Electronic Supplementary Information

Alcohol-Based Michaelis-Arbuzov Reaction: an Efficient and Environmentally-Benign Way for C-P(O) Bond Formation

Xiantao Ma,[a,b,c] Qing Xu,[a,b]* Huan Li,[a] Chenliang Su,[c] Lei Yu,[b] Xu Zhang,[b] Hongen Cao,[b] and Li-Biao Han[b,d]*

[a] *College of Chemistry and Materials Engineering, Wenzhou University, Wenzhou, Zhejiang 325035, China. Fax: (+)-86-577-86689302; Tel: (+)-86-138-57745327.*

[b] *Institute of Pesticide of School of Horticulture and Plant Protection and School of Chemistry and Chemical Engineering, Yangzhou University, Yangzhou, Jiangsu 225002, China.*

[c] *SZU-NUS Collaborative Innovation Center for Optoelectronic Science & Technology, Key Laboratory of Optoelectronic Devices and Systems of Ministry of Education and Guangdong Province, College of Optoelectronic Engineering, Shenzhen University, Shenzhen, Guangdong 518060, China.*

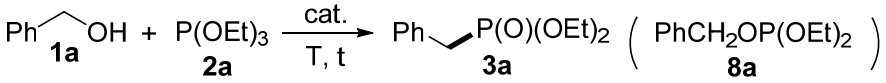
[d] *National Institute of Advanced Industrial Science and Technology (AIST), Tsukuba, Ibaraki 305-8565, Japan. Fax: (+)-81-29-8616344; Tel: (+)-(+)-81-29-8614855.*

E-mails: qing-xu@wzu.edu.cn; libiao-han@aist.go.jp

Table of contents

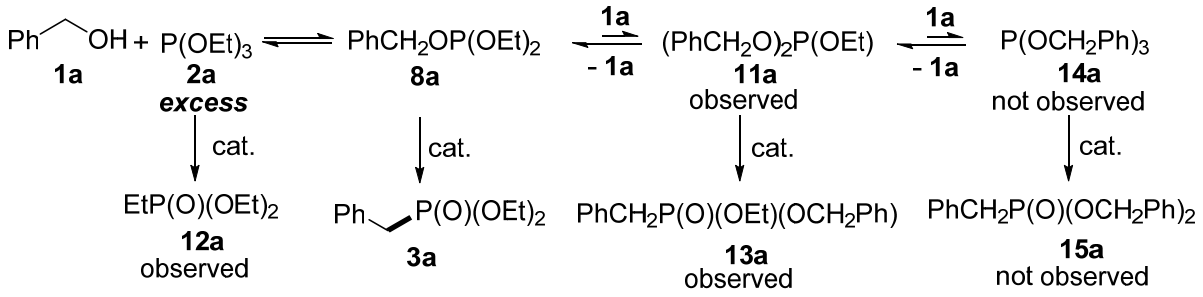
1. Detailed Condition Screening Tables

Table S1. Detailed catalyst screening and condition optimization for iodide-catalyzed coupling of $PhCH_2OH$ with $P(OEt)_3$ forming $PhCH_2P(O)(OEt)_2$.[a]



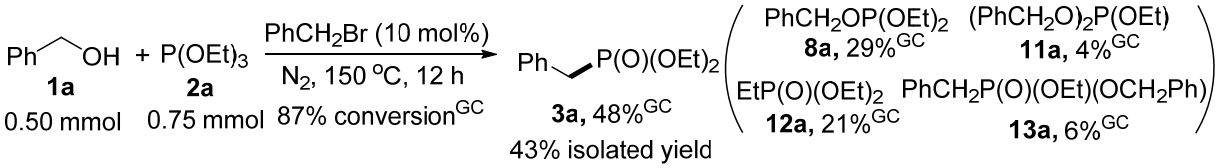
entry	cat. (mol%)	solvent	T, t	**3a/8a**[b]	**3a**%[c]
1[d]	$PhCH_2Br$ (10)	none	150 °C, 24 h	-	0
2[e,f]	$PhCH_2Br$ (10)	none	150 °C, 12 h	62/38	48 (43)
3[f]	$PhCH_2Br$ (10) *n*-Bu_4NI (10)	none	150 °C, 12 h	>99/1	94 (85)
4[f]	*n*-Bu_4NI (10)	none	150 °C, 12 h	>99/1	95 (90)
5[f]	*n*-Bu_4NI (2)	none	150 °C, 12 h	>99/1	95 (90)
6[f]	*n*-Bu_4NI (10)	none	125 °C, 24 h	>99/1	95 (90)
***7*[f]**	***n*-Bu_4NI (2)**	***none***	***125 °C, 24 h***	***>99/1***	***97 (90)***
8[e,f]	*n*-Bu_4NI (2)	none	100 °C, 24 h	25/75	23
9[f]	*n*-Bu_4NI (1)	none	125 °C, 24 h	>99/1	83
10[e,f]	*n*-Bu_4NI (2)	toluene	125 °C, 24 h	35/65	28
11[f]	*n*-Bu_4NI (2)	dioxane	125 °C, 24 h	95/5	89
12[f]	*n*-Bu_4NI (2)	MeCN	125 °C, 24 h	96/4	83
13[e,f]	*n*-Bu_4NBr (2)	none	125 °C, 24 h	49/51	40
14[e,f]	*n*-Bu_4NCl (2)	none	125 °C, 24 h	42/58	30
15[e,f]	KI (2)	none	125 °C, 24 h	55/45	39
16[f,g]	*n*-Bu_4NI (2)	none	125 °C, 24 h	>99/1	86
17[f,h]	*n*-Bu_4NI (2)	none	125 °C, 24 h	>99/1	90 (85)
18[f,i]	*n*-Bu_4NI (2)	none	125 °C, 24 h	>99/1	96 (90)
19[e,j]	none	none	125 °C, 24 h	1/99	<1
20[k]	*n*-Bu_4NI (2)	none	125 °C, 24 h	-	(90)

[a] Unless otherwise noted, the neat mixture of **1a** (0.50 mmol), **2a** (0.75 mmol, 1.5 equiv.), and a catalyst sealed under N_2 in a 20 mL Schlenk tube was heated and monitored by TLC/GC-MS. Although the single to triple transesterified phosphites $P(OEt)_2(OCH_2Ph)$ (**8a**), $P(OEt)(OCH_2Ph)_2$ (**11a**), and $P(OCH_2Ph)_3$ (**14a**) and their Michaelis-Arbuzov reaction products $PhCH_2P(O)(OEt)(OCH_2Ph)$ (**13a**) and $PhCH_2P(O)(OCH_2Ph)_2$ (**15a**), as well as **2a**'s Michaelis-Arbuzov reaction product $EtP(O)(OEt)_2$ (**12a**), are all potential byproducts of the reaction (**see the scheme in the next page**), **11a**, **12a**, and **13a** were mostly observed in trace yields, and **14a** and **15a** were not observed at all. This is because the three transesterification steps are all reversible equilibrium reactions, and the use of excess **2a** can drive the equilibriums to go leftward and consequently give the least amounts of the byproducts **11a**, **13a**, **14a**, and **15a**. [b] Determined by GC-MS. [c] GC yields (isolated yields in parentheses) based on **1a**. [d] $HP(O)(OEt)_2$ was used instead of **2a**. [e] Trace **11a** was also observed. [f] Trace **12a** and **13a** were also observed. [g] 1.2 equiv. **2a**. [h] 1.3 equiv. **2a**. [i] 2.0 equiv. **2a**. [j] The major product **8a** is too air sensitive to be isolated pure. [k] The reactants and catalyst were added to an unsealed tube reactor (20 mL) equipped with a normal condenser, and then heated at 125 °C under N_2 protection.

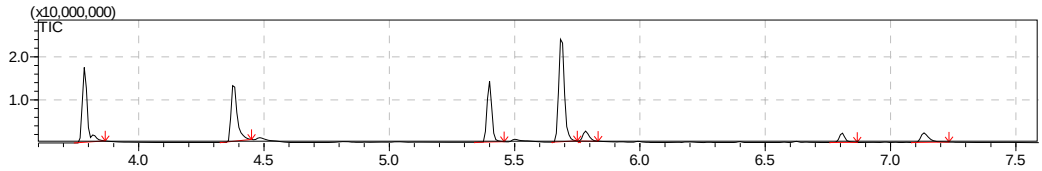


GC-MS Spectra and analysis of some key reactions in Table S1:

(1) GC-MS spectra of entry 2:



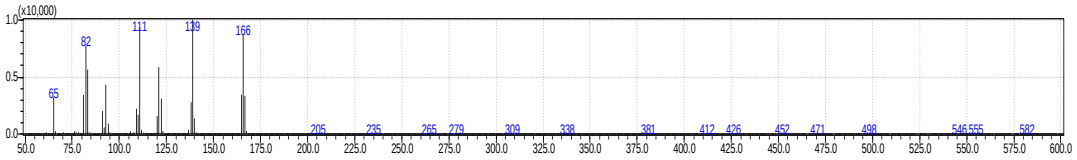
GC Spectra



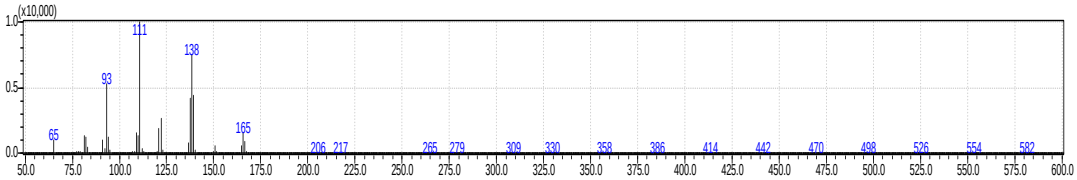
Ret.Time	Start Tm	End Tm	m/z	Area	Area%	Height	Height%	A/H	Mark
3.784	3.733	3.900	TIC	25203994	21.44	17410170	23.28	1.44	MI
4.379	4.325	4.450	TIC	22549691	19.18	12894942	17.24	1.74	MI
5.399	5.342	5.467	TIC	19151155	16.29	14123466	18.88	1.35	MI
5.687	5.633	5.742	TIC	37972237	32.30	23681276	31.66	1.60	MI
5.783	5.750	5.833	TIC	3993975	3.40	2328195	3.11	1.71	MI
6.806	6.758	6.867	TIC	3417989	2.91	2137788	2.86	1.59	MI
7.134	7.083	7.258	TIC	5266452	4.48	2224331	2.97	2.36	MI

MS Spectra

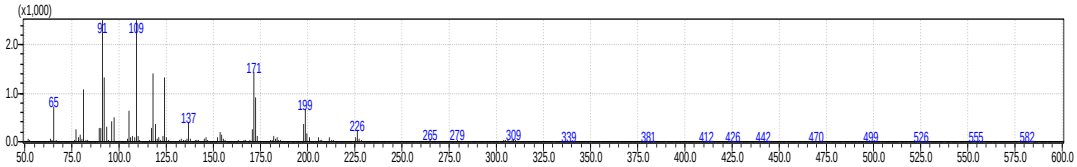
T =3.784 min, m/z = 166, $P(OEt)_3$ (**2a**)



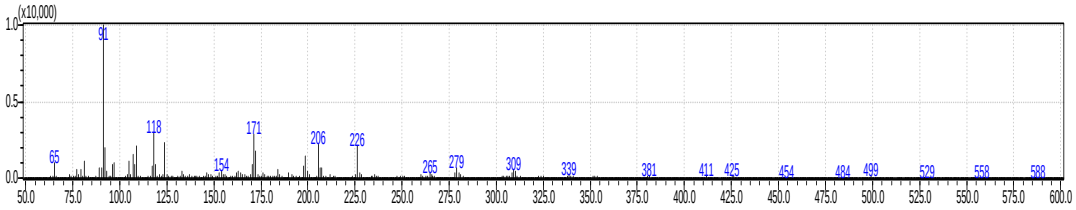
T = 4.379 min, m/z = 166, $EtP(O)(OEt)_2$ (**12a**)



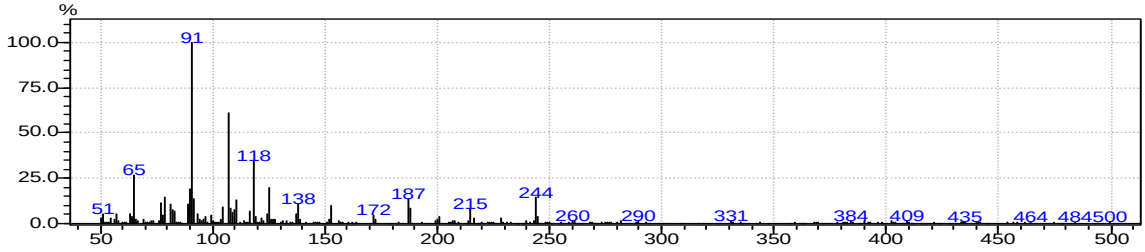
T = 5.399 min, m/z = 228, $P(OEt)_2(OCH_2Ph)$ (**8a**)



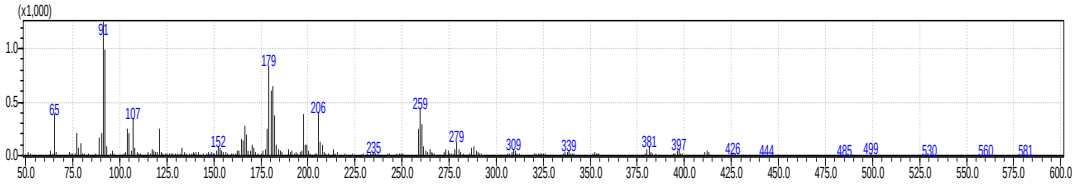
T = 5.687 min, m/z = 228, $PhCH_2P(O)(OEt)_2$ (**3a**)



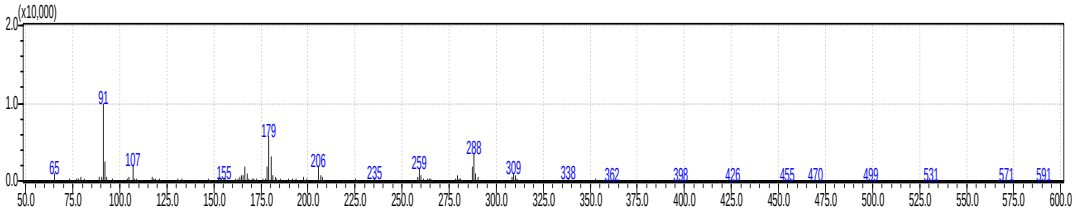
T = 5.783 min, m/z = 244, $P(O)(OEt)_2(OCH_2Ph)$ (formed by oxidation of **8a**)



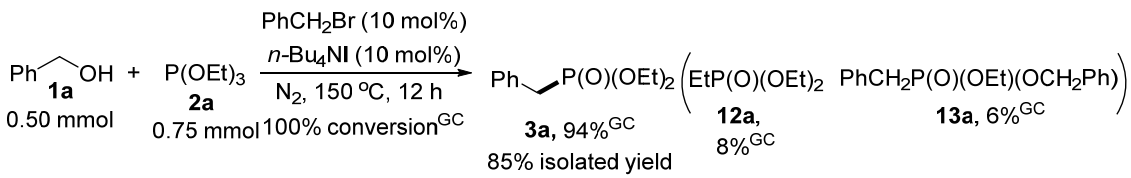
T = 6.806 min, m/z = = 290, $P(OEt)(OCH_2Ph)_2$ (**11a**)



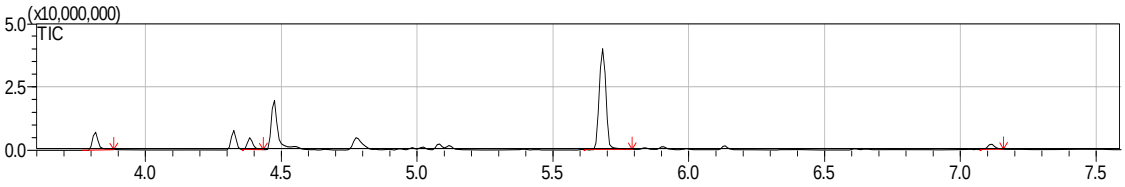
T = 7.134 min, m/z = 290, $PhCH_2P(O)(OEt)(OCH_2Ph)$ (**13a**)



(2) GC-MS spectra of entry 3:



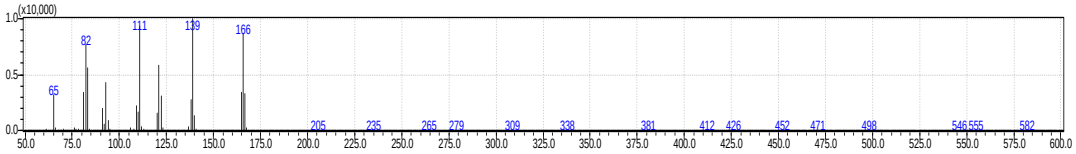
GC spectra



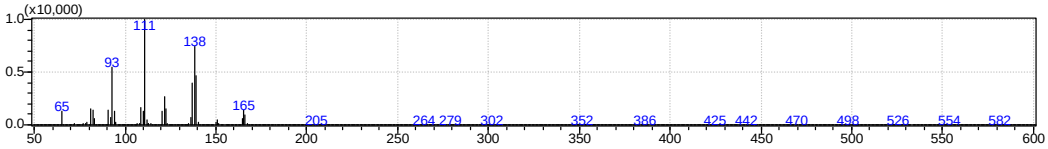
Ret.Time	Start Tm	End Tm	m/z	Area	Area%	Height	Height%	A/H	Mark
3.815	3.767	3.883	TIC	10331990	11.75	7025445	13.19	1.47	MI
4.384	4.358	4.433	TIC	6632360	7.54	4592510	8.62	1.45	MI
5.683	5.617	5.792	TIC	67286853	76.55	39710686	74.54	1.69	MI
7.113	7.075	7.158	TIC	3653848	4.16	1941977	3.65	1.87	MI

MS Spectra

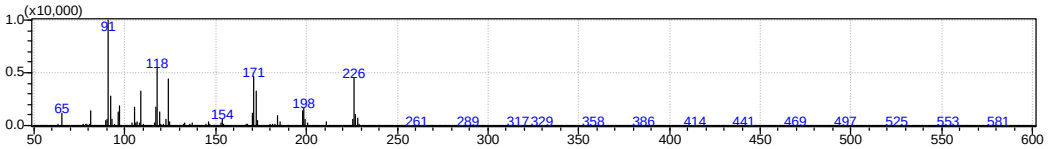
T = 3.815 min, m/z = 166, $P(OEt)_3$ (**2a**)



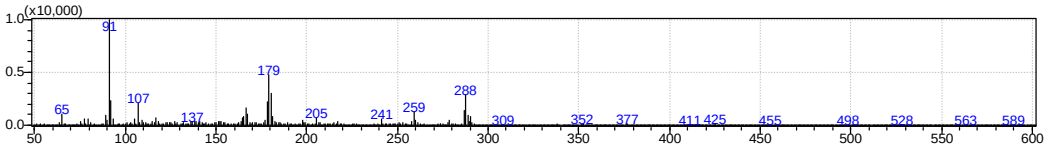
T = 4.384 min, m/z = 166, $EtP(O)(OEt)_2$ (**12a**)



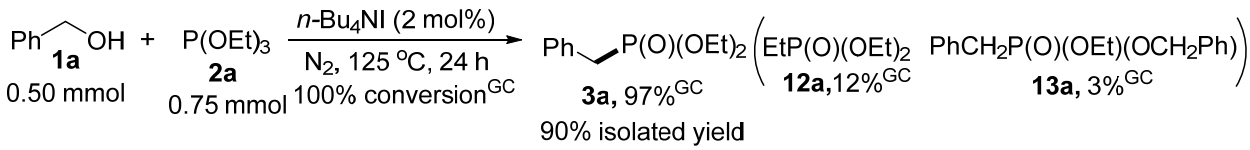
T = 5.683 min, m/z = 228, $PhCH_2P(O)(OEt)_2$ (**3a**)



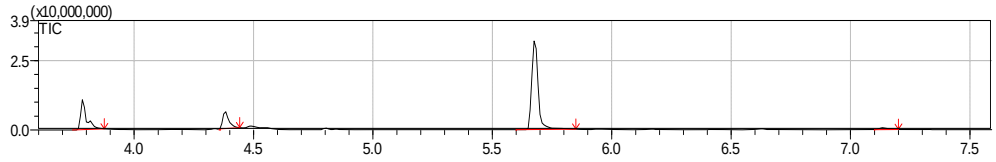
T = 7.113 min, m/z = 290, $PhCH_2P(O)(OEt)(OCH_2Ph)$ (**13a**)



(3) GC-MS spectra of entry 7 (the optimized standard reaction, entry 6 in the text):



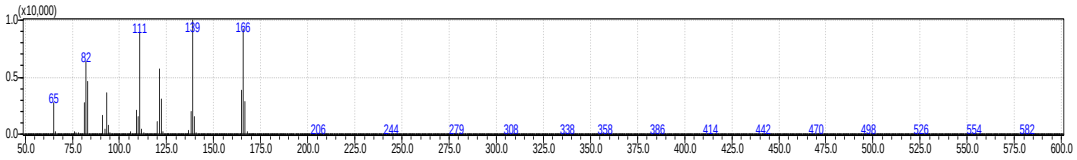
GC spectra



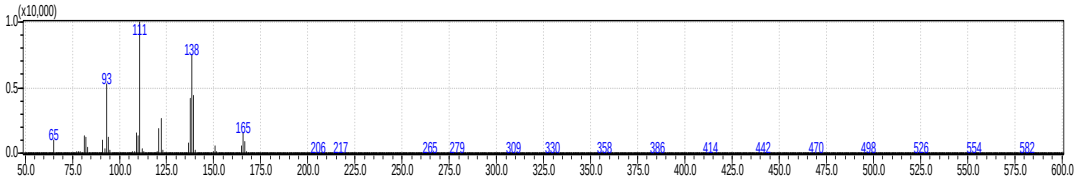
Ret.Time	Start Tm	End Tm	m/z	Area	Area%	Height	Height%	A/H	Mark
3.785	3.742	3.875	TIC	18183649	19.93	10763540	21.79	1.69	MI
4.381	4.358	4.442	TIC	11120391	12.19	6098954	12.34	1.82	MI
5.677	5.600	5.850	TIC	60322426	66.10	31895222	64.55	1.89	MI
7.135	7.100	7.200	TIC	1620357	1.78	649843	1.32	2.48	MI

MS spectra

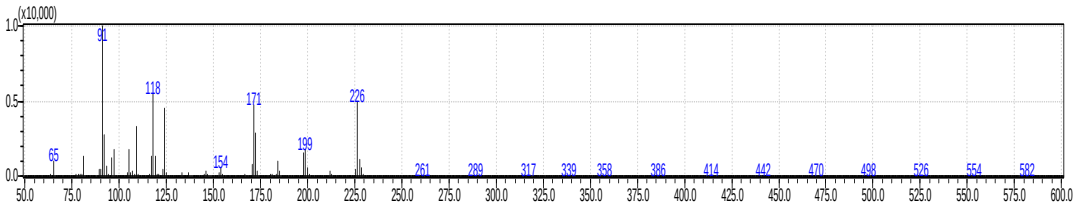
T = 3.785 min, m/z = 166, $P(OEt)_3$ (**2a**)



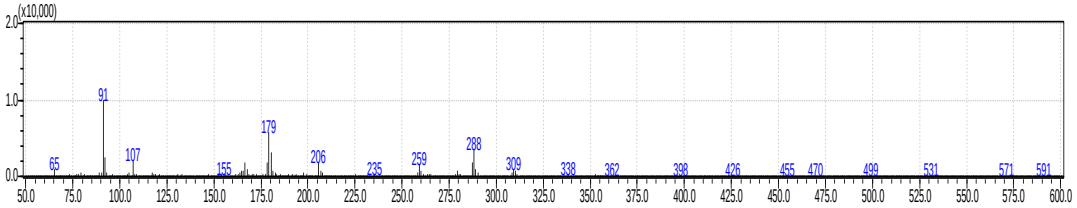
T = 4.381 min, m/z = 166, Et-P(O)$(OEt)_2$ (**12a**)



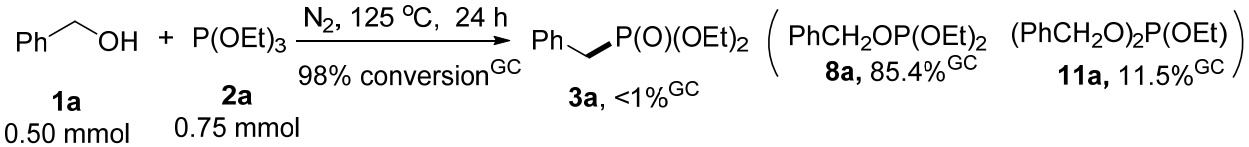
T = 5.677 min, $PhCH_2P(O)(OEt)_2$ (**3a**)



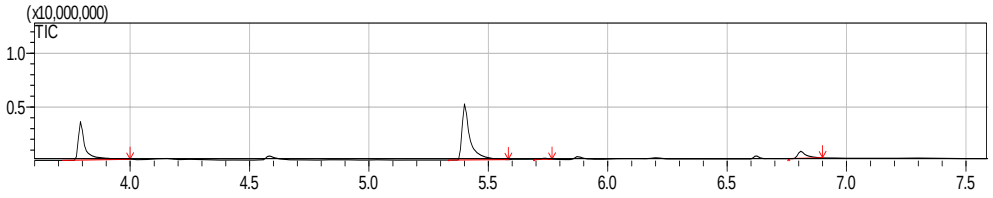
T = 7.135 min, m/z = 290, $PhCH_2P(O)(OEt)(OCH_2Ph)$ (**13a**)



(4) GC-MS spectra of entry 19 (the catalyst free reaction, entry 9 in the text):



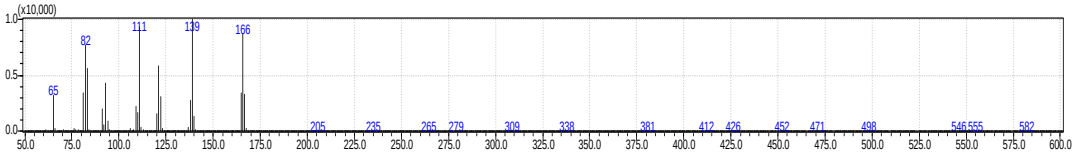
GC Spectra



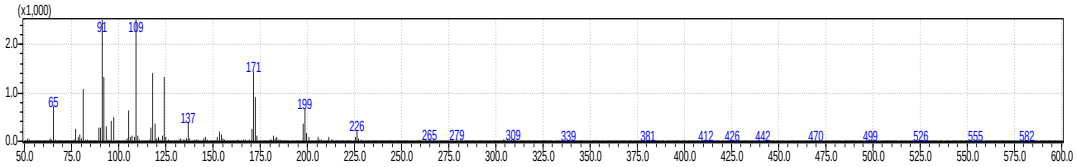
Ret.Time	Start Tm	End Tm	m/z	Area	Area%	Height	Height%	A/H	Mark
3.793	3.717	4.000	TIC	7215084	34.51	3588913	37.63	2.01	MI
5.401	5.333	5.583	TIC	11931753	57.07	5209637	54.62	2.29	MI
5.735	5.692	5.767	TIC	147512	0.71	91018	0.95	1.61	MI
6.809	6.758	6.900	TIC	1611820	7.71	648929	6.80	2.47	MI

MS Spectra

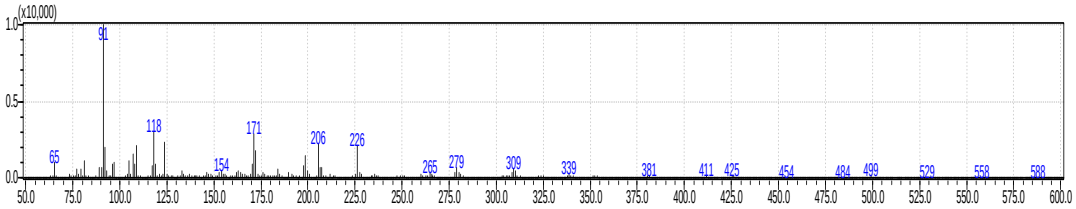
T = 3.793 min, m/z = 166, $P(OEt)_3$ (**2a**)



T = 5.401 min, m/z = 228, $P(OEt)_2(OCH_2Ph)$ (**8a**)



T = 5.735 min, $PhCH_2P(O)(OEt)_2$ (**3a**)



T = 6.890 min, m/z = 290, $P(OEt)(OCH_2Ph)_2$ (**11a**)

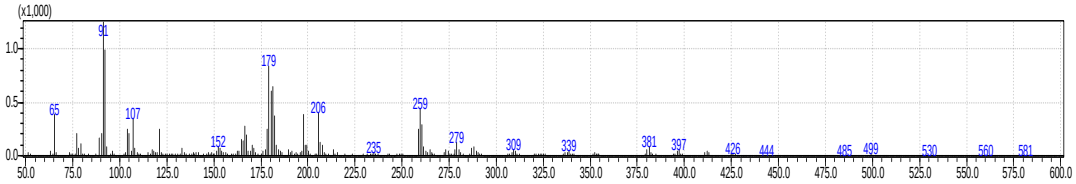
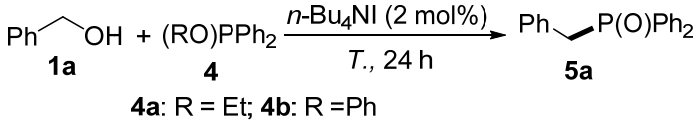


Table S2. Detailed condition screening for *n*-Bu_4NI-catalyzed preparation of alkyl phosphine oxide from alcohols.[a]



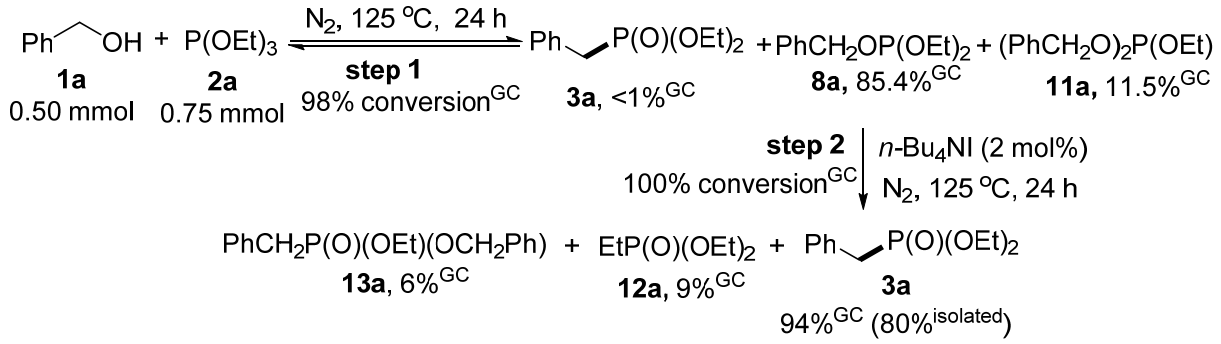
entry	**1a/4** (mmol)	**4**, R	T (^oC)	**6a**%[b]
1[c]	0.5/0.75	**4a**, Et	120	25
2[c]	0.5/0.75	**4a**, Et	100	54
3[d]	0.5/0.75	**4a**, Et	85	54
4[d]	0.5/0.75	**4a**, Et	60	(62)[e]
5[d]	0.5/0.6	**4a**, Et	85	58
6[d]	0.6/0.5	**4a**, Et	85	65
7[d]	***1.0/0.5***	***4a, Et***	***85***	***86***
8[d]	***0.5/0.75***	***4b, Ph***	***85***	***85***

[a] Unless otherwise noted, the mixture of **1a**, **4**, and *n*-Bu_4NI (3.7 mg, 2 mol%) sealed under N_2 in a 20 mL tube was heated for 24 h and monitored by TLC/GC-MS. [b] Isolated yields (GC yields in parentheses) based on the limiting **1a** or **4** used. [c] Considerable amounts of $P(O)Ph_2Et$ were observed at higher temperature due to an *n*-Bu_4NI-catalyzed reaction of **4a**. [d] Only trace amounts of $P(O)Ph_2Et$ were observed in the reactions at lower temperatures. [e] 25% GC yield of $PhCH_2OPPh_2$ was also observed.

2. Control Reactions for Mechanistic Studies

2.1 Confirmation of the formation of the reactive intermediates 8a by step-wise reaction of 1a and 2a

2.1.1 Step-wise reaction of 1a and 2a at the reaction temperature of 125 °C (eq. 4 in the text).



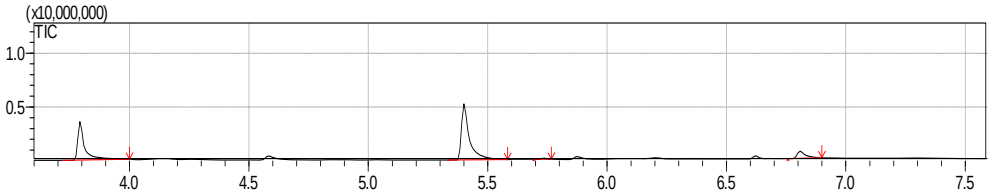
(1) Detailed procedure:

Step 1: A mixture of benzyl alcohol **1a** (54.0 mg, 0.50 mmol) and triethyl phosphite **2a** (125.0 mg, 0.75 mmol) sealed under nitrogen in a 20 mL schlenk tube was firstly stirred at 125 °C for 24 h and then analyzed by GC-MS, which showed that the conversion of **2a** was ca. 98% with **8a** being the major product.

Step 2: To the above reaction mixture was added *n*-Bu_4NI (3.7 mg, 2 mol%) under N_2. The mixture was then heated at 125 °C for 24 h and then analyzed by GC-MS, which showed that **3a** was generated as the major product in 94% GC yield. The reaction mixture was then purified by flash column chromatography on silica gel using ethyl acetate and petroleum ether (0~ 1/5) as the eluent to afford **3a** in 80% isolated yield.

(2) GC-MS spectra of step 1

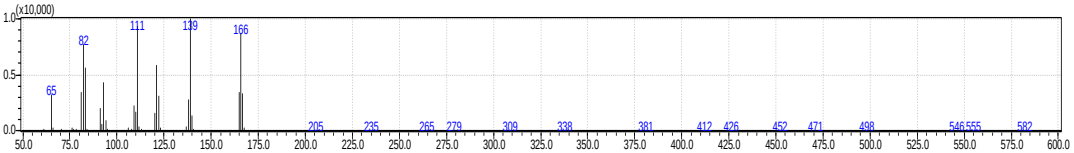
GC spectra



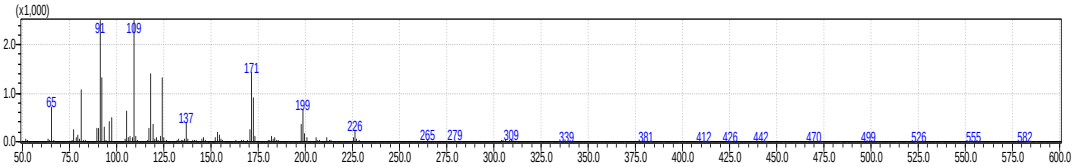
Ret.Time	Start Tm	End Tm	m/z	Area	Area%	Height	Height%	A/H	Mark
3.793	3.717	4.000	TIC	7215084	34.51	3588913	37.63	2.01	MI
5.401	5.333	5.583	TIC	11931753	57.07	5209637	54.62	2.29	MI
5.735	5.692	5.767	TIC	147512	0.71	91018	0.95	1.61	MI
6.809	6.758	6.900	TIC	1611820	7.71	648929	6.80	2.47	MI

MS Spectra

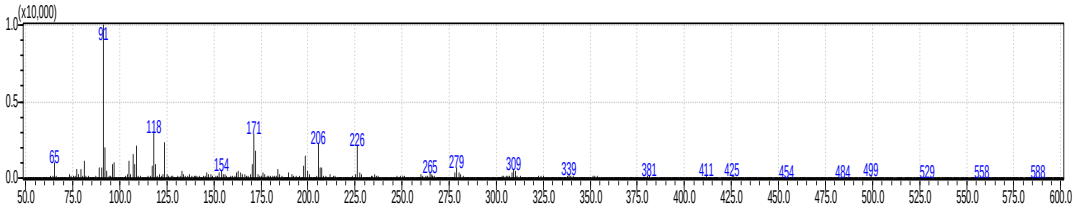
T = 3.793 min, m/z = 166, $P(OEt)_3$ (**2a**)



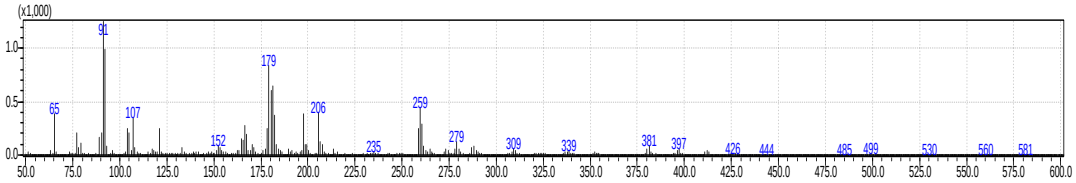
T = 5.401 min, m/z = 228, $P(OEt)_2(OCH_2Ph)$ (**8a**)



T = 5.735 min, $PhCH_2P(O)(OEt)_2$ (**3a**)

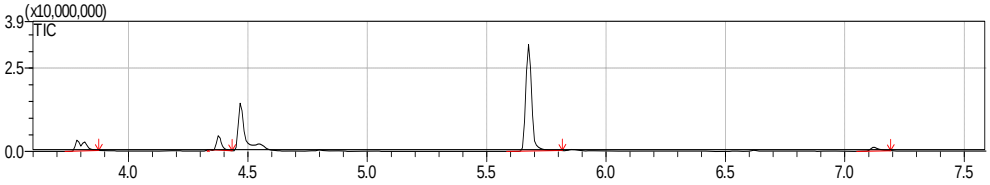


T = 6.890 min, m/z = 290, $P(OEt)(OCH_2Ph)_2$ (**11a**)



(3) GC-MS spectra of step 2

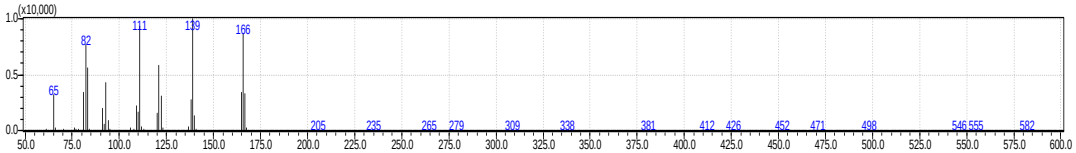
GC spectra



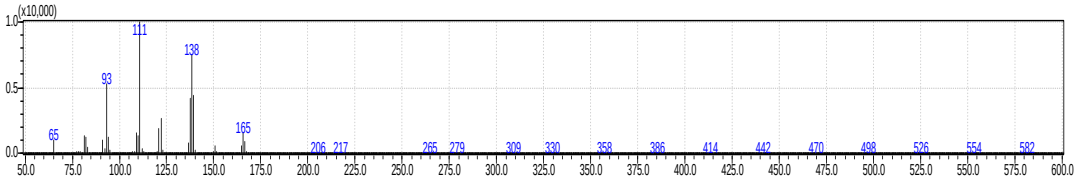
Ret.Time	Start Tm	End Tm	m/z	Area	Area%	Height	Height%	A/H	Mark
3.785	3.725	3.992	TIC	10078393	13.31	3320645	8.12	3.03	MI
4.377	4.350	4.433	TIC	6665223	8.80	4449274	10.87	1.50	MI
5.675	5.617	5.825	TIC	55702578	73.59	32035669	78.30	1.74	MI
7.121	7.042	7.267	TIC	3258414	4.30	1110015	2.71	2.94	MI

MS Spectra

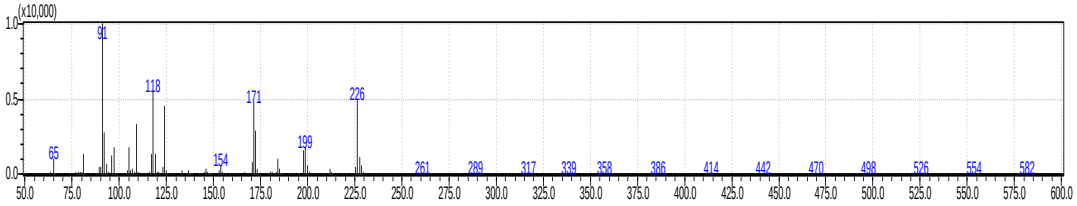
T = 3.786 min, m/z = 166, $P(OEt)_3$ (**2a**)



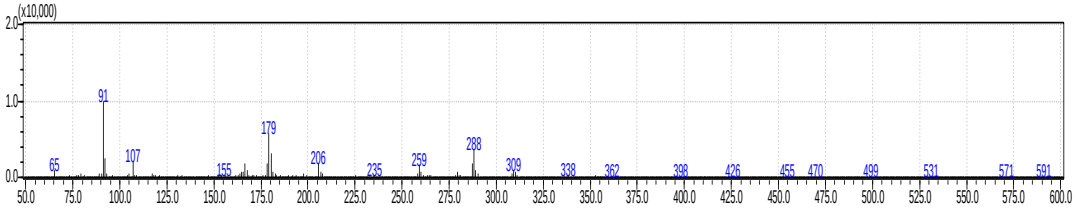
T = 4.377 min, m/z = 166, $EtP(O)(OEt)_2$ (**12a**)



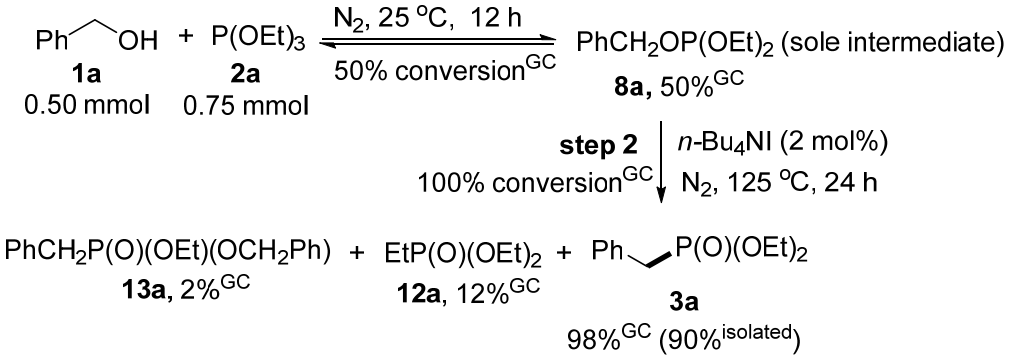
T = 5.675 min, $PhCH_2P(O)(OEt)_2$ (**3a**)



T = 7.121 min, m/z = 290, $PhCH_2P(O)(OEt)(OCH_2Ph)$ (**13a**)



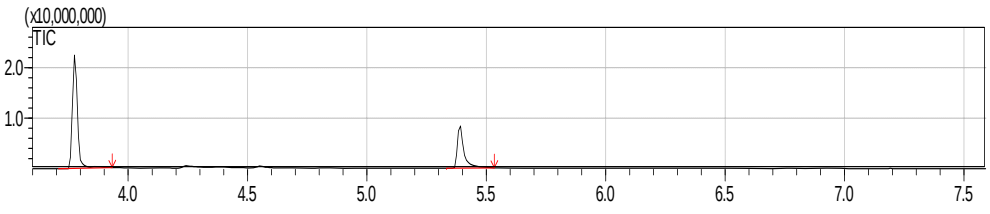
2.1.2 Step-wise reaction of 1a and 2a at room temperature (25 °C, reference 23 in the text)



(1) Procedure: Similar to the above reaction with only the step 1 conducted at room temperature (25 °C).

(2) GC-MS spectra of step 1

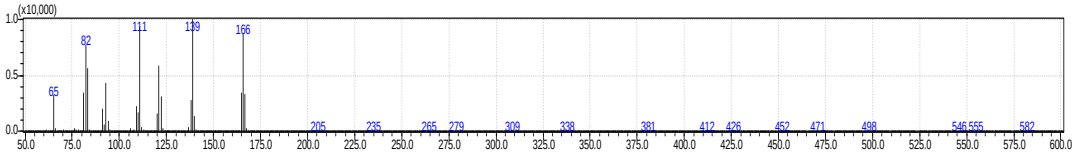
GC spectra



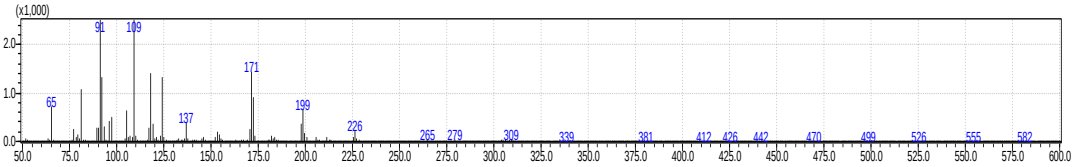
Ret.Time	Start Tm	End Tm	m/z	Area	Area%	Height	Height%	A/H	Mark
3.776	3.700	3.958	TIC	33499335	67.47	22432424	72.81	1.49	MI
5.390	5.308	5.542	TIC	16151895	32.53	8378267	27.19	1.93	MI

MS spectra

T = 3.776 min, m/z = 166, $P(OEt)_3$ (**2a**)

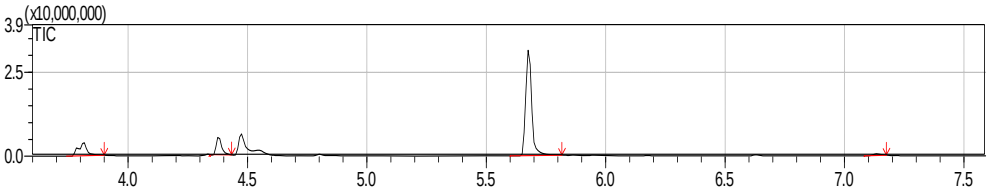


T = 5.390min, m/z = 228, $P(OEt)_2(OCH_2Ph)$ (**8a**)



(3) GC-MS spectra of step 2

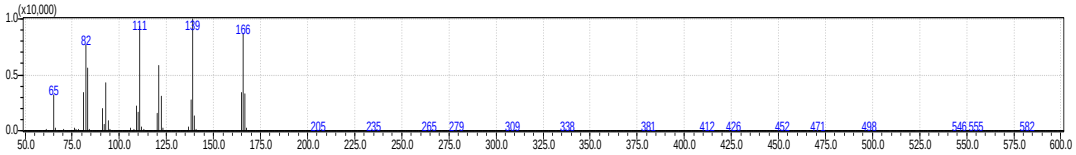
GC spectra



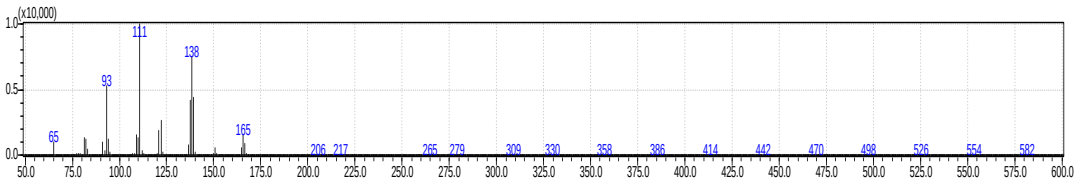
Ret.Time	Start Tm	End Tm	m/z	Area	Area%	Height	Height%	A/H	Mark
3.813	3.733	3.892	TIC	9746679	12.80	3835706	9.33	2.54	MI
4.378	4.308	4.425	TIC	9278573	12.19	5336003	12.98	1.73	MI
5.677	5.600	5.850	TIC	55673088	73.15	31362829	76.27	1.77	MI
7.135	7.067	7.200	TIC	1418481	1.86	583520	1.42	2.42	MI

MS spectra

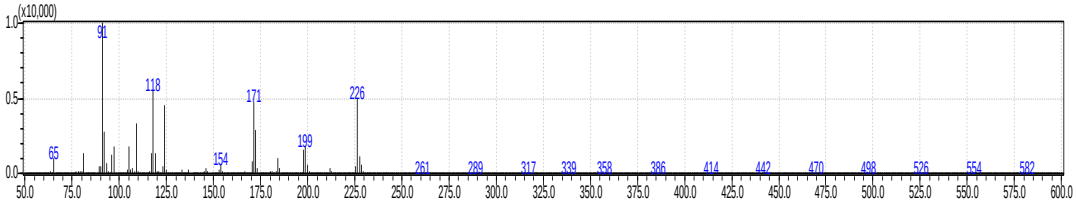
T = 3.813 min, m/z = 166, $P(OEt)_3$ (**2a**)



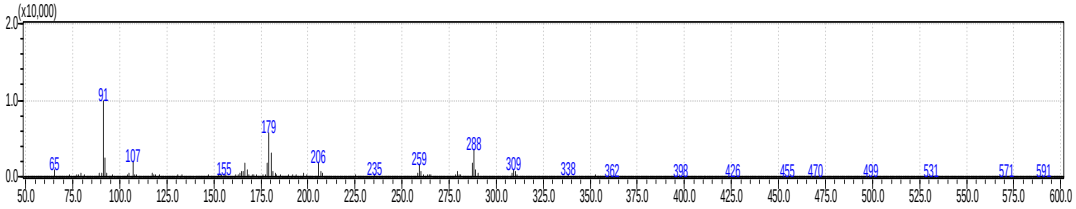
T = 4.378 min, m/z = 166, Et-P(O)$(OEt)_2$ (**12a**)



T = 5.677 min, $PhCH_2P(O)(OEt)_2$ (**3a**)



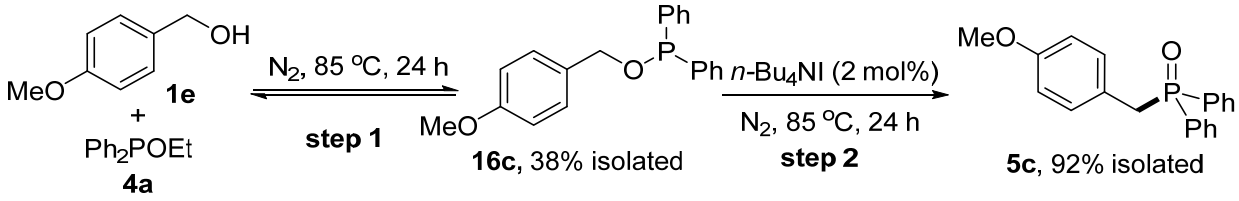
T = 7.135 min, m/z = 290, $PhCH_2P(O)(OEt)(OCH_2Ph)$ (**13a**)



2.1.3 Discussion and Conclusion

The transesterification reaction of benzyl alcohol **1a** and triethyl phosphite **2a** is so easy to occur that it can readily undergo even at 25 °C and give 50% GC yield of the new phosphite **8a** (step 1). This not only revealed that the transesterified phosphites **8** should most likely be the key reactive intermediates of the reaction, but also suggests that the transesterification step is a much more favorable and faster process than the conversion of intermediates **8** to products **3** (step 2) since the latter requires both the iodide catalyst and a much high reaction temperature such as 125 °C. However, since the reaction of **1** and **2** is a reversible equilibrium, their conversion to **8a** is not complete. Then, addition of *n*-Bu_4NI could drive the reaction to rightward to complete and effectively afford **3a** in a high yield.

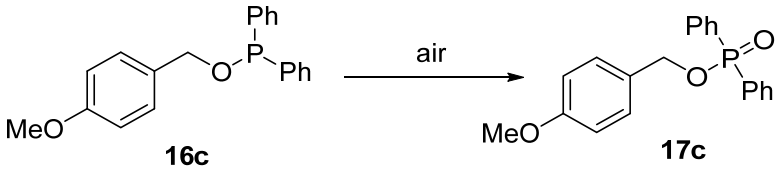
2.2 Confirmation of the formation of the reactive intermediate 16c by step-wise reaction of 1 and 4 (reference 23 in the text)



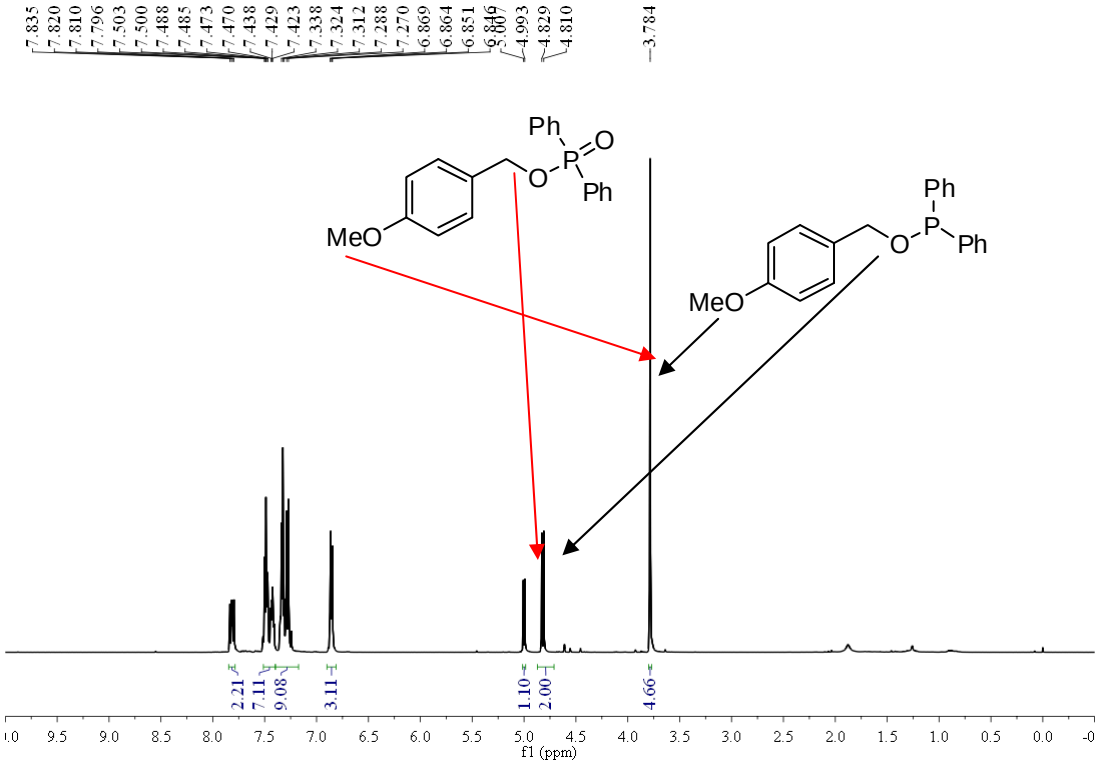
(1) Detailed procedure of step 1:

A mixture of 4-methoxybenzyl alcohol **1e** (138.0 mg, 1.0 mmol) and ethyl diphenyl phosphinite **4a** (115.0 mg, 0.50 mmol) was sealed under nitrogen in a 20 mL Schlenk tube, heated at 85 °C for 24 h, and analyzed by TLC/GC-MS. The reaction mixture was then purified by flash column chromatography on aluminium oxide using ethyl acetate and petroleum ether (0~ 1/5) as the eluent to give **16c** in 38% isolated yield.

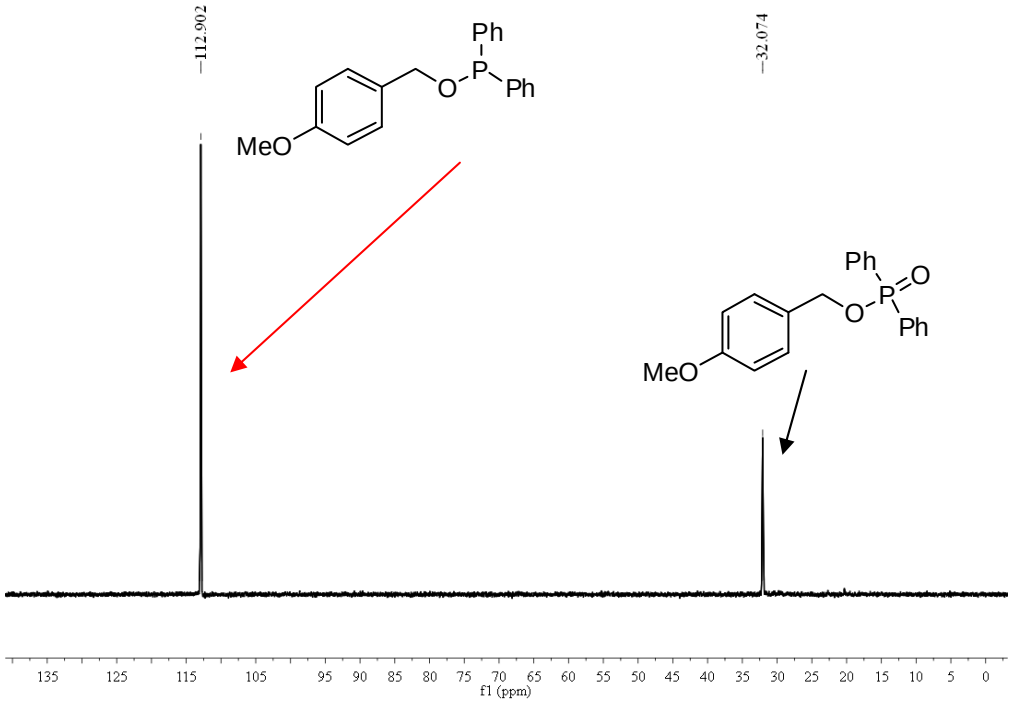
Note: Since **16c** is very sensitive toward air, it has already been partially oxidized before the column purification process. Therefore, it was obtained only in a low yield. As shown by the NMR spectra below, **16c** could even be partially oxidized during the NMR measurement.



^{1}H NMR



^{31}P NMR



4-Methoxybenzyl diphenylphosphinite (16c). Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ

7.55~7.40 (m, 6H), 7.35~7.23 (m, 6H), 6.86 (d, J = 9.0 Hz, 2H), 4.82 (d, J = 9.5 Hz, 2H), 3.78 (s, 3H). ^{31}P NMR (202 MHz, $CDCl_3$): δ 112.9. This compound was known: J.-L. Li, X.-J. Yang, Y. Wang, J.-T. Liu, *J. Fluo. Chem.* **2015**, *178*, 254.

4-Methoxybenzyl diphenyl phosphinate (17c). Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.85~7.79 (m, 4H), 7.50~7.40 (m, 2H), 7.35~7.20 (m, 6H), 7.13~7.17 (m, 1H), 6.86 (d, J = 9.0 Hz, 2H), 5.00 (d, J = 7.0 Hz, 1H), 3.78 (s, 3H). ^{31}P NMR (202 MHz, $CDCl_3$) δ 32.1. This compound was known: B. Xiong, Q. Ye, X. Feng, L. Zhu, T. Chen, Y. Zhou, C.-T. Au, S.-F. Yin *Tetrahedron* **2014**, 70, 9057.

(2) Detailed procedure of step 2:

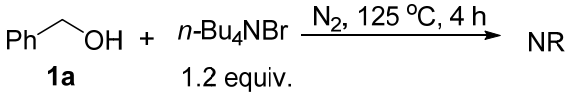
A mixture of 4-methoxybenzyl diphenylphosphinite **16c** (80.5 mg, 0.25 mmol) and n-Bu_4NI (1.9 mg, 2 mol%) was sealed under nitrogen in a 20 mL schlenk tube and heated at 85 ^{o}C for 24 h. The reaction mixture was then purified by flash column chromatography on silica gel using dichloromethane and methanol (100/0~ 15/1) as the eluent to give **5c** in 92% isolated yield.

(3) Discussion and Conclusion

The transesterified **16** should most likely be the key reactive intermediates in the reactions of alcohols **1** and phosphinites **4** as it was obtained in the blank reaction of **1e** and **4a** (step 1). They can also be transformed into the target phosphine oxides **5** by an n-Bu_4NI-catalyzed process (step 2).

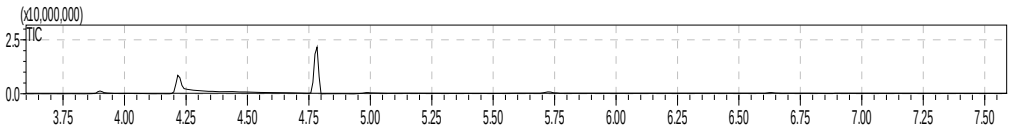
2.3 Confirmation of the Generation of Alkyl Halides Intermediates 10 in the Present Alcohol-Based Michaelis-Arbuzov Reaction (reference 25 in the text).

2.3.1 Blank Reaction of an Alcohol with Quantitative n-Bu_4NBr in the Absence of a Phosphite



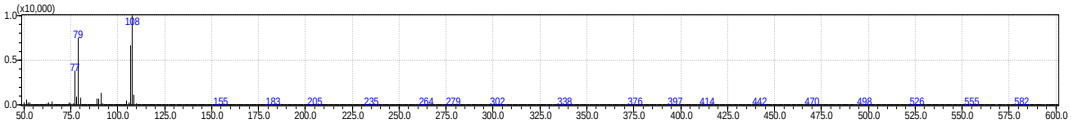
Detailed procedure: A neat mixture of benzyl alcohol **1a** (54.0 mg, 0.50 mmol) and n-Bu_4NBr (193.2 mg, 0.60 mmol, 1.2 equiv.) sealed under nitrogen in a 20 mL schlenk tube was heated at 125 ^{o}C for 4 h. The reaction mixture was then analyzed by GC-MS, which showed that no reaction occurred at all between benzyl alcohol **1a** and n-Bu_4NBr. See below spectra for details.

GC spectra for the reaction mixture

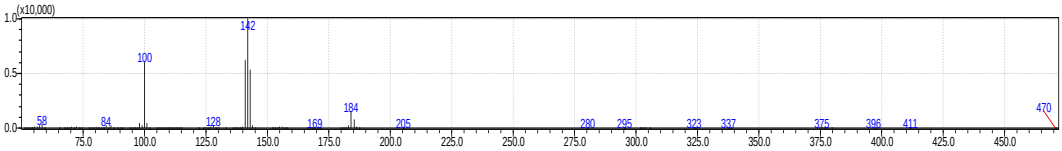


Ms spectra

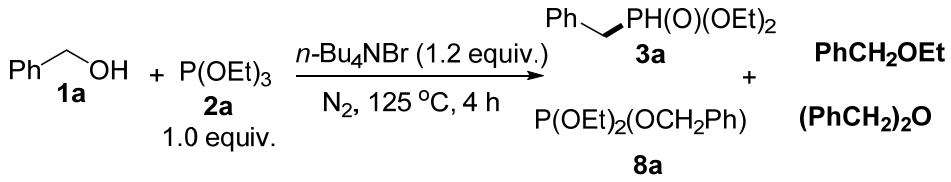
T = 4.219 min, m/z =108, **1a**



T = 4.781 min, m/z =185, $(n\text{-Bu})_3N$ (generated from $n\text{-Bu}_4NBr$)

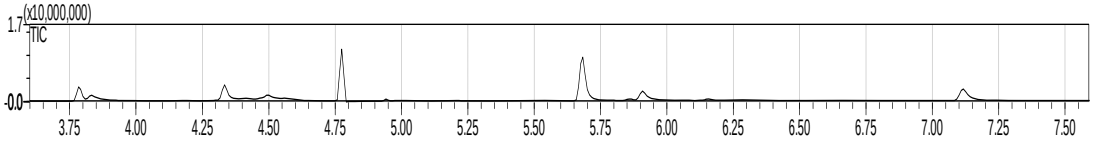


2.3.2 Reaction of an Alcohol with Quantitative *n*-Bu_4NBr in the Presence of a Phosphite



Detailed procedure: A mixture of benzyl alcohol **1a** (54.0 mg, 0.50 mmol), triethyl phosphite **2a** (83.0 mg, 0.50 mmol, 1.0 equiv.), and $n\text{-Bu}_4NBr$ (193.2 mg, 0.60 mmol, 1.2 equiv.) sealed under nitrogen in a 20 mL schlenk tube was heated at 125 ^oC for 4 h. The reaction mixture was then analyzed by GC-MS, which showed that, in addition to product **3a** and intermediate **8a**, benzyl ethyl ether $PhCH_2OEt$ and dibenzyl ether $(PhCH_2)_2O$ was also generated in considerable yields. See below spectra for details.

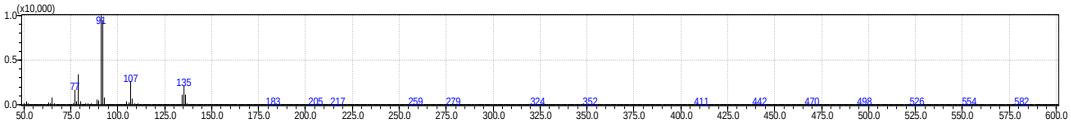
GC spectra of the reaction mixture:



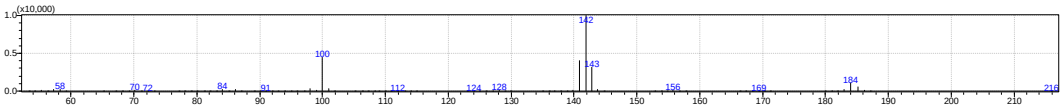
Ret.Time	Start Tm	End Tm	m/z	Area	Area%	Height	Height%	A/H	Mark
4.333	4.292	4.367	TIC	5486745	22.55	3335034	22.91	1.64	MI
5.420	5.375	5.467	TIC	297795	1.23	107329	0.74	2.77	MI
5.681	5.625	5.767	TIC	15597670	64.36	9378928	64.43	1.66	MI
5.908	5.858	5.958	TIC	2875759	11.86	1735009	11.92	1.66	MI

Ms spectra:

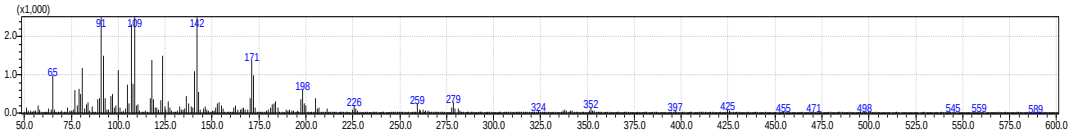
T = 4.333 min, m/z = 136, **$PhCH_2OEt$** (most possibly generated from the reaction of $PhCH_2Br$ and byproduct EtOH)



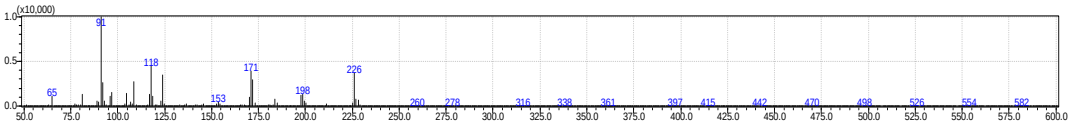
T = 4.775 min, m/z =185, $(n\text{-Bu})_3N$ (generated from $n\text{-Bu}_4NBr$)



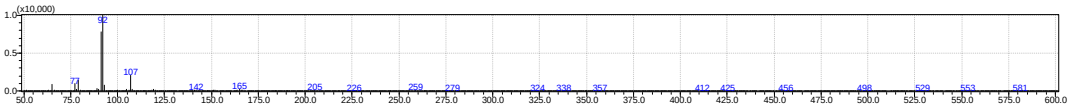
T = 5.420 min, m/z = 228, $P(OEt)_2(OCH_2Ph)$ (**8a**)



T = 5.681 min, m/z = 228, $PhCH_2P(O)(OEt)_2$ (**3a**)



T = 5.980 min, m/z = 198, **$(PhCH_2)_2O$** (most possibly generated from the reaction of $PhCH_2Br$ with the starting $PhCH_2OH$ **1a**)

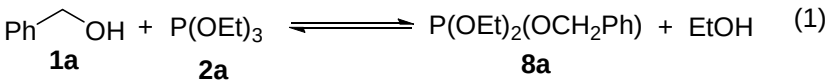


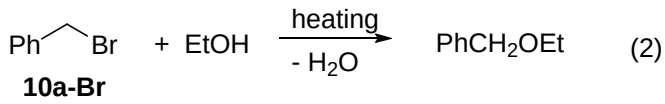
2.3.3 Discussion and Conclusion:

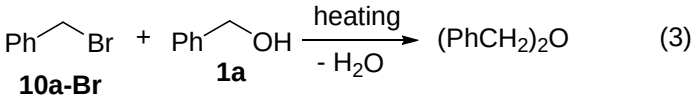
The results in **section 2.3.1** showed that alkyl halide intermediates **10** cannot be directly generated from the reaction of alcohols with *n*-Bu_4NX under the standard conditions (X = Br, I).

However, in the presence of a phosphite **(section 2.3.2)**, benzyl ethyl ether $PhCH_2OEt$ and dibenzyl ether $(PhCH_2)_2O$ could be generated in considerable yields. This suggested that the phosphite should have played a key role in the generation of the ethers $PhCH_2OEt$ and $(PhCH_2)_2O$.

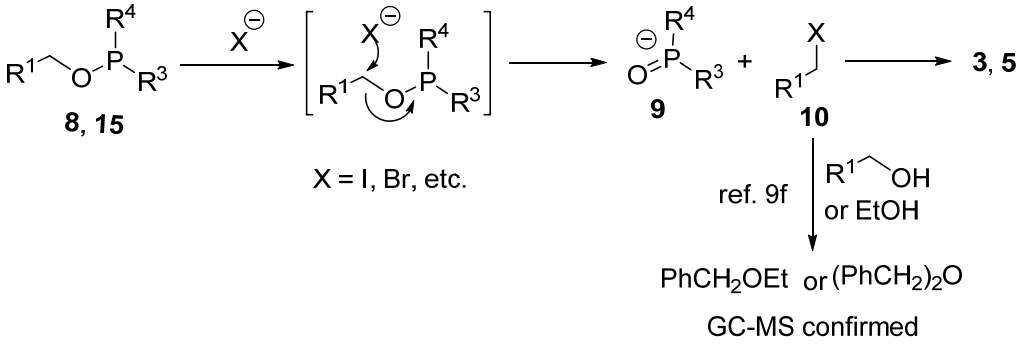
Since the reaction of **1a** and **2a** can release 1 equiv. of EtOH (eq. 1 below). And, in our previous studies, we have found that alcohols can react with alkyl halides to give ethers at heating (ref. 11d: Q. Xu, H. Xie, P. Chen, L. Yu, J. Chen, X. Hu, *Green Chem.* **2015**, *17*, 2774), it might be deduced that ethers $PhCH_2OEt$ and $(PhCH_2)_2O$ should have been generated from the reaction of $PhCH_2Br$ **(10a-Br)** with EtOH and $PhCH_2OH$ **1a** (eqs. 2-3 below).



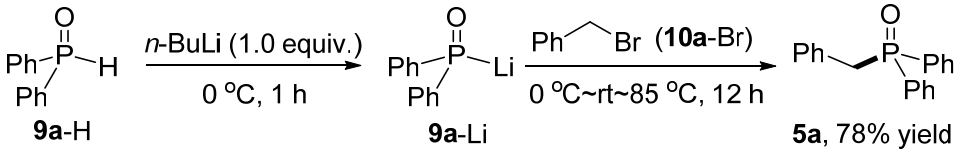




Consequently, the only way to generate the benzyl bromide **10a-Br** should have involved the phosphite **2a**, most possibly via the process we proposed in the mechanism of the reaction (Scheme 2 in the text and see also the one below). The above contrastive results could be the indirect confirmation of the production of alkyl halides **10** in the present alcohol-based Michaelis-Arbuzov reaction, further supporting the mechanism we proposed in Scheme 2.



2.4 Confirmation of the coupling between phosphoryl anion (9) and alkyl halide intermediates (10) (reference 26 in the text).



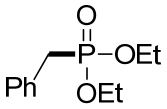
Procedure: To a stirred solution of **9a**-H (0.50 mmol, 101 mg) in THF (1.0 mL) in a 20 mL Schlenk tube was added *n*-BuLi (1.6 mmol/mL, 0.32 mL) at 0 °C under N_2 and stirred for more 1 h. Benzyl bromide **10a**-Br (0.50 mmol, 85.5 mg) was then added at 0 °C and the reaction mixture gradually warmed to room temperature in 1 h and to 85 °C for 12 h. After the reaction mixture was cooled to room temperature, it was purified by flash column chromatography on silica gel using dichloromethane and methanol (100/0~ 15/1) as the eluent, giving **5a** in 78% isolated yield.

3. Experimental

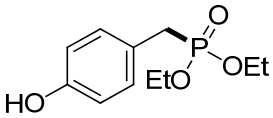
3.1 General. Unless otherwise noted, all chemicals were purchased and used without further purification. The purchased industrial-grade $P(OEt)_3$ (**2a**) was determined to be ca. 75% purity (others are $HP(OEt)_2$, $P(O)(OEt)_3$, etc.) by GC-MS analysis. It was then enriched by vacuum distillation, affording $P(OEt)_3$ (**2a**) in 95% purity which was further used in the work. All reactions were carried out in sealed Schlenk tubes (20 mL) under nitrogen atmosphere and monitored by TLC and/or GC-MS after heating. Products were purified by column chromatography on silica gel or aluminium oxide using petroleum ether and ethyl acetate (or dichloromethane and methanol) as the eluent. Unless otherwise noted, ^{1}H, ^{13}C and ^{31}P NMR spectra were measured on a Bruker Avance-III 500 instrument (500 MHz for ^{1}H, 125.4 MHz for ^{13}C NMR, and 202 MHz for ^{31}P NMR) using $CDCl_3$ as the solvent. Chemical shifts for ^{1}H and ^{13}C NMR were referred to internal Me_4Si (0 ppm) as the standard. Chemical shift for ^{31}P NMR was referred to 85% H_3PO_4. Mass spectra were measured on a Shimadzu GC-MS-QP2010 Plus spectrometer (EI). High resolution mass spectra (HRMS) were measured on a Bruker micrOTOF-Q II instrument (ESI).

3.2 Typical Procedure for *n*-Bu_4NI-Catalyzed Reaction of Alcohols and Phosphites/Phosphonites for Phosphonate and Phosphinate Synthesis. A neat mixture of benzyl alcohol **1a** (54.0 mg, 0.50 mmol), triethyl phosphite **2a** (124.5 mg, 0.75 mmol), and *n*-Bu_4NI (3.7 mg, 2 mol%) was sealed in a 20 mL Schlenk tube under nitrogen, heated at 125 ^{o}C for 24 h, and then monitored by TLC and/or GC-MS. The reaction mixture was then purified by flash column chromatography on silica gel using ethyl acetate and petroleum ether (0~ 1/5) as the eluent, giving **3a** in 90% isolated yield.

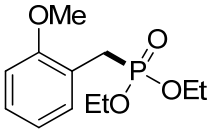
Typical Prcedure for Gram Scale Reaction of 1 and 2 for the Synthesis of 3. A neat mixture of benzyl alcohol **1a** (2.16 g, 20 mmol), triethyl phosphite **2a** (4.98 g, 30 mmol, 1.5 equiv.), and *n*-Bu_4NI (220.0 mg, 3 mol%) was sealed under nitrogen in a 20 mL Schlenk tube and heated at 130 ^{o}C for 24 h. The low-boiling compounds in the reaction mixture were then removed under vacuum. The residue was purified by flash column chromatography on silica gel using ethyl acetate and petroleum ether (0~ 1/5) as the eluent, giving **3a** in 90% (4.01 g) isolated yield.



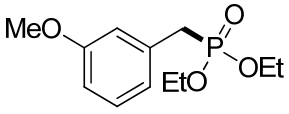
Diethyl benzylphosphonate (**3a**). Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.44 – 6.87 (m, 5H), 3.99 – 3.84 (m, 4H), 3.08 (d, J = 21.5 Hz, 2H), 1.17 (t, J = 7.0 Hz, 6H). ^{13}C NMR (125.4 MHz, $CDCl_3$): δ 131.62 (d, J = 9.0 Hz), 129.77 (d, J = 6.5 Hz), 128.50 (d, J = 3.0 Hz), 126.84 (d, J = 3.6 Hz), 62.09 (d, J = 6.8 Hz), 33.79 (d, J = 138.2 Hz), 16.34 (d, J = 6.0 Hz). ^{31}P NMR (202 MHz, $CDCl_3$): δ 26.48. This compound was known: W. Miao, Y. Gao, X. Li, Y. Gao, G. Tang, Y. Zhao, *Adv. Synth. Catal.* **2012**, *354*, 2659.



Diethyl 4-hydroxybenzylphosphonate (**3b**). Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.69 (brs, 1H), 7.03 (dd, J = 8.0, 2.0 Hz, 2H), 6.65 (d, J = 8.0 Hz, 2H), 4.29 – 3.83 (m, 4H), 3.06 (d, J = 21.0 Hz, 2H), 1.25 (t, J = 7.0 Hz, 6H). ^{13}C NMR (125.4 MHz, $CDCl_3$): δ 156.18 (d, J = 3.5 Hz), 130.67 (d, J = 6.5 Hz), 121.04 (d, J = 9.3 Hz), 115.99 (d, J = 3.0 Hz), 62.49 (d, J = 7.0 Hz), 32.59 (d, J = 139.6 Hz), 16.36 (d, J = 5.9 Hz). ^{31}P NMR (202 MHz, $CDCl_3$): δ 27.57. This compound was known: S. H. Boyer, H. Jiang, J. D. Jacintho, M. V. Reddy, H. Li, W. Li, R. Wu, *J. Med. Chem.* **2008**, *51*, 7075.

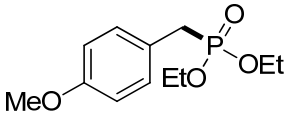


Diethyl 2-methoxybenzylphosphonate (**3c**). Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35 – 7.17 (m, 2H), 6.91 – 6.85 (m, 2H), 4.15 – 3.91 (m, 4H), 3.83 (d, J = 3.1 Hz, 3H), 3.25 (dd, J = 21.5, 3.0 Hz, 2H), 1.23 (td, J = 7.0, 3.5 Hz, 6H). ^{13}C NMR (125.4 MHz, $CDCl_3$): δ 157.22 (d, J = 5.1 Hz), 131.20 (d, J = 3.9 Hz), 128.12, 120.52, 120.25 (d, J = 8.1 Hz), 110.55, 61.85 (d, J = 5.5 Hz), 55.44, 26.64 (d, J = 139.4 Hz), 16.29 (d, J = 4.9 Hz). ^{31}P NMR (202 MHz, $CDCl_3$): δ 27.13. This compound was known: M. C. Hong, Y. K. Kim, J. Y. Choi, S. Q. Yang, H. Rhee, Y. H. Ryu, Y. Kim, *Bio. Med. Chem.* **2010**, *18*, 7724.

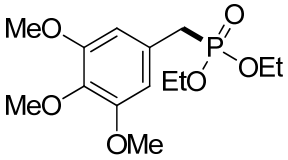


Diethyl 3-methoxybenzylphosphonate (**3d**). Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.27 – 7.20 (m, 1H), 6.96 – 6.84 (m, 2H), 6.80 (d, J = 8.0 Hz, 1H), 4.09 – 3.96 (m, 4H), 3.80 (s, 3H),

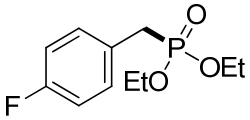
3.14 (d, J = 21.5 Hz, 2H), 1.25 (t, J = 7.0 Hz, 6H). ^{13}C NMR (125.4 MHz, $CDCl_3$); δ 159.63 (d, J = 3.1 Hz), 133.01 (d, J = 8.9 Hz), 129.44 (d, J = 3.0 Hz), 122.16 (d, J = 6.6 Hz), 115.30 (d, J = 6.5 Hz), 112.55 (d, J = 3.5 Hz), 62.12 (d, J = 6.8 Hz), 55.16, 33.80 (d, J = 138.1 Hz), 16.36 (d, J = 6.0 Hz). ^{31}P NMR (202 MHz, $CDCl_3$): δ 26.35. This compound was known: M. C. Hong, Y. K. Kim, J. Y. Choi, S. Q. Yang, H. Rhee, Y. H. Ryu, Y. Kim, *Bio. Med. Chem.* **2010**, *18*, 7724.



Diethyl 4-methoxybenzylphosphonate (**3e**). Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.14 (dd, J = 8.5, 2.5 Hz, 2H), 6.78 (d, J = 8.5 Hz, 2H), 4.04 – 3.85 (m, 4H), 3.72 (s, 3H), 3.02 (d, J = 21.0 Hz, 2H), 1.17 (t, J = 7.0 Hz, 6H). ^{13}C NMR (125.4 MHz, $CDCl_3$): δ 158.60 (d, J = 3.4 Hz), 130.74 (d, J = 6.6 Hz), 123.45 (d, J = 9.2 Hz), 114.01 (d, J = 2.8 Hz), 62.06 (d, J = 6.8 Hz), 55.24, 32.79 (d, J = 139.1 Hz), 16.38 (d, J = 6.0 Hz). ^{31}P NMR (202 MHz, $CDCl_3$): δ 26.88. This compound was known: W. Miao, Y. Gao, X. Li, Y. Gao, G. Tang, Y. Zhao, *Adv. Synth. Catal.* **2012**, *354*, 2659.

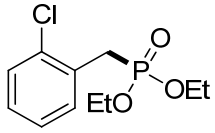


Diethyl 3,4,5-trimethoxybenzylphosphonate (**3f**). Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.53 (d, J = 2.5 Hz, 2H), 4.18 – 3.98 (m, 4H), 3.86 (s, 6H), 3.83 (s, 3H), 3.10 (d, J = 21.5 Hz, 2H), 1.28 (t, J = 7.0 Hz, 6H). ^{13}C NMR (125.4 MHz, $CDCl_3$): δ 153.12 (d, J = 3.2 Hz), 136.93 (d, J = 4.0 Hz), 127.02 (d, J = 8.9 Hz), 106.82 (d, J = 6.7 Hz), 62.18 (d, J = 6.8 Hz), 60.85 (d, J = 2.1 Hz), 56.08, 33.91 (d, J = 138.9 Hz), 16.43 (d, J = 6.0 Hz). ^{31}P NMR (202 MHz, $CDCl_3$): δ 26.41. This compound was known: M. Murias, N. Handler, T. Erker, K. Pleban, G. Ecker, P. Saiko, W. Jäger, *Bio. Med. Chem.* **2004**, *12*, 5571.

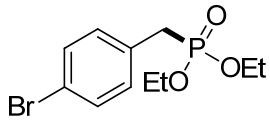


Diethyl 4-fluorobenzylphosphonate (**3g**). Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.29 – 7.24 (m, 2H), 7.00 (t, J = 8.5 Hz, 2H), 4.07 – 3.90 (m, 4H), 3.12 (d, J = 21.5 Hz, 2H), 1.25 (t, J = 7.0 Hz, 6H). ^{13}C NMR (125.4 MHz, $CDCl_3$): δ 161.93 (dd, J = 245.3, 3.9 Hz), 131.24 (dd, J = 7.9, 6.7 Hz), 127.31 (dd, J = 9.2, 3.3 Hz), 115.41 (dd, J = 21.5, 3.0 Hz), 62.18 (d, J = 6.8 Hz),

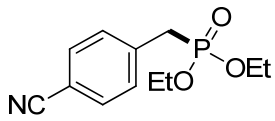
32.90 (d, J = 139.2 Hz), 16.35 (d, J = 6.0 Hz). ^{31}P NMR (202 MHz, $CDCl_3$): δ 26.15 (d, J = 5.7 Hz). This compound was known: Miao, W., Gao, Y., Li, X., Gao, Y., Tang, G., Zhao, Y. *Adv. Synth. Catal.* **2012**, *354*, 2659.



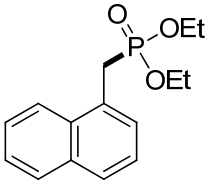
Diethyl 2-chlorobenzylphosphonate (**3h**). Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37 (d, J = 7.5 Hz, 1H), 7.31 (d, J = 7.5 Hz, 1H), 7.19 – 7.09 (m, 2H), 4.01 – 3.95 (m, 4H), 3.31 (d, J = 22.0 Hz, 2H), 1.19 (t, J = 7.0 Hz, 6H). ^{13}C NMR (125.4 MHz, $CDCl_3$): δ 134.29 (d, J = 8.3 Hz), 131.74 (d, J = 5.2 Hz), 130.08 (d, J = 9.0 Hz), 129.60 (d, J = 3.0 Hz), 128.29 (d, J = 3.6 Hz), 126.83 (d, J = 3.4 Hz), 62.24 (d, J = 6.7 Hz), 30.77 (d, J = 139.3 Hz), 16.32 (d, J = 6.1 Hz). ^{31}P NMR (202 MHz, $CDCl_3$): δ 25.23. This compound was known: N. Doubina, S. A. Paniagua, A. V. Soldatova, A. K. Jen, S. R. Marder, C. K. Luscombe, *Macromolecules* **2011**, *44*, 512.



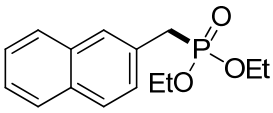
Diethyl 4-bromobenzylphosphonate (**3i**). Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.44 (d, J = 8.0 Hz, 2H), 7.17 (dd, J = 8.0, 2.0 Hz, 2H), 4.10 – 3.94 (m, 4H), 3.09 (d, J = 21.5 Hz, 2H), 1.25 (t, J = 7.0 Hz, 6H). ^{13}C NMR (125.4 MHz, $CDCl_3$): δ 131.64 (d, J = 3.0 Hz), 131.43 (d, J = 6.6 Hz), 130.78 (d, J = 9.1 Hz), 120.93 (d, J = 4.6 Hz), 62.22 (d, J = 6.8 Hz), 33.28 (d, J = 138.7 Hz), 16.37 (d, J = 5.9 Hz). ^{31}P NMR (202 MHz, $CDCl_3$): δ 25.51. This compound was known: W. Miao, Y. Gao, X. Li, Y. Gao, G. Tang, Y. Zhao, *Adv. Synth. Catal.* **2012**, *354*, 2659.



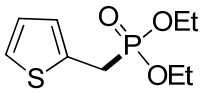
Diethyl 4-cyanobenzylphosphonate (**3j**). Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.62 (d, J = 8.0 Hz, 2H), 7.43 (dd, J = 8.0, 2.0 Hz, 2H), 4.23 – 3.80 (m, 4H), 3.21 (d, J = 22.5 Hz, 2H), 1.26 (t, J = 7.0 Hz, 6H). ^{13}C NMR (125.4 MHz, $CDCl_3$): δ 137.58 (d, J = 9.2 Hz), 132.25 (d, J = 3.1 Hz), 130.55 (d, J = 6.5 Hz), 118.70 (d, J = 2.2 Hz), 110.84 (d, J = 3.8 Hz), 62.40 (d, J = 6.8 Hz), 34.11 (d, J = 137.8 Hz), 16.34 (d, J = 6.0 Hz). ^{31}P NMR (202 MHz, $CDCl_3$): δ 24.42. This compound was known: W. Miao, Y. Gao, X. Li, Y. Gao, G. Tang, Y. Zhao, *Adv. Synth. Catal.* **2012**, *354*, 2659.



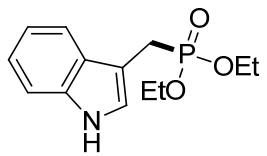
Diethyl (naphthalen-1-ylmethyl)phosphonate (**3l**). Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.10 (d, J = 8.5 Hz, 1H), 7.84 (d, J = 8.0 Hz, 1H), 7.76 (d, J = 8.5 Hz, 1H), 7.63 – 7.37 (m, 4H), 3.99 – 3.87 (m, 4H), 3.64 (d, J = 22.0 Hz, 2H), 1.15 (t, J = 7.0 Hz, 6H). ^{13}C NMR (125.4 MHz, $CDCl_3$): δ 133.90 (d, J = 2.8 Hz), 132.07 (d, J = 5.2 Hz), 128.61, 128.46 (d, J = 7.6 Hz), 128.09 (d, J = 9.9 Hz), 127.74 (d, J = 4.2 Hz), 126.06, 125.73, 125.37 (d, J = 4.1 Hz), 124.43 (d, J = 1.5 Hz), 62.16 (d, J = 6.8 Hz), 30.84 (d, J = 139.2 Hz), 16.29 (d, J = 6.0 Hz). ^{31}P NMR (202 MHz, $CDCl_3$): δ 26.26. This compound was known: L. Rout, S. Regati, C. G. Zhao, *Adv. Synth. Catal.* **2011**, *353*, 3340.



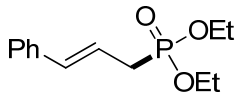
Diethyl (naphthalen-2-ylmethyl)phosphonate (**3m**). Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.82– 7.73 (m, 4H), 7.48 – 7.42 (m, 3H), 4.20 – 3.90 (m, 4H), 3.32 (d, J = 21.7 Hz, 2H), 1.23 (t, J = 7.0 Hz, 6H). ^{13}C NMR (125.4 MHz, $CDCl_3$): δ 133.45 (d, J = 3.1 Hz), 132.34 (d, J = 2.6 Hz), 129.16 (d, J = 9.5 Hz), 128.48 (d, J = 8.4 Hz), 128.14 (d, J = 2.5 Hz), 127.91 (d, J = 5.1 Hz), 127.63 (dd, J = 5.9, 1.4 Hz), 126.14 (d, J = 0.8 Hz), 125.74 (d, J = 1.4 Hz), 62.20 (d, J = 6.7 Hz), 33.98 (d, J = 138.1 Hz), 16.40 (d, J = 5.9 Hz). ^{31}P NMR (202 MHz, $CDCl_3$): δ 26.33. This compound was known: W. Miao, Y. Gao, X. Li, Y. Gao, G. Tang, Y. Zhao, *Adv. Synth. Catal.* **2012**, *354*, 2659.



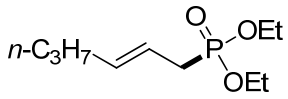
Diethyl (thiophen-2-ylmethyl)phosphonate (**3n**). Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.19 (d, J = 5.0 Hz, 1H), 7.00 – 6.94 (m, 2H), 4.11 – 4.00 (m, 4H), 3.38 (d, J = 20.5 Hz, 2H), 1.28 (t, J = 7.0 Hz, 6H). ^{13}C NMR (125.4 MHz, $CDCl_3$): δ 132.43 (d, J = 10.2 Hz), 127.34 (d, J = 8.5 Hz), 127.05 (d, J = 3.3 Hz), 124.74 (d, J = 3.9 Hz), 62.43 (d, J = 6.7 Hz), 27.98 (d, J = 143.9 Hz), 16.36 (d, J = 6.0 Hz). ^{31}P NMR (202 MHz, $CDCl_3$): δ 24.24. This compound was known: W. Miao, Y. Gao, X. Li, Y. Gao, G. Tang, Y. Zhao, *Adv. Synth. Catal.* **2012**, *354*, 2659.



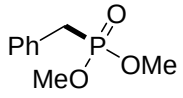
Diethyl ((1H-indol-3-yl)methyl)phosphonate (**3o**). Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.75 (brs, 1H), 7.55 (d, J = 8.0 Hz, 1H), 7.36 – 7.17 (m, 1H), 7.12 – 7.00 (m, 3H), 4.11 – 3.74 (m, 4H), 3.24 (d, J = 20.0 Hz, 2H), 1.15 (t, J = 6.5 Hz, 6H). ^{13}C NMR (125.4 MHz, $CDCl_3$): δ 136.06, 127.44 (d, J = 5.4 Hz), 123.91 (d, J = 7.3 Hz), 121.95, 119.39, 118.78, 111.33, 104.54 (d, J = 9.1 Hz), 62.19 (d, J = 6.2 Hz), 23.12 (d, J = 142.9 Hz), 16.42 (d, J = 5.5 Hz). ^{31}P NMR (202 MHz, $CDCl_3$): δ 27.87. This compound was known: M. N. Greco, M. J. Hawkins, E. T. Powell, H. R. Almond, L. de Garavilla, J. Hall, A. M. Cantwell, *J. Med. Chem.* **2007**, *50*, 1727.



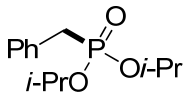
Diethyl cinnamylphosphonate (**3p**). Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.28 (d, J = 7.5 Hz, 2H), 7.25 (t, J = 7.5 Hz, 2H), 7.15 (t, J = 7.5 Hz, 1H), 6.45 (dd, J = 16.0, 5.0 Hz, 1H), 6.09 (dt, J = 16.0, 7.5 Hz, 1H), 4.10 – 3.99 (m, 4H), 2.69 (dd, J = 22.5, 7.5 Hz, 2H), 1.24 (t, J = 7.0 Hz, 7H). ^{13}C NMR (125.4 MHz, $CDCl_3$): δ 136.79 (d, J = 3.4 Hz), 134.71 (d, J = 14.9 Hz), 128.56, 127.60, 126.22 (d, J = 1.9 Hz), 118.76 (d, J = 12.0 Hz), 62.09 (d, J = 6.7 Hz), 31.06 (d, J = 138.9 Hz), 16.47 (d, J = 6.0 Hz). ^{31}P NMR (202 MHz, $CDCl_3$): δ 26.94. This compound was known: W. Miao, Y. Gao, X. Li, Y. Gao, G. Tang, Y. Zhao, *Adv. Synth. Catal.* **2012**, *354*, 2659.



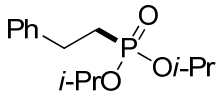
(*E*)-Diethyl hex-2-en-1-ylphosphonate (**3q**). Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.75 – 5.52 (m, 1H), 5.44 – 5.36 (m, 1H), 4.21 – 3.98 (m, 4H), 2.56 (dd, J = 21.5, 7.5 Hz, 2H), 2.12 – 1.93 (m, 2H), 1.41 – 1.36 (m, 2H), 1.32 (t, J = 7.0 Hz, 6H), 0.90 (t, J = 7.5 Hz, 3H). ^{13}C NMR (125.4 MHz, $CDCl_3$): δ 136.05 (d, J = 14.5 Hz), 118.51 (d, J = 11.2 Hz), 61.83 (d, J = 6.6 Hz), 34.64 (d, J = 2.3 Hz), 30.44 (d, J = 139.7 Hz), 22.30 (d, J = 3.6 Hz), 16.42 (d, J = 6.0 Hz), 13.56. ^{31}P NMR (202 MHz, $CDCl_3$): δ 28.12. This compound was known: V. Hornillos, M. Pérez, M. Fañanás‐Mastral, B. L. Feringa, *Chem. Eur. J.* **2013**, *19*, 5432.



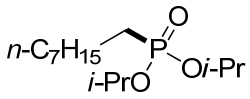
Dimethyl benzylphosphonate (**3r**). Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 – 7.19 (m, 5H), 3.66 (d, J = 10.8 Hz, 3H), 3.17 (d, J = 21.5 Hz, 2H). ^{13}C NMR (125.4 MHz, $CDCl_3$) δ 131.24 (d, J = 9.1 Hz), 129.70 (d, J = 6.6 Hz), 128.62 (d, J = 2.8 Hz), 126.98 (d, J = 3.5 Hz), 52.86 (d, J = 6.8 Hz), 32.89 (d, J = 138.3 Hz). ^{31}P NMR (202 MHz, $CDCl_3$) δ 28.90. This compound was known: W. Miao, Y. Gao, X. Li, Y. Gao, G. Tang, Y. Zhao, *Adv. Synth. Catal.* **2012**, *354*, 2659.



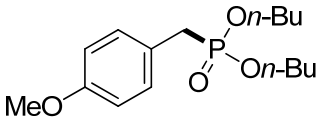
Diisopropyl benzylphosphonate (**3s**). Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.51 – 7.13 (m, 5H), 4.60 (dq, J = 12.5, 6.5 Hz, 2H), 3.11 (d, J = 21.5 Hz, 2H), 1.27 (d, J = 6.0 Hz, 6H), 1.16 (d, J = 6.5 Hz, 6H). ^{13}C NMR (125.4 MHz, $CDCl_3$): δ 132.00 (d, J = 9.0 Hz), 129.90 (d, J = 6.6 Hz), 128.36 (d, J = 3.0 Hz), 126.71 (d, J = 3.6 Hz), 70.58 (d, J = 7.0 Hz), 34.82 (d, J = 139.7 Hz), 24.06 (d, J = 3.8 Hz), 23.78 (d, J = 5.0 Hz). ^{31}P NMR (202 MHz, $CDCl_3$): δ 26.65. This compound was known: K. Xu, H. Hu, F. Yang, Y. Wu, *Eur. J. Org. Chem.* **2013**, 319.



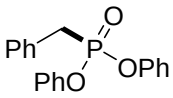
Diisopropyl phenethylphosphonate (**3t**). Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.31 – 7.27 (m, 2H), 7.22 – 7.19 (m, 3H), 4.75 – 4.68 (m, 2H), 2.93 – 2.87 (m, 2H), 2.07 – 1.97 (m, 2H), 1.33 (d, J = 6.0 Hz, 6H), 1.31 (d, J = 6.5 Hz, 6H). ^{13}C NMR (125.4 MHz, $CDCl_3$): δ 141.22 (d, J = 18.1 Hz), 128.54, 128.04, 126.25, 70.03 (d, J = 6.7 Hz), 28.92 (d, J = 139.8 Hz), 28.82 (d, J = 4.5 Hz), 24.08, 24.05. ^{31}P NMR (202 MHz, $CDCl_3$): δ 28.68. This compound was known: M. Kyoda, T. Yokoyama, H. Maekawa, T. Ohno, I. Nishiguchi, *Synlett.* **2001**, 1535.



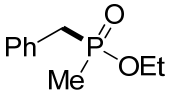
Diisopropyl octylphosphonate (**3u**). Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.76 – 4.58 (m, 2H), 1.75 – 1.51 (m, 4H), 1.46 – 1.20 (m, 22H), 0.88 (t, J = 7.0 Hz, 3H). ^{13}C NMR (125.4 MHz, $CDCl_3$): δ 69.69 (d, J = 6.7 Hz), 31.79 30.62 (d, J = 17.2 Hz), 29.04, 26.99 (d, J = 141.6 Hz), 24.06 (d, J = 4.5 Hz), 24.05, 22.61, 22.55 (d, J = 5.3 Hz), 14.05. ^{31}P NMR (202 MHz, $CDCl_3$): δ 30.71. Calcd for $C_{14}H_{32}O_3P$ (M+H): 279.2089; found: 279.2110.



Dibutyl 4-methoxybenzylphosphonate (**3v**). Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.21 (d, J = 7.0 Hz, 2H), 6.84 (d, J = 8.0 Hz, 2H), 3.98 – 3.88 (m, 4H), 3.79 (s, 3H), 3.09 (d, J = 21.1 Hz, 2H), 1.61 – 1.48 (m, 4H), 1.38 – 1.30 (m, 4H), 0.89 (t, J = 7.5 Hz, 6H). ^{13}C NMR (125.4 MHz, $CDCl_3$): δ 158.6 (d, J = 3.3 Hz), 130.7 (d, J = 6.6 Hz), 123.6 (d, J = 9.3 Hz), 114.0 (d, J = 2.7 Hz), 65.8 (d, J = 7.0 Hz), 55.3, 32.7 (d, J = 138.8 Hz), 32.6 (d, J = 5.9 Hz), 18.7, 13.6. ^{31}P NMR (202 MHz, $CDCl_3$): δ 26.76. Calcd for $C_{16}H_{27}O_4P$ (M+H): 315.1725; found: 315.1720.



Diphenyl benzylphosphonate (**3w**). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.42 – 7.22 (m, 9H), 7.13 (t, J = 7.5 Hz, 2H), 7.03 (d, J = 7.5 Hz, 4H), 3.51 (d, J = 21.5 Hz, 1H). ^{13}C NMR (125.4 MHz, $CDCl_3$): δ 150.41 (d, J = 9.2 Hz), 130.33 (d, J = 9.5 Hz), 130.09 (d, J = 7.0 Hz), 129.69, 128.75 (d, J = 3.1 Hz), 127.35 (d, J = 3.8 Hz), 125.10, 120.53 (d, J = 4.4 Hz), 33.87 (d, J = 139.2 Hz). ^{31}P NMR (202 MHz, $CDCl_3$): δ 19.53. This compound was known: Q. Yao, S. Levchik, *Tetrahedron Lett.* **2006**, *47*, 227.



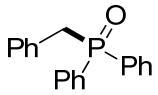
Ethyl benzyl(methyl)phosphinate (**3x**). Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.42 – 7.18 (m, 5H), 4.21 – 3.89 (m, 2H), 3.15 (d, J = 17.5 Hz, 2H), 1.36 (d, J = 13.5 Hz, 3H), 1.29 (t, J = 7.0 Hz, 3H). ^{13}C NMR (125.4 MHz, $CDCl_3$): δ 132.1 (d, J = 7.2 Hz), 129.6 (d, J = 5.7 Hz), 128.7 (d, J = 2.7 Hz), 126.9 (d, J = 3.3 Hz), 60.5 (d, J = 6.6 Hz), 38.0 (d, J = 88.3 Hz), 16.6 (d, J = 5.9 Hz), 13.4 (d, J = 94.7 Hz). ^{31}P NMR (202 MHz, $CDCl_3$): δ 51.04. T. Novak, J. Deme, K. Ludanyi, G. Keglevich, *Heteroatom Chem.* **2008**, *19*, 28.

3.3 Typical Procedures for *n*-Bu_4NI-Catalyzed Reaction of Alcohols and Phosphinites for Phosphine Oxide Synthesis.

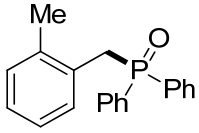
Method A: A neat mixture of benzyl alcohol **1a** (108.0 mg, 1.0 mmol, 2.0 equiv.), ethyl diphenylphosphinite **4a** (115.0 mg, 0.50 mmol), and *n*-Bu_4NI (3.7 mg, 2 mol%) was sealed in a

20 mL schlenk tube under nitrogen, heated at 85 °C for 24 h, and monitored by TLC and/or GC-MS. The reaction mixture was then purified by flash column chromatography on silica gel using dichloromethane and methanol (100/0~ 15/1) as the eluent, giving **5a** in 86% isolated yield.

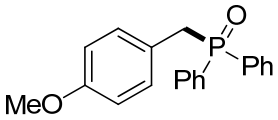
Method B: A neat mixture of benzyl alcohol **1a** (54.0 mg, 0.50 mmol), phenyl diphenylphosphinite **4b** (209.0 mg, 0.75 mmol, 1.5 equiv.), and *n*-Bu_4NI (3.7 mg, 2 mol%) was sealed in a 20 mL schlenk tube under nitrogen, heated at 85 °C for 24 h, and then monitored by TLC and/or GC-MS. The reaction mixture was then purified by flash column chromatography on silica gel using dichloromethane and methanol (100/0~ 15/1) as the eluent, giving **5a** in 85% isolated yield.



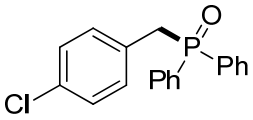
Benzyldiphenylphosphine oxide (**5a**). Colorless solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.84 – 7.60 (m, 4H), 7.60 – 7.36 (m, 6H), 7.27 – 7.13 (m, 3H), 7.18 – 6.92 (m, 2H), 3.66 (d, J = 14.0 Hz, 2H). ^{13}C NMR (125.4 MHz, $CDCl_3$): δ 132.24 (d, J = 98.4 Hz), 131.79 (d, J = 2.7 Hz), 131.19 (d, J = 9.1 Hz), 131.16 (d, J = 6.4 Hz), 130.16 (d, J = 5.2 Hz), 128.49 (d, J = 11.7 Hz), 128.37 (d, J = 2.5 Hz), 126.79 (d, J = 2.9 Hz), 38.15 (d, J = 66.3 Hz). ^{31}P NMR (202 MHz, $CDCl_3$): δ 29.45. This compound was known: F. Wang, M. Qu, F. Chen, Q. Xu, M. Shi, *Chem. Commun.* **2012**, *48*, 8580.



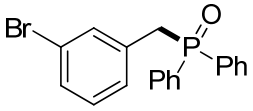
(2-Methylbenzyl)diphenylphosphine oxide (**5b**). Colorless solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.62 – 7.55 (m, 4H), 7.46 – 7.28 (m, 6H), 7.02 – 6.78 (m, 4H), 3.59 (d, J = 14.0 Hz, 2H), 2.06 (s, 3H). ^{13}C NMR (125.4 MHz, $CDCl_3$): δ 137.5 (d, J = 5.4 Hz), 132.5 (d, J = 98.4 Hz), 131.8 (d, J = 2.7 Hz), 131.2 (d, J = 9.1 Hz), 130.7 (d, J = 4.6 Hz), 130.4 (d, J = 2.6 Hz), 129.7 (d, J = 8.2 Hz), 128.5 (d, J = 11.6 Hz), 127.0 (d, J = 3.1 Hz), 125.7 (d, J = 2.8 Hz), 35.3 (d, J = 66.7 Hz), 20.0. ^{31}P NMR (202 MHz, $CDCl_3$): δ 29.64. This compound was known: S. Montel, T. Jia, P. J. Walsh, *Org. Lett.* **2014**, *16*, 130.



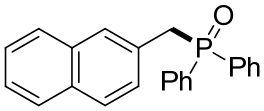
(4-Methoxybenzyl)diphenylphosphine oxide (**5c**). Colorless solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.87 – 7.61 (m, 4H), 7.60 – 7.36 (m, 6H), 7.02 (dd, J = 8.5, 2.0 Hz, 2H), 6.73 (d, J = 8.5 Hz, 2H), 3.74 (s, 3H), 3.59 (d, J = 13.5 Hz, 2H). ^{13}C NMR (125.4 MHz, $CDCl_3$): δ 158.54 (d, J = 2.9 Hz), 132.42 (d, J = 98.0 Hz), 131.76 (d, J = 2.7 Hz), 131.19 (d, J = 9.3 Hz), 131.13 (d, J = 5.8 Hz), 128.49 (d, J = 11.6 Hz), 122.91 (d, J = 8.1 Hz), 113.91 (d, J = 2.5 Hz), 55.20, 37.12 (d, J = 67.5 Hz). ^{31}P NMR (202 MHz, $CDCl_3$): δ 29.44. This compound was known: F. Wang, M. Qu, F. Chen, Q. Xu, M. Shi, *Chem. Commun.* **2012**, *48*, 8580.



(4-Chlorobenzyl)diphenylphosphine oxide (**5d**). Colorless solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.70 (d, J = 7.5 Hz, 2H), 7.67 (d, J = 8.0 Hz, 2H), 7.55 – 7.42 (m, 6H), 7.15 (d, J = 8.5 Hz, 2H), 7.04 (d, J = 8.0 Hz, 2H), 3.61 (d, J = 13.5 Hz, 2H). ^{13}C NMR (125.4 MHz, $CDCl_3$): δ 132.86 (d, J = 3.6 Hz), 132.02 (d, J = 98.9 Hz), 131.96 (d, J = 2.7 Hz), 131.38 (d, J = 5.3 Hz), 131.11 (d, J = 9.2 Hz), 129.72 (d, J = 8.1 Hz), 128.60 (d, J = 11.9 Hz), 128.54 (d, J = 3.6 Hz), 37.48 (d, J = 66.2 Hz). ^{31}P NMR (202 MHz, $CDCl_3$): δ 29.07. This compound was known: F. Wang, M. Qu, F. Chen, Q. Xu, M. Shi, *Chem. Commun.* **2012**, *48*, 8580.

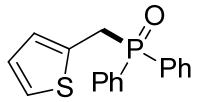


(3-Bromobenzyl)diphenylphosphine oxide (**5e**). Colorless solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.73 – 7.65 (m, 4H), 7.59 – 7.39 (m, 6H), 7.34 – 7.25 (m, 2H), 7.12 – 6.98 (m, 2H), 3.60 (d, J = 14.0 Hz, 2H). ^{13}C NMR (125.4 MHz, $CDCl_3$): δ 133.56 (d, J = 7.9 Hz), 133.03 (d, J = 5.4 Hz), 132.01 (d, J = 2.7 Hz), 131.94 (d, J = 99.1 Hz), 131.11 (d, J = 9.2 Hz), 129.89 (dd, J = 17.2, 2.7 Hz), 128.77 (d, J = 5.1 Hz), 128.61 (d, J = 11.8 Hz), 122.26 (d, J = 2.9 Hz), 37.83 (d, J = 65.8 Hz). ^{31}P NMR (202 MHz, $CDCl_3$): δ 29.21. This compound was known: X. Liu, P. Braunstein, *Inorg. Chem.* **2013**, *52*, 7367.

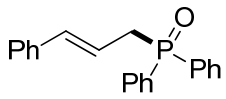


(Naphthalen-2-ylmethyl)diphenylphosphine oxide (**5f**). Colorless solid. ^{1}H NMR (500 MHz,

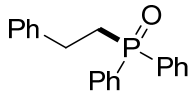
$CDCl_3$): δ 7.77 – 7.64 (m, 7H), 7.57 (br, 1H), 7.50 (t, J = 7.5 Hz, 2H) 7.44 – 7.37 (m, 6H), 7.24 (t, J = 8.0 Hz, 1H), 3.81 (d, J = 14.0 Hz, 2H). ^{13}C NMR (125.4 MHz, $CDCl_3$): δ 133.33 (d, J = 2.6 Hz), 132.33 (d, J = 98.4 Hz), 132.26 (d, J = 2.0 Hz), 131.85 (d, J = 2.6 Hz), 131.20 (d, J = 9.1 Hz), 129.03 (d, J = 6.7 Hz), 128.78 (d, J = 8.2 Hz), 128.54 (d, J = 11.7 Hz), 128.21 (d, J = 4.2 Hz), 127.95 (d, J = 1.9 Hz), 127.64, 127.57 (d, J = 0.9 Hz), 125.99, 125.67 (d, J = 0.6 Hz), 38.37 (d, J = 66.4 Hz). ^{31}P NMR (202 MHz, $CDCl_3$): δ 29.46. J. Yang, T. Chen, L.-B. Han, *J. Am. Chem. Soc.* **2015**, *137*, 1782.



Diphenyl(thiophen-2-ylmethyl)phosphine oxide (**5g**). Colorless solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.80 – 7.68 (m, 4H), 7.60 – 7.45 (m, 6H), 7.14 – 7.07 (m, 1H), 6.92 – 6.82 (m, 2H), 3.89 (d, J = 11.5 Hz, 2H). ^{13}C NMR (125.4 MHz, $CDCl_3$): δ 132.11 (d, J = 50.6 Hz) 131.98, 131.90, 131.20 (d, J = 9.2 Hz), 128.57 (d, J = 11.8 Hz), 127.83 (d, J = 6.6 Hz), 127.01 (d, J = 2.5 Hz), 124.88 (d, J = 2.8 Hz), 32.62 (d, J = 68.8 Hz). ^{31}P NMR (202 MHz, $CDCl_3$): δ 28.71. Calcd for $C_{17}H_{16}OPS$ (M+H): 299.0659; found: 299.0664.

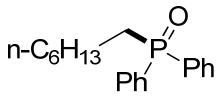


Cinnamyldiphenylphosphine oxide (**5h**). Colorless solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.85 – 7.60 (m, 4H), 7.63 – 7.37 (m, 6H), 7.30 – 7.06 (m, 5H), 6.42 (dd, J = 16.0, 4.0 Hz, 1H), 6.29 – 5.98 (m, 1H), 3.29 (dd, J = 15.0, 7.5 Hz, 2H). ^{13}C NMR (125.4 MHz, $CDCl_3$): δ 136.79 (d, J = 3.1 Hz), 135.64 (d, J = 12.1 Hz), 132.47 (d, J = 98.3 Hz), 131.91 (d, J = 2.7 Hz), 131.09 (d, J = 9.2 Hz), 128.64 (d, J = 11.7 Hz), 128.47, 127.57, 126.24 (d, J = 1.6 Hz), 118.45 (d, J = 9.7 Hz), 35.60 (d, J = 68.7 Hz). ^{31}P NMR (202 MHz, $CDCl_3$): δ 30.06. This compound was known: Y. G. Zhang, X. L. Liu, Z. Y. He, X. M. Li, H.-J. Kang, S.- K. Tian, *Chem. Eur. J.* **2014**, *20*, 2765.



Phenethyldiphenylphosphine oxide (**5i**). Colorless solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.82 – 7.72 (m, 4H), 7.55 – 7.45 (m, 6H), 7.27 – 7.12 (m, 5H), 2.97 – 2.90 (m, 2H), 2.62 – 2.55 (m, 2H). ^{13}C NMR (125.4 MHz, $CDCl_3$): δ 141.18 (d, J = 15.3 Hz), 132.78 (d, J = 97.8 Hz), 131.83 (d, J = 2.7 Hz), 130.80 (d, J = 9.3 Hz), 128.74 (d, J = 11.7 Hz), 128.62, 128.07, 126.34, 31.90

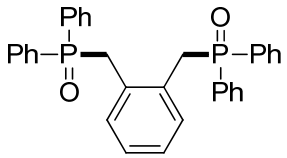
(d, J = 69.9 Hz), 27.55 (d, J = 3.1 Hz). ^{31}P NMR (202 MHz, $CDCl_3$): δ 31.64. This compound was known: W. Miao, Y. Gao, X. Li, Y. Gao, G. Tang, Y. Zhao, *Adv. Synth. Catal.* **2012**, *354*, 2659.



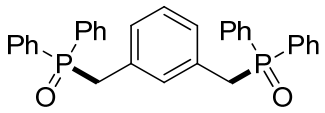
Heptyldiphenylphosphine oxide (**5j**). Colorless solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.77 – 7.71 (m, 4H), 7.54 – 7.44 (m, 6H), 2.30 – 2.22 (m, 2H), 1.75 – 1.51 (m, 2H), 1.50 – 1.33 (m, 2H), 1.30 – 1.17 (m, 6H), 0.85 (d, J = 6.5 Hz, 3H). ^{13}C NMR (125.4 MHz, $CDCl_3$): δ 133.22 (d, J = 97.7 Hz), 131.61 (d, J = 2.6 Hz), 130.76 (d, J = 9.2 Hz), 128.60 (d, J = 11.6 Hz), 31.53, 30.92 (d, J = 14.6 Hz), 29.73 (d, J = 72.1 Hz), 28.72, 22.53, 21.40 (d, J = 3.9 Hz), 14.00. ^{31}P NMR (202 MHz, $CDCl_3$): δ 32.72. This compound was known: S. H. Bertz, G. Dabbagh, *J. Am. Chem. Soc.* **1981**, *103*, 5932.

3.4 Typical Procedures for *n*-Bu_4NI-Catalyzed Reaction of Diols and Phosphinites for Bisphosphine oxide Synthesis (Modified Method B). A neat mixture of 1,2-benzenedimethanol (69.0 mg, 0.50 mmol), phenyl diphenylphosphinite **4b** (417.0 mg, 1.5 mmol, 1.5 equiv.), and *n*-Bu_4NI (9.3 mg, 5 mol%) was sealed in a 20 mL schlenk tube under nitrogen, heated at 85 ^{o}C for 24 h, and then monitored by TLC and/or GC-MS. After completion, the reaction mixture was purified by flash column chromatography on silica gel using dichloromethane and methanol (100/0~ 15/1) as the eluent, giving **5k** in 61% isolated yield.

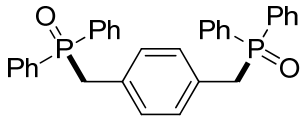
Typical Procedure for Gram Scale Reaction of a Diol and 4 for the Synthesis of 5. A neat mixture of 1,2-benzenedimethanol (1.38 g, 10 mmol), phenyl diphenylphosphinite **4b** (8.34 g, 30 mmol, 1.5 equiv.), and *n*-Bu_4NI (184.5 mg, 5 mol%) was sealed under nitrogen in a 100 mL Schlenk tube and heated at 85 ^{o}C for 24 h. The reaction mixture was then washed with ethyl acetate/petroleum ether to give crude (1,2-phenylenebis(methylene))bis(diphenylphosphine oxide) (**5k**). The crude **5k** was then subjected to recrystallisation in ethyl acetate and dichloromethane to afford 60% isolated yield of white crystals **5k** (3.04 g).



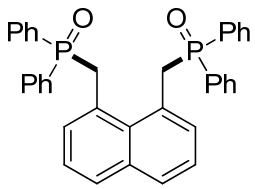
(1,2-Phenylenebis(methylene))bis(diphenylphosphine oxide) (**5k**). Colorless solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.68 (t, J = 9.0 Hz, 8H), 7.52 – 7.38 (m, 12H), 6.90 – 6.83 (m, 2H), 6.75 – 6.68 (m, 2H), 3.96 (d, J = 12.5 Hz, 4H). ^{13}C NMR (125.4 MHz, $CDCl_3$): δ 132.57 (d, J = 98.7 Hz), 131.79, 131.68, 131.49 (d, J = 2.9 Hz), 131.21 (d, J = 9.1 Hz), 128.51 (d, J = 9.3 Hz), 126.65, 35.44 (d, J = 66.1 Hz). ^{31}P NMR (202 MHz, $CDCl_3$): δ 31.05. This compound was known: S. P. Bew, R. A. Brimage, D. L. Hughes, L. Legentil, S. V. Sharma, M. A. Wilson, *J. Org. Chem.* **2007**, *72*, 2655.



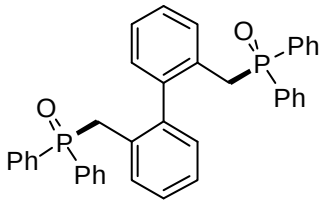
(1,3-Phenylenebis(methylene))bis(diphenylphosphine oxide) (**5l**). Colorless solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.71 – 7.57 (m, 8H), 7.52 – 7.40 (m, 12H), 7.15 (s, 1H), 6.93 (t, J = 7.5 Hz, 1H), 6.84 (d, J = 7.5 Hz, 2H), 3.58 (d, J = 13.5 Hz, 4H). ^{13}C NMR (125.4 MHz, $CDCl_3$): δ 132.05 (d, J = 99.0 Hz), 132.26 (d, J = 10.6 Hz), 132.25, 131.83, 131.27 (d, J = 10.1 Hz), 131.15 (d, J = 9.4 Hz), 128.52 (d, J = 12.0 Hz), 128.30, 37.82 (d, J = 66.3 Hz). ^{31}P NMR (202 MHz, $CDCl_3$): δ 30.93. This compound was known: D. Duncan, E. G. Hope, K. Singh, A. M, Stuart, *Dalton Trans.* **2011**, *40*, 1998.



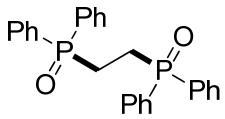
(1,4-Phenylenebis(methylene))bis(diphenylphosphine oxide) (**5m**). Colorless solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.73 – 7.60 (m, 8H), 7.52 (t, J = 7.5 Hz, 4H), 7.43 (t, J = 7.0 Hz, 8H), 6.94 (br, 4H), 3.61 (d, J = 13.0 Hz, 4H). ^{13}C NMR (125.4 MHz, $CDCl_3$): δ 132.24 (d, J = 99.1 Hz), 131.79, 131.15 (d, J = 9.0 Hz), 130.17, 128.53 (d, J = 12.3 Hz), 128.47 (d, J = 12.0 Hz), 37.79 (d, J = 66.4 Hz). ^{31}P NMR (202 MHz, $CDCl_3$): δ 31.24. This compound was known: E. N. Tsvetkov，N. A. Bondarenko，I. G. Malakhova，M. I. Kabachnik, *Synthesis* **1986**, 198.



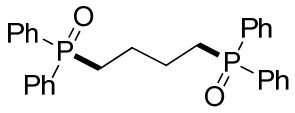
(Naphthalene-1,8-diylbis(methylene))bis(diphenylphosphine oxide) (**5n**). Colorless solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.72 – 7.60 (m, 10H), 7.45 (t, J = 7.5 Hz, 4H), 7.36 – 7.31 (m, 8H), 7.04 (t, J = 7.5 Hz, 2H), 6.82 (d, J = 6.5 Hz, 2H), 4.77 (d, J = 12.5 Hz, 4H). ^{13}C NMR (125.4 MHz, $CDCl_3$): δ 136.14, 132.77 (d, J = 98.9 Hz), 132.38, 132.24, 131.61 (d, J = 2.4 Hz), 131.34 (d, J = 9.2 Hz), 129.54 (d, J = 3.5 Hz), 128.43 (d, J = 11.8 Hz), 127.77 (d, J = 8.9 Hz), 124.35 (d, J = 3.0 Hz), 38.47 (d, J = 67.2 Hz). ^{31}P NMR (202 MHz, $CDCl_3$): δ 31.60. Calcd for $C_{36}H_{32}O_2P_2$ (M+H): 557.1799; found: 557.1800.



([1,1'-Biphenyl]-2,2'-diylbis(methylene))bis(diphenylphosphine oxide) (**5o**). Colorless solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.60 (d, J = 7.8 Hz, 2H), 7.53 – 7.35 (m, 12H), 7.33 – 7.18 (m, 10H), 7.06 (t, J = 7.5 Hz, 2H), 6.40 (d, J = 7.5 Hz, 2H), 3.46 – 3.19 (m, 4H). ^{13}C NMR (125.4 MHz, $CDCl_3$): δ 140.59 (d, J = 6.6 Hz), 131.79 (d, J = 2.4 Hz), 131.58 (d, J = 2.7 Hz), 131.11 (d, J = 8.9 Hz), 130.54 (d, J = 4.4 Hz), 130.47 (d, J = 1.5 Hz), 128.56 (d, J = 11.6 Hz), 128.34 (d, J = 11.8 Hz), 127.61 (d, J = 2.4 Hz), 126.77 (d, J = 2.4 Hz), 33.88 (d, J = 66.8 Hz). ^{31}P NMR (202 MHz, $CDCl_3$): δ 30.36. Calcd for $C_{38}H_{33}O_2P_2$ (M+H): 583.1956; found: 583.1967.

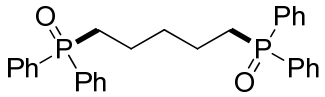


Ethane-1,2-diylbis(diphenylphosphine oxide) (**5p**). Colorless solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.72 (d, J = 5.0 Hz, 8H), 7.55 – 7.42 (m, 12H), 2.55 (s, 4H). ^{13}C NMR (125.4 MHz, $CDCl_3$): δ 132.03, 131.99 (d, J = 100.4 Hz), 130.80 (t, J = 4.7 Hz), 128.83 (t, J = 5.8 Hz), 21.59 (dd, J = 65.3, 32.6 Hz). ^{31}P NMR (202 MHz, $CDCl_3$): δ 32.70. This compound was known: Y. Sagaa, D. Han, S.-I. Kawaguchia, A. Ogawaa, L.-B. Han, *Chem. Commun.* **2008**, *37*, 4493. *Tetrahedron Lett.* **2015**, *56*, 5303.



Butane-1,4-diylbis(diphenylphosphine oxide) (**5q**). Colorless solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.77 – 7.52 (m, 8H), 7.50 – 7.28 (m, 12H), 2.31– 2.18 (m, 4H), 1.75 – 1.60 (m, 4H). ^{13}C NMR (125.4 MHz, $CDCl_3$): δ 132.69 (d, J = 98.5 Hz), 131.77 (d, J = 2.5 Hz), 130.73 (d, J

= 9.3 Hz), 128.68 (d, J = 11.7 Hz), 29.32 (d, J = 71.6 Hz), 22.86 (dd, J = 15.5, 3.6 Hz). ^{31}P NMR (202 MHz, $CDCl_3$): δ 33.14. This compound was known: M.J. Petersson, W. A. Loughlin, I, D. Jenkins, *Chem. Commun.* **2008**, *37*, 4493.

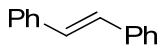


Pentane-1,5-diylbis(diphenylphosphine oxide) (**5r**). Colorless solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.80 – 7.62 (m, 8H), 7.55 – 7.42 (m, 12H), 2.28 – 2.16 (m, 4H), 1.67 – 1.47 (m, 6H). ^{13}C NMR (125.4 MHz, $CDCl_3$): δ 132.90 (d, J = 98.3 Hz), 131.71 (d, J = 2.6 Hz), 130.74 (d, J = 9.3 Hz), 128.65 (d, J = 11.6 Hz), 31.82 (t, J = 14.1 Hz), 29.27 (d, J = 71.9 Hz), 20.87 (d, J = 3.8 Hz). ^{31}P NMR (202 MHz, $CDCl_3$): δ 33.73. This compound was known: N. Platzer, F. Dardoise, W. Bergeret, J. C. Gautier, S. Raynal, *Phosphorus und Sulfur* **1986**, *27*, 275.

3.5 Applications of the Alcohol-Based Michaelis-Arbuzov Reaction in One-Pot Synthesis.

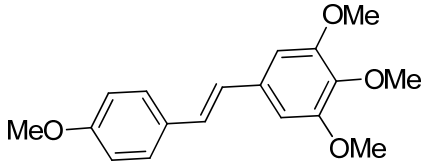
Typical Procedure for One-Pot Gram-Scale Synthesis of Substituted Stillbenes (Figure 2a in the text). A neat mixture of benzyl alcohol **1a** (2.16 g, 20 mmol), triethyl phosphite **2a** (4.98 g, 30.0 mmol, 1.5 equiv.), and *n*-Bu_4NI (220.0 mg, 3 mol%) was sealed under nitrogen in a 20 mL Schlenk tube and heated at 130 ^{o}C for 24 h. The low-boiling compounds in the reaction mixture were then removed under vacuum to afford the crude diethyl benzylphosphonate **3a**.

Dry DMF (30 mL) was then added to the above crude diethyl benzylphosphonate **3a** under N_2 and the solution was transferred to a three-necked-flask (100 mL). To the above **3a**/DMF solution in the three-necked-flask cooled at 0 ^{o}C was added successively sodium methoxide (2.24 g, 40 mmol) and benzaldehyde (20 mmol). The mixture was then stirred at room temperature under N_2 for 12 h, and poured into 250 mL ice-water. The precipitate was filtered off. The filtrate was collected and concentrated. The reaction residue was then subjected to recrystallization in ethyl acetate and petroleum ether to give **6a** as white crystals in 71% isolated yield (2.56 g).



(*E*)-Stillbene (**6a**). Colorless solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.51 (d, J = 7.5 Hz, 4H),

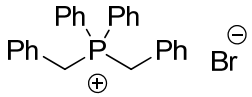
7.35 (t, J = 7.5 Hz, 4H), 7.25 (t, J = 7.5 Hz, 2H), 7.11 (s, 2H). ^{13}C NMR (125.4 MHz, $CDCl_3$): δ 137.39, 128.75, 128.70, 127.63, 126.54. This compound was known: D.-J. Dong, H.-H. Li, S.-K. Tian, *J. Am. Chem. Soc.* **2010**, *132*, 5018.



(*E*)-3,4,4'5-Tetramethoxystillbene (**6b**). Colorless solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.44 (d, J = 8.5 Hz, 2H), 6.97 (d, J = 16.0 Hz, 1H), 6.90 (dd, J = 12.0, 3.5 Hz, 3H), 6.72 (s, 2H), 3.92 (s, 6H), 3.86 (s, 3H), 3.83 (s, 3H). ^{13}C NMR (125.4 MHz, $CDCl_3$): δ 159.35, 153.43, 133.45, 130.08, 127.79, 127.63, 126.61, 114.20, 103.52, 60.94, 56.16, 55.33. This compound was known: D.-J. Dong, H.-H. Li, S.-K. Tian, *J. Am. Chem. Soc.* **2010**, *132*, 5018.

Detailed Procedures for One-pot Synthesis of a Phosphine Ligand (Figure 2b in the text). A neat mixture of benzyl alcohol **1a** (108.0 mg, 1.0 mmol, 2.0 equiv.), ethyl diphenylphosphinite **4a** (115.0 mg, 0.50 mmol), and *n*-Bu_4NI (3.7 mg, 2 mol%) was sealed under nitrogen in a 20 mL Schlenk tube and heated at 85 ^{o}C for 24 h. The reaction mixture was then washed with ethyl acetate to give the crude benzyldiphenylphosphine oxide **5a**.

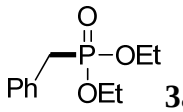
To the crude phosphine oxide **5a** was added dry THF (1 mL), triethoxyl hydrosilane (1.5 mmol, 3.0 equiv.), and titanium (IV) isopropoxide (14.2 mg, 10 mol%) under nitrogen. The reaction mixture was then heated at 80 ^{o}C for 1 h and cooled to room temperature to give the crude benzyldiphenylphosphine **7a**. Since **7a** is air-sensitive and not isolable by usual procedures, benzyl bromide (171 mg, 1 mmol, 2.0 equiv.) was added to **7a** and then heated at 80 ^{o}C under nitrogen for 1 h. The target dibenzyldiphenylphosphonium bromide $[PPh_2(CH_2Ph)_2]Br$ was obtained in 78% yield by filtration and wash with ethyl acetate.



Dibenzyldiphenylphosphonium Bromide. Colorless solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.81 – 7.62 (m, 2H), 7.55 (d, J = 7.5 Hz, 1H), 7.14 (t, J = 7.0 Hz, 1H), 7.10 – 6.92 (m, 2H), 4.95 (d, J = 14.5 Hz, 1H). ^{13}C NMR (125.4 MHz, $CDCl_3$): δ 134.75 (d, J = 2.7 Hz), 134.29 (d, J = 8.8

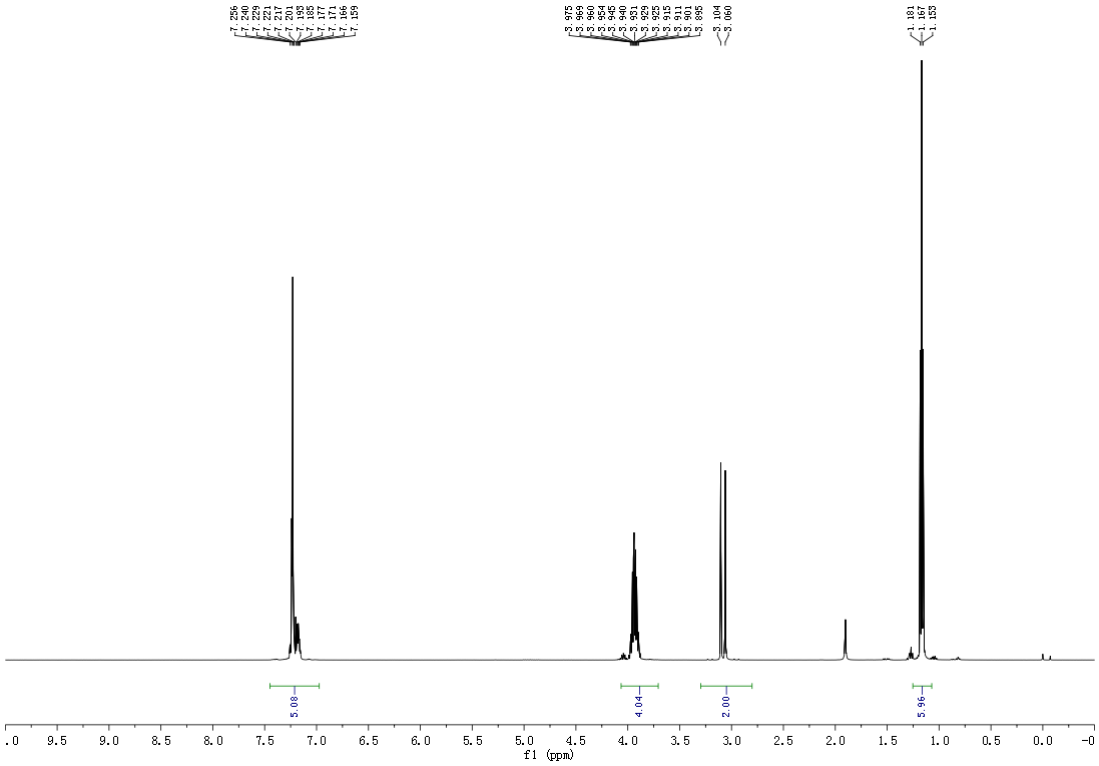
Hz), 130.71 (d, J = 5.5 Hz), 129.61 (d, J = 12.2 Hz), 128.71 (d, J = 3.1 Hz), 128.05 (d, J = 3.7 Hz), 127.55 (d, J = 8.7 Hz), 116.41 (d, J = 82.7 Hz), 29.53 (d, J = 45.2 Hz). ^{31}P NMR (202 MHz, $CDCl_3$): δ 26.70. This compound was known: N. J. Lawrence, F. Muhammad, *Tetrahedron* **1998**, *54*, 15361.

4. NMR spectra of the products

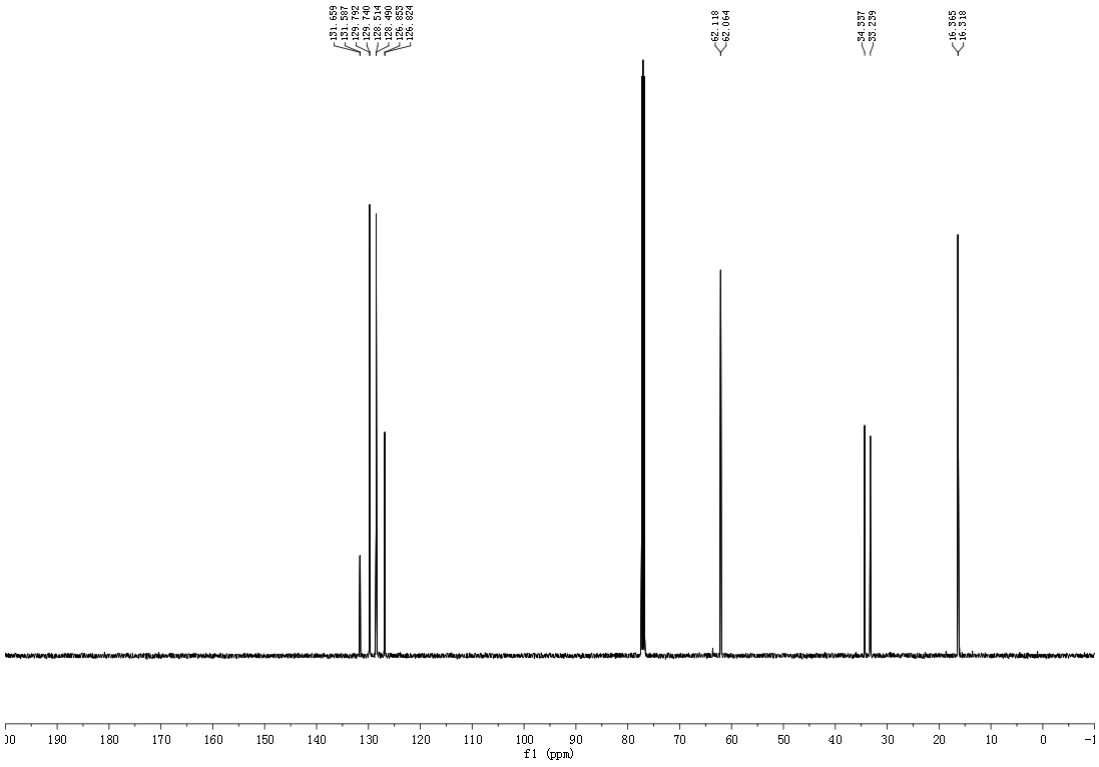


3a

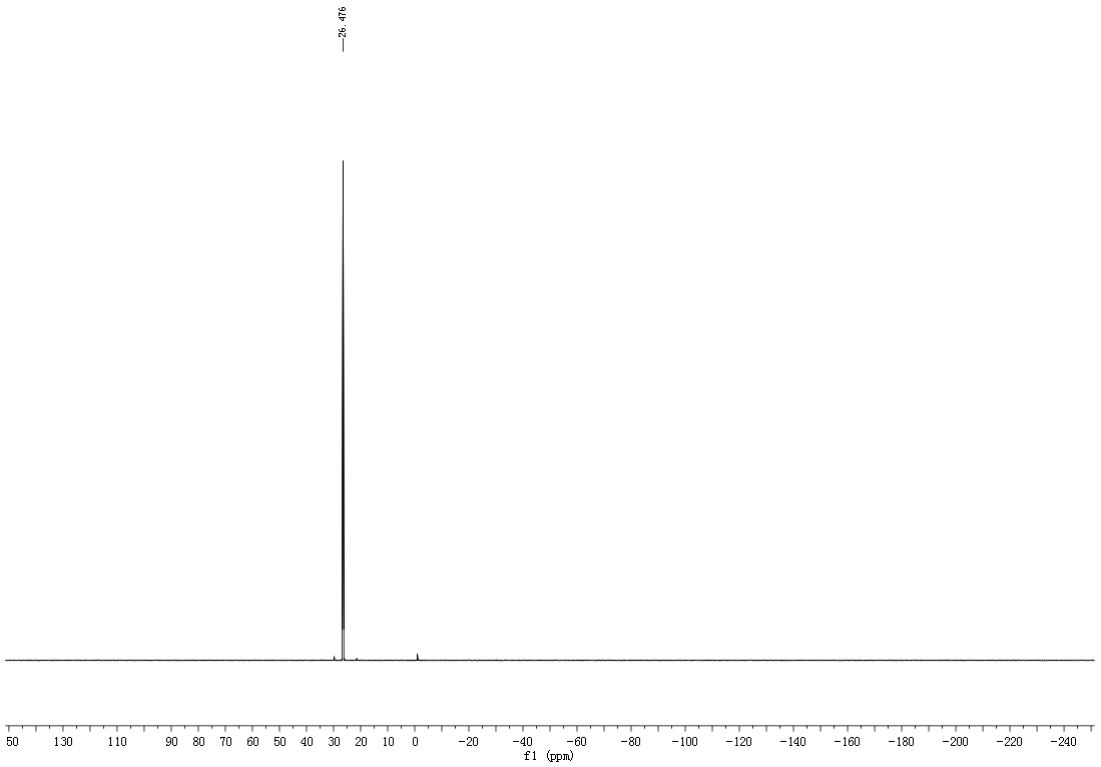
^{1}H NMR

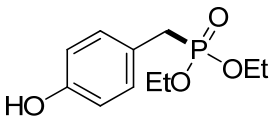


^{13}C NMR



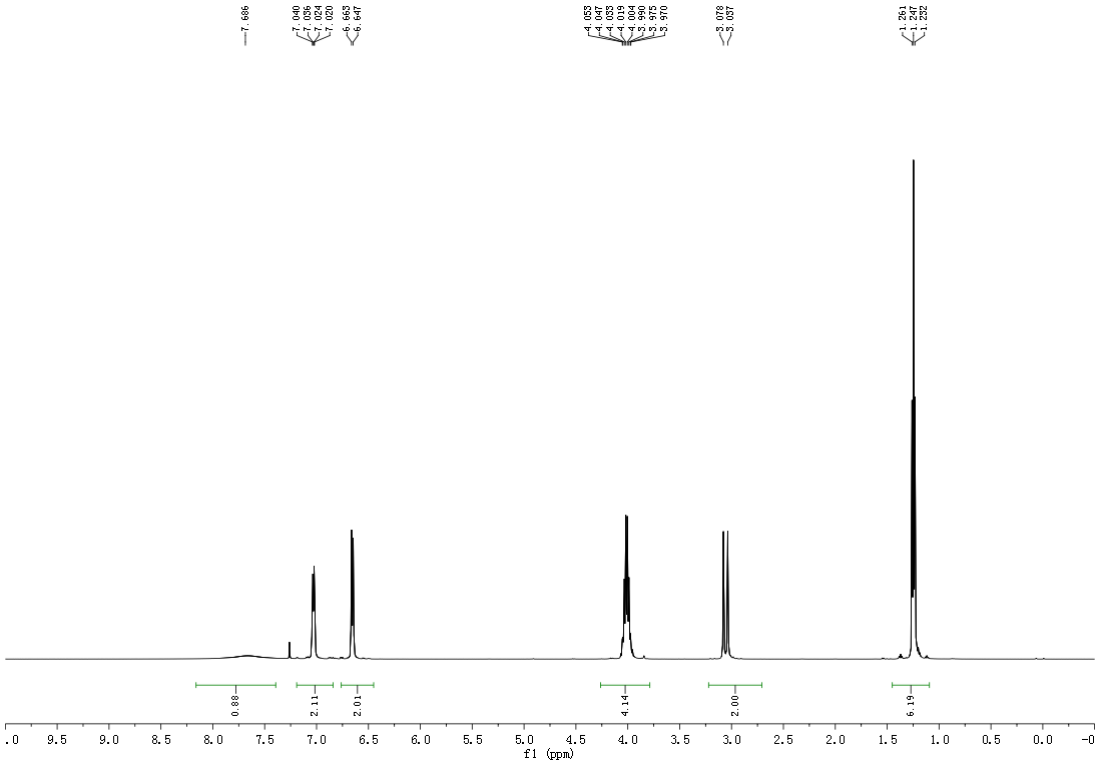
^{31}P NMR



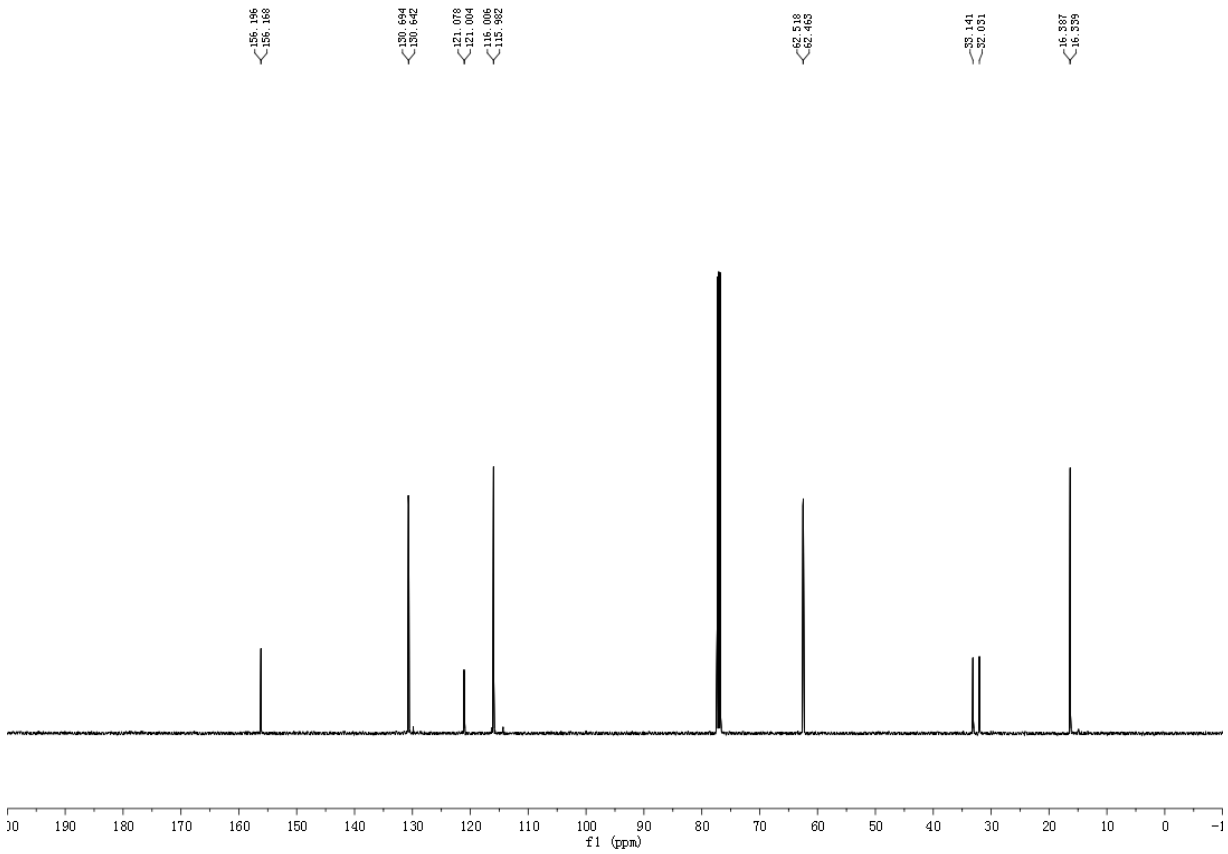


3b

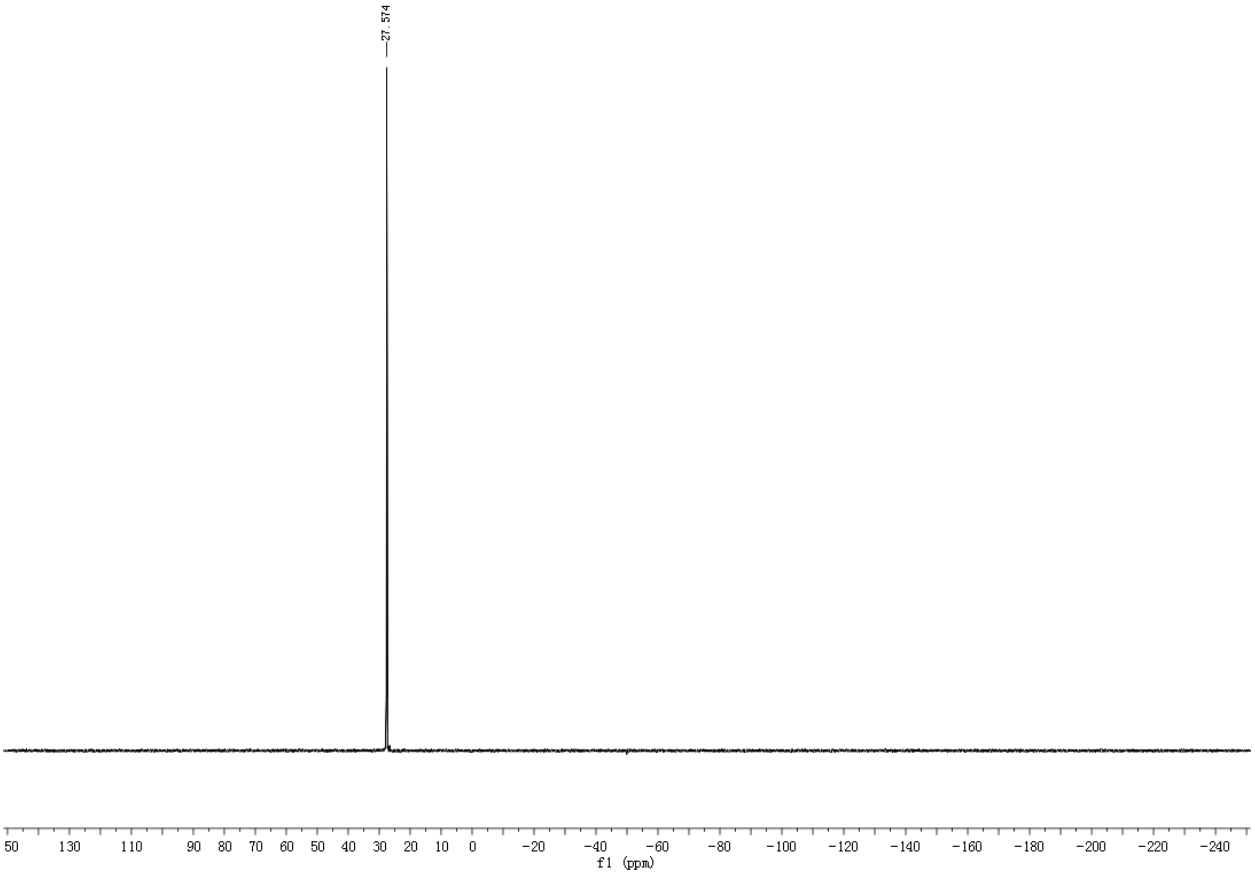
^{1}H NMR

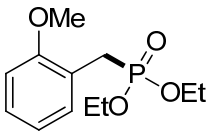


^{13}C NMR



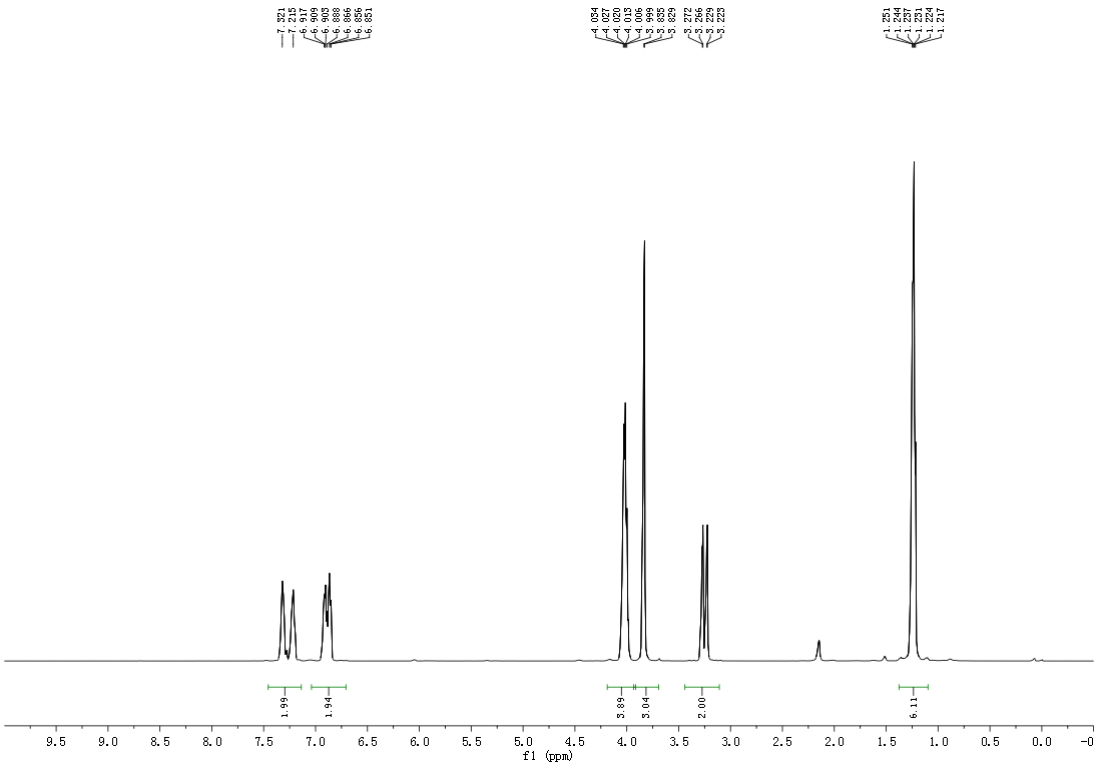
^{31}P NMR



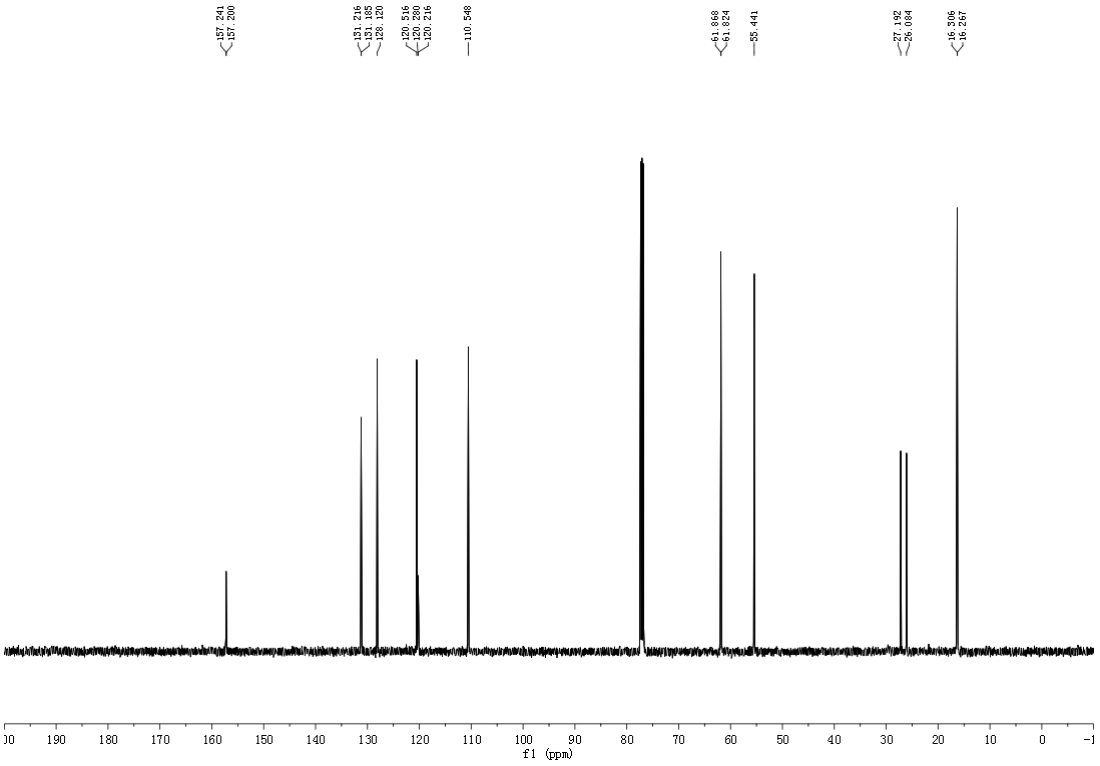


3c

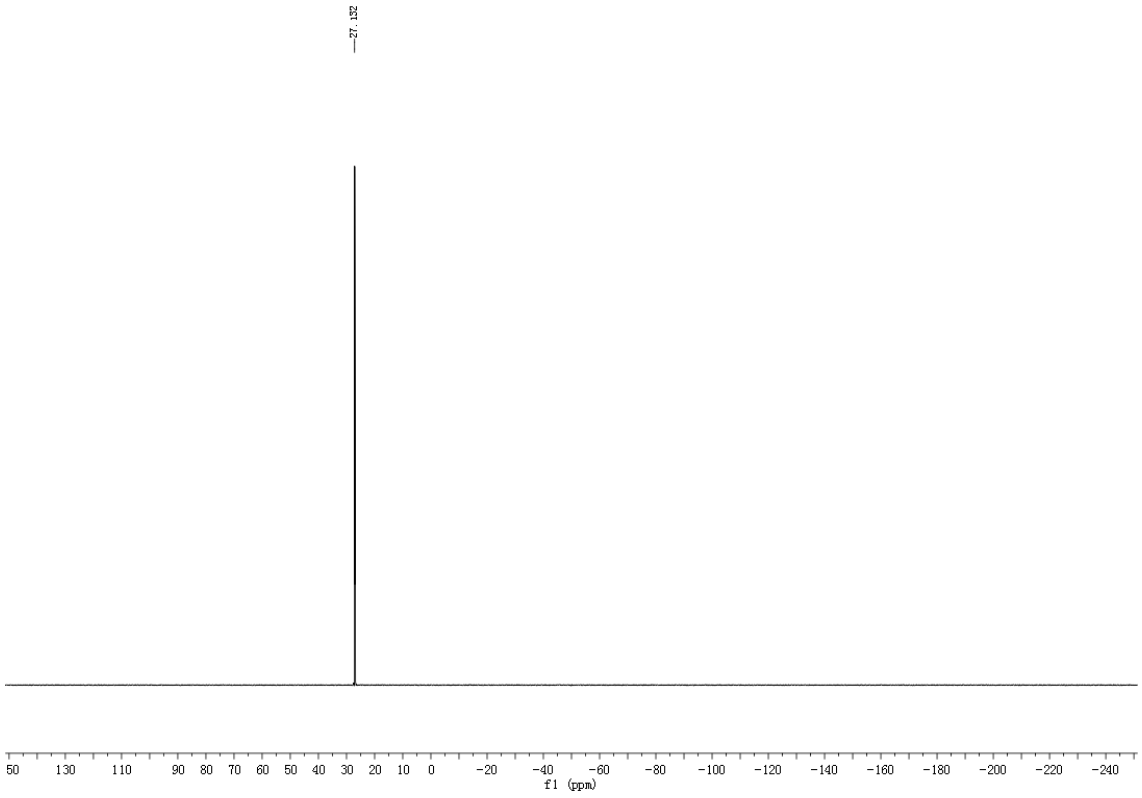
^{1}H NMR

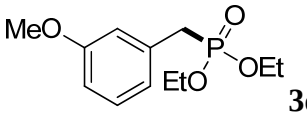


^{13}C NMR



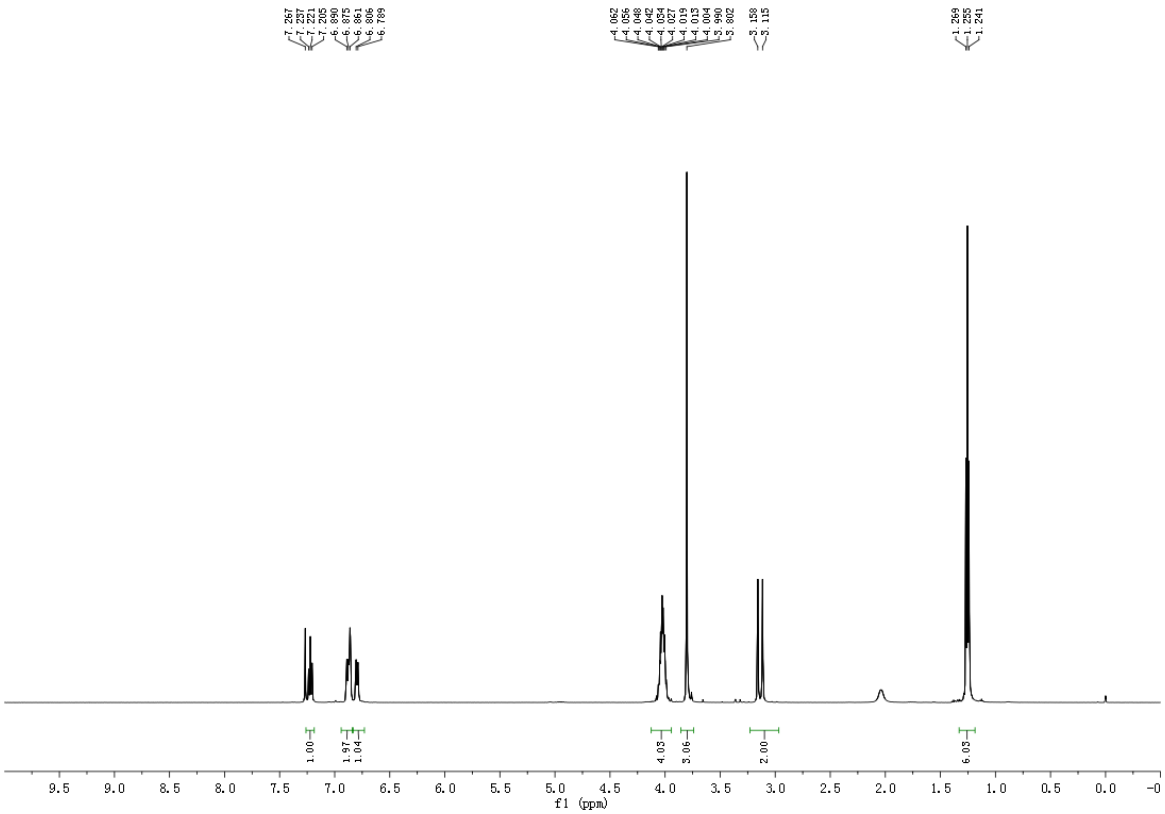
^{31}P NMR



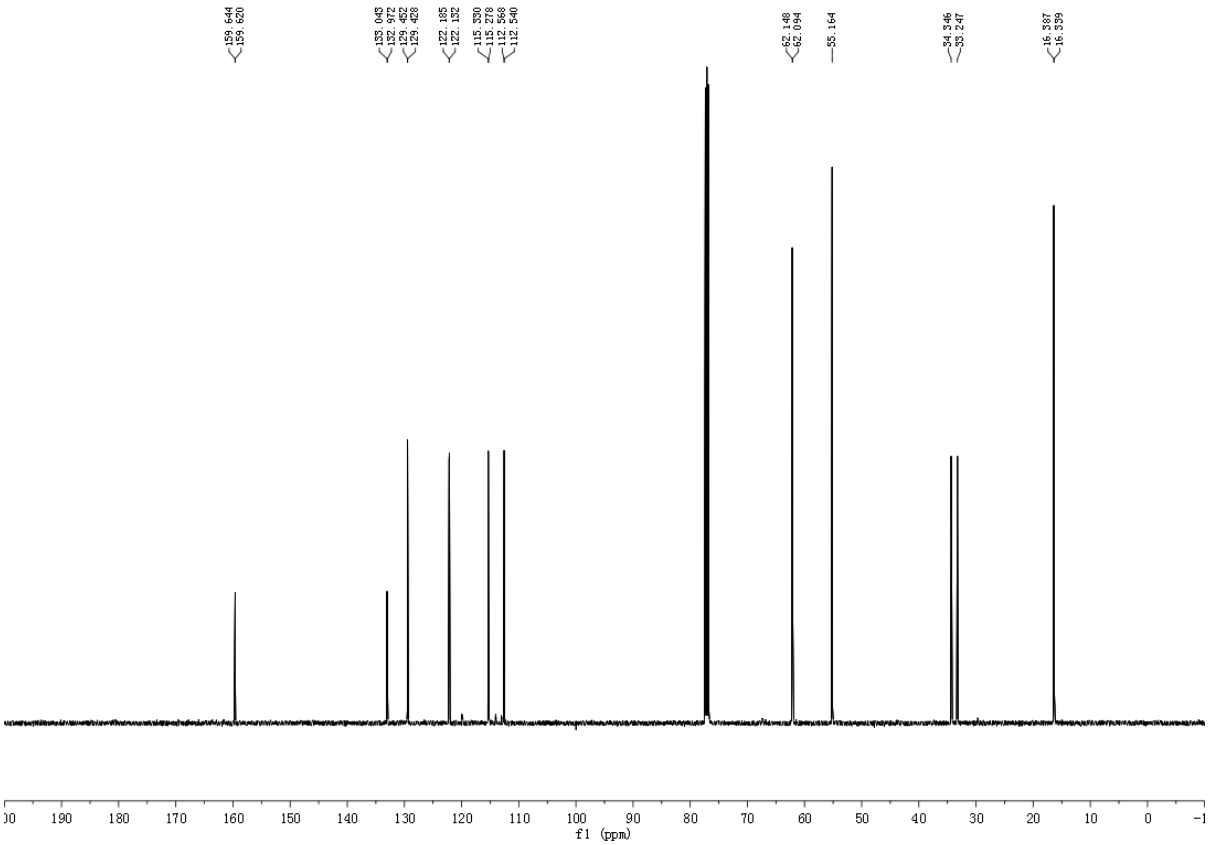


3d

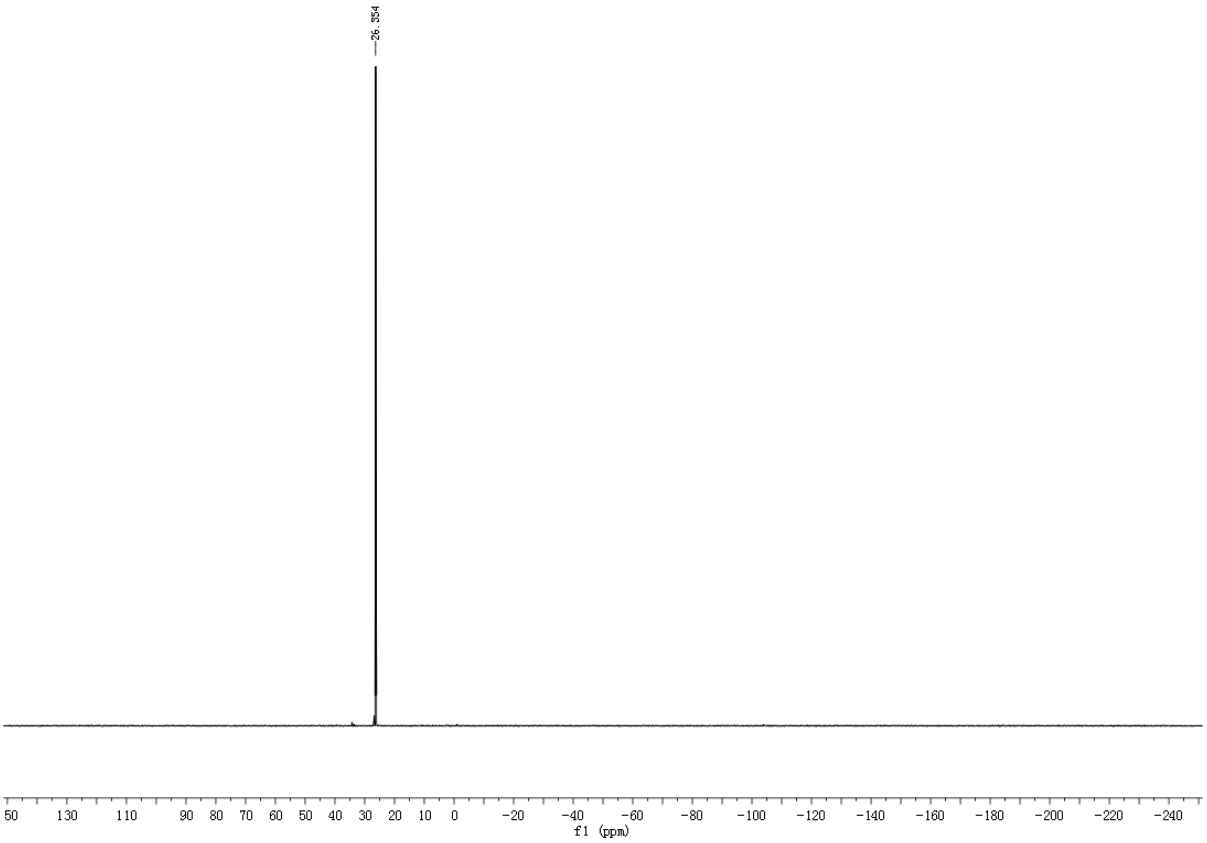
^{1}H NMR

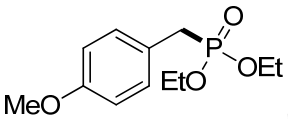


^{13}C NMR



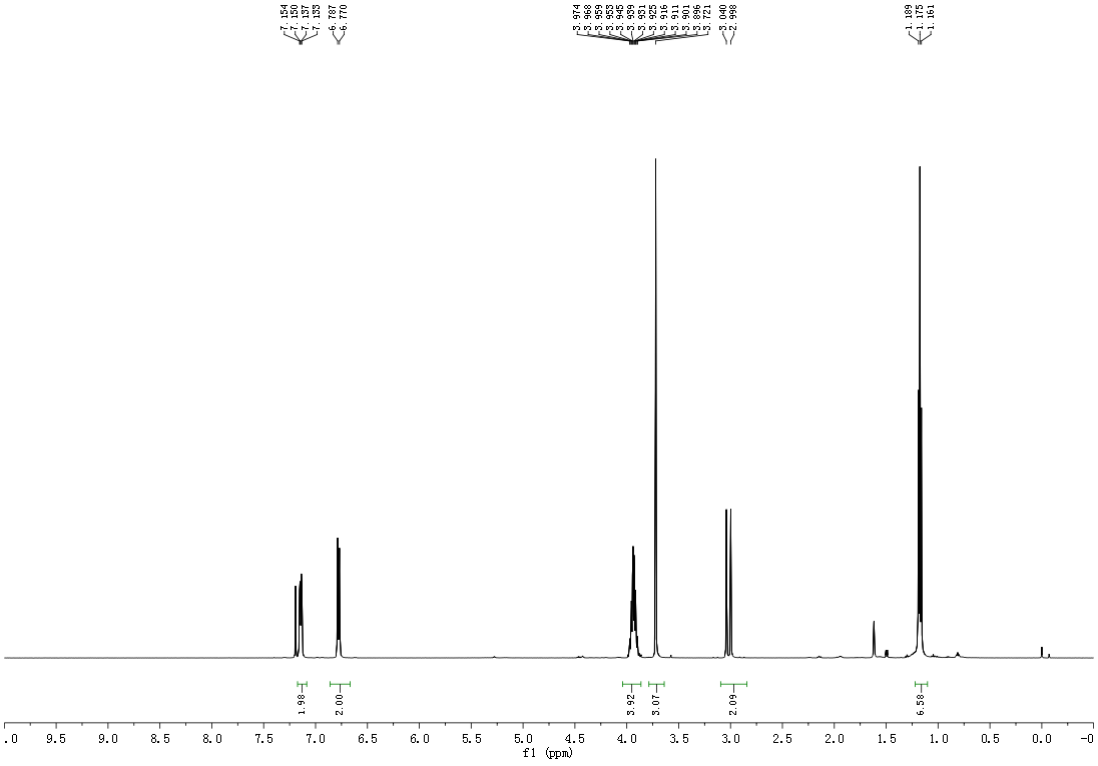
^{31}P NMR



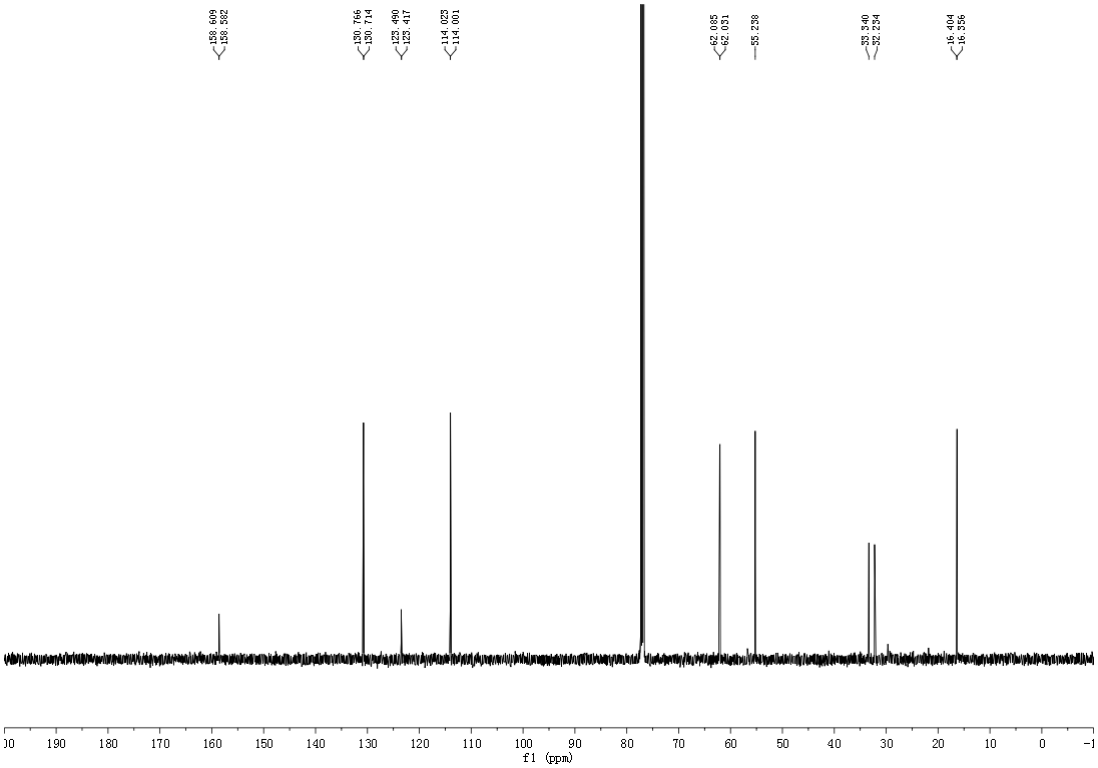


3e

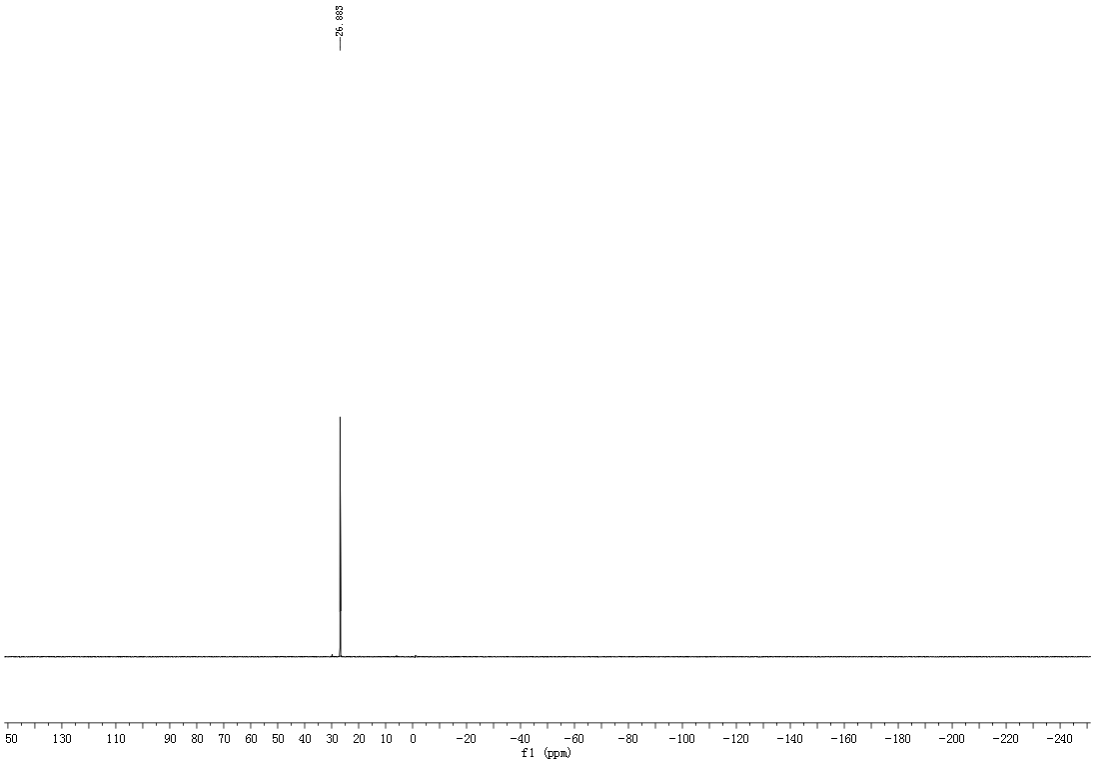
^{1}H NMR

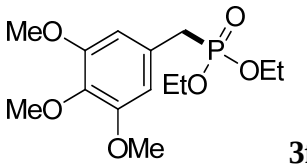


^{13}C NMR



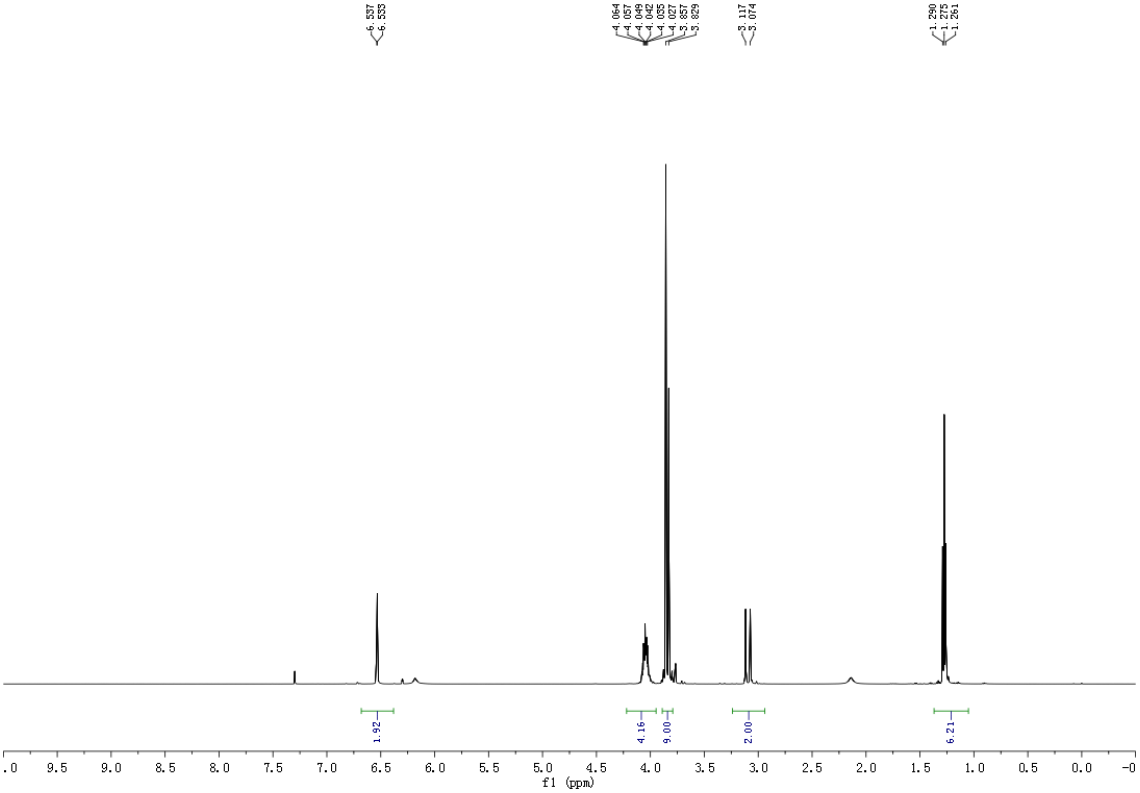
^{31}P NMR



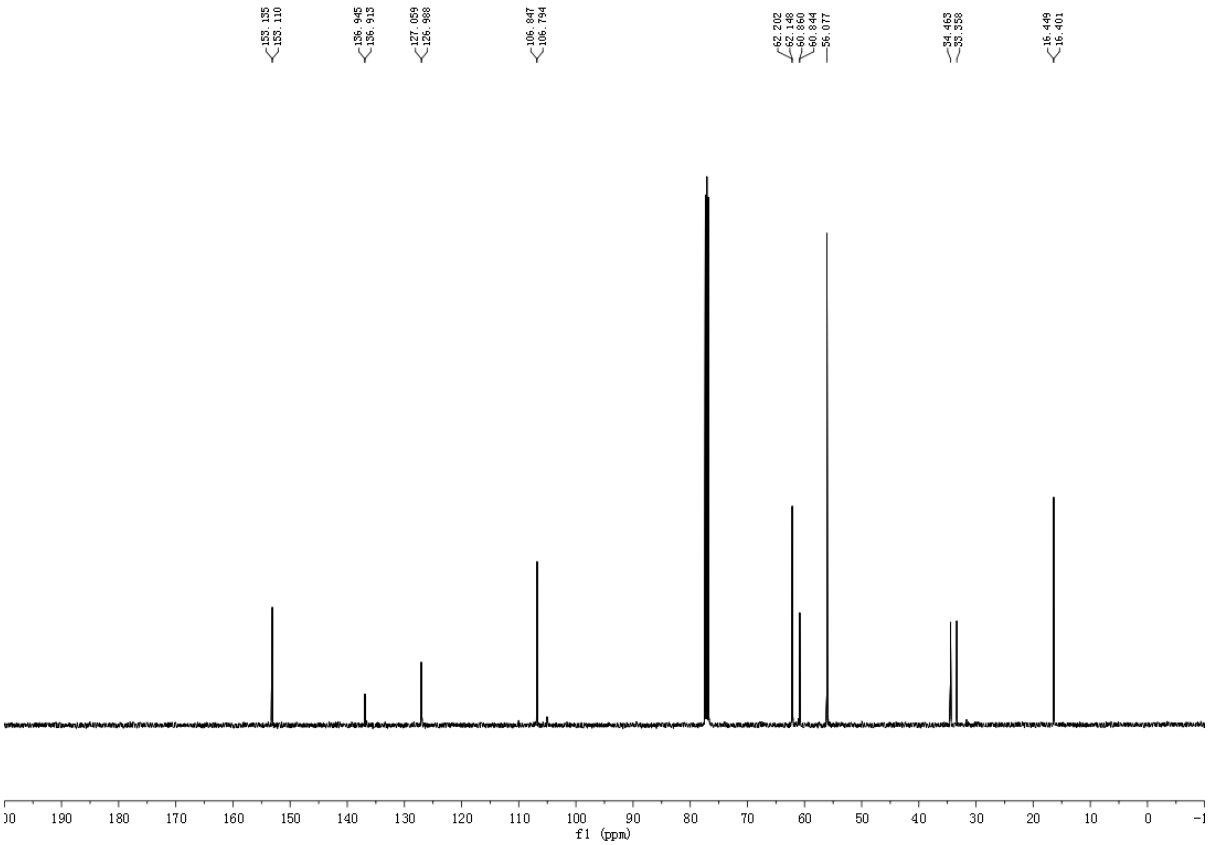


3f

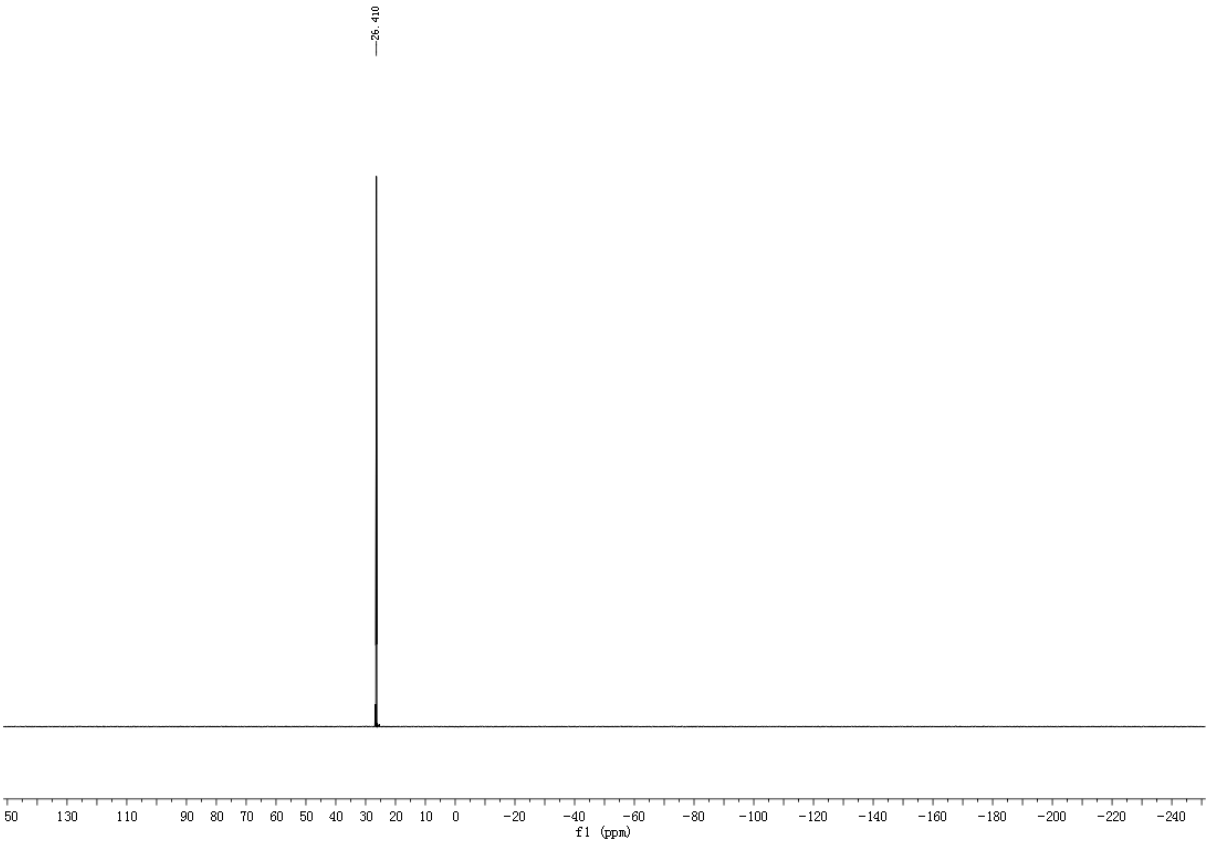
^{1}H NMR

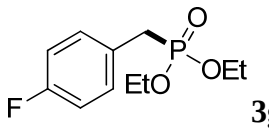


^{13}C NMR



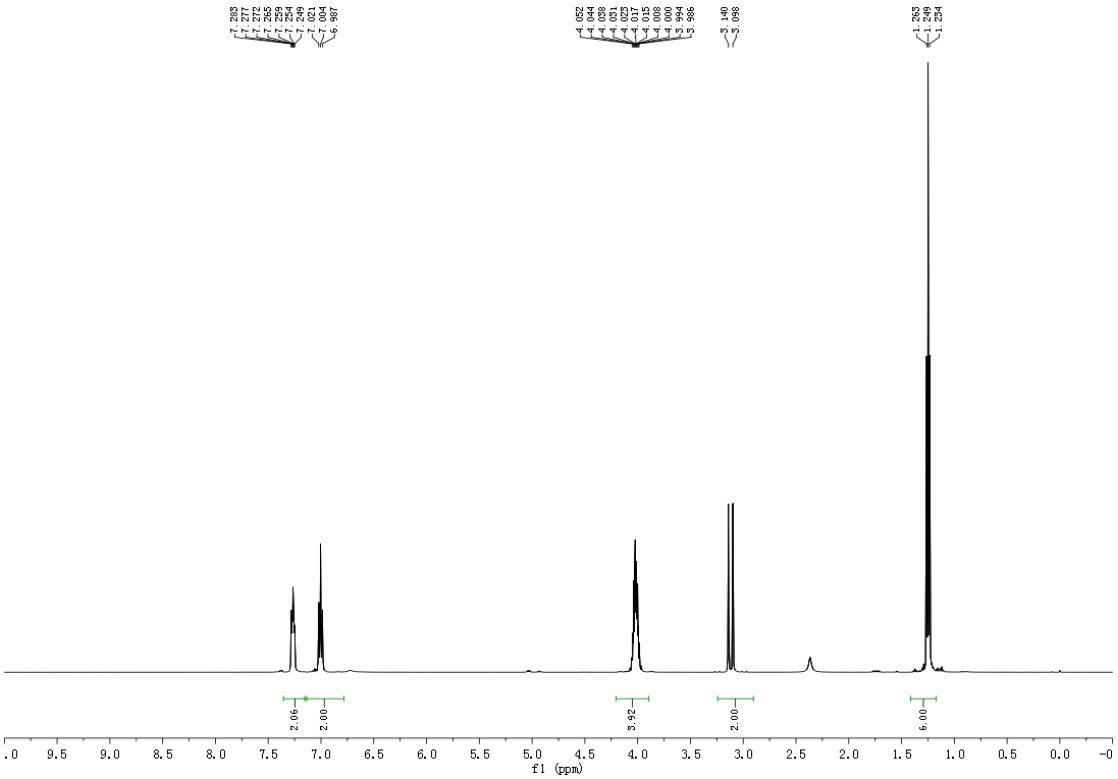
^{31}P NMR



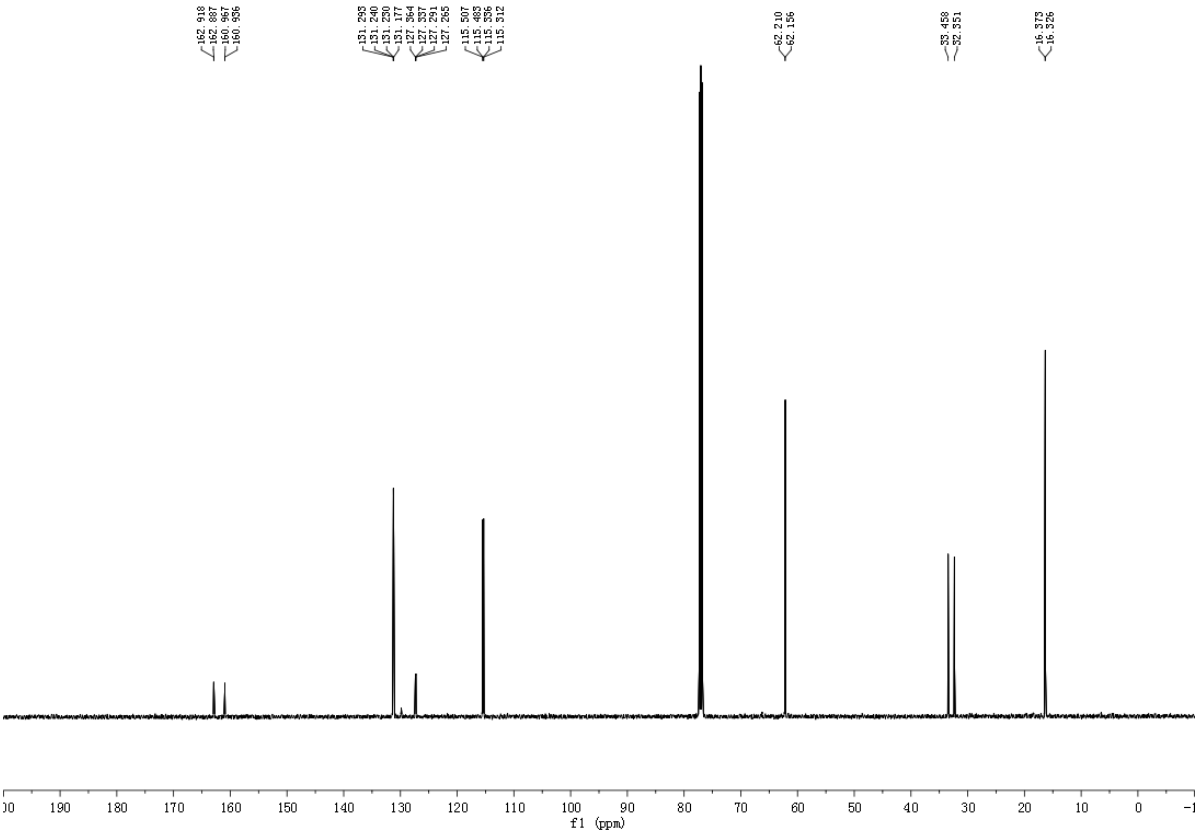


3g

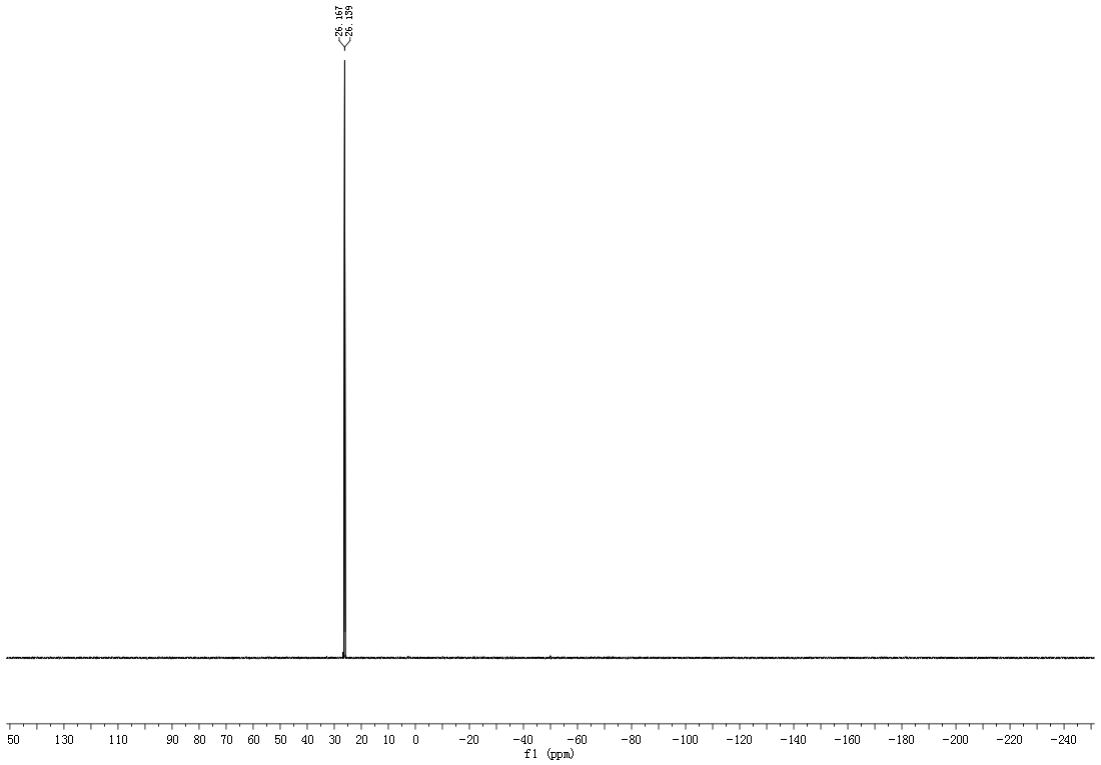
^{1}H NMR

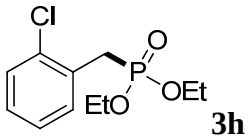


^{13}C NMR



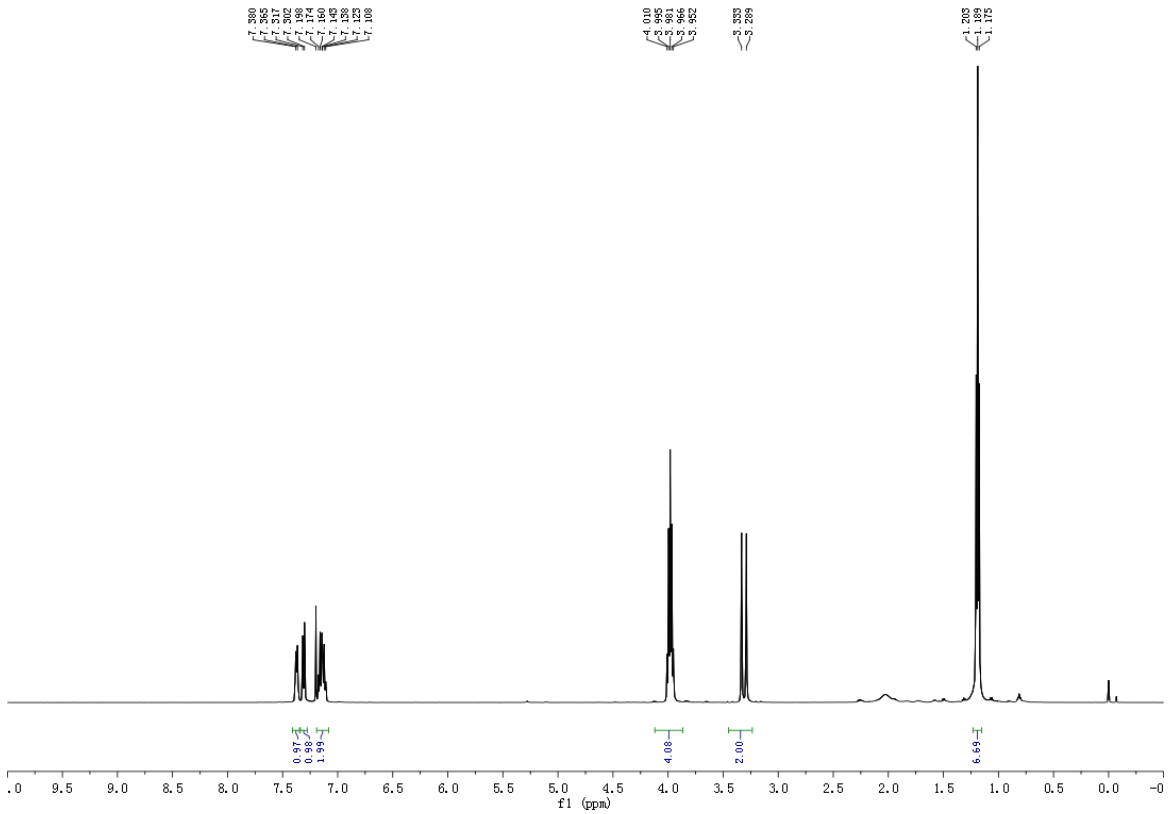
^{31}P NMR



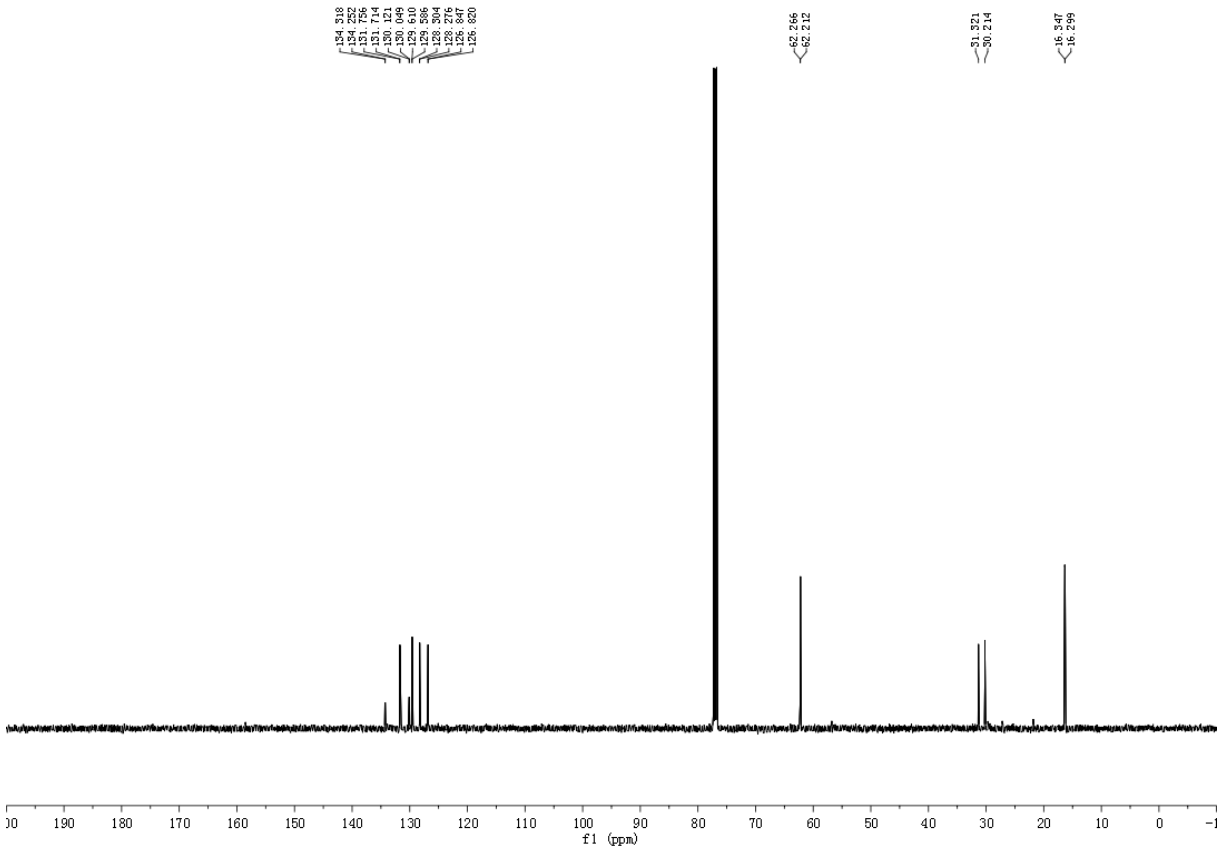


3h

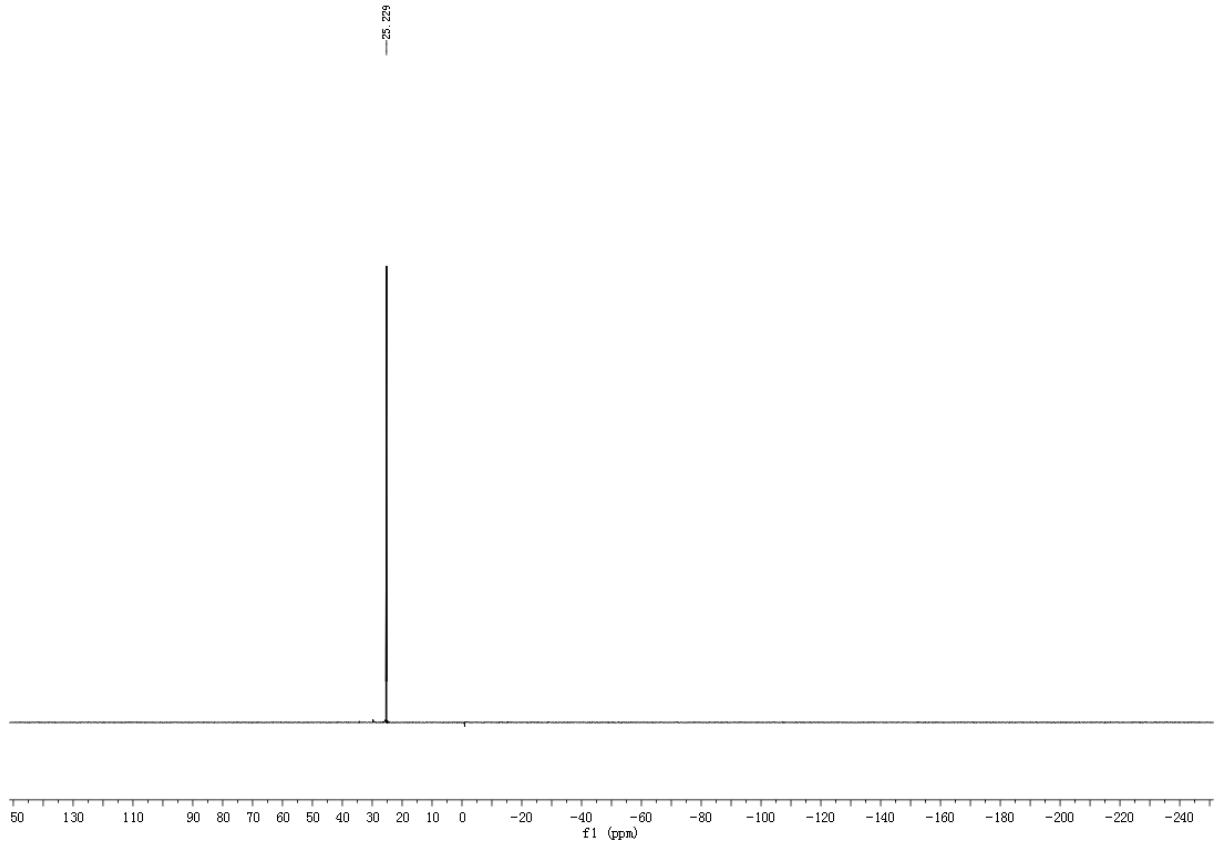
^{1}H NMR

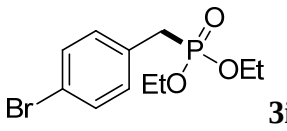


^{13}C NMR



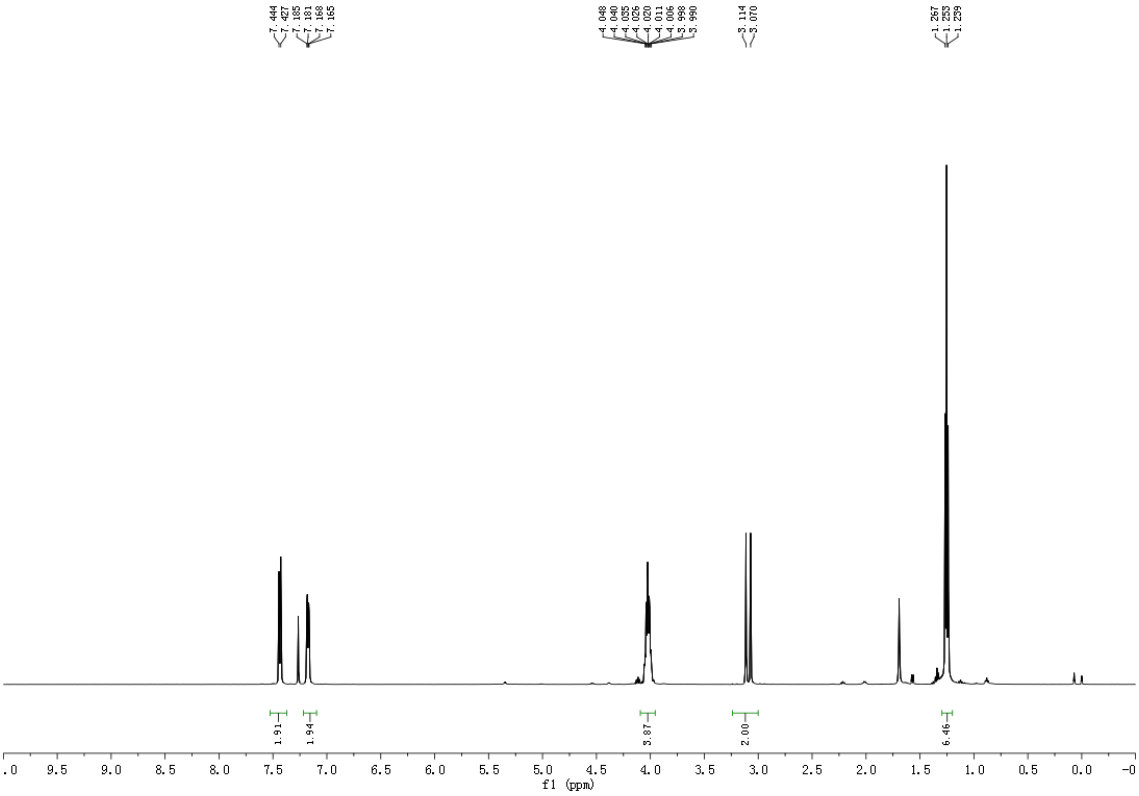
^{31}P NMR



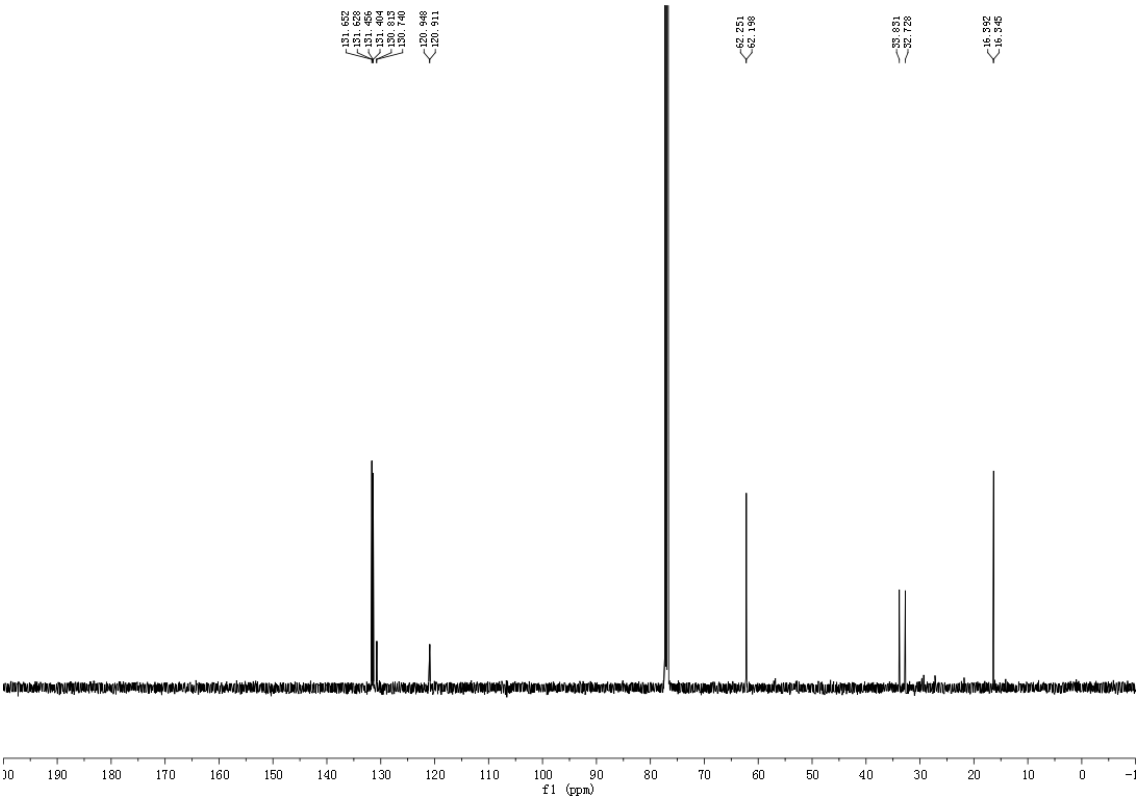


3i

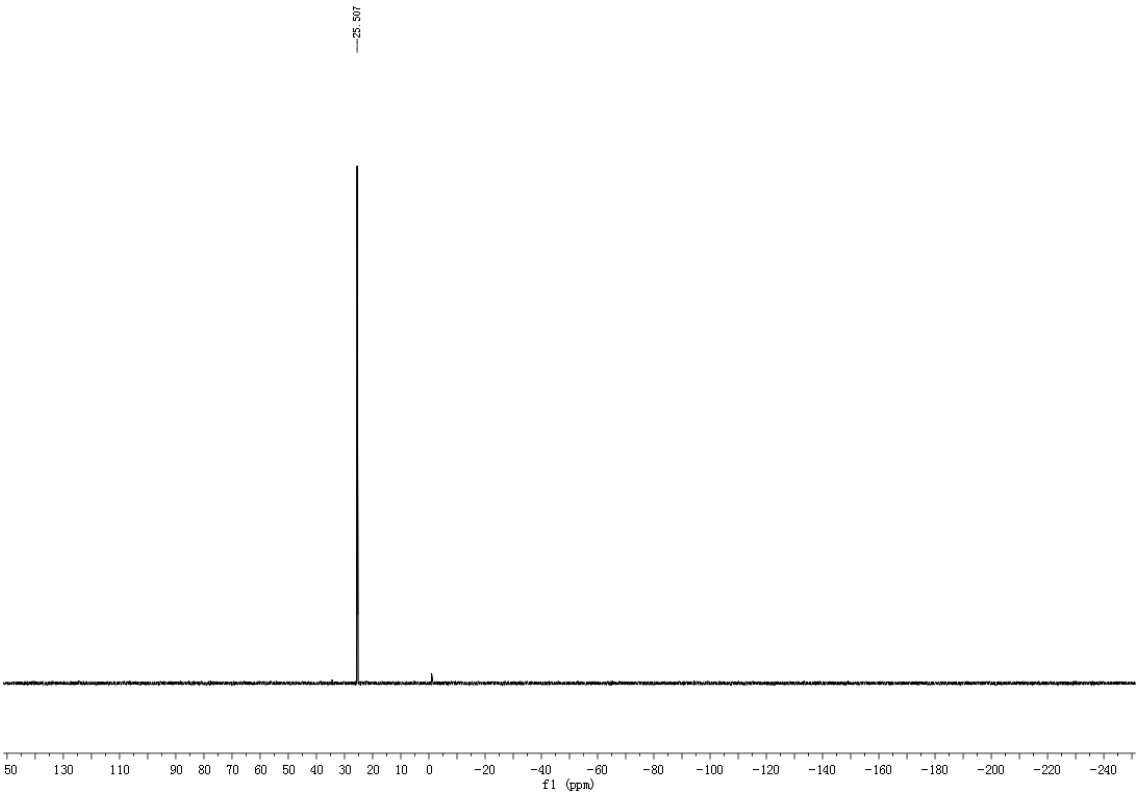
^{1}H NMR

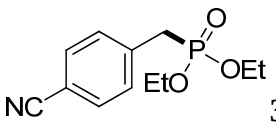


^{13}C NMR



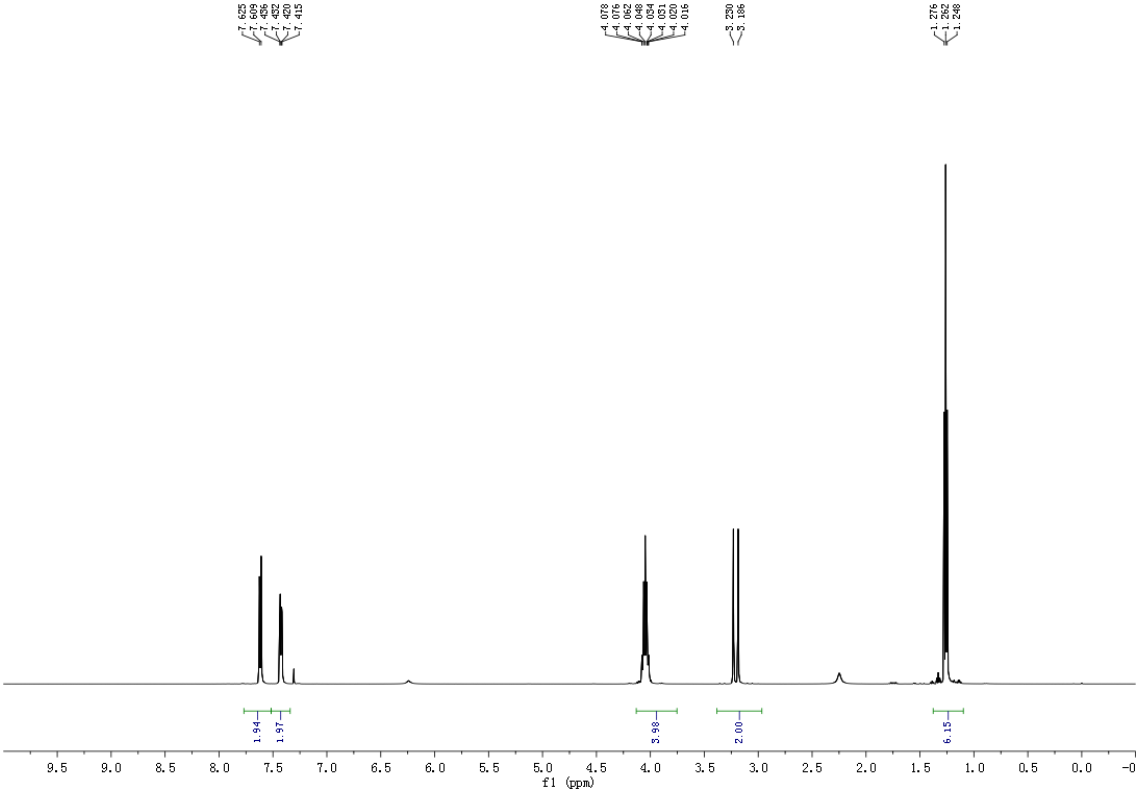
^{31}P NMR



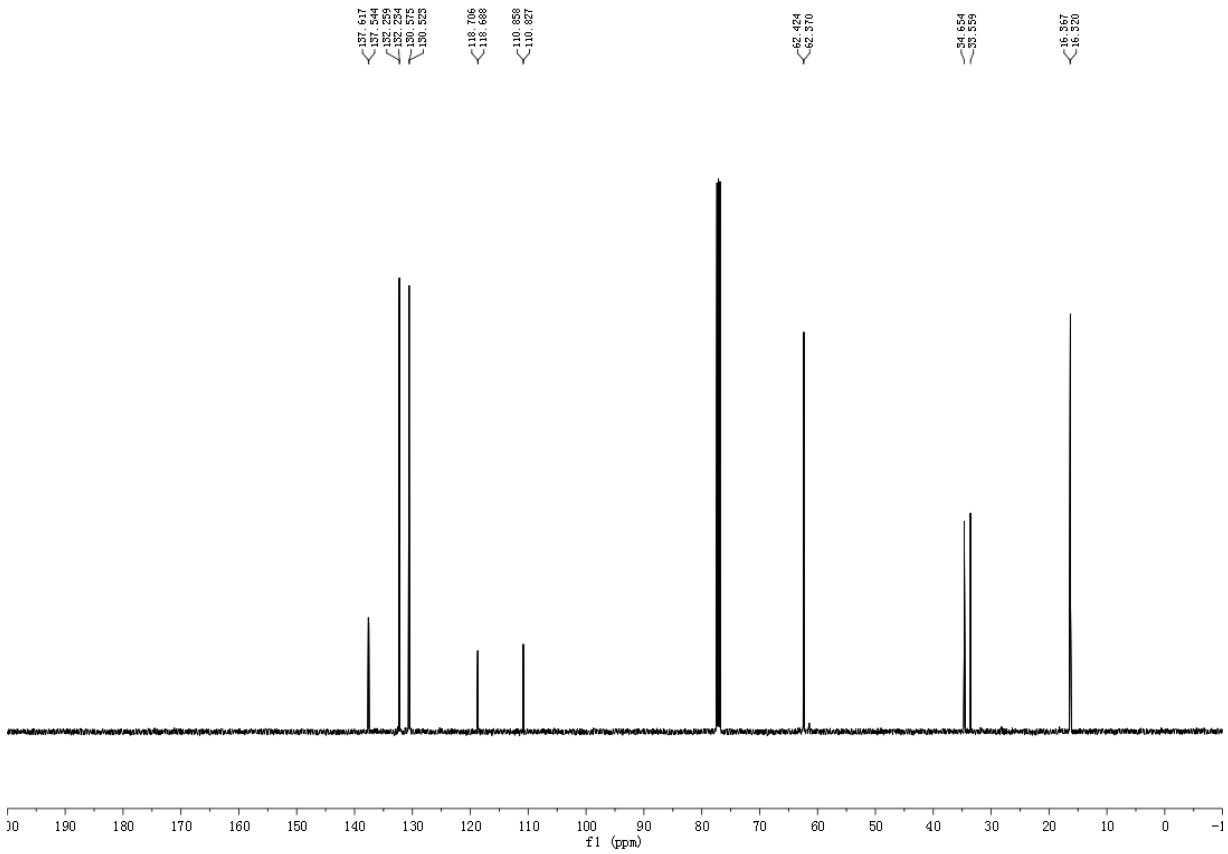


3j

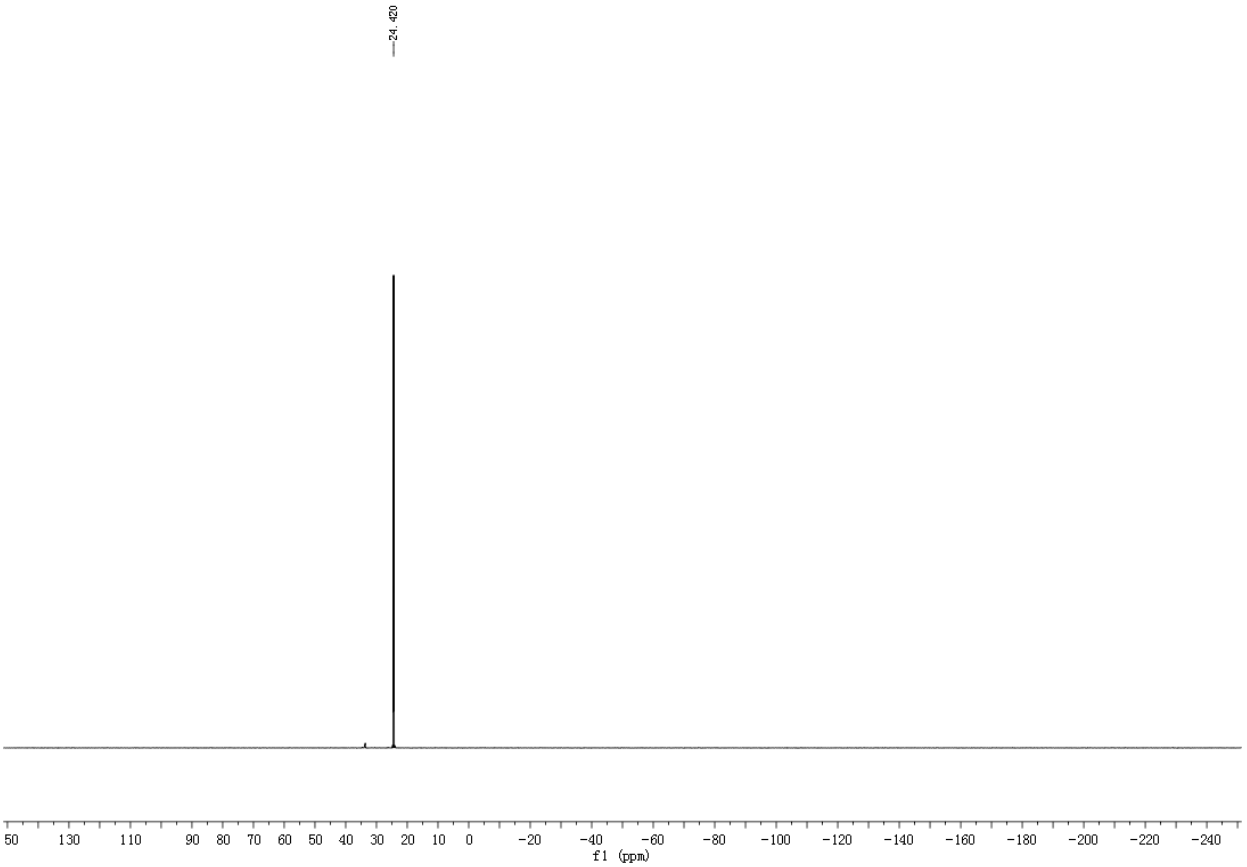
^{1}H NMR

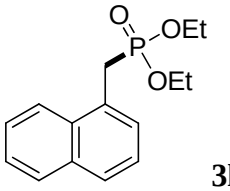


^{13}C NMR



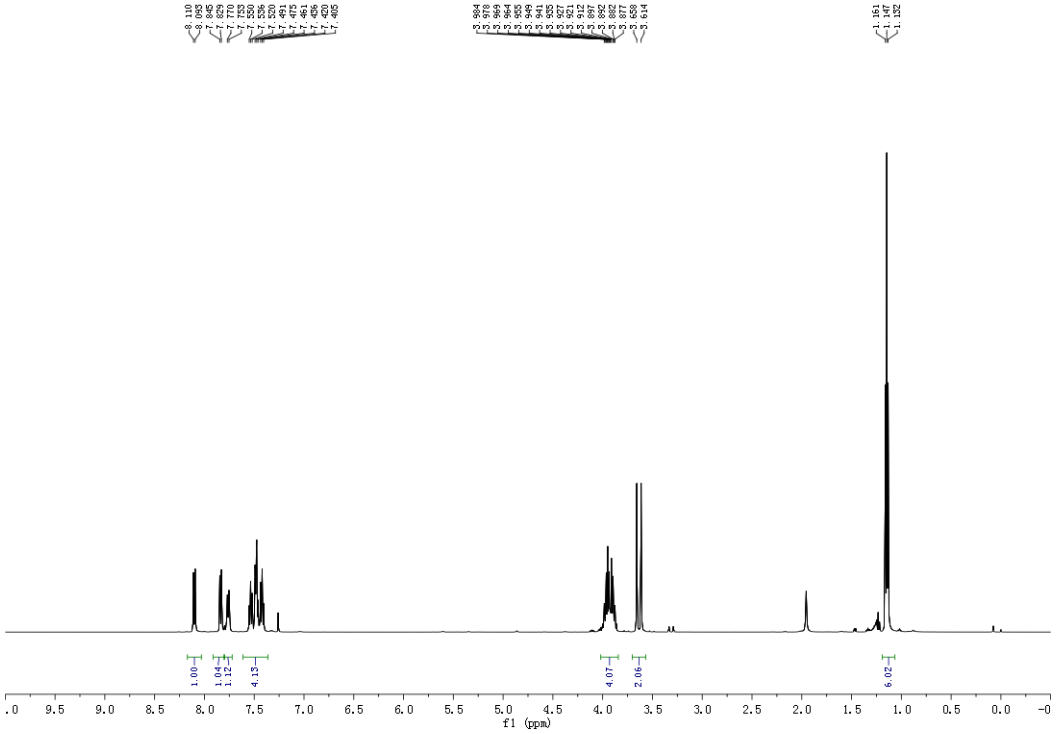
^{31}P NMR



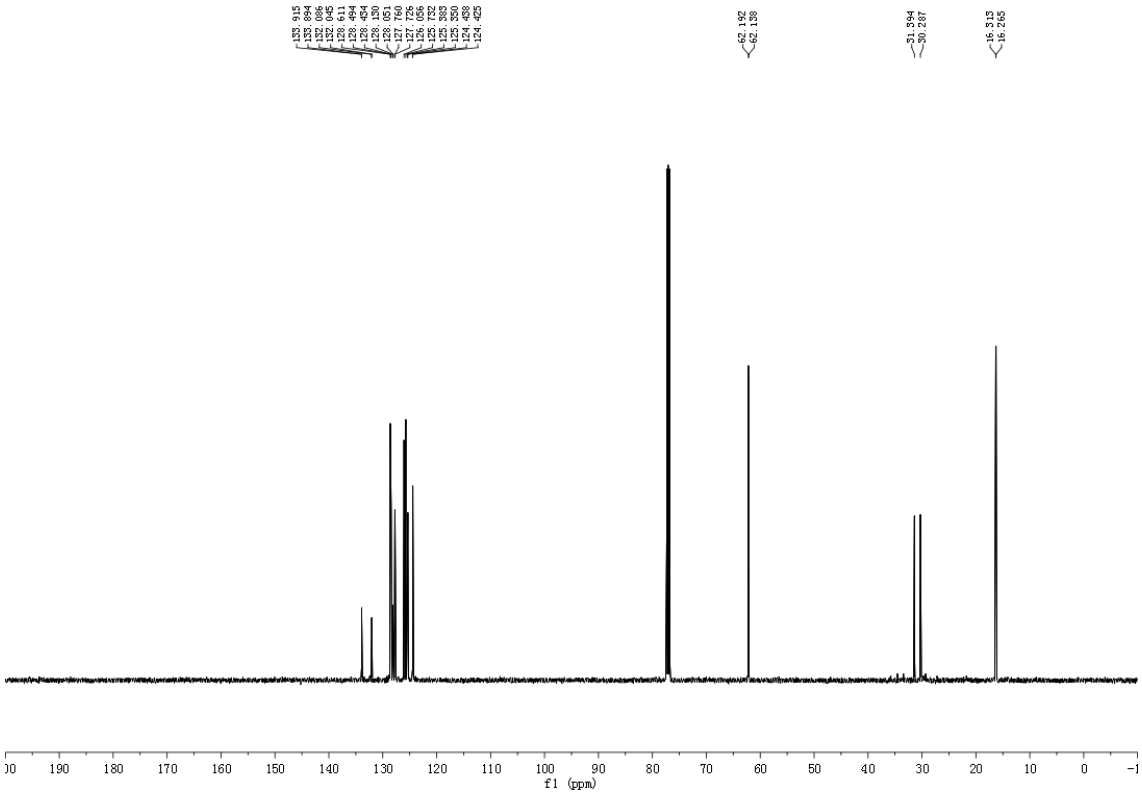


3l

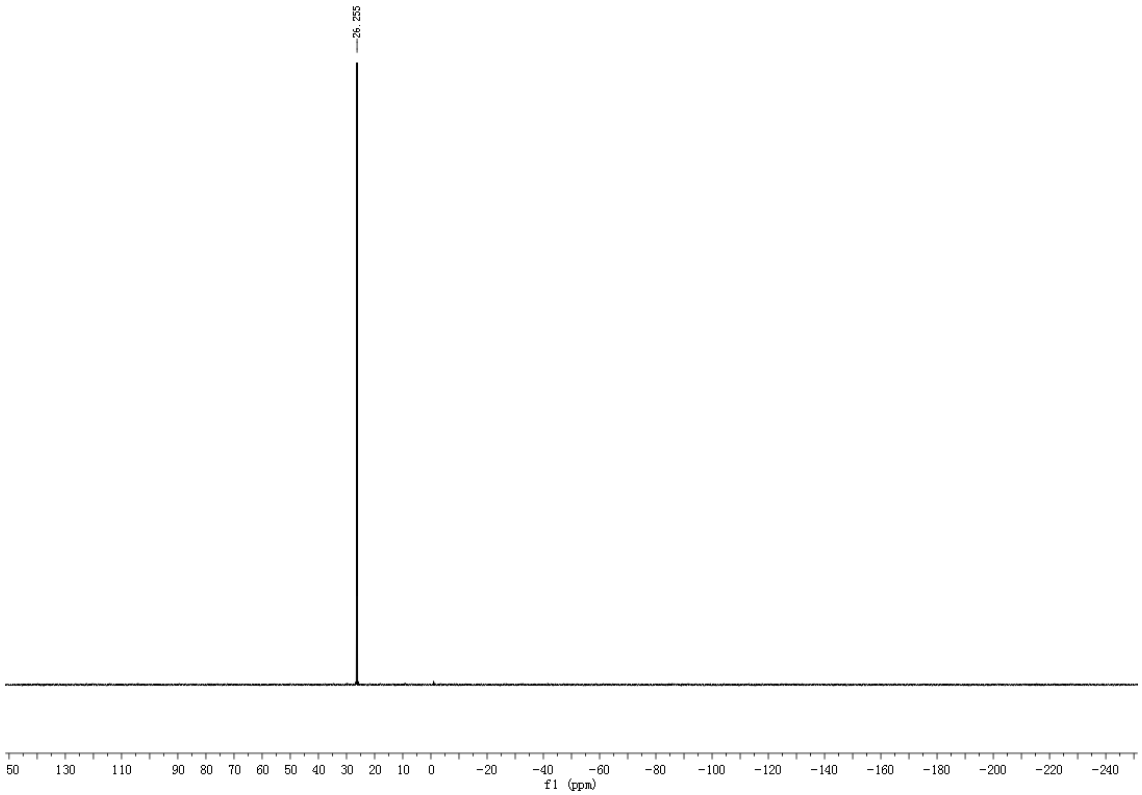
^{1}H NMR

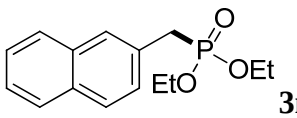


^{13}C NMR



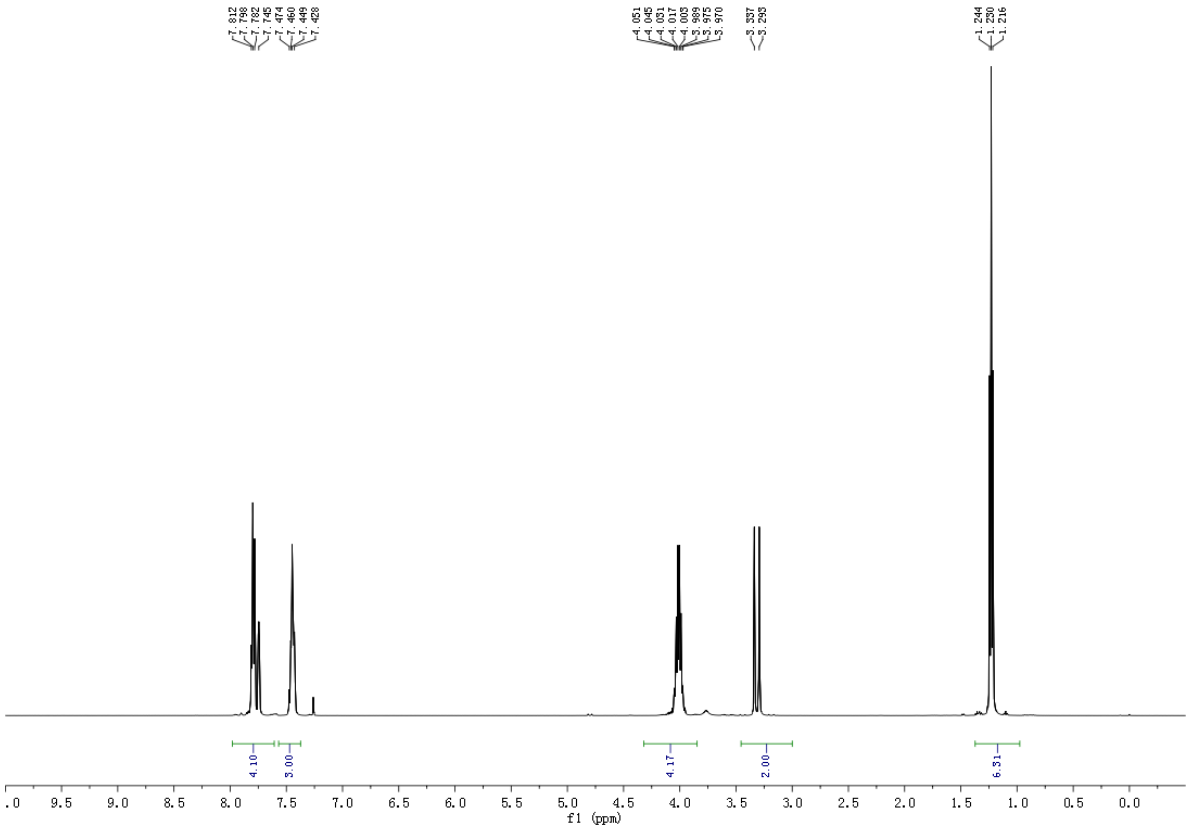
^{31}P NMR



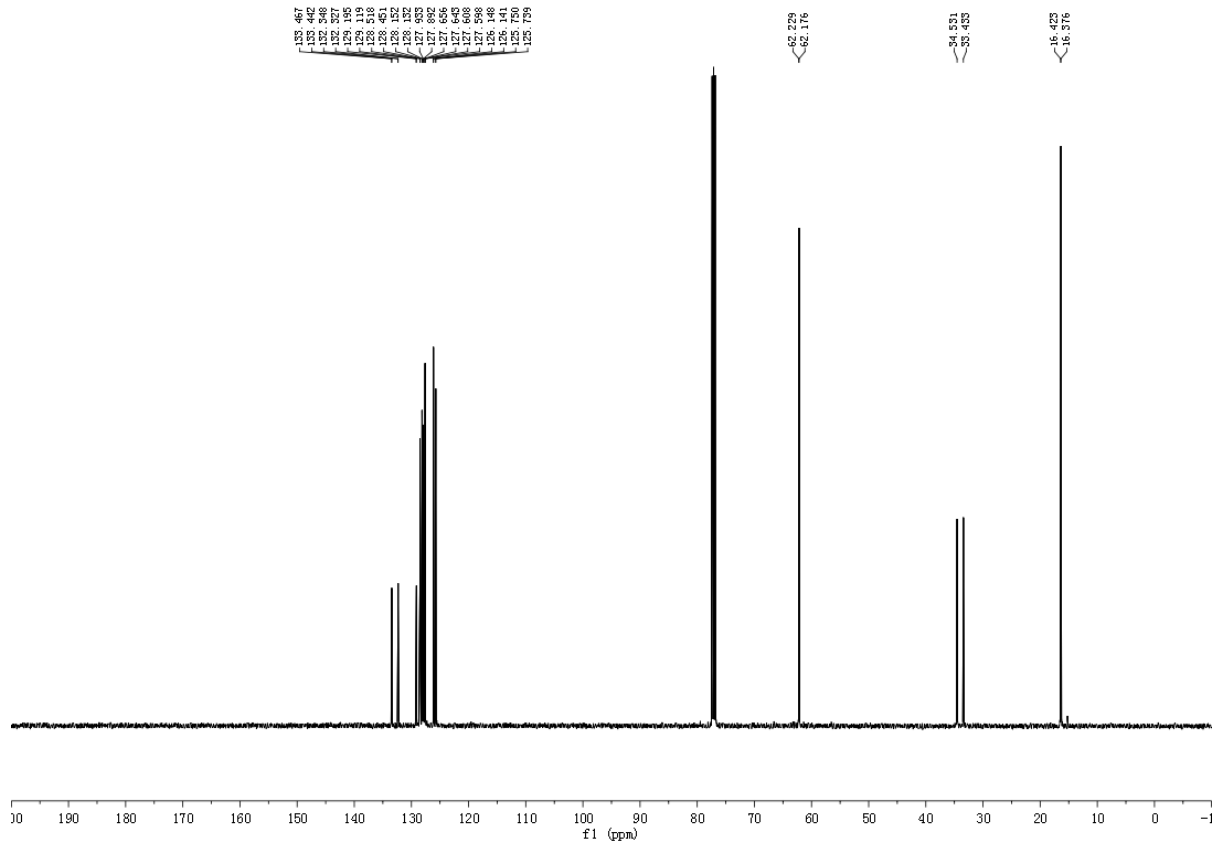


3m

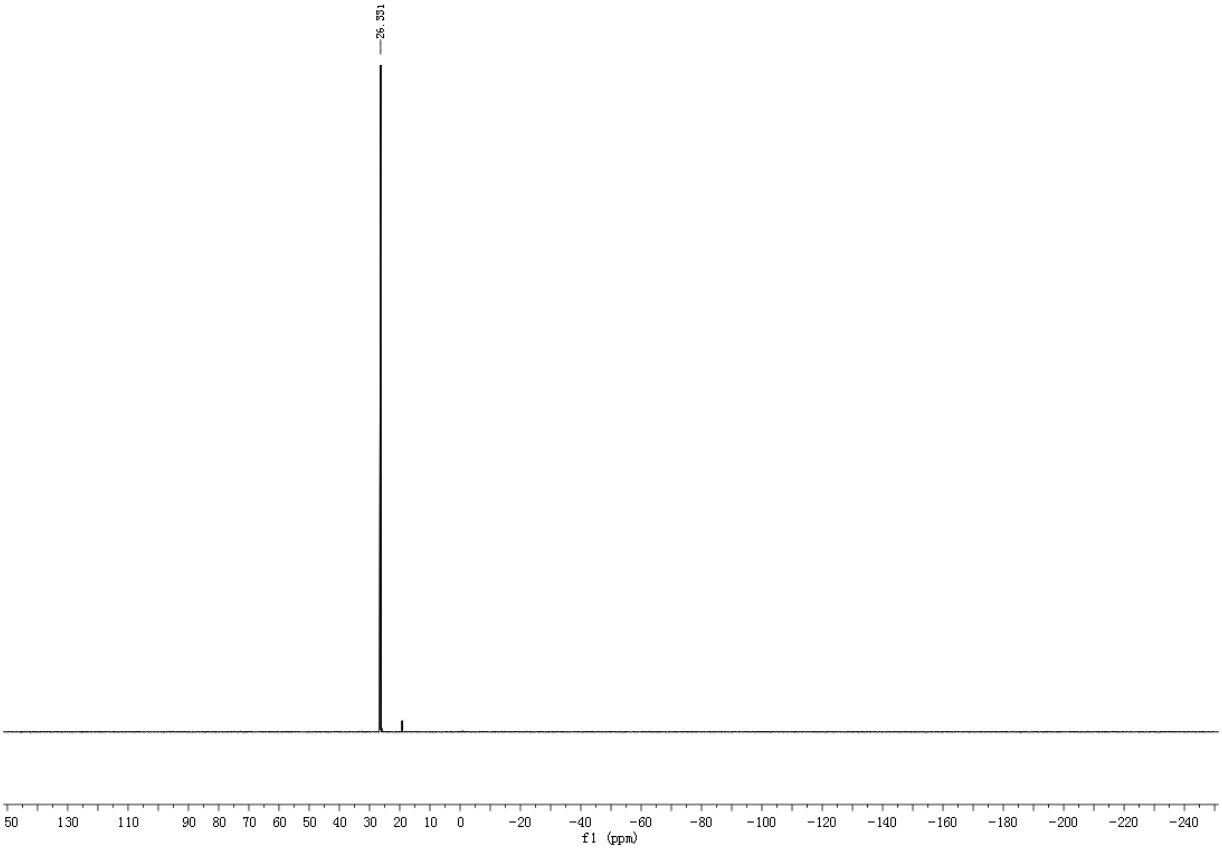
^{1}H NMR

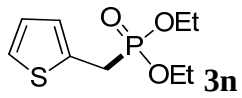


^{13}C NMR



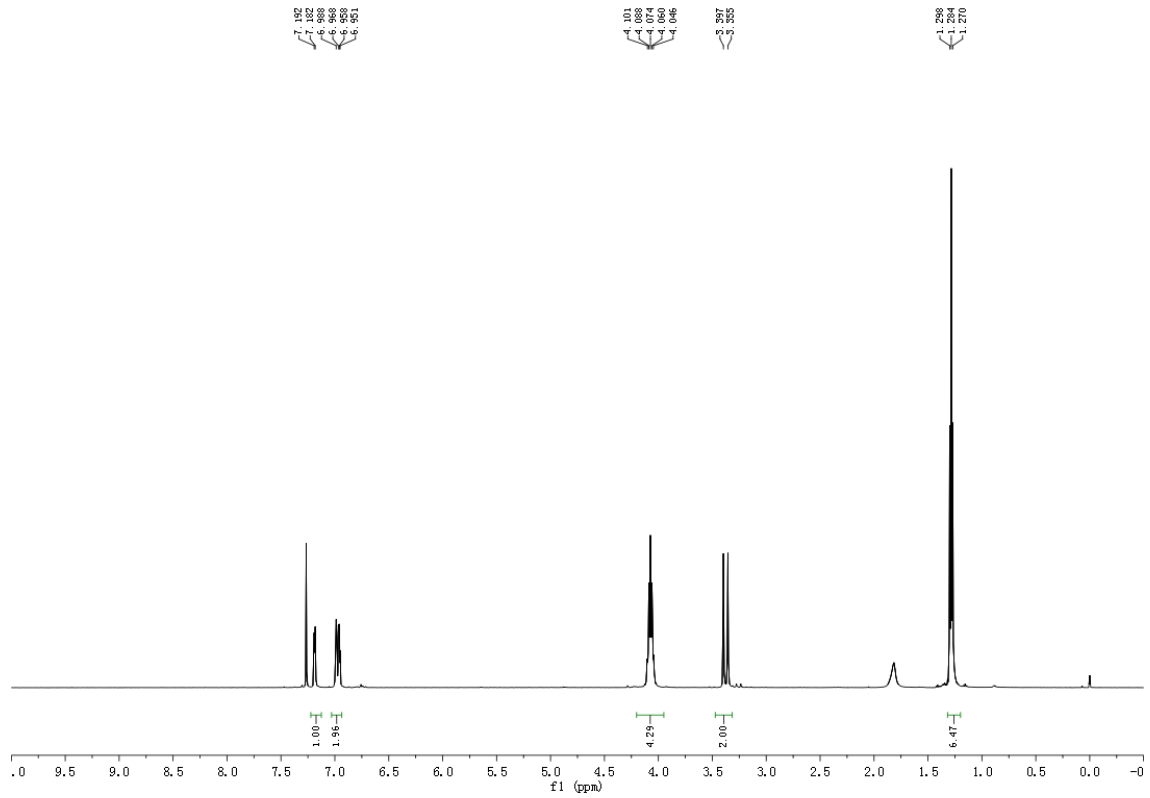
^{31}P NMR



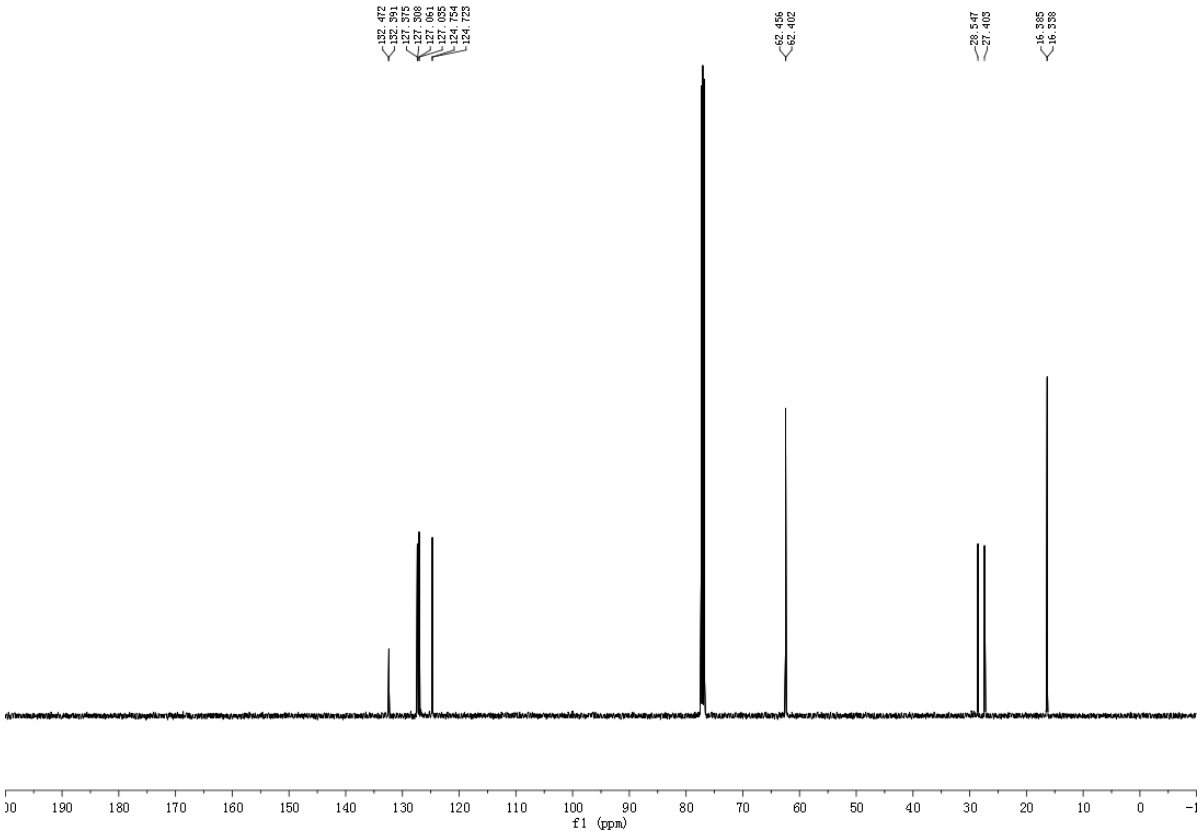


3n

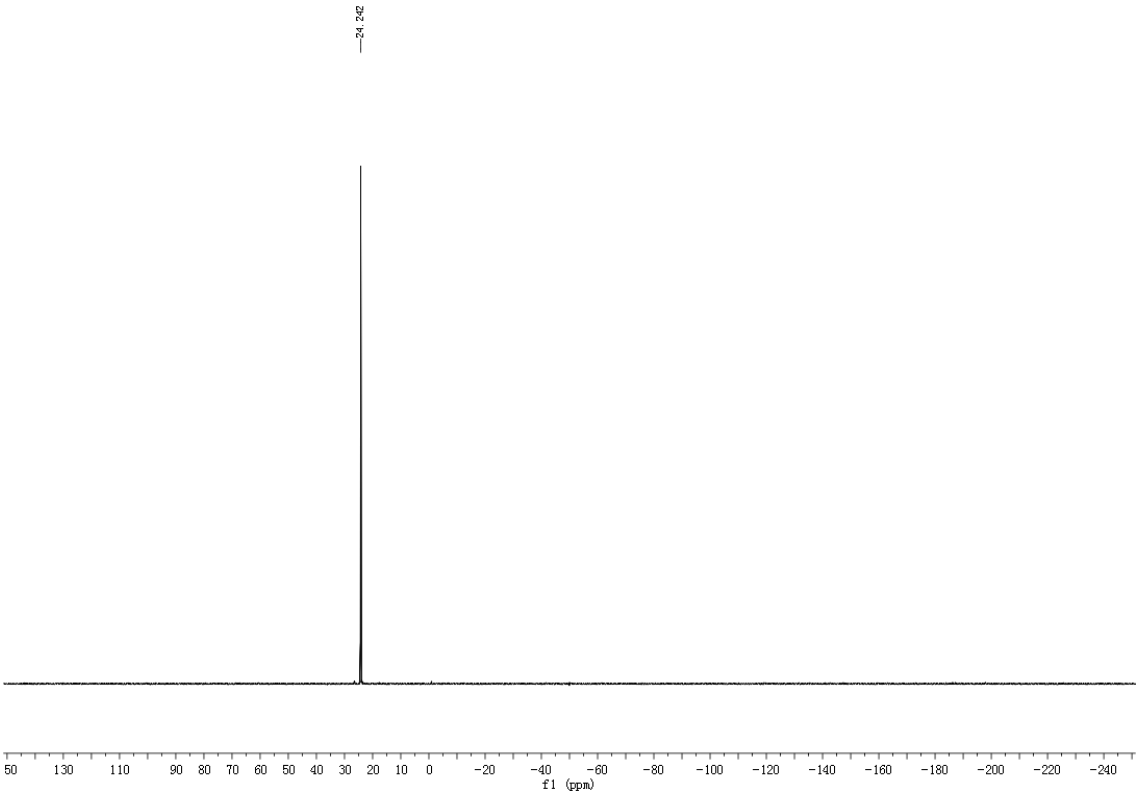
^{1}H NMR

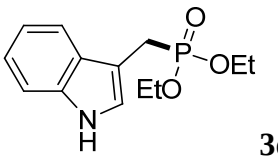


^{13}C NMR



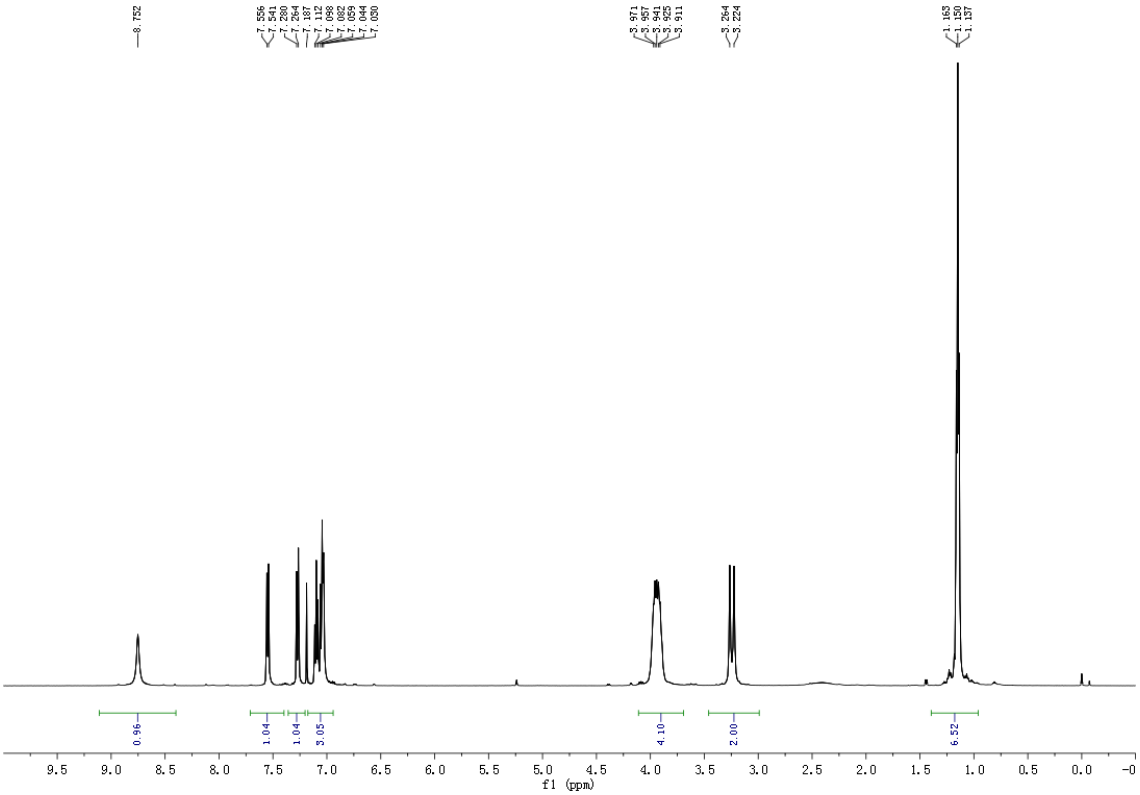
^{31}P NMR



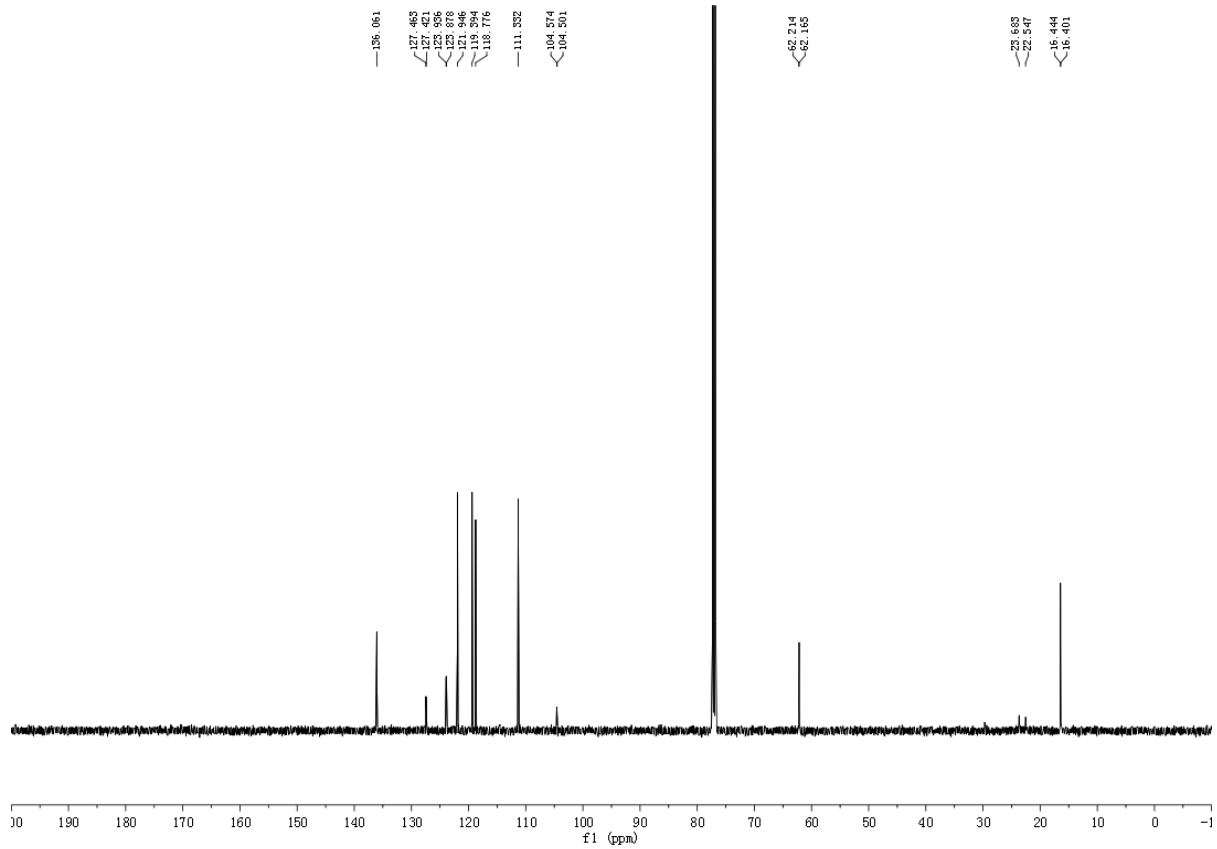


3o

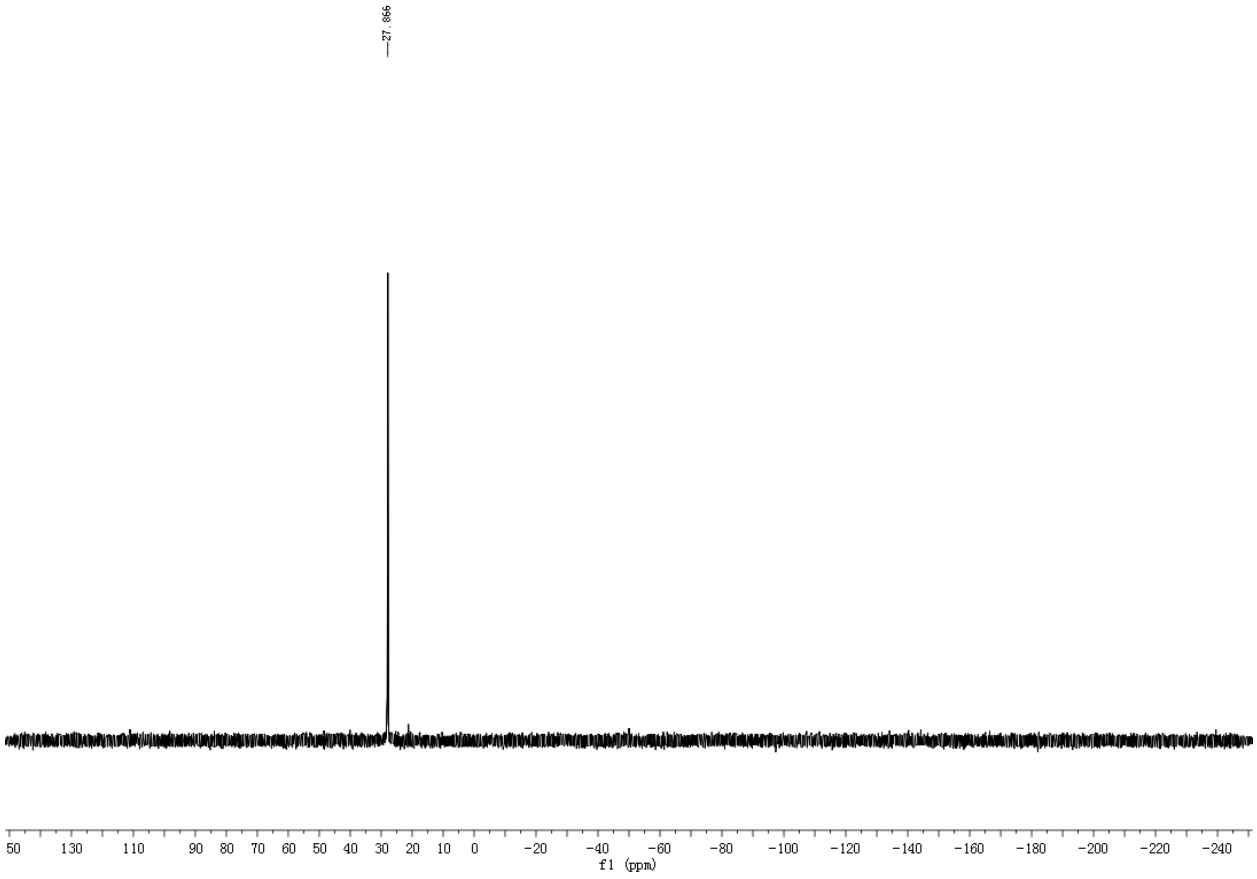
^{1}H NMR

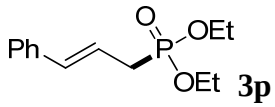


^{13}C NMR



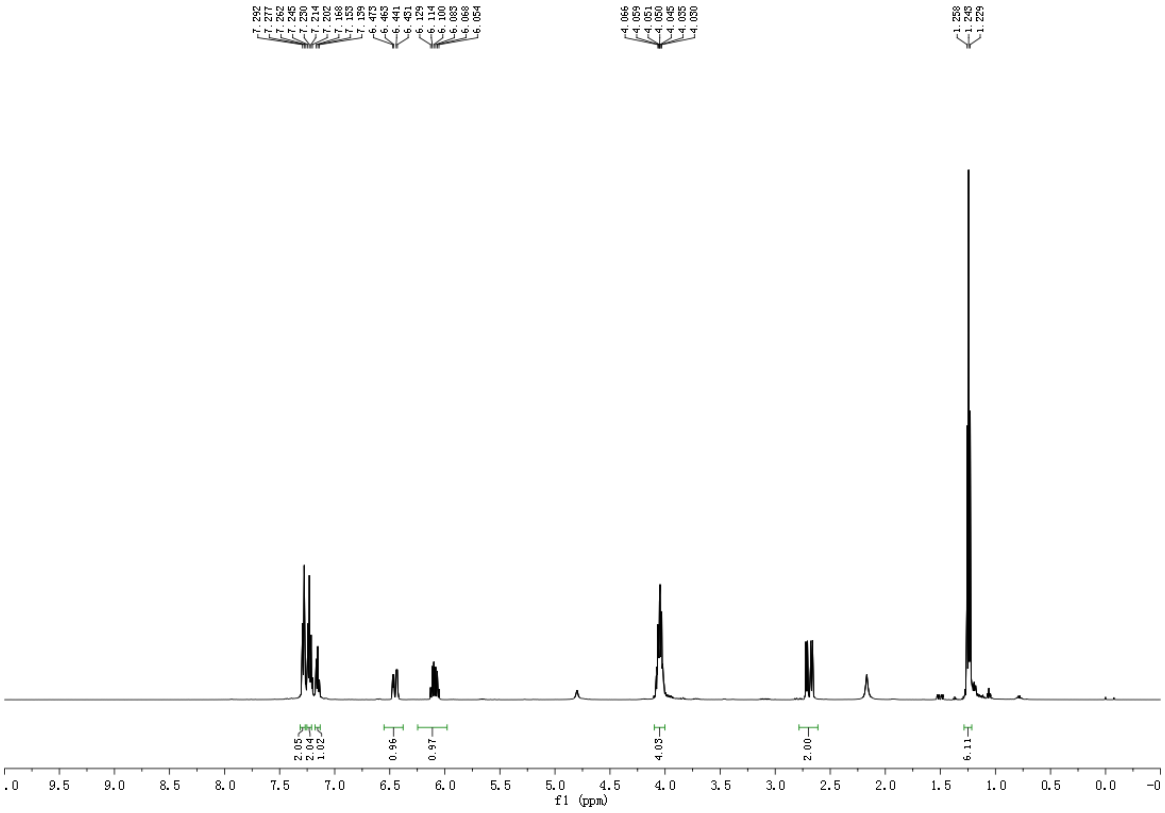
^{31}P NMR



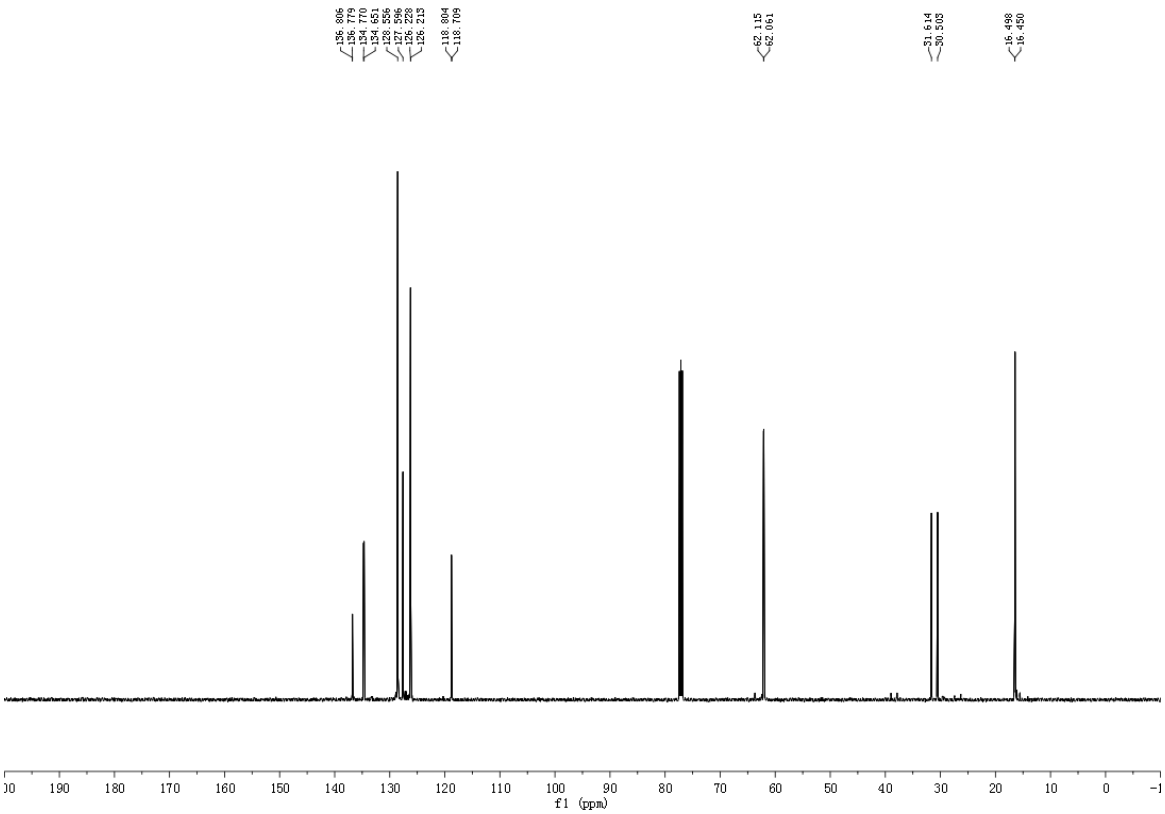


3p

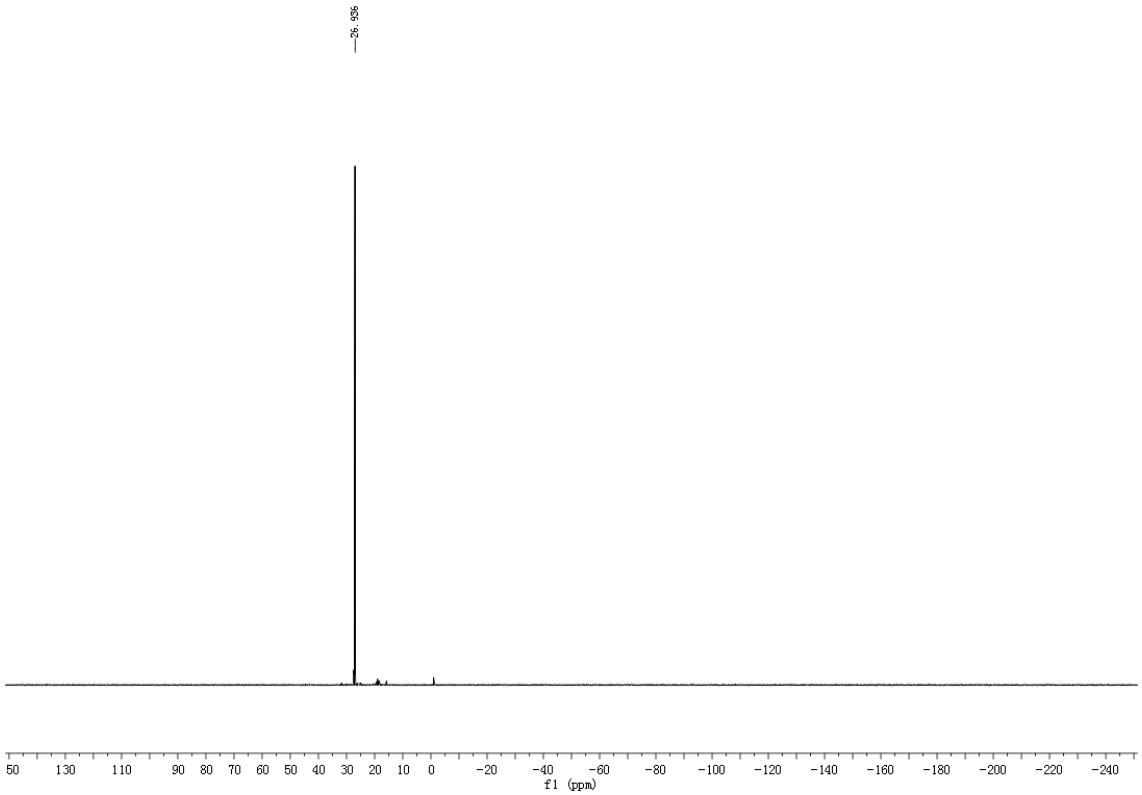
^{1}H NMR

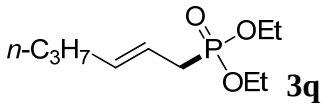


^{13}C NMR



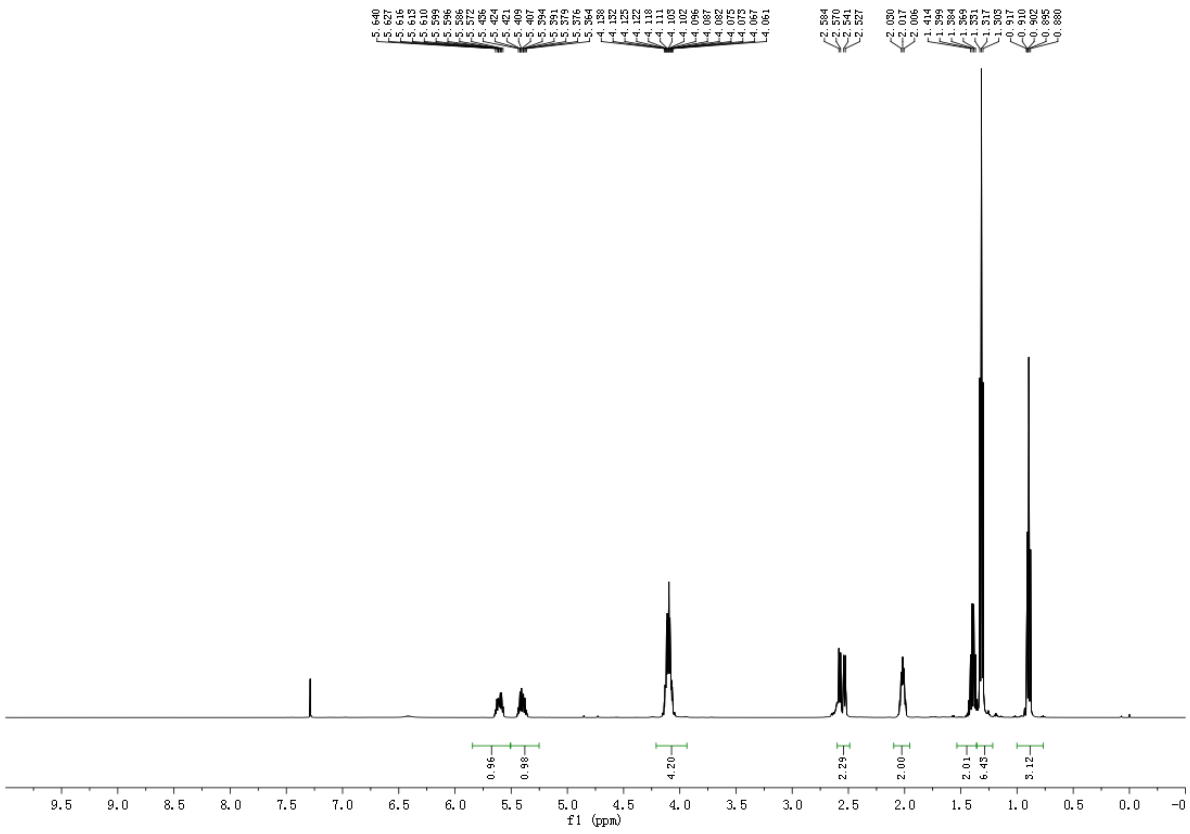
^{31}P NMR



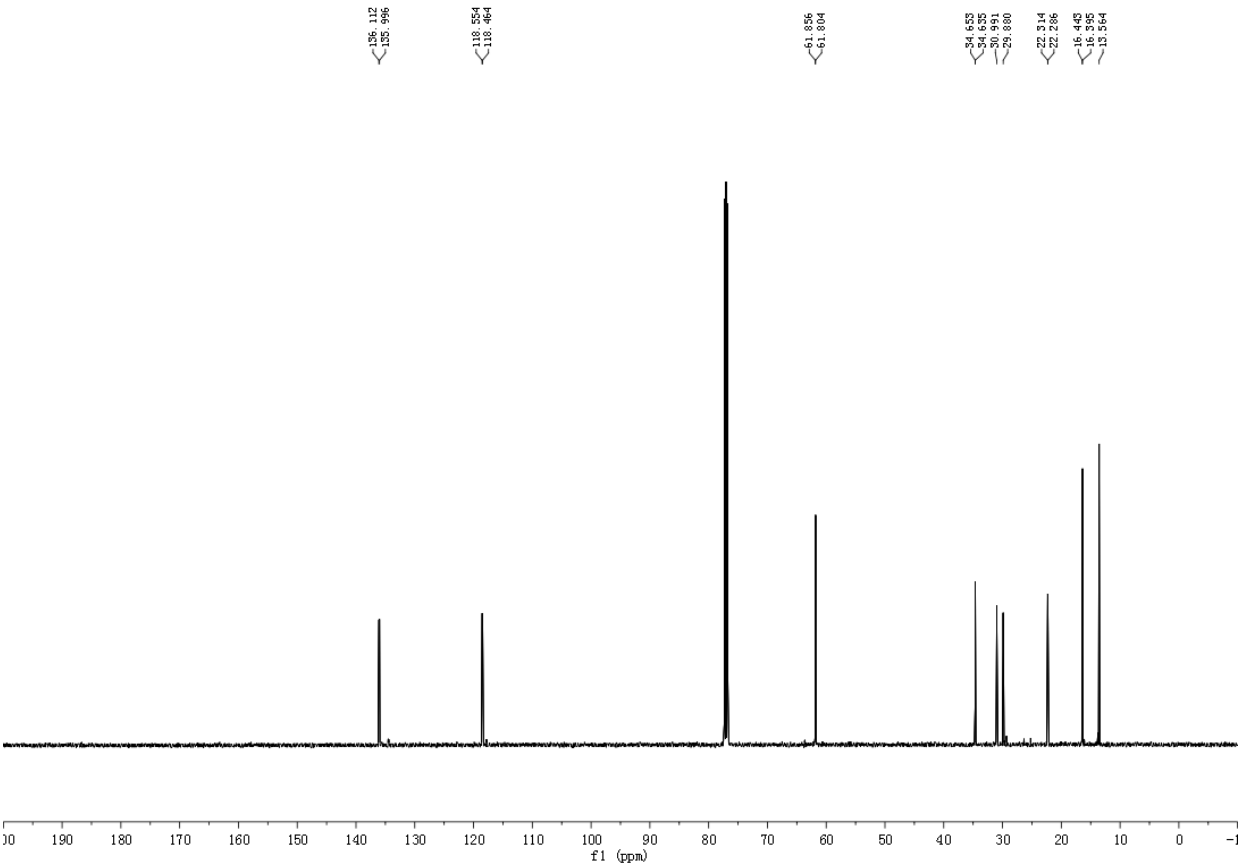


3q

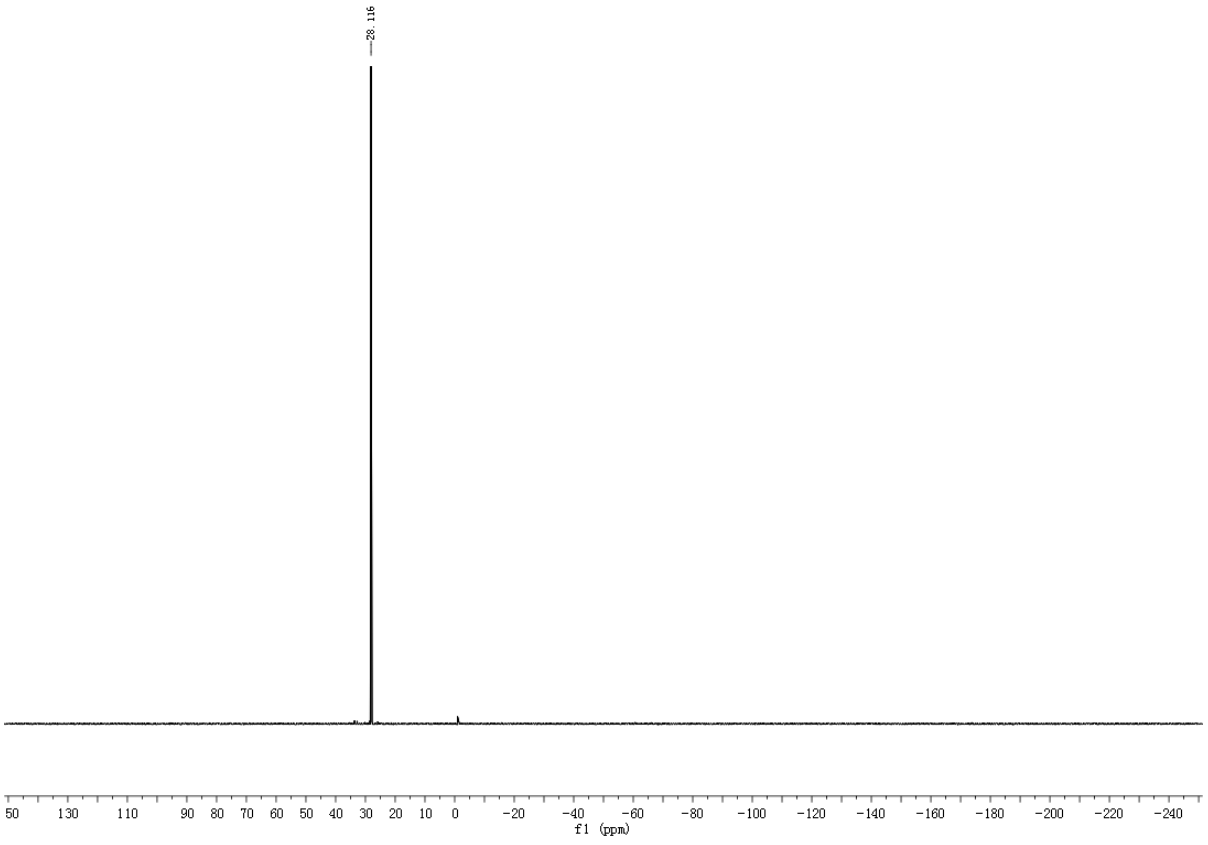
^{1}H NMR

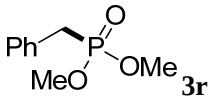


^{13}C NMR



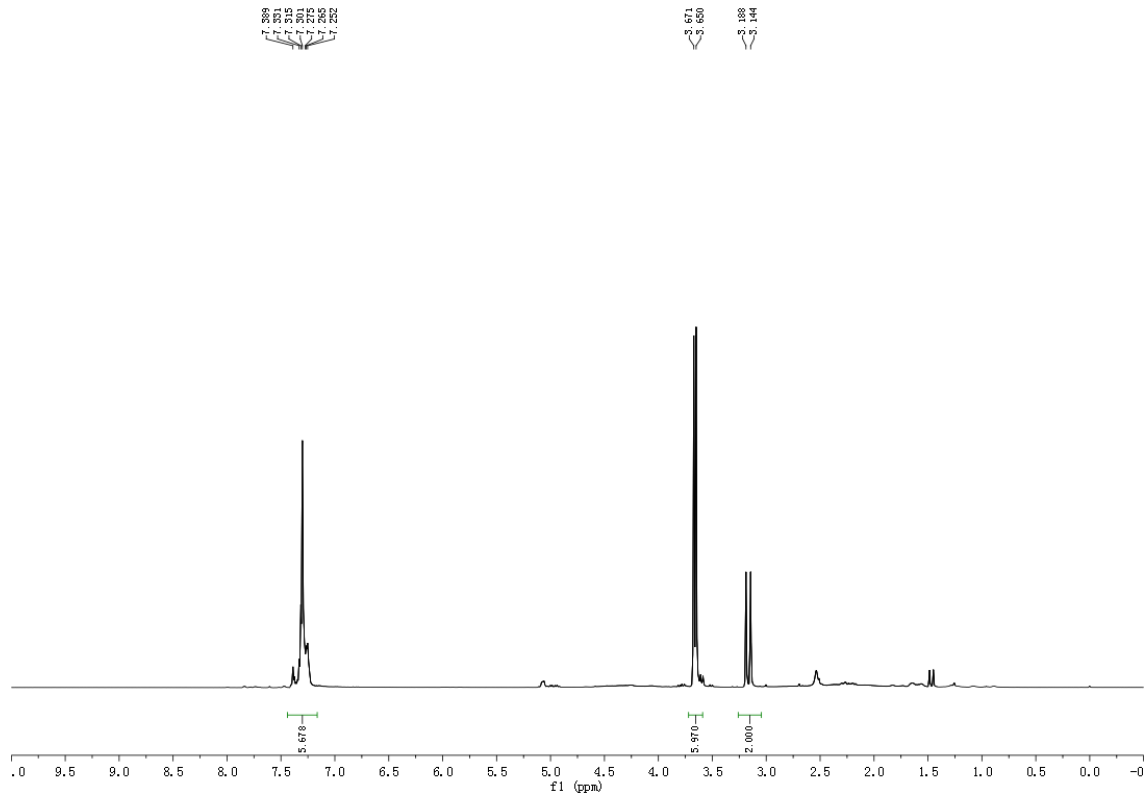
^{31}P NMR



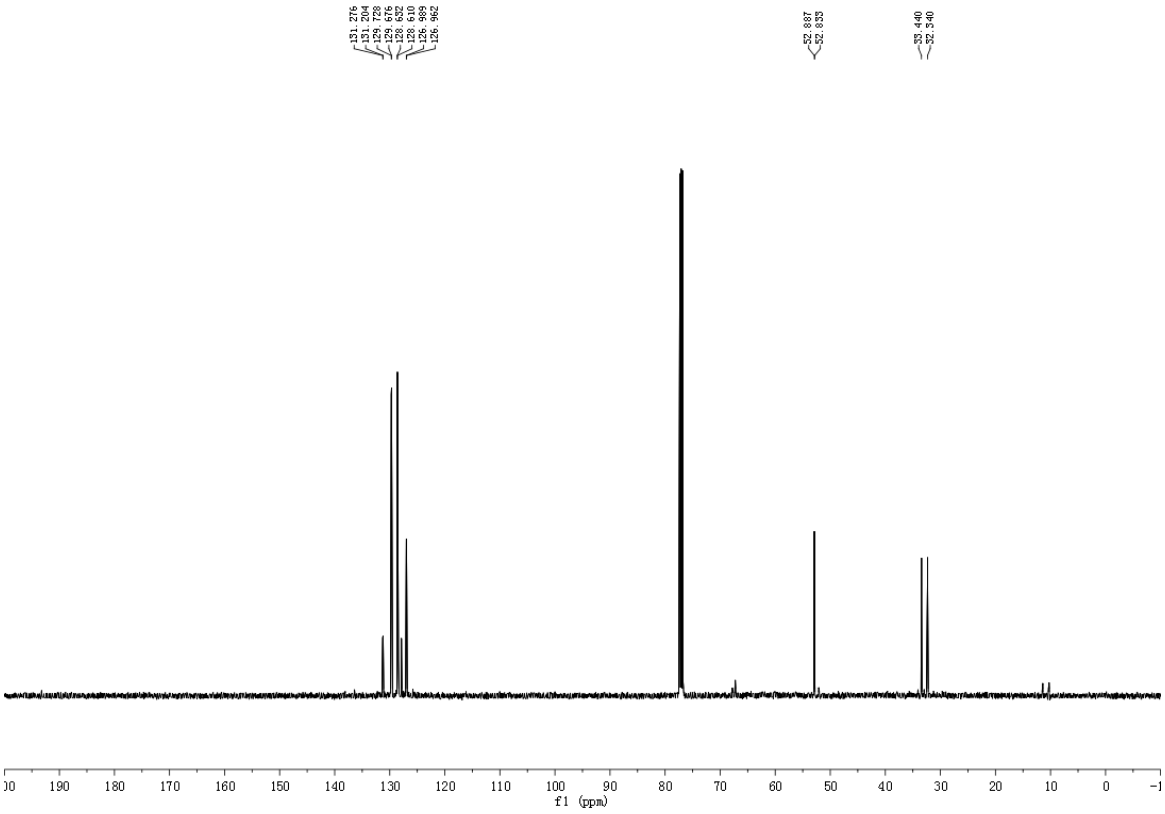


3r

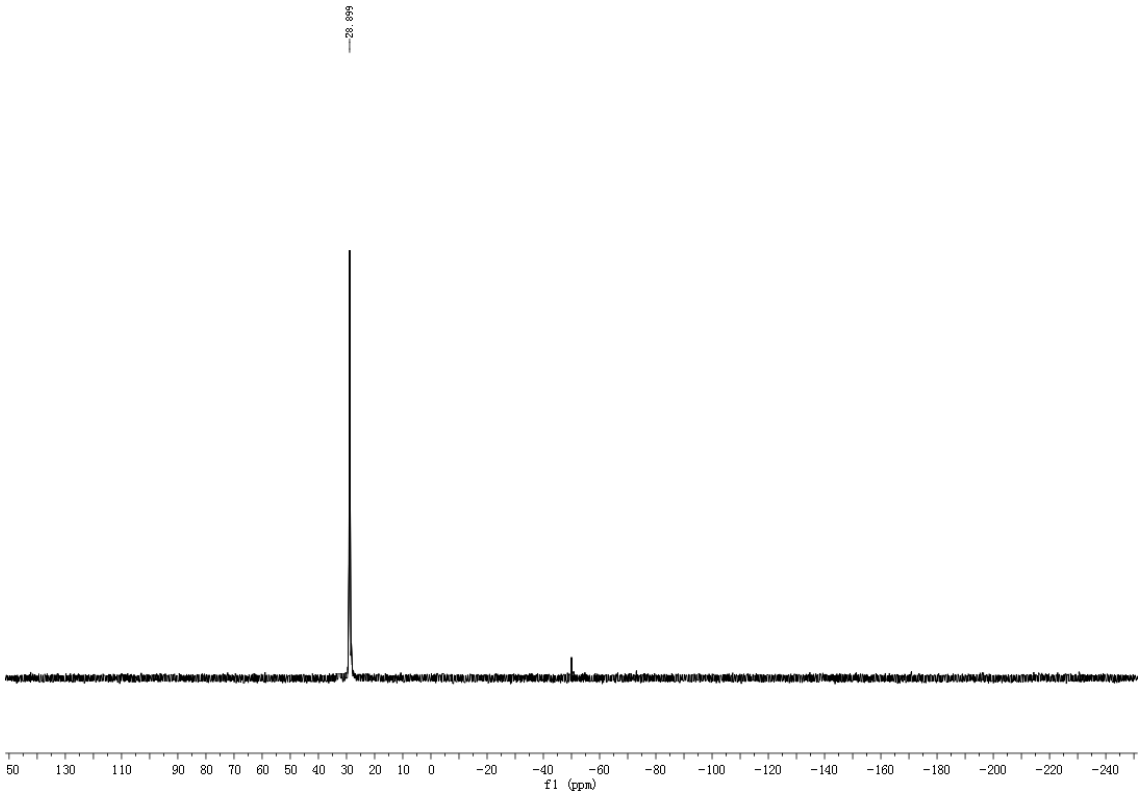
^{1}H NMR

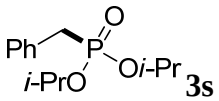


^{13}C NMR



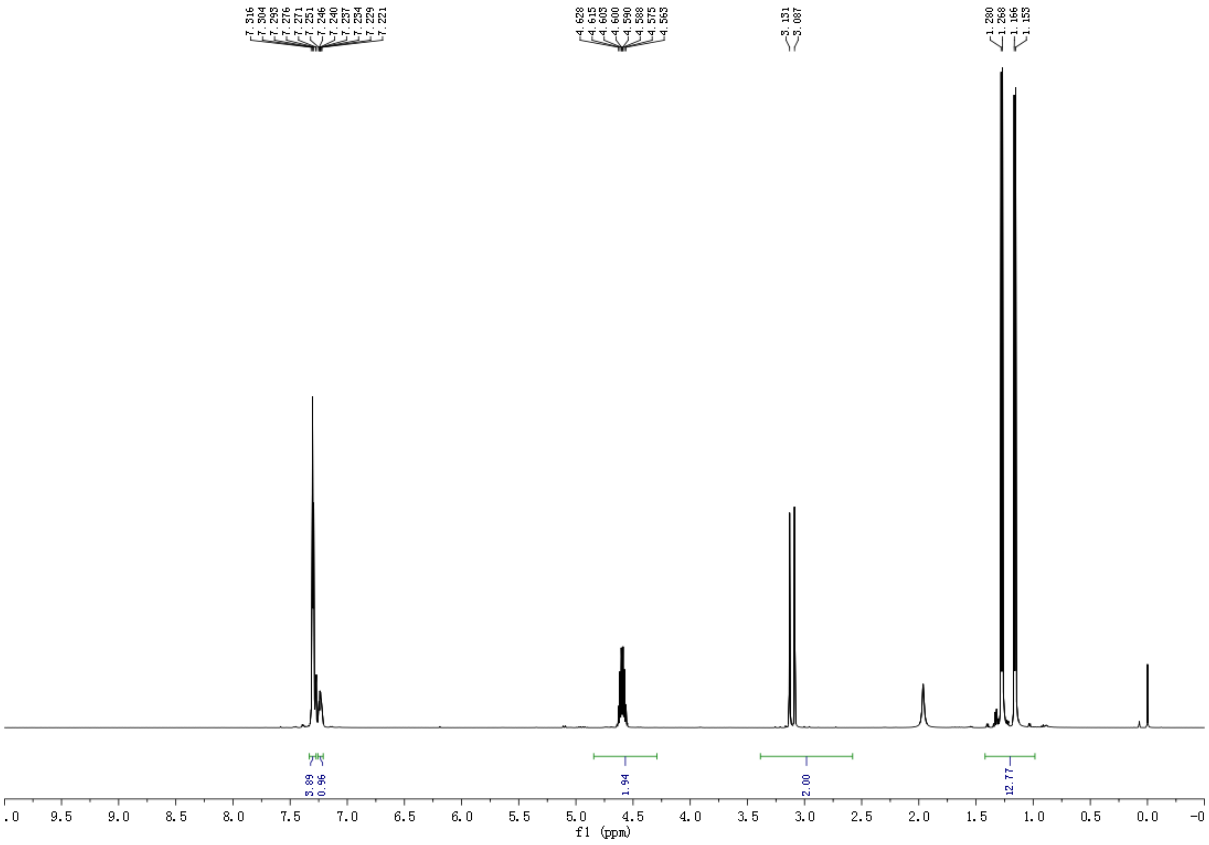
^{31}P NMR



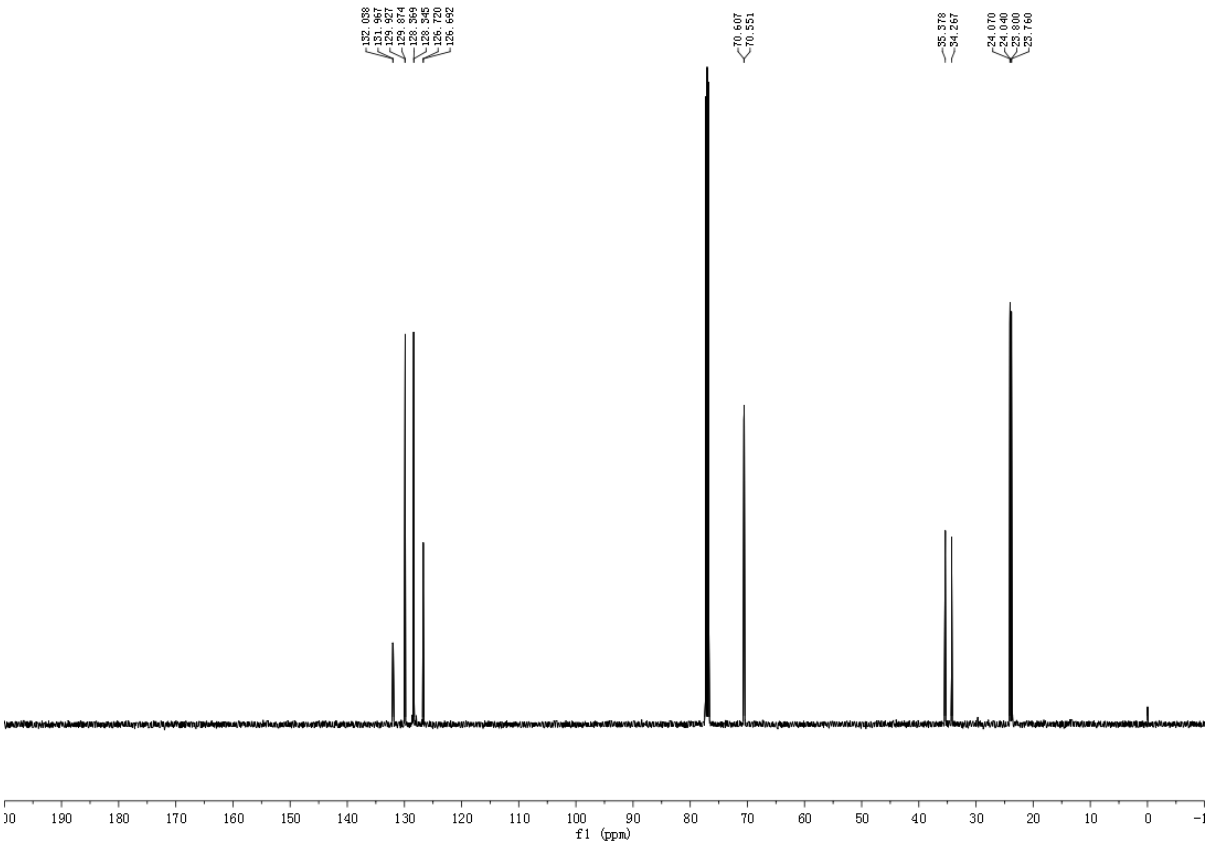


3s

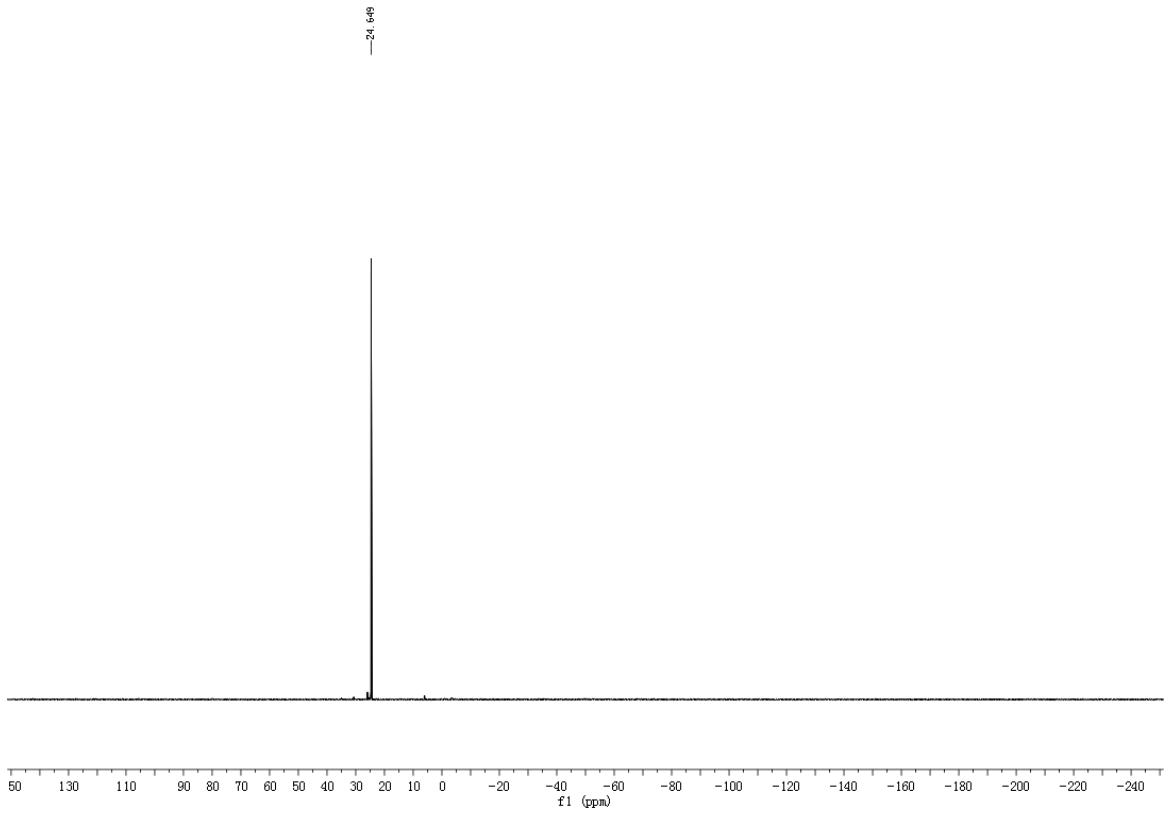
^{1}H NMR

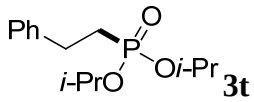


^{13}C NMR



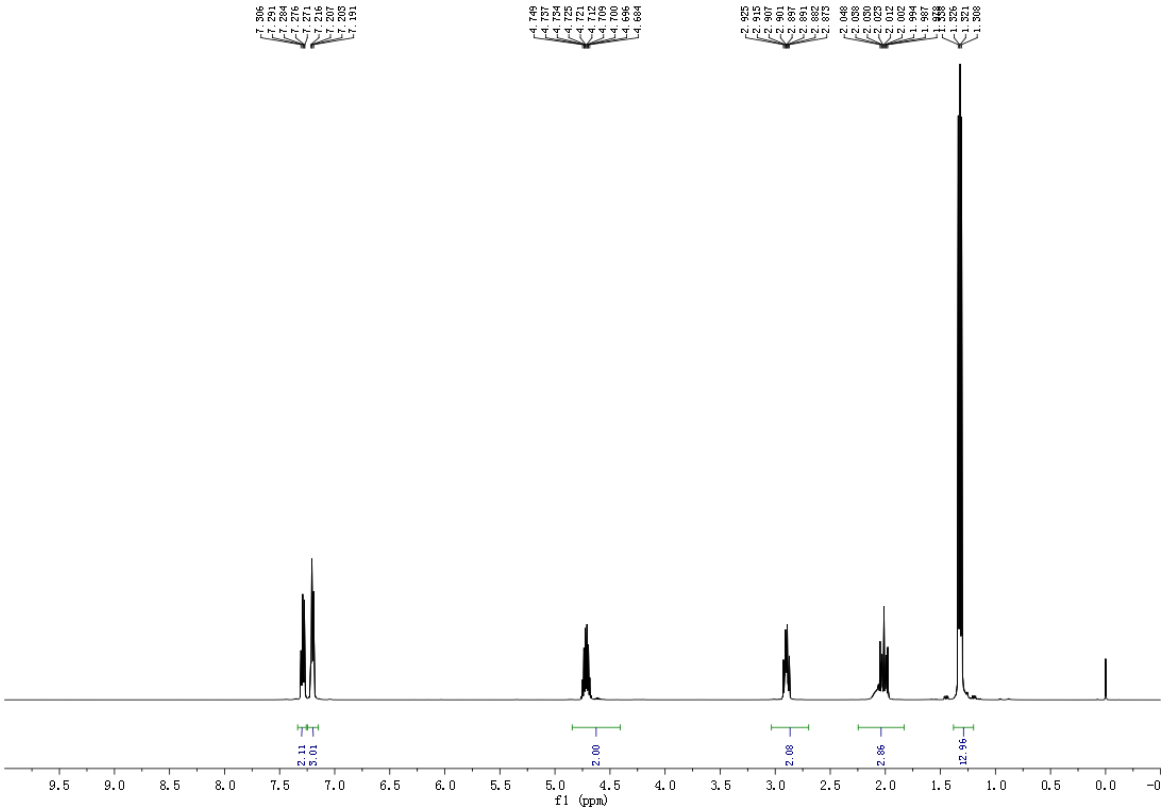
^{31}P NMR



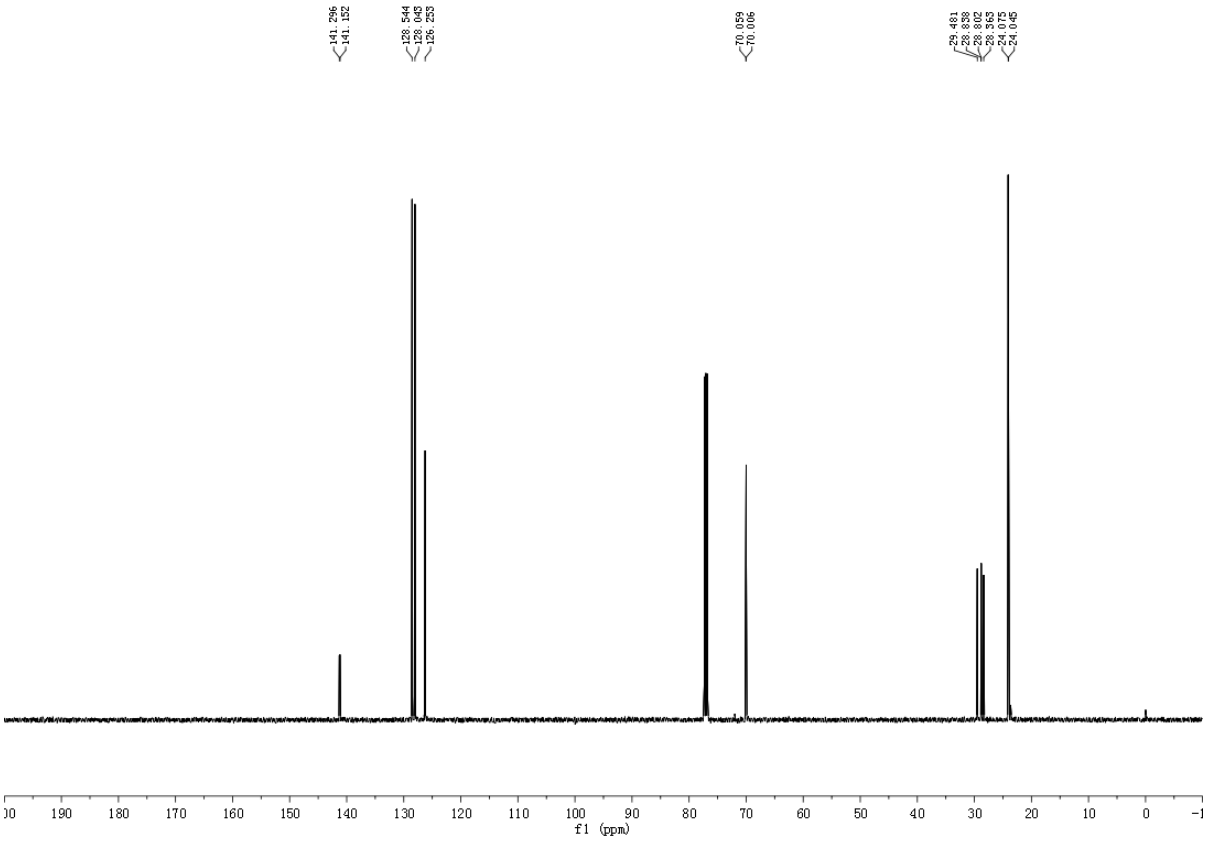


3t

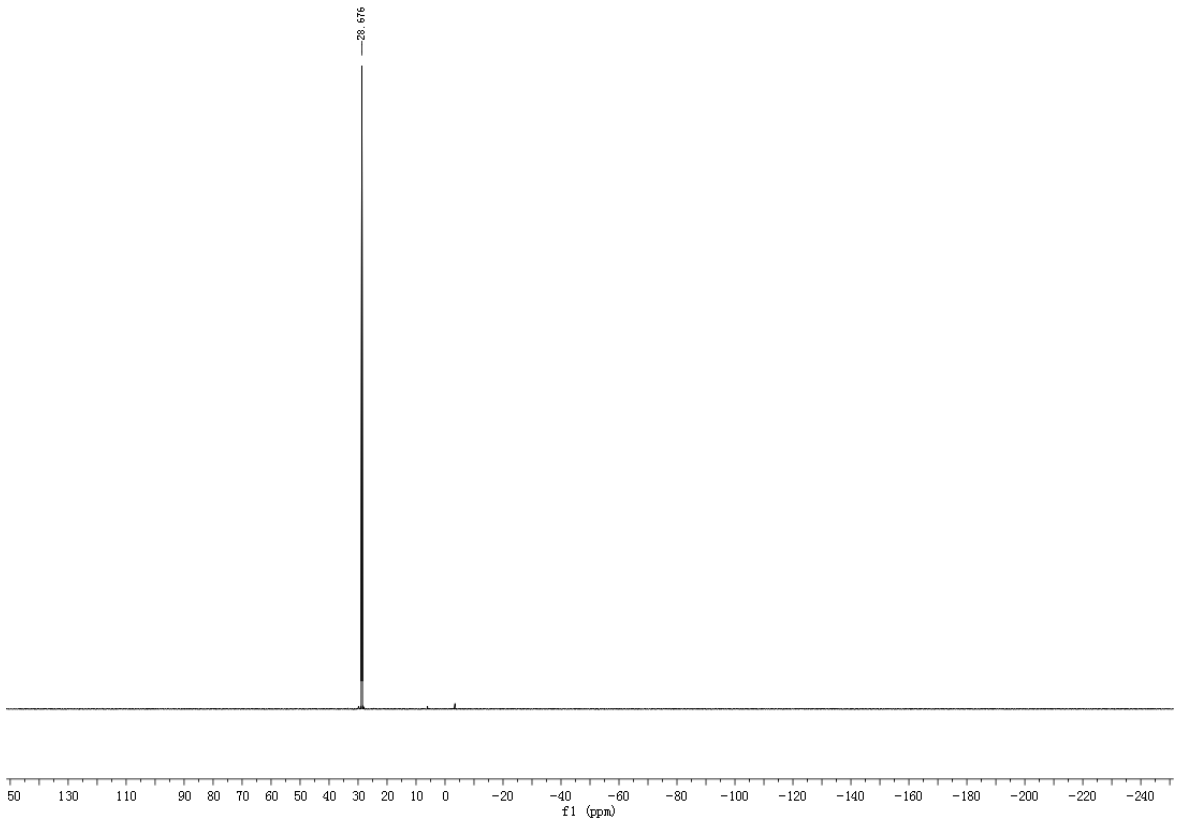
^{1}H NMR

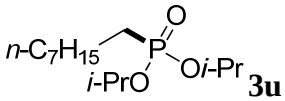


^{13}C NMR



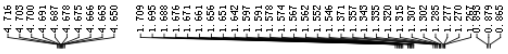
^{31}P NMR

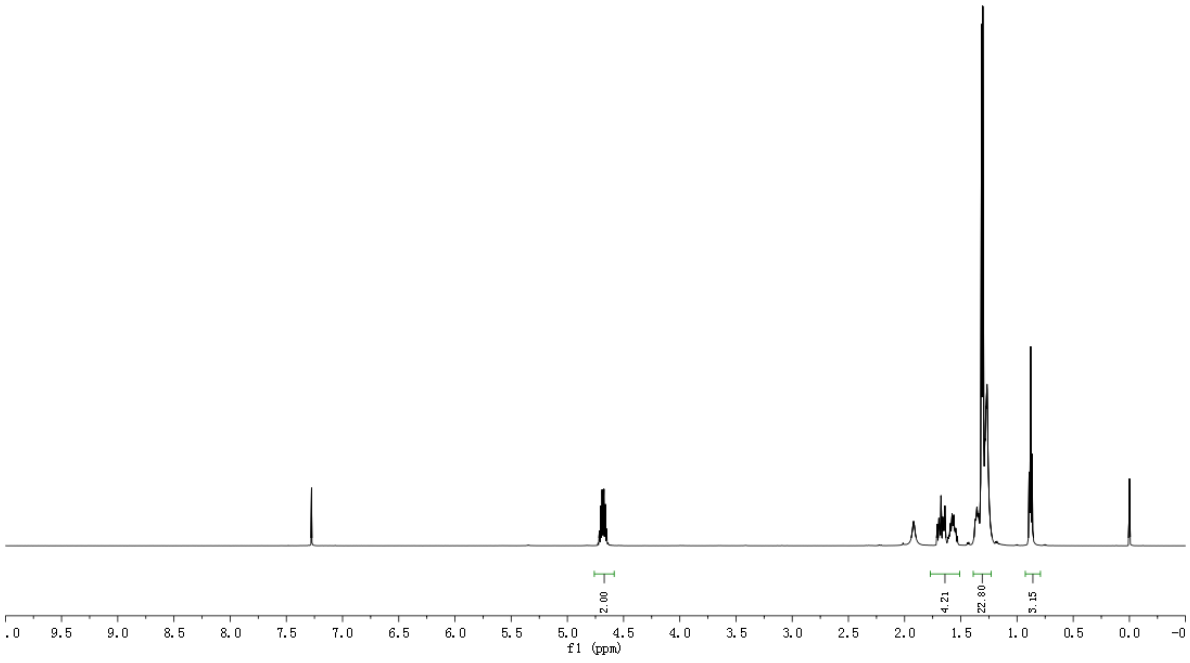




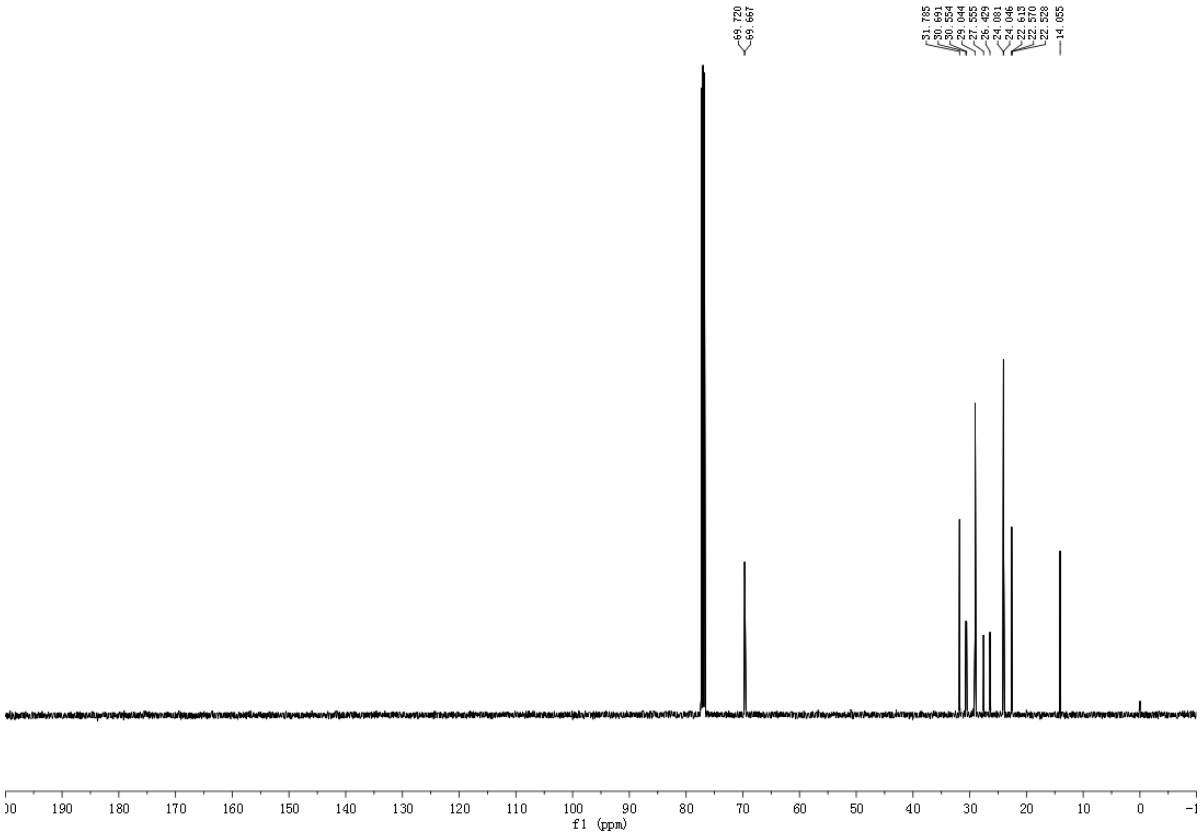
3u

^{1}H NMR

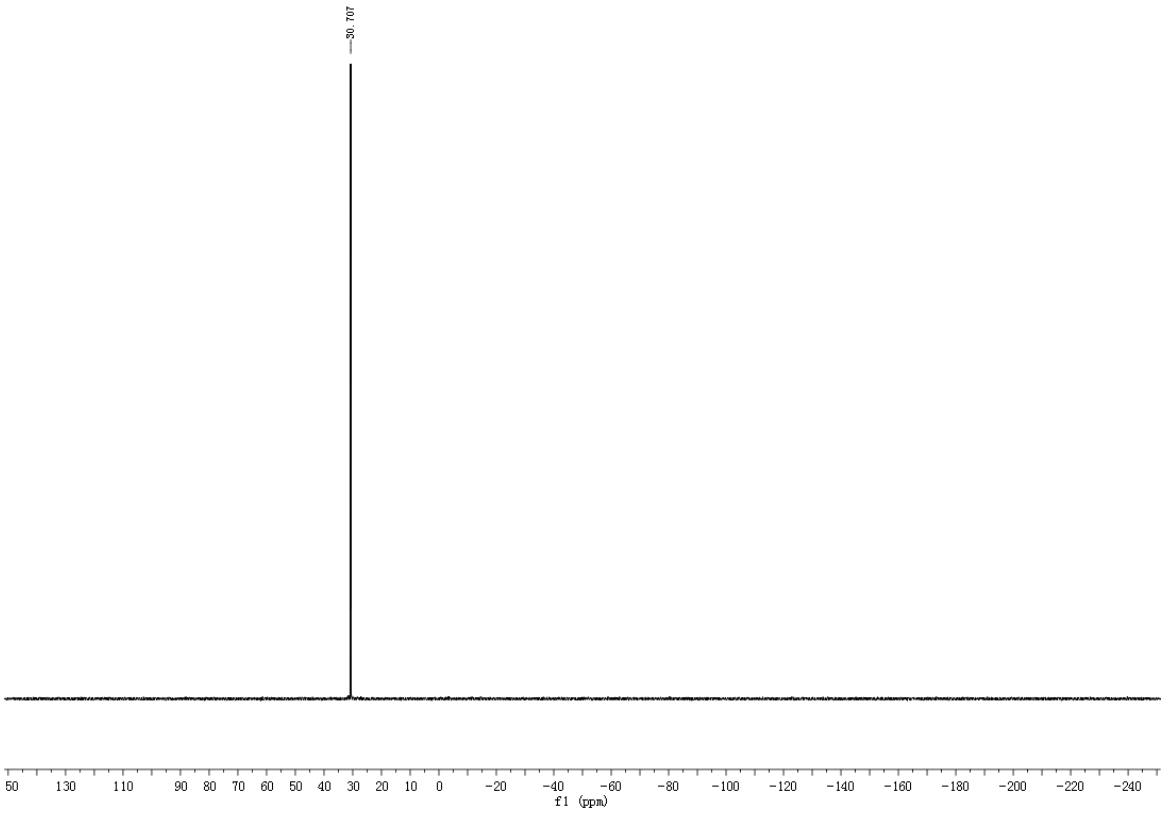


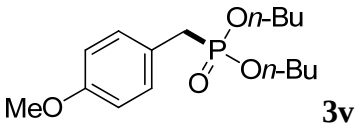


^{13}C NMR



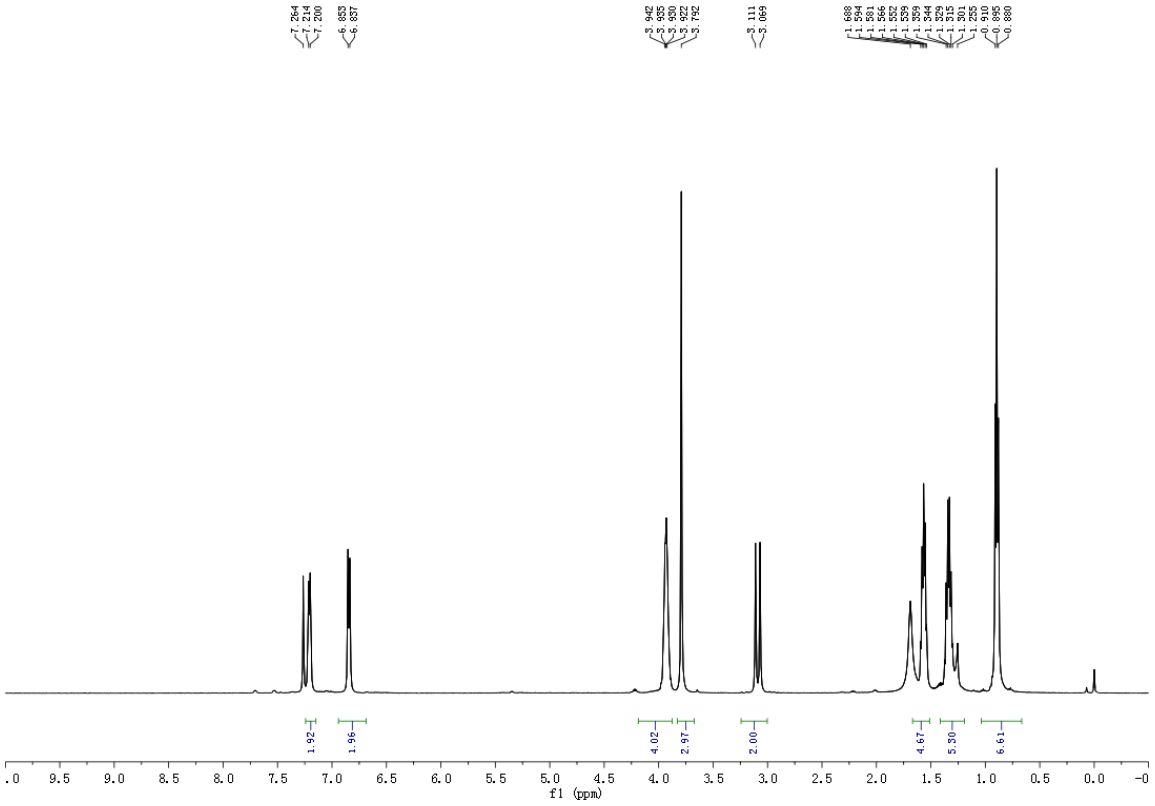
^{31}P NMR



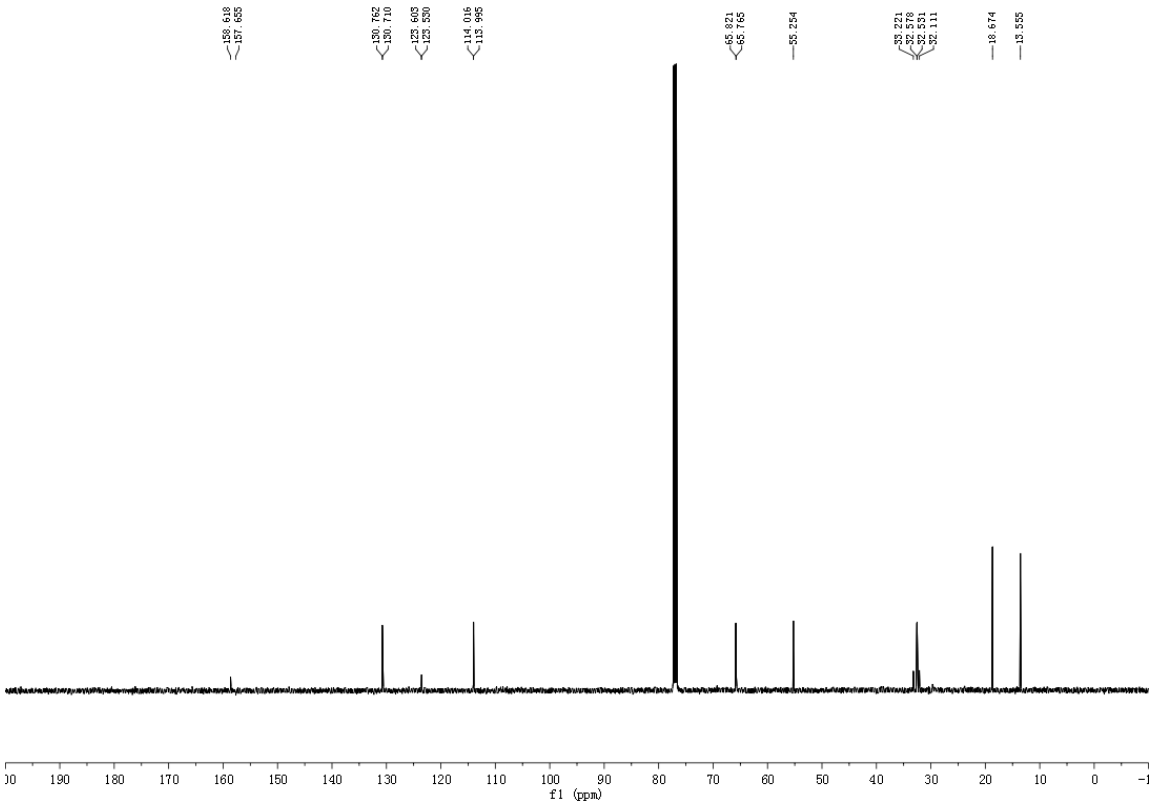


3v

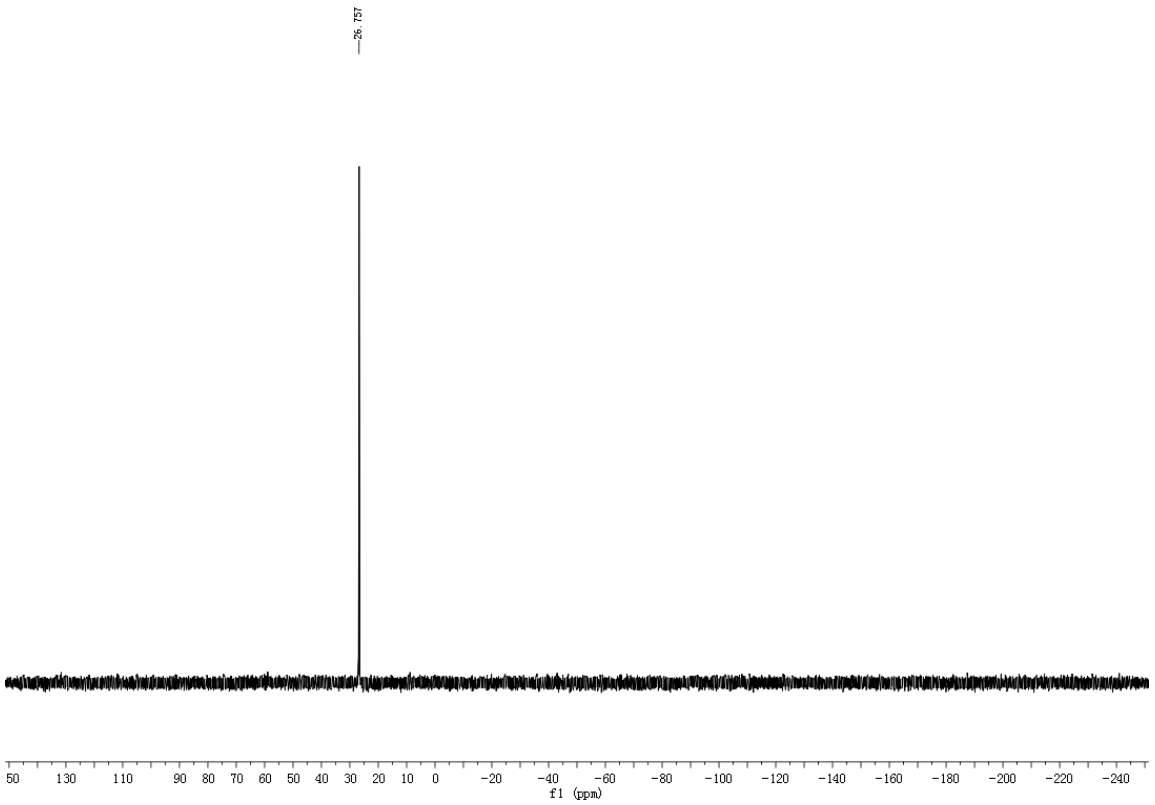
^{1}H NMR

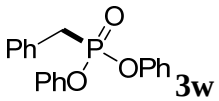


^{13}C NMR



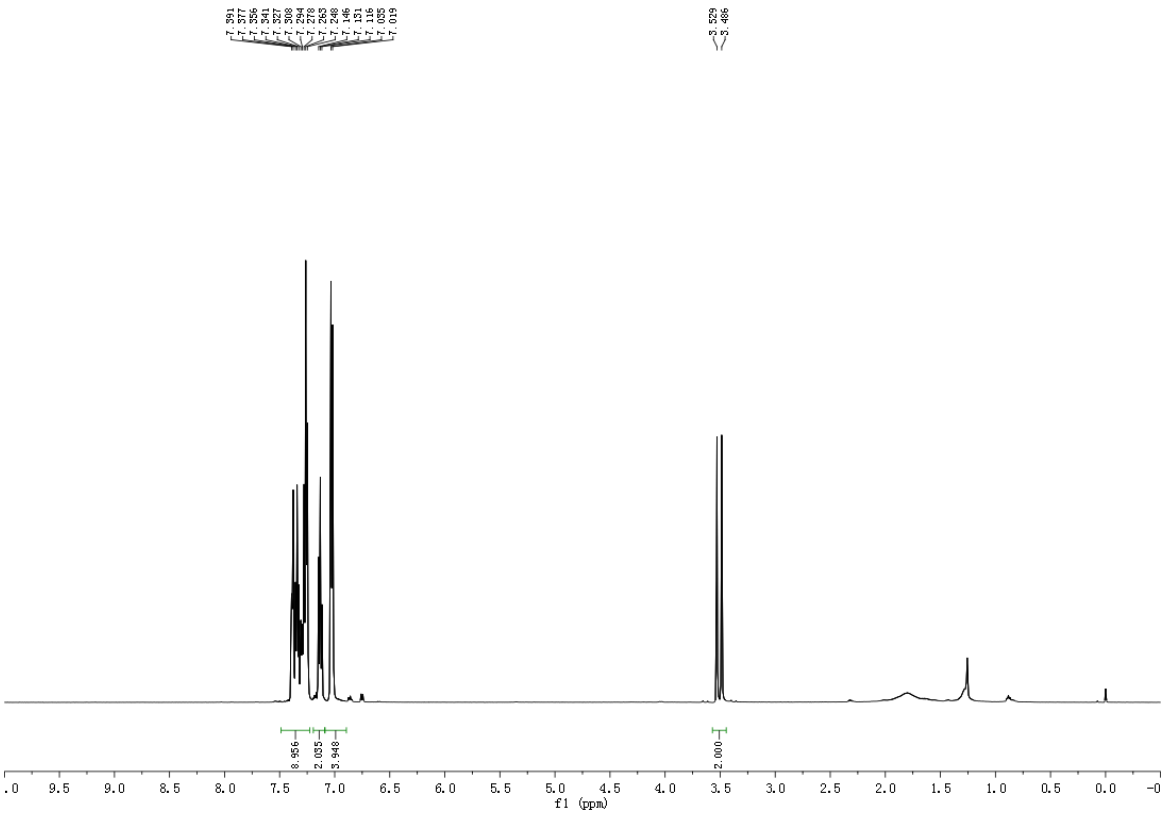
^{31}P NMR



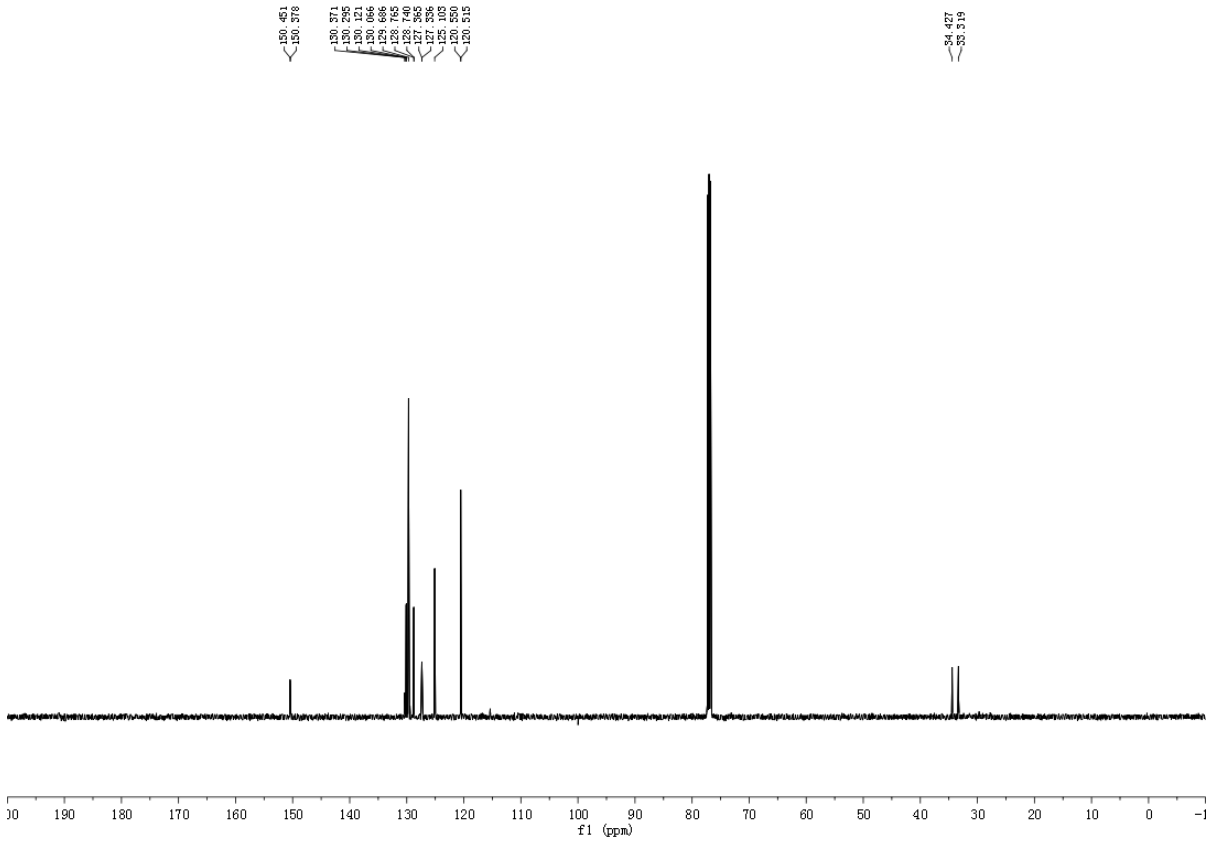


3w

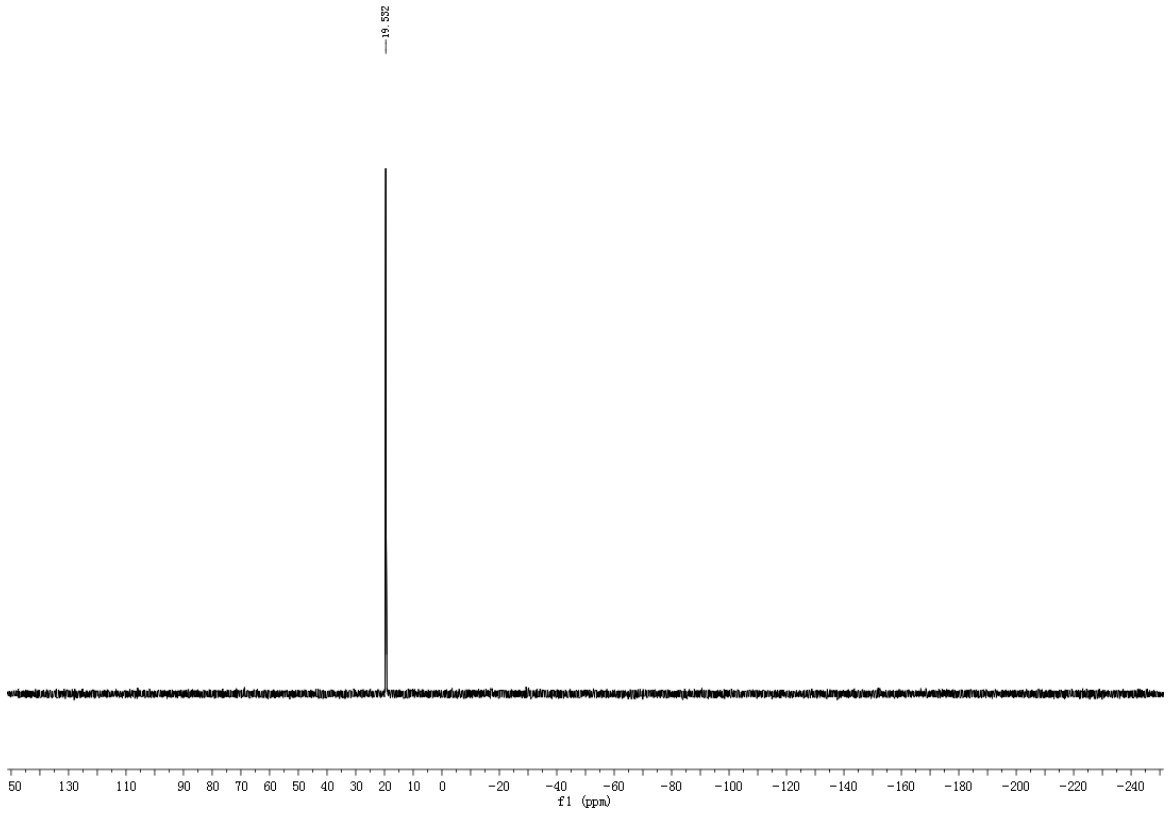
^{1}H NMR

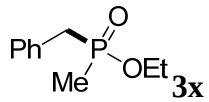


^{13}C NMR



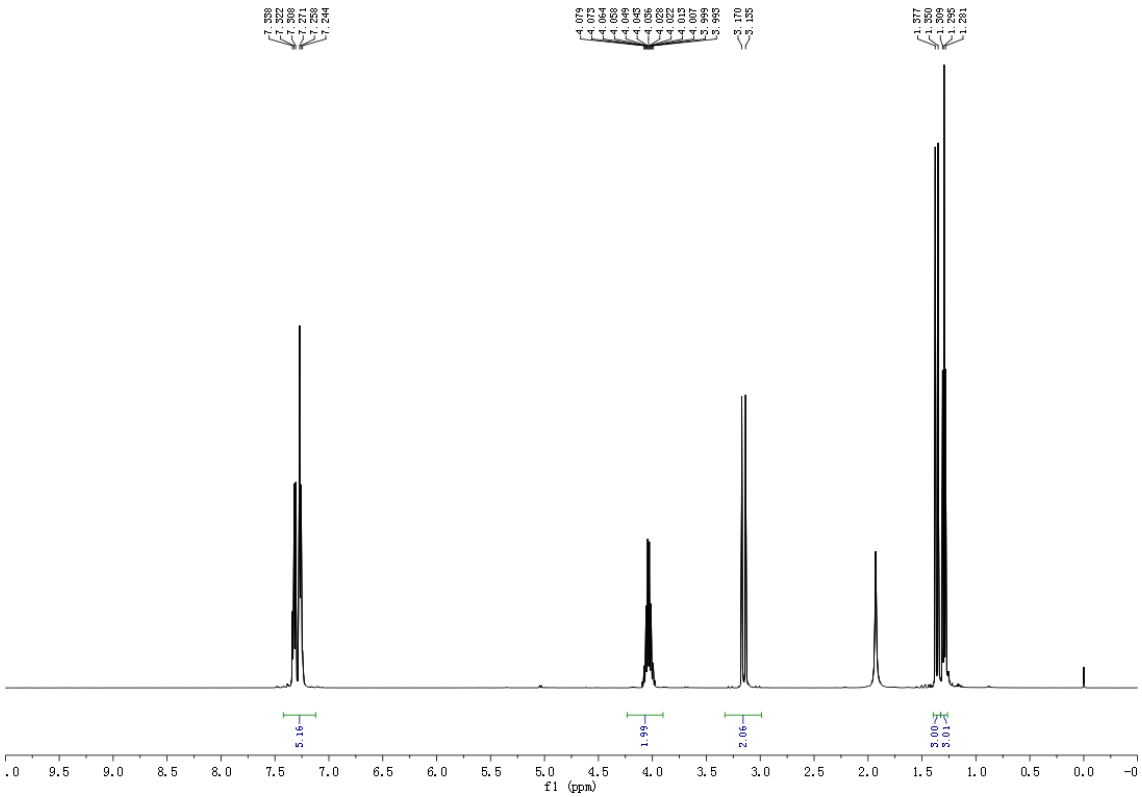
^{31}P NMR



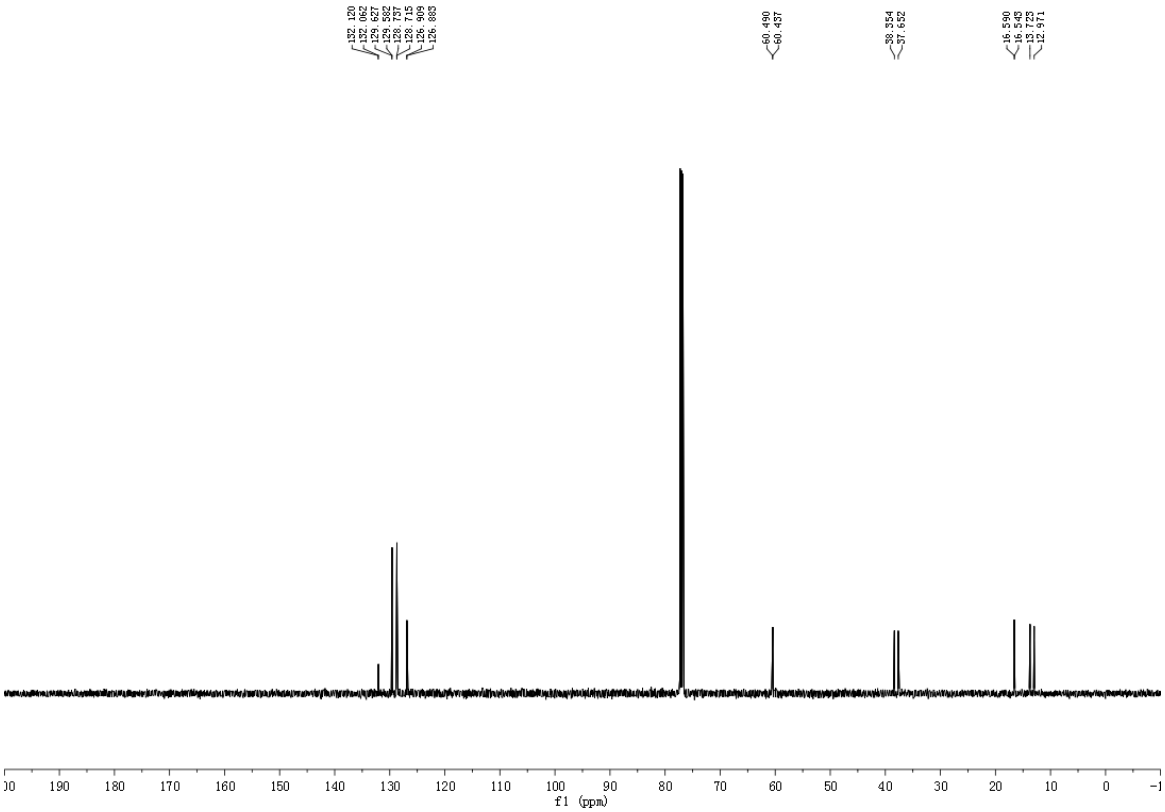


3x

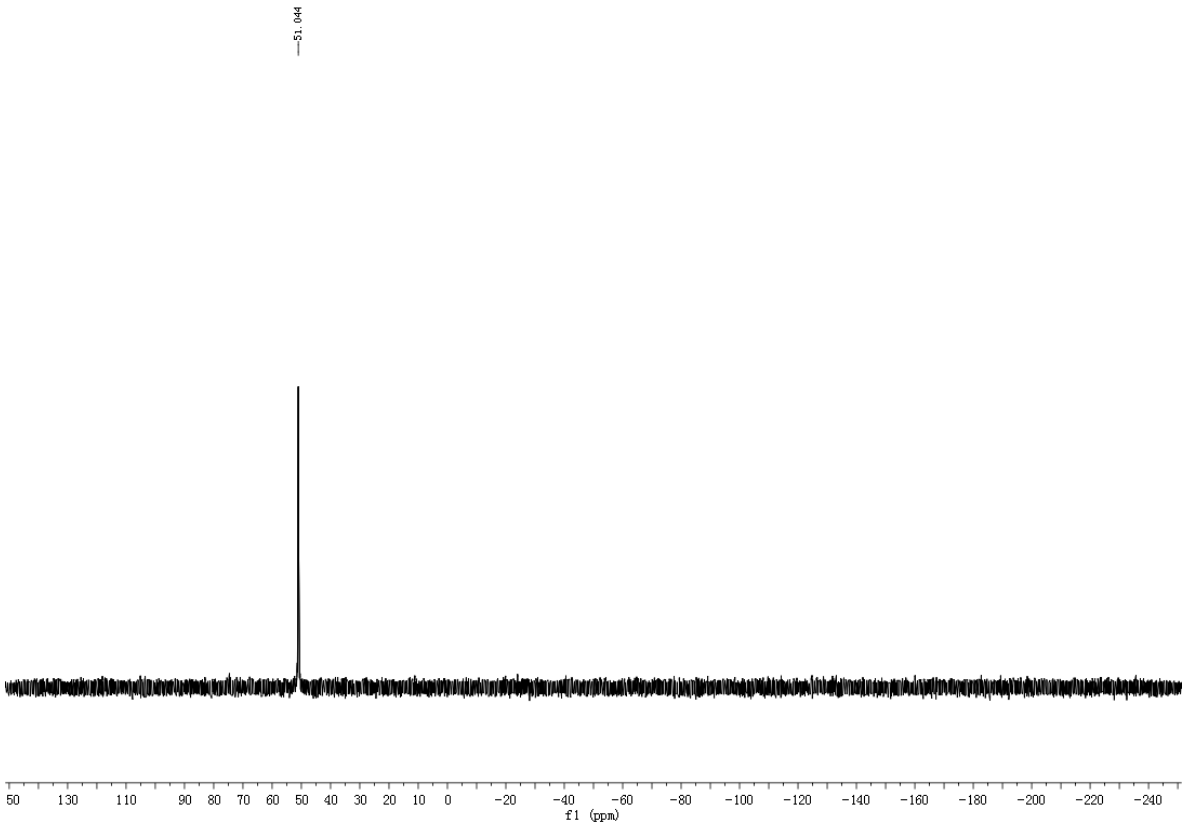
^{1}H NMR

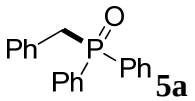


^{13}C NMR



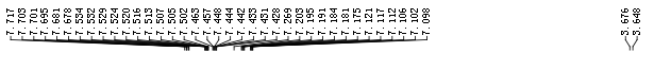
^{31}P NMR

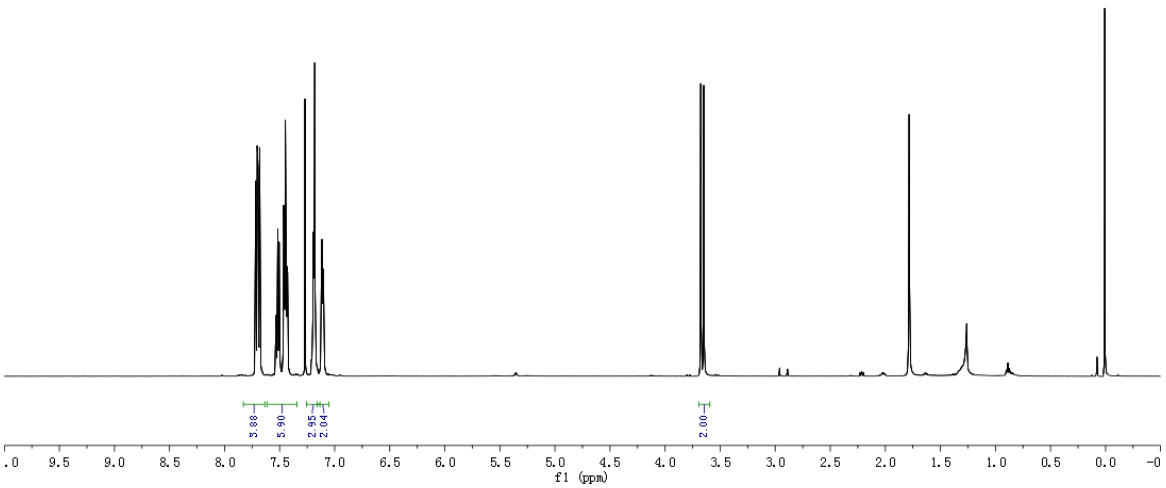




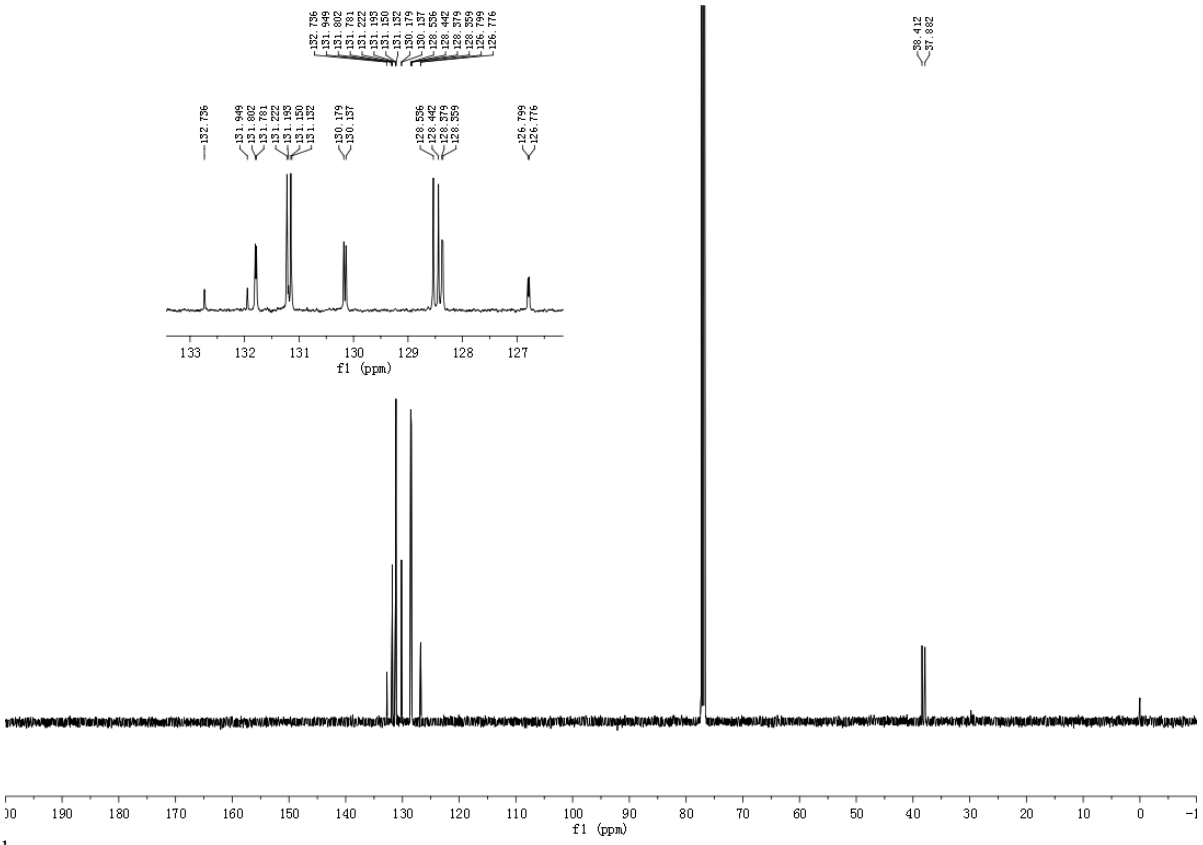
5a

^{1}H NMR

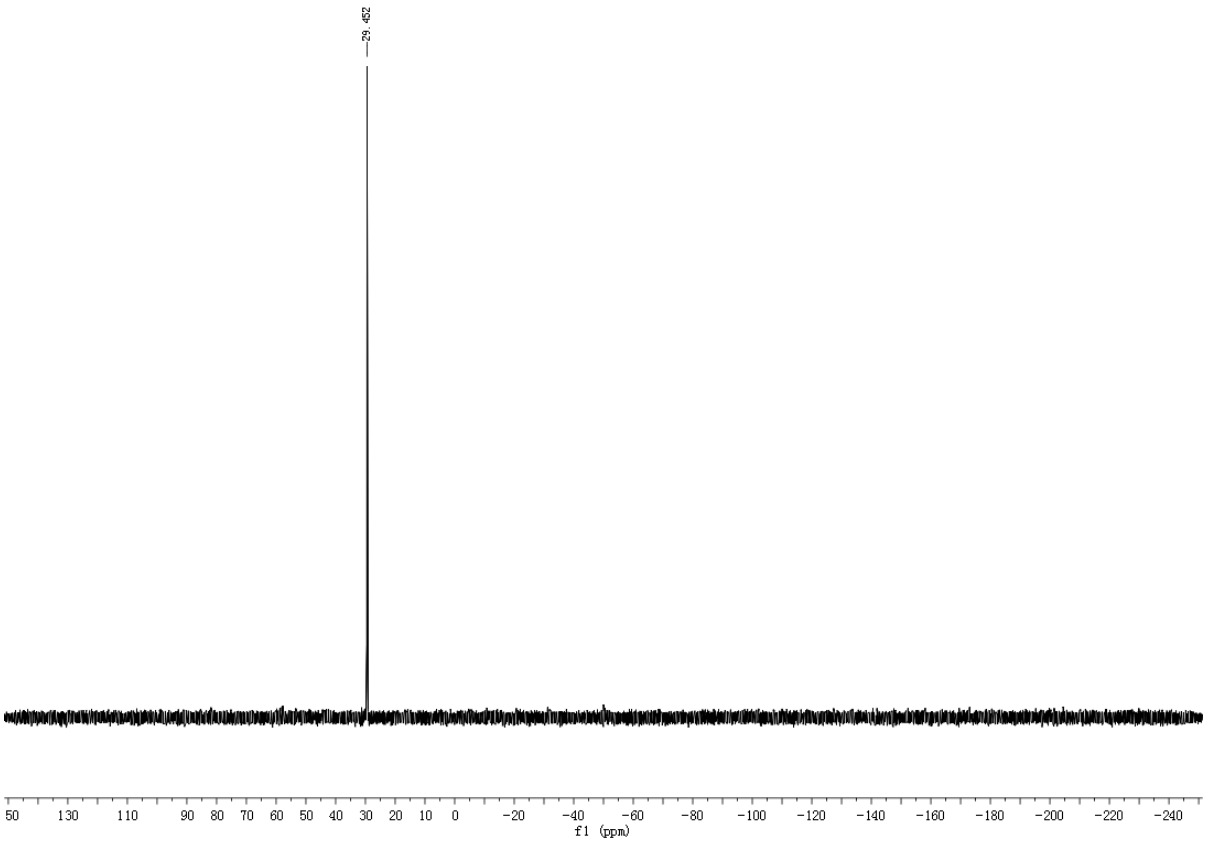


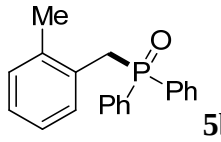


^{13}C NMR



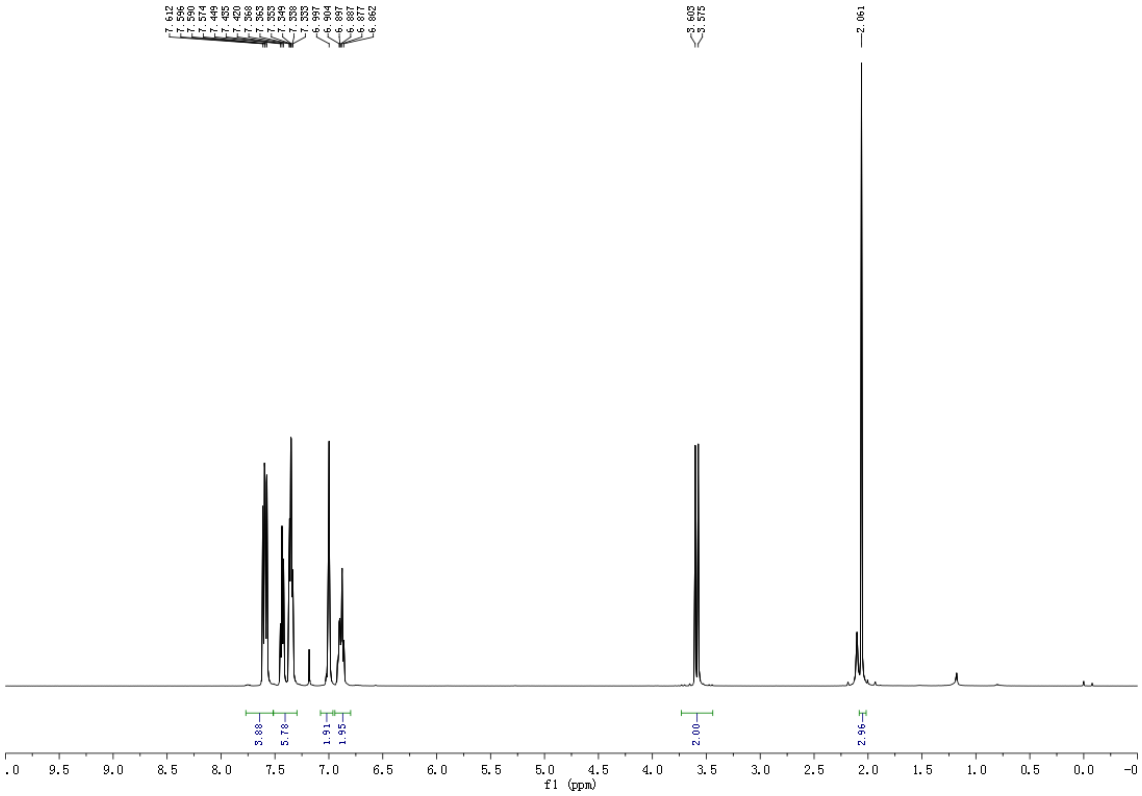
^{31}P NMR



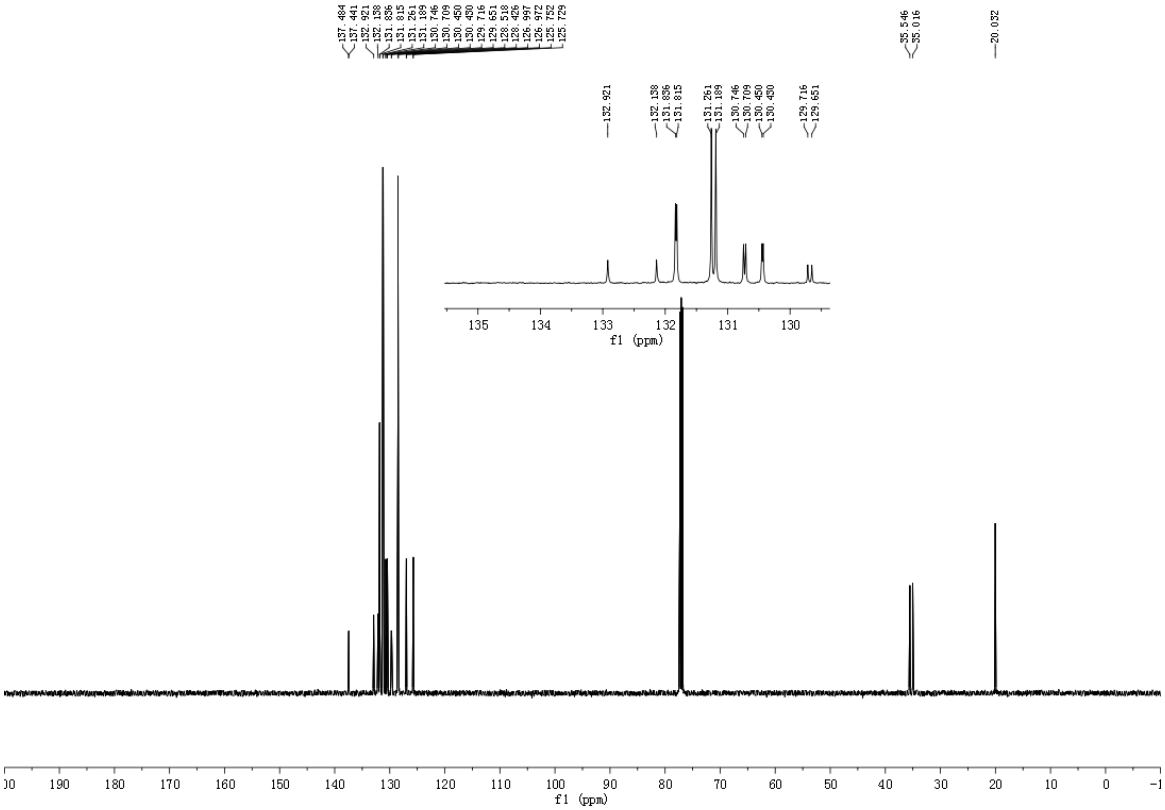


5b

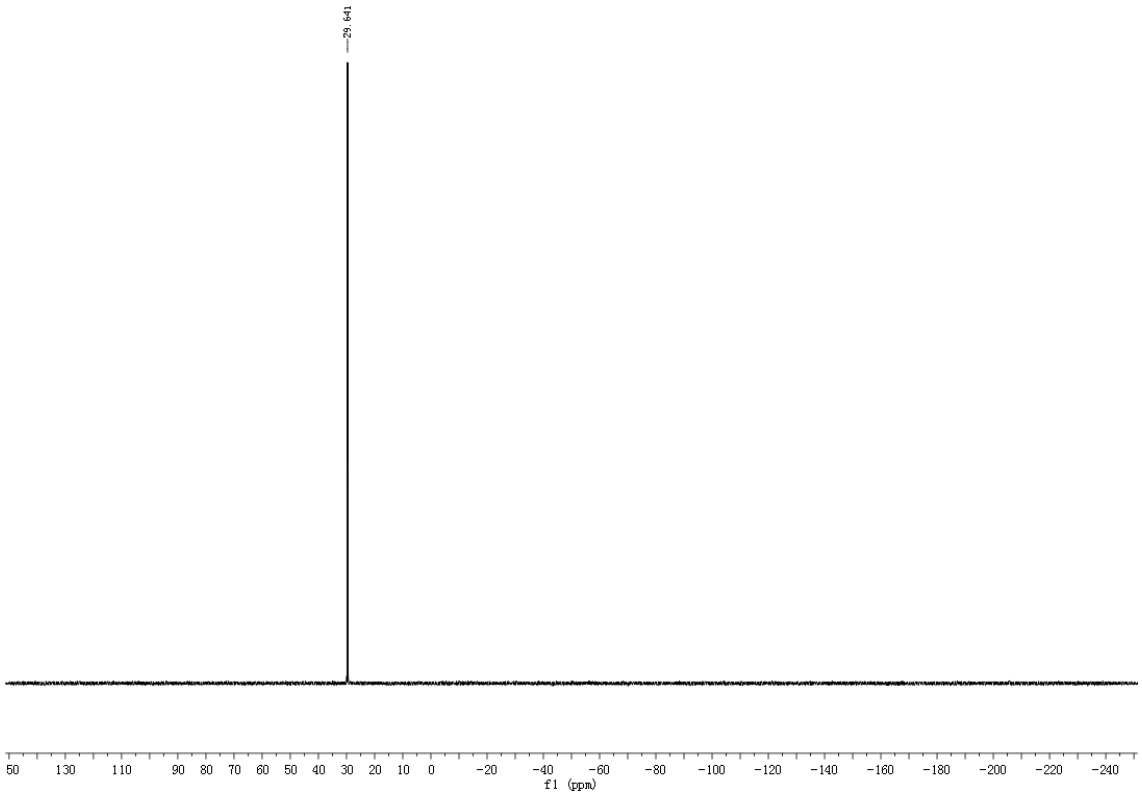
^{1}H NMR

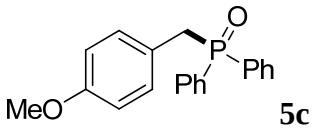


^{13}C NMR



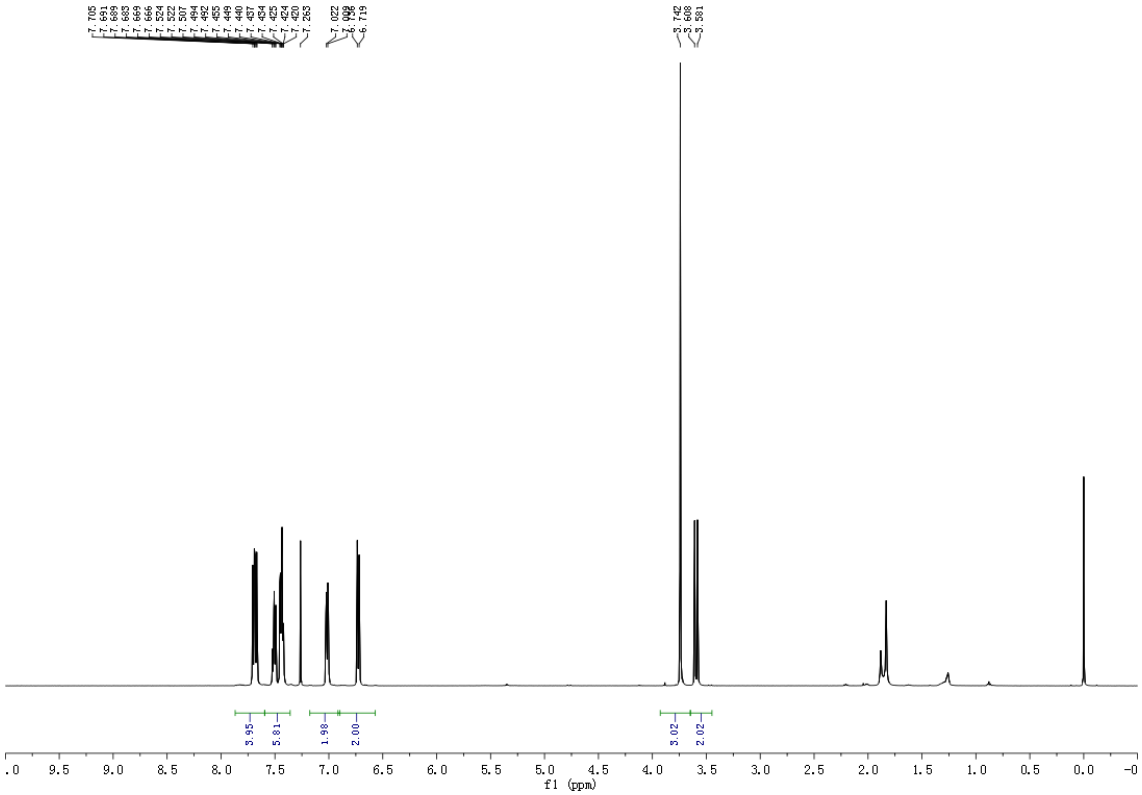
^{31}P NMR



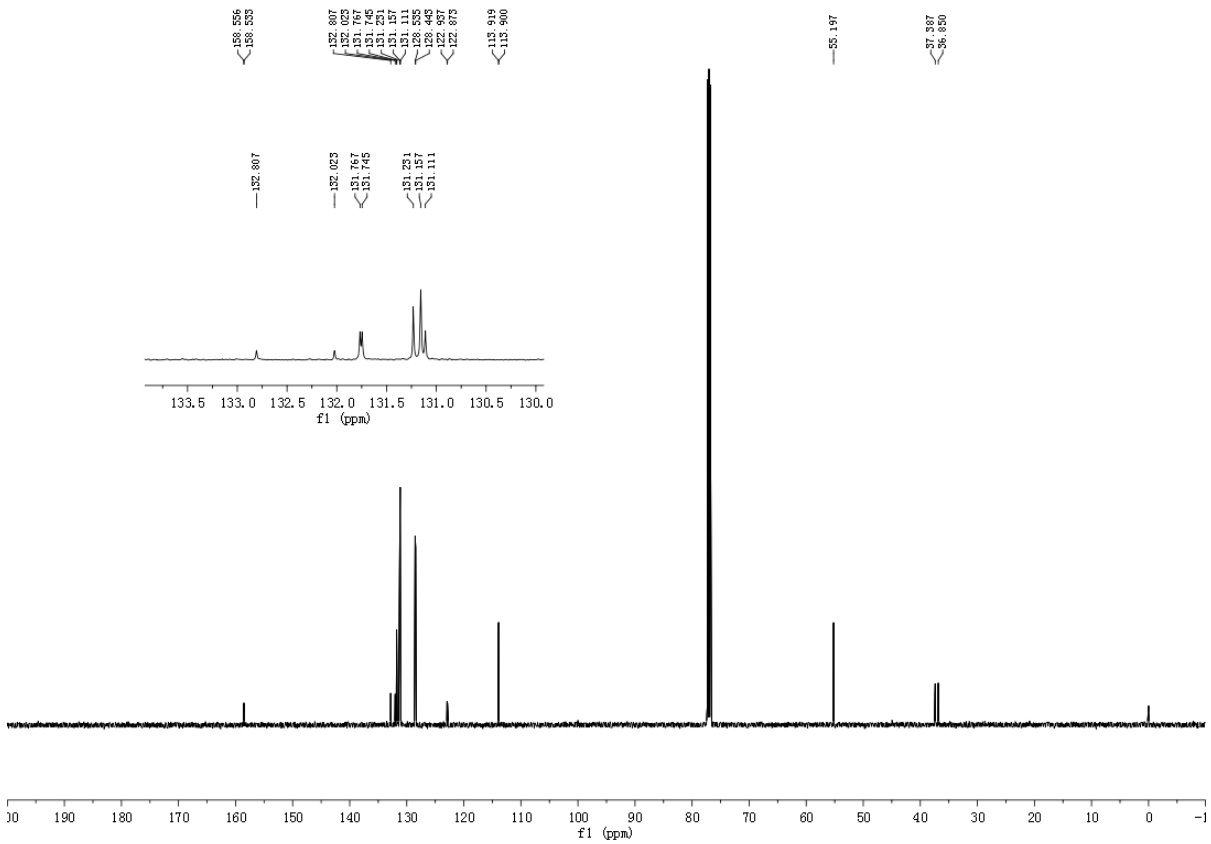


5c

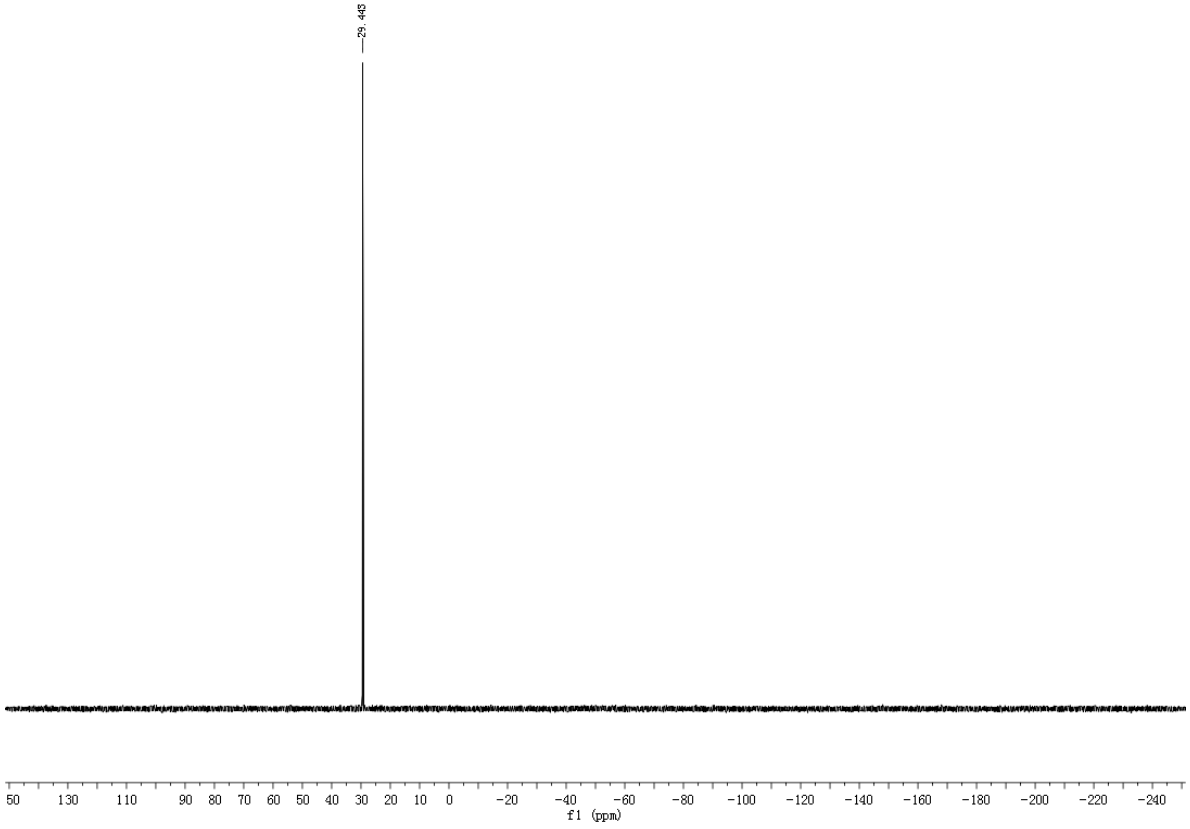
^{1}H NMR

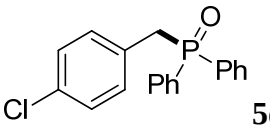


^{13}C NMR



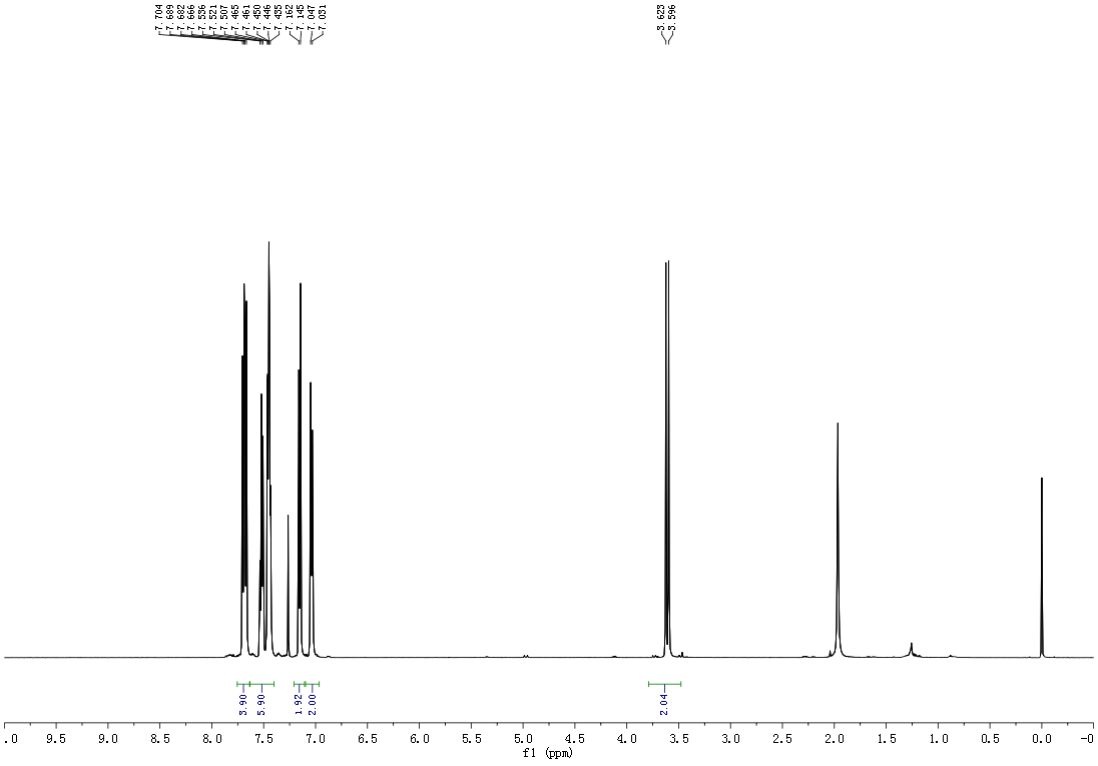
^{31}P NMR



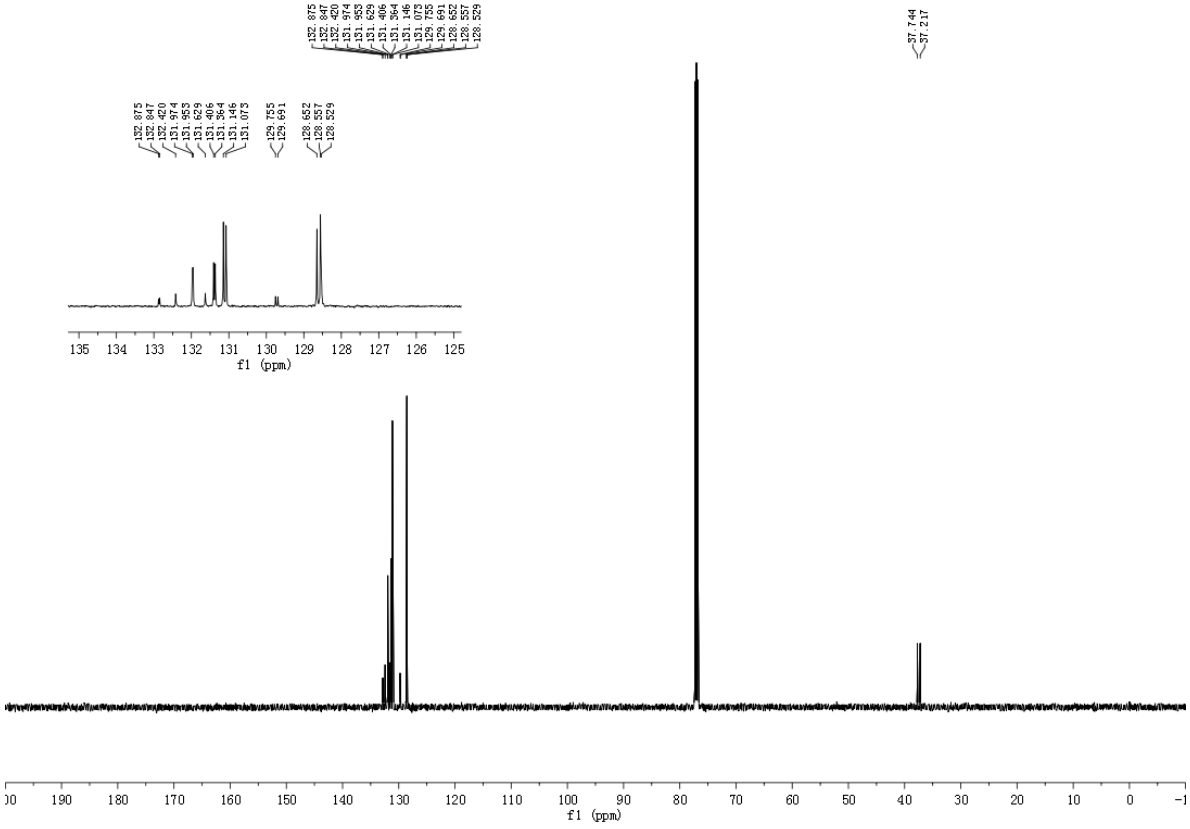


5d

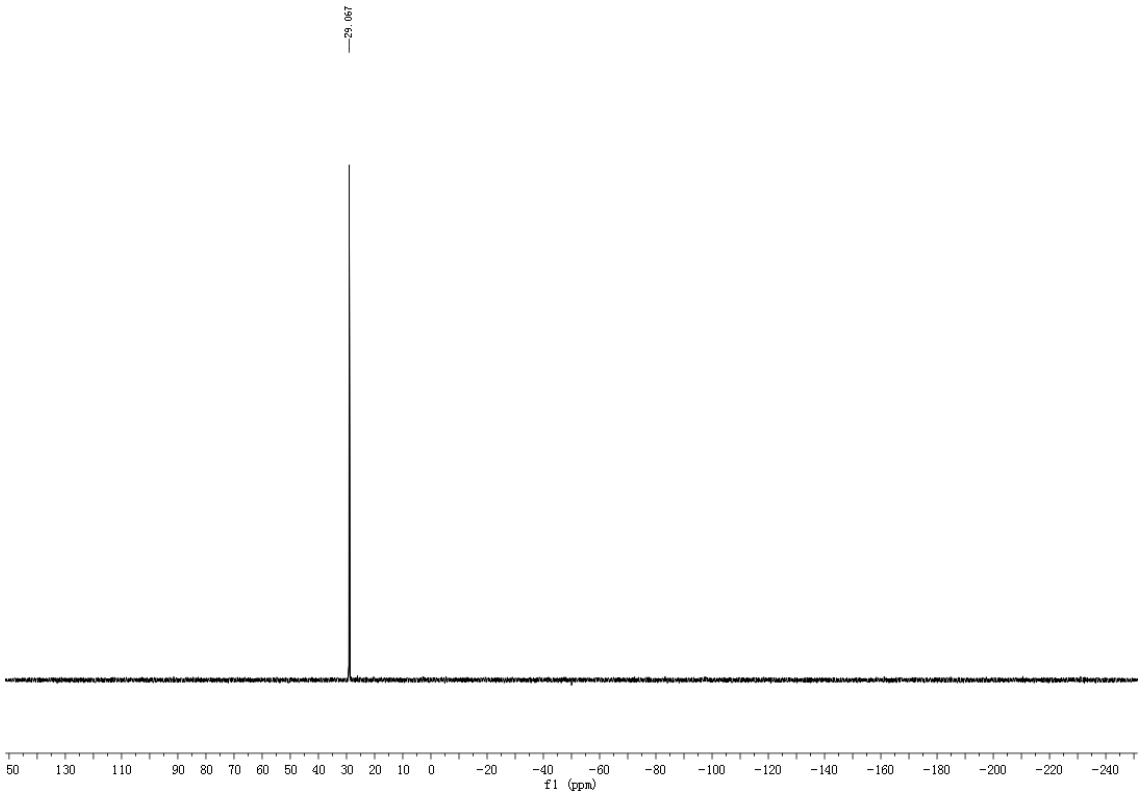
^{1}H NMR

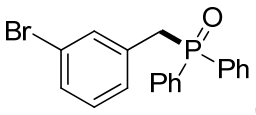


^{13}C NMR



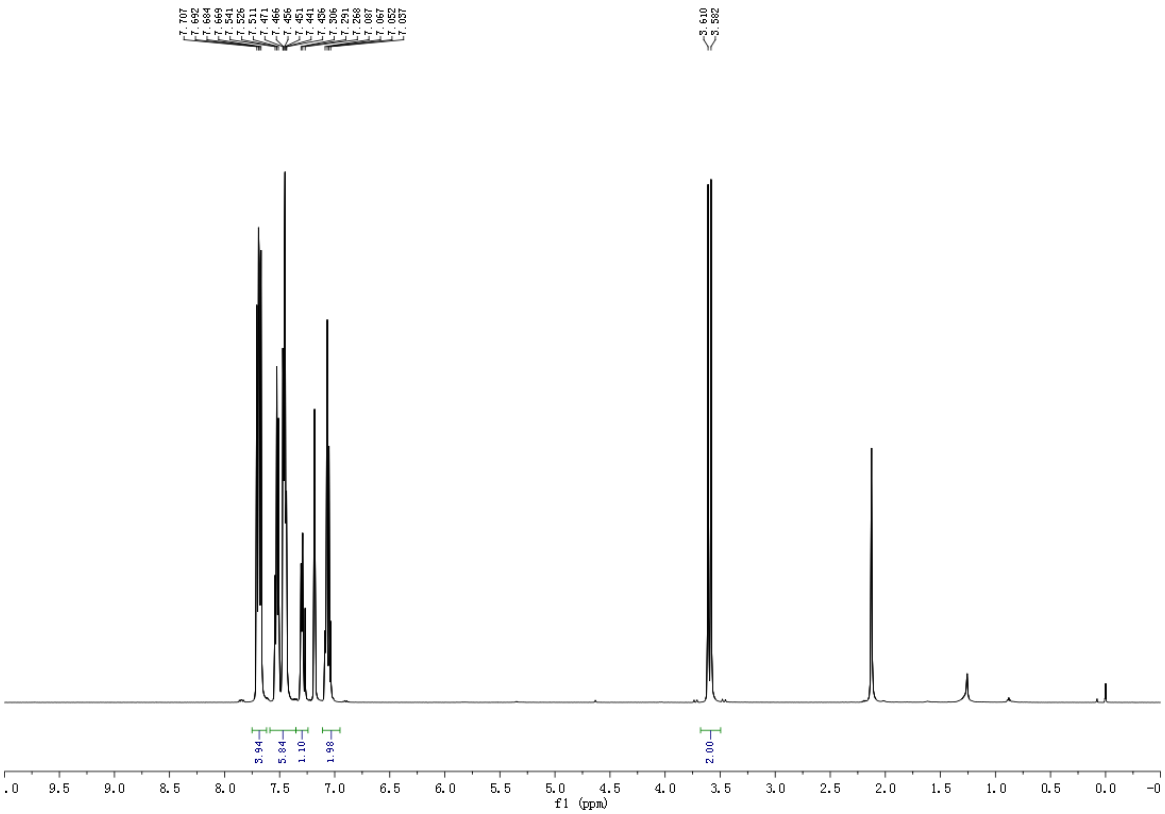
^{31}P NMR



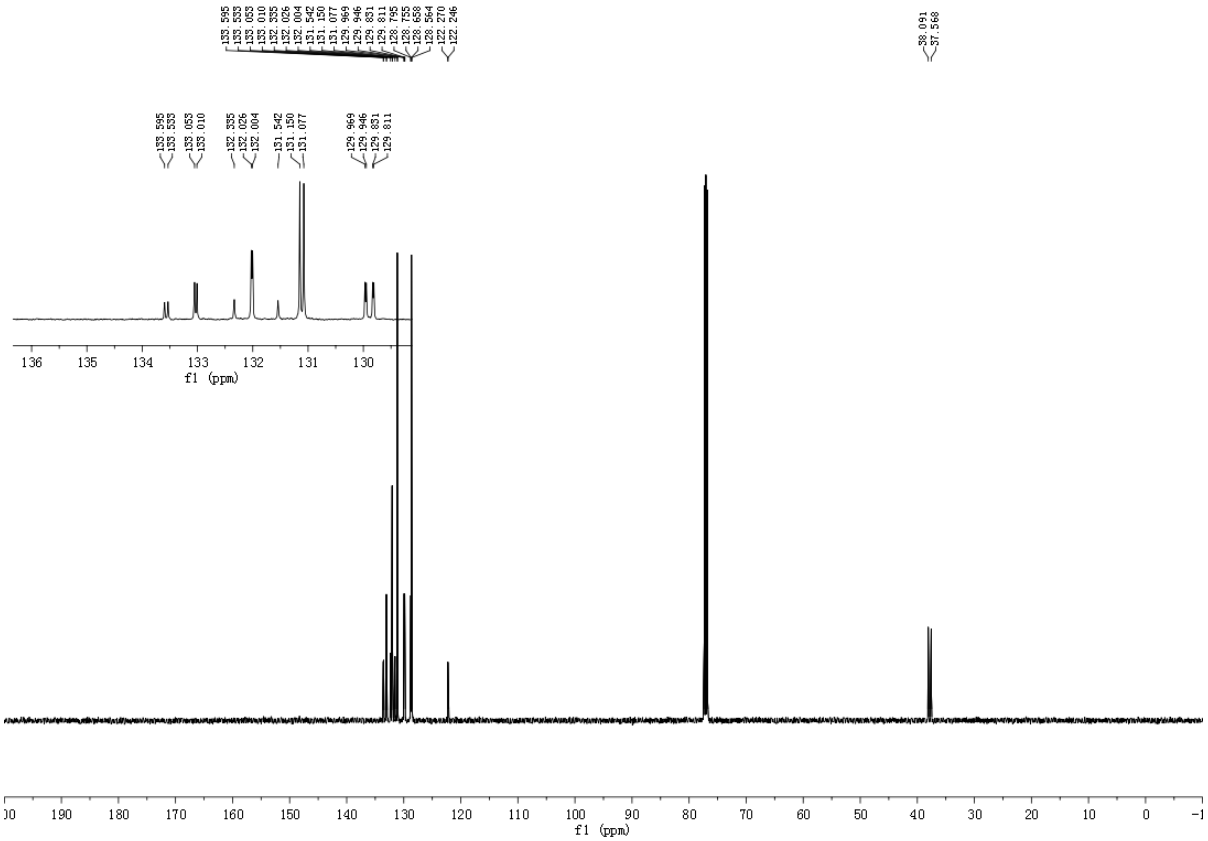


5e

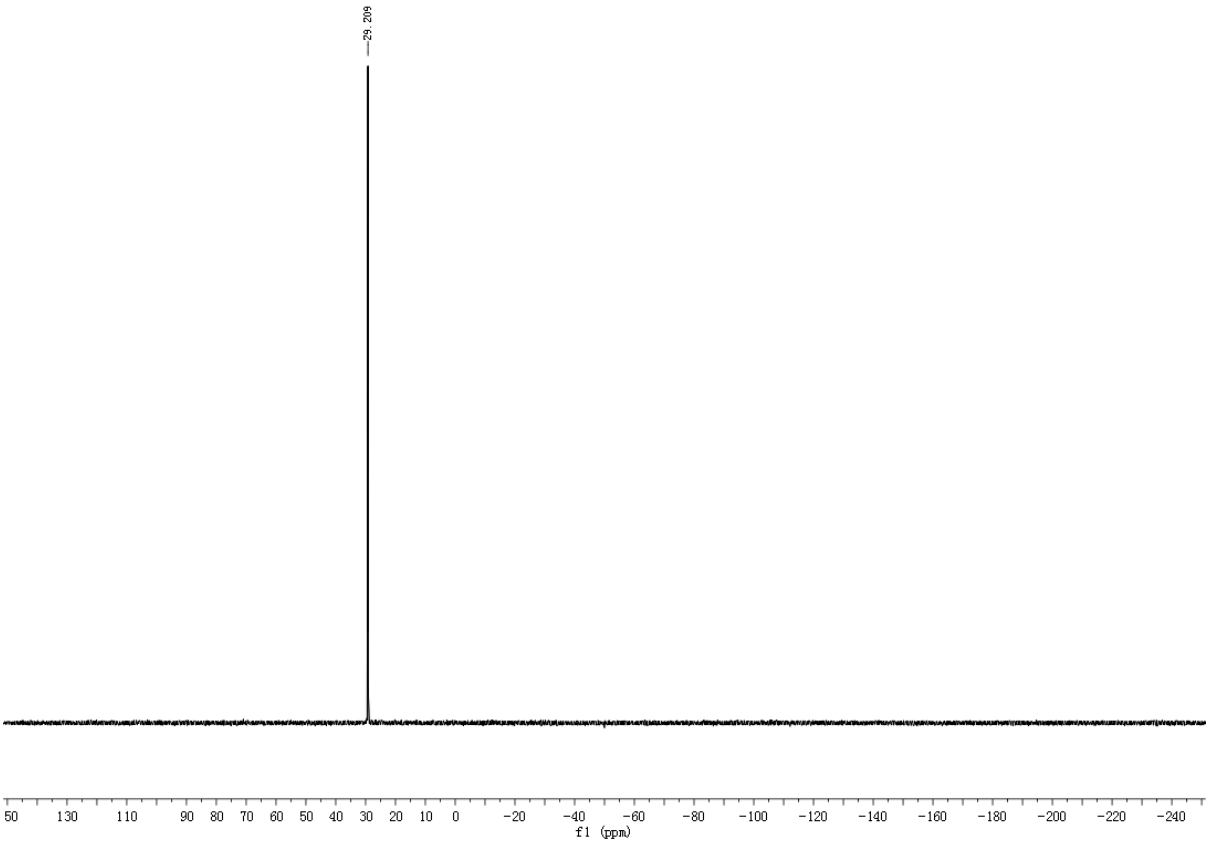
^{1}H NMR

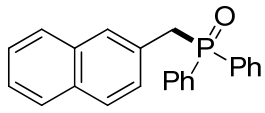


^{13}C NMR



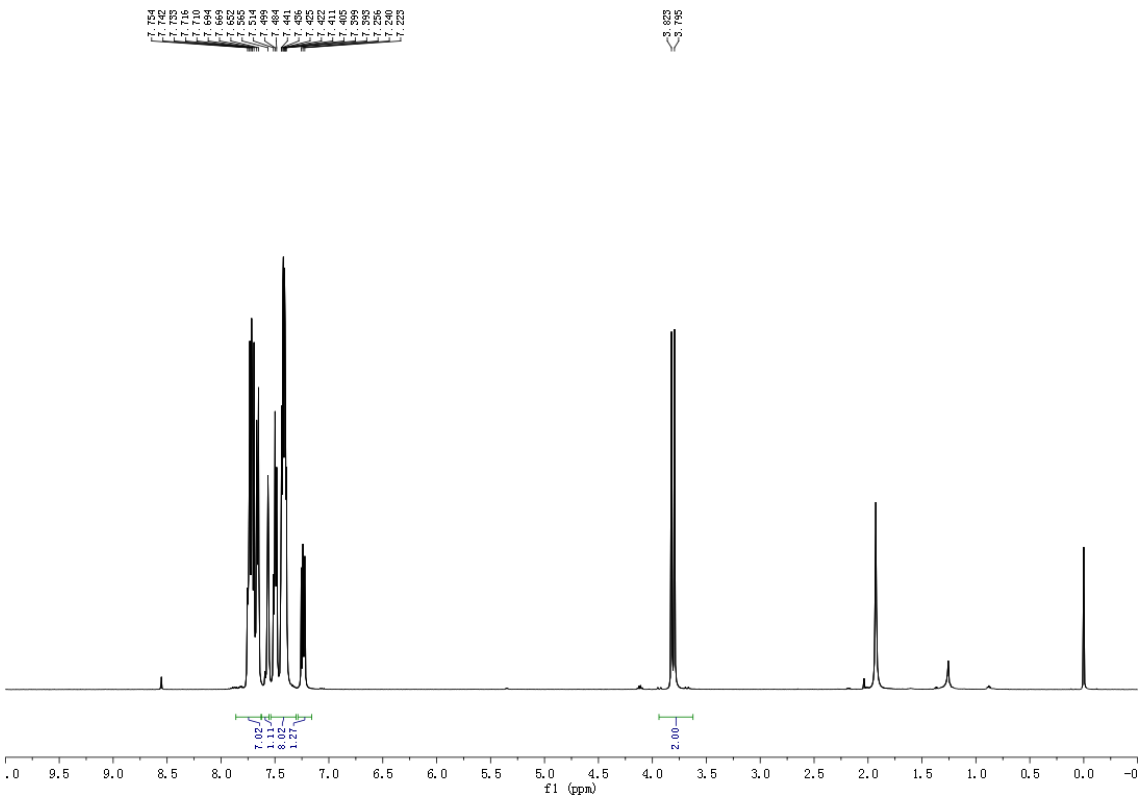
^{31}P NMR



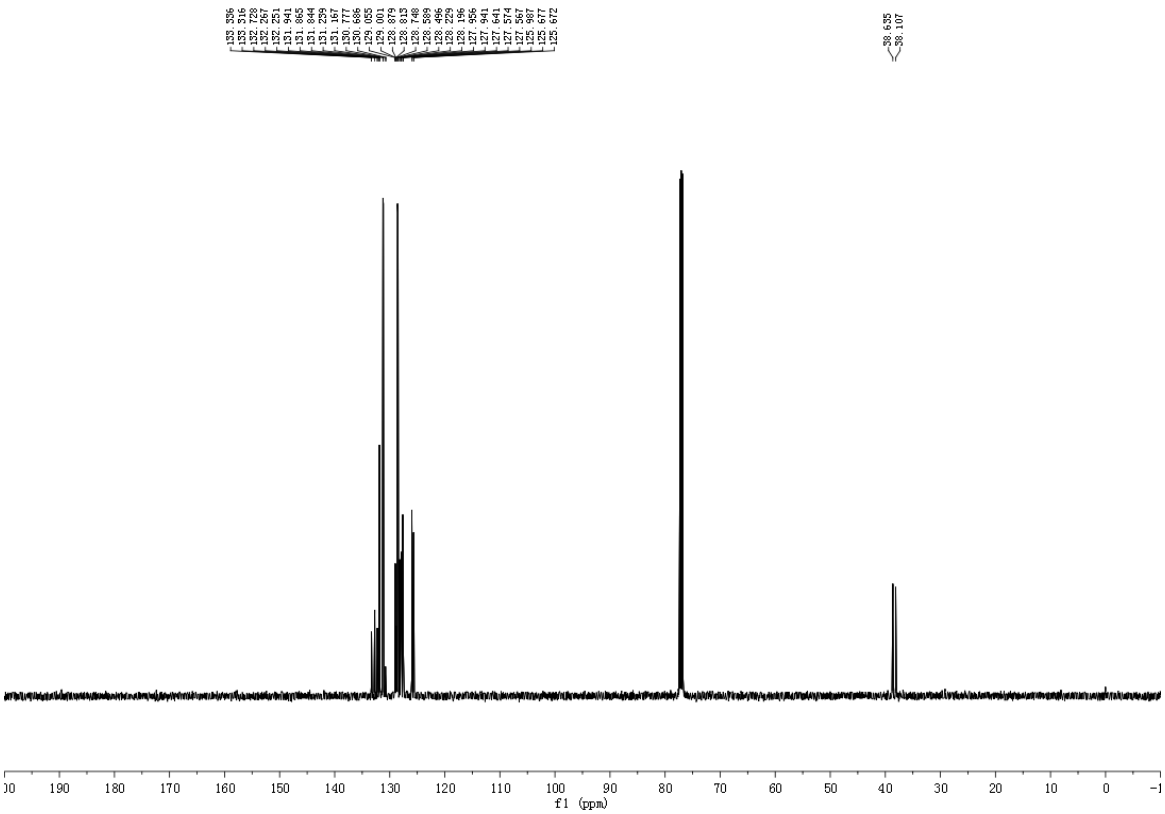


5f

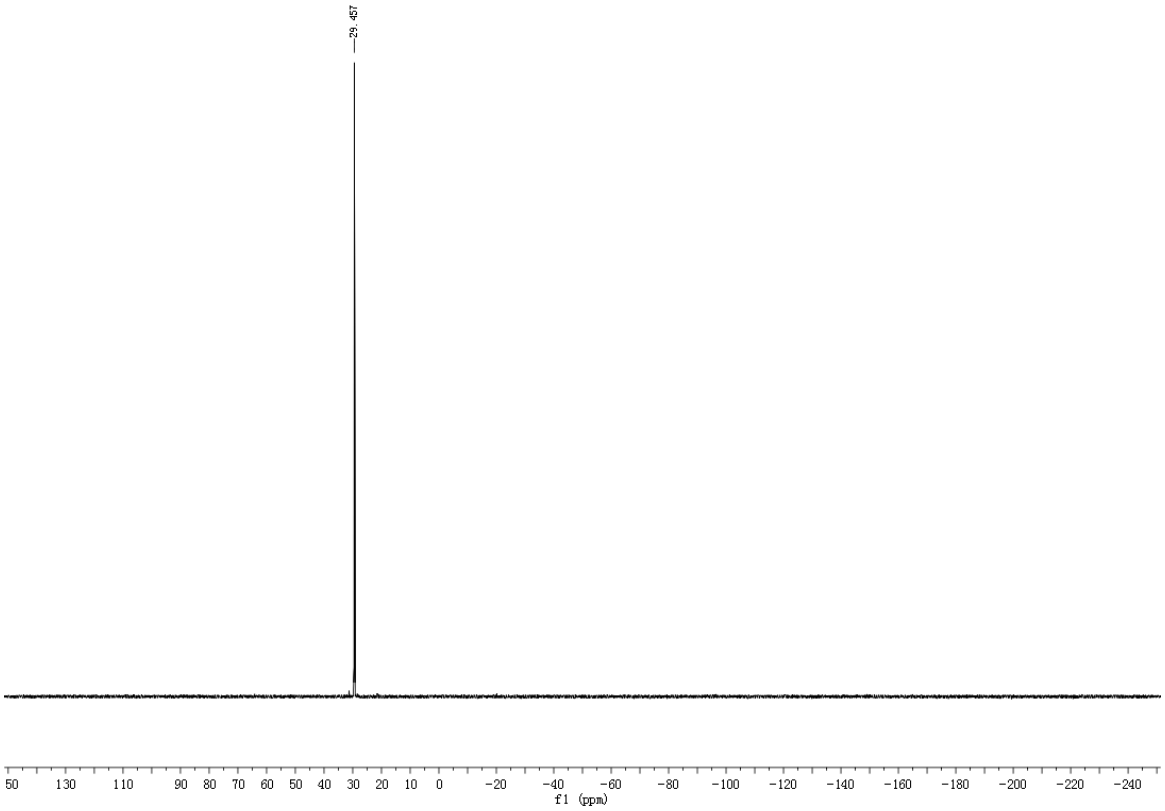
^{1}H NMR

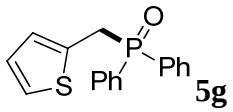


^{13}C NMR



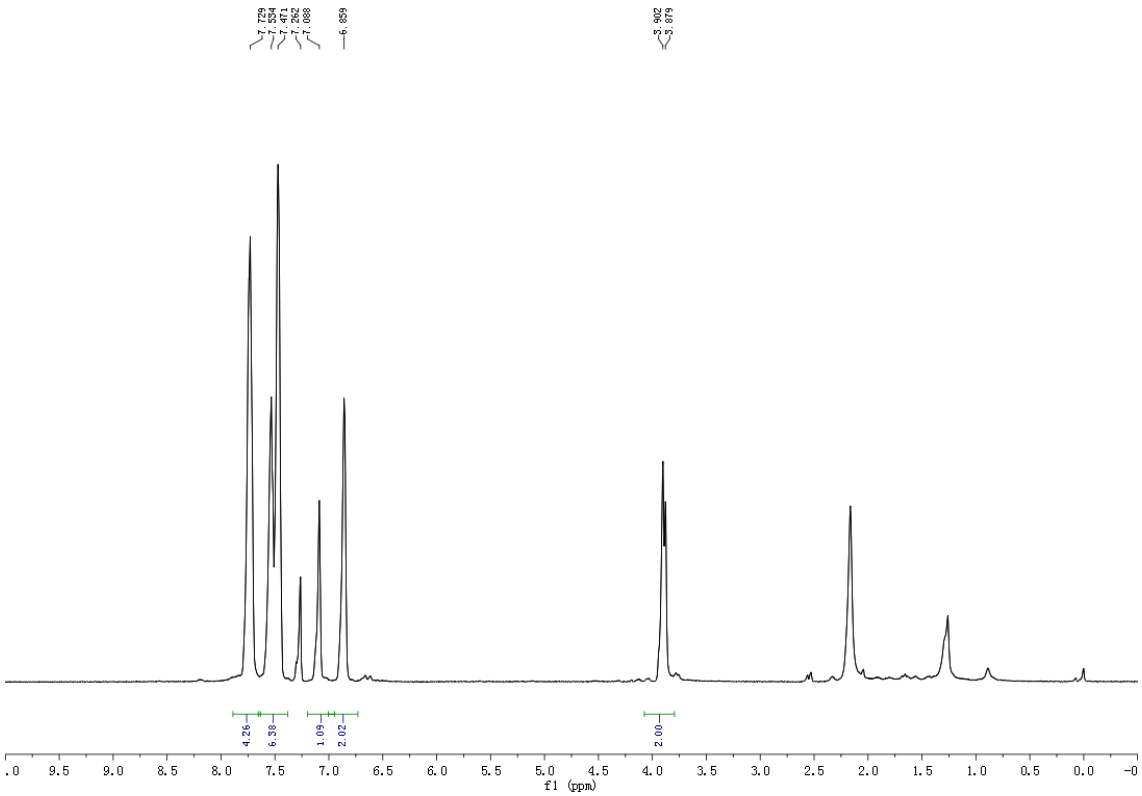
^{31}P NMR



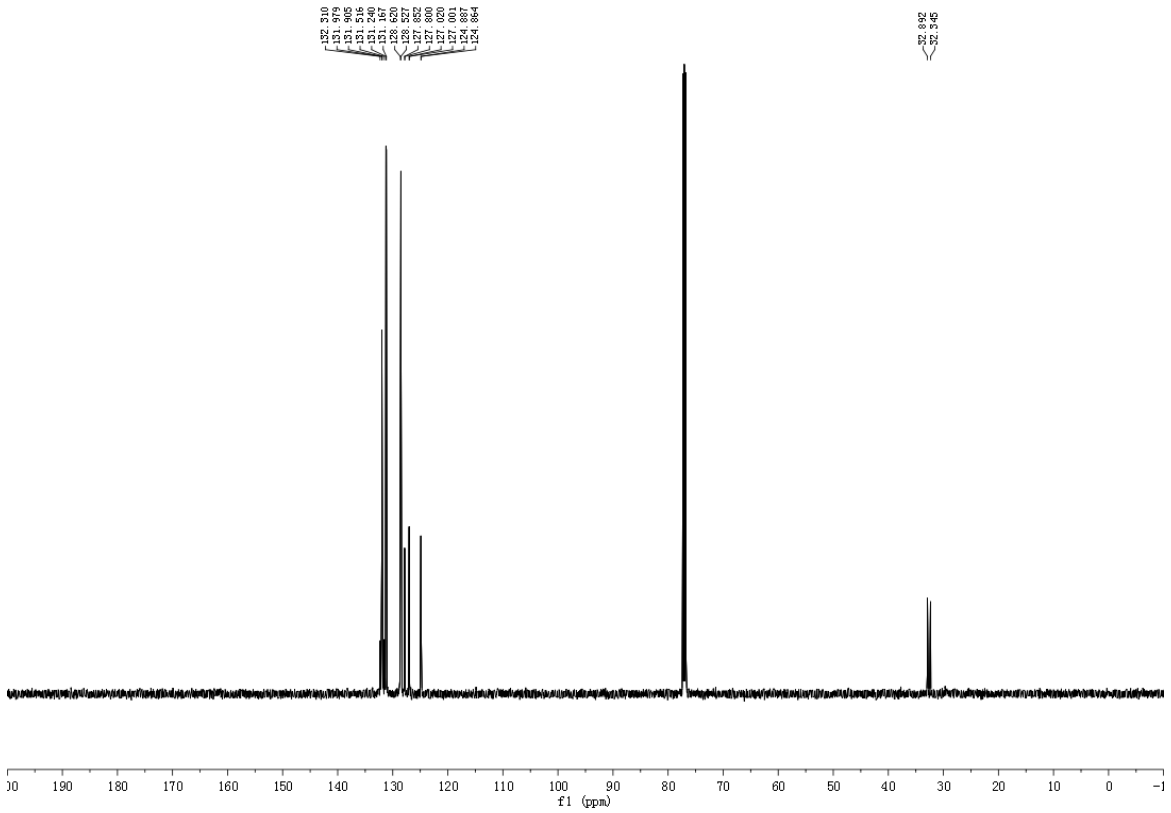


5g

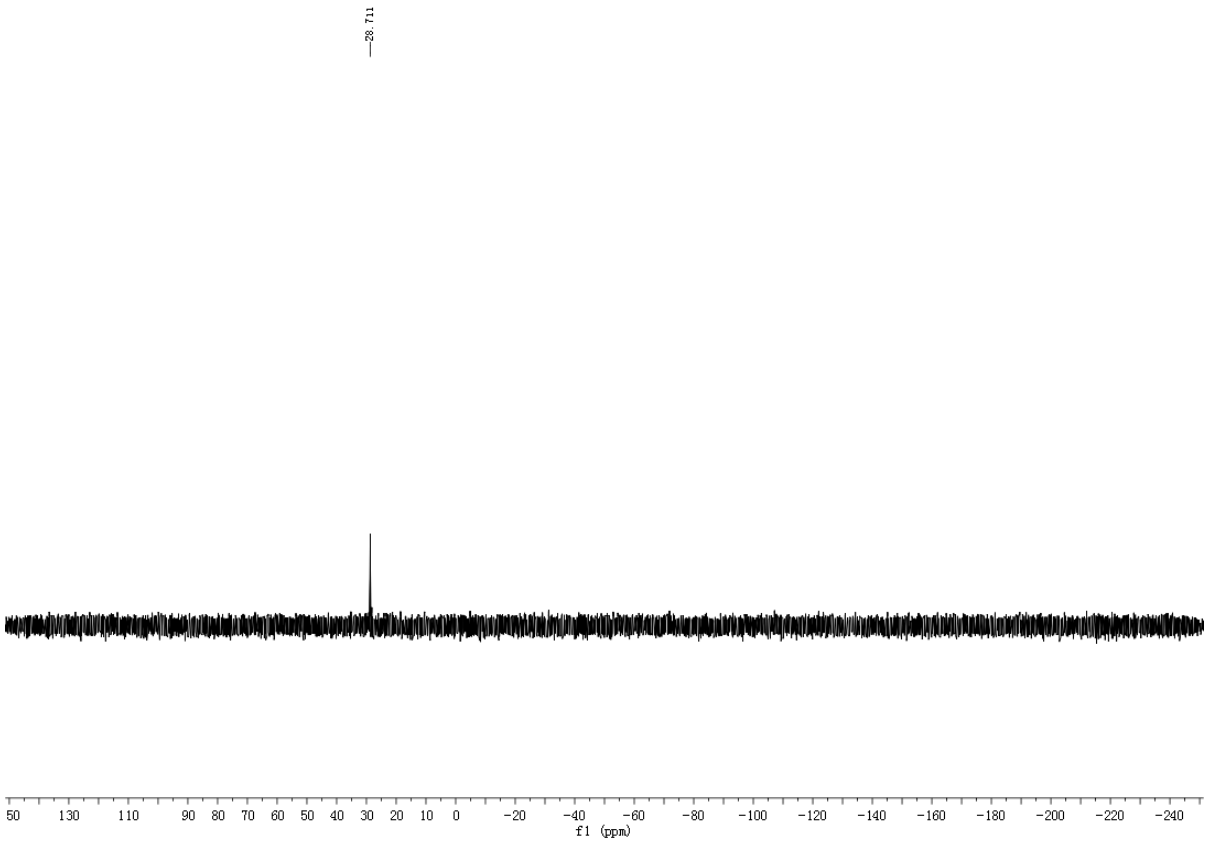
^{1}H NMR

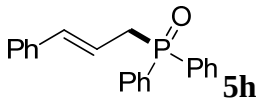


^{13}C NMR



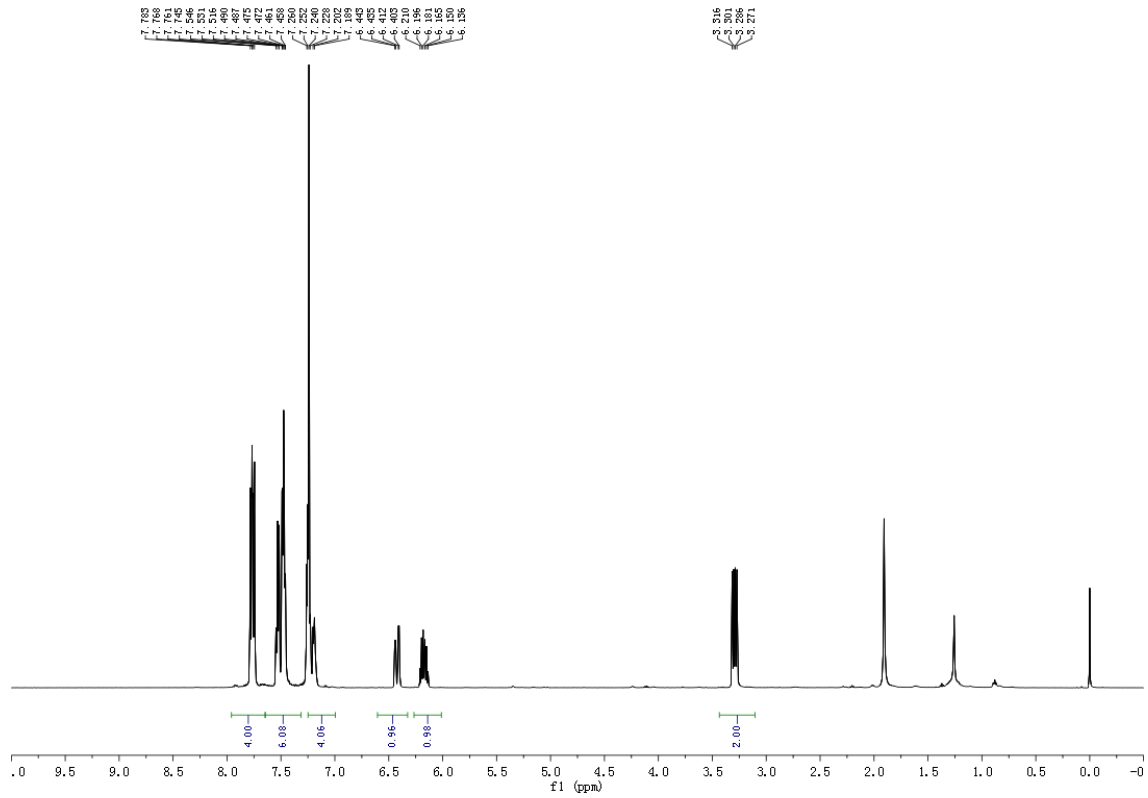
^{31}P NMR



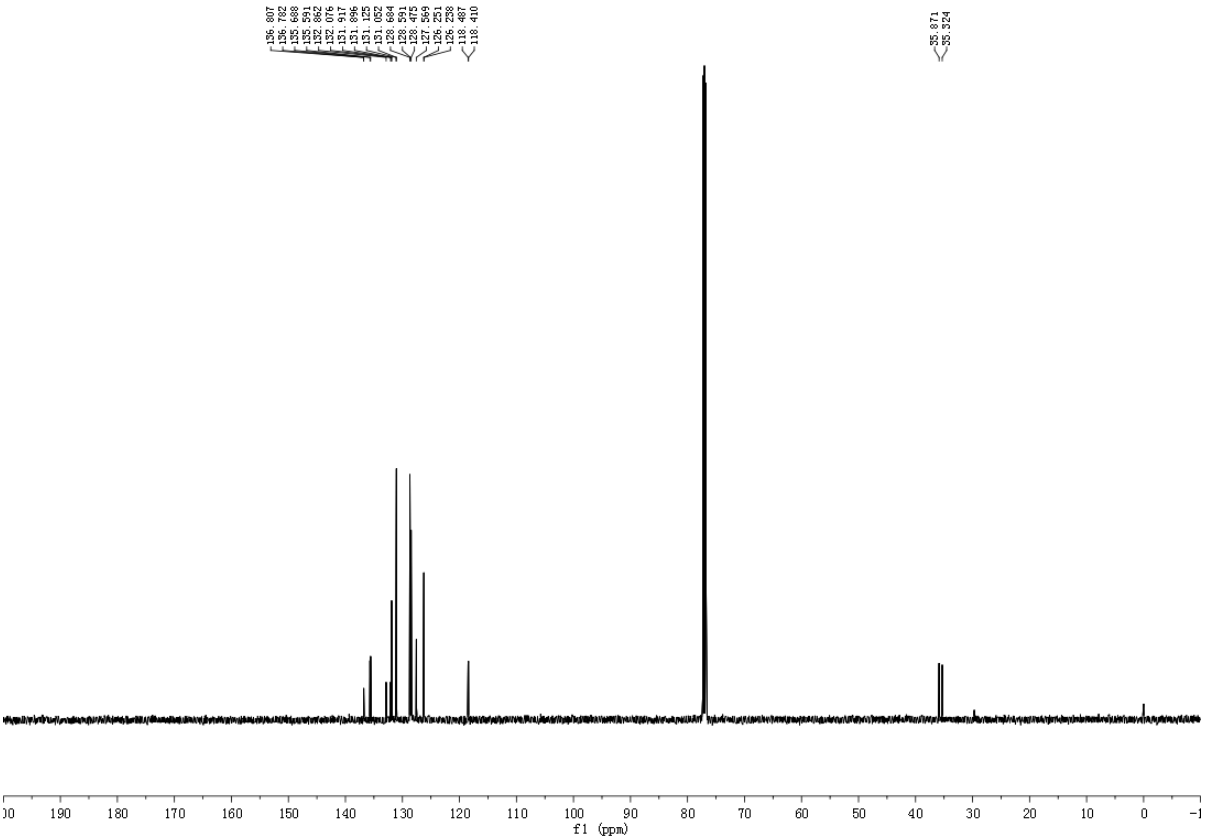


5h

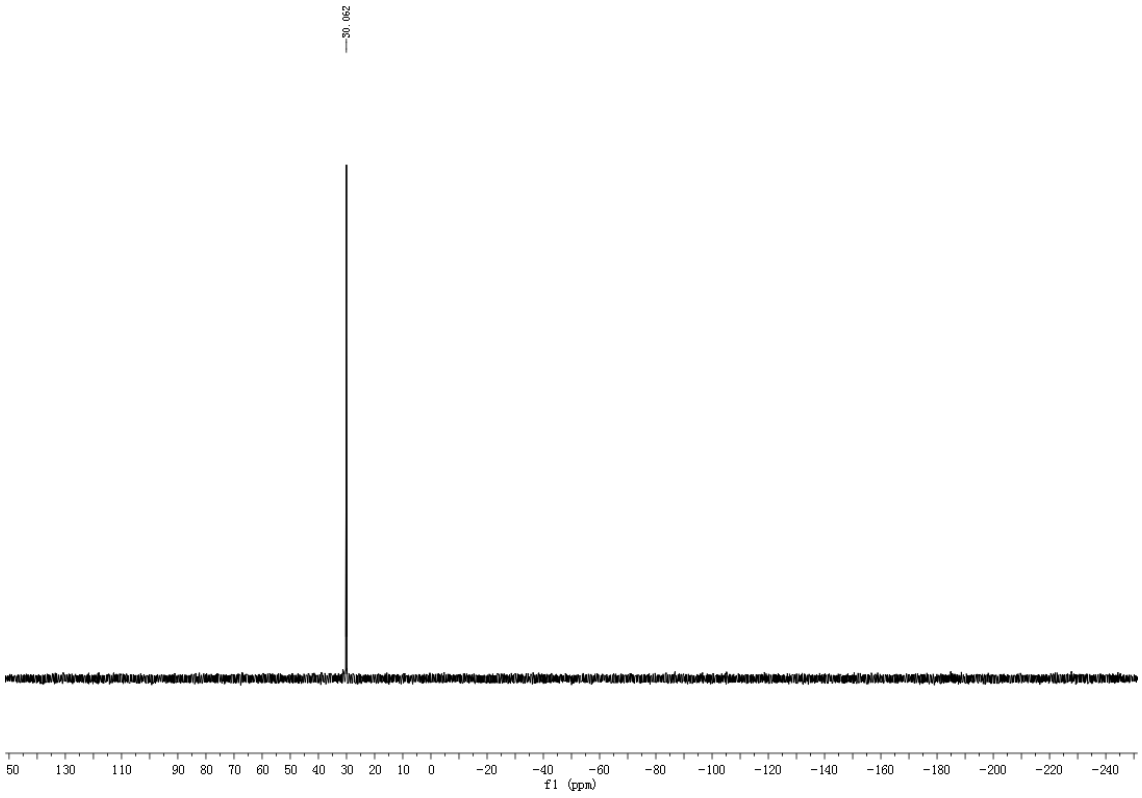
^{1}H NMR

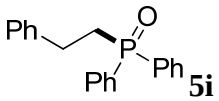


^{13}C NMR



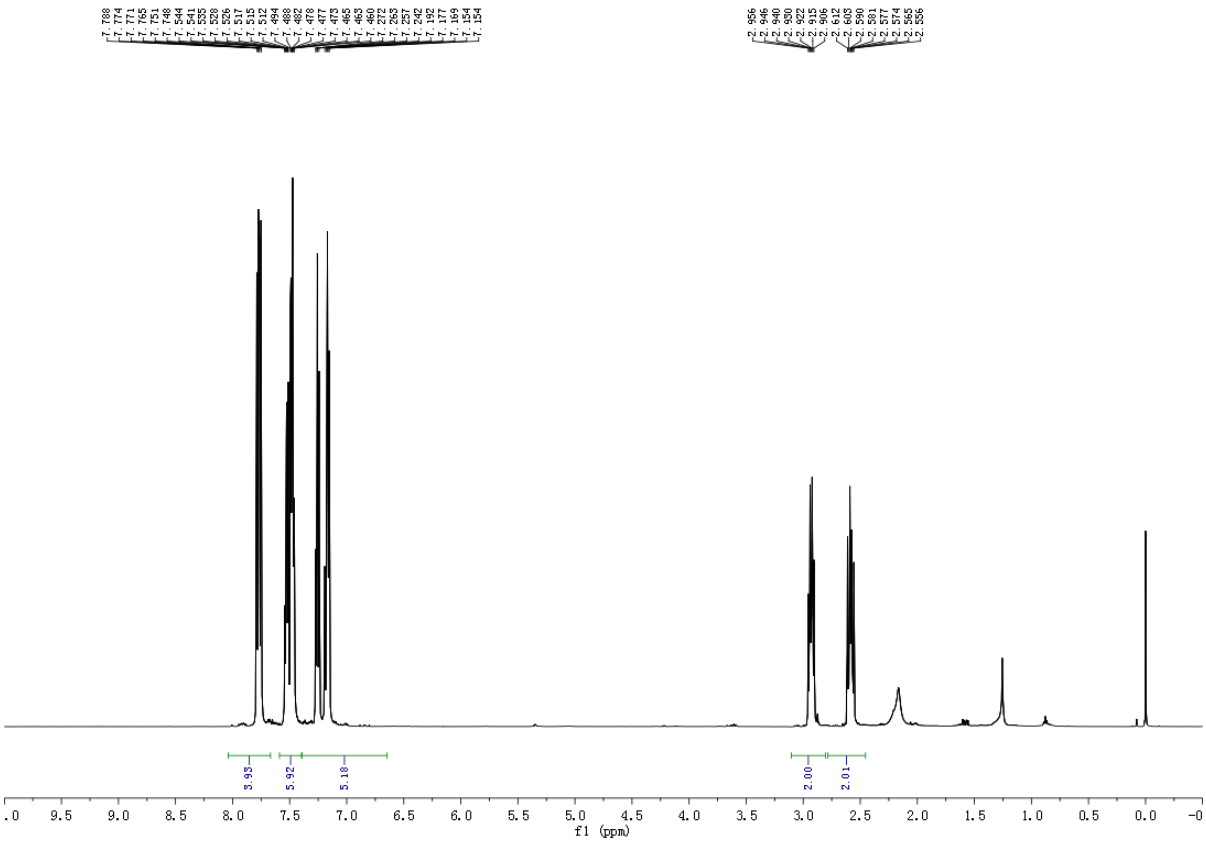
^{31}P NMR



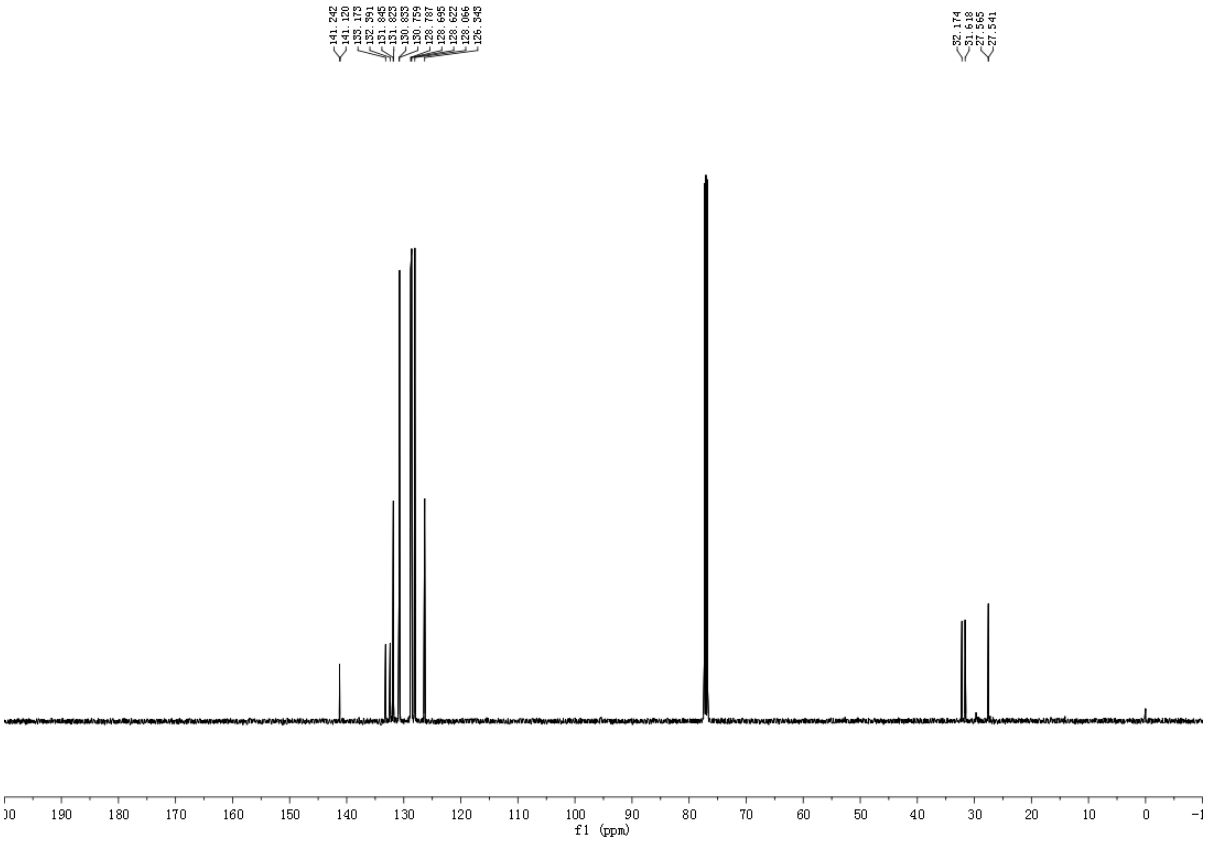


5i

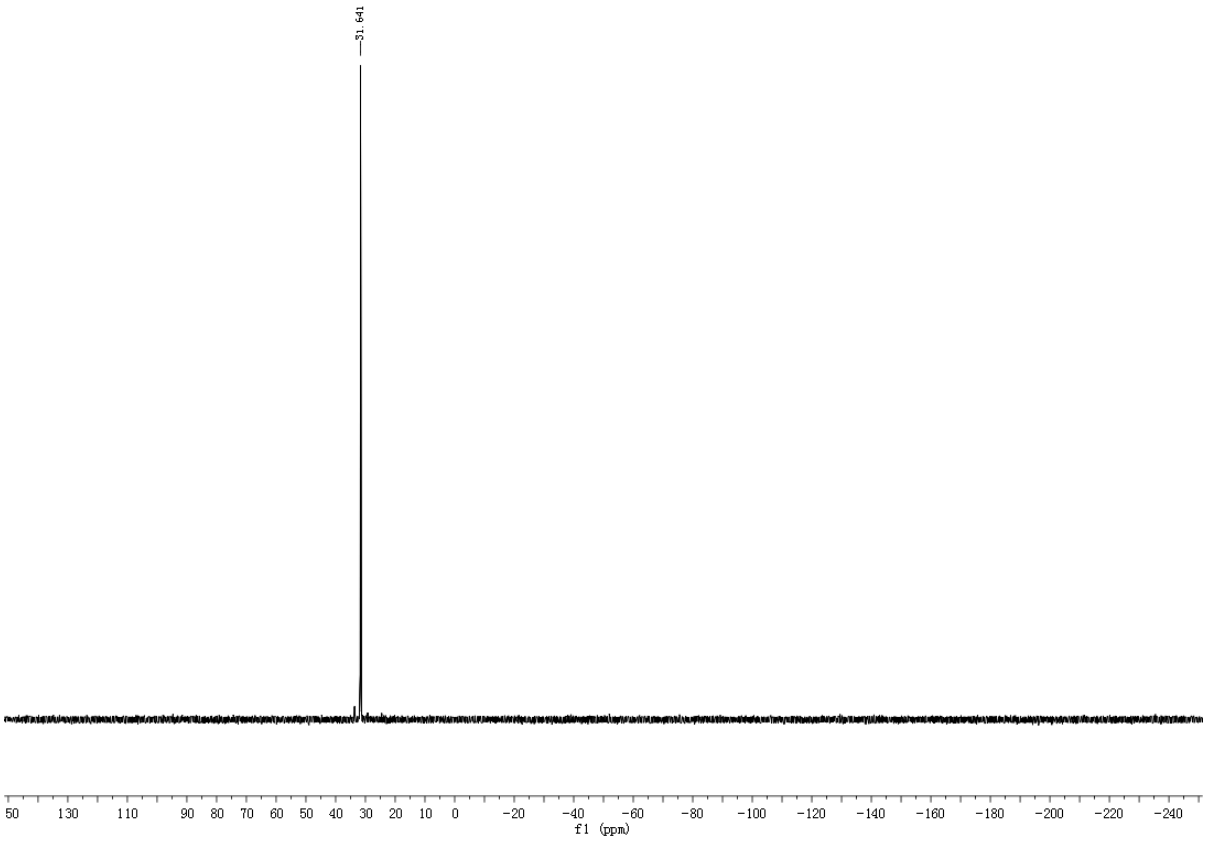
^{1}H NMR

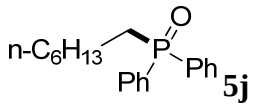


^{13}C NMR



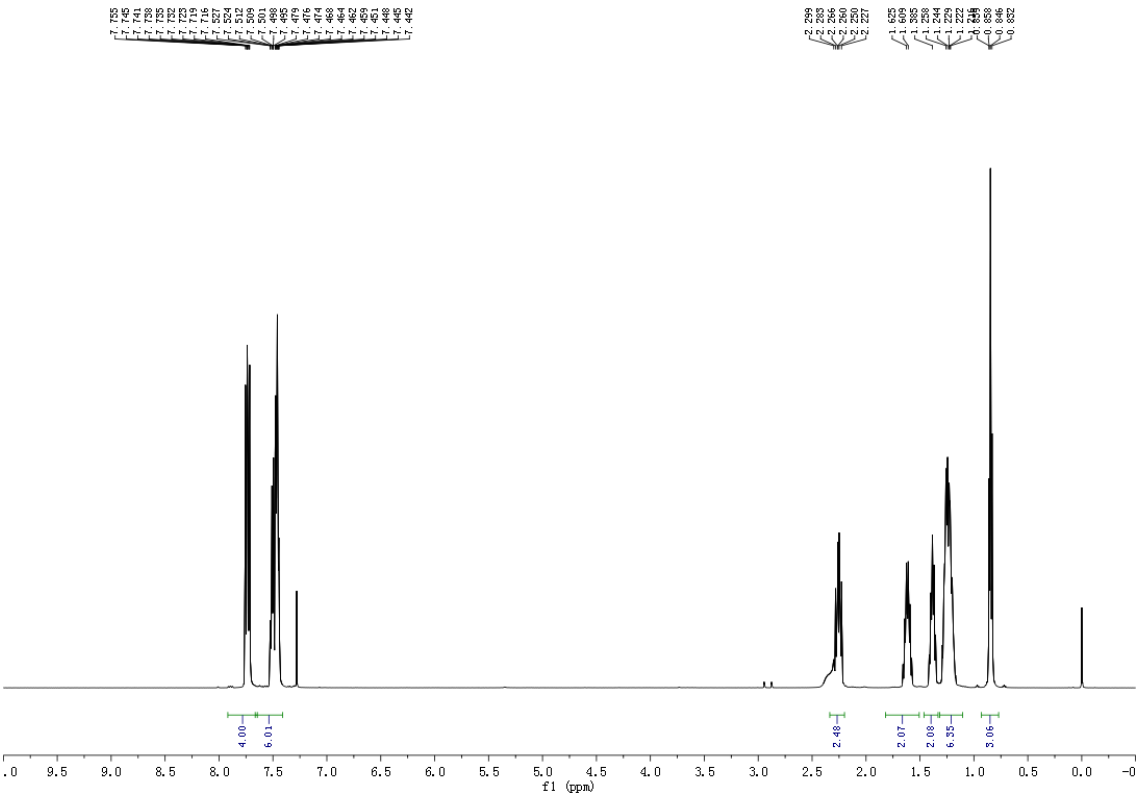
^{31}P NMR



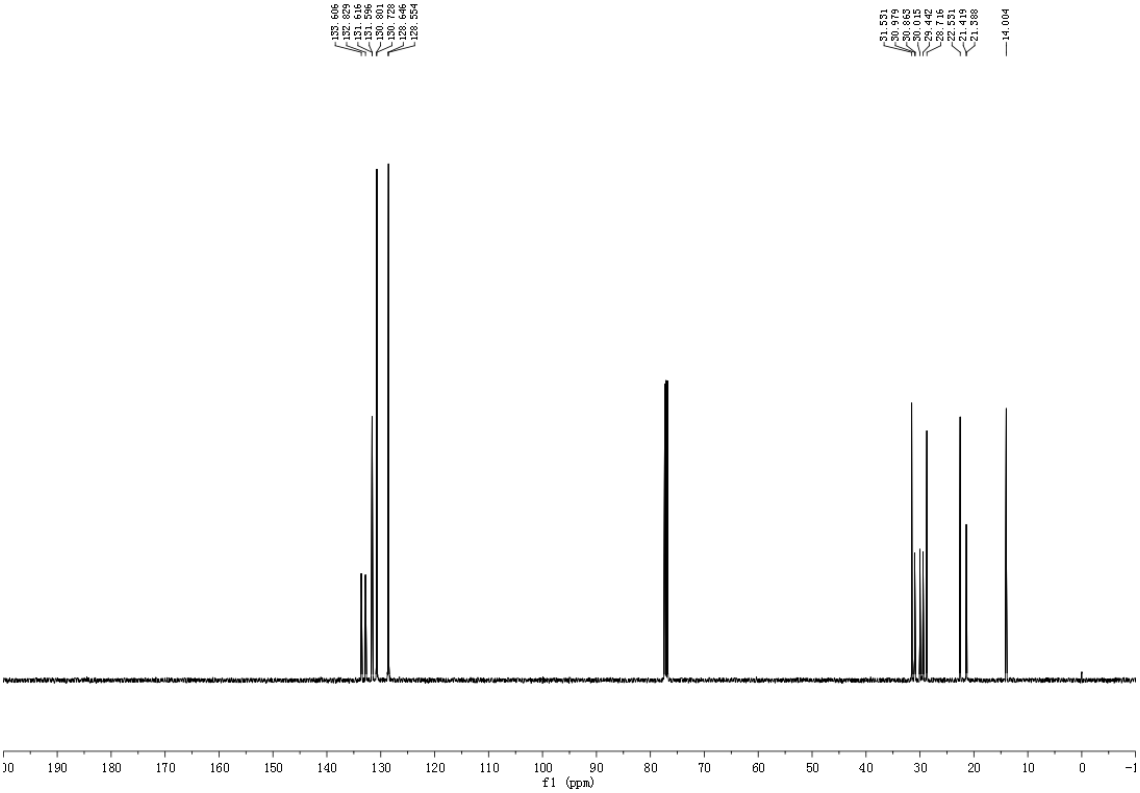


5j

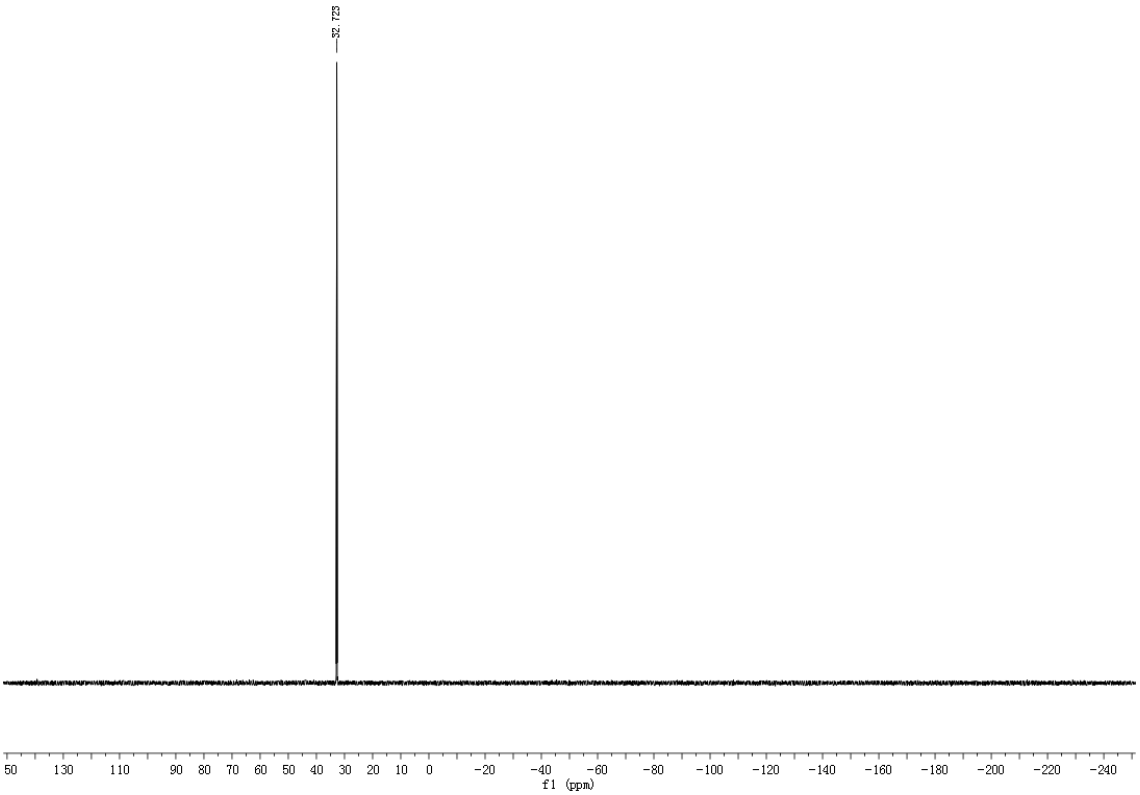
^{1}H NMR

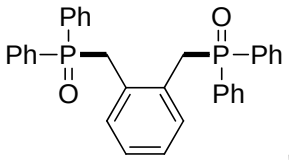


^{13}C NMR



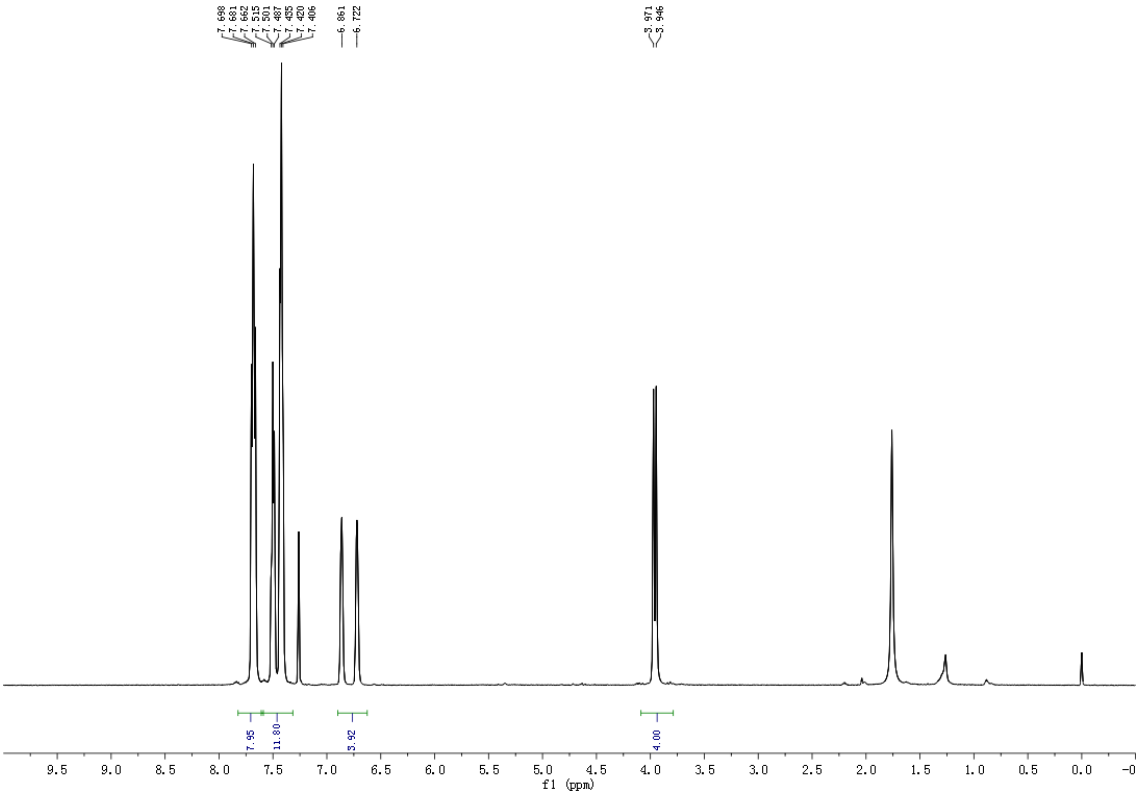
^{31}P NMR



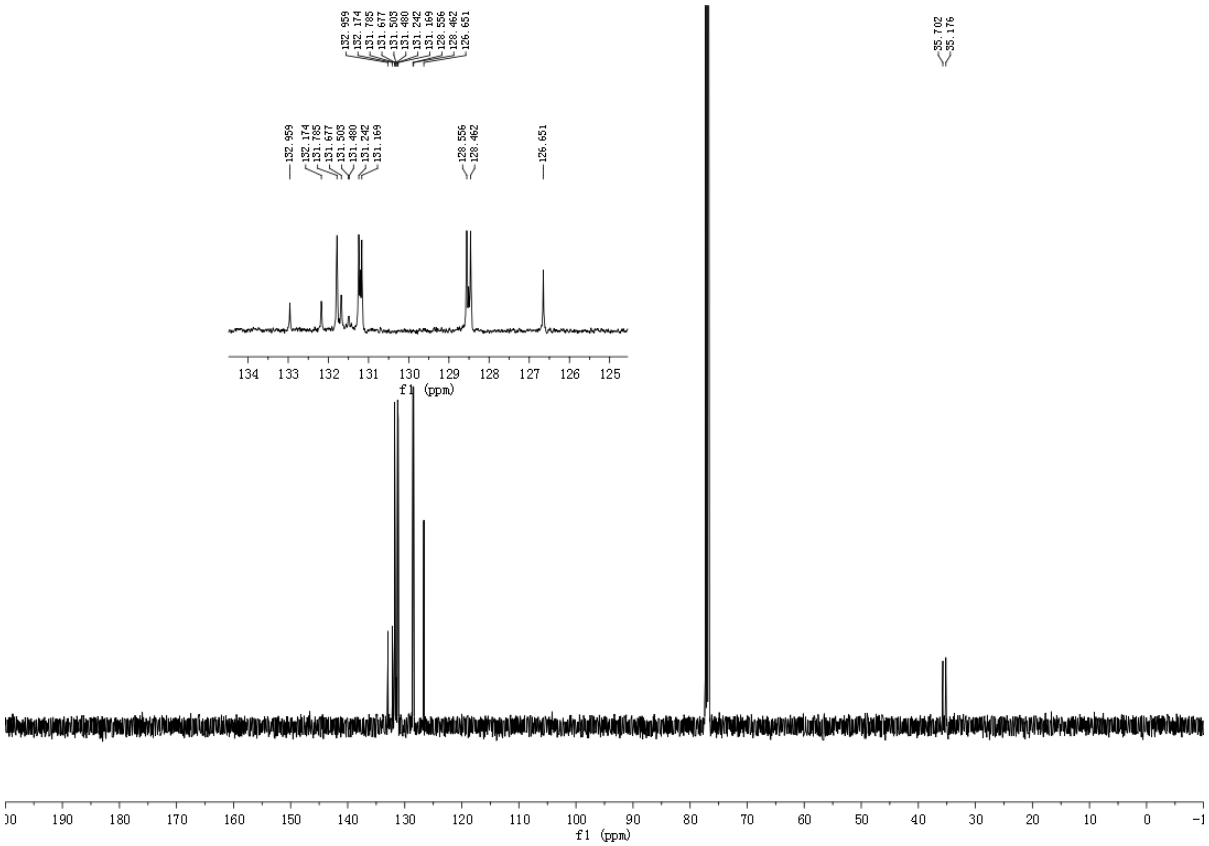


5k

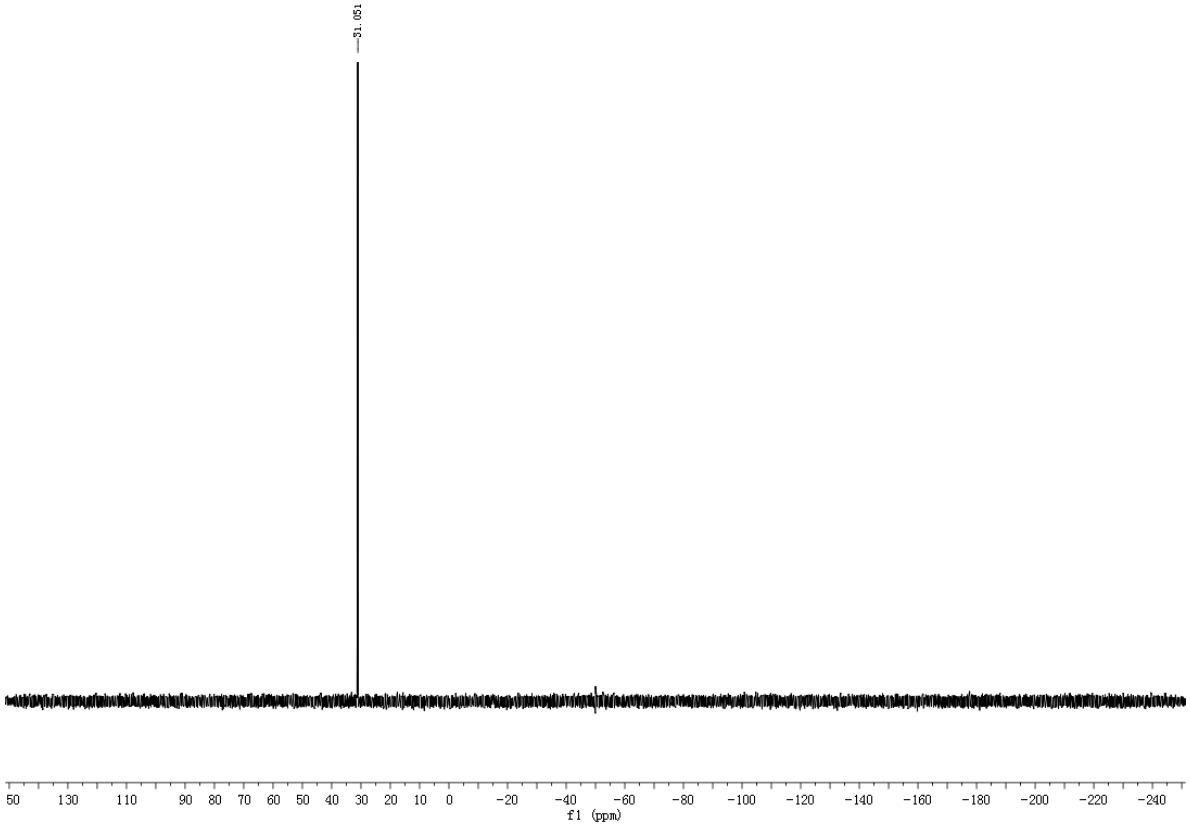
^{1}H NMR

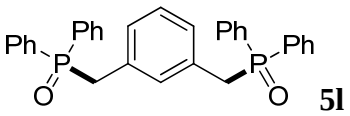


^{13}C NMR



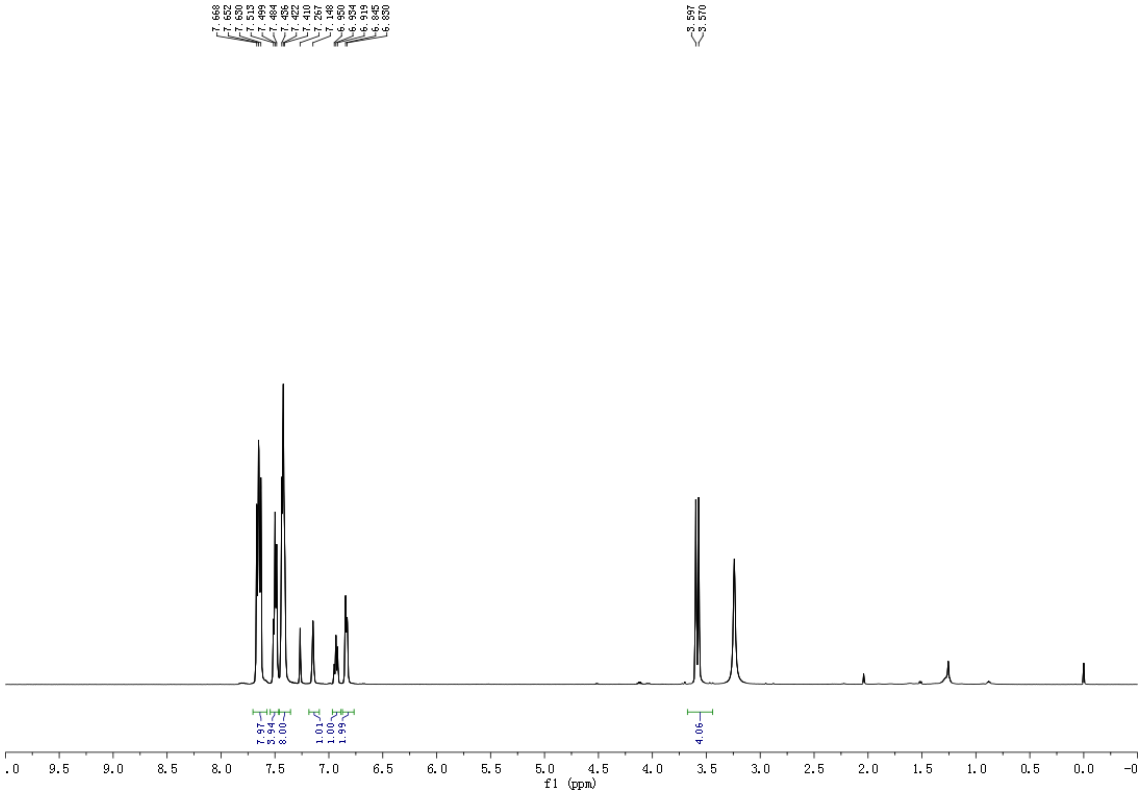
^{31}P NMR



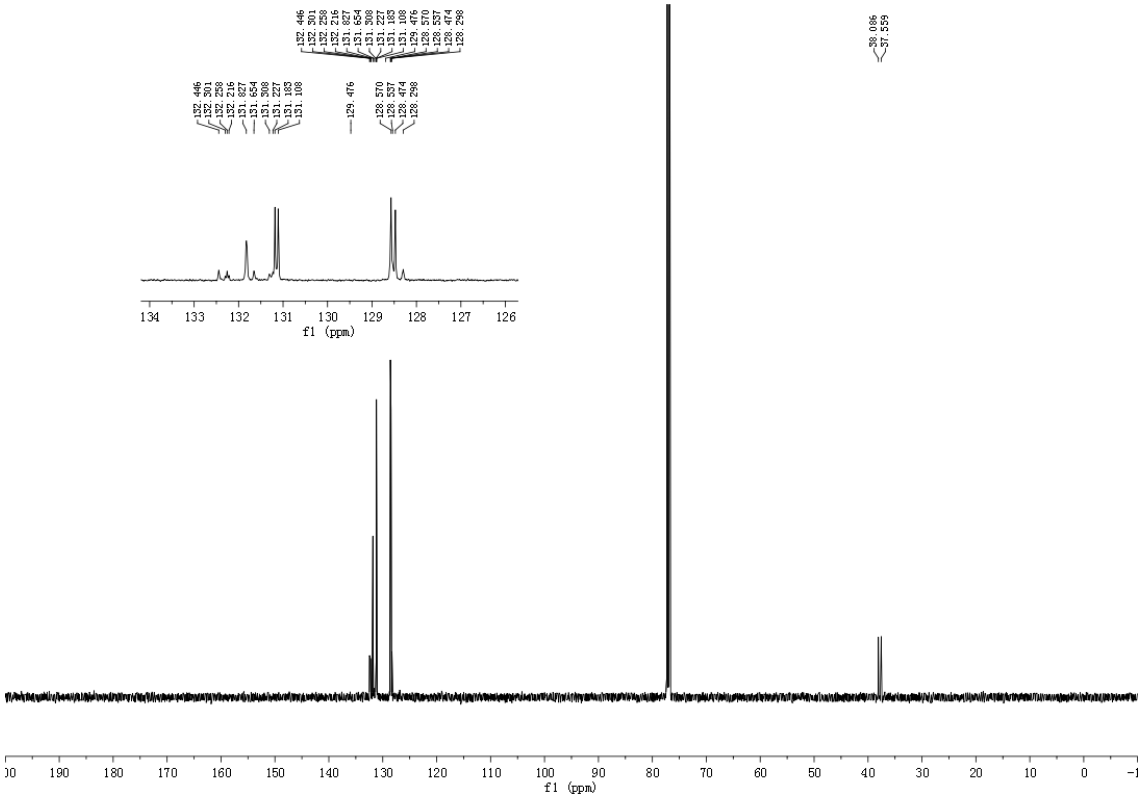


5l

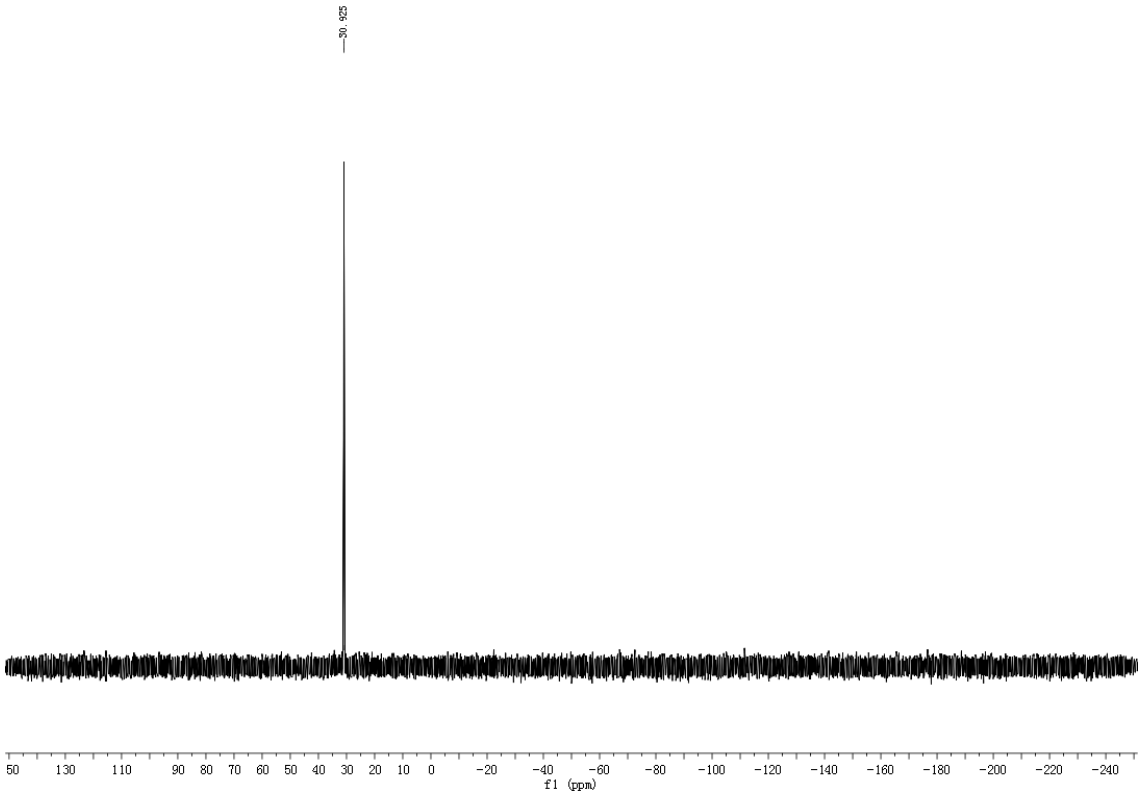
^{1}H NMR

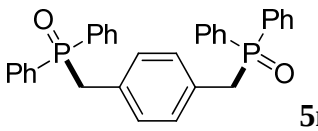


^{13}C NMR



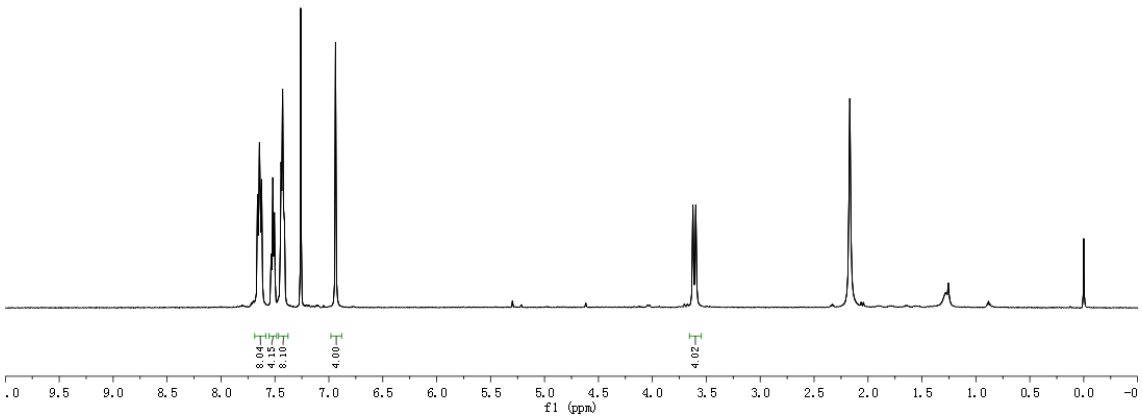
^{31}P NMR



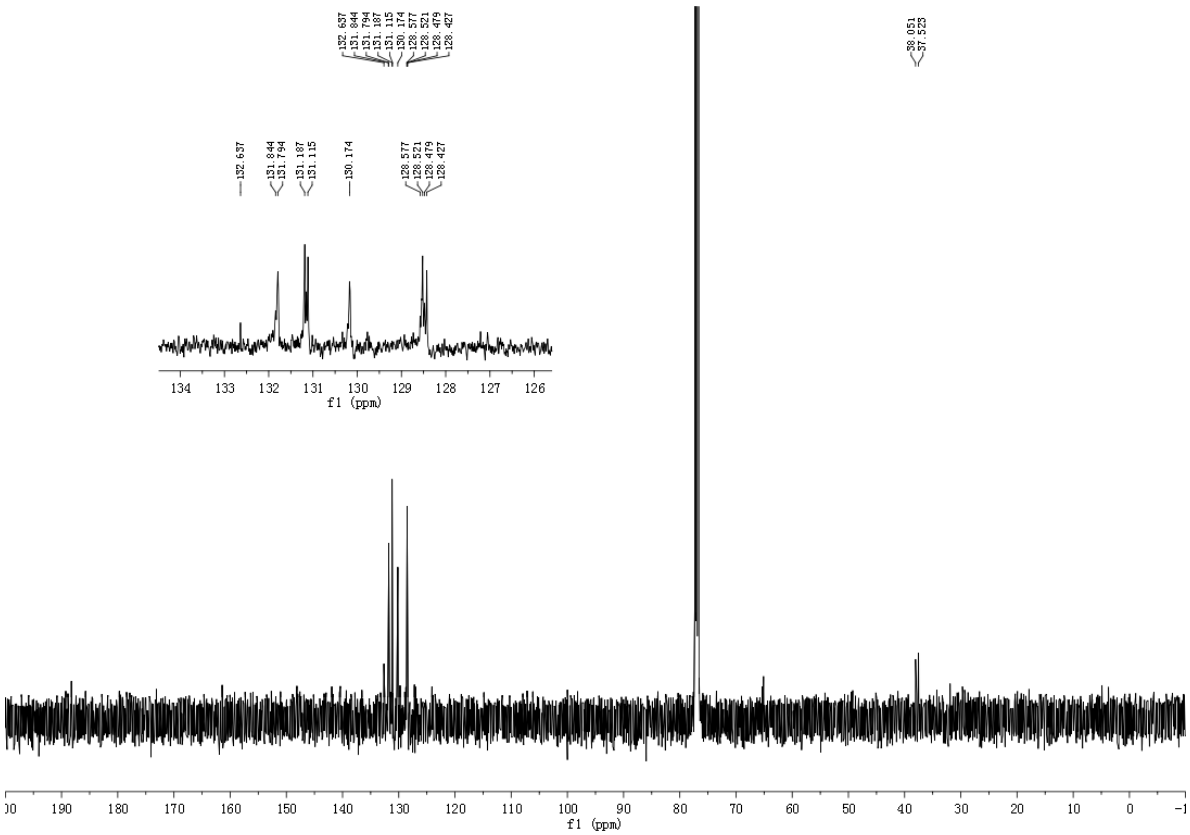


5m

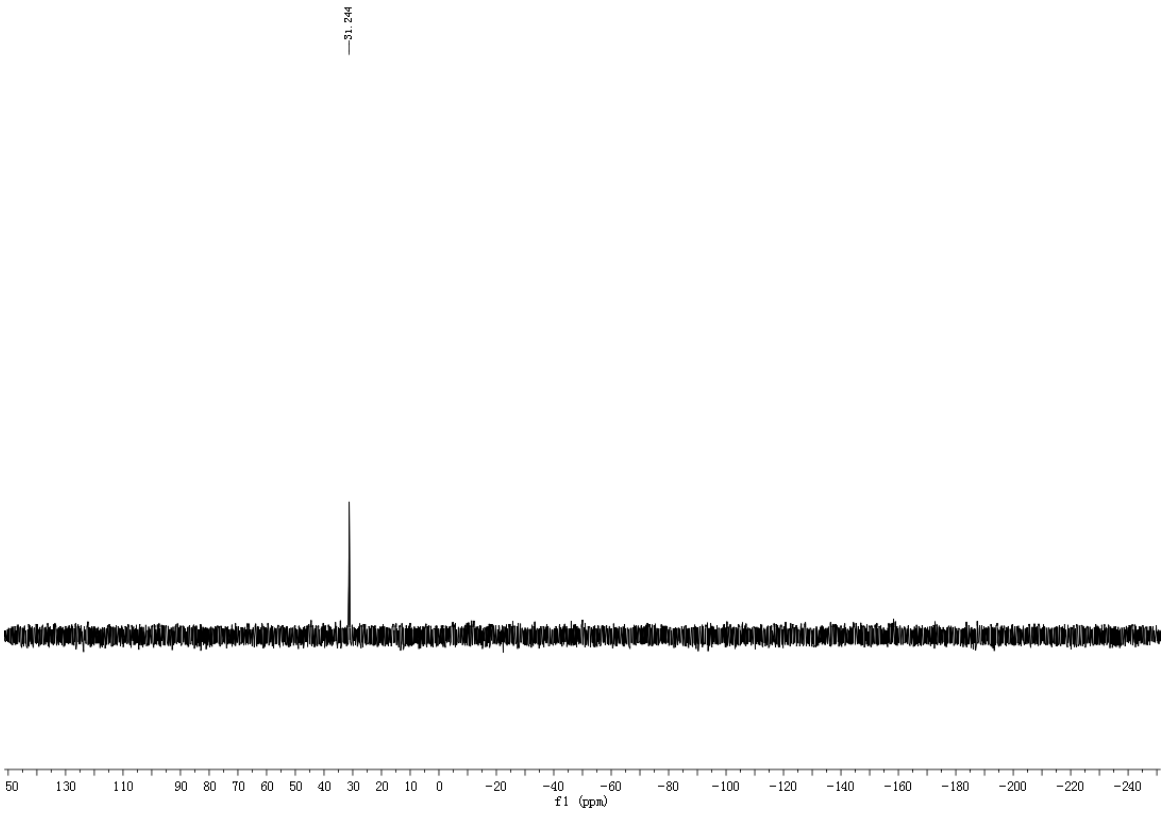
^{1}H NMR

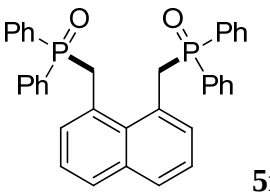


^{13}C NMR



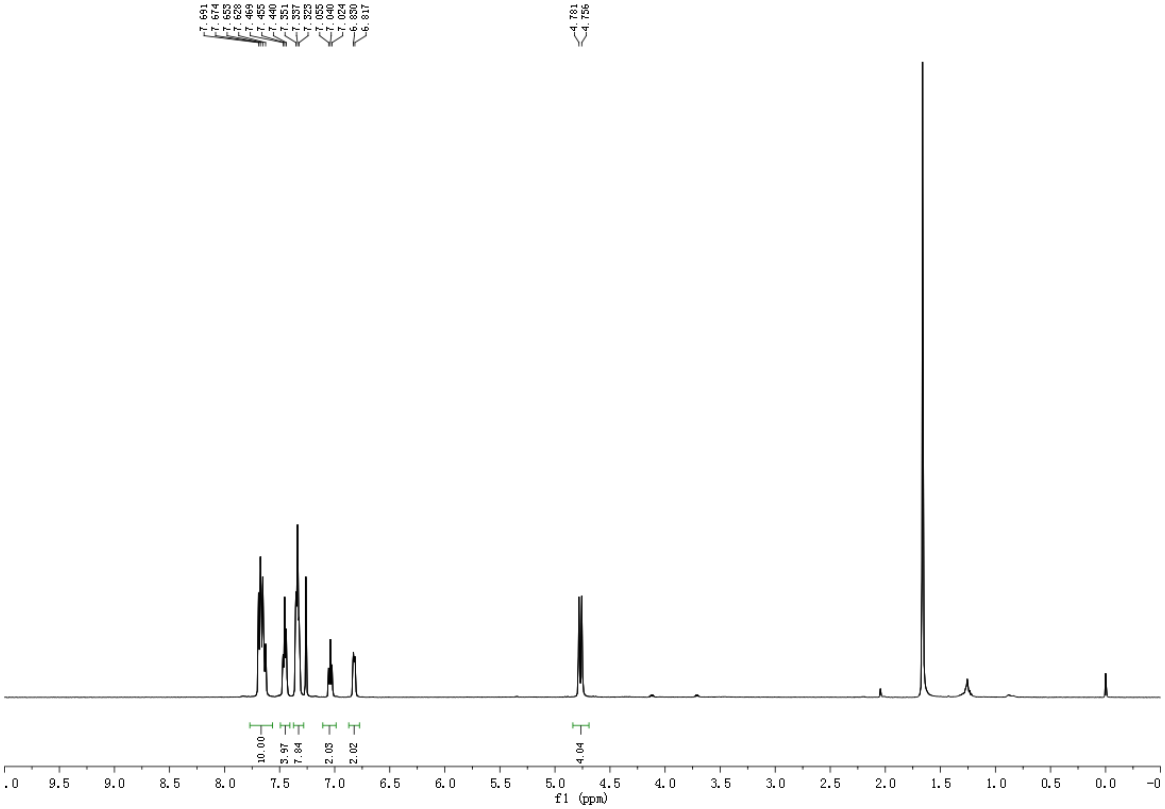
^{31}P NMR



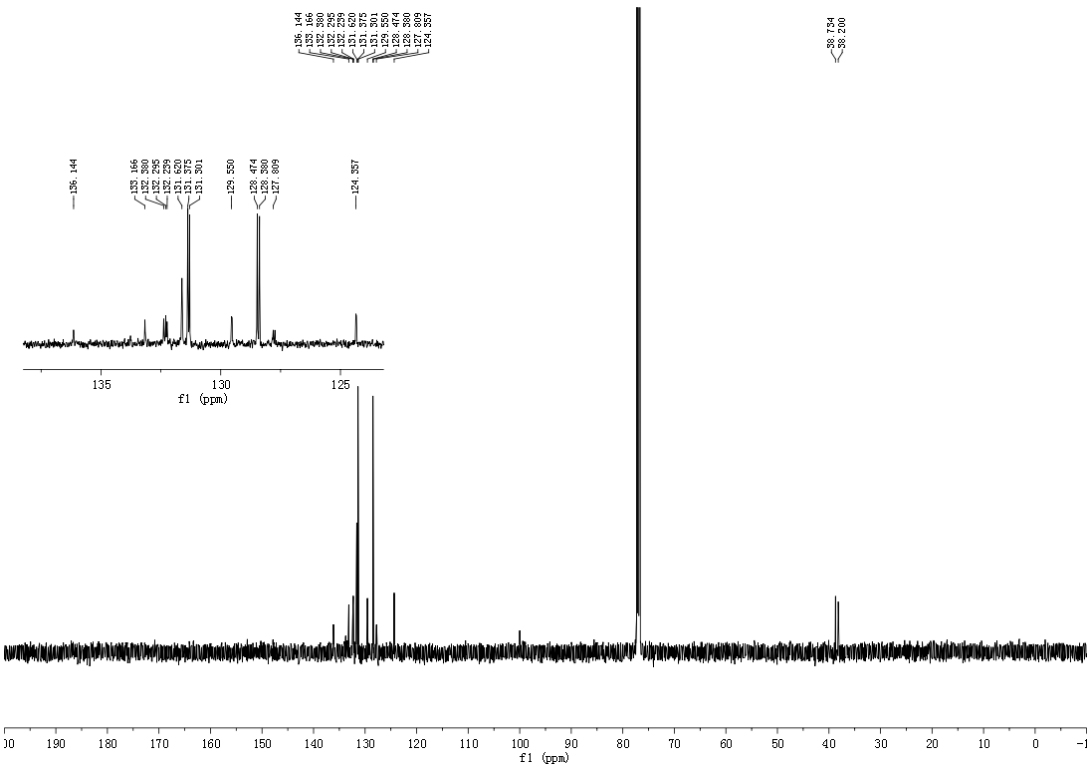


5n

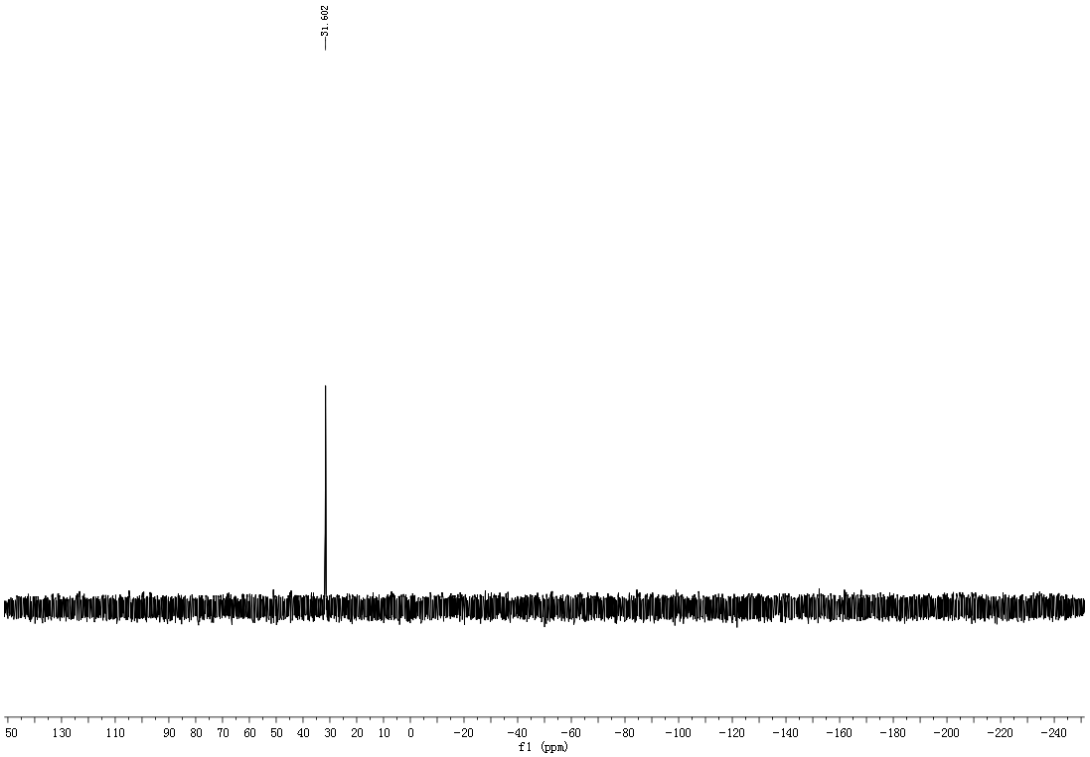
^{1}H NMR

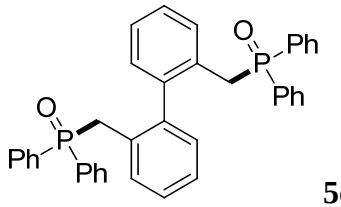


^{13}C NMR



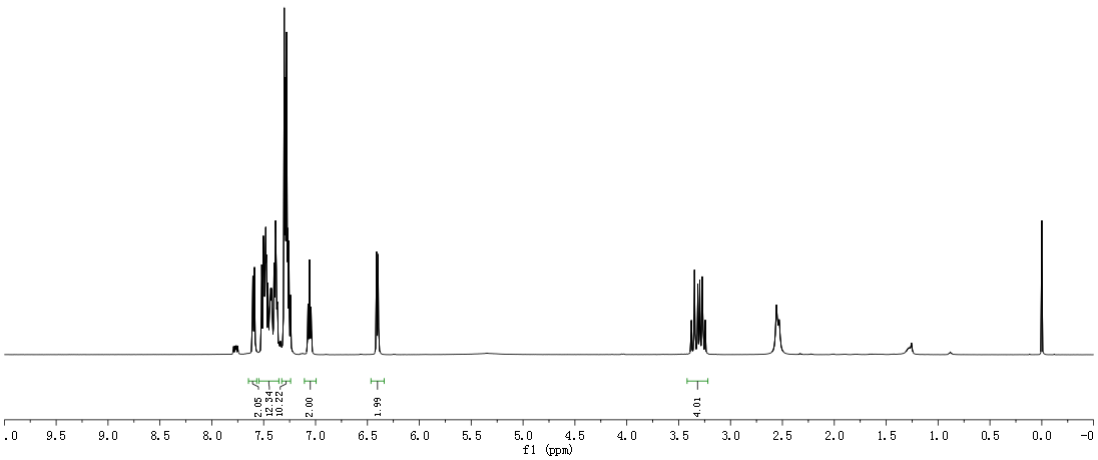
^{31}P NMR



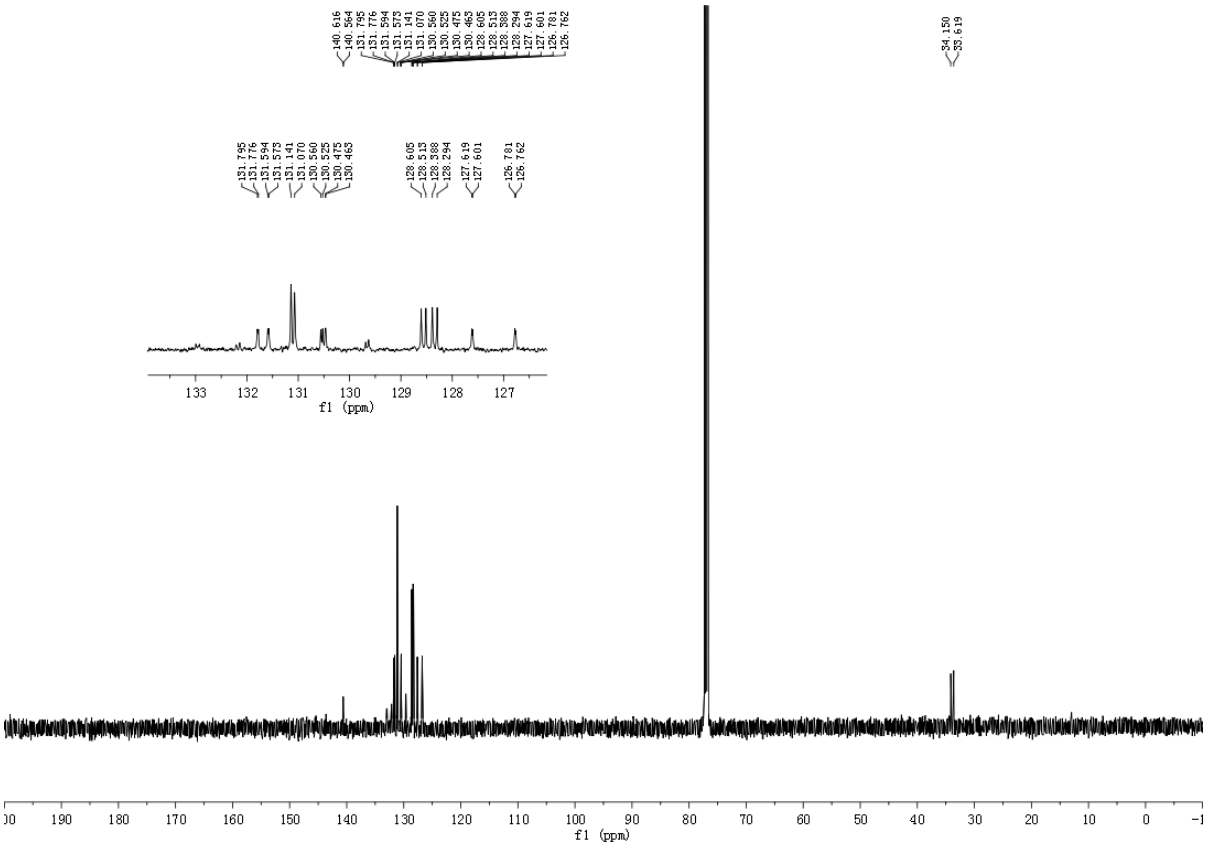


5o

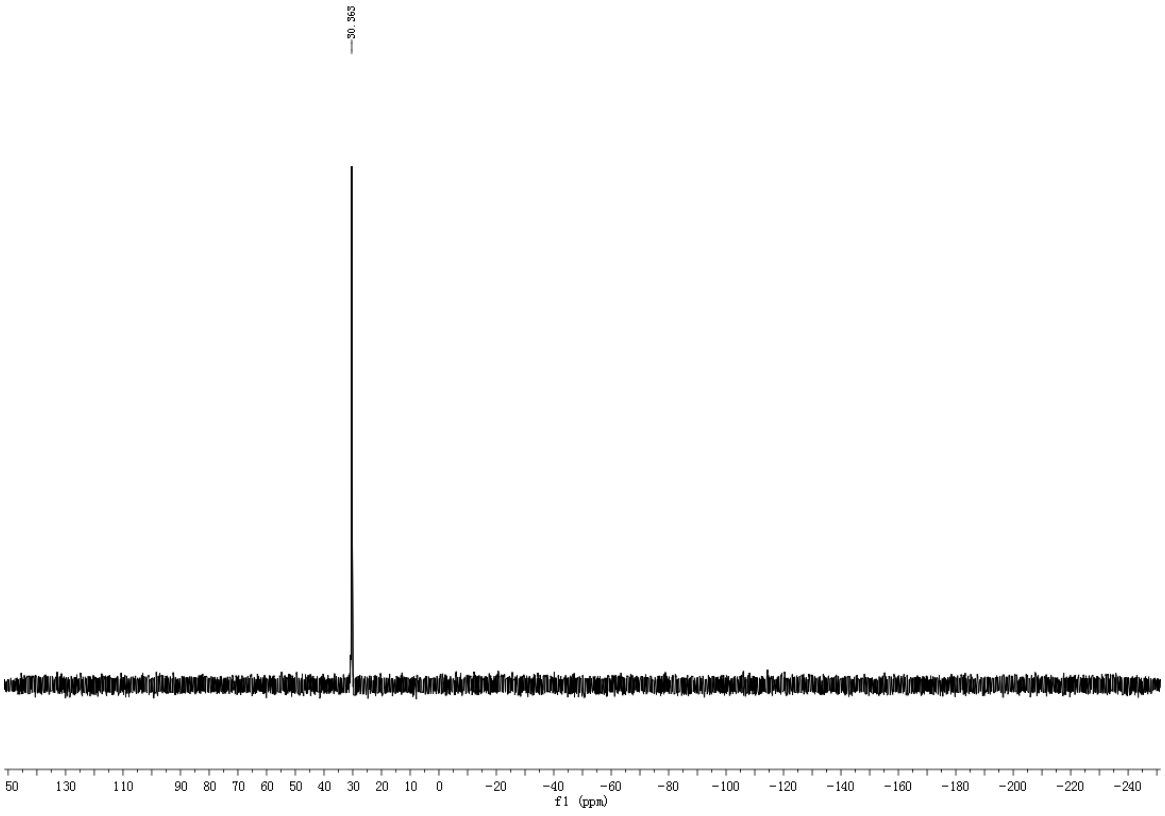
^{1}H NMR

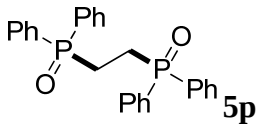


^{13}C NMR



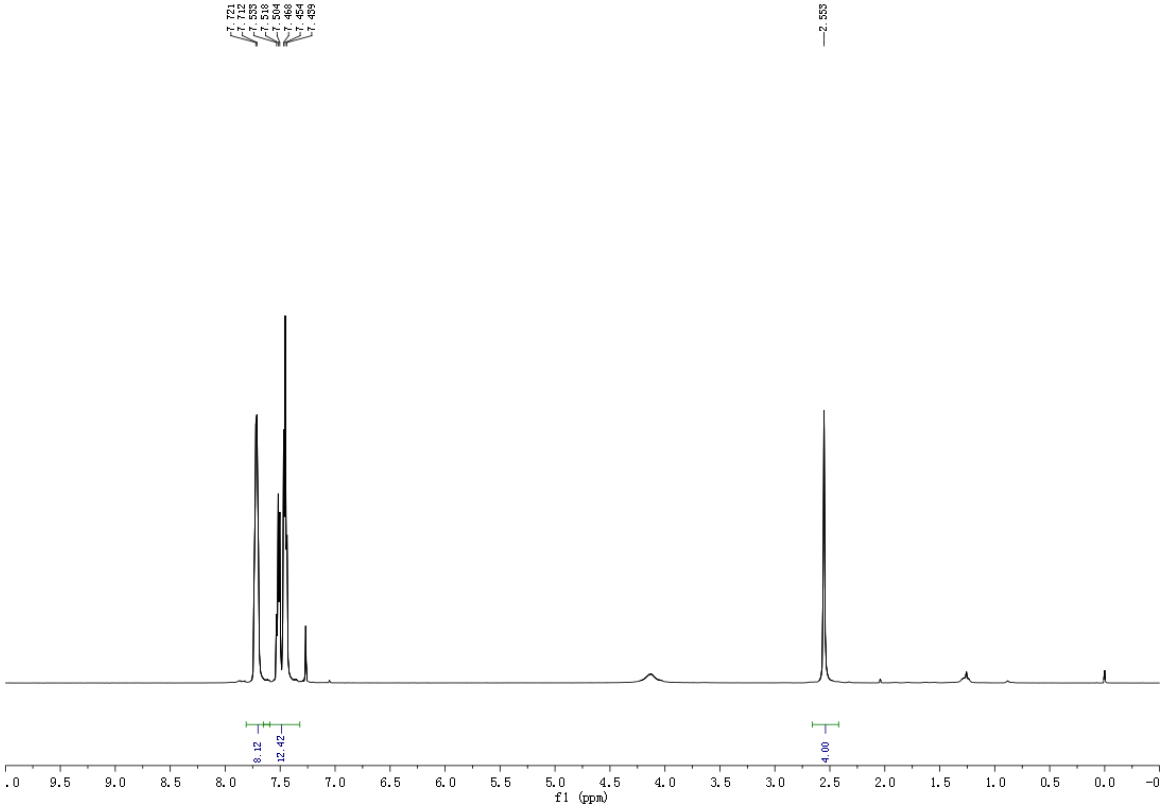
^{31}P NMR



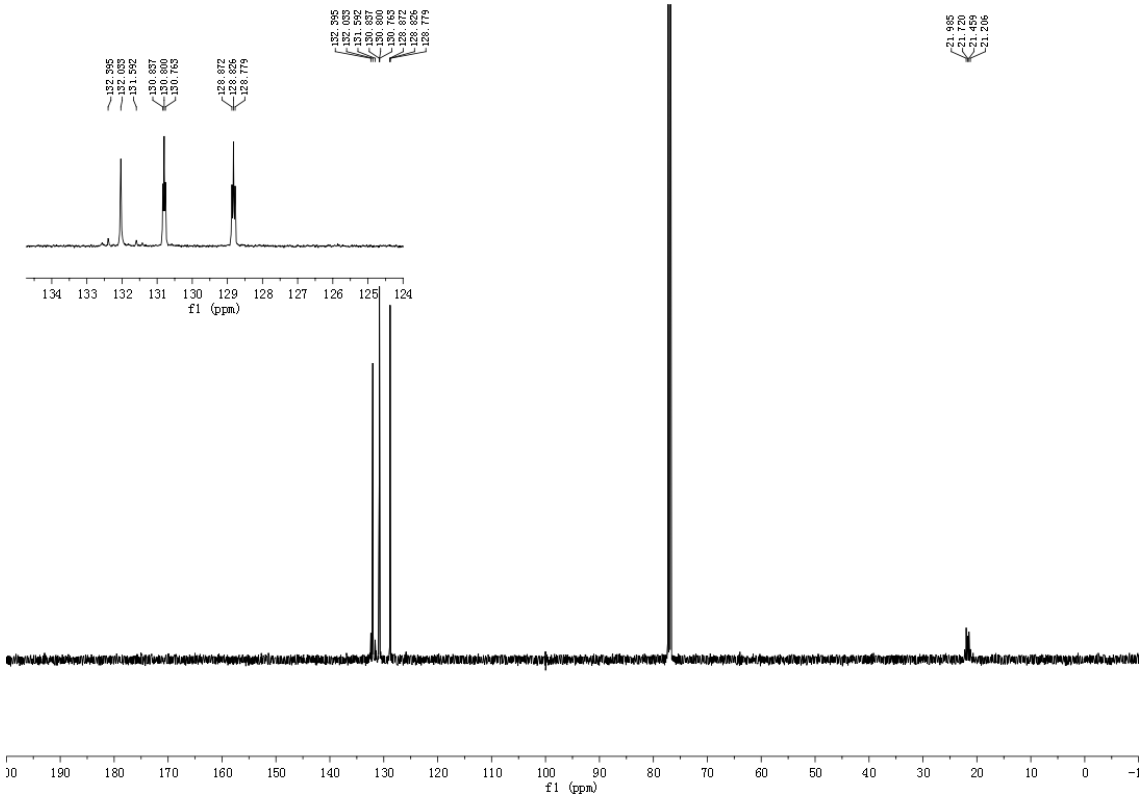


5p

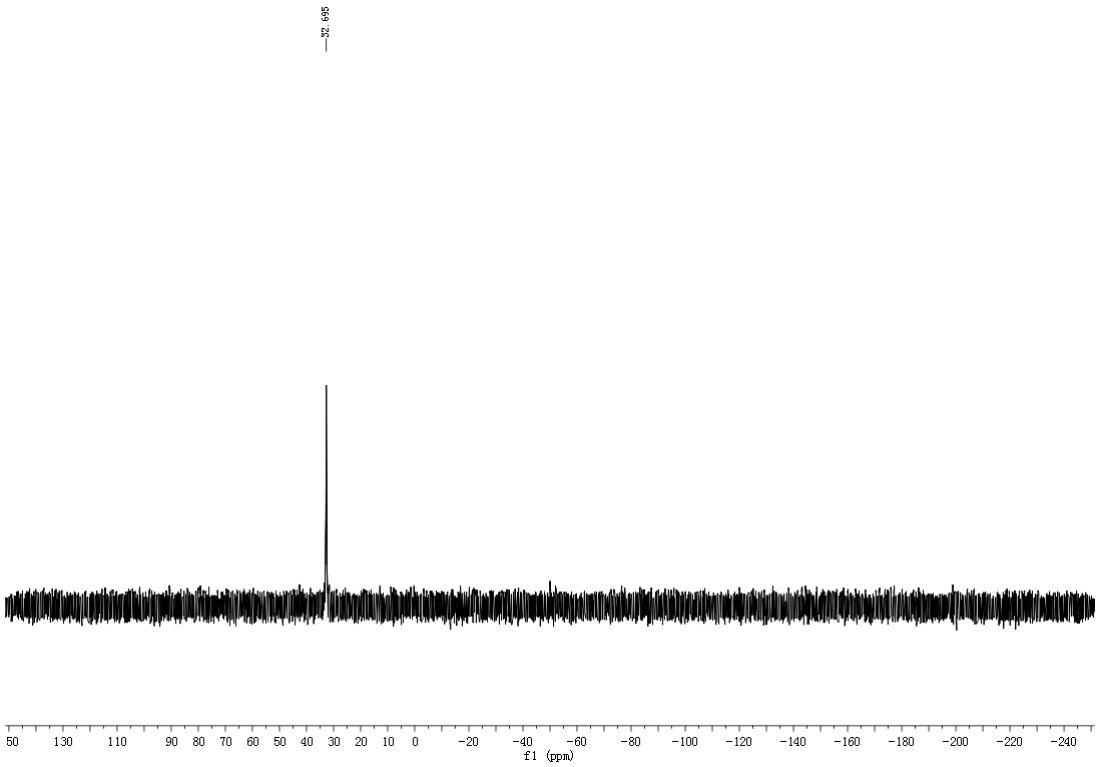
^{1}H NMR

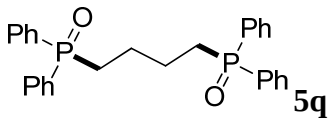


^{13}C NMR



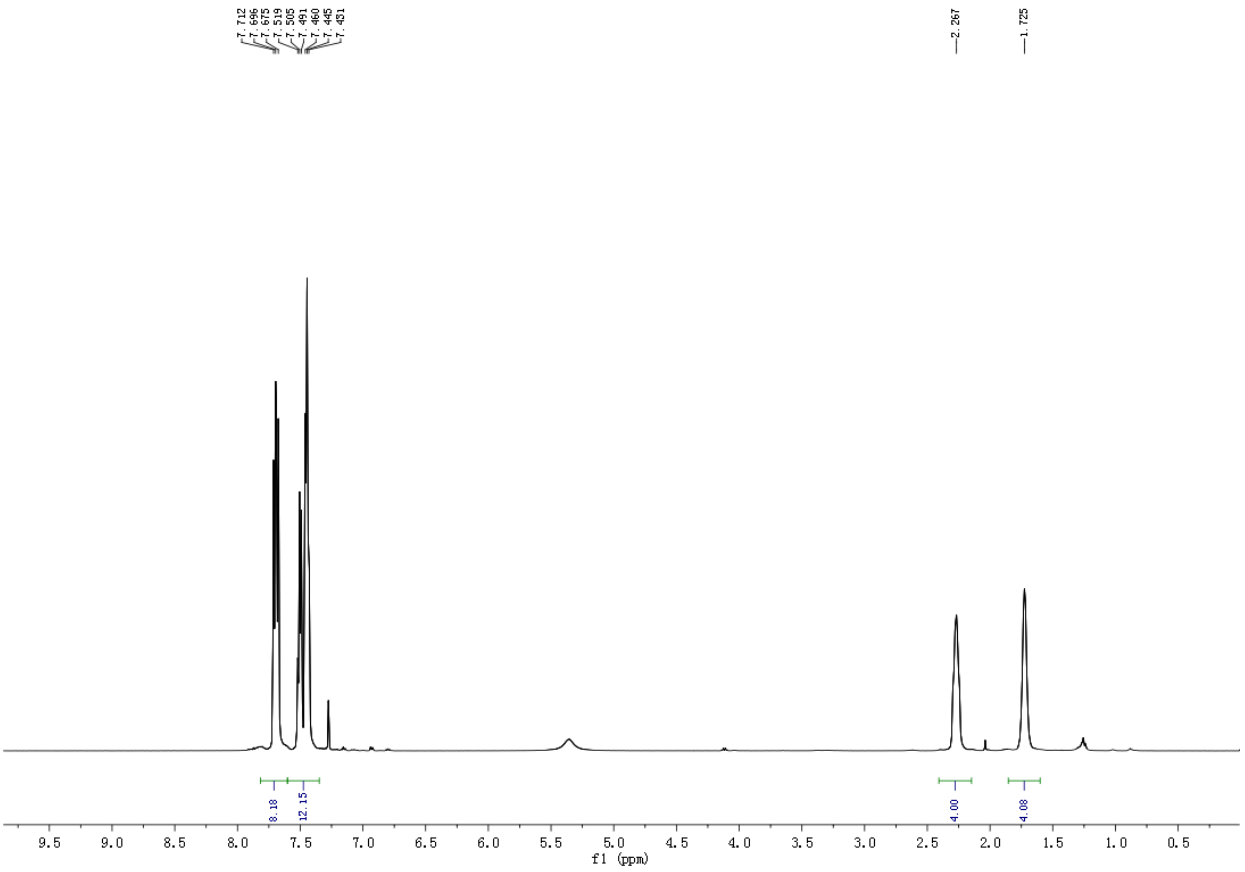
^{31}P NMR



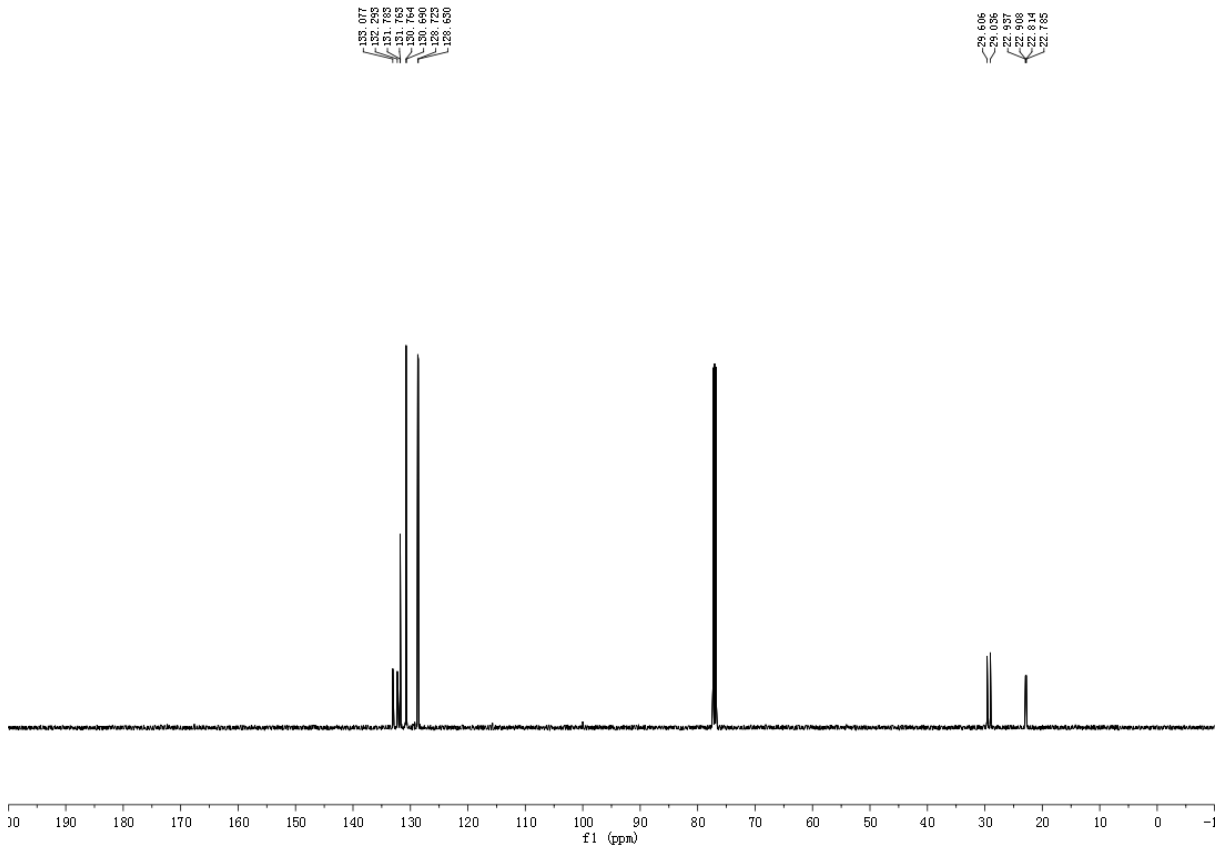


5q

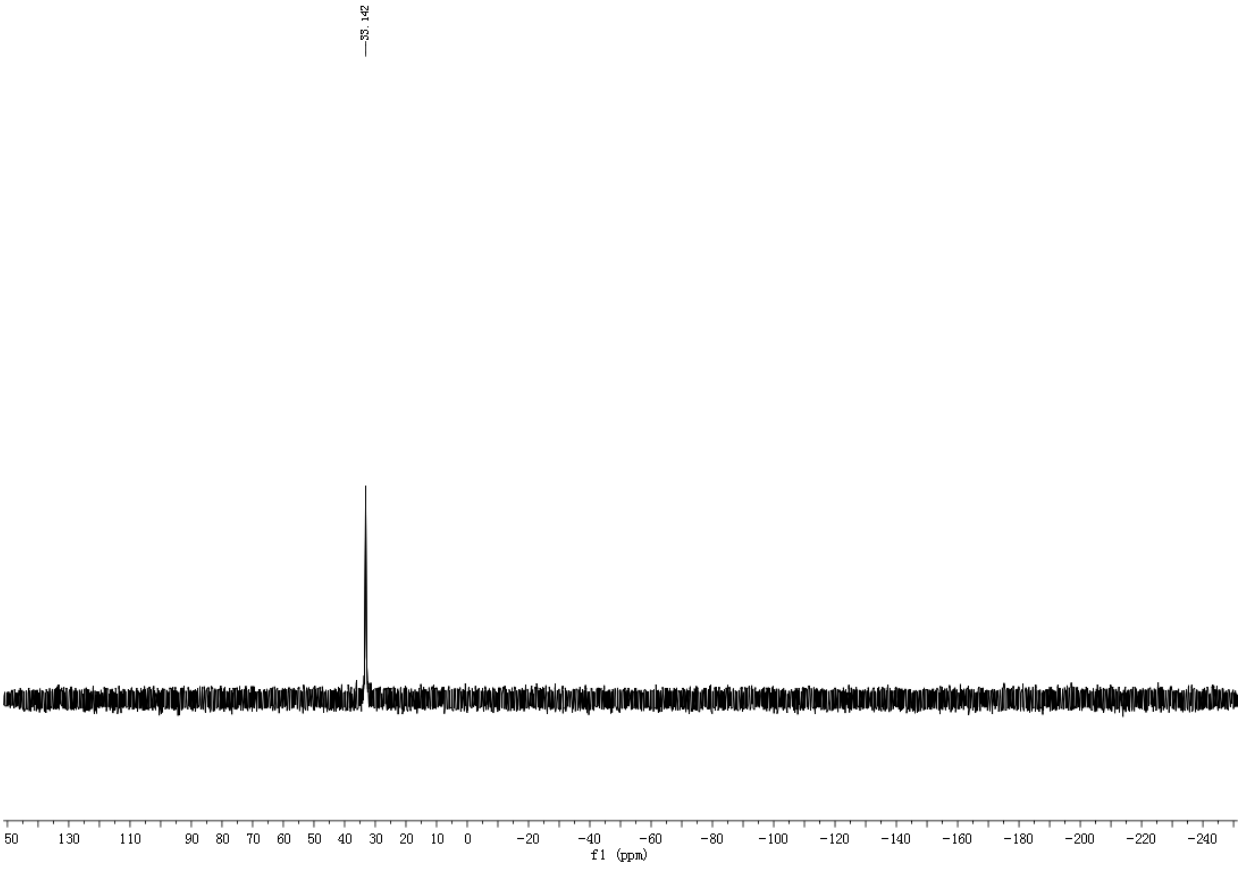
^{1}H NMR

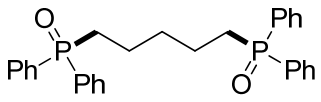


^{13}C NMR



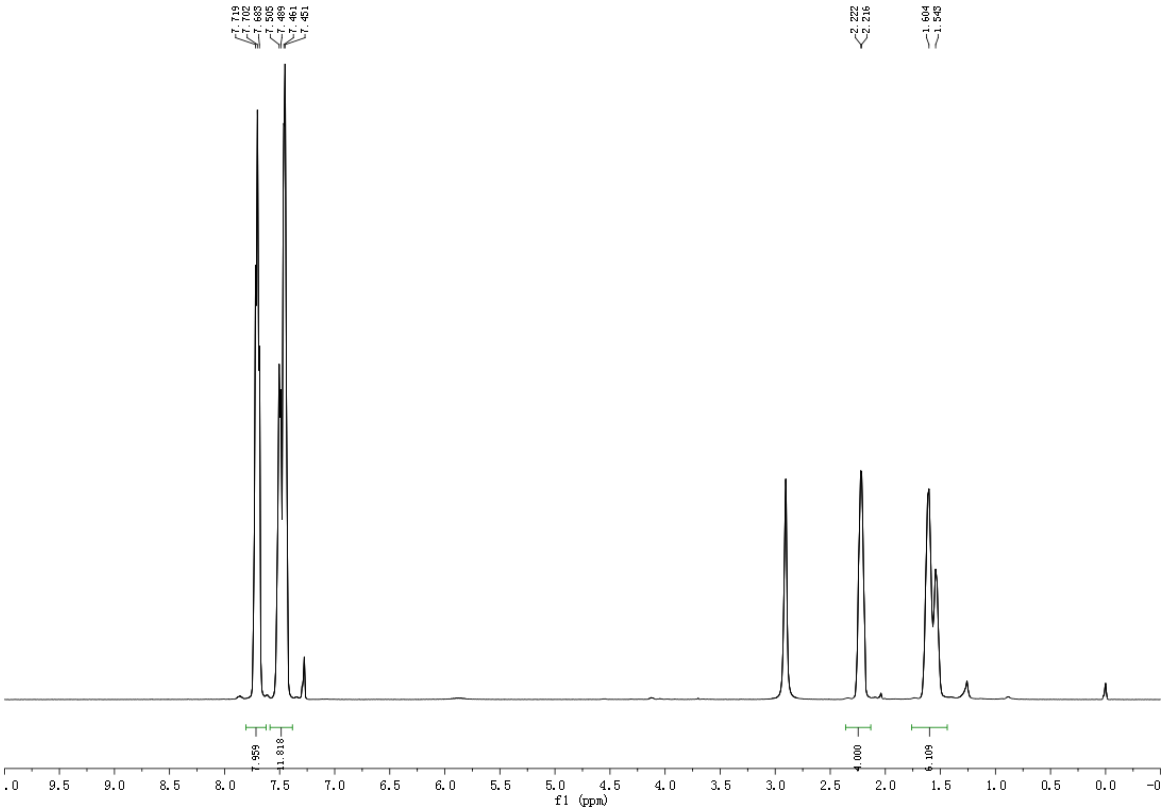
^{31}P NMR



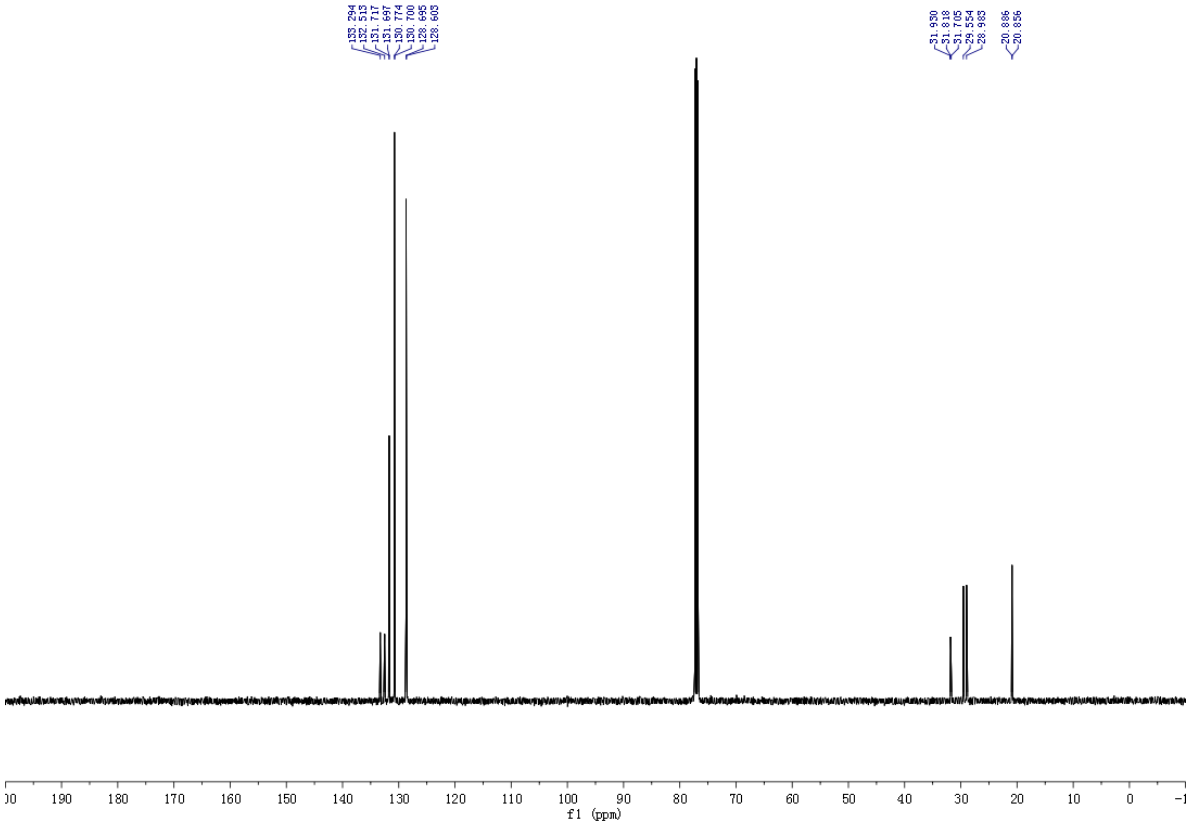


5r

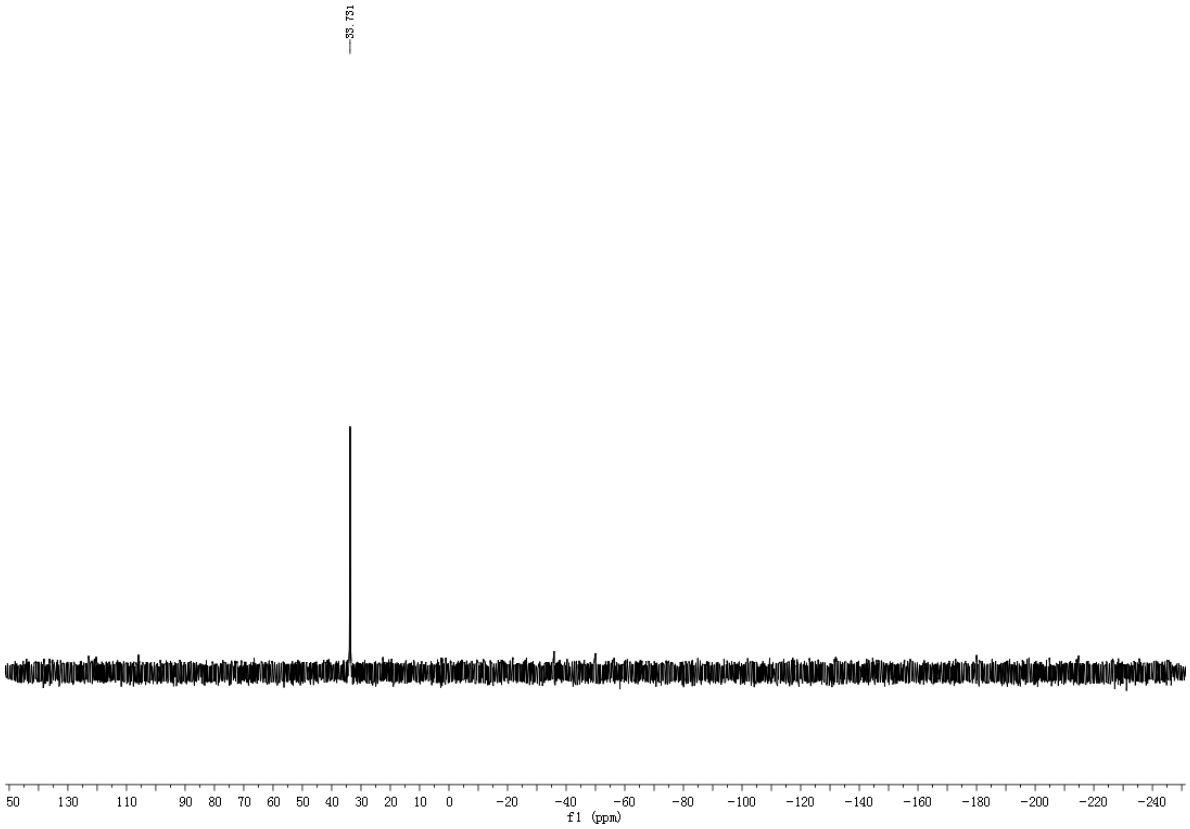
^{1}H NMR

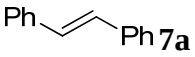


^{13}C NMR



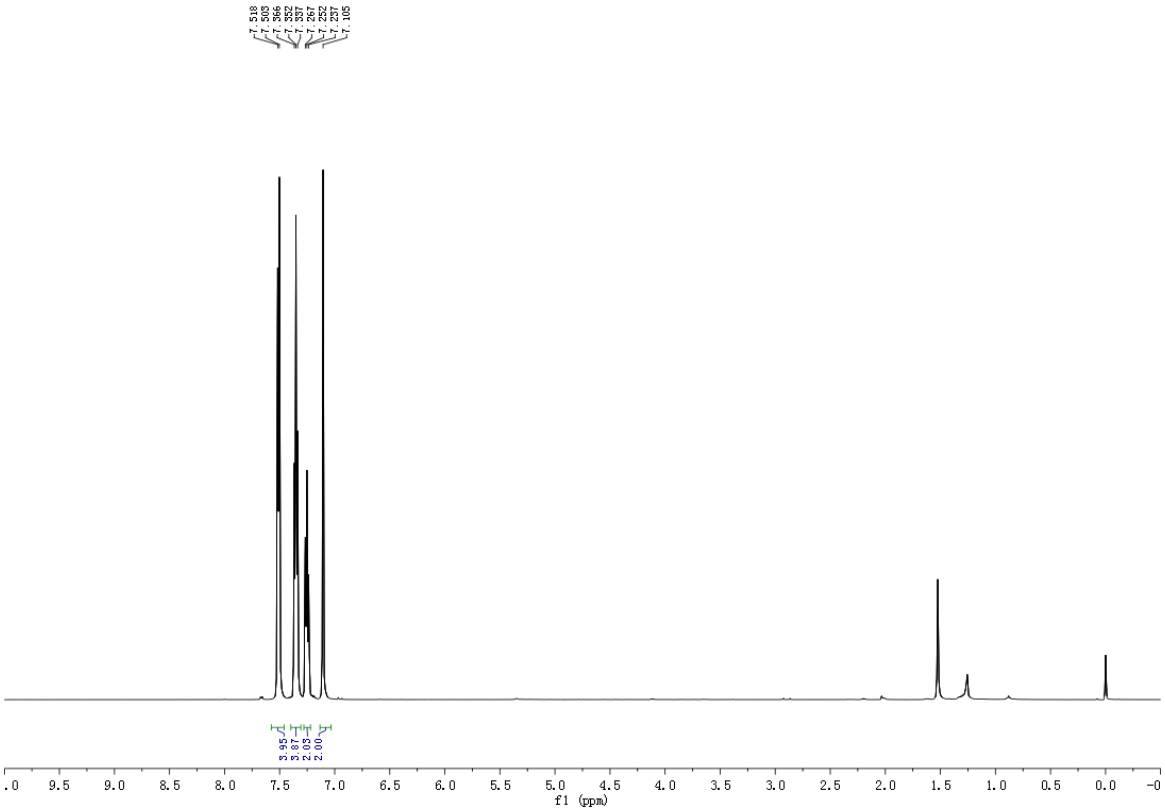
^{31}P NMR


33.791
50 130 110 90 80 70 60 50 40 30 20 10 0 -20 -40 -60 -80 -100 -120 -140 -160 -180 -200 -220 -240
f1 (ppm)

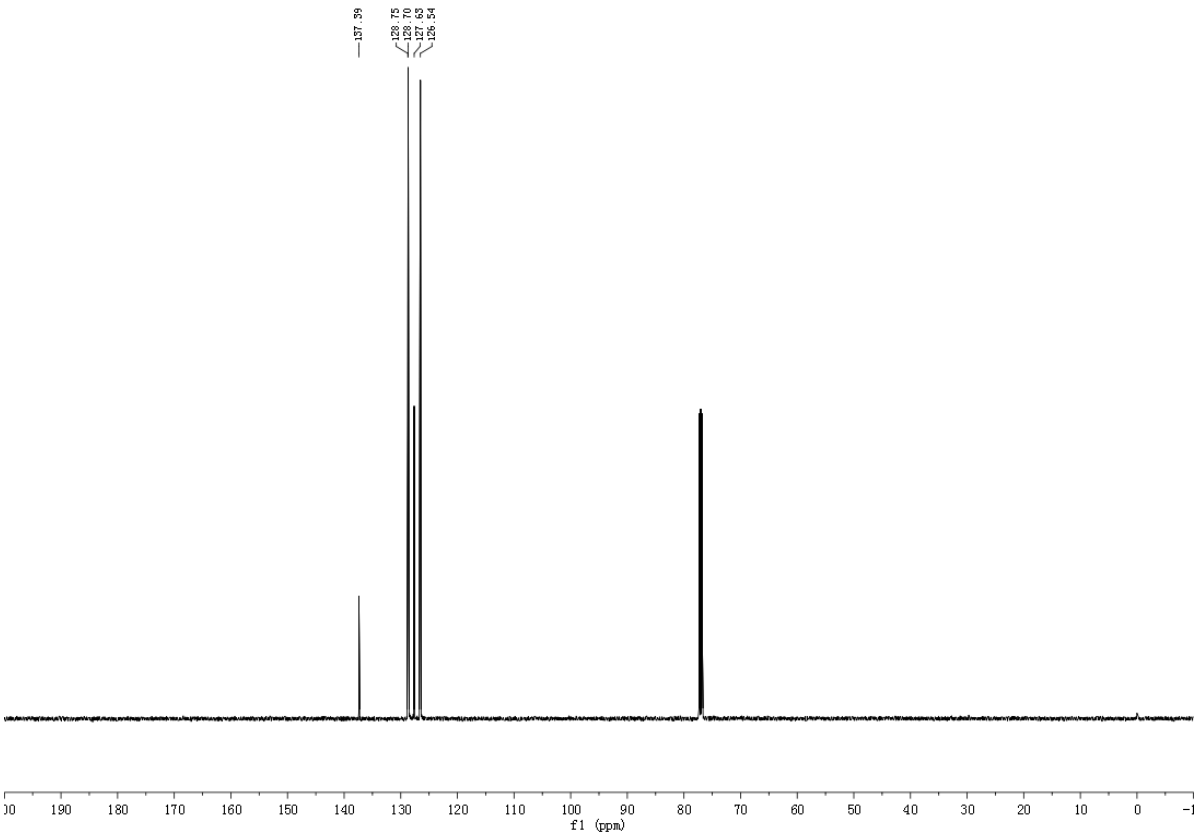


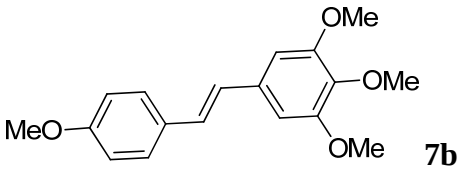
7a

^{1}H NMR



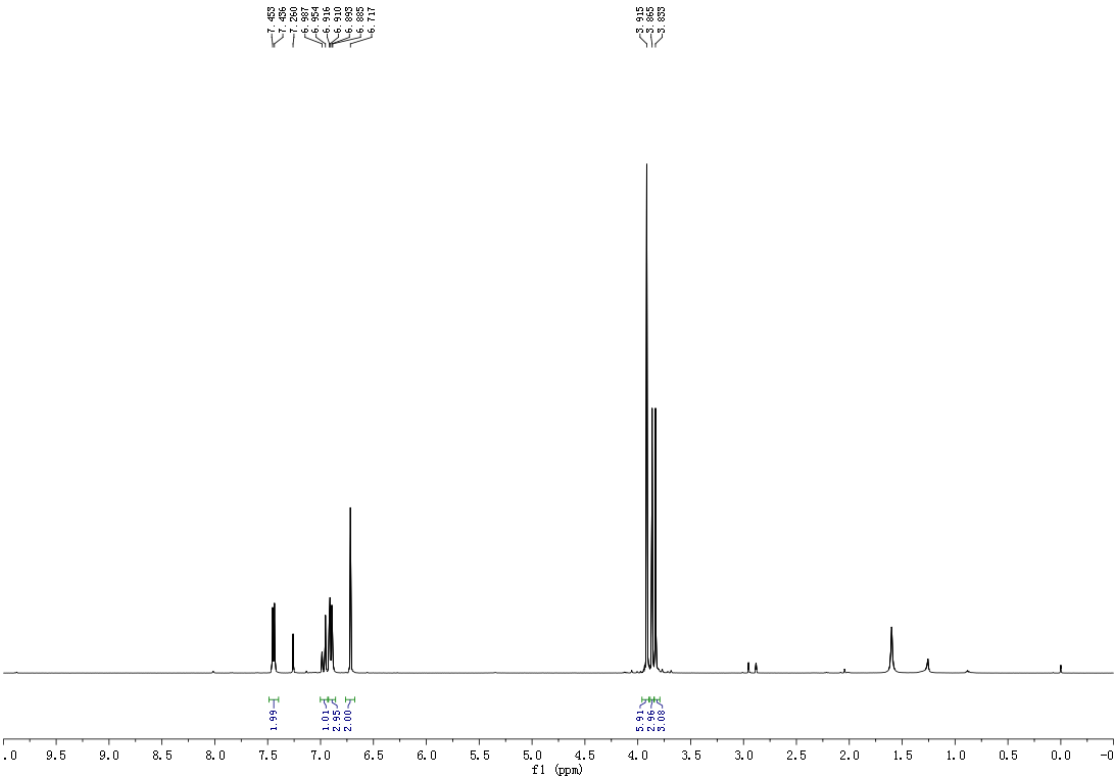
^{13}C NMR



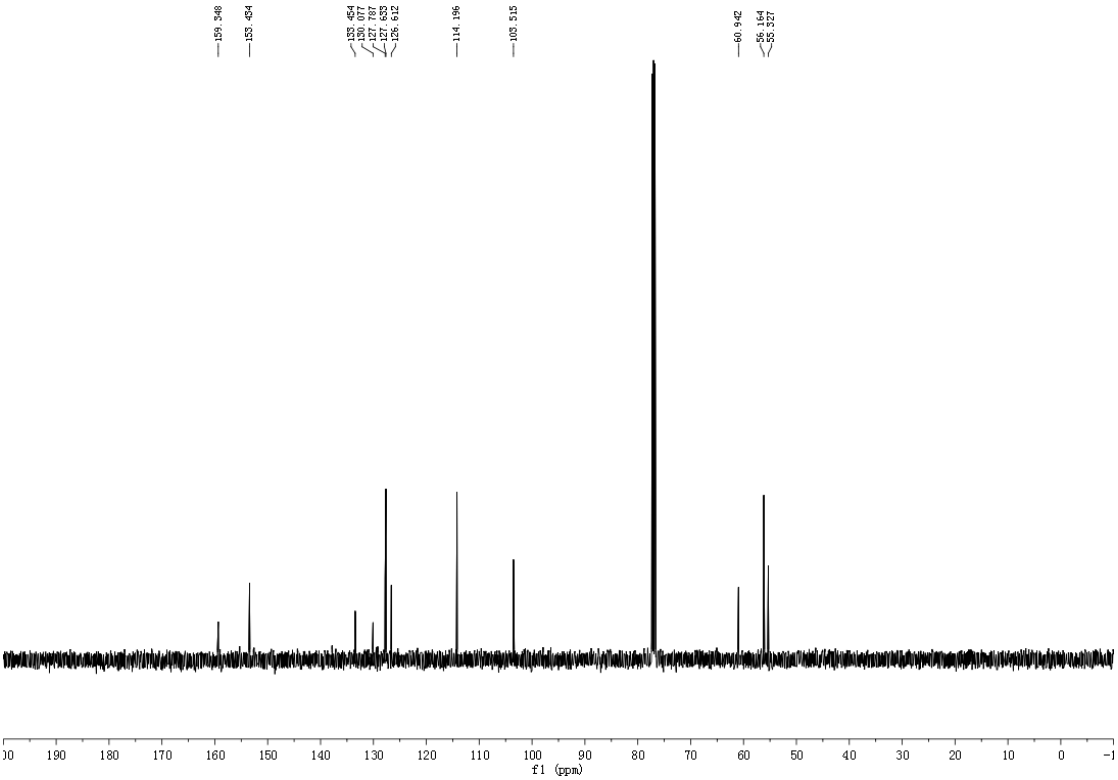


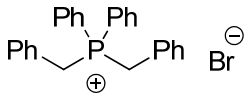
7b

^{1}H NMR

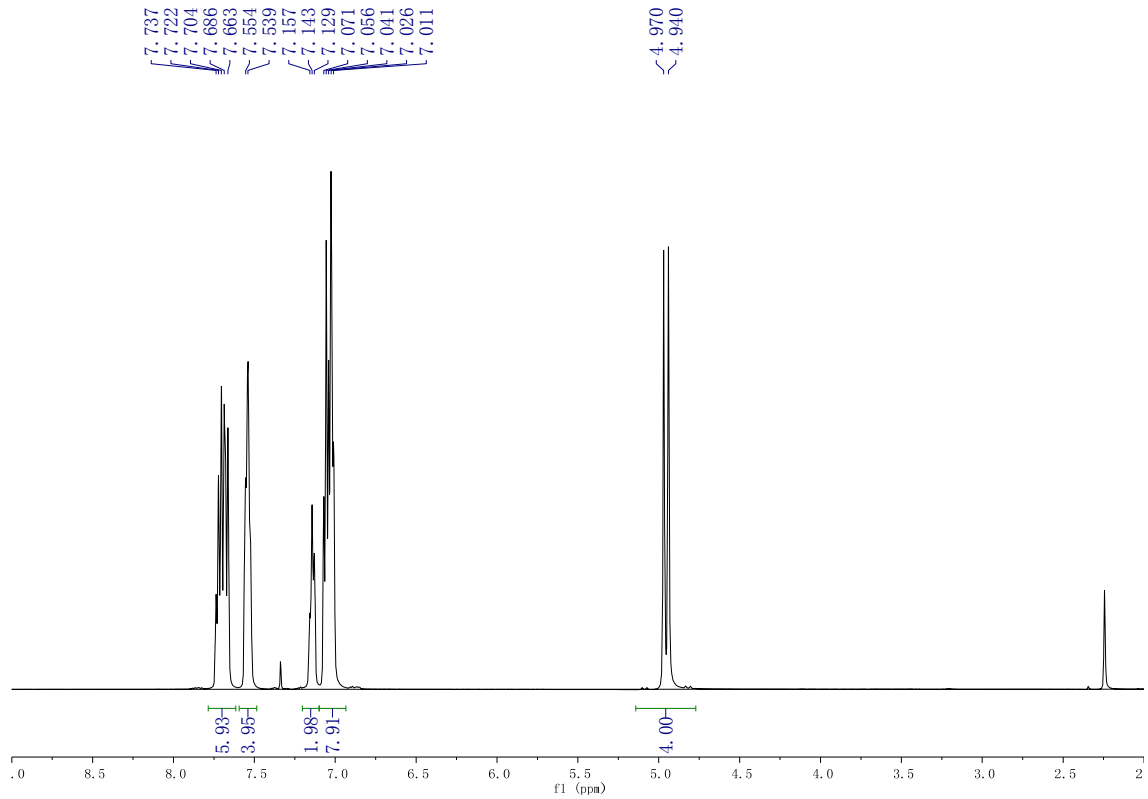


^{13}C NMR

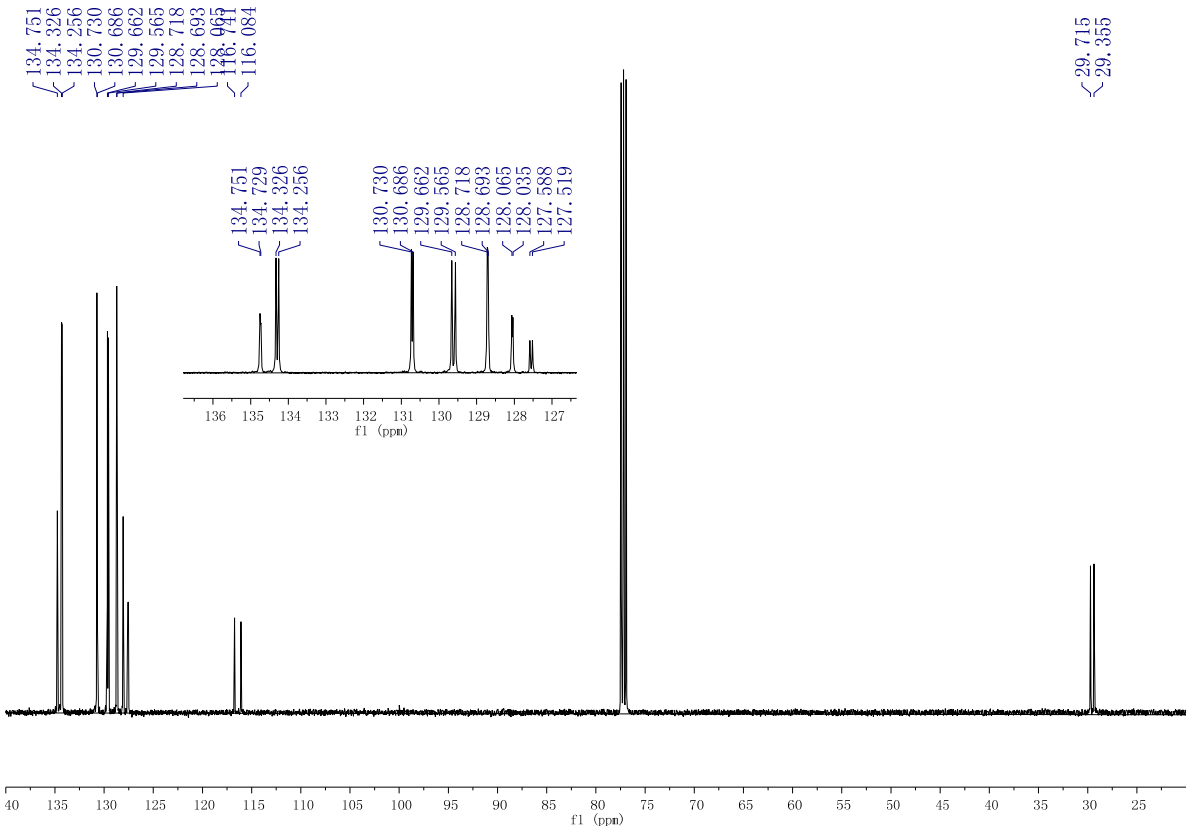




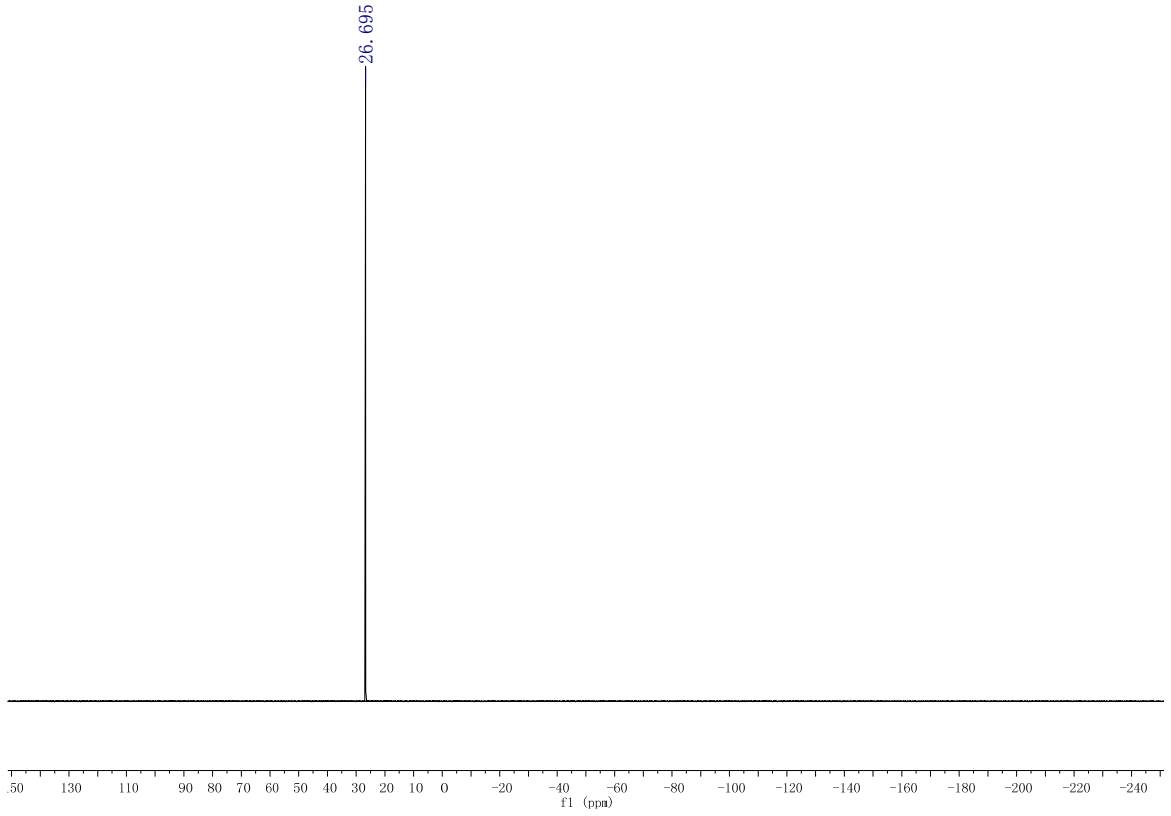
^{1}H NMR



^{13}C NMR



^{31}P NMR


26.695
50 130 110 90 80 70 60 50 40 30 20 10 0 -20 -40 -60 -80 -100 -120 -140 -160 -180 -200 -220 -240
f1 (ppm)