Supporting information

for

Experimental study on the microreactor-assisted synthesis of phosphinic chlorides with varying steric hindrance

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Table S1. Energetics of the phosphine oxide **1** tautomerization at various temperatures (kcal/mol)

temp. [°C]	route	solvent	free substrates	reactant complex	TS 0_1 [ΔG‡]	product complex	free products [ΔG]
25	(**1**)	CCl_4	0.0	---	59.7	---	10.8
		toluene	0.0	---	59.8	---	10.9
		CH_2Cl_2	0.0	---	60.6	---	12.1
		acetonitrile	0.0	---	60.9	---	12.5
	(**2**)	CCl_4	0.0	0.5	33.8	19.1	21.5
		toluene	0.0	0.7	34.0	19.9	21.7
		CH_2Cl_2	0.0	2.2	36.2	22.9	24.1
		acetonitrile	0.0	2.5	37.3	24.1	25.0
60	(**1**)	toluene	0.0	---	59.8	---	10.8
		CH_2Cl_2	0.0	---	60.6	---	12.1
		acetonitrile	0.0	---	60.9	---	12.5

	(**2**)	toluene	0.0	1.8	35.4	20.8	21.7
		CH_2Cl_2	0.0	3.5	37.7	24.3	24.1
		acetonitrile	0.0	3.8	38.8	25.4	25.0
100	(**1**)	toluene	0.0	---	59.8	---	10.8
	(**2**)		0.0	3.3	37.1	22.3	21.7

Table S2. Energetics of the phosphine oxide **3** tautomerization at various temperatures (kcal/mol).

temp. [°**C**]	route	solvent	free substrates	reactant complex	TS 0_1 [$\Delta G^{\ddagger}$]	product complex	free products [ΔG]
25	(**1**)	CCl_4	0.0	---	60.0	---	11.4
		toluene	0.0	---	60.1	---	11.5
		CH_2Cl_2	0.0	---	61.0	---	12.9
		acetonitrile	0.0	---	61.2	---	13.3
	(**2**)	CCl_4	0.0	-1.1	32.8	18.9	22.8
		toluene	0.0	-1.5	32.9	19.2	23.0
		CH_2Cl_2	0.0	1.5	35.9	23.2	25.8
		acetonitrile	0.0	2.3	36.8	24.0	26.7
60	(**1**)	CH_2Cl_2	0.0	---	61.0	---	12.9
		acetonitrile	0.0	---	61.2	---	13.3
	(**2**)	CH_2Cl_2	0.0	3.0	37.5	24.7	25.8
		acetonitrile	0.0	3.9	38.5	25.5	26.6
100	(**1**)	CCl_4	0.0	---	60.0	---	11.4
		toluene	0.0	---	59.8	---	10.8
		CH_2Cl_2	0.0	---	61.0	---	12.9
		acetonitrile	0.0	---	61.2	---	13.3
	(**2**)	CCl_4	0.0	1.8	36.3	22.0	22.7
		toluene	0.0	1.3	36.4	22.3	22.9
		CH_2Cl_2	0.0	4.6	39.5	26.4	25.8
		acetonitrile	0.0	5.7	40.4	27.1	26.6
110	(**1**)	acetonitrile	0.0	---	61.2	---	13.3
	(**2**)		0.0	6.1	40.9	27.5	26.6
120	(**1**)	toluene	0.0	---	60.0	---	11.4
	(**2**)		0.0	2.0	37.3	23.2	22.9
140	(**1**)	toluene	0.0	---	60.0	---	11.4
	(**2**)		0.0	2.8	38.2	24.0	22.8

Table S3. Energetics of the phosphine oxide **2** tautomerization at various temperatures (kcal/mol).

temp. [°C]	route	solvent	free substrates	reactant complex	TS 0_1 [$\Delta G^{\ddagger}$]	product complex	free products [ΔG]
25	(**1**)	CCl_4	0.0	---	59.5	---	9.8
		toluene	0.0	---	59.6	---	9.9
		CH_2Cl_2	0.0	---	60.4	---	10.9
		acetonitrile	0.0	---	60.6	---	11.3
	(**2**)	CCl_4	0.0	-2.0	31.9	16.2	19.5
		toluene	0.0	-1.8	32.1	16.5	19.8
		CH_2Cl_2	0.0	0.0	33.5	19.6	21.9
		acetonitrile	0.0	0.1	34.0	20.5	22.5
60	(**1**)	CH_2Cl_2	0.0	---	63.3	---	10.8
		acetonitrile	0.0	---	60.6	---	11.3

	(**2**)	CH_2Cl_2	0.0	1.6	35.1	21.2	21.7
		acetonitrile	0.0	1.6	35.7	22.6	22.6
80	(**1**)	CH_2Cl_2	0.0	---	63.3	---	10.9
	(**2**)		0.0	2.4	36.1	22.1	21.8
100	(**1**)	CCl_4	0.0	---	59.6	---	9.8
		toluene	0.0	---	59.7	---	9.9
		acetonitrile	0.0	---	60.6	---	11.2
	(**2**)	CCl_4	0.0	1.3	35.7	19.8	19.6
		toluene	0.0	1.5	36.0	20.1	19.8
		acetonitrile	0.0	3.2	37.6	24.5	22.4

Table S4. Energetics of the reaction of phosphine oxide **1** with CCl_4 at various temperatures (kcal/mol).

temp. [°**C**]	solvent	free substrates	reactant complex	TS 1_1 [ΔG‡]	$P^{(V)}$ compound	TS 2_1 [ΔG‡]	product complex	free products [ΔG]
25	CCl_4	0.0	3.5	51.6	0.5	5.7	-45.6	-47.7
	toluene	0.0	3.5	51.6	0.5	5.6	-45.6	-48.0
	CH_2Cl_2	0.0	3.7	50.9	0.7	4.3	-46.1	-49.1
	acetonitrile	0.0	3.6	50.6	0.8	3.9	-46.2	-49.4
60	toluene	0.0	4.5	52.6	2.0	6.9	-44.6	-48.0
	CH_2Cl_2	0.0	4.6	51.9	2.2	5.6	-45.1	-49.2
	acetonitrile	0.0	4.6	51.6	2.2	5.3	-45.2	-49.6
100	toluene	0.0	5.6	60.6	3.7	8.5	-43.5	-48.1

Table S5. Energetics of the reaction of phosphine oxide **3** with CCl_4 at various temperatures (kcal/mol).

temp. [°**C**]	solvent	free substrates	reactant complex	TS 1_2 [ΔG‡]	$P^{(V)}$ compound	TS 2_2 [ΔG‡]	product complex	free products [ΔG]
25	CCl_4	0.0	1.7	47.5	-2.0	0.9	-49.2	-48.8
	toluene	0.0	3.4	50.4	-0.3	4.5	-46.7	-49.0
	CH_2Cl_2	0.0	3.3	49.3	0.0	3.4	-47.2	-50.1
	acetonitrile	0.0	3.5	48.8	0.1	2.8	-47.5	-50.5
60	CH_2Cl_2	0.0	4.2	50.3	1.5	4.8	-46.3	-50.2
	acetonitrile	0.0	4.4	50.1	1.7	4.2	-46.4	-50.6
100	CCl_4	0.0	3.8	49.7	1.1	3.9	-47.1	-49.0
	toluene	0.0	5.5	52.6	2.9	7.5	-44.7	-49.1
	CH_2Cl_2	0.0	5.3	51.4	3.2	6.4	-45.1	-50.3
	acetonitrile	0.0	5.6	50.8	3.2	5.4	-45.4	-50.7
110	acetonitrile	0.0	5.8	51.1	3.6	5.8	-45.2	-50.7
120	toluene	0.0	4.4	51.6	2.2	6.7	-45.7	-49.2
140	toluene	0.0	3.4	50.5	1.4	5.8	-46.7	-49.3

Table S6. Energetics of the reaction of phosphine oxide **2** with CCl_4 at various temperatures (kcal/mol).

temp. [°C]	solvent	free substrates	reactant complex	TS 1_3 [ΔG‡]	$P^{(V)}$ compound	TS 2_3 [ΔG‡]	product complex	free products [ΔG]
25	CCl_4	0.0	2.6	52.2	1.2	6.9	-44.7	-46.4
	toluene	0.0	2.6	52.2	1.3	7.1	-44.6	-46.6
	CH_2Cl_2	0.0	3.0	51.6	1.7	5.9	-44.5	-47.5
	acetonitrile	0.0	3.0	51.4	1.8	5.5	-44.5	-47.8
60	CH_2Cl_2	0.0	3.9	52.6	3.2	7.3	-43.5	-47.6
	acetonitrile	0.0	3.9	52.4	3.3	6.9	-43.5	-48.0
80	CH_2Cl_2	0.0	4.5	53.2	4.0	8.1	-42.9	-47.7
100	CCl_4	0.0	4.6	54.4	4.2	9.8	-42.7	-46.7
	toluene	0.0	4.5	54.4	4.3	10.0	-42.6	-46.7
	acetonitrile	0.0	5.0	53.5	5.0	8.5	-42.4	-48.1

Table S7. Technical specification of used microreactor.

	Asia 120 Microreactor
Wetter materials	glass, quartz
Temperature range	-20 °C to +250 °C[a]
Maximum pressure	30 bar
Inside diameter of connection tubing	0.5 mm
Connection tubing material	PTFE, FEP
Type of mixer	Double T-mixer

[a] up to 150 °C.

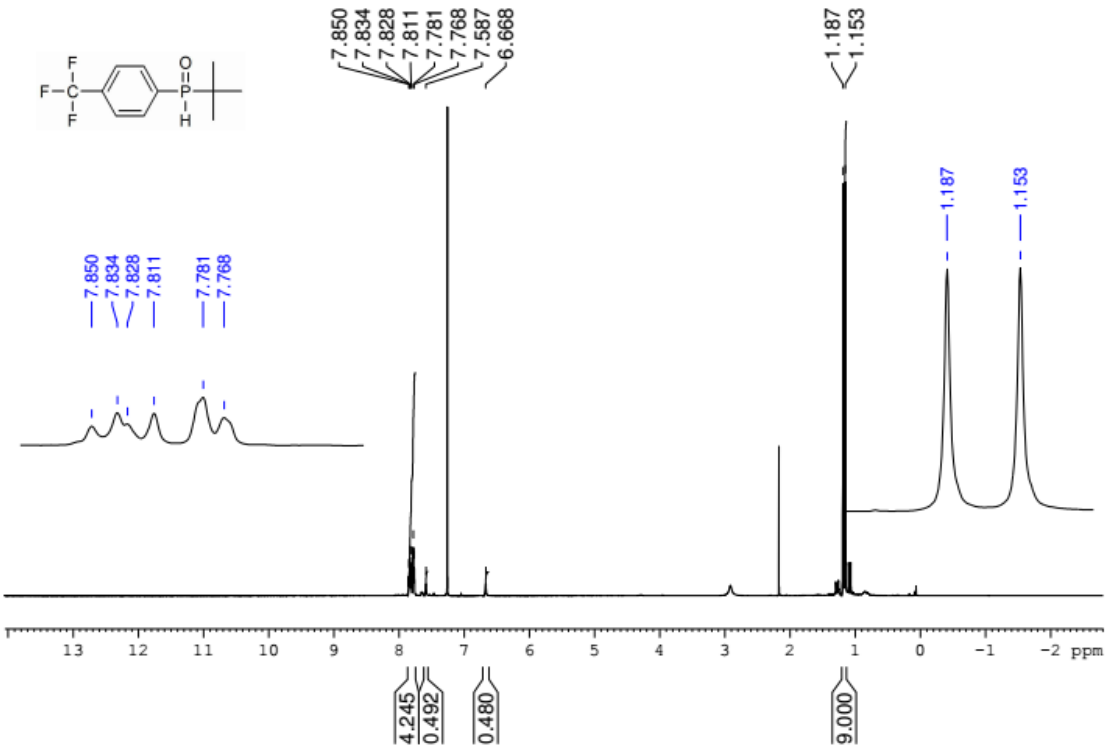


Figure S1: ^{1}H NMR (500 MHz, $CDCl_3$) of **2**.

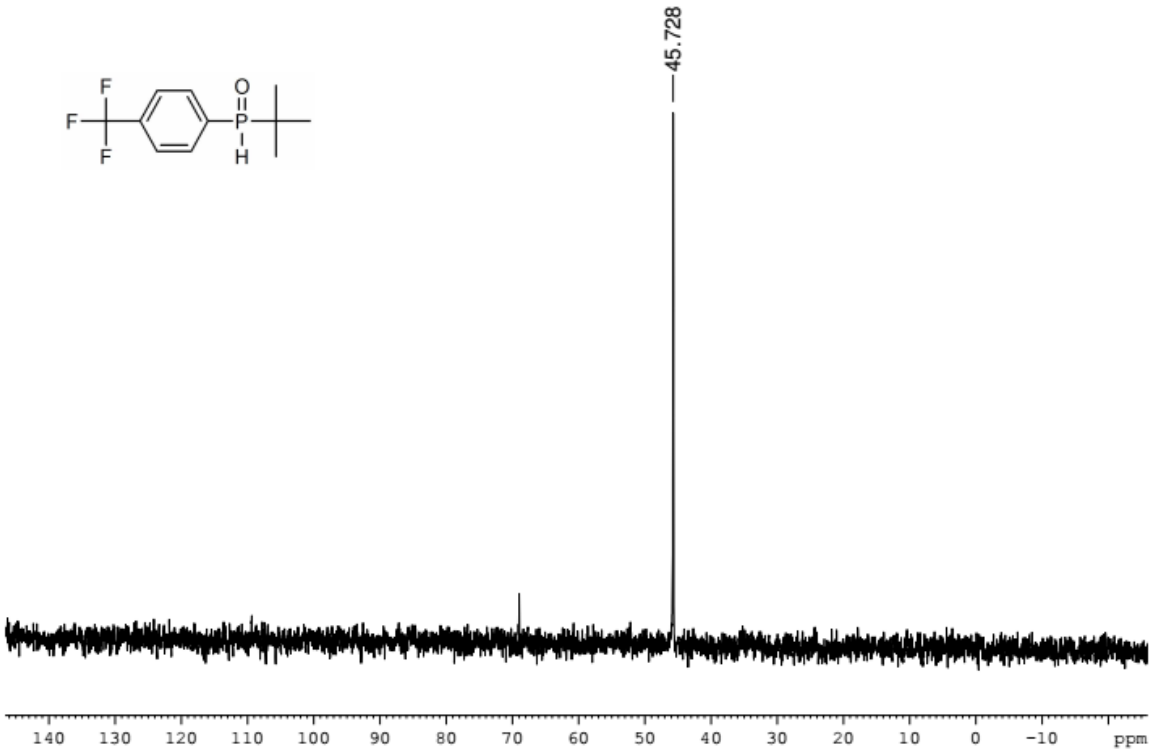


Figure S2: ^{31}P NMR (81 MHz, $CDCl_3$) of **2**.

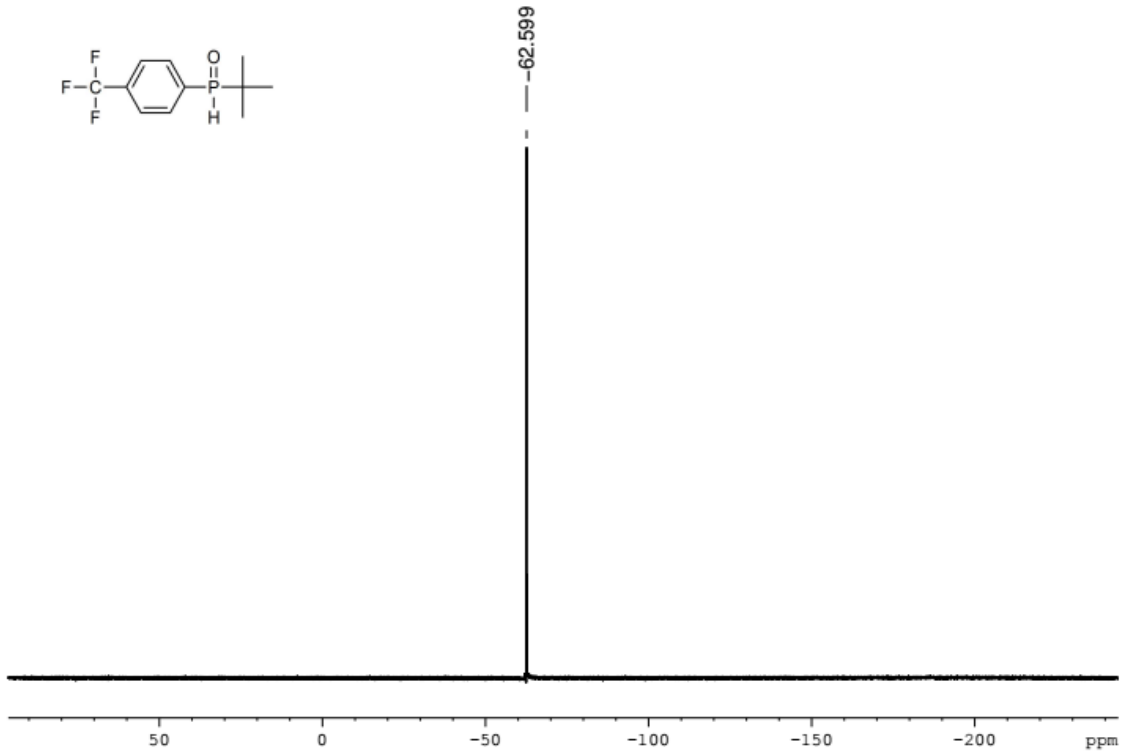


Figure S3: ^{19}F NMR (188 MHz, $CDCl_3$) of **2**.

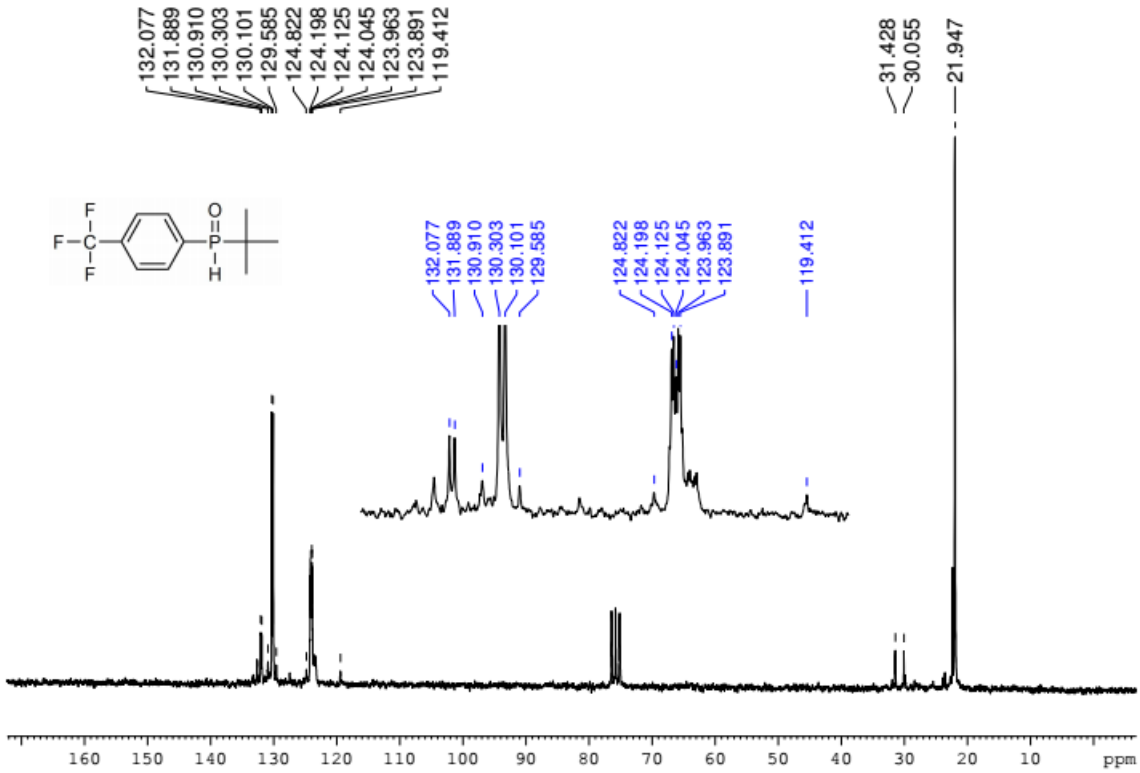


Figure S4: ^{13}C NMR (50 MHz, $CDCl_3$) of **2**.

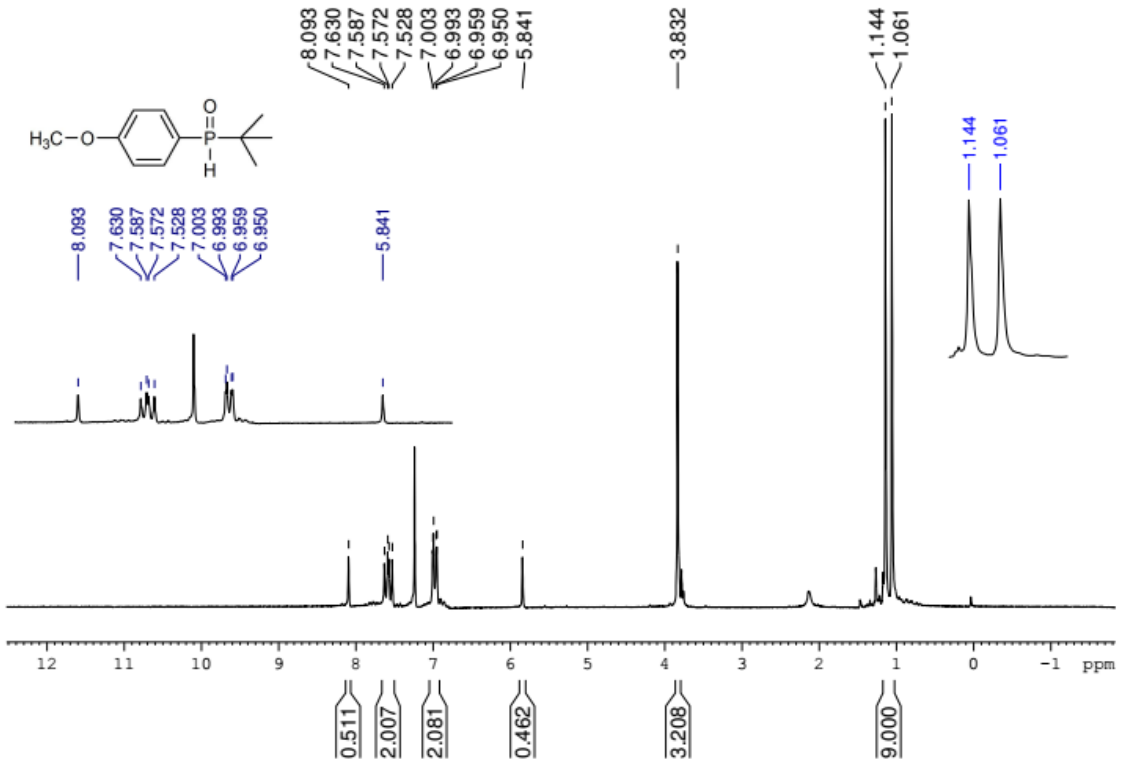


Figure S5: ^{1}H NMR (200 MHz, $CDCl_3$) of **3**.

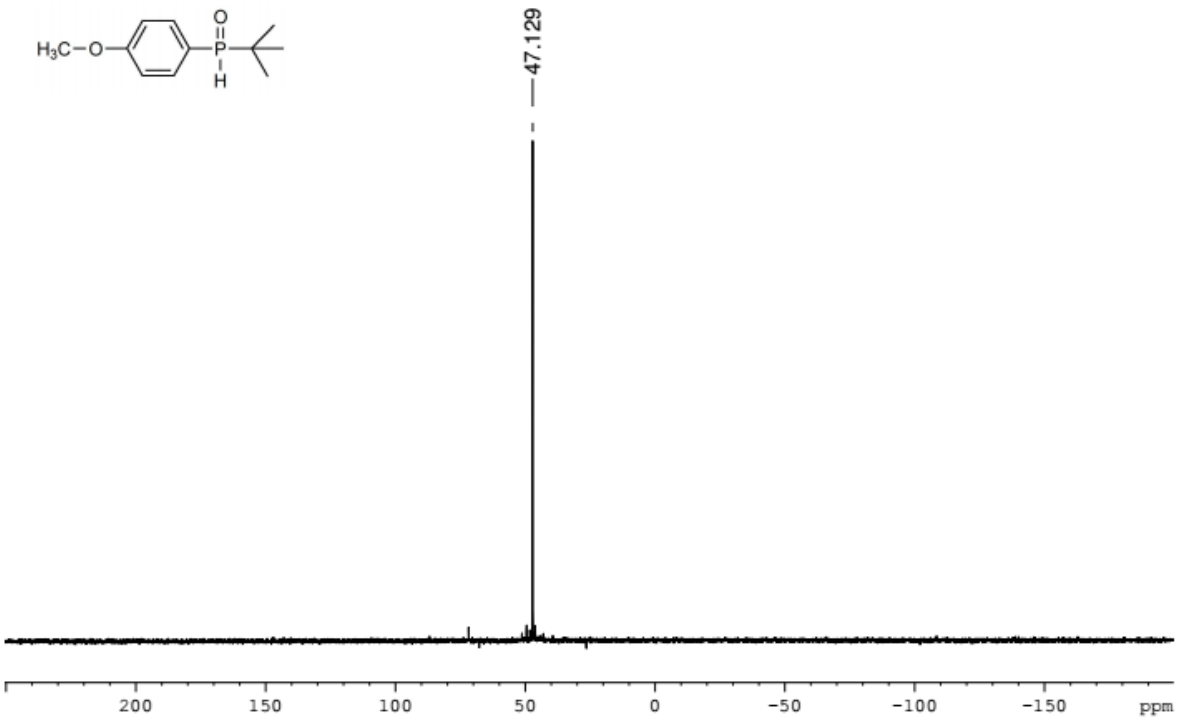


Figure S6: ^{31}P NMR (81 MHz, $CDCl_3$) of **3**.

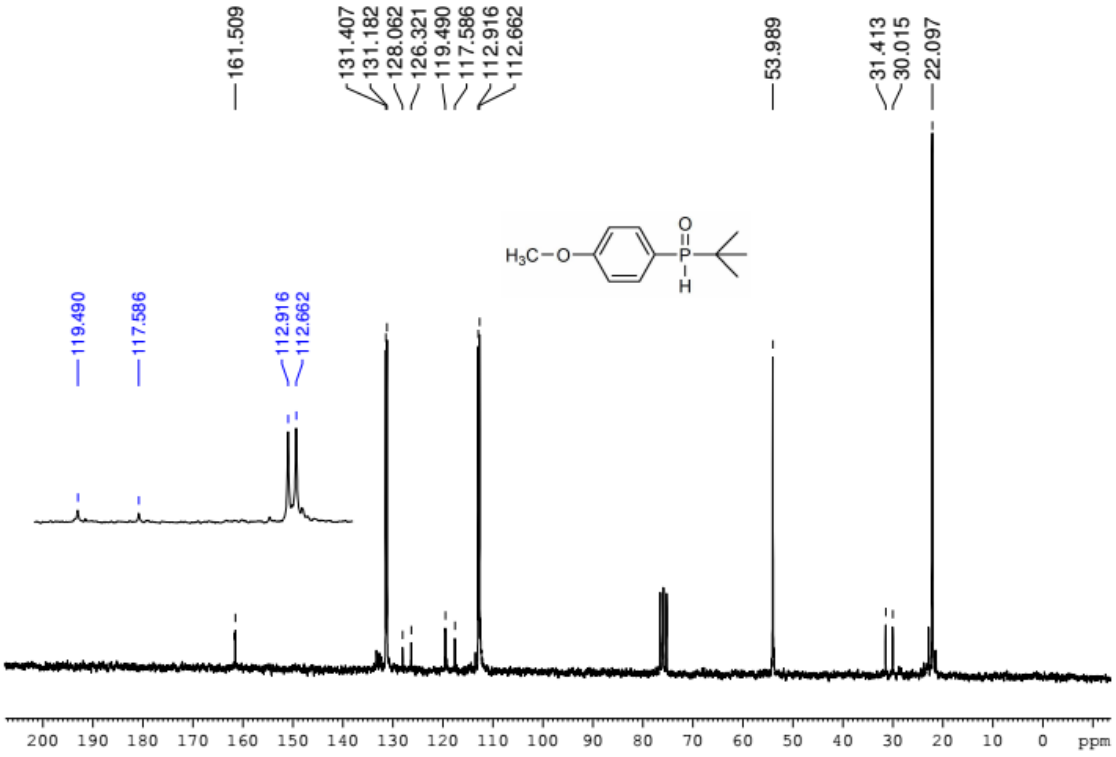


Figure S7: ^{13}C NMR (50 MHz, $CDCl_3$) of **3**.

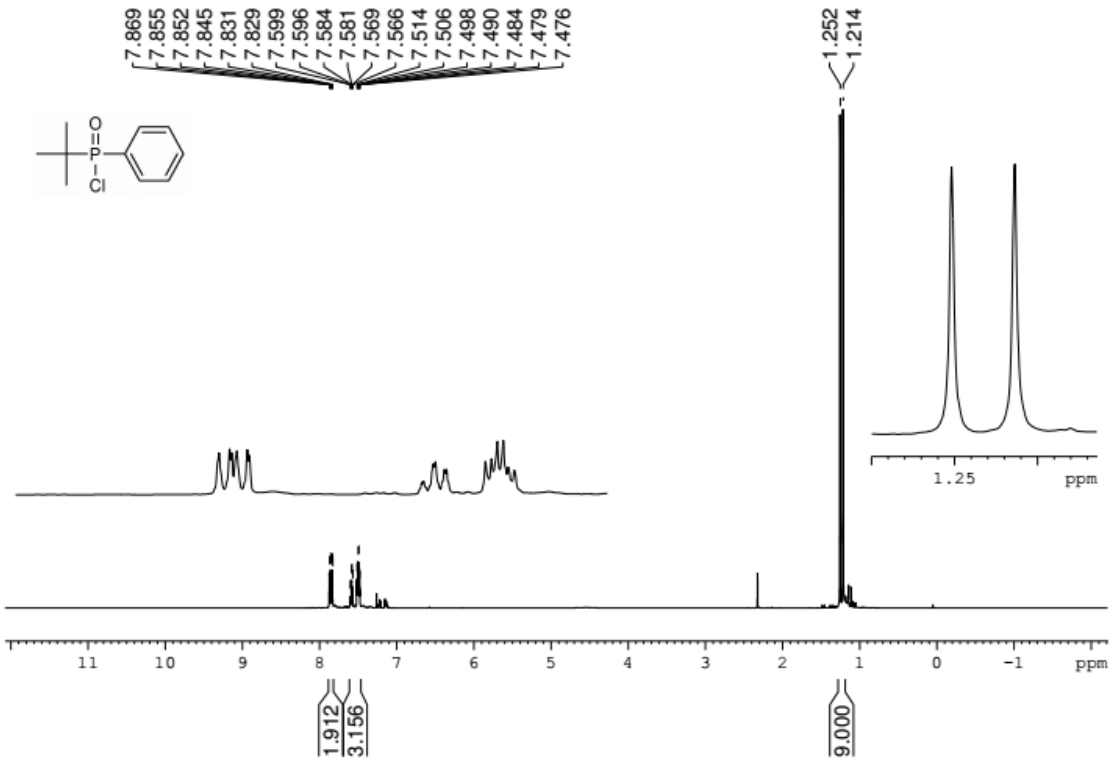


Figure S8: ^{1}H NMR (500 MHz, $CDCl_3$) of **4** and **(S)-4**.

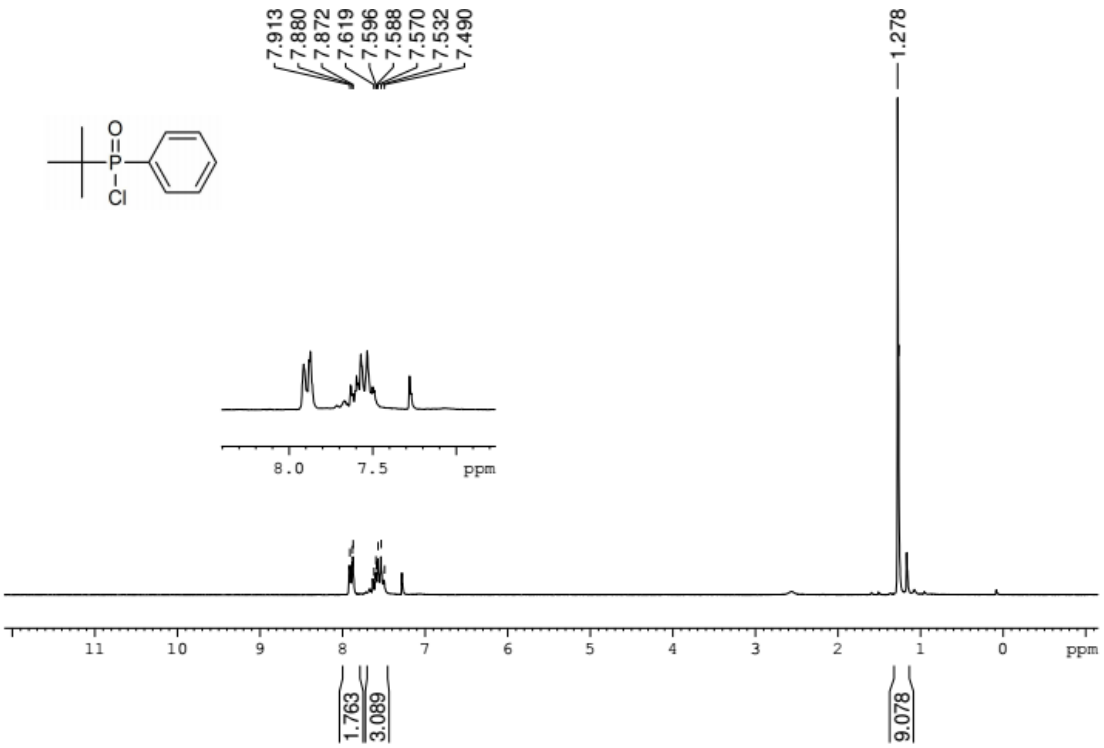


Figure S9: $^{1}H\{^{31}P\}$ NMR (200 MHz, $CDCl_3$) of **4** and **(S)-4**.

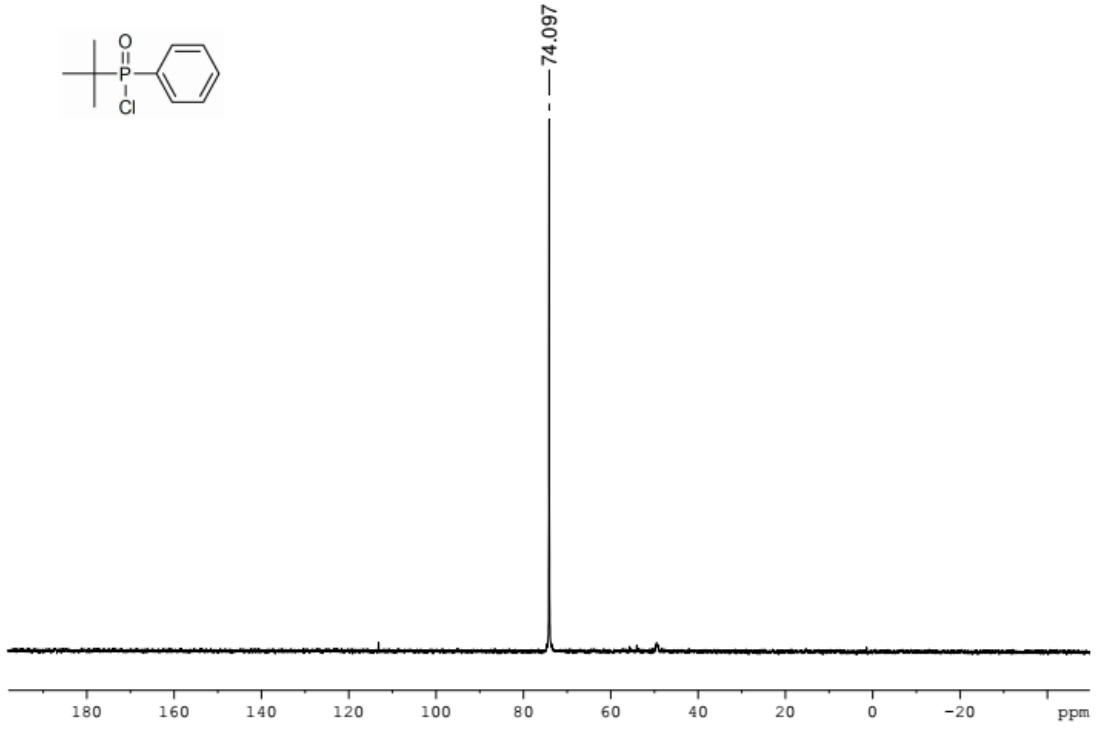


Figure S10: ^{31}P NMR (81 MHz, $CDCl_3$) of **4** and **(S)-4**.

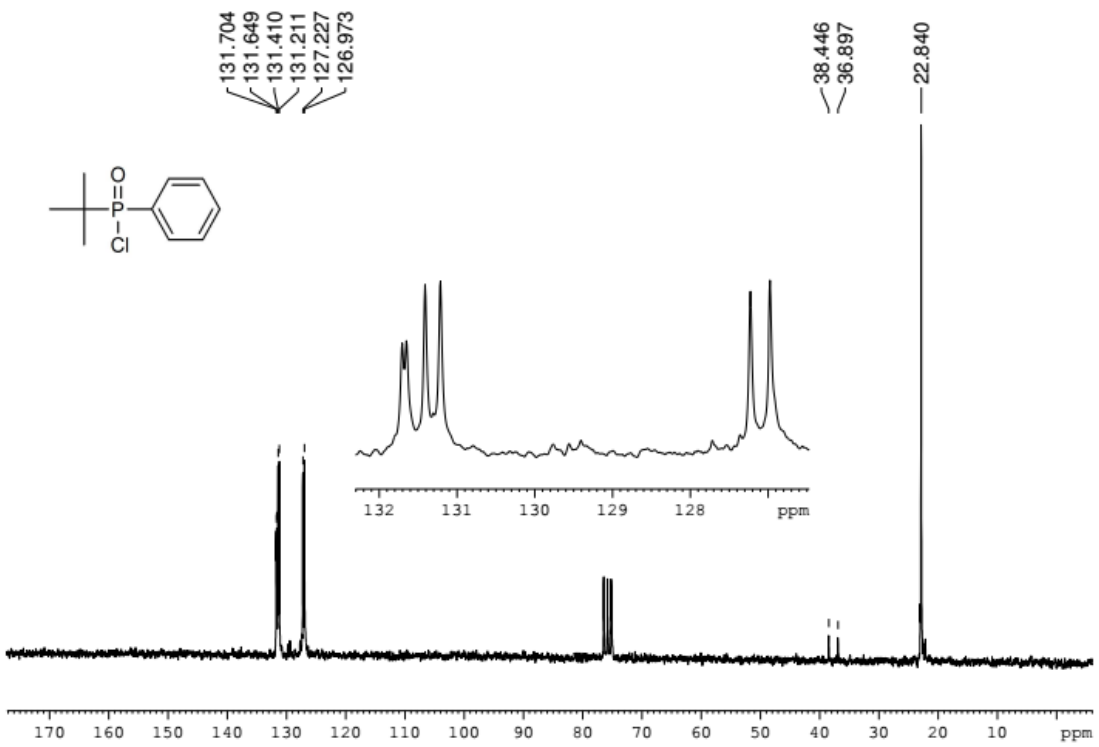


Figure S11: ^{13}C NMR (50 MHz, $CDCl_3$) of **4** and **(S)-4**.

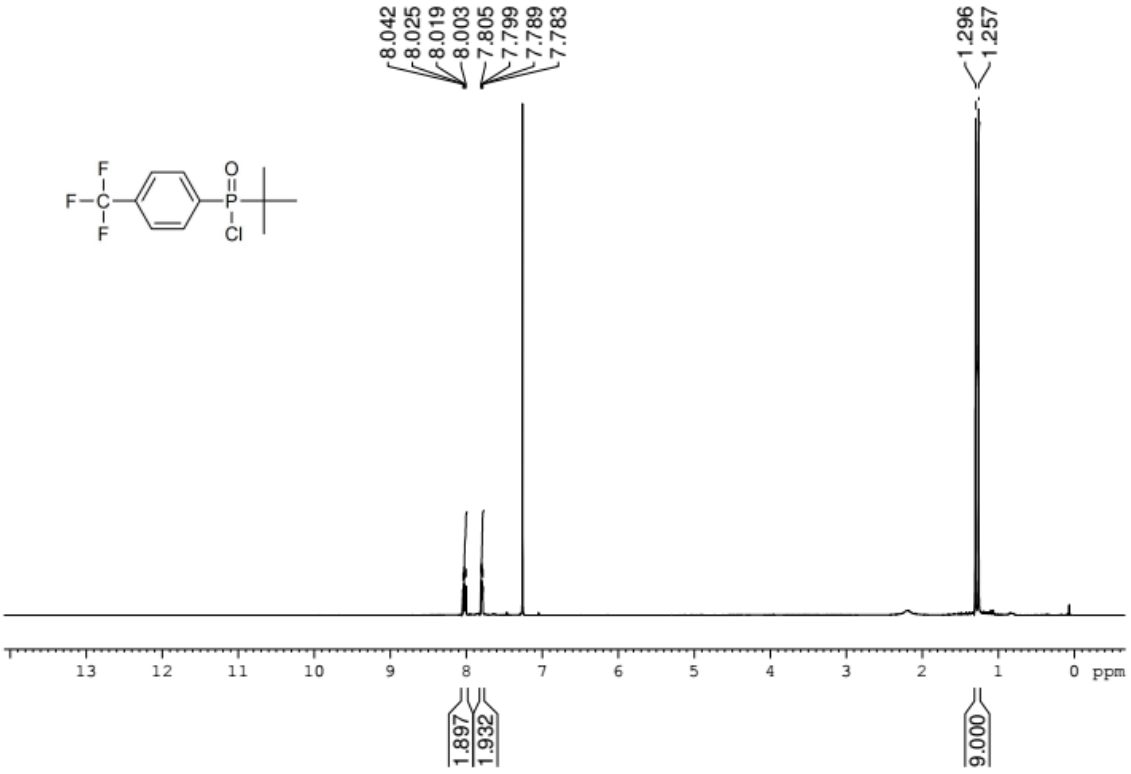


Figure S12: ^{1}H NMR (500 MHz, $CDCl_3$) of **5**.

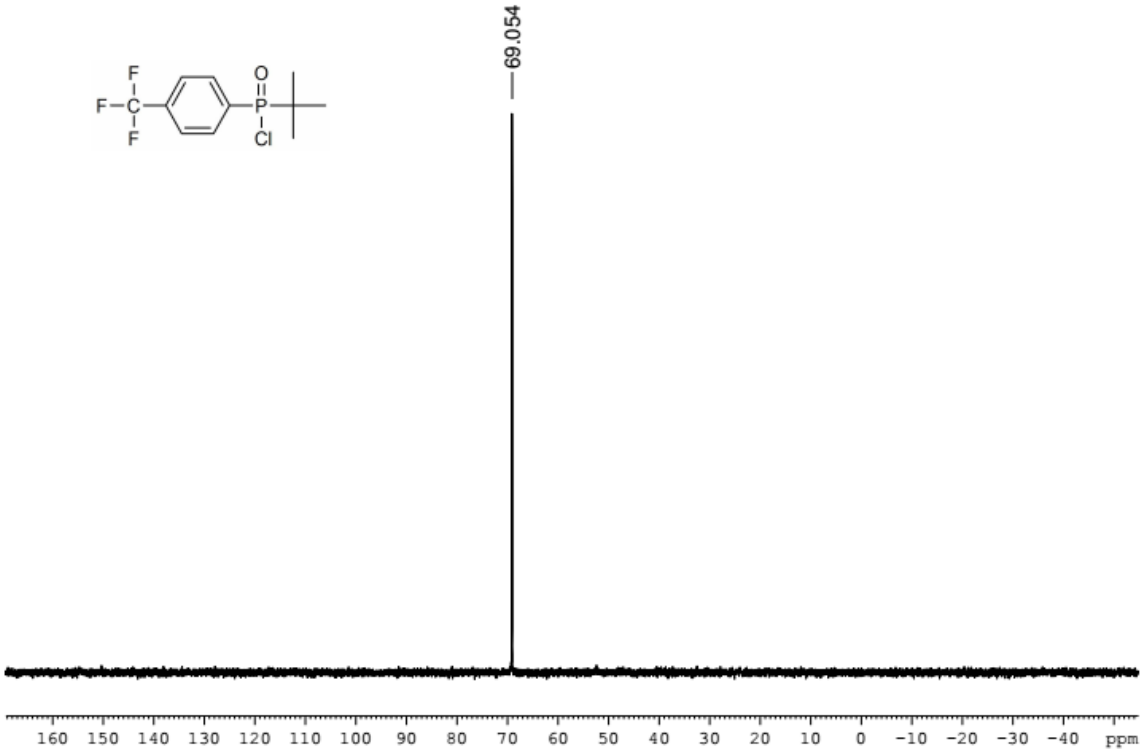


Figure S13: ^{31}P NMR (202 MHz, $CDCl_3$) of **5**.

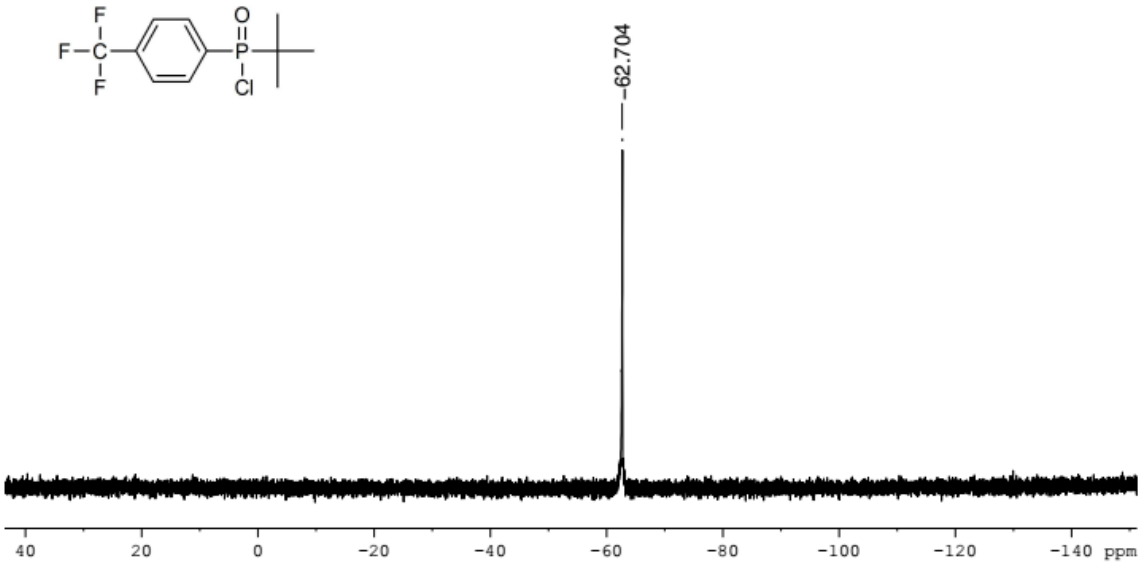


Figure S14: ^{19}F NMR (188 MHz, $CDCl_3$) of **5**.

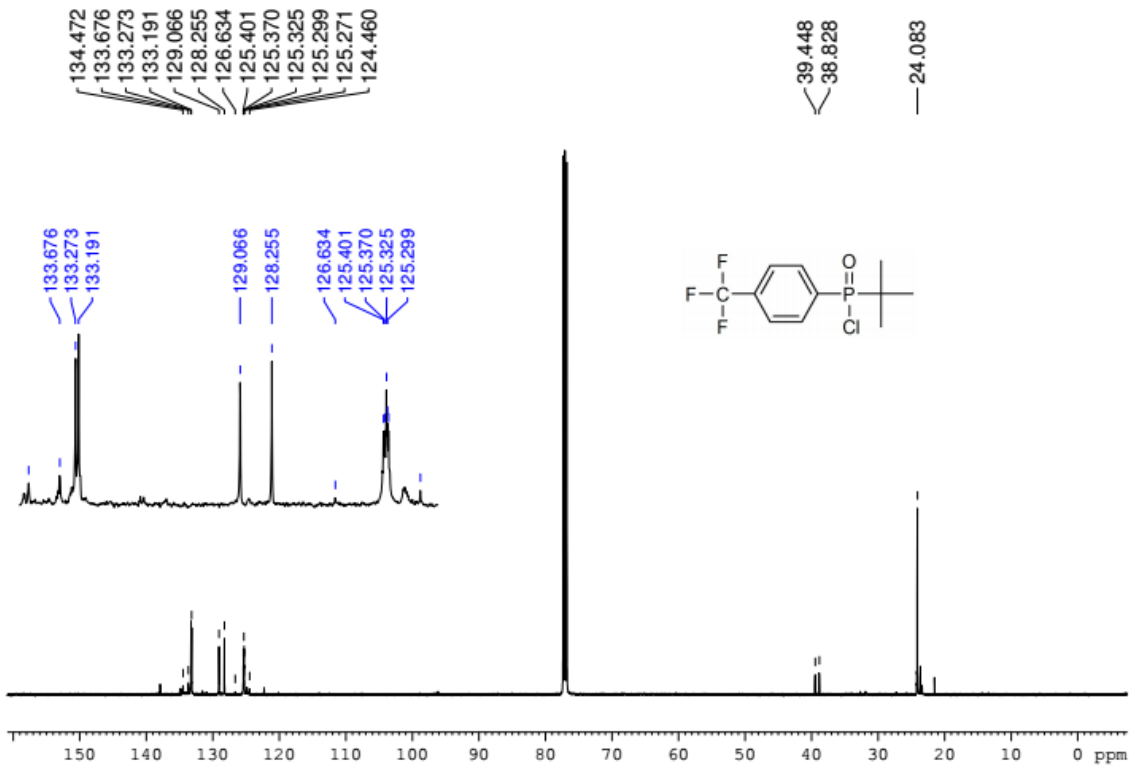


Figure S15: ^{13}C NMR (125 MHz, $CDCl_3$) of **5**.

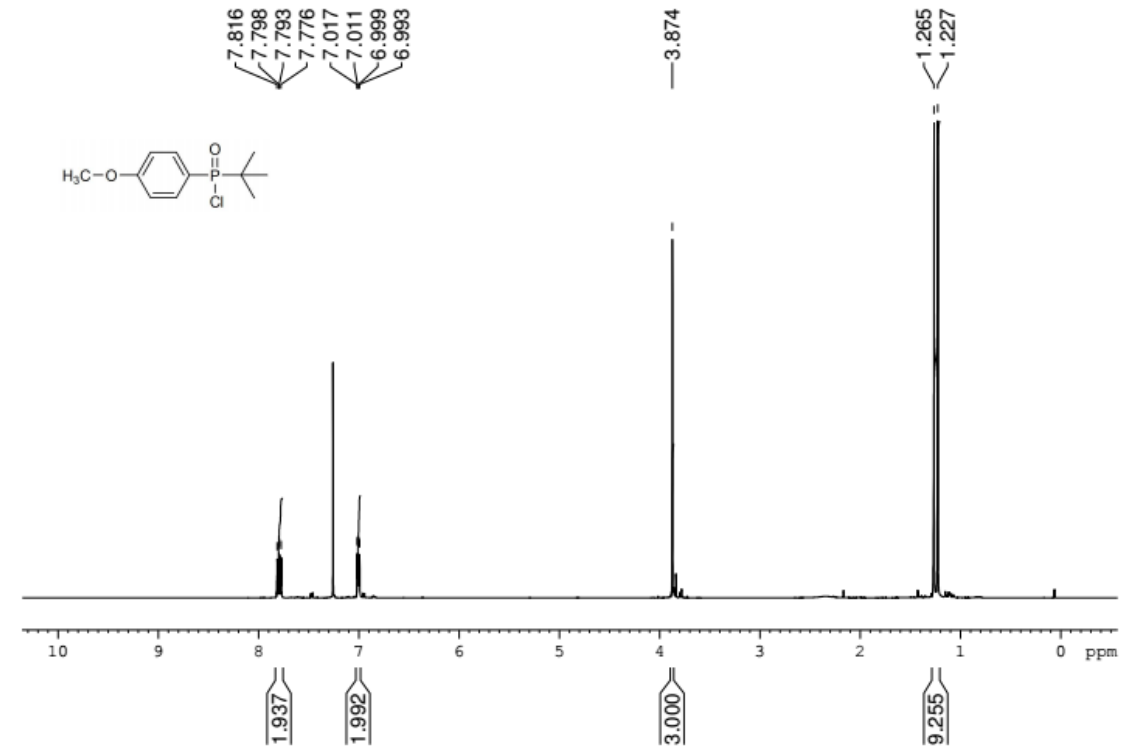


Figure S16: ^{1}H NMR (500 MHz, $CDCl_3$) of **6**.

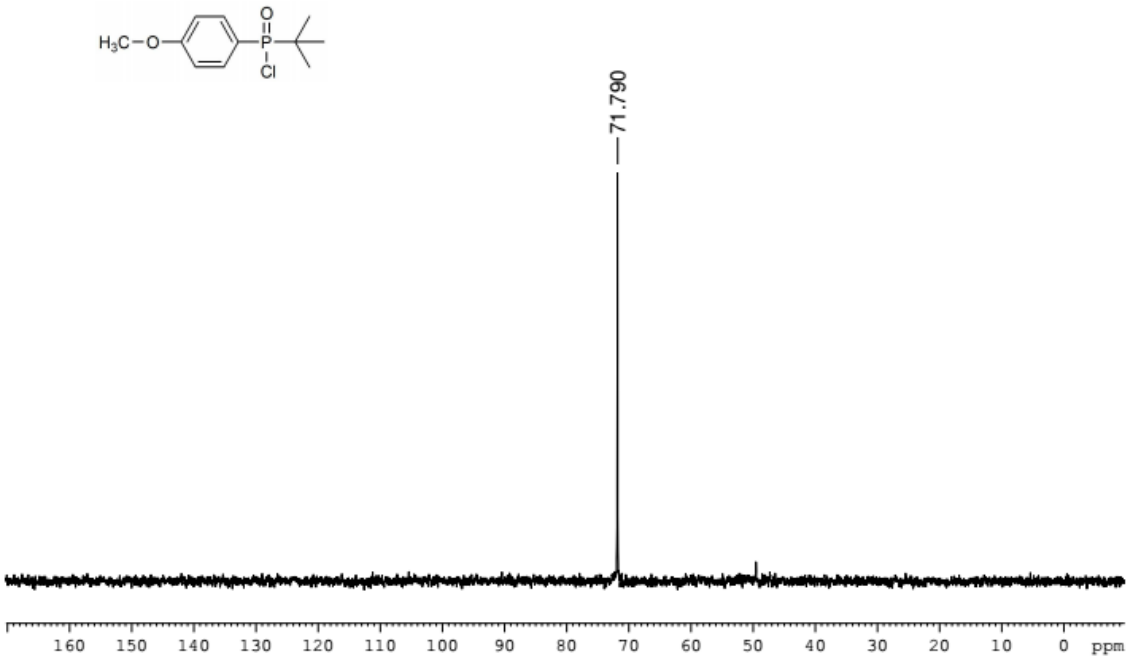


Figure S17: ^{31}P NMR (81 MHz, $CDCl_3$) of **6**.

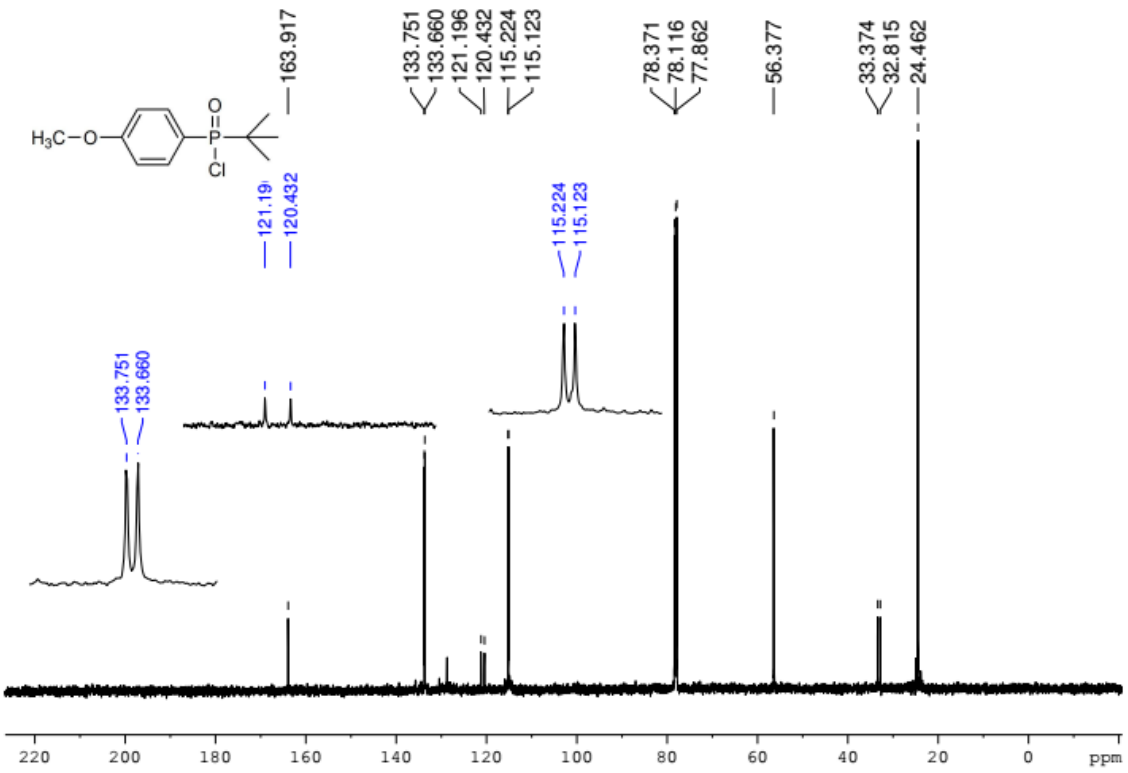


Figure S18: ^{13}C NMR (125 MHz, $CDCl_3$) of **6**.

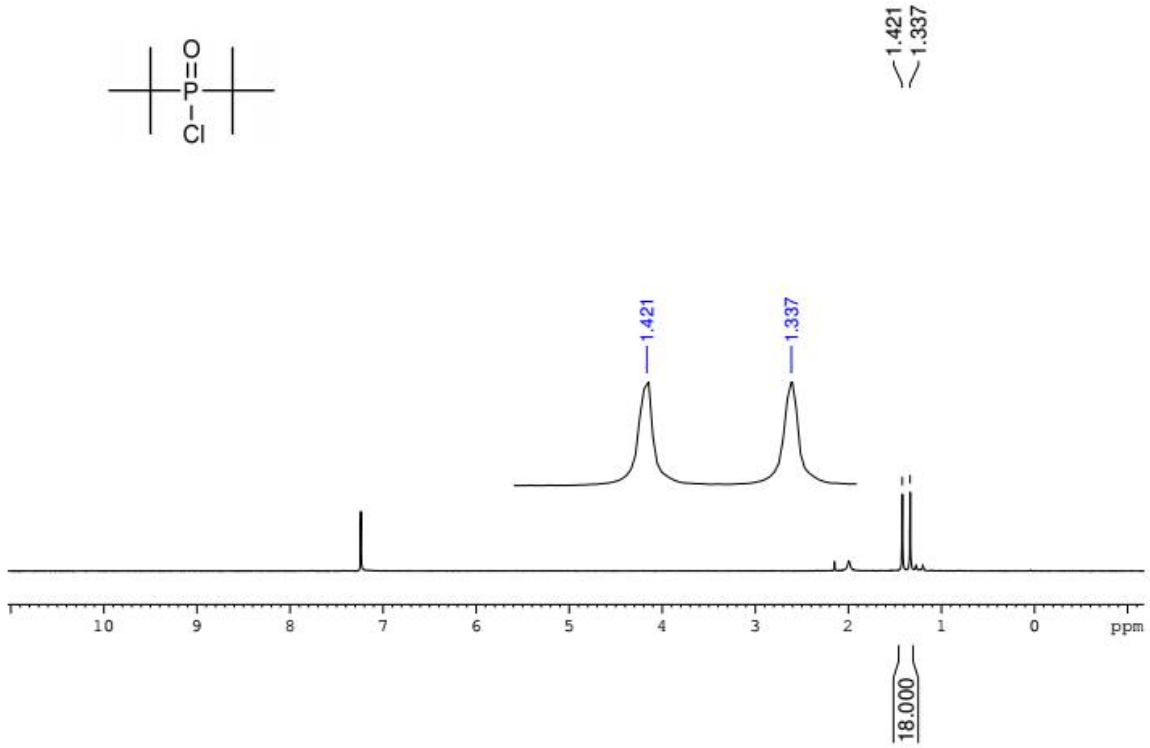


Figure S19: ^{1}H NMR (200 MHz, $CDCl_3$) of **8**.

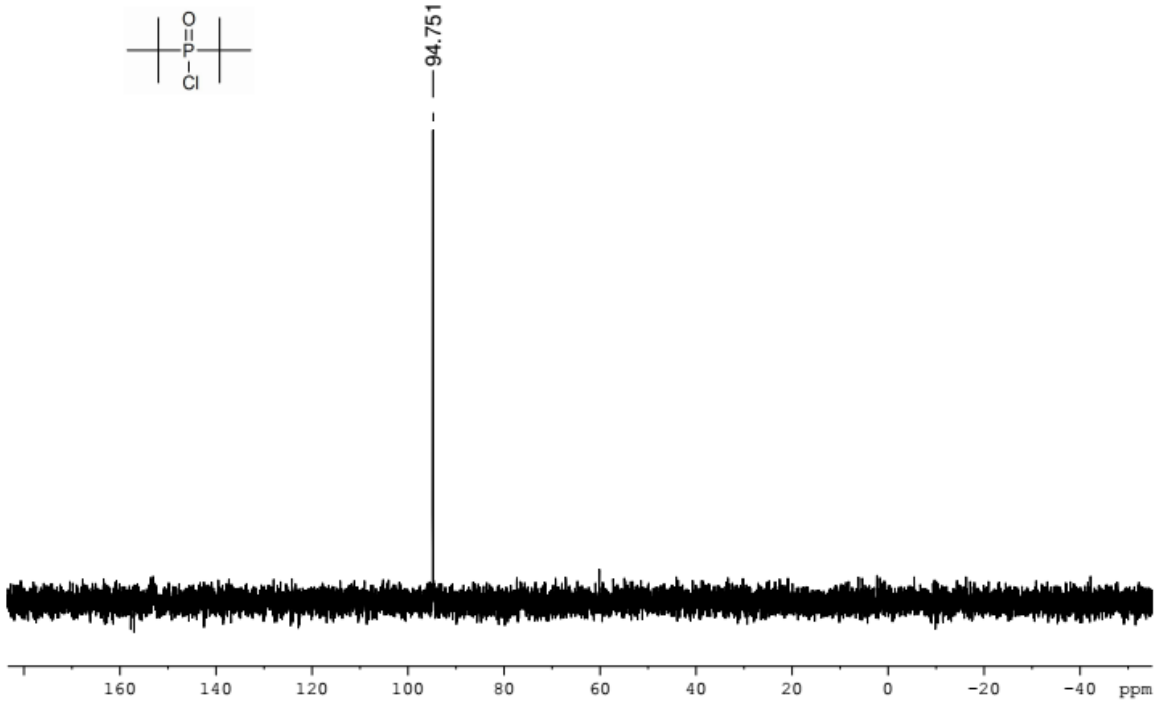


Figure S20: ^{31}P NMR (202 MHz, $CDCl_3$) of **8**.

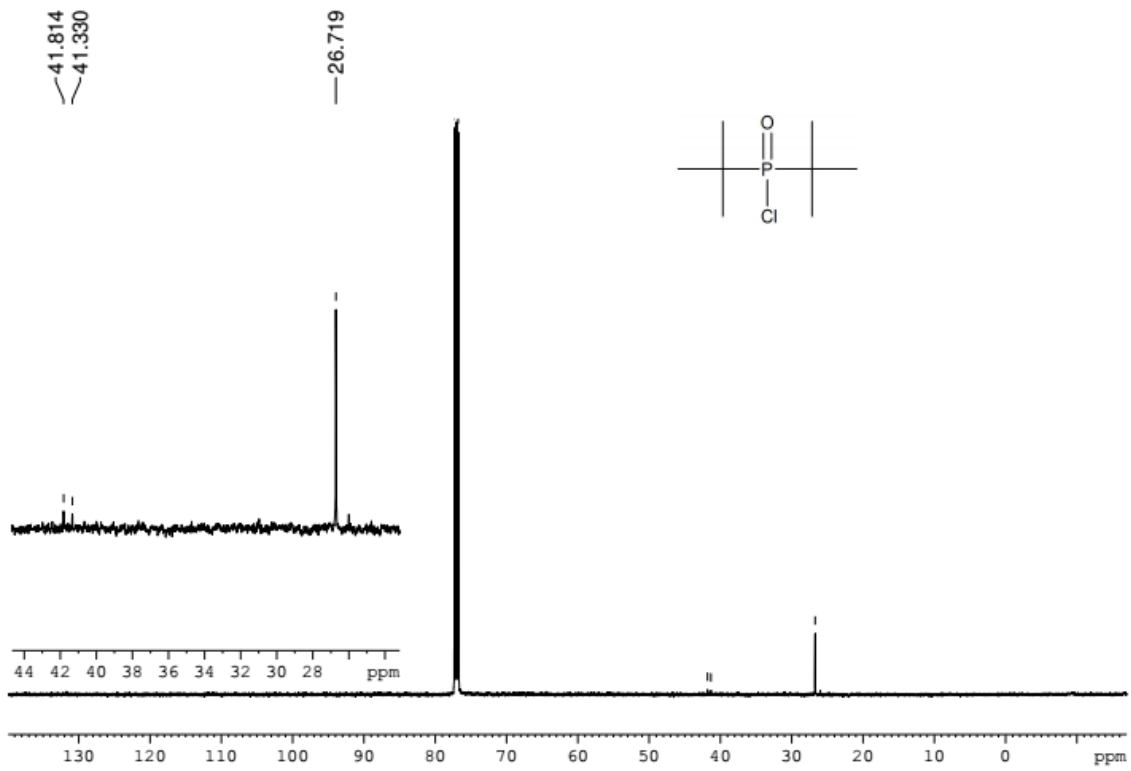


Figure S21: ^{13}C NMR (125 MHz, $CDCl_3$) of **8**.

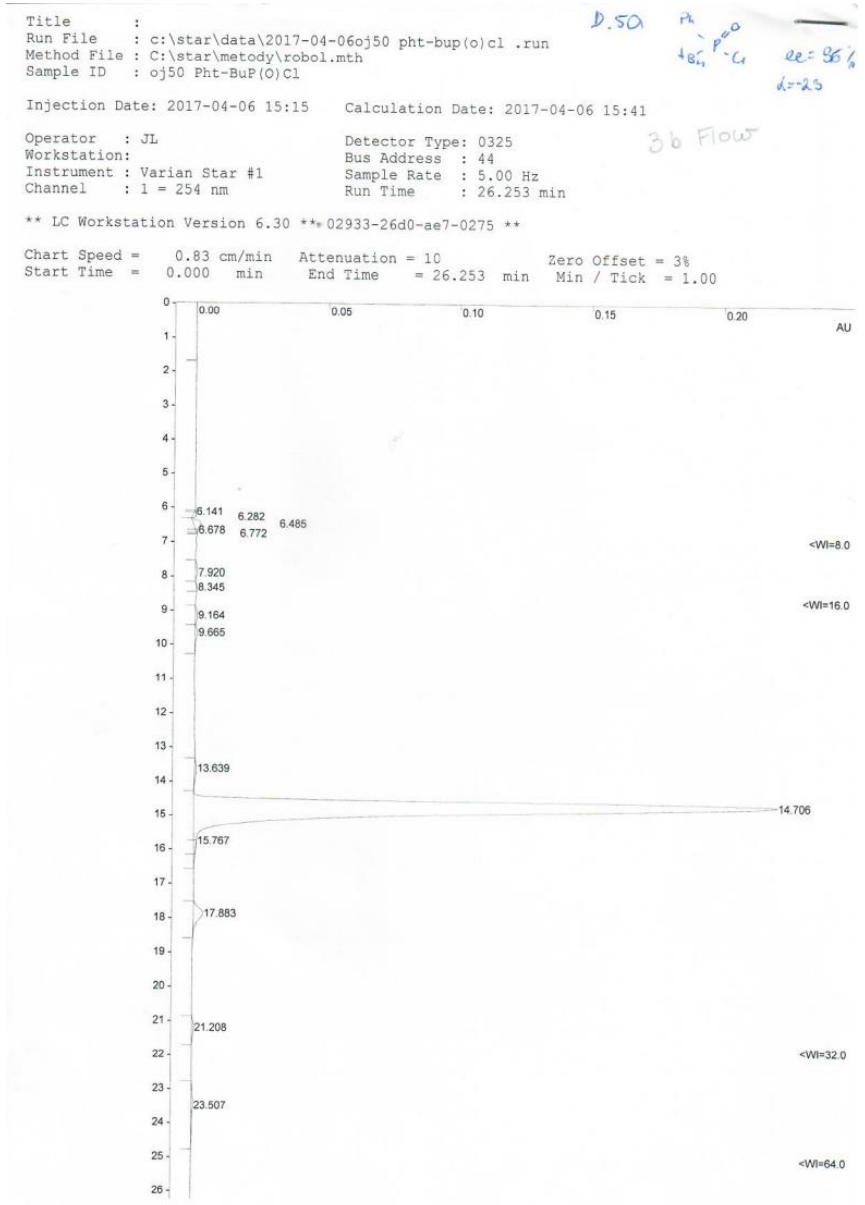
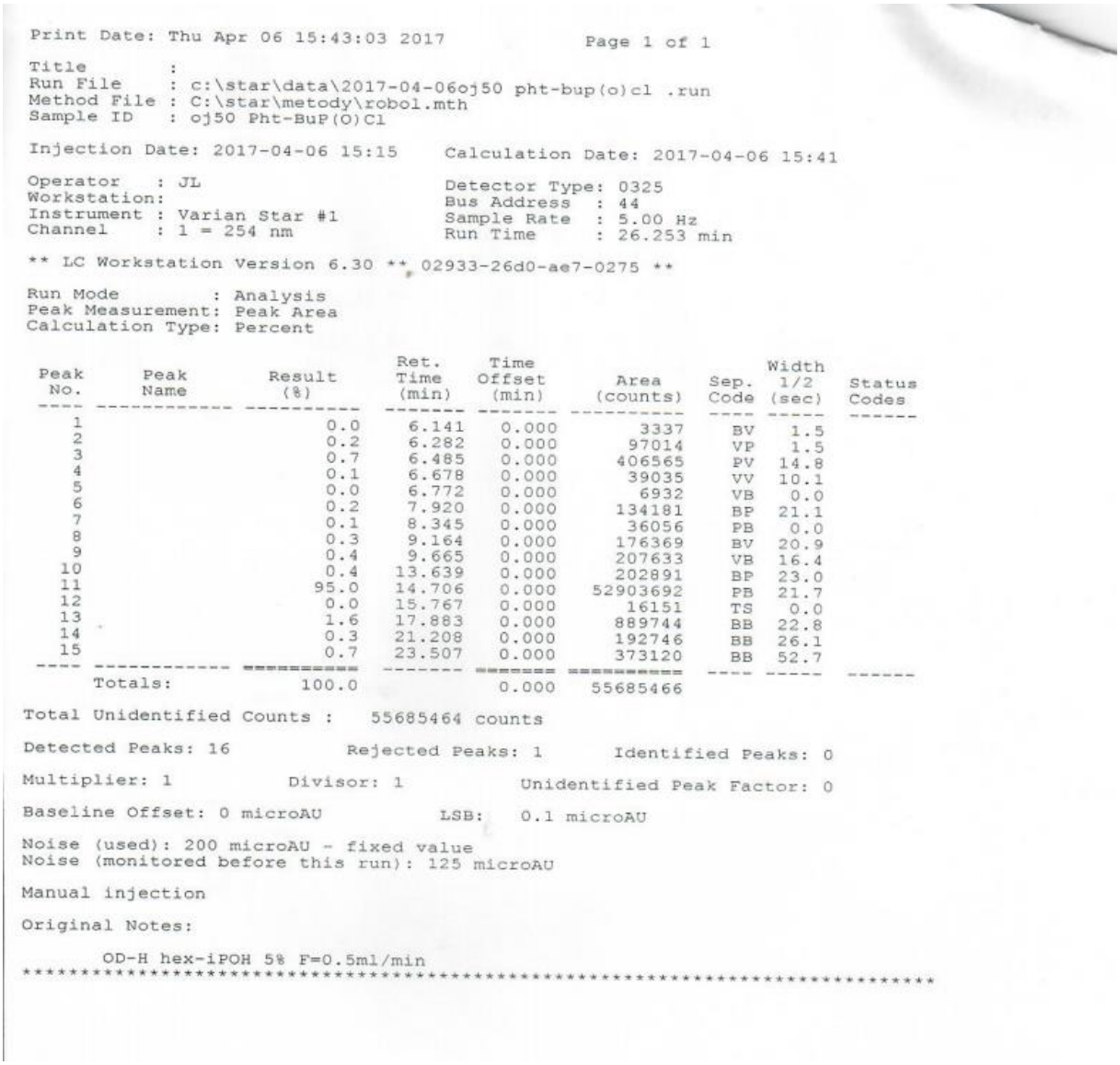


Figure S22: HPLC of **(S)-4 (flow)**



Print Date: Thu Apr 06 15:43:03 2017 Page 1 of 1

Title :
Run File : c:\star\data\2017-04-06oj50 pht-bup(o)cl .run
Method File : C:\star\metody\robol.mth
Sample ID : oj50 Pht-BuP(O)Cl

Injection Date: 2017-04-06 15:15 Calculation Date: 2017-04-06 15:41

Operator : JL
Workstation:
Instrument : Varian Star #1
Channel : 1 = 254 nm

Detector Type: 0325
Bus Address : 44
Sample Rate : 5.00 Hz
Run Time : 26.253 min

** LC Workstation Version 6.30 ** 02933-26d0-ae7-0275 **

Run Mode : Analysis
Peak Measurement: Peak Area
Calculation Type: Percent

Peak No.	Peak Name	Result (%)	Ret. Time (min)	Time Offset (min)	Area (counts)	Sep. Code	Width 1/2 (sec)	Status Codes
1		0.0	6.141	0.000	3337	BV	1.5	
2		0.2	6.282	0.000	97014	VP	1.5	
3		0.7	6.485	0.000	406565	PV	14.8	
4		0.1	6.678	0.000	39035	VV	10.1	
5		0.0	6.772	0.000	6932	VB	0.0	
6		0.2	7.920	0.000	134181	BP	21.1	
7		0.1	8.345	0.000	36056	PB	0.0	
8		0.3	9.164	0.000	176369	BV	20.9	
9		0.4	9.665	0.000	207633	VB	16.4	
10		0.4	13.639	0.000	202891	BP	23.0	
11		95.0	14.706	0.000	52903692	PB	21.7	
12		0.0	15.767	0.000	16151	TS	0.0	
13		1.6	17.883	0.000	889744	BB	22.8	
14		0.3	21.208	0.000	192746	BB	26.1	
15		0.7	23.507	0.000	373120	BB	52.7	
	Totals:	100.0		0.000	55685466			

Total Unidentified Counts : 55685464 counts

Detected Peaks: 16 Rejected Peaks: 1 Identified Peaks: 0

Multiplier: 1 Divisor: 1 Unidentified Peak Factor: 0

Baseline Offset: 0 microAU LSB: 0.1 microAU

Noise (used): 200 microAU - fixed value
Noise (monitored before this run): 125 microAU

Manual injection

Original Notes:

OD-H hex-iPOH 5% F=0.5ml/min

Figure S23: HPLC of **(S)-4** (**flow**)

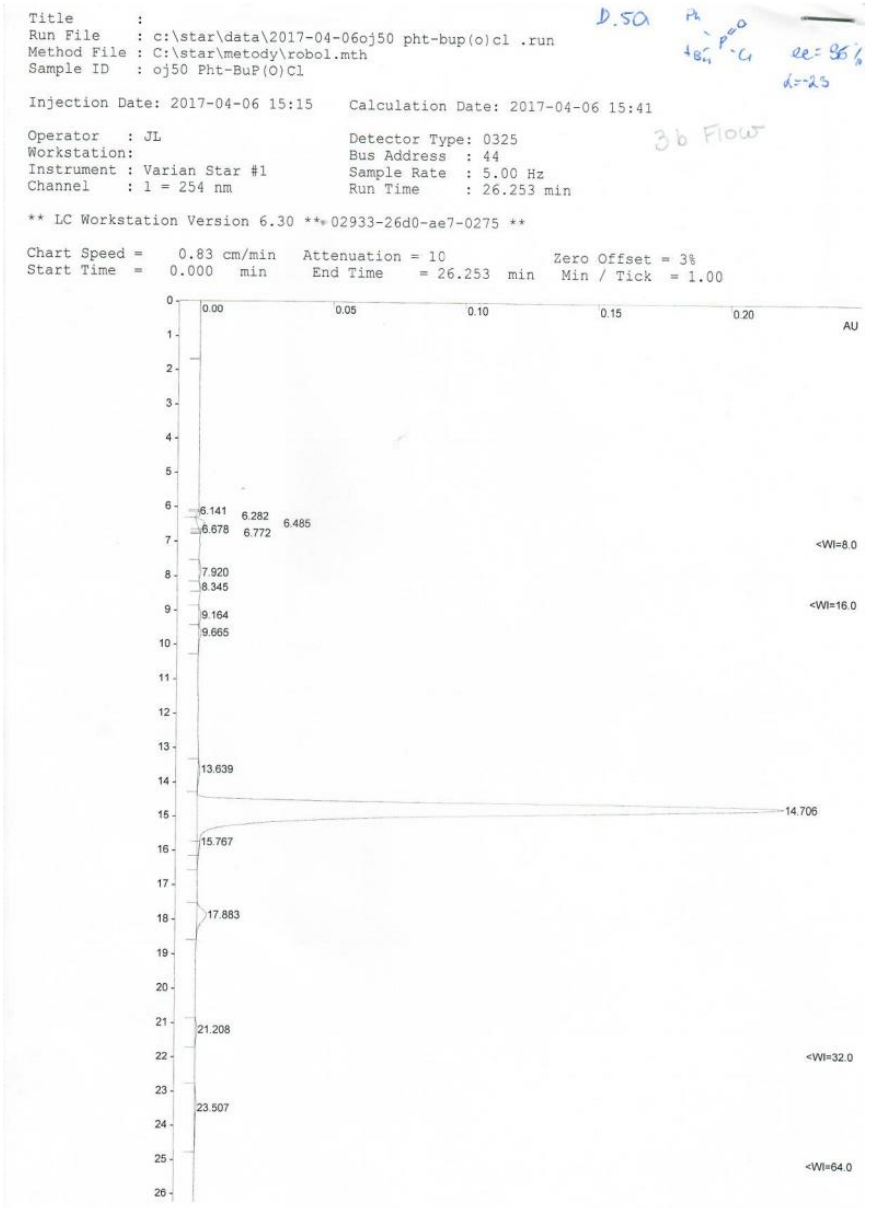
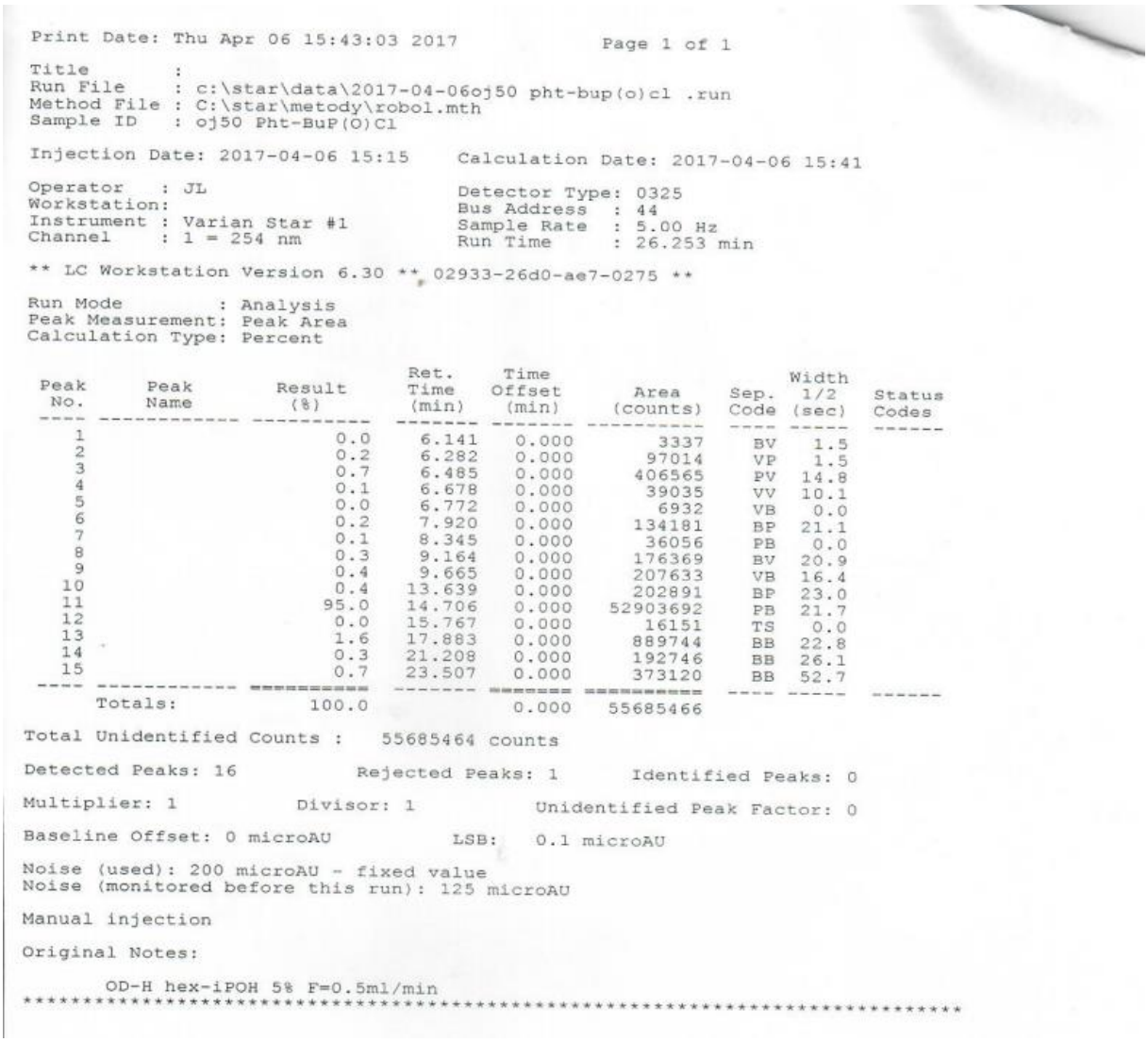


Figure S24: HPLC of **(S)-4 (batch)**



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Title :
Run File : c:\star\data\2017-04-06oj50 pht-bup(o)cl .run
Method File : C:\star\metody\robol.mth
Sample ID : oj50 Pht-BuP(O)Cl

Injection Date: 2017-04-06 15:15 Calculation Date: 2017-04-06 15:41

Operator : JL
Workstation:
Instrument : Varian Star #1
Channel : 1 = 254 nm

Detector Type: 0325
Bus Address : 44
Sample Rate : 5.00 Hz
Run Time : 26.253 min

** LC Workstation Version 6.30 ** 02933-26d0-ae7-0275 **

Run Mode : Analysis
Peak Measurement: Peak Area
Calculation Type: Percent

Peak No.	Peak Name	Result (%)	Ret. Time (min)	Time Offset (min)	Area (counts)	Sep. Code	Width 1/2 (sec)	Status Codes
1		0.0	6.141	0.000	3337	BV	1.5	
2		0.2	6.282	0.000	97014	VP	1.5	
3		0.7	6.485	0.000	406565	PV	14.8	
4		0.1	6.678	0.000	39035	VV	10.1	
5		0.0	6.772	0.000	6932	VB	0.0	
6		0.2	7.920	0.000	134181	BP	21.1	
7		0.1	8.345	0.000	36056	PB	0.0	
8		0.3	9.164	0.000	176369	BV	20.9	
9		0.4	9.665	0.000	207633	VB	16.4	
10		0.4	13.639	0.000	202891	BP	23.0	
11		95.0	14.706	0.000	52903692	PB	21.7	
12		0.0	15.767	0.000	16151	TS	0.0	
13		1.6	17.883	0.000	889744	BB	22.8	
14		0.3	21.208	0.000	192746	BB	26.1	
15		0.7	23.507	0.000	373120	BB	52.7	
	Totals:	100.0		0.000	55685466			

Total Unidentified Counts : 55685464 counts

Detected Peaks: 16 Rejected Peaks: 1 Identified Peaks: 0

Multiplier: 1 Divisor: 1 Unidentified Peak Factor: 0

Baseline Offset: 0 microAU LSB: 0.1 microAU

Noise (used): 200 microAU - fixed value
Noise (monitored before this run): 125 microAU

Manual injection

Original Notes:

OD-H hex-iPOH 5% F=0.5ml/min

Figure S25: HPLC of **(S)-4** (**batch**)

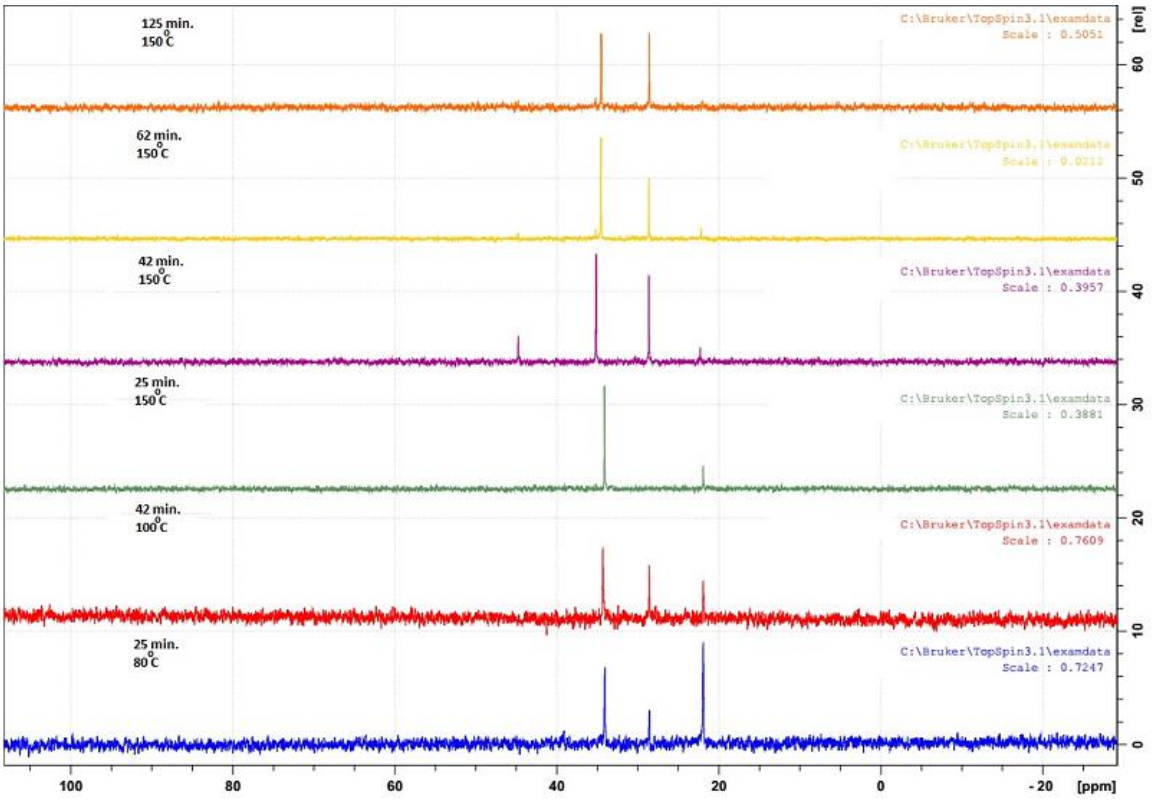

Figure S26: ^{31}P NMR (81 MGz, $CDCl_3$) details of conversion of diphenylphosphine oxide (**9**) against temperature and residence time under flow conditions.