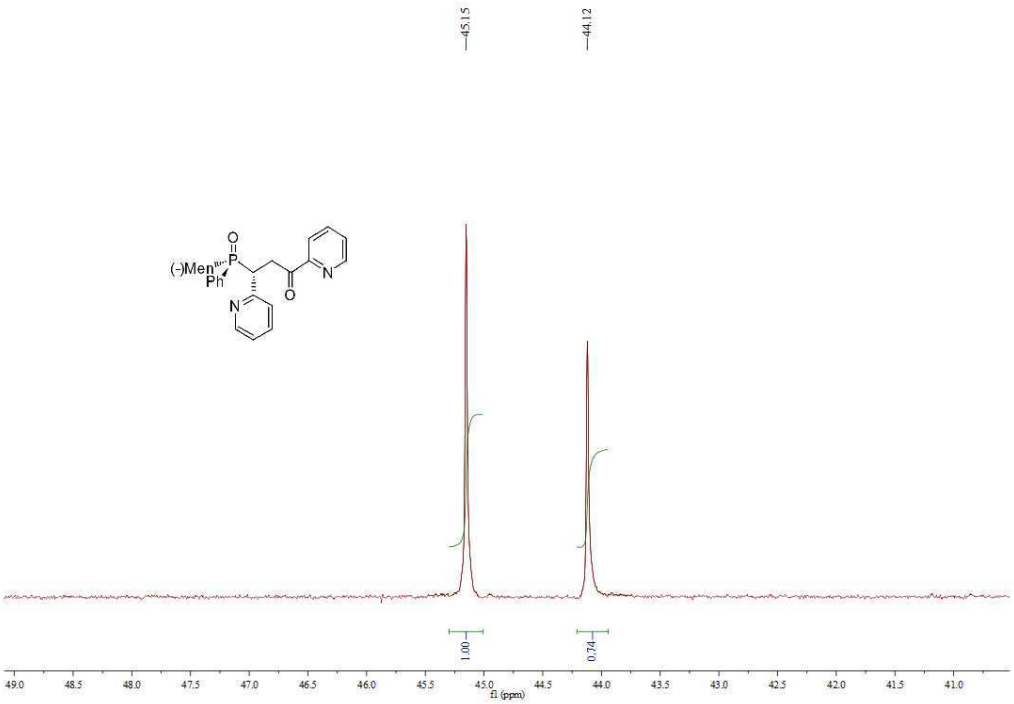


^{13}C-NMR spectroscopy of isolated 3w

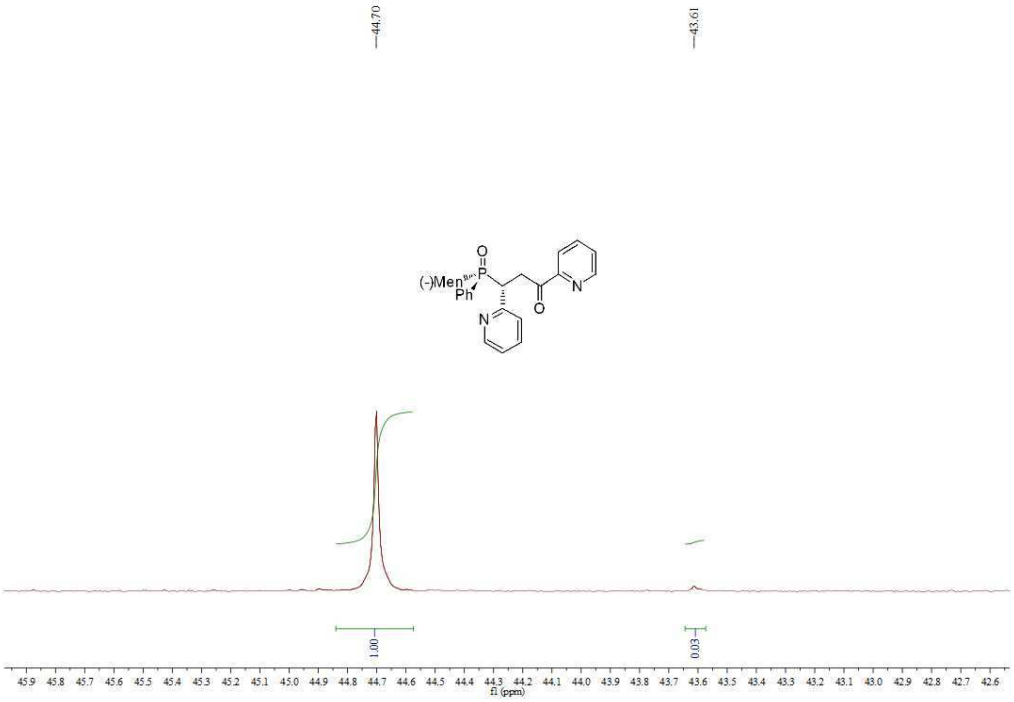


(S_P,*R*)-4-[(–)-Menthylphenylphosphoryl]-1-pyridyl-4- pyridylpropan-2-one, 3x'

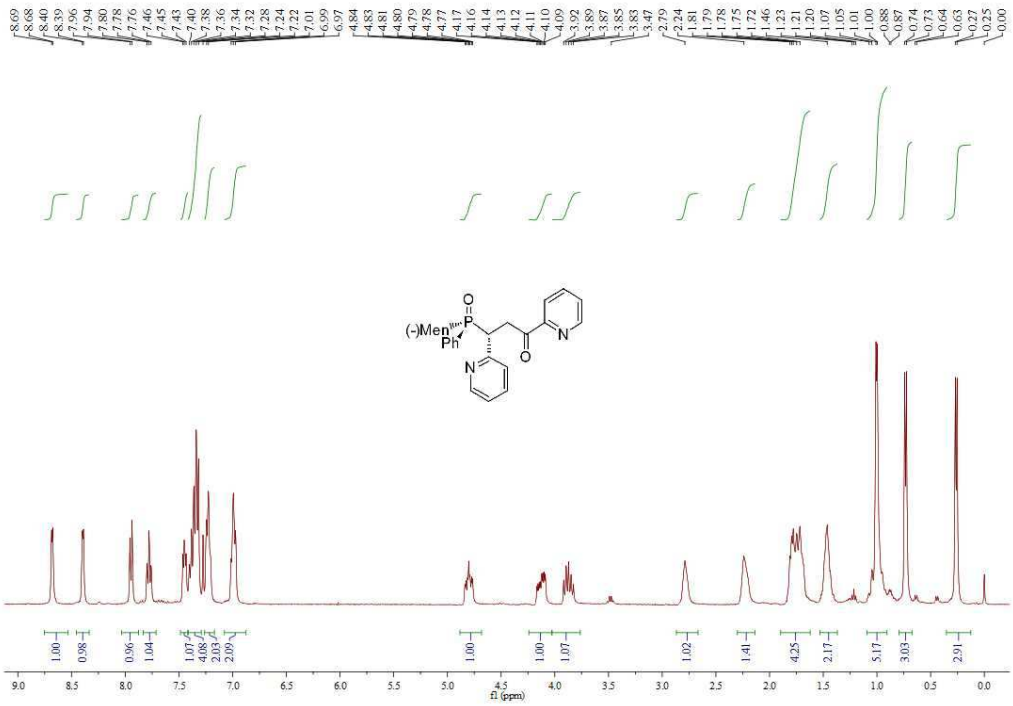
^{31}P-NMR spectroscopy of crude 3x/3x'=43:57



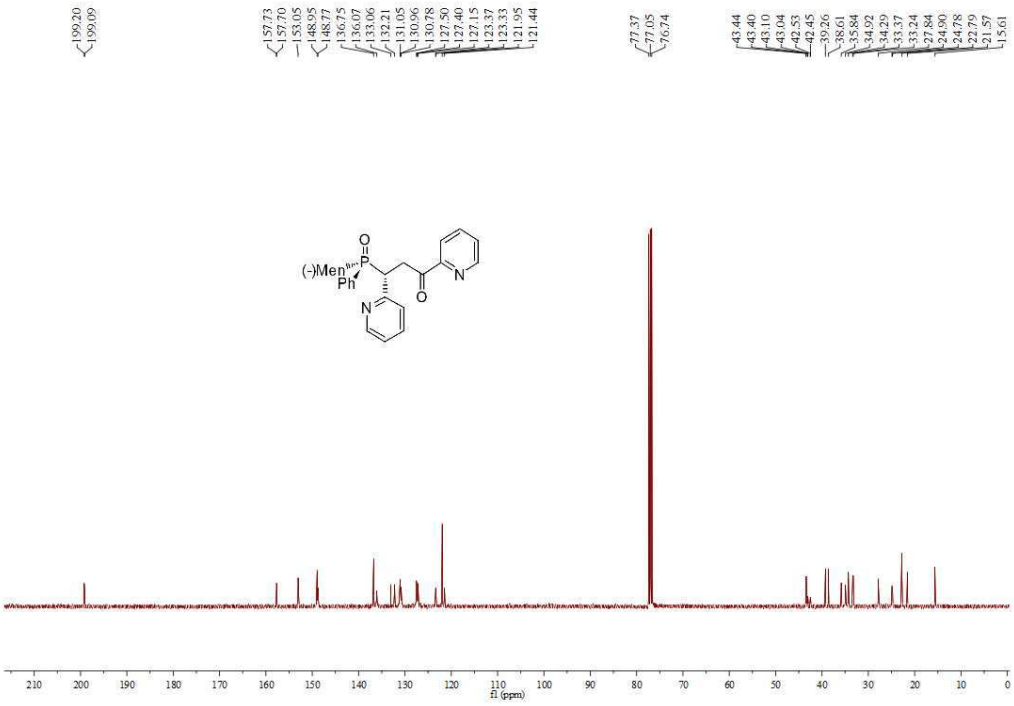
^{31}P-NMR spectroscopy of isolated 3x/3x'=3:97



^{1}H-NMR spectroscopy of isolated 3x/3x'=3:97

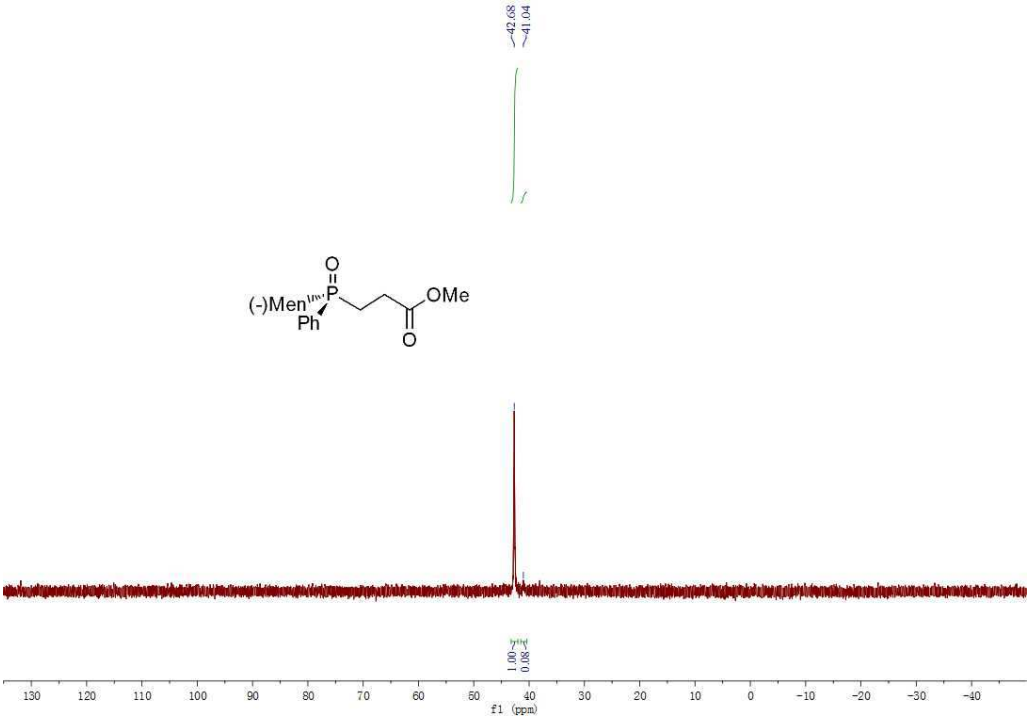


^{13}C-NMR spectroscopy of isolated 3x/3x'=3:97

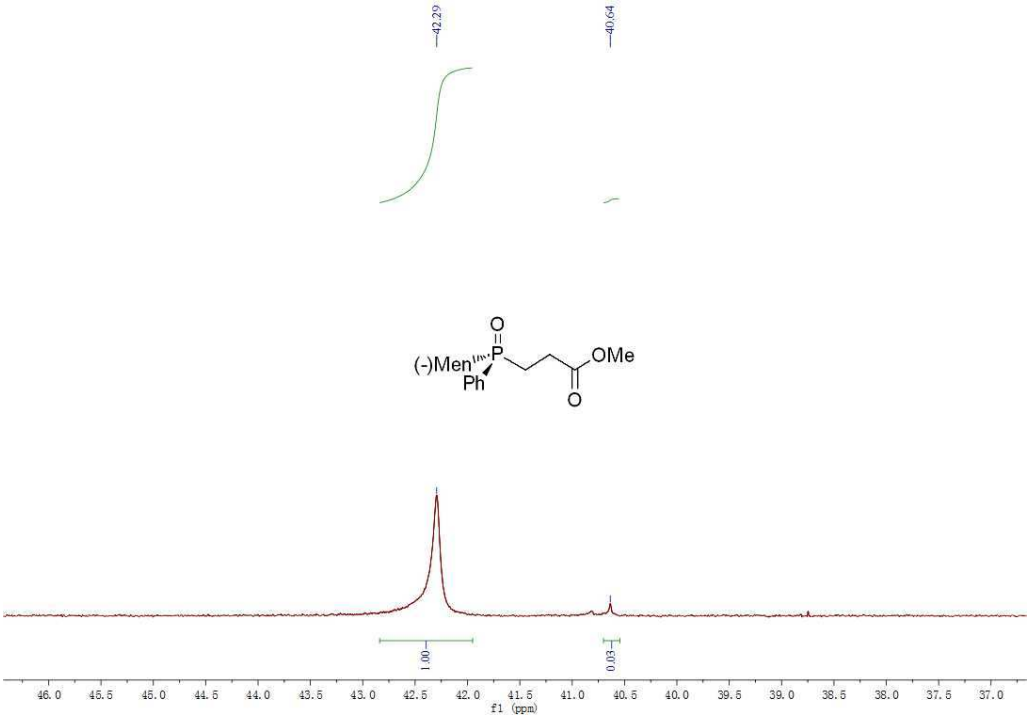


Methyl (S_P)-3-[(–)-Menthylphenylphosphoryl]propanoate, 5a

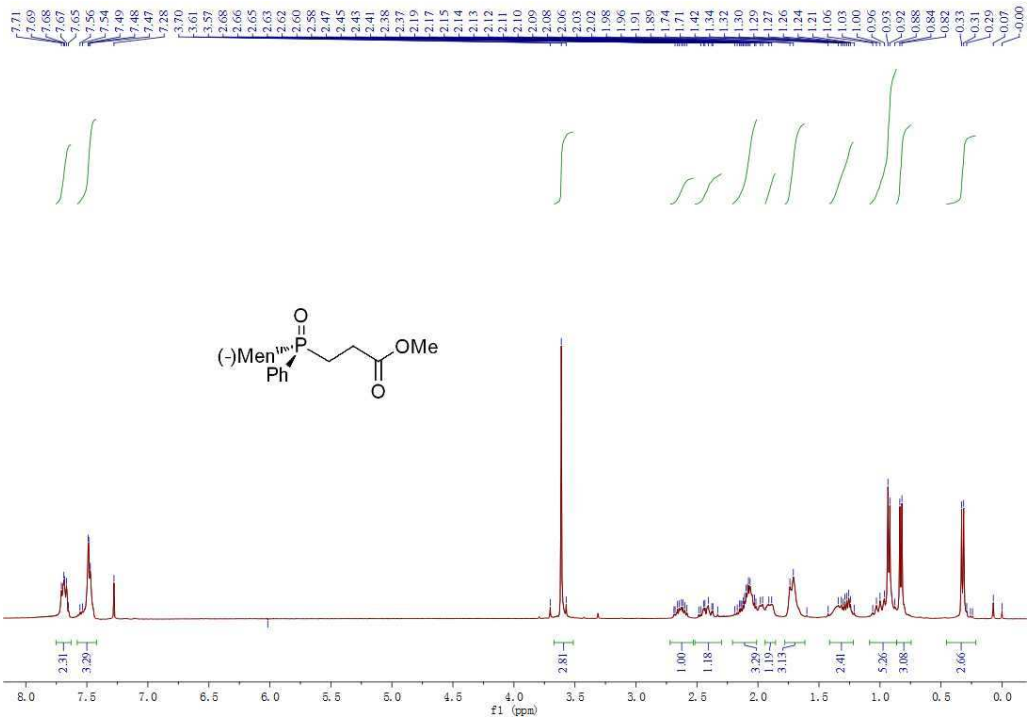
^{31}P-NMR spectroscopy of crude 5a



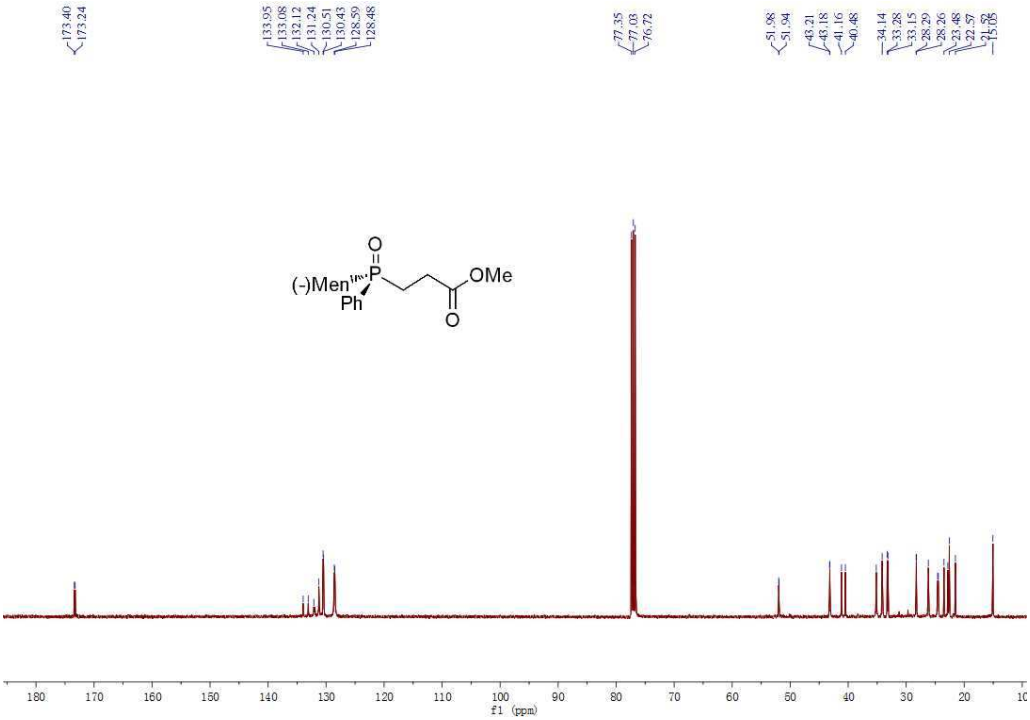
^{31}P-NMR spectroscopy of isolated 5a



^{1}H-NMR spectroscopy of isolated 5a

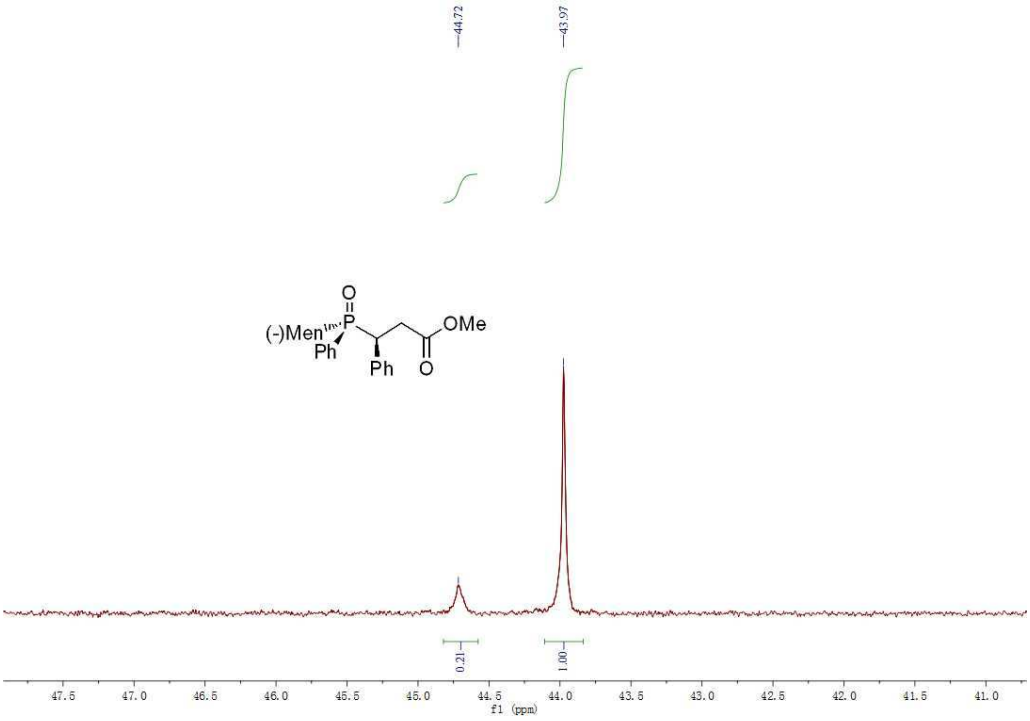


^{13}C-NMR spectroscopy of isolated 5a

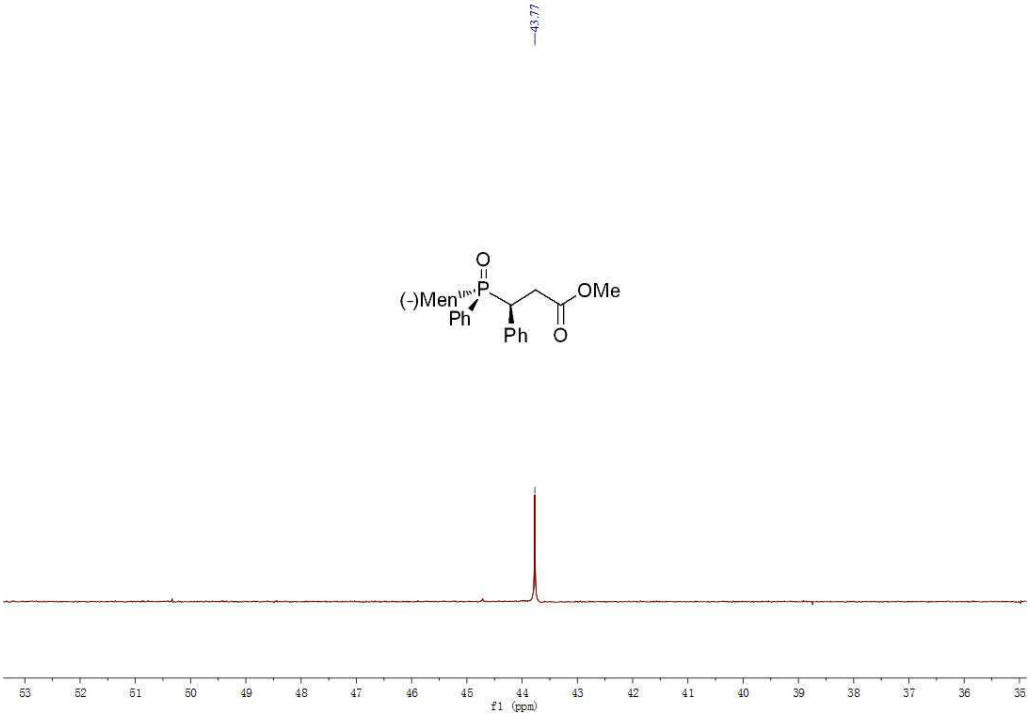


Methyl (S_P)-3-[(–)-Menthylphenylphosphoryl]-3-phenylpropanoate, 5b

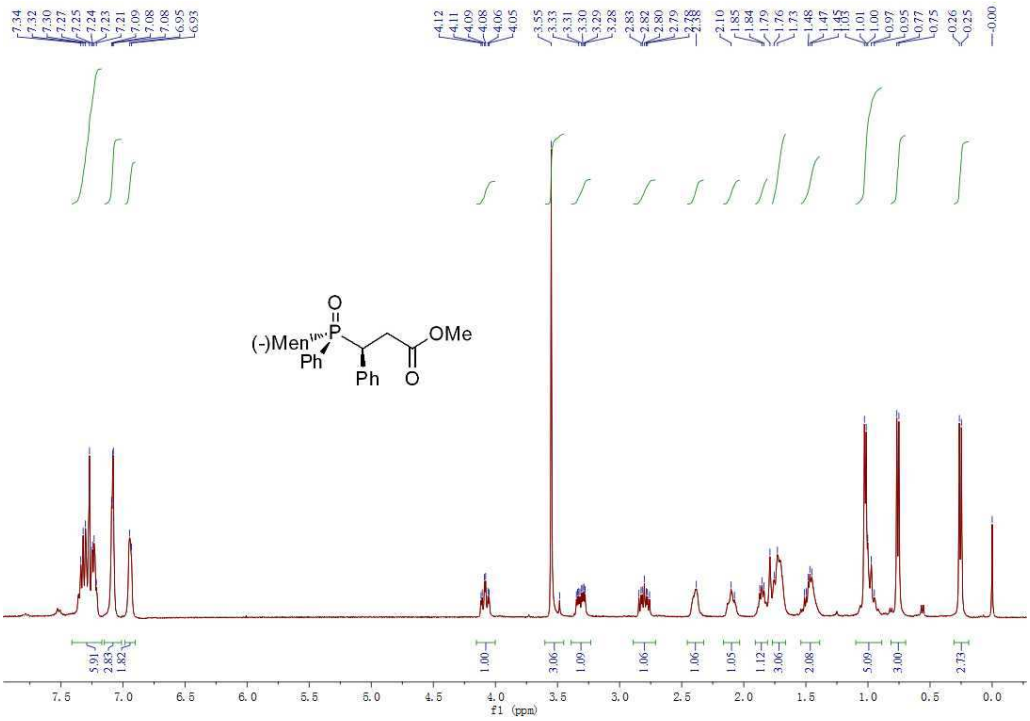
^{31}P-NMR spectroscopy of crude 5b/5b'=83:17



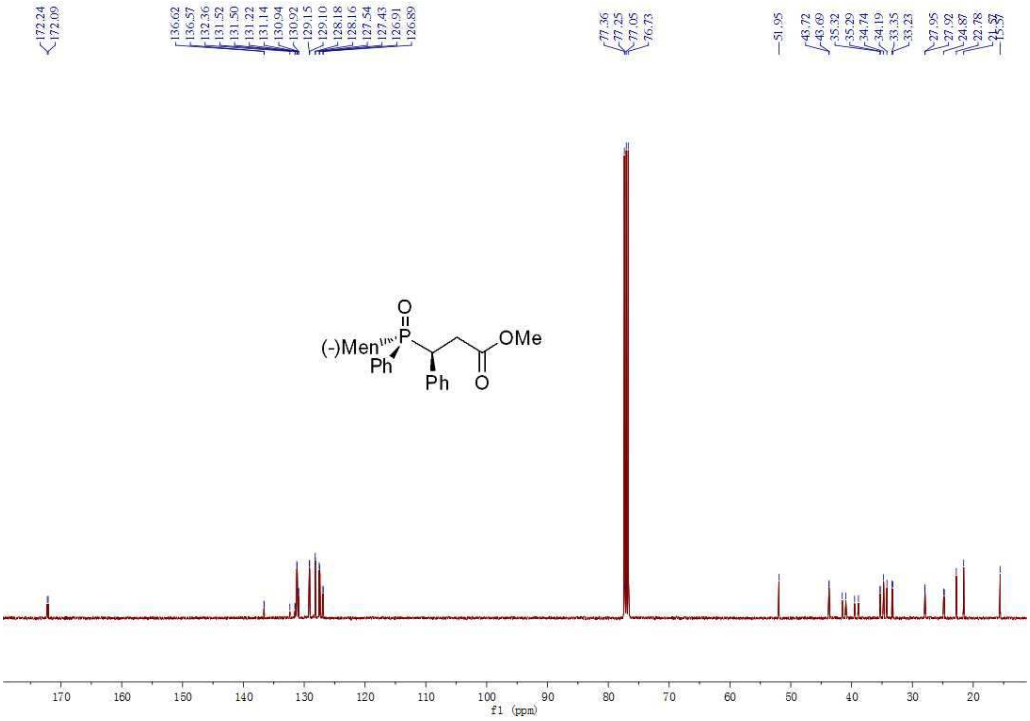
^{31}P-NMR spectroscopy of isolated 5b



^{1}H-NMR spectroscopy of isolated 5b

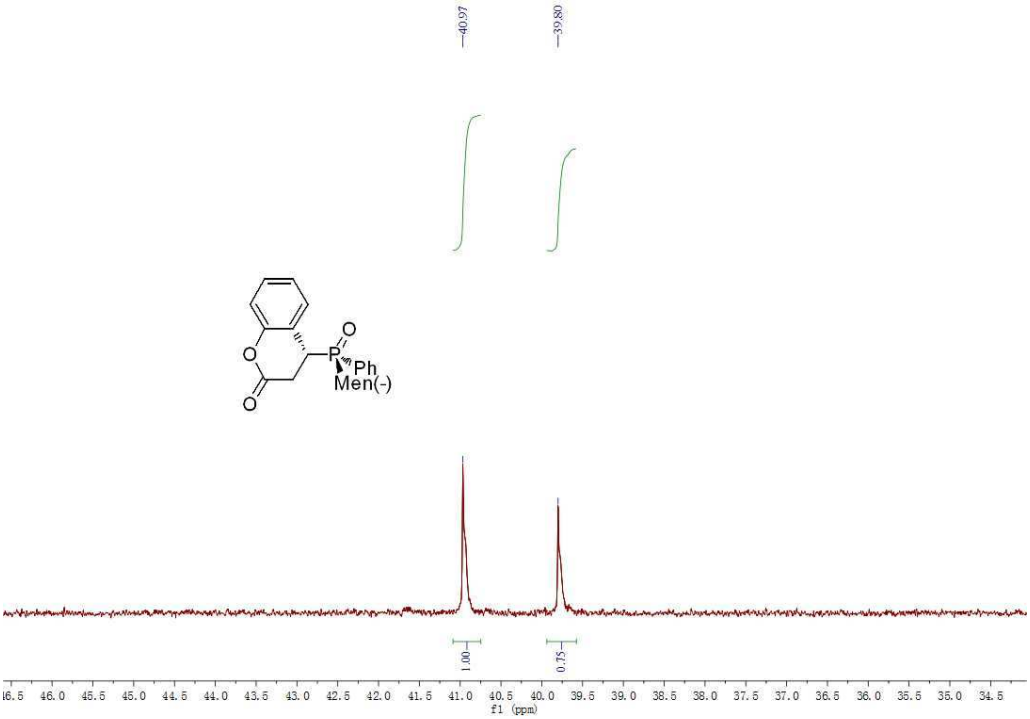


^{13}C-NMR spectroscopy of isolated 5b

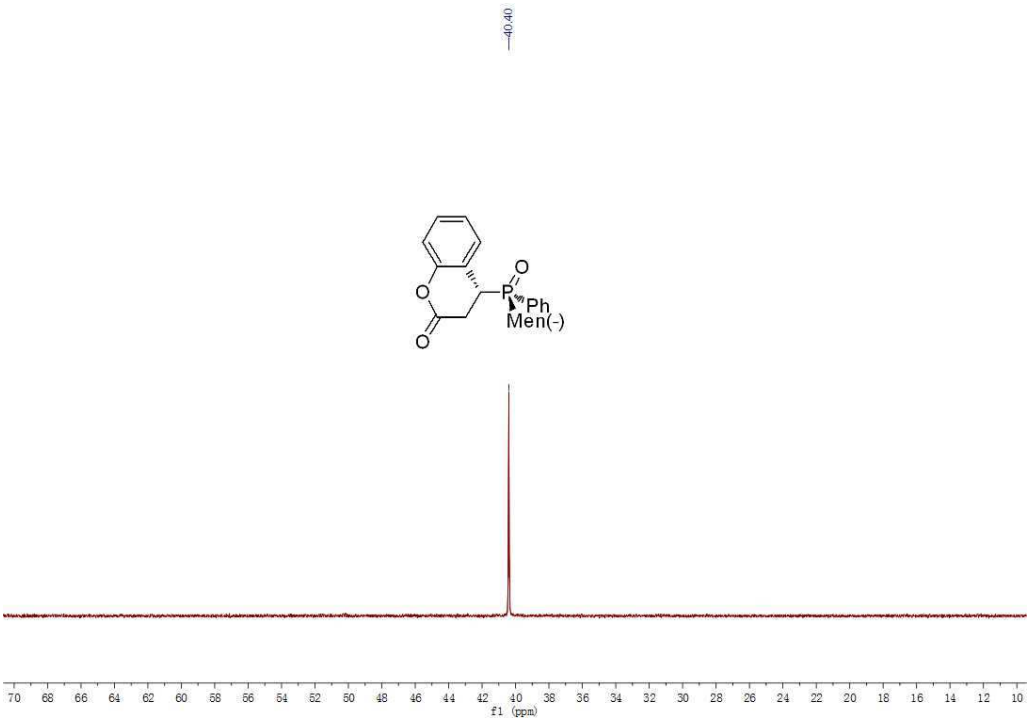


(S_P,*R*)-4-[(–)-Menthylphenylphosphoryl]-4-chroman-2-one, 5c'

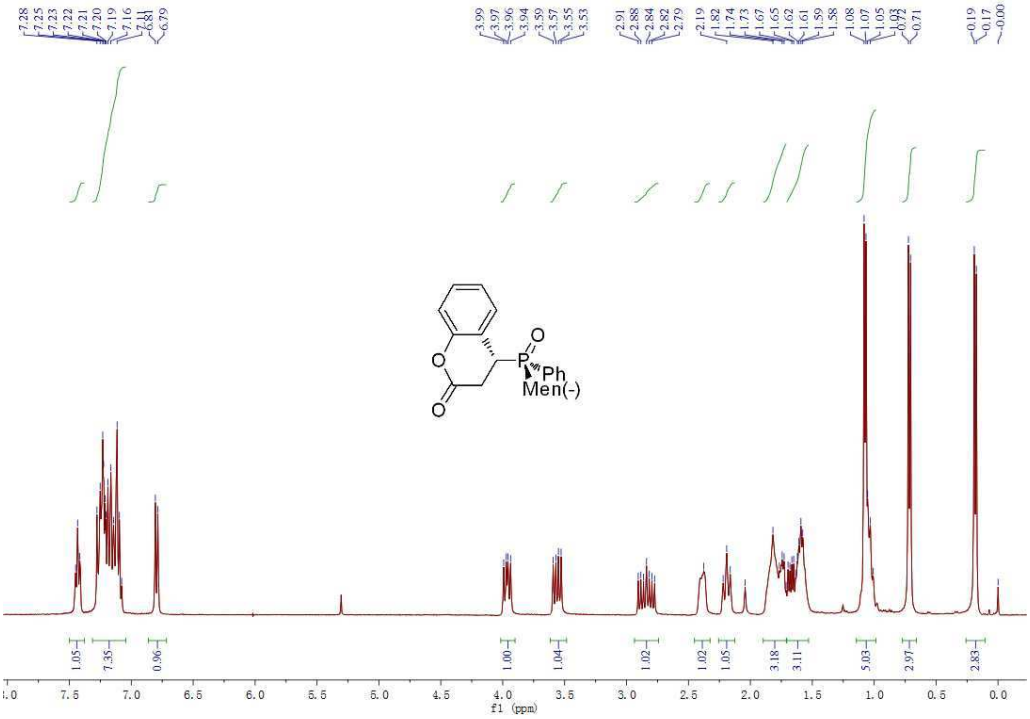
^{31}P-NMR spectroscopy of crude 5c/5c'=43:57



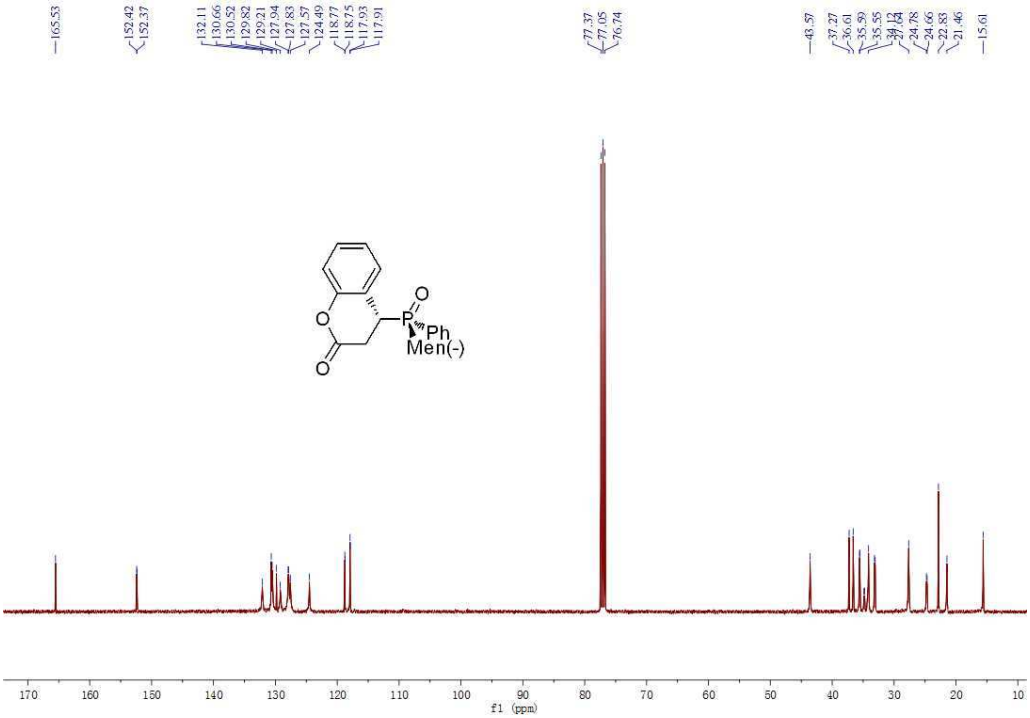
^{31}P-NMR spectroscopy of isolated 5c'



^{1}H-NMR spectroscopy of isolated 5c'

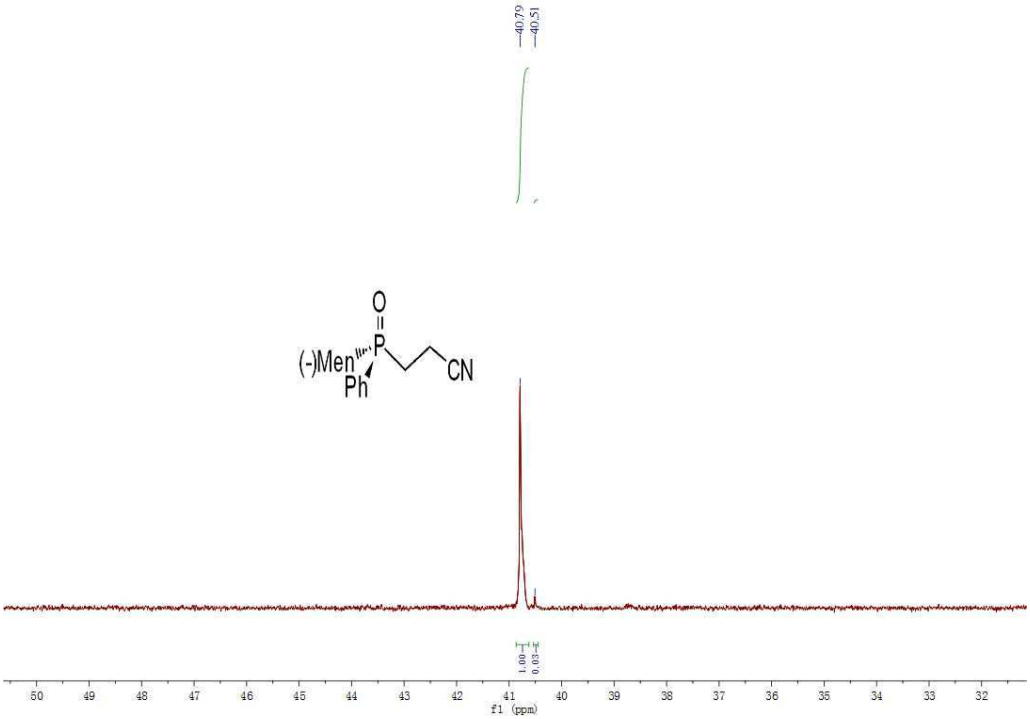


^{13}C-NMR spectroscopy of isolated 5c'

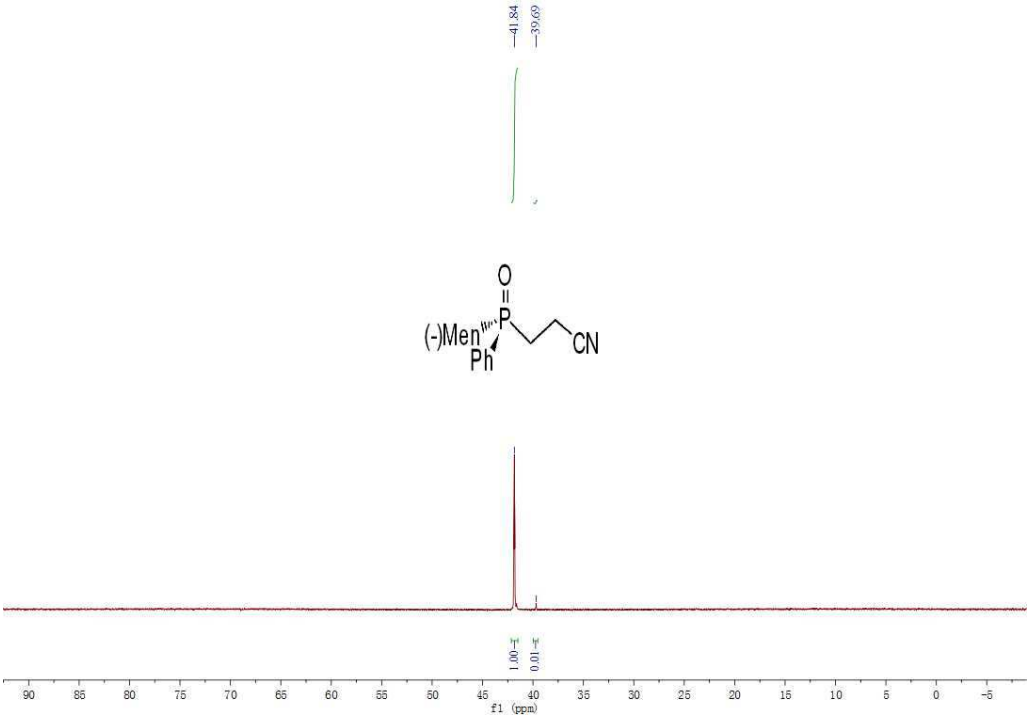


(S_P)-[(–)-Menthylphenylphosphoryl]propanenitrile, 5d

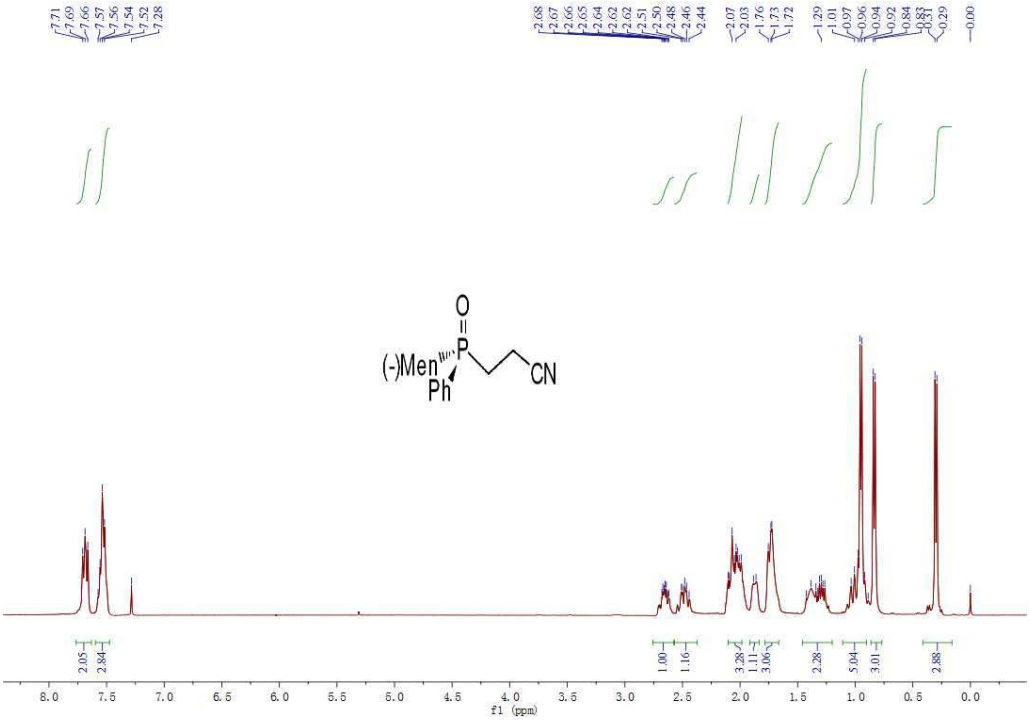
^{31}P-NMR spectroscopy of crude 5d



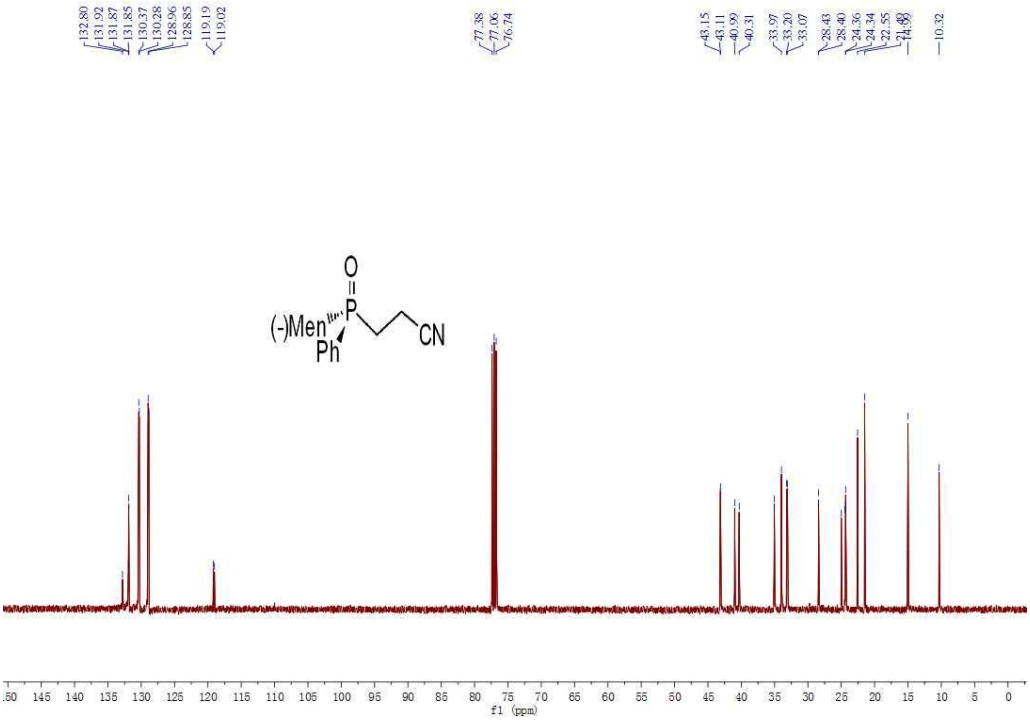
^{31}P-NMR spectroscopy of isolated 5d



^{1}H-NMR spectroscopy of isolated 5d

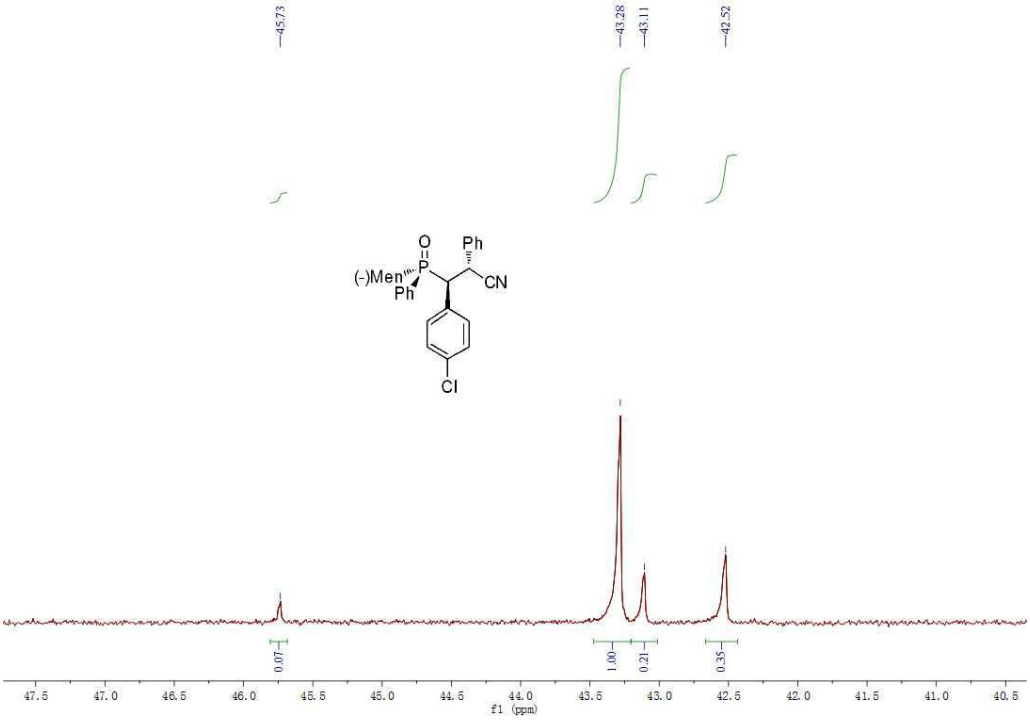


^{13}C-NMR spectroscopy of isolated 5d

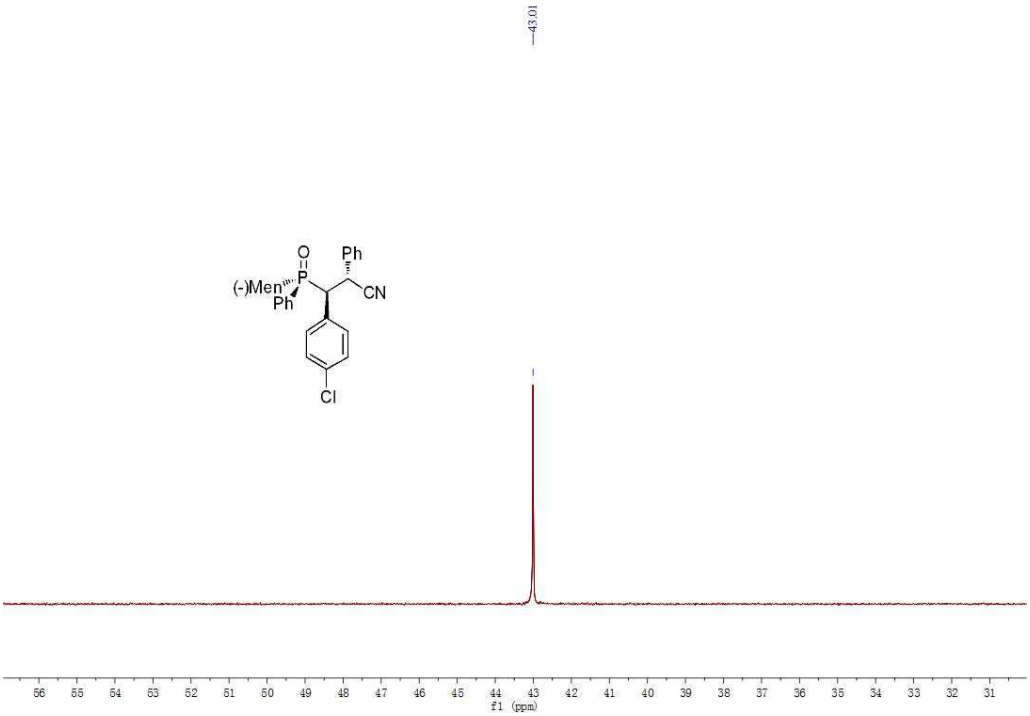


(S_P,*2R,3S*)-3-[(–)-Menthylphenylphosphoryl]-2-phenyl-3-(*p*-chlorophenyl)propanenitrile, 5e

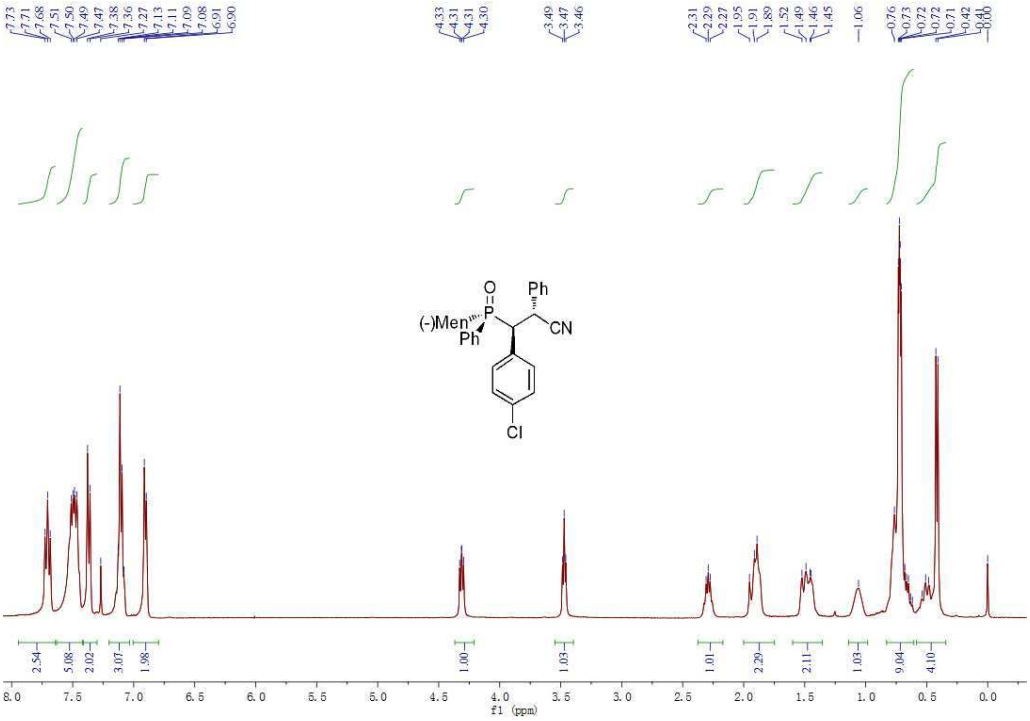
^{31}P-NMR spectroscopy of crude product, the ratio of four stereomers: 22:13:61:4



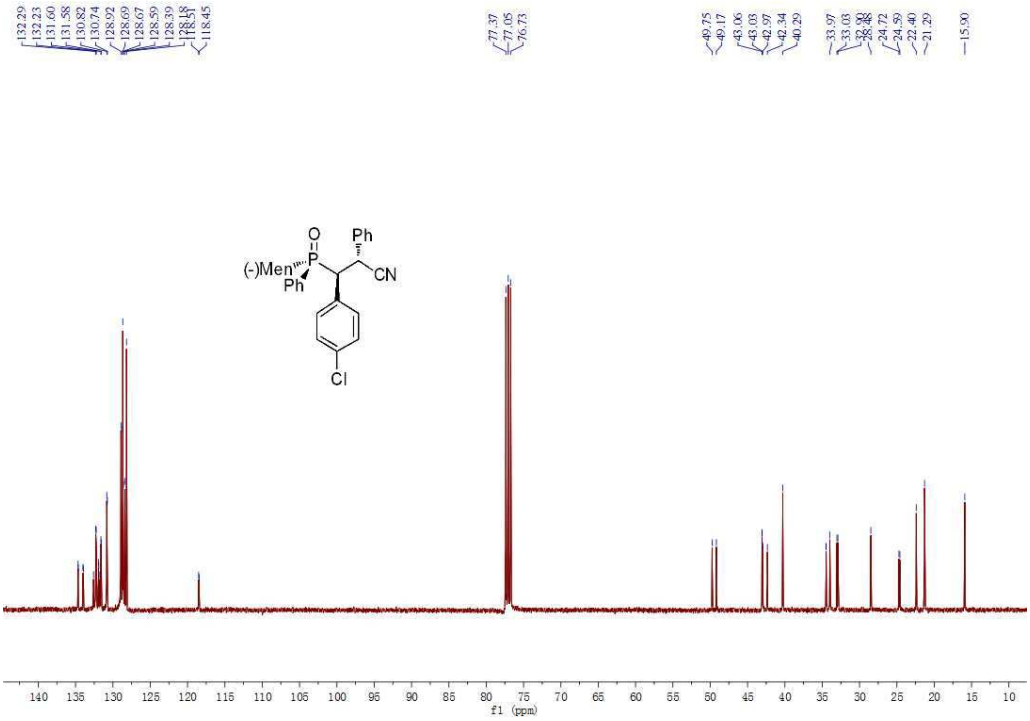
^{31}P-NMR spectroscopy of isolated 5e



^{1}H-NMR spectroscopy of isolated 5e

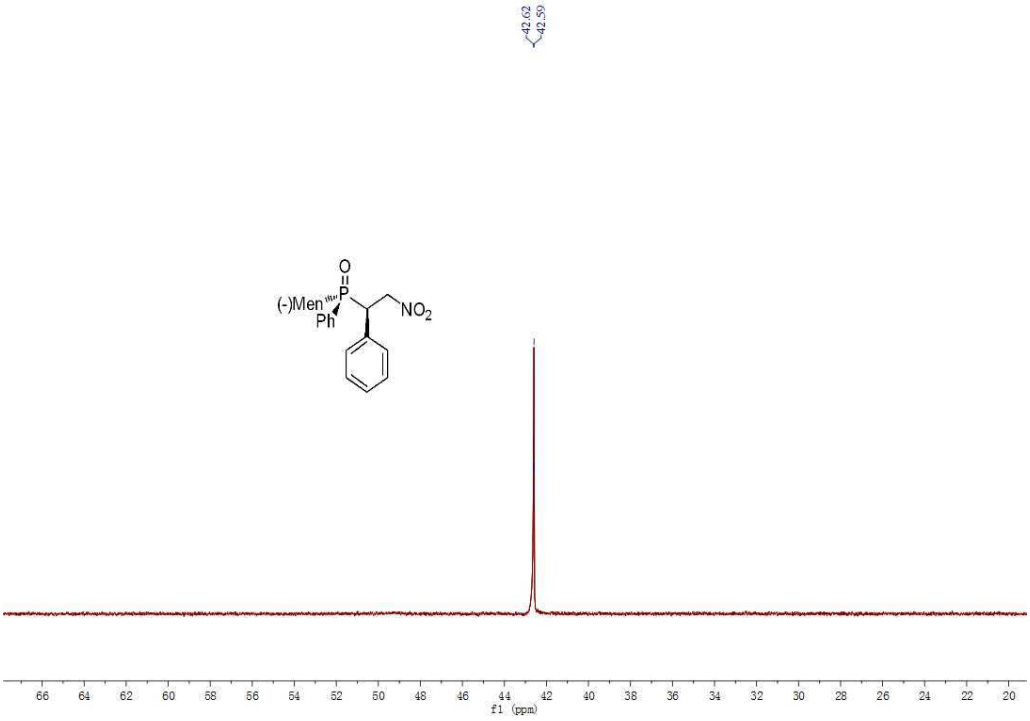


^{13}C-NMR spectroscopy of isolated 5e

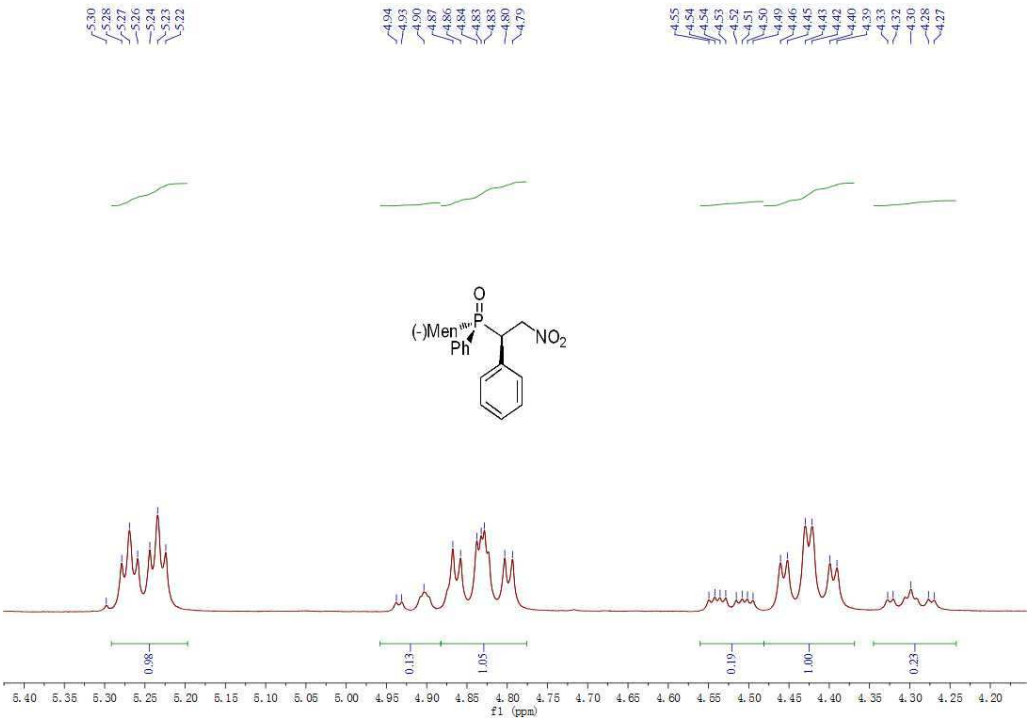


(S_P,S)-(–)-Menthylphenyl-2-nitro-1-phenylethyl phosphine oxide, 5f

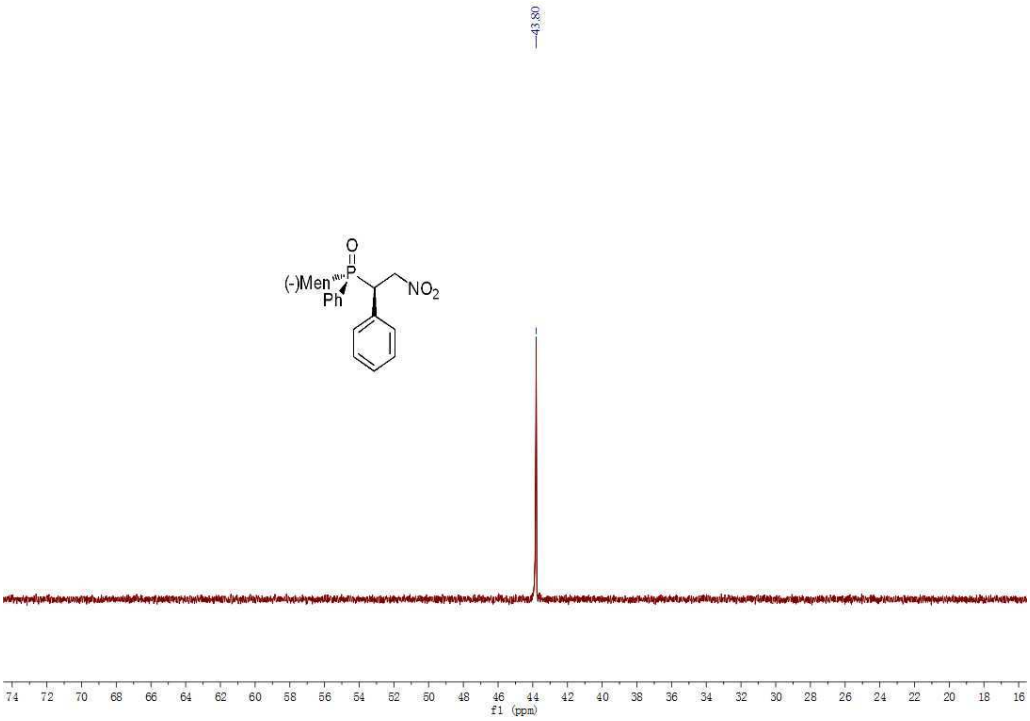
^{31}P-NMR spectroscopy of crude 5f /5f'=81:19



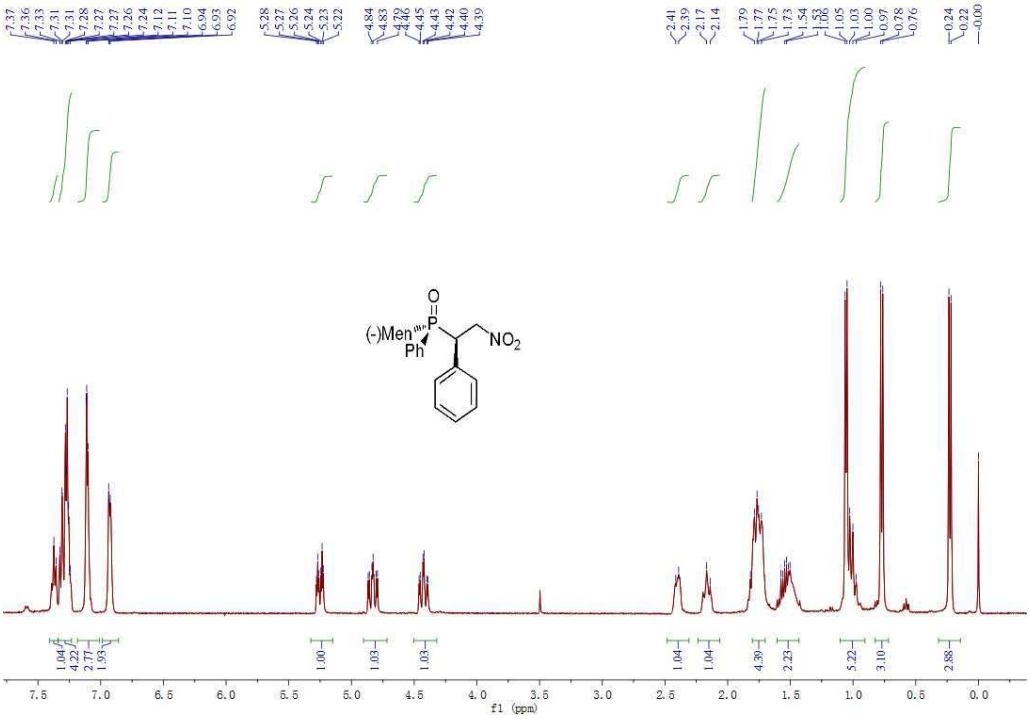
^{1}H-NMR spectroscopy of crude 5f/5f'=81:19



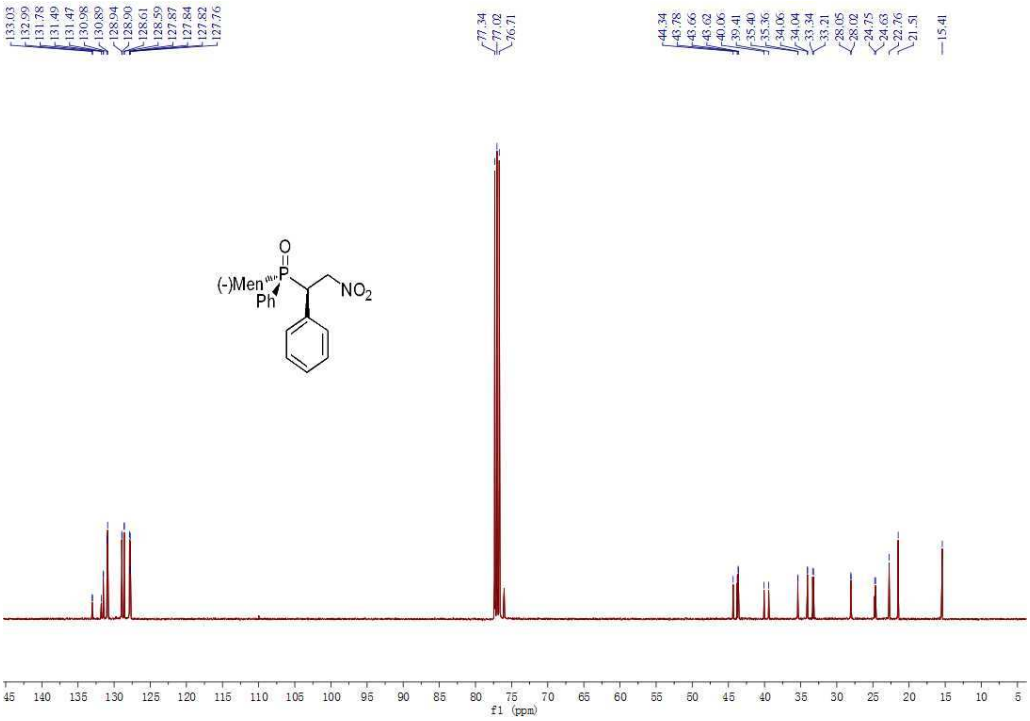
^{31}P-NMR spectroscopy of isolated 5f



^{1}H-NMR spectroscopy of isolated 5f

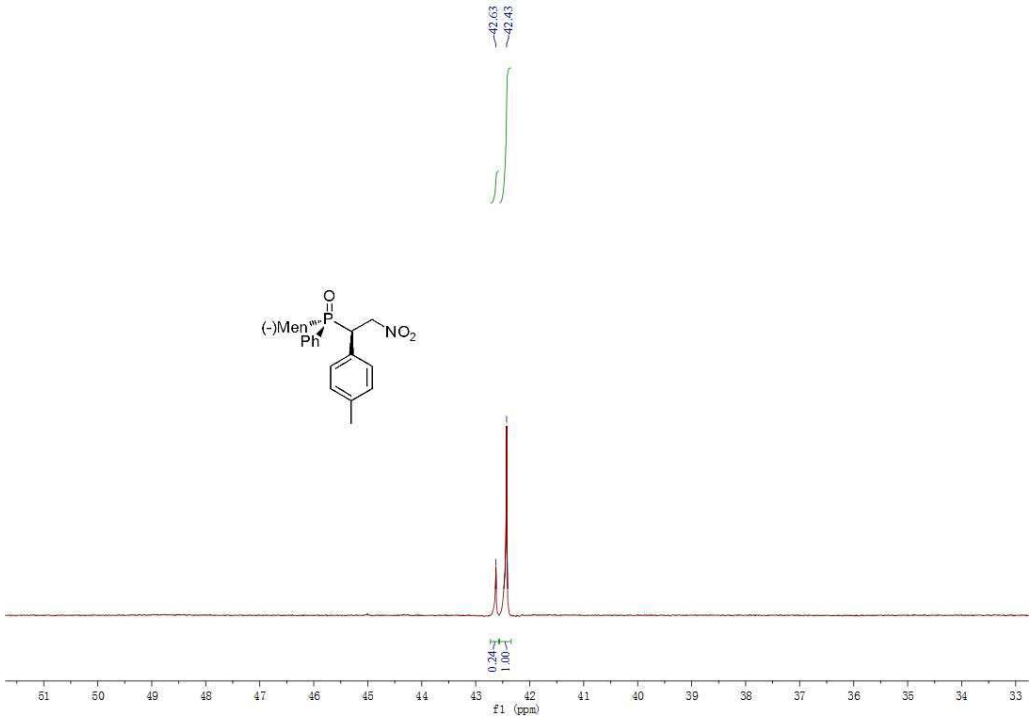


^{13}C-NMR spectroscopy of isolated 5f

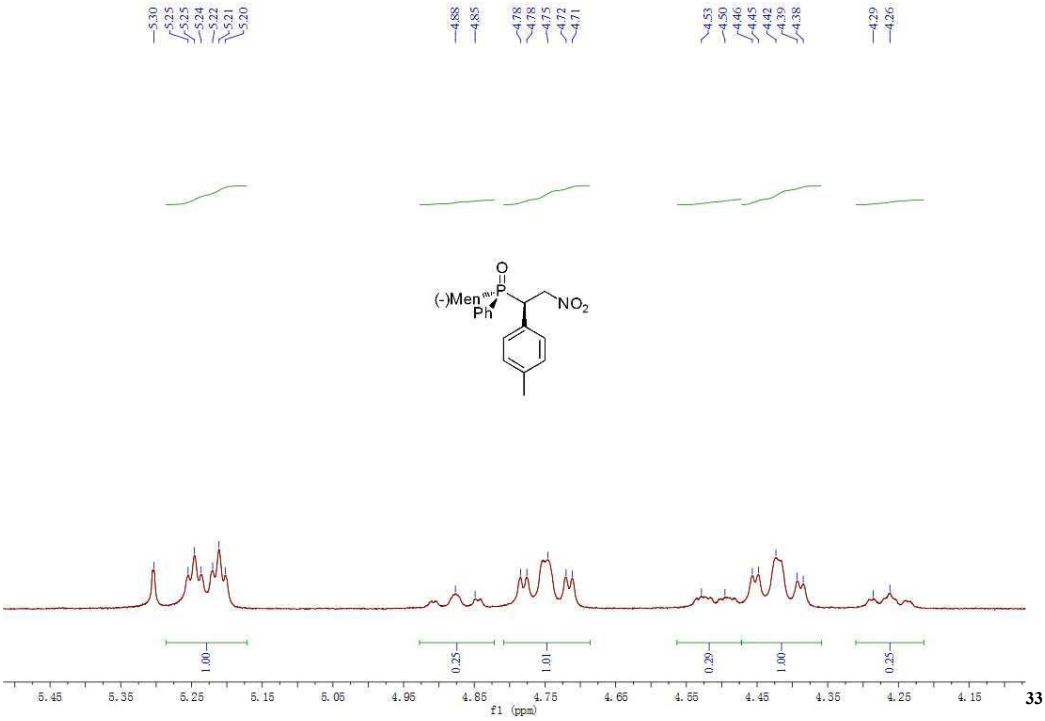


(S_P,S)-(–)-Menthylphenyl-2-nitro-1-*p*-methylphenylethyl phosphine oxide, 5g

^{31}P-NMR spectroscopy of crude 5g/5g'=80:20

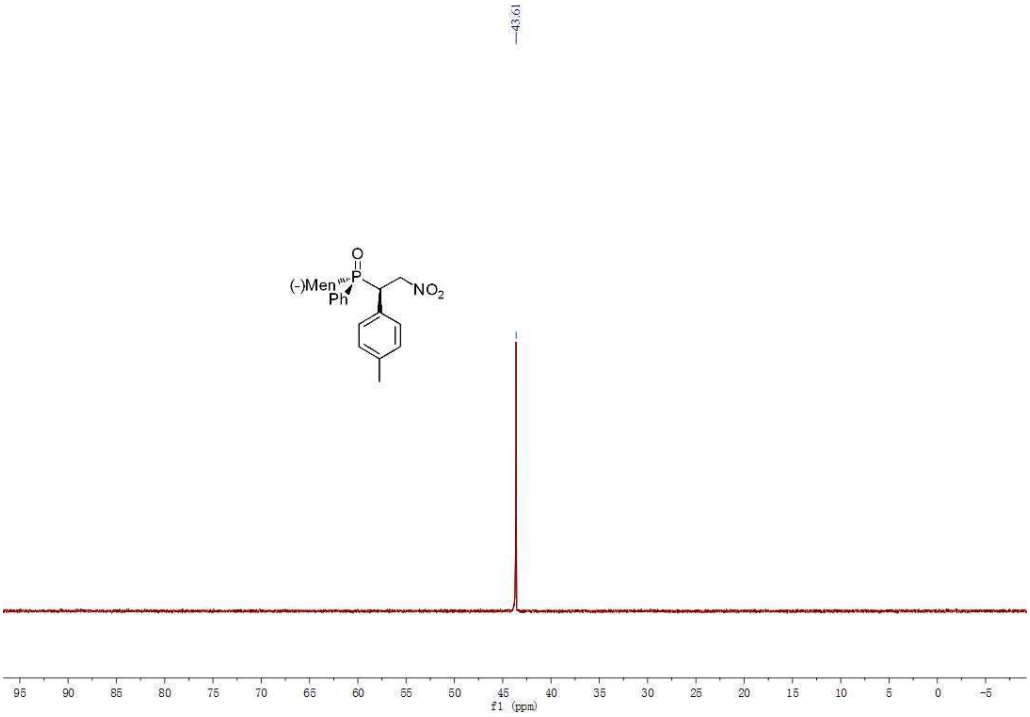


^{1}H-NMR spectroscopy of crude 5g/5g'=80:20

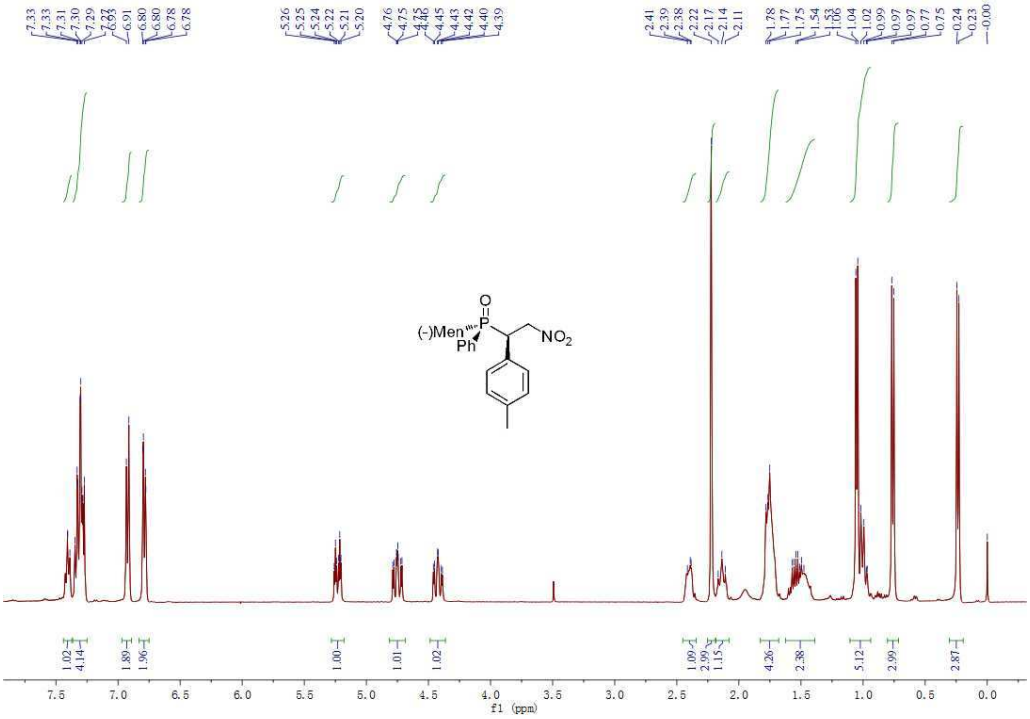


33

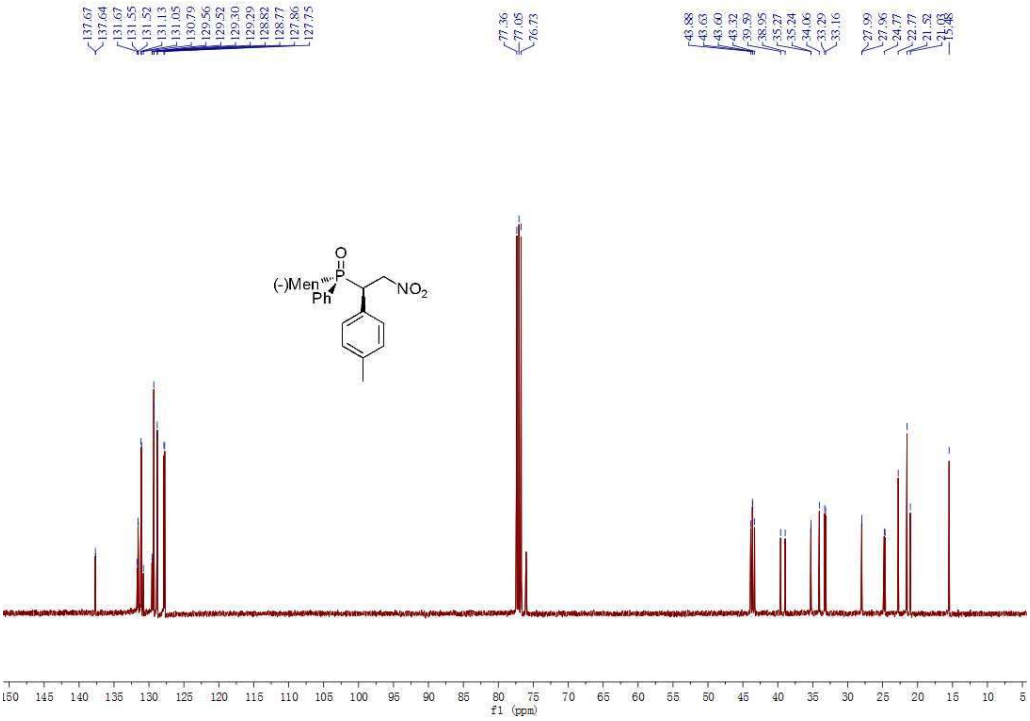
^{31}P-NMR spectroscopy of isolated 5g



^{1}H-NMR spectroscopy of isolated 5g

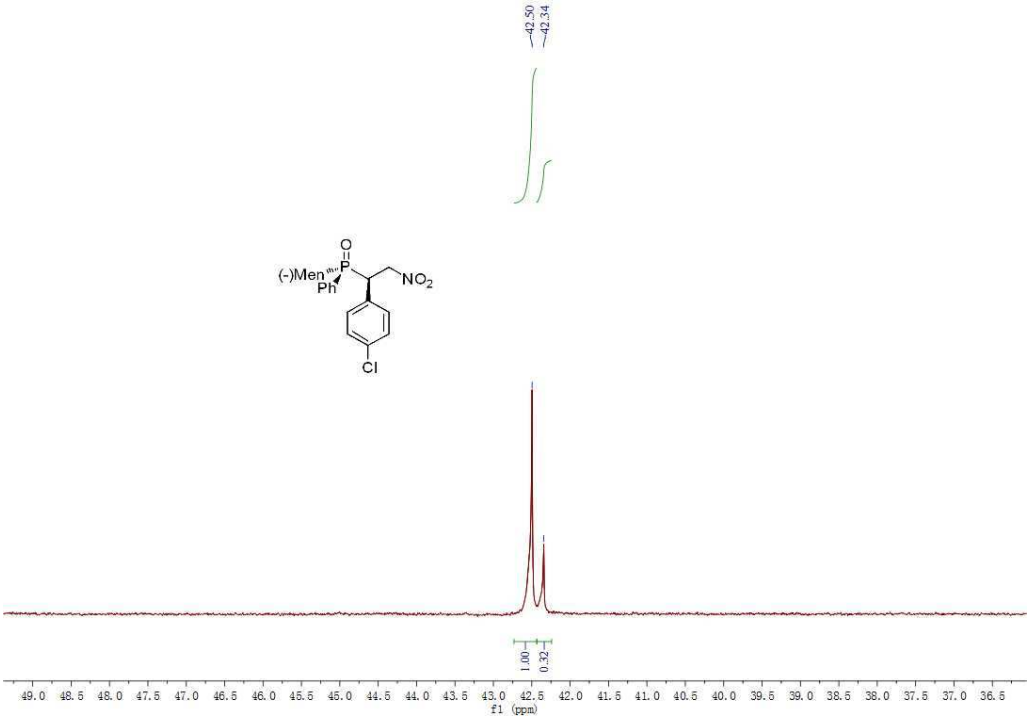


^{13}C-NMR spectroscopy of isolated 5g

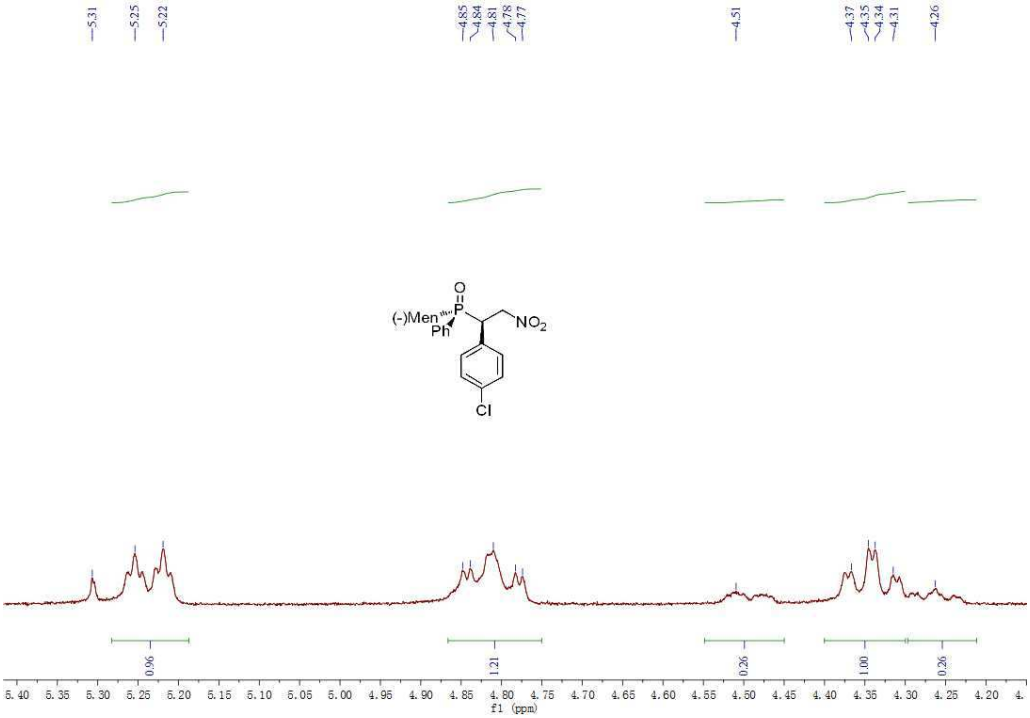


(S_P,S)-(–)-Menthylphenyl-2-nitro-1-*p*-chlorophenylethyl phosphine oxide, 5h

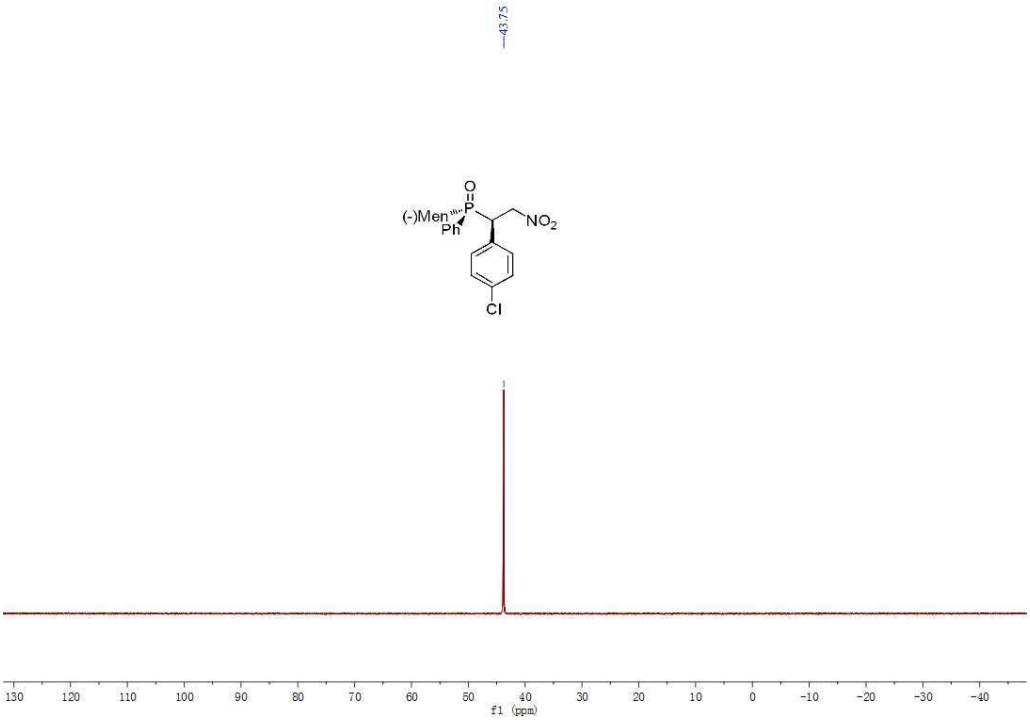
^{31}P-NMR spectroscopy of crude 5h/5h'=79:21



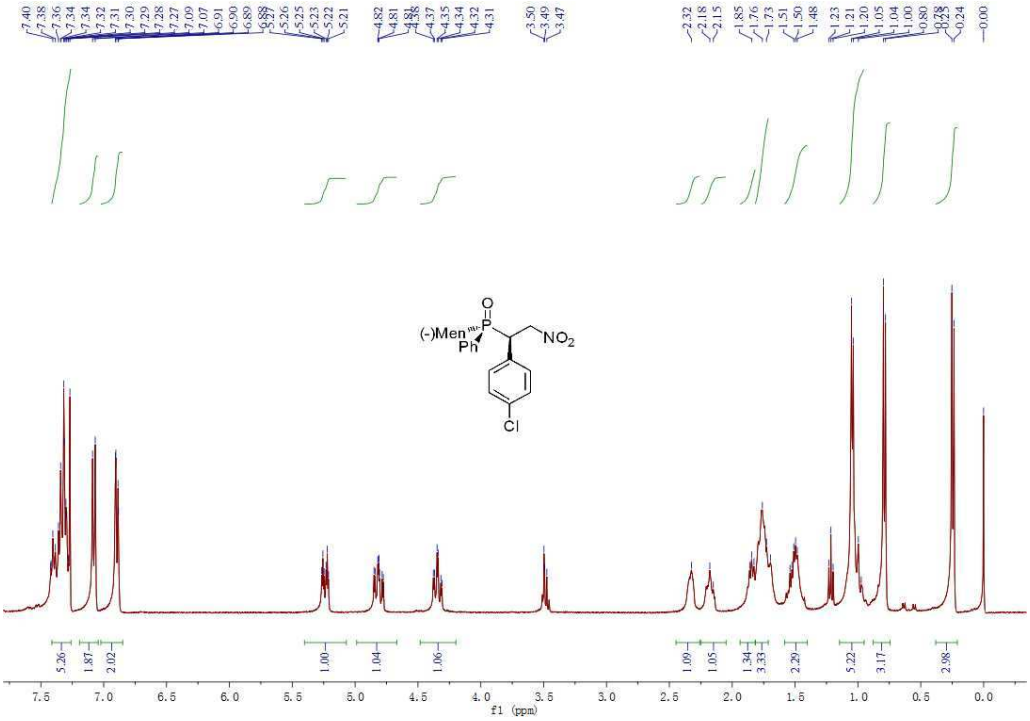
^{1}H-NMR spectroscopy of crude 5h/5h'=79:21



^{31}P-NMR spectroscopy of isolated 5h



^{1}H-NMR spectroscopy of isolated 5h



^{13}C-NMR spectroscopy of isolated 5h