SUPPORTING INFORMATION

for

Multimetallic Pd- and Ni-Catalyzed C(sp^2)–P Cross-Coupling under Aqueous Micellar Conditions

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General Information

Reagents were purchased at the highest quality from commercial vendors (Sigma-Aldrich, TCI Europe, Strem, Fluorochem, Across (Europe), Acros Pharmatech Ltd. (China)) and used without further purification. $Pd(OAc)_2$ was purchased from Sigma-Aldrich (cat. no. 520764); $Pd[P(t\text{-}Bu)_3]_2$, from Sigma-Aldrich (cat. no. 676578) and TCI Europe (cat. no. B3161); $NiCl_2.6H_2O$, from Strem (cat. no. 93-2810); XantPhos, from TCI Europe (cat. no. B2709); 1,10-phenanthroline (phen), from Sigma-Aldrich (cat. no. 131377); Zn nanopowder (40-60 nm avg. part. size), from Sigma-Aldrich (cat. no. 578002); TPGS-750-M, from Sigma-Aldrich (cat. no. 763896); diethyl *H*-phosphonate (**3**, 98% purity), dibenzyl H-phosphonate (**73**, technical grade), ethyl phenyl *H*-phosphinate (**86**, 94% purity) and diphenylphosphine oxide (**97**, 97% purity), from Sigma-Aldrich (cat. no. D99234, D36607, 415642, 287881, respectively); di-*iso*-propyl *H*-phosphonate (**72**), from TCI Europe; and dimethylphosphine oxide (**98**, 95% purity), from BioSynth (UK, cat. no. FD166291).

Reaction progress was monitored by LC-MS analysis and/or thin-layer chromatography (TLC) using TLC 60G F_{254} glass plates (Merck) and short-wave UV light for visualization and/or $KMnO_4$ and heat as a developing agent. All yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous material, unless stated otherwise.

Flash column chromatography was performed using E. Merck silica (60, particle size 0.043–0.063 mm), and preparative TLC (pTLC) was performed on TLC 60G F_{254} glass plates (Merck) or PLC Silica gel 60 F_{254} glass plates (1 mm thickness, Merck). Preparative reverse-phase HPLC purification was performed on an Ecom ECS28P0X compact preparative system equipped with a TOY18DAD800 L DAD detector using a C18 column (Teledyne Isco, RediSep Gold® C18Aq 50g, cat. no. 692203561) or a C8 column (Interchim, puriFlash® 200 C8 15µM F0040, cat. no. PT-C8-F0040) and eluting with HPLC-grade water, methanol (VWR) and acetonitrile (VWR) containing 0.1 vol % trifluoroacetic acid.

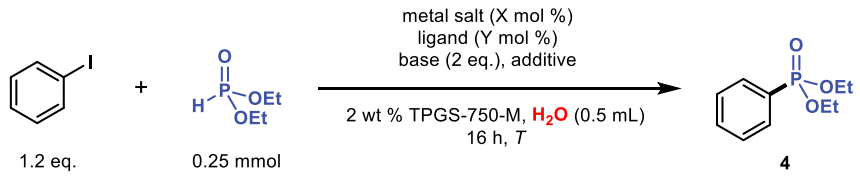
NMR spectra were recorded on a Bruker Avance III HD spectrometer with a BBFI probe (operating at 400 MHz for ^{1}H, 100 MHz for ^{13}C, 162 MHz for ^{31}P, 376 MHz for ^{19}F, and 128 MHz for ^{11}B) and a Bruker Avance III spectrometer with a cryo-probe (5 mm TCI ^{1}H/^{13}C/^{15}N/D Z/GRD, operating at 600 MHz for ^{1}H and 151 MHz for ^{13}C) at a corrected temperature of 25 °C. All ^{13}C and ^{31}P spectra are proton decoupled. NMR spectra were calibrated using residual nondeuterated solvent ($CHCl_3$ at 7.26 ppm in ^{1}H NMR, 77.16 ppm in ^{13}C NMR; CH_3CN at 1.94 ppm in ^{1}H NMR, 1.32 and 118.26 ppm in ^{13}C NMR; CH_3OH at 3.31 ppm in ^{1}H NMR, 49.0 ppm in ^{13}C NMR; benzene at 7.16 ppm in ^{1}H NMR, 128.06 ppm in ^{13}C NMR). Chemical shifts in ^{31}P, ^{19}F, and ^{11}B NMR spectra were not referenced. Coupling constants (*J*) are reported in Hertz (Hz). The following abbreviations were used to explain signal multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. All NMR data were processed and interpreted using the software package MestReNova.

HRMS data were recorded on a LTQ Orbitrap XL spectrometer or Agilent 6530 accurate-mass QTOF.

Optimization Experiments

All screening and optimization experiments were performed at 0.25-mmol reaction scale following the procedure described in *General procedure A/B*.

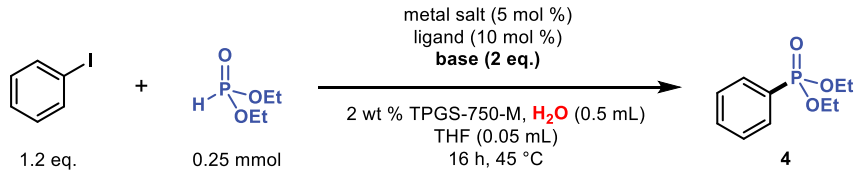
Initial Micellar Transition Metal-Catalyzed C(sp^2)–P Cross-Coupling in Water



entry	metal salt (X mol %)	ligand (Y mol %)	base (2 eq.)	additive/co-solvent	temperature	^{31}P NMR yield[a]
1	SPhos Pd G3 (5)		Et_3N		rt	traces
2	$Pd(OAc)_2$ (5)	XantPhos (10)	Et_3N		rt	30%
3	$Pd(OAc)_2$ (5)	XantPhos (10)	Et_3N		45 °C	21%
4	$Pd(OAc)_2$ (5)	XantPhos (10)	Et_3N	THF (0.05 mL)	45 °C	49%
5	$Pd(OAc)_2$ (5)	DavePhos (10)	Et_3N	THF (0.05 mL)	45 °C	12%
6	$Pd(OAc)_2$ (5)	P(*t*-Bu)$_3$.HBF_4 (10)	Et_3N	THF (0.05 mL)	45 °C	53%
7	$Pd(OAc)_2$ (5)	dppp (10)	Et_3N	THF (0.05 mL)	45 °C	<5%
8	$Pd(OAc)_2$ (5)	dppf (10)	Et_3N	THF (0.05 mL)	45 °C	16%
9	$Pd(OAc)_2$ (5)	BPhen (10)	Et_3N	THF (0.05 mL)	45 °C	ND
10	$Pd(OAc)_2$ (5)	JohnPhos (10)	Et_3N	THF (0.05 mL)	45 °C	22%
11	$Pd(OAc)_2$ (1)	P(*t*-Bu)$_3$.HBF_4 (2)	2,6-lutidine	THF (0.05 mL)	45 °C	45%
12	$Pd(OAc)_2$ (1)	PCy_3.HBF_4 (2)	2,6-lutidine	THF (0.05 mL)	45 °C	ND
13	$Pd(OAc)_2$ (1)	APhos (2)	2,6-lutidine	THF (0.05 mL)	45 °C	25%
14	$Pd(OAc)_2$ (1)	PEPPSI Pd IPr (1)	2,6-lutidine	THF (0.05 mL)	45 °C	ND
15	Ni(XantPhos)Cl_2 (10)		Et_3N	Zn (2 eq.)	rt	ND
16	$NiBr_2$.glyme (1)	phen (2 mol %)	2,6-lutidine	nano Zn (0.5 eq.), THF (0.05 mL)	45 °C	67%
17	$NiBr_2$.glyme (2)	phen (4 mol %)	2,6-lutidine	nano Zn (0.5 eq.), THF (0.05 mL)	45 °C	quantitative (67%)
18	$NiBr_2$.glyme (2)	dtbbpy (4 mol %)	2,6-lutidine	nano Zn (0.5 eq.), THF (0.05 mL)	45 °C	quantitative
19	$Cu(OAc)_2$.H_2O (2.5)	DMEDA (10)	2,6-lutidine	THF (0.05 mL)	45 °C	ND
20	$Cu(OAc)_2$.H_2O (2.5)	phen (5)	2,6-lutidine	THF (0.05 mL)	45 °C	ND
21	$Cu(MeCN)_4$.BF_4 (2.5)	DMEDA (10)	2,6-lutidine	THF (0.05 mL)	45 °C	ND
22	$Cu(MeCN)_4$.BF_4 (2.5)	phen (5)	2,6-lutidine	THF (0.05 mL)	45 °C	ND

Figure S1. Combinations of $Pd(OAc)_2$ with XantPhos or P(*t*-Bu)$_3$ ligands were initially identified as the most efficient catalyst for micellar C(sp^2)–P cross-coupling reaction in water, subsequently identifying effective Ni-catalyzed conditions (entries 15-18). No product was detected under the Cu-catalyzed conditions tested in this study (entries 19-22). [a] ^{31}P NMR yields were determined by integrating all ^{31}P resonances; this approach has been previously used by Montchamp *et al.* (please refer to *J. Am. Chem. Soc.* **2002**, *124*, 9386–9387 and *Org. Lett.* **2011**, *13*, 3270–3273). Isolated yields are reported in italics. ND = not detected.

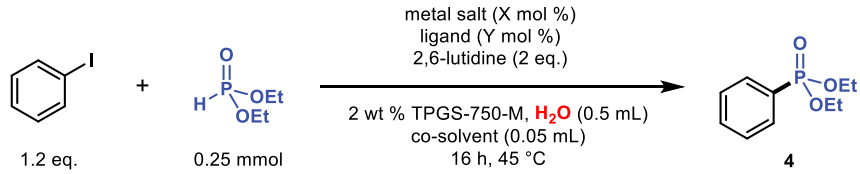
Screening of Micellar Pd-Catalyzed C(sp^2)–P Cross-Coupling in Water: Base Effect



entry	metal salt (X mol %)	ligand (Y mol %)	base (2 eq.)	additive/co-solvent	temperature	^{31}P NMR yield[a]
1	$Pd(OAc)_2$ (5)	XantPhos (10)	Et_3N	THF (0.05 mL)	45 °C	49%
2	$Pd(OAc)_2$ (5)	XantPhos (10)	*t*-BuOK	THF (0.05 mL)	45 °C	ND
3	$Pd(OAc)_2$ (5)	XantPhos (10)	Cs_2CO_3	THF (0.05 mL)	45 °C	traces
4	$Pd(OAc)_2$ (5)	XantPhos (10)	K_3PO_4	THF (0.05 mL)	45 °C	<5 %
5	$Pd(OAc)_2$ (5)	XantPhos (10)	*i*-Pr_2NEt	THF (0.05 mL)	45 °C	26%
6	$Pd(OAc)_2$ (5)	XantPhos (10)	DBU	THF (0.05 mL)	45 °C	<5%
7	$Pd(OAc)_2$ (5)	XantPhos (10)	2,6-lutidine	THF (0.05 mL)	45 °C	88%
8	$Pd(OAc)_2$ (2.5)	XantPhos (5)	(*n*-Bu)$_3$N	EtOAc (0.05 mL)	45 °C	57%
9	$Pd(OAc)_2$ (2.5)	XantPhos (5)	Cy_2NMe	EtOAc (0.05 mL)	45 °C	ND

Figure S2. The highest yields of micellar C(sp^2)–P cross-coupling reactions were achieved when using 2,6-lutidine base (entry 7). [a] ^{31}P NMR yields were determined by integrating all ^{31}P resonances. ND = not detected.

Screening of Micellar Pd-Catalyzed C(sp^2)–P Cross-Coupling in Water: Pd Loading, Co-Solvent



entry	metal salt (X mol %)	ligand (Y mol %)	base (2 eq.)	additive/co-solvent	temperature	^{31}P NMR yield[a]
1	$Pd(OAc)_2$ (5)	XantPhos (10)	2,6-lutidine	THF (0.05 mL)	45 °C	88%
2	$Pd(OAc)_2$ (2.5)	XantPhos (5)	2,6-lutidine	THF (0.05 mL)	45 °C	quantitative
3	$Pd(OAc)_2$ (2.5)	XantPhos (2.5)	2,6-lutidine	THF (0.05 mL)	45 °C	quantitative
4	$Pd(OAc)_2$ (1)	XantPhos (1)	2,6-lutidine	THF (0.05 mL)	45 °C	quantitative (*91%*)
5	$Pd(OAc)_2$ (2.5)	XantPhos (5)	2,6-lutidine	toluene (0.05 mL)	45 °C	95%
6	$Pd(OAc)_2$ (2.5)	XantPhos (5)	2,6-lutidine	1,4-dioxane (0.05 mL)	45 °C	80%
7[#]	$Pd(OAc)_2$ (1)	XantPhos (1)	2,6-lutidine	THF (0.05 mL)	45 °C	88%
8*	$Pd(OAc)_2$ (1)	XantPhos (1)	2,6-lutidine	THF (0.05 mL)	45 °C	50%

Figure S3. Decreasing the Pd catalyst loading increased the yield of the micellar C(sp^2)–P cross-coupling reaction (entry 4). [a] ^{31}P NMR yields were determined by integrating all ^{31}P resonances. Isolated yields are reported in italics. ND = not detected. [#] The reaction was run at ambient temperature (~20 °C). * $P(OEt)_3$ was used instead of $HP(O)(OEt)_2$.

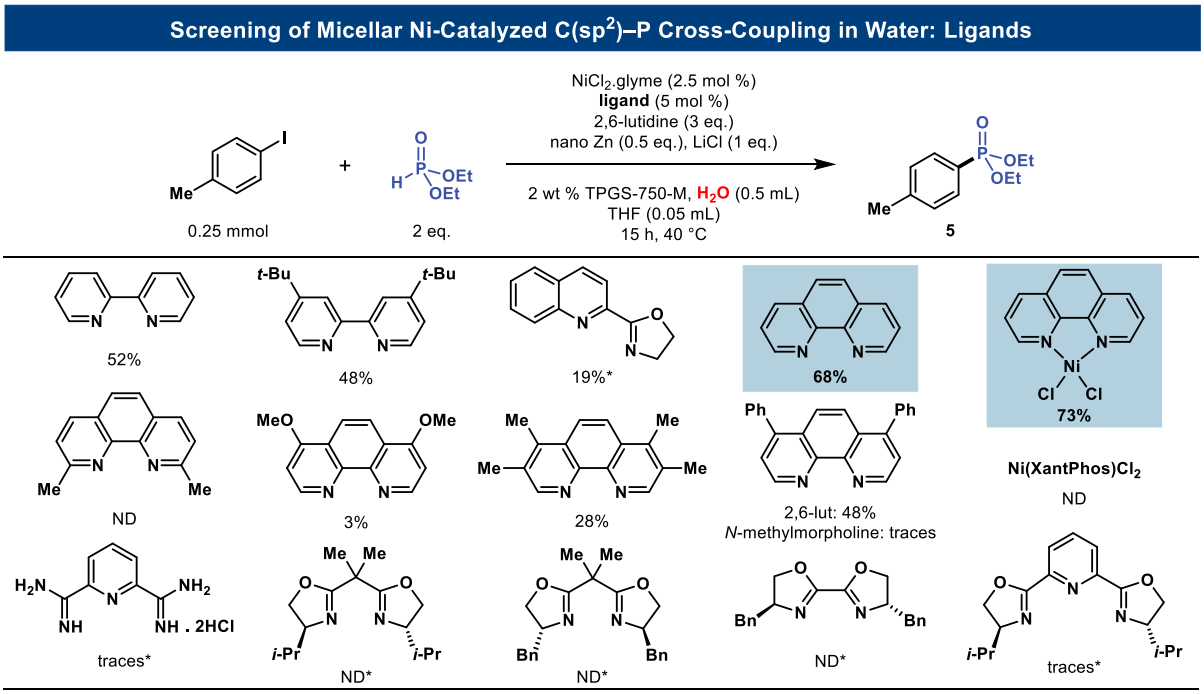
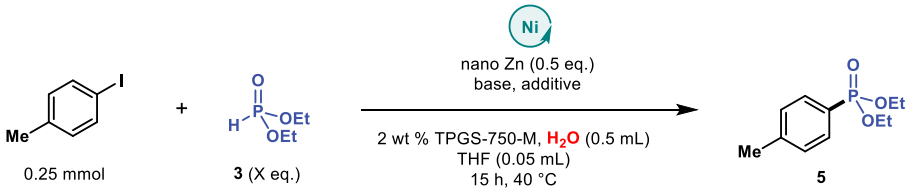


Figure S4. Screening of ligands in Ni-catalyzed micellar C(sp^2)–P cross-coupling reactions showed that 1,10-phenanthroline is the most effective ligand. Yields were determined by ^{1}H NMR using CH_2Br_2 as an internal standard. ND = not detected. * LiBr was used instead of LiCl.

Screening of Micellar Ni-Catalyzed C(sp^2)–P Cross-Coupling in Water: Additives

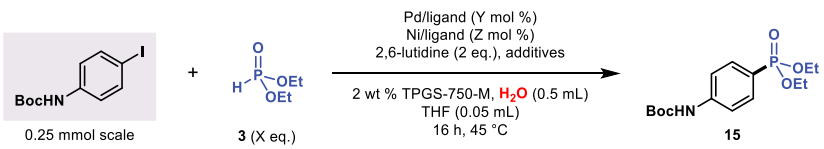


entry	**3** (X eq.)	Ni/ligand (2.5/5 mol %)	base	additives/deviation	yield[a]
1	2	$NiCl_2$.glyme/phen	2,6-lutine (3 eq.)	LiCl (1 eq.)	68%
2	2	$NiCl_2$.glyme/phen	2,6-lutine (3 eq.)	LiBr (1 eq.)	82% (*84%*)
3	2	$NiCl_2$.glyme/phen	2,6-lutine (3 eq.)	LiI (1 eq.)	78%
4	2	$NiCl_2$.glyme/phen	2,6-lutine (3 eq.)	$MgCl_2$ (1 eq.)	76%
5	2	$NiCl_2$.glyme/phen	2,6-lutine (3 eq.)	$ZnBr_2$ (1 eq.)	41%
6	2	$NiCl_2$.glyme/phen	2,6-lutine (3 eq.)	KBr (1 eq.)	73%
7	2	$NiCl_2$.glyme/phen	2,6-lutine (3 eq.)	NaI (1 eq.)	74%
8	2	$NiCl_2$.glyme/phen	2,6-lutine (3 eq.)	LiCl (1 eq.), phthalimide (0.25 eq.)	80%
9	2	$NiCl_2$.glyme/-	2,6-lutine (3 eq.)	LiCl (1 eq.), dimethyl fumarate (0.1 eq.)	ND
10	2	$NiCl_2$.glyme/phen	Et_3N (3 eq.)	LiBr (1 eq.)	ND
11	2	$Ni(acac)_2$/phen	2,6-lutine (3 eq.)	LiBr (1 eq.)	82%
12	2	$NiCl_2.6H_2O$/phen	2,6-lutine (3 eq.)	LiBr (1 eq.)	78%
13	1.5	$Ni(phen)_3Cl_2$	2,6-lutine (3 eq.)	LiBr (1 eq.)	77%
14	1.5	$Ni(PPh_3)_2Cl_2$/phen	2,6-lutine (3 eq.)	LiBr (1 eq.)	71%
15	1.1	$NiCl_2$.glyme/phen	2,6-lutine (3 eq.)	LiBr (1 eq.)	83%
16	1.5	$NiCl_2$.glyme/phen	2,6-lutine (3 eq.)	LiBr (1 eq.), toluene (0.05 mL)	90% (*84 %*)
17	1.5	$NiCl_2$.glyme/phen	2,6-lutine (3 eq.)	LiBr (1 eq.), EtOAc (0.05 mL)	90% (*81%*)
18	1.5	$NiCl_2$.glyme/phen	2,6-lutine (3 eq.)	LiBr (1 eq.), no co-solvent	75%
19	2	Ni(COD)DQ/phen	2,6-lutine (3 eq.)	LiCl (1 eq.)	ND

Figure S5. Additive and co-solvent screening in Ni-catalyzed micellar C(sp^2)–P cross-coupling reactions showed that LiBr (additive) and EtOAc (co-solvent) enhance the reaction. [a] Yields were determined by ^1H NMR using CH_2Br_2 as an internal standard. Isolated yields are reported in italics. ND = not detected.

After identifying effective reactions conditions for Pd- and Ni-catalyzed micellar C(sp^2)–P cross-coupling of 4-iodobenzene and 4-iodotoluene with **3**, we tested the cross-coupling of other (hetero)aryl halides under these conditions, albeit to no avail. Therefore, we screened combinations of Pd and Ni catalytic systems, eventually establishing effective *multimetallic* and *dual-ligand* micellar C(sp^2)–P cross-coupling reaction conditions.

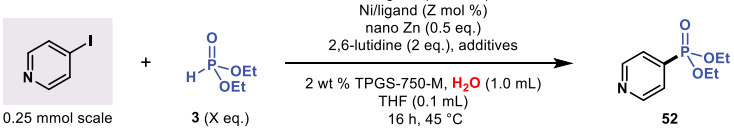
Additional Screening Experiments of Micellar C(sp^2)–P Cross-Coupling in Water



entry	**3** (X eq.)	Pd cat. (Y mol %)	Ni cat. (Z mol %)	additives	yield[a]
1	0.8 : 1	$Pd(OAc)_2$/XantPhos (1/1)		LiCl (1 eq.)	24%
2	2	$Pd(OAc)_2$/XantPhos (1/2)	$NiCl_2$.DME/Bphen (1/2.5)	nano Zn (0.5 eq.), LiCl (1 eq.)	49%
3	2	$Pd[P(t\text{-}Bu)_3]_2$ (2.5)		LiCl (1 eq.), KOAc (0.2 eq.)	traces
4	2.5	$Pd(OAc)_2$/dppf (1/1)	$NiCl_2$.DME/Bphen (1/2)	nano Zn (0.5 eq.), LiCl (1 eq.)	42%
5	2	$Pd(OAc)_2$/XantPhos (2.5/2.5)	$NiCl_2$.DME/phen (2.5/5)	nano Zn (0.5 eq.), LiCl (1 eq.), KOAc (0.5 eq.)	*98%*
6*	2	$Pd(OAc)_2$/XantPhos (2.5/2.5)	$Ni(phen)_3Cl_2$ (1)	nano Zn (0.5 eq.), LiBr (1 eq.)	*95%*

Figure S6. [a] Yields were determined by ^{1}H NMR using CH_2Br_2 as an internal standard. Isolated yields are reported in italics. ND = not detected. * 3 equivalents of 2,6-lutidine.

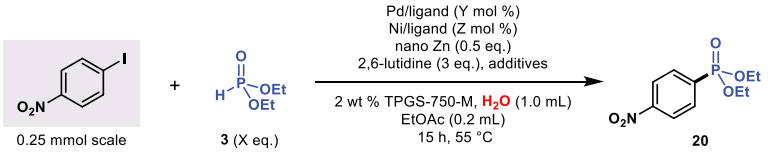
Additional Screening Experiments of Micellar C(sp^2)–P Cross-Coupling in Water



entry	**3** (X eq.)	Pd cat. (Y mol %)	Ni cat. (Z mol %)	additives/deviation	yield[a]
1	2.5	$Pd(OAc)_2$/XantPhos (1/1)	$NiCl_2$.DME/Bphen (1/2)	LiCl (1 eq.)	15%
2	2.5	$Pd(OAc)_2$/dppf (1/1)	$NiCl_2$.DME/Bphen (1/2)	LiCl (1 eq.)	ND
3*	2.5	$Pd(OAc)_2$/Cy-XantPhos (2.5/2.5)	$Ni(Bphen)_2Br_2$ (2.5)	LiCl (1 eq.), KOAc (0.1 eq.)	ND
4*	2.5	$Pd(OAc)_2$/DPEphos (2.5/2.5)	$Ni(Bphen)_2Br_2$ (2.5)	LiCl (1 eq.), KOAc (0.1 eq.)	12%
5*	2.5	$Pd(OAc)_2$/dppb (2.5/2.5)	$Ni(Bphen)_2Br_2$ (2.5)	LiCl (1 eq.), KOAc (0.1 eq.)	ND
6*	2.5	$Pd(OAc)_2$/dtbpf (2.5/2.5)	$Ni(Bphen)_2Br_2$ (2.5)	LiCl (1 eq.), KOAc (0.1 eq.)	ND
7*	2.5	$Pd(OAc)_2$/XantPhos/PPh_3 (2.5/2.5/5)	$Ni(Bphen)_2Br_2$ (2.5)	LiCl (1 eq.), KOAc (0.1 eq.)	16%
8*	2.5		$NiCl_2$.DME/phen (2.5/5)	LiBr (1 eq.)	ND
9*	2	$Pd(OAc)_2$/XantPhos (2.5/2.5)	$NiCl_2$.DME/phen (2.5/5)	acetone (0.2 mL), LiBr (1 eq.)	33%
10*	2	$Pd(OAc)_2$/XantPhos (2.5/2.5)	$Ni(phen)_3Cl_2$ (5)	EtOAc (0.2 mL), LiBr (1 eq.), 55 °C	83% (*89%*)
11*	2	$Pd(OAc)_2$/XantPhos (2.5/2.5)	$Ni(phen)_3Cl_2$ (2.5)	EtOAc (0.2 mL), LiBr (1 eq.), KOAc (0.2 eq.), 55 °C	82%
12*	2	$Pd(OAc)_2$/XantPhos (2.5/2.5)	$Ni(phen)_3Cl_2$ (2.5)	EtOAc (0.2 mL), LiBr (1 eq.)	42%

Figure S7. [a] Yields were determined by ^{1}H NMR using CH_2Br_2 as an internal standard. Isolated yields are reported in italics. ND = not detected. * 3 equivalents of 2,6-lutidine.

Additional Screening Experiments of Micellar C(sp^2)–P Cross-Coupling in Water

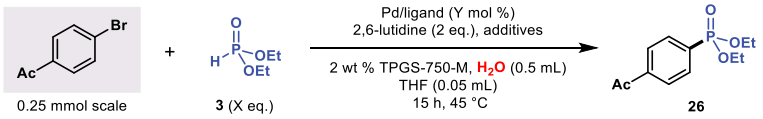


0.25 mmol scale | **3** (X eq.) | **20**

entry	**3** (X eq.)	Pd cat. (Y mol %)	Ni cat. (Z mol %)	additives/deviation	yield[a]
1	1.2	$Pd(OAc)_2$/XantPhos (2.5/2.5)	$Ni(phen)_3Cl_2$ (2.5)	LiBr (1 eq.)	*86%*
2	1.7	$Pd(OAc)_2$/XantPhos (2.5/2.5)	$Ni(phen)_3Cl_2$ (2.5)	LiBr (1 eq.), 40 °C	52%
3	1.7	$Pd(OAc)_2$/XantPhos (1/2)	$NiCl_2$.DME/Bphen (1/2)	H_2O/THF (10:1, 0.55 mL), LiCl (1 eq.), 2,6-lut (2 eq.), 45 °C	7%
4	1.7	$Pd(OAc)_2$/P(*t*-Bu)$_3$.HBF_4 (5/10)		LiBr (1 eq.), KOAc (0.5 eq.), 55 °C	41%
5*	1.7	$Pd(OAc)_2$/P(*t*-Bu)$_3$.HBF_4 (2.5/5)		acetone (0.2 mL), LiBr (1 eq.)	35%
6*	1.7	$Pd(OAc)_2$/P(*t*-Bu)$_3$.HBF_4 (2.5/5)		THF (0.2 mL), LiBr (1 eq.)	20%
7*	1.7	$Pd(OAc)_2$/P(*t*-Bu)$_3$.HBF_4 (2.5/5)		LiBr (1 eq.)	35%

Figure S8. Cross-coupling of 1-iodo-4-nitrobenzene was challenging mainly due to its high crystallinity and thus poor solubility under micellar conditions. Optimal cross-coupling conditions (entry 1) were reached by increasing the reaction volume from 0.55 to 1.2 mL, using EtOAc co-solvent, and increasing the reaction temperature to 55 °C (*cf.* entry 2). [a] Yields were determined by ^{1}H NMR using CH_2Br_2 as an internal standard. Isolated yields are reported in italics. ND = not detected. * More lipophilic HP(O)(O*n*-Bu)$_2$ was used instead of HP(O)(OEt)$_2$ (**3**).

Additional Screening Experiments of Micellar C(sp^2)–P Cross-Coupling in Water

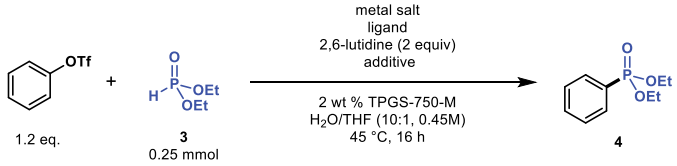


0.25 mmol scale | **3** (X eq.) | **26**

entry	**3** (X eq.)	Pd cat. (Y mol %)	additives/deviation	yield[a]
1	2	Pd[P(*t*-Bu)$_3$]$_2$ (2.5)	LiCl (1 eq.)	11%
2	2	Pd[P(*t*-Bu)$_3$]$_2$ (2.5)	LiCl (1 eq.), KOAc (0.1 eq.)	47%
3	2	Pd[P(*t*-Bu)$_3$]$_2$ (2.5)	LiCl (1 eq.), KOAc (0.5 eq.)	72%
4	2	Pd[P(*t*-Bu)$_3$]$_2$ (2.5)	LiCl (1 eq.), KOAc (1 eq.)	42%
5	2	Pd[P(*t*-Bu)$_3$]$_2$/$Pd(OAc)_2$ (2.5/2.5)	LiCl (1 eq.)	76%
6	2	Pd[P(*t*-Bu)$_3$]$_2$/$Pd(OAc)_2$ (1.25/1.25)	LiCl (1 eq.), KOAc (0.5 eq.)	18%
7	2	Pd[P(*t*-Bu)$_3$]$_2$/$Pd(OAc)_2$/XantPhos (2.5/1/1)	EtOAc (0.1 mL), LiBr (1 eq.)	*89%*

Figure S9. Screening experiments with 4-bromoacetophenone (model aryl bromide) revealed that dual-ligand Pd-catalyzed conditions afford **26** in the highest yield (entry 7). Adding KOAc in the reaction also increased yields of **26** (entries 2-4). [a] Yields were determined by ^{1}H NMR using CH_2Br_2 as an internal standard. Isolated yields are reported in italics.

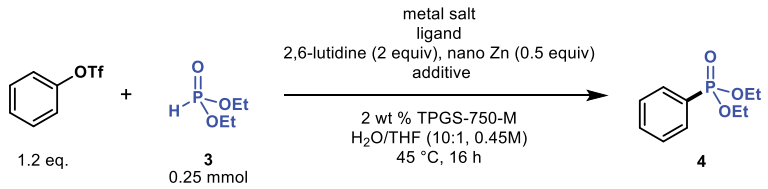
Micellar C(sp^2)–P Cross-Coupling of Aryl Triflates in Water, part 1



entry	metal salt (X mol %)	ligand (Y mol %)	additive/deviation	^{31}P NMR yield
1	$Pd(OAc)_2$ (2.5%)	XantPhos (2.5%)		ND
2	$Pd(OAc)_2$ (2.5%)	dppp (2.5%)		ND
3	$Pd(OAc)_2$ (2.5%)	dppf (2.5%)		13%
4	$NiBr_2$.glyme (2%)	phen (4%)	nano Zn (1 equiv)	traces
5	$Pd(OAc)_2$ (2.5%)	dppf (3%)	65 hours	34%
6	$Pd(OAc)_2$ (2.5%)	P(*t*-Bu)$_3$ (2.5%)		ND
7	$PdCl_2$ (2.5%)	dppf (3%)		12%
8	$Pd(TFA)_2$ (2.5%)	dppf (3%)		11%
9	$Pd(OAc)_2$ (2.5%)	dppf (2.5%), P(*t*-Bu)$_3$ (2.5%)		18%
10	$Pd(OAc)_2$ (2.5%)	dppf (3%)	LiBr (0.5 equiv)	ND
11	$Pd(OAc)_2$ (2.5%)	dppf (3%)	KF (0.5 equiv)	22%
12	$Pd(OAc)_2$ (2.5%)	dppf (3%)	TBAI (0.5 equiv)	ND
13	$Pd(OAc)_2$ (2.5%)	dppf (3%)	*t*-BuTMG instead of 2,6-lut.	traces
14	$Pd(OAc)_2$ (2.5%)	dppf (3%)	*N*-Me-morpholine instead of 2,6-lut.	38%
15	$Pd(OAc)_2$ (2.5%)	dppf (9%)		17%
16	$Pd(OAc)_2$ (2.5%), $NiBr_2$.glyme (2.5%)	dppf (3%), phen (7%)	nano Zn (0.5 equiv), KF (1 equiv)	64%
17	$Pd(OAc)_2$ (2.5%), $NiBr_2$.glyme (2.5%)	dppf (3%), Bphen (7%)	nano Zn (0.5 equiv), KF (1equiv)	73%
18	$Pd(OAc)_2$ (2.5%), $NiBr_2$.glyme (2.5%)	dppf (3%), bpy (7%)	nano Zn (0.5 equiv), KF (1 equiv)	67%
19	$Pd(OAc)_2$ (2.5%), $NiBr_2$.glyme (2.5%)	dppf (3%), phen (7%)	nano Zn (0.5 equiv), LiCl (1 equiv)	94% (*41%*)
20	$Pd(OAc)_2$ (2.5%), $NiBr_2$.glyme (2.5%)	dppf (3%), phen (7%)	nano Zn (0.5 equiv)	64%
21	$Pd(OAc)_2$ (2.5%), $NiBr_2$.glyme (2.5%)	dppf (3%), Bphen (7%)	nano Zn (0.5 equiv), LiCl (1 equiv)	82% (*56%*)
22	$Pd(OAc)_2$ (2.5%), $NiCl_2$.glyme (2.5%)	dppf (3%), phen (7%)	nano Zn (0.5 equiv), LiCl (1 equiv)	73%
23	$Pd(OAc)_2$ (2.5%), $NiCl_2$.glyme (2.5%)	dppf (3%), Bphen (7%)	nano Zn (0.5 equiv), LiCl (1 equiv), 55 °C	traces
24	$Pd(OAc)_2$ (2.5%), $NiCl_2$.glyme (2.5%)	XantPhos(3%), Bphen (7%)	nano Zn (0.5 equiv), LiCl (1 equiv), 55 °C	ND
25	$Pd(OAc)_2$ (2.5%), $NiBr_2$.glyme (2.5%)	dppf (3%), PCy_3 (7%)	nano Zn (0.5 equiv), LiCl (1 equiv)	7%
26	$Pd(OAc)_2$ (2.5%), $NiCl_2$.XantPhos (2.5%)	dppf (3%)	nano Zn (0.5 equiv), LiCl (1 equiv)	trace
27	$Pd(OAc)_2$ (2.5%), $NiCl_2$.dppf (2.5%)	dppf (3%)	nano Zn (0.5 equiv), LiCl (1 equiv)	20%
28	$Pd(OAc)_2$ (2.5%), $NiCl_2$.dppp (2.5%)	dppf (3%)	nano Zn (0.5 equiv), LiCl (1 equiv)	ND
29	$Pd(OAc)_2$ (2.5%), Ni(COD)DQ (2.5%)	dppf (3%), Bphen (7%)	nano Zn (0.5 equiv), LiCl (1 equiv)	80% (35% ^{1}H NMR)
30	$Pd(OAc)_2$ (2.5%), $NiBr_2$.glyme (2.5%)	P*t*-Bu$_3$ (6%), Bphen (7%)	nano Zn (0.5 equiv), LiCl (1 equiv)	ND
31	$Pd(OAc)_2$ (2.5%), $NiBr_2$.glyme (2.5%)	dppf (3%), terpy (3%)	nano Zn (0.5 equiv), LiCl (1 equiv)	12/57% (12% ^{1}H NMR)
32	$Pd(OAc)_2$ (2.5%), $NiBr_2$.glyme (2.5%)	dtbpf (3%), Bphen (7%)	nano Zn (0.5 equiv), LiCl (1 equiv)	ND
33	$Pd(OAc)_2$ (2.5%), $Fe(acac)_3$ (2.5%)	dppf (3%), dppBz (3%)	nano Zn (0.5 equiv), LiCl (1 equiv)	ND
34	$Pd(OAc)_2$ (2.5%), $NiBr_2$.glyme (2.5%)	dppf (3%), Bphen (7%)	nano Zn (0.5 equiv), LiCl (1 equiv)	93% (61% ^{1}H NMR)
35	$Pd(OAc)_2$ (2.5%), $NiBr_2$.glyme (2.5%)	dppf (3%), Bphen (7%)	Mn (0.5 equiv), LiCl (1 equiv)	ND
36	$Pd(OAc)_2$ (2.5%), $NiBr_2$.glyme (2.5%)	dppf (3%), Bphen (7%)	nano Zn (1 equiv), LiCl (1 equiv)	89% (33% ^{1}H NMR)
37	$Pd(OAc)_2$ (2.5%), $NiBr_2$.glyme (2.5%)	dppf (3%), Bphen (7%)	nano Zn (0.25 equiv), LiCl (1 equiv)	74% (34% ^{1}H NMR)
38	$Pd(OAc)_2$ (2.5%), $NiBr_2$.glyme (2.5%)	dppf (3%), Bphen (7%)	nano Zn (0.5 equiv), LiCl (3 equiv)	24%
39	$Pd(OAc)_2$ (2.5%), $NiBr_2$.glyme (2.5%)	dppf (3%), Bphen (7%)	nano Zn (0.5equiv), $MgCl_2$ (3 equiv)	24%
40	$Pd(OAc)_2$ (2.5%), $NiBr_2$.glyme (2.5%)	dppf (3%), Bphen (7%)	nano Zn (0.5 equiv), NaCl (3 equiv)	14%
41	$Pd(OAc)_2$ (2.5%), $NiBr_2$.glyme (2.5%)	dppf (3%), Bphen (7%)	nano Zn (0.5 equiv), LiCl (1 equiv), 10 vol % HFIP	<5% (^{1}H NMR)
42	$Pd(OAc)_2$ (2.5%), $NiBr_2$.glyme (2.5%)	dppf (3%), Bphen (7%)	nano Zn (0.5 equiv), LiCl (1 equiv), 10 vol % DME	11% (^{1}H NMR)
43	$Pd(OAc)_2$ (2.5%), $NiBr_2$.glyme (2.5%)	dppf (3%), Bphen (7%)	nano Zn (0.5 equiv), LiCl (1 equiv), 10 vol % EG	40% (^{1}H NMR)
44	$Pd(OAc)_2$ (2.5%), $NiBr_2$.glyme (2.5%)	dppf (3%), Bphen (7%)	nano Zn (0.5 equiv), LiCl (1 equiv), 10 vol % acetone	38% (^{1}H NMR)
45	$Pd(OAc)_2$ (2.5%), $NiBr_2$.glyme (2.5%)	dppf (3%), Bphen (7%)	nano Zn (0.5 equiv), LiCl (1 equiv), 10 vol % toluene	traces (^{1}H NMR)
46	$Pd(OAc)_2$ (2.5%), $NiBr_2$.glyme (2.5%)	dppf (3%), Bphen (7%)	nano Zn (0.5 equiv), LiCl (1 equiv), 10 vol % 1,4-dioxane	25% (^{1}H NMR)

Figure S10. Screening experiments with phenyl trifluoromethanesulfonate (model aryl triflate), part 1. Yields were determined by ^{31}P NMR spectroscopy and/or ^{1}H NMR with CH_2Br_2 as an internal standard. Isolated yields are reported in italics. HFIP = 1,1,1,3,3,3-hexafluoro-2-propanol, DME = 1,2-dimethoxyethane, EG = ethylene glycol. The highest isolated yields were achieved under *multimetallic* Pd/Ni conditions using dppf and phen/Bphen ligands (entries 19 and 21).

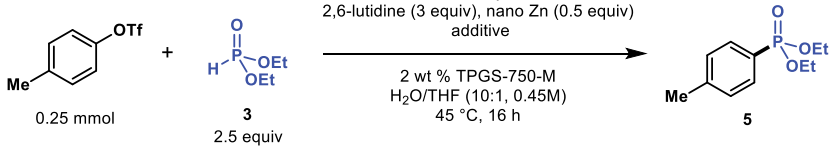
Micellar C(sp^2)–P Cross-Coupling of Aryl Triflates in Water, part 2



entry	metal salt (X mol %)	ligand (Y mol %)	additive/deviation	^{31}P NMR yield
1	$Pd(OAc)_2$ (2.5%), $NiBr_2$.glyme (2.5%)	dppf (2.5%), Bphen (7%)	2,4,6-collidine instead of 2,6-lut.	81% (40% ^{1}H NMR)
2	$Pd(OAc)_2$ (2.5%), $NiBr_2$.glyme (2.5%)	dppf (2.5%), Bphen (7%)	1,2,2,6,6-pentamethylpiperidine instead of 2,6-lut.	trace
3	$Pd(OAc)_2$ (2.5%), $NiBr_2$.glyme (2.5%)	dppf (2.5%), Bphen (7%)	*N*-methylmorpholine instead of 2,6-lut.	19% (^{1}H NMR)
4	$Pd(OAc)_2$ (2.5%), $NiBr_2$.glyme (2.5%)	dppf (2.5%), Bphen (7%)	LiCl (1 equiv), dimethylfumarate (0.25 equiv)	traces (messy)
5	$Pd(OAc)_2$ (2.5%), $NiBr_2$.glyme (2.5%)	dppf (2.5%), Bphen (7%)	phthalimide (0.25 equiv)	30% (^{1}H NMR)
6	$Pd(OAc)_2$ (2.5%), $NiBr_2$.glyme (2.5%)	dppf (2.5%), Bphen (7%)	$NaPF_6$ (0.5 equiv)	ND
7	$Pd(OAc)_2$ (2.5%), $NiBr_2$.glyme (2.5%)	dppf (2.5%), Bphen (7%)	$Zn(OTf)_2$ (0.5 equiv)	ND
8	$Pd(OAc)_2$ (2.5%), $NiBr_2$.glyme (2.5%)	dppf (2.5%), Bphen (7%)	$Mg(OTf)_2$ (0.5 equiv)	ND
9	$Pd(OAc)_2$ (2.5%), $NiBr_2$.glyme (2.5%)	dppf (2.5%), Bphen (7%)	LiF (1 equiv)	38% (^{1}H NMR)
10	$Pd(OAc)_2$ (2.5%), $NiBr_2$.glyme (2.5%)	dppf (2.5%), Bphen (7%)	CsF (1 equiv)	21% (^{1}H NMR)
11	$Pd(OAc)_2$ (2.5%), $Ni(OAc)_2.4H_2O$ (1%)	dppf (2.5%), Bphen (2%)		traces
12	$Pd(OAc)_2$ (2.5%), $Ni(acac)_2$ (1%)	dppf (2.5%), Bphen (2%)	LiCl (1 equiv)	37%

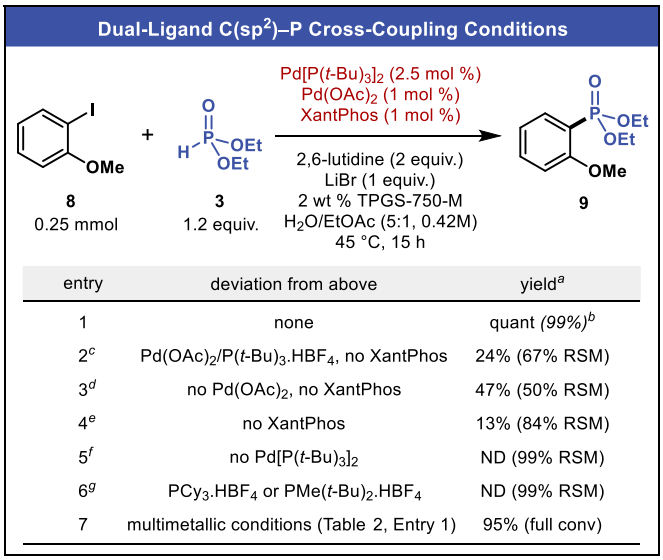
Figure S11. Screening experiments with phenyl trifluoromethanesulfonate (model aryl triflate), part 2. Yields were determined by ^{31}P NMR spectroscopy and/or ^{1}H NMR with CH_2Br_2 as an internal standard. Isolated yields are reported in italics. Weakly coordinating anions (OTf, PF_6) inhibit the reaction (entries 6-8).

Micellar C(sp^2)–P Cross-Coupling of Aryl Triflates in Water, part 3



entry	Pd catalyst (X mol %)	Ni catalyst (Y mol %)	additive/deviation	^{31}H NMR yield
1	$Pd(OAc)_2$/dppf (2.5/3%)	$NiBr_2$.DME/Bphen (2.5/7%)	LiCl (1 equiv)	49% (*51%*)
2	$Pd(OAc)_2$/dppf (1/1%)	$NiBr_2$.DME/Bphen (1/2%)	LiCl (1 equiv)	25%
3	$Pd(OAc)_2$/dppf (1/1%)	$Ni(Bphen)_2Br_2$ (1%)	LiCl (1 equiv)	34%
4	$Pd(OAc)_2$/dppf (5/6%)	$Ni(Bphen)_2Br_2$ (5%)	LiCl (1 equiv)	60%
5	$Pd(OAc)_2$/dppf (1/1%)	$Ni(Bphen)_2Br_2$ (5%)	LiCl (1 equiv)	30%
6	$Pd(OAc)_2$/dppf (5/6%)	$Ni(Bphen)_2Br_2$ (1%)	LiCl (1 equiv)	55%
7	$Pd(OAc)_2$/dppf (2.5/3%)	$Ni(Bphen)_2Br_2$ (2%)	KF (0.5 equiv)	26%
8	$Pd(OAc)_2$/dppf (2.5/3%)	$Ni(Bphen)_2Br_2$ (2%)	KF (0.5 equiv), LiCl (1 equiv)	52%
9	$Pd(OAc)_2$/dppf (2.5/3%)	$Ni(Bphen)_2Br_2$ (2%)	LiCl (1 equiv), DMAP (0.25 equiv)	41%

Figure S12. Screening experiments with *p*-tolyl trifluoromethanesulfonate (model aryl triflate). Yields were determined by ^{1}H NMR with CH_2Br_2 as an internal standard. Isolated yields are reported in italics.



entry	deviation from above	yield[a]
1	none	quant *(99%)*[b]
2[c]	$Pd(OAc)_2$/P(*t*-Bu)$_3$.HBF_4, no XantPhos	24% (67% RSM)
3[d]	no $Pd(OAc)_2$, no XantPhos	47% (50% RSM)
4[e]	no XantPhos	13% (84% RSM)
5[f]	no Pd[P(*t*-Bu)$_3$]$_2$	ND (99% RSM)
6[g]	$PCy_3.HBF_4$ or PMe(*t*-Bu)$_2$.HBF_4	ND (99% RSM)
7	multimetallic conditions (Table 2, Entry 1)	95% (full conv)

Figure S13. Dual-ligand C(sp^2)–P cross-coupling conditions under micellar catalysis conditions (more detailed Table 3 of the manuscript). [a]Yields determined by ^{1}H NMR using CH_2Br_2 internal standard. [b]Isolated yield. The reactions were performed using *General procedure B* with the following modifications: [c]**3** (2 equiv), $Pd(OAc)_2$ (5 mol %), P(*t*-Bu)$_3$.HBF_4 (10 mol %), 18 h at 50 °C. [d]**3** (2 equiv), Pd[(P(*t*-Bu)$_3$]$_2$ (5 mol %), KOAc (0.5 equiv), 18 h at 50 °C. [e]**3** (2 equiv), Pd[P(*t*-Bu$_3$)]$_2$ (2.5 mol %), $Pd(OAc)_2$ (2.5 mol %), 18 h at 50 °C. [f]**3** (2 equiv), $Pd(OAc)_2$ (2.5 mol %), XantPhos (2.5 mol %). [g]**3** (2 equiv), $Pd(OAc)_2$ (5 mol %), $PCy_3.HBF_4$ of PMe(*t*-Bu)$_2$.HBF_4 (10 mol %), 18 h at 50 °C. RSM = recovered starting material. ND = not detected.

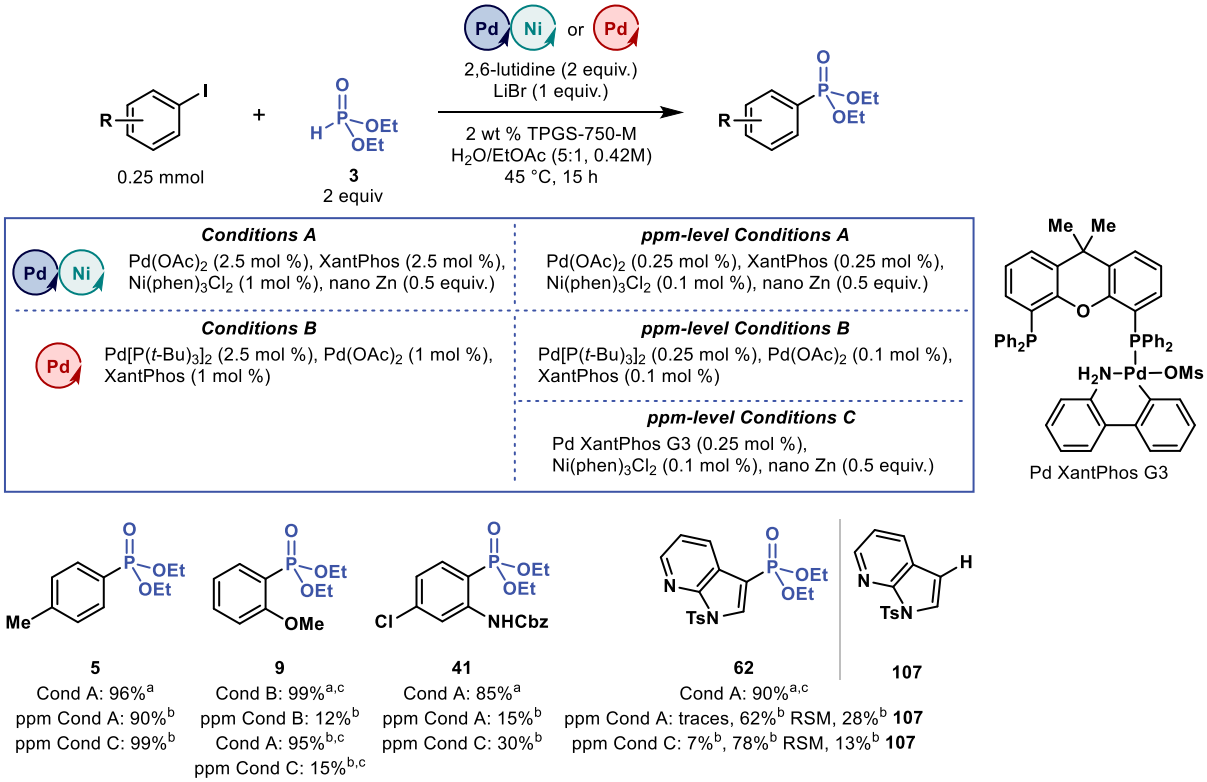


Figure S14. Comparison of optimized reaction conditions for multimetallic and dual-ligand C(sp^2)–P cross-coupling with an initial reaction condition using ppm-level catalysis. For the latter, General procedure A/B were used with the following modification. The catalysts were added into the reaction mixture as a stock solution (0.1 mL; the stock solution was prepared by combining 2.5 mol % $Pd(OAc)_2$, 2.5 mol % XantPhos, and 1 mol % $Ni(phen)_3Cl_2$ in 1.0 mL of 2 wt % TPGS-750-M in H_2O and stirring at laboratory temperature for 1 hour under Ar before use). Stock catalyst solutions containing Pd[P(*t*-Bu)$_3$]$_2$/$Pd(OAc)_2$/XantPhos and Pd XantPhos G3/ $Ni(phen)_3Cl_2$ were prepared in a similar manner. [a]Isolated yield. [b]Determined by ^{1}H NMR analysis with CH_2Br_2 as an internal standard. [c]1.2 equiv of **3**. RSM = recovered starting material.

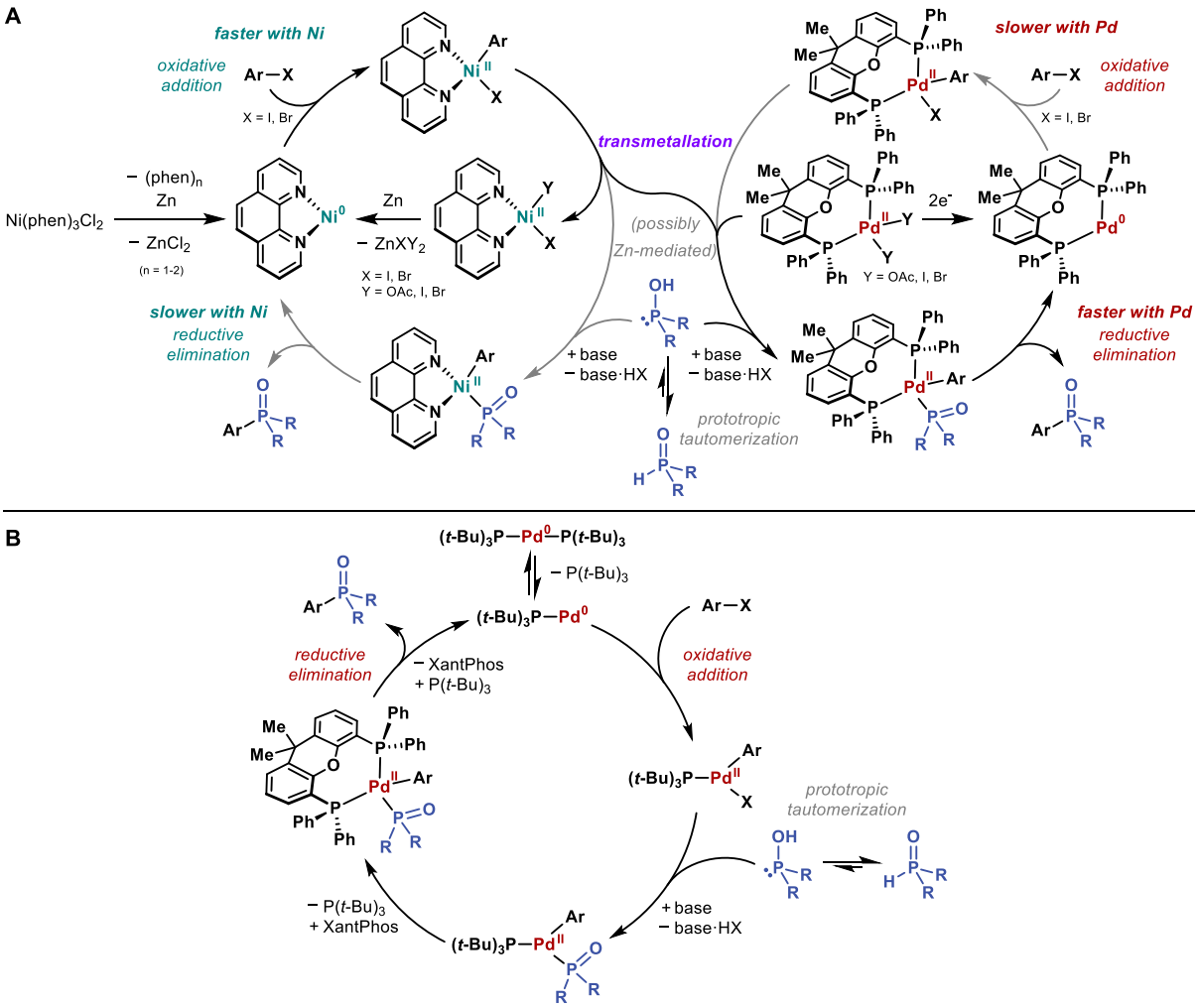
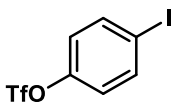


Figure S15. Plausible mechanism for A) multimetallic and B) dual-ligand C(sp^2)–P cross-coupling reactions. Please note, that acetates [supplied in $Pd(OAc)_2$] also affect the reaction performance; however, their exact role (*e.g.*, being bound to Pd centers and facilitating coordination of phosphorus nucleophiles) in the *micellar* C(sp^2)–P coupling mechanism currently remains unclear. Please refer to refs. 23c-d and 23h for mechanistic studies on C(sp^2)–P coupling *in organic solvents*.

Substrate Synthesis

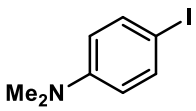
The nickel catalyst used in this study, $Ni(phen)_3Cl_2$,[1] is a free-flowing, non-hygroscopic complex prepared simply by mixing 1,10-phenanthroline (3 equiv) with $NiCl_2.6H_2O$ (1 equiv) in refluxing anhydrous methanol for 1 hour. After cooling to laboratory temperature, the resulting pink precipitate was filtered and thoroughly dried under high-vacuum to afford $Ni(phen)_3Cl_2$.

4-Iodophenyl trifluoromethanesulfonate (SI-1)



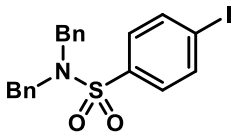
SI-1 was prepared according to a previously reported procedure from 4-iodophenol.[2]

4-Iodo-*N*,*N*-dimethylaniline (SI-2)



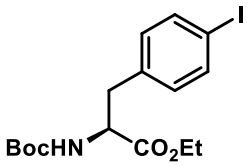
SI-2 was prepared according to a previously reported procedure from 4-iodoaniline.[3]

***N*,*N*-Dibenzyl-4-iodobenzenesulfonamide (SI-3)**



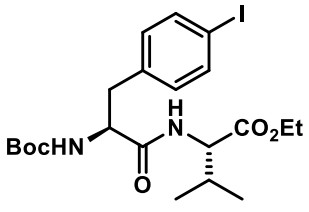
SI-3 was prepared according to a previously reported procedure from 4-iodobenzenesulfonyl chloride and dibenzylamine.[4]

Ethyl (*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(4-iodophenyl)propanoate (SI-4)



SI-4 was prepared according to a previously reported procedure from *N*-Boc-4-iodophenylalanine.[5]

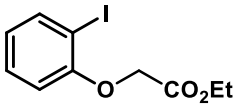
Ethyl ((*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(4-iodophenyl)propanoyl)-L-valinate (SI-5)



SI-5 was prepared according to the micellar COMU-mediated peptide coupling procedure.[6] A test-tube was charged with *N*-Boc-4-iodophenylalanine (430 mg, 1.1 mmol), 2,6-lutidine (361 µL, 3.1 mmol), 2 wt % TPGS-750-M in H_2O (2.0 mL) and a magnetic stir bar. After stirring at laboratory temperature for 5 minutes, L-valine ethyl ester hydrochloride (182 mg, 1.0 mmol) and COMU (471 mg, 1.1 mmol) were added to the reaction mixture. The reaction mixture was stirrer at laboratory temperature for 16 hours. The reaction mixture was then extracted with EtOAc (3 × 4 mL). Combined organic extracts were washed with 1M aq. HCl (3 × 10 mL), sat. aq. $NaHCO_3$ (4 × 10 mL), sat. aq. K_2CO_3 (3 × 10 mL), dried over Na_2SO_4 and concentrated under reduced pressure to afford **SI-5** as a light-yellow solid (432 mg, 83%), containing trace amounts of TPGS-750-M but **SI-5** was used with no further purification in the $C(sp^2)$–P cross-coupling reaction.

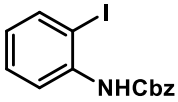
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58 (d, *J* = 8.9 Hz, 2H), 6.94 (d, *J* = 8.0 Hz, 2H), 6.45 (d, *J* = 8.4 Hz, 1H), 5.08 (d, *J* = 8.4 Hz, 1H), 4.42 (dd, *J* = 8.8, 4.8 Hz, 1H), 4.34–4.29 (m, 1H), 4.16 (q, *J* = 7.2 Hz, 2H), 3.05–2.96 (m, 2H), 2.14–2.06 (m, 1H), 1.40 (s, 9H), 1.25 (t, *J* = 7.2 Hz, 3H), 0.87 (d, *J* = 6.8 Hz, 3H, overlapped), 0.85 (d, *J* = 6.8 Hz, 3H, overlapped) ppm;
^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 171.4, 170.9, 137.7, 136.4, 131.5, 92.4, 70.7, 61.4, 57.3, 55.7, 37.7, 31.4, 28.4, 18.9, 17.8, 14.3 ppm;
HRMS (ESI-TOF) calc'd for $C_{21}H_{32}O_5N_2I$ $[M+H]^+$: 519.13504, found 519.13493.

Ethyl 2-(2-iodophenoxy)acetate (SI-6)



SI-6 was prepared according to a previously reported procedure from 2-iodophenol and ethyl 2-bromoacetate.[7]

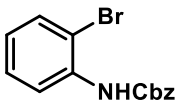
Benzyl (2-iodophenyl)carbamate (6)



6 was prepared according to a modified procedure using 2-iodoaniline instead of 2-bromoaniline.[8] To a solution of 2-iodoaniline (3.0 g, 13.7 mmol) and pyridine (1.7 mL, 20.6 mmol) in EtOAc (30 mL) was slowly added benzyl chloroformate (2.4 mL, 16.5 mmol) dropwise at 0 °C. The reaction mixture was then allowed to warm to laboratory temperature and stirred for 2 hours. The reaction mixture was then diluted with H_2O (50 mL) and EtOAc (20 mL), organic phase was separated, washed with 1M aq. HCl (2 × 50 mL), sat. aq. $NaHCO_3$ (50 mL), dried over Na_2SO_4 and concentrated under reduced pressure. Hexane (~20 mL) was added to the residue and the mixture was then placed in a freezer (-28 °C) overnight. The formed precipitate was then filtered, washed with cold hexane (2 × 5 mL) and dried to afford **6** as an off-white solid (3.8 g, 79%).

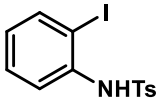
Spectral data match previously reported results,[9] and ^{1}H NMR data are provided here for convenience.
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.08 (d, *J* = 8.0 Hz, 1H), 7.76 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.45–7.31 (m, 6H), 7.02 (br s, 1H), 6.80 (ddd, *J* = 9.2, 7.6, 1.6 Hz, 1H), 5.23 (s, 2H) ppm.

Benzyl (2-bromophenyl)carbamate (SI-7)



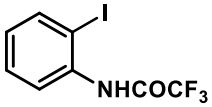
SI-7 was prepared according to a previously reported procedure from 2-bromoaniline.[8]

***N*-(2-iodophenyl)-4-toluenesulfonamide (SI-8)**



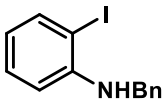
SI-8 was prepared according to a previously reported procedure from 2-iodoaniline.[10]

2,2,2-Trifluoro-*N*-(2-iodophenyl)acetamide (SI-9)



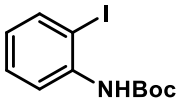
SI-9 was prepared according to a previously reported procedure from 2-iodoaniline.[11]

***N*-Benzyl-2-iodoaniline (SI-10)**



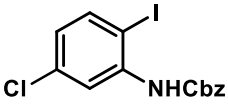
SI-10 was prepared according to a previously reported procedure from 2-iodoaniline.[12]

***tert*-Butyl (2-iodophenyl)carbamate (SI-11)**



SI-11 was prepared according to a previously reported procedure from 2-iodoaniline.[13]

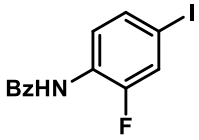
Benzyl (5-chloro-2-iodophenyl)carbamate (SI-12)



SI-12 was prepared according to a modified Cbz-protection procedure.[8] To a solution of 5-chloro-2-iodoaniline (1.014 g, 4.0 mmol) and pyridine (451 µL, 5.6 mmol) in EtOAc (10 mL) was slowly added benzyl chloroformate (685 µL, 4.8 mmol) dropwise at laboratory temperature. After 2 hours, the reaction was diluted with H_2O (20 mL) and EtOAc (25 mL), organic phase was separated, washed with 1M aq. HCl (2 × 20 mL), sat. aq. $NaHCO_3$ (20 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The solid residue was dissolved in minimal amount of CH_2Cl_2 (1 vol) and hexane was added (4 vol). Upon stirring, precipitate formed and was then filtered, washed with hexane (2 × 10 mL) and hexane/CH_2Cl_2 (5:1, 5 mL) and dried to afford **SI-12** as a white solid (550 mg, 35%).

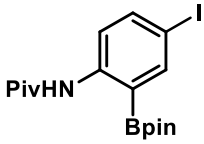
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.19 (d, *J* = 2.4 Hz, 1H), 7.65 (d, *J* = 8.4 Hz, 1H), 7.45–7.35 (m, 5H), 7.03 (br s, 1H), 6.81 (dd, *J* = 8.4, 2.4 Hz, 1H), 5.30 (s, 2H) ppm;
^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 153.0, 139.47, 139.43, 135.7, 135.6, 128.8, 128.7, 128.6, 125.2, 120.1, 67.7 ppm;
HRMS (ESI-TOF) calc'd for $C_{14}H_{11}O_2NClINa$ $[M+Na]^+$: 409.94152, found 409.94145.

***N*-(2-Fluoro-4-iodophenyl)benzamide (SI-13)**



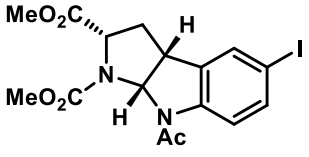
SI-13 was prepared according to a previously reported procedure from 2-fluoro-4-iodoaniline.[14]

***N*-(4-Iodo-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)pivalamide (SI-14)**



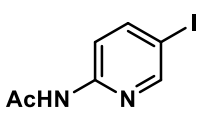
SI-14 was prepared according to a previously reported procedure from *N*-(4-iodophenyl)pivalamide.[15]

Iodide SI-15



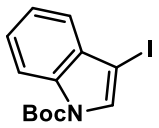
SI-15 was prepared according to a previously reported procedure.[16]

tert-Butyl 3-iodo-1*H*-indole-1-carboxylate (SI-16)



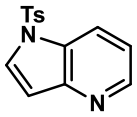
SI-16 was prepared according to a previously reported procedure from 2-amino-5-iodopyridine.[17]

tert-Butyl 3-iodo-1*H*-indole-1-carboxylate (SI-17)



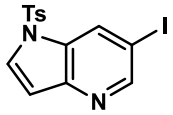
SI-17 was prepared according to a previously reported procedure from indole.[18]

1-Tosyl-1*H*-pyrrolo[3,2-*b*]pyridine (SI-18)



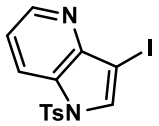
SI-18 was prepared according to a previously reported procedure.[19]

6-Iodo-1-tosyl-1*H*-pyrrolo[3,2-*b*]pyridine (SI-19)



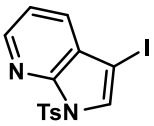
SI-19 was prepared according to a previously reported procedure from **SI-18**.[20]

3-Iodo-1-tosyl-1*H*-pyrrolo[3,2-*b*]pyridine (SI-20)



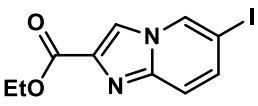
SI-20 was prepared according to a previously reported procedure procedure.[21]

3-Iodo-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridine (SI-21)



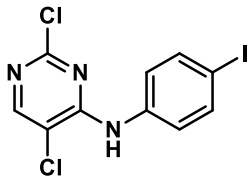
SI-21 was prepared according to a previously reported procedure.[21]

Ethyl 6-iodoimidazo[1,2-*a*]pyridine-2-carboxylate (SI-22)



SI-22 was prepared according to a previously reported procedure.[22]

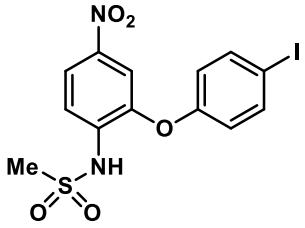
2,5-Dichloro-*N*-(4-iodophenyl)pyrimidin-4-amine (SI-23)



SI-23 was prepared according to a previously reported micellar S_NAr procedure.[23] A test-tube was charged with 4-iodoaniline (110 mg, 0.5 mmol), $K_3PO_4 \cdot H_2O$ (115 mg, 0.5 mmol) and a magnetic stir bar. Then 2 wt % TPGS-750-M in H_2O (1.0 mL) was added, followed by 2,4,5-trichloropyrimidine (**114**, 57.3 µL, 0.5 mmol), and the reaction mixture was stirred at laboratory temperature for 24 hours. The reaction mixture was extracted by EtOAc (3 × ~1 mL) and combined organic extracts were concentrated under reduced pressure. The residue was purified by pTLC (hexane/EtOAc 7:2) to afford **SI-23** as an off-white solid (159 mg, 87%).

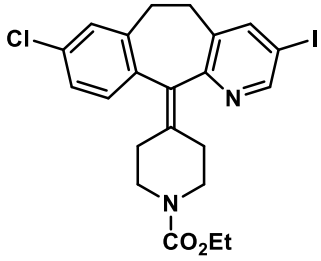
Spectral data match previously reported results,[24] and $^1H/^{13}C$ NMR data are provided here for convenience.
R_f = 0.25 (hexane/EtOAc 4:1). Stain: UV active, $KMnO_4$;
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.17 (s, 1H), 7.69–7.65 (m, 2H), 7.41–7.37 (m, 2H), 7.24 (bs, 1H) ppm;
$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 158.1, 156.2, 154.8, 138.1, 136.7, 122.9, 113.9, 88.7 ppm;

Iodo-nimesulide SI-24



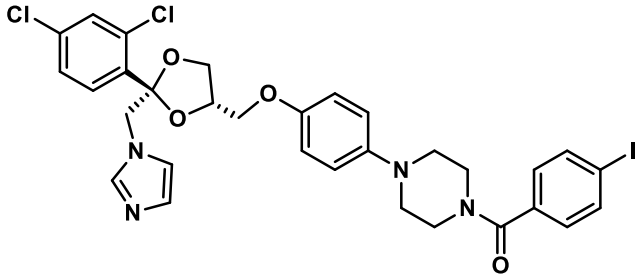
SI-24 was prepared according to a previously reported procedure from nimesulide.[25]

Iodo-loratadine SI-25



SI-25 was prepared according to a previously reported procedure from loratadine.[20]

Iodide SI-26

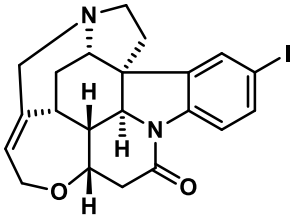


SI-26 was prepared according to the micellar COMU-mediated peptide coupling procedure.[6] A small vial was charged with 4-iodobenzoic acid (273 mg, 1.0 mmol), 2,6-lutidine (361 µL, 3.1 mmol), 2 wt % TPGS-750-M in H_2O (4.0 mL), THF (0.5 mL) and a magnetic stir bar. After stirring at laboratory temperature for 5 minutes, *des*-acetylketoconazole[26] (531 mg, 1.0 mmol) and COMU (471 mg, 1.1 mmol) were added to the reaction mixture. The reaction mixture was vigorously stirrer at 40 °C for 15 hours. Then the reaction mixture was extracted with EtOAc (3 × 10 mL). Combined organic extracts were washed with sat. aq.

K_2CO_3 (6 × 10 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The solid residue was purified by flash column chromatography (2.5% MeOH in EtOAc/CH_2Cl_2 1:1 → 5% MeOH in CH_2Cl_2 → 10% MeOH in CH_2Cl_2) to afford **SI-26** as a solid (597 mg) contaminated with traces of TPGS-750-M. The solid was further purified by dissolving in EtOAc (10 mL) and washing with dist. H_2O (3 × 10 mL), organic phase was dried over $MgSO_4$ and concentrated under reduced pressure to afford **SI-26** as an off-white foamy solid (486 mg, 68%), containing traces of TPGS-750-M which is difficult to remove. Therefore; **SI-26** was used with no further purification in the C(sp^2)–P cross-coupling reaction.

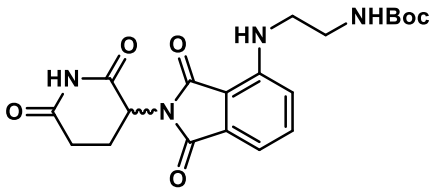
R_f = 0.26 (5% MeOH in CH_2Cl_2). Stain: UV active, $KMnO_4$;
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (d, *J* = 8.4 Hz, 2H), 7.57 (d, *J* = 8.4 Hz, 1H), 7.50 (s, 1H), 7.45 (d, *J* = 2.0 Hz, 1H), 7.24 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.16 (d, *J* = 8.4 Hz, 2H), 6.96 (d, *J* = 8.8 Hz, 2H), 6.86 (d, *J* = 9.2 Hz, 2H), 6.75 (d, *J* = 9.2 Hz, 2H), 4.48 (d, *J* = 14.8 Hz, 1H), 4.41 (d, *J* = 14.8 Hz, 1H), 4.34–4.30 (m, 1H), 3.88 (br s, 2H, overlapped), 3.87–3.83 (m, 1H, overlapped), 3.73–3.67 (m, 3H), 3.53 (br s, 1H), 3.26 (dd, *J* = 9.6, 6.8 Hz, 1H), 3.10 (br s, 2H), 2.99 (br s, 2H) ppm;
^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 169.5, 153.1, 145.7, 138.9, 137.8, 135.9, 135.1, 134.7, 133.1, 131.4, 129.6, 128.9, 128.6, 127.3, 121.3, 118.9, 115.3, 108.1, 74.8, 70.6, 67.7, 67.6, 51.3, 51.1 (br, 2 × C), 47.9 (br), 42.4 (br) ppm;
HRMS (ESI-TOF) calc'd for $C_{31}H_{30}O_4N_4Cl_2I$ $[M+H]^+$: 719.06833, found 719.06810.

Iodo-strychnine SI-27



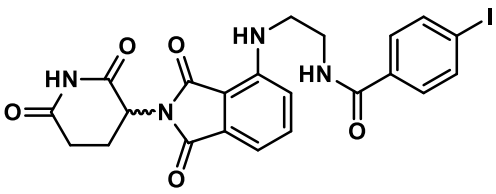
SI-27 was prepared according to a previously reported procedure from strychnine.[25]

***tert*-Butyl (2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethyl)carbamate (SI-28)**



SI-28 was prepared according to a modified procedure.[27] To a solution of 4-fluorothalidomide (207.2 mg, 0.75 mmol) in anhydrous dioxane (10 ml) was added *N*-Boc-ethylenediamine (130.6 µL, 0.83 mmol) and (*i*-Pr)$_2$NEt (392.0 µL, 2.25 mmol) under argon. The reaction mixture was heated at 100 °C for 17 hours under argon. The color of the reaction mixture gradually changed from yellow to dark green. Then the reaction solution was then diluted with dist. H_2O (20 mL) and extracted with EtOAc (3 × 20 mL). The combined organic phases were washed with 10 wt % aq. citric acid (30 mL), sat. aq. $NaHCO_3$ (30 mL), brine (30 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flask column chromatography (hexane/EtOAc 1:1, R_f = 0.25, visible yellow spot, $KMnO_4$ stain) to afford **SI-28** as a yellow solid (103 mg, 33%). Spectroscopic data match previously reported results.[27]

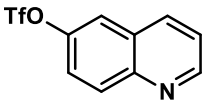
***N*-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethyl)-4-iodobenzamide (SI-29)**



Trifluoroacetic acid (0.5 mL) was dropwise added to a solution of **SI-28** (103 mg, 0.25 mmol) in CH_2Cl_2 (2 mL) at 0 °C. The reaction mixture was then allowed to warm to laboratory temperature and stirred for 3 hours. The reaction progress was monitored by TLC. Upon completion, the reaction mixture was concentrated under reduced pressure and co-evaporated with CH_2Cl_2 (2 × 1 mL) and toluene (2 × 1 mL). The crude product was used directly in the next step. To a solution of 4-iodobenzoic acid (72 mg, 0.29 mmol) and $(i\text{-Pr})_2$NEt (217 µL, 1.25 mmol) in anhydrous DMF (5 mL) cooled at 0 °C under argon was added HATU (110 mg, 0.29 mmol) and the reaction was stirred at laboratory temperature for 1 hour. Then, a solution of the deprotected amine in anhydrous DMF (2 mL) was added dropwise over 1 min and the reaction mixture was stirred at laboratory temperature for 18 hours. The reaction mixture was concentrated under reduced pressure and the residue was purified by column chromatography (hexane/EtOAc 1:3) to afford **SI-29** as a yellow solid (128 mg, 94%).

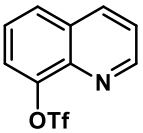
R_f = 0.50 (hexane/EtOAc 1:3). Stain: UV active, visible yellow spot.
^{1}H NMR (600 MHz, $CDCl_3$/DMSO-d_6 ~ 5:1): δ 10.92 (s, 1H), 8.52 (s, 1H), 7.68 (d, *J* = 8.3 Hz, 2H), 7.54 (d, *J* = 8.3 Hz, 2H), 7.43 (t, *J* = 7.2 Hz, 1H), 7.03 (d, *J* = 8.6 Hz, 1H), 6.95 (d, *J* = 7.0 Hz, 1H), 6.6 (s, 1H), 4.87 (dd, *J* = 12.6, 5.4 Hz, 1H), 3.49 (s, 4H), 2.76–2.59 (m, 4H) ppm;
^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$/DMSO-d_6 ~ 5:1): δ 171.8, 169.0, 168.6, 166.9, 166.5, 146.1, 136.7, 135.5, 133.5, 132.0, 128.7, 116.3, 110.5, 109.6, 97.7, 48.3, 41.1, 38.8, 31.0, 22.13 ppm;
HRMS (ESI-TOF) calc'd for $C_{22}H_{20}O_5N_4I$ $[M+H]^+$: 547.04729, found 547.04680.

Quinolin-6-yl trifluoromethanesulfonate (SI-30)



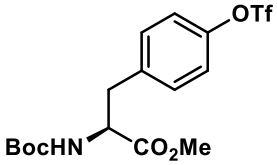
SI-30 was prepared according to a previously reported procedure.[28]

Quinolin-8-yl trifluoromethanesulfonate (SI-31)



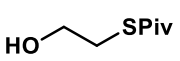
SI-31 was prepared according to a previously reported procedure.[29]

Triflate SI-32



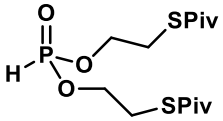
SI-32 was prepared according to a previously reported procedure.[30]

_S_-(2-hydroxyethyl) 2,2-dimethylpropanethioate (109)



109 was prepared according to a previously reported procedure.[31]

Bis-SATE _H_-phosphonate 74



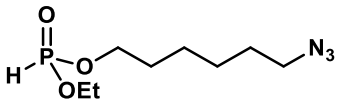
_S_-(2-Hydroxyethyl) 2,2-dimethylpropanethioate (**109**, 2.0 g, 12.33 mmol) was added dropwise to diphenyl _H_-phosphonate (**108**, 1.19 mL, 5.60 mmol, technical grade) at room temperature under argon, followed by the addition of anhydrous pyridine (993 µL, 12.33 mmol). The reaction mixture was stirred at laboratory temperature for 24 hours. Purification by flash column chromatography (hexane/EtOAc 3:1 → 1:1) afforded **74** as a colorless oil (1.794 g, 86%).

Spectral data match previously reported results,[32] and $^{1}H/^{31}P$ NMR data are provided here for convenience.

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.86 (d, $J_{P–H}$ = 708.0 Hz, 1H), 4.20–4.08 (m, 4H), 3.14 (t, J = 6.8 Hz, 4H), 1.23 (s, 18H) ppm;

^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 7.63 ppm.

6-Azidohexyl ethyl _H_-phosphonate (83)



A solution of 6-azidohexan-1-ol (425.3 µL, 3.0 mmol) and pyridine (604.1 µL, 7.5 mmol) in anhydrous dioxane (5 mL) was slowly added dropwise to a solution of ethyl dichlorophosphite (342.8 µL, 3.0 mmol) in anhydrous dioxane (3 mL) at 0 °C under argon. The reaction mixture was then allowed to warm to laboratory temperature and stirred for 1.5 hours. Dist. H_2O (59.4 µL, 3.3 mmol) in dioxane (3 mL) was added dropwise into the reaction mixture which was then stirred for additional 30 minutes at laboratory temperature. Resulting reaction mixture with white precipitate was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography (hexane/EtOAc 1:1) to afford **83** as a colorless oil (317 mg, 45%). Efforts to further purify **83** by chromatography failed due to its decomposition on silica gel.

R_f = 0.25 (hexane/EtOAc 1:1). Stain: $KMnO_4$;

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.79 (d, J_{P-H} = 693.0 Hz, 1H), 4.17–4.01 (m, 4H), 3.25 (t, J = 6.8 Hz, 2H), 1.73–1.53 (m, 4H), 1.40 (m, 4H), 1.34 (t, J = 7.1 Hz, 3H) ppm;

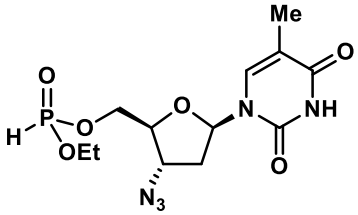
^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 7.54 ppm;

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 65.6 (d, J = 6.2 Hz), 61.9 (d, J = 5.8 Hz), 51.37, 30.3 (d, J = 6.2 Hz), 28.8, 26.3, 25.2, 16.4 (d, J = 6.2 Hz) ppm;

HRMS (ESI-TOF) calc'd for $C_8H_{18}O_3N_3NaP$ $[M+Na]^+$: 258.09780, found 258.09776.

Note: Compound **83** decomposes during column chromatography and pTLC so we advise to perform its purification rapidly and store **83** in a refrigerator.

***H*-phosphonate 85**

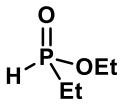


Ethyl dichlorophosphite (143 µL, 1.25 mmol) was added to anhydrous dioxane (1.5 ml) and anhydrous THF (2.0 ml) under argon and the resulting mixture was cooled to –20 °C. To this mixture, a solution of AZT (334.1 mg, 1.25 mmol) and anhydrous pyridine (252 µL, 3.13 mmol) in anhydrous dioxane (2.5 mL) and anhydrous THF (2.0 mL) was added dropwise over 10 minutes. The reaction mixture was then allowed to warm to laboratory temperature and stirred for 1 hour. Dist. H_2O (25 µL, 38 mmol) in THF (1.5 mL) was then added dropwise and the reaction was stirred at laboratory temperature for 40 minutes. The reaction mixture was concentrated under reduced pressure, the residue was dissolved in CH_2Cl_2 (15 mL), washed with 1M aq. HCl (10 mL), brine (10 mL), dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash column chromatography (CH_2Cl_2 → CH_2Cl_2/EtOAc 3:2) afforded **85** as a colorless oil (309 mg, 69%) as a mixture of diastereomers in 1:1.1 ratio (determined by ^{31}P NMR).

R_f = 0.33 (DCM/EtOAc 1:2). Stain: UV active, $KMnO_4$;
^{1}H NMR (mixture of diastereoisomers, 400 MHz, $CDCl_3$): δ 9.38 (br s, 2H), 6.92* and 6.91* (2 × d, 2 × *J* = 705.0 Hz, 2 × 1H), 7.35 (dd, *J* = 11.2, 1.2 Hz, 2H), 6.18 (td, *J* = 6.5, 2.7 Hz, 2H), 4.38–4.15 (m, 10H), 4.04–4.00 (m, 2H), 2.48–2.32 (m, 4H), 1.93 and 1.92 (s, 2 × 3H), 1.37 (td, *J* = 7.1, 2.6 Hz, 6H) ppm;
^{31}P{^{1}H} NMR (mixture of diastereoisomers, 162 MHz, $CDCl_3$): δ 8.38* and 7.84* ppm;
^{13}C{^{1}H} NMR (mixture of diastereoisomers, 100 MHz, $CDCl_3$): δ 163.9, 150.4, 135.4 (d, *J* = 12.6 Hz), 111.7 (d, *J* = 5.6 Hz), 85.23* and 85.21*, 82.29* and 82.28* (2 × d, 2 × *J* = 6.6 Hz), 64.35* and 64.25* (2 × d, 2 × *J* = 5.6 Hz), 62.86* and 62.81* (2 × d, 2 × *J* = 5.1 Hz), 60.1 (d, *J* = 1.6 Hz), 37.5 (d, *J* = 3.3 Hz), 16.4 (d, *J* = 5.8 Hz), 12.5 (d, *J* = 2.8 Hz) ppm;
HRMS (ESI-TOF) calc'd for $C_{12}H_{19}O_6N_5P$ $[M+H]^+$: 360.10675, found 360.10668.

Note: ^{13}C signals were only tentatively assigned to each of the diastereomers, which are difficult to distinguish.

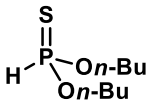
Ethyl ethyl-*H*-phosphinate (87)



Prepared according to a modified previously reported procedure.[33] A flame-dried round bottom flask with a magnetic stir bar was charged with $P(OEt)_3$ (10.0 mL, 58.0 mmol) and anhydrous THF (50 mL) under argon. Then EtMgBr (3.0M in Et_2O, 19.3 mL, 58.0 mmol) was added dropwise over 10 minutes at laboratory temperature. The reaction mixture was heated at 65 °C over 4 hours and then, upon cooling to laboratory temperature, quenched by slowly adding 6M aq. HCl (~12 mL) and pH was adjusted to 2. The reaction mixture was then concentrated under reduced pressure to remove THF. The resulting oily residue was dissolved in CH_2Cl_2 (100 mL) and washed with dist. H_2O (2 × 60 mL). The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by short-path vacuum distillation and the fractions containing the product (100-130 °C/25 mbar) were combined to afford **87** as a colorless liquid (1.558 g, 22%).

Spectral data match the previous report[33] and the $^1H/^{31}P$ NMR data are provided here for convenience.
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.01 (d, $J_{P–H}$ = 528.0 Hz, 1H), 4.18–3.98 (m, 2H), 1.79–1.68 (m, 2H), 1.34–3.30 (m, 3H), 1.16–1.07 (m, 3H) ppm;
^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 40.73 ppm.

Di-*n*-butyl *H*-thiophosphonate (94)



In a well-ventilated fume hood, a two-necked round bottom flask containing Lawesson's reagent (2.02 g, 5.0 mmol), fitted with a reflux condenser, and capped with septa was evacuated/back-filled with Ar three times. Anhydrous toluene (10 mL) and di-*n*-butyl *H*-phosphonate (976 μL, 5.0 mmol) were then added using syringes. The reaction mixture was subsequently refluxed for 4 hours under Ar. Upon cooling, toluene was evaporated under nitrogen flow (compressed air can be used instead). The remaining solids were dissolved in a minimal amount of CH_2Cl_2 and subjected to column chromatography (hexane/CH_2Cl_2 10:1 → 3.5:1). Fractions containing the product ($KMnO_4$ stain) were combined and evaporated to afford **94** as a colorless liquid (901 mg, 86%).

The compound **94** has been previously prepared and described in multiple reports,[34] and $^{1}H/^{31}P/^{13}C$ NMR data are provided here for convenience.

R_f = 0.14 (hexane). Stain: $KMnO_4$;

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (d, $J_{P–H}$ = 648.0 Hz, 1H), 4.14–4.00 (m, 4H), 1.66 (quintet, *J* = 8.0 Hz, 4H), 1.40 (sextet, *J* = 7.6 Hz, 4H), 0.93 (t, *J* = 7.2 Hz, 6H) ppm;

^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 69.93 ppm;

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 66.1 (d, *J* = 7.0 Hz), 32.3 (d, *J* = 7.1 Hz), 18.9, 13.7 ppm.

General Procedures

Preparation of the TPGS-750-M stock solution

TPGS-750-M (2 wt %) was weighted into a larger vial to which a rod-shape magnetic stirring bar was added. The vial was capped with a septum and evacuated/back-filled with Ar three times and fitted with an Ar balloon. HPLC-grade water (98 wt %), previously degassed by sparging Ar while sonicating for at least 1 hour, was then added using a syringe. The contents of the flask were then vigorously stirred at room temperature under Ar for >6 hours (overnight at larger scales), forming a homogenous solution. The TPGS-750-M solution can be used for at least 1 week if kept under argon atmosphere.

General procedure A (Conditions A, *multimetallic* C(sp^2)–P cross-coupling)

A test tube or a small vial containing aryl iodide/bromide (0.25 mmol, *if solid*), H–P(O) compound (0.50 mmol, *if solid*), $Pd(OAc)_2$ (1.4 mg, 6.25 μmol, 2.5 mol %), XantPhos (3.6 mg, 6.25 μmol, 2.5 mol %), $Ni(phen)_3Cl_2$ (1.7 mg, 2.50 μmol, 1 mol %), nano Zn powder (8.1 mg, 0.125 mmol) and LiBr (21.7 mg, 0.25 mmol) and a magnetic stirring bar was capped with a septum, evacuated/back-filled with argon three times and fitted with an Ar balloon. Then, degassed EtOAc (0.1 mL, degassed by bubbling Ar for at least 15 minutes) and 2 wt % aqueous solution of TPGS-750-M (0.5 mL) were added. Lastly, under positive Ar pressure, the vial was quickly opened and aryl iodide/bromide (0.25 mmol, *if liquid)*, 2,6-lutidine (58.0 μL, 0.50 mmol), and H–P(O) compound (0.50 mmol, *if liquid*) were added using a micropipette. The vial was capped with the septum again, sealed with electrical tape, and placed in a pre-heated oil bath set at 40-45 °C and 850 rpm (both temperature and vigorous stirring are *crucial* for the reaction; splashing and depositing of solids on walls may result in incomplete conversion). After 15 hours, the reaction mixture was diluted with 1M aq. HCl (~1 mL), *except for compounds containing basic functional groups*, and extracted with EtOAc (3 × ~1-2 mL). Combined organic extracts were evaporated to dryness (40 °C, <30 mbar). If required, excess 2,6-lutidine and **3** can be removed under high vacuum (b.p.(2,6-lutidine, atm. pressure) = 143-145 °C, b.p.(**3**, atm. pressure) = 187-188 °C). The crude products were analyzed by $^1H/^{31}P$ NMR using CH_2Br_2 as an internal standard and/or directly purified by chromatography.

General procedure B (Conditions B, *dual-ligand* C(sp^2)–P cross-coupling)

A test tube or a small vial containing aryl iodide/bromide (0.25 mmol, *if solid*), H–P(O) compound (0.50 mmol, *if solid*), $Pd[P(t\text{-}Bu)_3]_2$ (3.2 mg, 6.25 μmol, 2.5 mol %), $Pd(OAc)_2$ (0.6 mg, 2.50 μmol, 1 mol %), XantPhos (1.4 mg, 2.50 μmol, 1 mol %) and LiBr (21.7 mg, 0.25 mmol) and a magnetic stirring bar was capped with a septum, evacuated/back-filled with argon three times and fitted with an Ar balloon. Then, degassed EtOAc (0.1 mL, degassed by bubbling Ar for at least 15 minutes) and 2 wt % aqueous solution of TPGS-750-M (0.5 mL) were added. Lastly, under positive Ar pressure, the vial was quickly opened and aryl iodide/bromide (0.25 mmol, *if liquid)*, 2,6-lutidine (58.0 μL, 0.50 mmol), and H–P(O) compound (0.50 mmol, *if liquid*) were added using a micropipette. The vial was capped with the septum again, sealed with electrical tape, and placed in a pre-heated oil bath set at 40-45 °C and 850 rpm (both temperature and vigorous stirring are *crucial* for the reaction; splashing and depositing of solids on walls may result in incomplete conversion). After 15 hours, the reaction mixture was diluted with 1M aq. HCl (~1 mL), *except for compounds containing basic functional groups*, and extracted with EtOAc (3 × ~1-2 mL). Combined organic extracts were evaporated to dryness (40 °C, <30 mbar). If required, excess 2,6-lutidine and **3** can be removed under high vacuum (b.p.(2,6-lutidine, atm. pressure)

= 143-145 °C, b.p.(**3**, atm. pressure) = 187-188 °C). The crude products were analyzed by $^{1}H/^{31}P$ NMR using CH_2Br_2 as an internal standard and/or directly purified by chromatography.

Minor modifications are indicated in the procedures for each substrate. These modifications most commonly involve performing the reaction at a higher dilution (*e.g.*, 0.25 mmol of substrate in 1.0 mL of 2 wt % TPGS-750-M in H_2O and 0.2 mL EtOAc) to improve solubilization, using 1.2 equivalents of **3** (instead of 2 equivalents), using 3 equivalents of 2,6-lutidine (instead of 2 equivalents), and heating at 50-55 °C (instead of 40-45°C).

Common Questions and Troubleshooting

How do I monitor the reaction?
Micellar C(sp^2)–P cross-coupling reactions can be monitored by standard TLC and (preferably) LC-MS analysis as the products are readily protonated in conventional electrospray ion sources.

How do I choose between Conditions A and Conditions B?
With the current knowledge of the catalytic systems, the choice is mostly empirical. Conditions A provided good yields across a wide range of substrates and phosphorus nucleophiles. Moreover, under Conditions A, reactions with heteroaryl halides and cross-couplings with **97** performed better than under Conditions B. We suggest using Conditions B for the reactions of aryl bromides, *ortho*-substituted iodobenzenes, and **98**. When conversion is low, increasing the reaction temperature to 55 °C may be helpful. In a few cases (*e.g.*, cross-coupling reactions of **50** and **51** with **3** and 3-iodo-7-azaindole derivative **SI-21** with **98**), we observed virtually quantitative catalytic transfer hydrogenation, affording the corresponding Ar–H by-products. All our attempts to avoid this side-reactions have failed so far.

How do I select the reaction volume?
In most cases, we run 0.25-mmol scale reactions in 0.5 mL of 2 wt %TPGS-750-M in H_2O and 0.1 mL of EtOAc (0.42M concertation of the substrate). However, highly crystalline substates (*e.g.*, 1-nitro-4-nitrobenzene, 4-iodopyridine) and/or with a mass exceeding approximately 100 mg (at 0.25 mmol scale) do not readily dissolve. Instead, they tend to stick to the walls, ultimately decreasing the reaction conversion and yield. In these cases, we suggest decreasing the concentration to 0.21M by using 1.0 mL of 2 wt % TPGS-750-M in H_2O and 0.2 mL of EtOAc and/or increasing the reaction temperature to 55 °C to facilitate solubilization. Alternatively, other co-solvents may be used, such as *n*-butanol, which outperformed EtOAc in difficult C(sp^2)–P cross-coupling reactions (data not included in this manuscript).

How do I purify the product?
The C(sp^2)–P cross-coupling products can be isolated by standard flash column chromatography or pTLC using short-wave UV light and/or $KMnO_4$ stain for visualization. If needed, trace amounts of **3** or 2,6-lutidine can be removed under high vacuum (b.p.(2,6-lutidine, atm. pressure) = 143-145 °C, b.p.(**3**, atm. pressure) = 187-188 °C).

How do I isolate highly polar aryl dimethyl phosphine oxide products?
Cross-coupling reactions with dimethylphosphine oxide (**98**) afford highly polar phosphine oxides, which are also considerably soluble in water, thereby decreasing the isolated yields, in some cases, upon EtOAc extraction during work-up. Instead of extraction, we suggest subjecting the entire reaction mixture to preparative C8 or C18 HPLC.

Does the reaction work with no surfactant?
In some cases, the reaction still works with no surfactant (*i.e.*, "on-water"), albeit with low yields, depending on the substrate.

Can I increase the reaction temperature above 55 °C?
We run micellar C(sp^2)–P cross-coupling reactions with **98** at 60 °C to increase reaction conversion rates and yields. However, temperatures ranging from 45 to 55 °C are most often sufficient for this purpose. Some reactions worked efficiently even at room temperature (15-20 °C). When using PEG-containing surfactants (including TPGS-750-M), increasing the reaction temperature above a specific temperature

(approximately 75 °C for TPGS-750-M) weakens hydrogen bonds between the PEG chains and water, eventually precipitating the surfactant.

Is the micellar C(sp^2)–P cross-coupling scalable?
Yes, we have included 3 examples of reactions performed at larger scales (see the corresponding section below). The scale-up experiments were performed with no modifications to the used General procedures.

What are the current limitations of this methodology in terms of scope?
Our method showed a broad substrate scope and functional group-tolerance. However, we encountered some limitations. In particular, *ortho*-substituted iodobenzenes bearing OH, NH_2, NO_2 and CO_2H groups provided phosphonate products in poor yields (<20% by ^1H NMR with CH_2Br_2 as an internal standard). Similarly, 2-iodopyridine and 2-iodopyrazine afforded no cross-coupling products. Despite affording the target products in serviceable yields (40-86%), cross-coupling reactions with some phosphorus nucleophiles (**87**, **97**, and **98**) still require further optimization to reach their full efficiency. Nevertheless, the recently reported surfactant Savie,[35] which enhances the efficiency of many transformations under micellar conditions in water, may enable us to perform C(sp^2)–P cross-coupling reactions at higher temperatures, at which the TPGS-750-M surfactant reaches its cloud point. These more forcing conditions may be the key to efficient cross-coupling reactions with poorly reactive (hetero)aryl halides and with strongly coordinating phosphorus nucleophiles (such as **87**, **97**, and **98**), and our laboratory is actively pursuing this line of research.

Calculation of PMI Values and E Factors and Comparison With Those of Literature Procedures

Densities (at 25 °C): EtOAc 0.897 g/mL; THF 0.889 g/mL; MeCN 0.796 g/mL; toluene 0.867 g/mL; Et_2O 0.713 g/mL; 1,4-dioxane 1.033 g/mL, CH_2Cl_2 1.326 g/mL; water 1.0 g/mL.

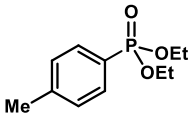
$$PMI = \frac{mass_{reactant} + mass_{reagents} + mass_{catalysts} + mass_{EtOAc\ rxn\&extraction} + mass_{water\&surfactant}}{mass_{product}}$$

$$E\ factor\ (inc.water, exc.\ extration) = \frac{mass\ of\ waste(EtOAc_{rxn}) + mass\ of\ water}{mass\ of\ product}$$

$$E\ factor\ (inc.water\ and\ extration) = \frac{mass\ of\ waste(EtOAc_{rxn}) + mass\ of\ water + mass\ of\ waste(EtOAc_{ext})}{mass\ of\ product}$$

Phosphonate 6

$$PMI = \frac{0.0545 + (0.0691 + 0.0536 + 0.0081 + 0.0217) + (0.0014 + 0.0036 + 0.0017) + (3.1 \times 0.897) + (0.5 \times 1.0)}{0.0550} = \frac{3.4943}{0.0550} = \mathbf{63.5\ g\ g^{-1}}$$



$$E\ factor\ (inc.water, exc.\ extration) = \frac{(0.1 \times 0.897) + (0.5 \times 1.0)}{0.0550} = \mathbf{10.7}$$

$$E\ factor\ (inc.water\ and\ extration) = \frac{(3.1 \times 0.897) + (0.5 \times 1.0)}{0.0550} = \mathbf{59.6}$$

Comparison with literature (ref. 36 from the main text, *J. Am. Chem. Soc.* **1990**, 4324):

$$PMI = \frac{0.448 + (0.378 + 0.303) + (0.313) + (5.0 \times 0.796) + (10.0 \times 1.0) + (mass\ of\ waste_{extraction})}{0.480} = \frac{15.422}{0.480} = \mathbf{32.1\ g\ g^{-1}}\ (\textbf{\textit{see note}})$$

$$E\ factor\ (exc.\ extration) = \frac{(5.0 \times 0.796) + (10.0 \times 1.0)}{0.480} = \mathbf{29.1}$$

$$E\ factor\ (inc.\ extration) = \frac{(5.0 \times 0.796) + (10.0 \times 1.0) + (mass\ of\ waste_{extraction})}{0.480} = \textbf{\textit{not determined}}^*$$

*Volumes of benzene and Et_2O used for extractions were not disclosed. Thus, the actual PMI is higher.

Comparison with literature (ref. 25b from the main text, *J. Org. Chem.* **2006**, 5020):

$$PMI = \frac{0.2180 + (0.1519 + 0.6516) + (0.0191 + 0.0461) + (3.0 \times 0.867) + (10.0 \times 0.713)}{0.1552} = \frac{10.8177}{0.1552} = \mathbf{69.7\ g\ g^{-1}}$$

$$E\ factor\ = \frac{(3.0 \times 0.867) + (10.0 \times 0.713)}{0.1552} = \mathbf{62.7}$$

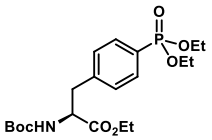
Comparison with literature (Angew. Chem. Int. Ed. **2017**, 12718):

$$PMI = \frac{0.0463 + (0.0138 + 0.0152) + (0.0011 + 0.0043) + (0.8 \times 1.033) + (1.0 \times 1.326)}{0.0219} = \frac{2.2331}{0.0219} = \mathbf{102.0\ g\ g^{-1}}$$

$$E\ factor\ = \frac{(0.8 \times 1.033) + (1.0 \times 1.326)}{0.0219} = \mathbf{98.3}$$

Phosphonate 28

$$PMI = \frac{0.1048 + (0.0691 + 0.0536 + 0.0081 + 0.0217) + (0.0014 + 0.0036 + 0.0017) + (3.1 \times 0.897) + (0.5 \times 1.0)}{0.0940} = \frac{3.5447}{0.0940} = \mathbf{37.7\ g\ g^{-1}}$$



$$E\ factor\ (inc.water, exc.\ extration) = \frac{(0.1 \times 0.897) + (0.5 \times 1.0)}{0.0940} = \mathbf{6.3}$$

$$E\ factor\ (inc.water\ and\ extration) = \frac{(3.1 \times 0.897) + (0.5 \times 1.0)}{0.0940} = \mathbf{34.9}$$

Comparison with literature (ref. 45, *Tetrahedron Lett.* **2007**, 4051):

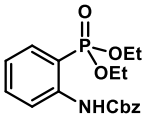
$$PMI = \frac{2.4 + (1.2 + 1.2) + (0.1982) + (100 \times 0.796) + (250 \times 1.0) + (100 \times 0.897)}{2.1} = \frac{424.298}{2.1} = \mathbf{202.0\ g\ g^{-1}}$$

$$E\ factor\ (exc.\ extration\ workup) = \frac{(100 \times 0.796)}{2.1} = \mathbf{37.9}$$

$$E\ factor\ (inc.\ extration\ workup) = \frac{(100 \times 0.796) + (250 \times 1.0) + (100 \times 0.897)}{2.1} = \mathbf{199.7}$$

Phosphonate 7

$$PMI = \frac{0.0883 + (0.0414 + 0.0536 + 0.0081 + 0.0217) + (0.0014 + 0.0036 + 0.0017) + (3.1 \times 0.897) + (0.5 \times 1.0)}{0.0850} = \frac{3.5005}{0.0850} = \mathbf{41.2\ g\ g^{-1}}$$

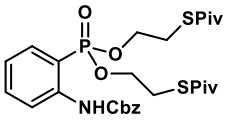


$$E\ factor\ (inc.water, exc.\ extration) = \frac{(0.1 \times 0.897) + (0.5 \times 1.0)}{0.0850} = \mathbf{6.9}$$

$$E\ factor\ (inc.water\ and\ extration) = \frac{(3.1 \times 0.897) + (0.5 \times 1.0)}{0.0850} = \mathbf{38.6}$$

Phosphonate 77

$$PMI = \frac{0.0883 + (0.1111 + 0.0536 + 0.0217) + (0.0032 + 0.0014 + 0.0006) + (3.1 \times 0.897) + (0.5 \times 1.0)}{0.1310} = \frac{3.5606}{0.1310} = \mathbf{27.2\ g\ g^{-1}}$$

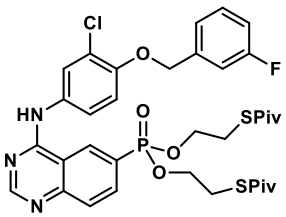


$$E\ factor\ (inc.water, exc.\ extration) = \frac{(0.1 \times 0.897) + (0.5 \times 1.0)}{0.1310} = \mathbf{4.5}$$

$$E\ factor\ (inc.water\ and\ extration) = \frac{(3.1 \times 0.897) + (0.5 \times 1.0)}{0.1310} = \mathbf{25.0}$$

Phosphonate 80

$$PMI = \frac{0.0631 + (0.0696 + 0.0286 + 0.0109) + (0.0016 + 0.0003 + 0.0007) + (3.2 \times 0.897) + (1.0 \times 1.0)}{0.0930} = \frac{4.0434}{0.0930} = \mathbf{43.5\ g\ g^{-1}}$$



$$E\ factor\ (inc.water, exc.\ extration) = \frac{(0.2 \times 0.897) + (1.0 \times 1.0)}{0.0930} = \mathbf{12.7}$$

$$E\ factor\ (inc.water\ and\ extration) = \frac{(3.2 \times 0.897) + (1.0 \times 1.0)}{0.0930} = \mathbf{41.6}$$

ICP Analysis

Measuring procedure

Analysis was conducted at IOCB Prague, The Czech Republic, using inductively coupled plasma optical emission spectroscopy (ICP-OES) with electrothermal vaporization of sample (ETV). Samples were accurately weighed (weighing accuracy 1 µg, single dose about 1 -2 mg) into graphite boats and inserted into a graphite furnace of the ETV unit (ETV 4000c, Spectral Systems, Fürstenfeldbruck, Germany), where a predefined temperature program was run. The temperature program consisted of a pyrolytic phase (45 s, Tmax 550 °C), fast heating phase (5 s, 2200°C) and a prolonged evaporating phase (15 s, 2200 °C). The analytes evaporated and were transferred to plasma, and the emitted characteristic radiation was processed with the ICP-OES spectrometer (SPECTRO Arcos SOP, SPECTRO Analytical Instruments, Kleve, Germany). Four analytical lines of nickel and five lines of palladium with different sensitivity were observed and evaluated according to measured concentration. Samples were analyzed at minimum in duplicate, more measurements were carried out when sufficient amount of material was available. Calibration was performed with standard aqueous solutions in range from 0 to 0,2 µg/kg absolute quantity (prepared from certified solutions (Analytika s r.o., Prague, The Czech Republic)) depending on the content of analytes in the sample and the sensitivity of their analytical lines. LODs were up to 0.01 mg/kg for Pd and 0.002 mg/kg for Ni.

Optical emission spectrometry with inductively coupled plasma and electrothermal vaporization (ETV-ICP-OES)

Method principle: Electrothermal vaporization represents an alternative way of sample introduction to ICP-OES. The sample is weighted into graphite boats and inserted into a graphite furnace. In the furnace, sample is heated according to chosen temperature program up to a maximum of 3000 °C. During this heating the sample decomposes and analytes evaporate. A small amount of CCl_2F_2 (2 ml/min) is added to the furnace during heating to transform elements into their more volatile compounds. A stream of argon flows through the furnace, carrying vapors and dry aerosol to a high-temperature plasma.

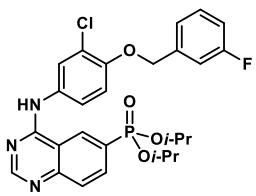
Unlike in the common ICP-OES, when ETV is used, element´s signal is not constant during the analysis (compounds evaporate at different temperatures and therefore at different moments) and therefore transient signal needs to be recorded.

Electrothermal vaporization improves limits of detection of ICP-OES (up to units of µg/kg in the material itself), lowers sample consumption and enables analysis without sample preparation. Another advantage is removal of interferences by optimization of temperature program so that interfering elements evaporate at different moments.

Depending on sample type and content of elements to be determined, one analysis needs 0.5-5 mg of sample. Analysis of such small amounts brings higher demands on sample homogeneity.

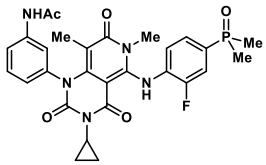
Results of the Pd and Ni ICP analysis

Compound **79**



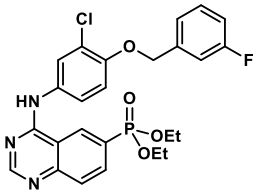
	Calculated 26-Sep-23 12:19:31 PM				
sample mass (mg)				1.362	1.478
Integration Window	Unit	**Mean**	**Rsd**	- 2 -	- 1 -
Ni-231.604-53	mg/kg	4.81	0.69	4.83	4.78
Ni-232.003-54	mg/kg	4.61	1.69	4.66	4.55
Pd-324.270-54	mg/kg	50.6	2.7	51.5	49.6
Pd-340.458-54	mg/kg	51.1	3.23	52.2	49.9
Pd-344.140-54	mg/kg	48.4	0.94	48.1	48.8
Pd-360.955-54	mg/kg	51.4	0.25	51.5	51.3

Compound **102**



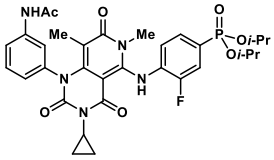
	Calculated 26-Sep-23 12:20:16 PM				
sample mass (mg)				1.651	1.823
Integration Window	Unit	**Mean**	**Rsd**	- 2 -	- 1 -
Ni-231.604-53	mg/kg	0.366	2.83	0.358	0.373
Pd-324.270-54	mg/kg	36.8	9.04	34.4	39.1
Pd-340.458-54	mg/kg	36.9	9.05	34.5	39.2
Pd-344.140-54	mg/kg	33.6	8.02	31.7	35.5
Pd-360.955-54	mg/kg	34.5	8.99	32.3	36.7

Compound **66**



	Calculated 26-Sep-23 12:21:16 PM				
sample mass (mg)				1.818	1.458
Integration Window	Unit	**Mean**	**Rsd**	- 2 -	- 1 -
Ni-174.828-53	mg/kg	11.1	47.22	7.39	14.8
Ni-231.604-53	mg/kg	11	61.94	6.15	15.7
Pd-344.140-54	mg/kg	67.9	3.83	69.7	66.1

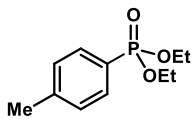
Compound **81**



	Calculated 26-Sep-23 12:21:40 PM				
sample mass (mg)				1.471	1.247
Integration Window	Unit	**Mean**	**Rsd**	- 2 -	- 1 -
Ni-231.604-53	mg/kg	0.897	21.38	1.03	0.761
Pd-324.270-54	mg/kg	14.1	23.92	16.5	11.7
Pd-340.458-54	mg/kg	14.1	23.84	16.5	11.8
Pd-344.140-54	mg/kg	14.6	18.17	16.4	12.7
Pd-360.955-54	mg/kg	13.8	22.28	16	11.6

C(sp^2)–P Cross-Coupling Products

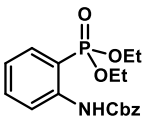
Diethyl *p*-tolylphosphonate (5)



Prepared according to General procedure A using 4-iodotoluene (**2**, 54.5 mg, 0.25 mmol) and diethyl *H*-phosphonate (**3**, 66.0 μL, 0.50 mmol). The crude product was purified by pTLC (hexane/EtOAc 1:1) to afford **5** as a viscous light-yellow oil (55.0 mg, 96%).

Spectral data match previously reported results,[36] and ^{1}H/^{31}P NMR data are provided here for convenience.
R_f = 0.20 (hexane/EtOAc 1:1). Stain: UV active, $KMnO_4$;
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72–7.67 (m, 2H), 7.28–7.25 (m, 2H), 4.17–4.00 (m, 4H), 2.39 (s, 3H), 1.31 (t, *J* = 6.8 Hz, 6H) ppm;
^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 19.54 ppm.

Benzyl (2-(diethoxyphosphoryl)phenyl)carbamate (7)

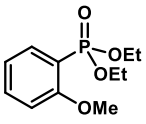


Prepared according to General procedure A using benzyl (2-iodophenyl)carbamate (**6**, 88.3 mg, 0.25 mmol) and diethyl *H*-phosphonate (**3**, 38.6 μL, 0.30 mmol). The crude product was purified by pTLC (hexane/EtOAc 2:1) to afford **7** as a viscous light-yellow oil (85.0 mg, 94%).

The compound has been prepared previously;[37] however, no spectral data has been reported yet.
R_f = 0.43 (hexane/EtOAc 2:1). Stain: UV active, $KMnO_4$;
^{1}H NMR (400 MHz, $CDCl_3$): δ 10.05 (s, 1H), 8.37 (t, *J* = 7.2 Hz, 1H), 7.59–7.50 (m, 2H), 7.43–7.41 (m, 2H), 7.37–7.29 (m, 3H), 7.09–7.05 (m, 1H), 5.21 (s, 2H), 4.19–3.99 (m, 4H), 1.31 (t, *J* = 7.2 Hz, 6H) ppm;
^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 19.46 ppm;
^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 153.6, 142.9 (d, *J* = 7.1 Hz), 136.3, 134.1 (d, *J* = 2.0 Hz), 132.6 (d, *J* = 6.1 Hz), 128.5, 128.3, 128.2, 122.2 (d, *J* = 14.1 Hz), 119.3 (d, *J* = 12.1 Hz), 113.3 (d, *J* = 179.0 Hz), 66.8, 62.6 (d, *J* = 6.1 Hz), 16.3 (d, *J* = 7.1 Hz) ppm;
HRMS (ESI-TOF) calc'd for $C_{18}H_{23}O_5NP$ $[M+H]^+$: 364.13084, found 364.13063.

7 was also prepared according to General procedure B using benzyl (2-bromophenyl)carbamate (**SI-7**, 76.5 mg, 0.25 mmol) and diethyl *H*-phosphonate (**3**, 66.0 μL, 0.50 mmol). The reaction was performed at 55 °C. The crude product was purified by pTLC (hexane/EtOAc 2:1) to afford **7** as a light-yellow oil (41.0 mg, 45%). General procedure A using **SI-7** and **3** afforded no product (96% RSM by ^{1}H NMR with CH_2Br_2 as an internal standard).

Diethyl (2-methoxyphenyl)phosphonate (9)

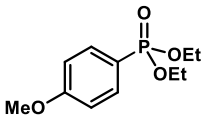


Prepared according to General procedure B using 2-iodoanisole (32.5 μL, 58.5 mg, 0.25 mmol) and diethyl *H*-phosphonate (**3**, 38.6 μL, 0.30 mmol). The crude product was purified by pTLC (hexane/EtOAc 2:1) to afford **9** as a light-yellow oil (61.0 mg, 99%).

Spectral data match previously reported results,[38] and ^{1}H/^{31}P NMR data are provided here for convenience.

R_f = 0.45 (hexane/EtOAc 2:1). Stain: UV active;
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81 (ddd, *J* = 14.8, 7.6, 1.6 Hz, 1H), 7.52–7.48 (m, 1H), 7.01 (ddd, *J* = 7.6, 3.6, 1.2 Hz, 1H), 6.96–6.92 (m, 1H), 4.23–4.07 (m, 4H), 3.90 (s, 3H), 1.33 (t, *J* = 6.8 Hz, 6H) ppm;
^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 17.17 ppm.

Diethyl (4-methoxyphenyl)phosphonate (10)

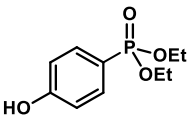


Prepared according to General procedure A using 4-iodoanisole (58.5 mg, 0.25 mmol) and diethyl *H*-phosphonate (**3**, 38.6 μL, 0.30 mmol). The crude product was purified by pTLC (hexane/EtOAc 2:3) to afford **10** as a light-yellow oil (55.0 mg, 90%).

Spectral data match previously reported results,[36] and ^{1}H/^{31}P NMR data are provided here for convenience.
R_f = 0.40 (hexane/EtOAc 2:3). Stain: UV active;
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77–7.71 (m, 2H), 6.97–6.94 (m, 2H), 4.16–3.99 (m, 4H), 3.84 (s, 3H), 1.30 (t, *J* = 6.8 Hz, 6H) ppm;
^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 19.71 ppm.

10 was also prepared according to General procedure B using benzyl 4-bromoanisole (31.4 μL, 0.25 mmol) and diethyl *H*-phosphonate (**3**, 66.0 μL, 0.50 mmol). The reaction was performed at 55 °C. The crude product was purified by pTLC (hexane/EtOAc 2:3) to afford **10** as a light-yellow oil (29.0 mg, 47%).

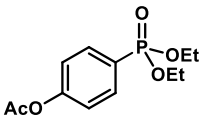
Diethyl (4-hydroxyphenyl)phosphonate (11)



Prepared according to General procedure A using 4-iodophenol (55.0 mg, 0.25 mmol) and diethyl *H*-phosphonate (**3**, 66.0 μL, 0.50 mmol). The crude product was purified by pTLC (hexane/EtOAc 1:4) to afford **11** as a light-yellow solid (38.0 mg, 66%).

Spectral data match previously reported results,[38] and ^{1}H/^{31}P NMR data are provided here for convenience.
R_f = 0.20–0.25 (hexane/EtOAc 1:4). Stain: UV active, $KMnO_4$;
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60–7.54 (m, 2H), 6.89–6.86 (m, 2H), 4.09–3.93 (m, 4H), 2.39 (s, 3H), 1.26 (t, *J* = 7.2 Hz, 6H) ppm;
^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 21.01 ppm.

4-(Diethoxyphosphoryl)phenyl acetate (12)

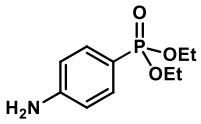


Prepared according to General procedure B using 4-iodophenyl acetate (65.5 mg, 0.25 mmol) and diethyl *H*-phosphonate (**3**, 66.0 μL, 0.50 mmol). The crude product was purified by pTLC (hexane/EtOAc 1:1) to afford **12** as a light-brown oil (68.0 mg, 99%).

Spectral data match previously reported results,[39] and ^{1}H/^{31}P NMR data are provided here for convenience.
R_f = 0.34 (hexane/EtOAc 1:1). Stain: UV active;

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86–7.80 (m, 2H), 7.21–7.18 (m, 2H), 4.19–4.02 (m, 4H), 2.31 (s, 3H), 1.32 (t, *J* = 7.2 Hz, 6H) ppm;
^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 17.89 ppm.

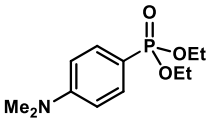
Diethyl (4-aminophenyl)phosphonate (13)



Prepared according to modified General procedure B using 4-iodoaniline (54.8 mg, 0.25 mmol), diethyl *H*-phosphonate (**3**, 66.0 μL, 0.50 mmol), Pd[P(*t*-Bu)$_3$]$_2$ (6.6 mg, 12.5 μmol), KOAc (12.5 mg, 0.125 mmol), LiBr (21.7 mg, 0.25 mmol), 2,6-lutidine (58.0 μL, 0.50 mmol), 2 wt % TPGS-750-M in H_2O (1.0 mL) and EtOAc (0.2 mL). The reaction was performed at 60 °C. The crude product was purified by pTLC (7% MeOH in CH_2Cl_2) to afford **13** as a white solid (34.0 mg, 59%).

Spectral data match previously reported results,[38] and ^{1}H/^{31}P NMR data are provided here for convenience.
R_f = 0.43 (7% MeOH in CH_2Cl_2). Stain: UV active;
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59–7.54 (m, 2H), 6.69–6.66 (m, 2H), 4.13–3.96 (m, 4H), 1.29 (t, *J* = 7.2 Hz, 6H) ppm;
^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 20.97 ppm.

Diethyl (4-(dimethylamino)phenyl)phosphonate (14)

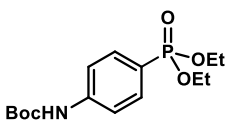


Prepared according to modified General procedure B using 4-iodo-*N*,*N*-dimethylaniline (**SI-2**, 61.8 mg, 0.25 mmol), diethyl *H*-phosphonate (**3**, 66.0 μL, 0.50 mmol), Pd[P(*t*-Bu)$_3$]$_2$ (6.6 mg, 12.5 μmol), KOAc (12.5 mg, 0.125 mmol), LiBr (21.7 mg, 0.25 mmol), 2,6-lutidine (58.0 μL, 0.50 mmol), 2 wt % TPGS-750-M in H_2O (0.5 mL) and EtOAc (0.1 mL). The reaction was performed at 55 °C. The crude product was purified by pTLC (hexane/EtOAc 1:2) to afford **14** as a clear crystalline solid (43.0 mg, 70%, 97% brsm) and starting 4-iodo-*N*,*N*-dimethylaniline (19.0 mg).

Spectral data match previously reported results,[40] and ^{1}H/^{31}P NMR data are provided here for convenience.
R_f = 0.33 (hexane/EtOAc 1:2). Stain: UV active;
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66–7.61 (m, 2H), 6.71–6.68 (m, 2H), 4.14–3.96 (m, 4H), 3.01 (s, 6H), 1.29 (t, *J* = 7.2 Hz, 6H) ppm;
^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 21.88 ppm.

Note: Cross-coupling of **SI-2** with **3** using General procedure A afforded **14** in 40% yield (^{1}H NMR with CH_2Br_2 as an internal standard).

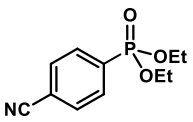
***tert*-Butyl (4-(diethoxyphosphoryl)phenyl)carbamate (15)**



Prepared according to modified General procedure A using *tert*-butyl (4-iodophenyl)carbamate (79.8 mg, 0.25 mmol), diethyl *H*-phosphonate (**3**, 66.0 μL, 0.50 mmol), 2,6-lutidine (87.0 μL, 0.75 mmol), 2 wt % TPGS-750-M in H_2O (0.5 mL) and THF (0.05 mL). The crude product was purified by pTLC (hexane/EtOAc 3:2) to afford **15** as a beige solid (78.0 mg, 95%).

Spectral data match previously reported results,[41] and $^{1}H/^{31}P$ NMR data are provided here for convenience.
R_f = 0.41 (hexane/EtOAc 2:3). Stain: UV active, $KMnO_4$;
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74–7.69 (m, 2H), 7.50–7.47 (m, 2H), 6.92 (br s, 1H), 4.15–3.98 (m, 4H), 1.51 (s, 9H), 1.29 (t, *J* = 7.2 Hz, 6H) ppm;
^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 19.18 ppm.

Diethyl (4-cyanophenyl)phosphonate (16)

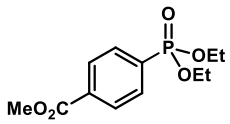


Prepared according to General procedure A using 4-iodobenzonitrile (57.3 mg, 0.25 mmol) and diethyl *H*-phosphonate (**3**, 38.6 μL, 0.275 mmol). The crude product was purified by pTLC (hexane/EtOAc 2:3) to afford **16** as a colorless crystalline solid (43.0 mg, 72%).

Spectral data match previously reported results,[41] and $^{1}H/^{31}P$ NMR data are provided here for convenience.
R_f = 0.44 (hexane/EtOAc 2:3). Stain: UV active;
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94–7.89 (m, 2H), 7.77–7.74 (m, 2H), 4.23–4.06 (m, 4H), 1.33 (t, *J* = 7.2 Hz, 6H) ppm;
^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 15.33 ppm.

16 was also prepared according to modified General procedure B using 4-bromobenzonitrile (45.5 mg, 0.25 mmol), diethyl *H*-phosphonate (**3**, 66.0 μL, 0.50 mmol), 2 wt % TPGS-750-M in H_2O (1.0 mL) and EtOAc (0.2 mL). The reaction was performed at 55 °C. The crude product was purified by pTLC (hexane/EtOAc 2:3) to afford **16** as a colorless crystalline solid (59.0 mg, 99%).

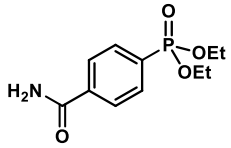
Methyl 4-(diethoxyphosphoryl)benzoate (17)



Prepared according to General procedure A using methyl 4-iodobenzoate (65.5 mg, 0.25 mmol) and diethyl *H*-phosphonate (**3**, 38.6 μL, 0.30 mmol). The crude product was purified by pTLC (hexane/EtOAc 2:3) to afford **17** as a clear crystalline solid (57.0 mg, 84%).

Spectral data match previously reported results,[36] and $^{1}H/^{31}P$ NMR data are provided here for convenience.
R_f = 0.42 (hexane/EtOAc 2:3). Stain: UV active;
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12–8.09 (m, 2H), 7.91–7.85 (m, 2H), 4.21–4.03 (m, 4H), 3.94 (s, 3H), 1.32 (t, *J* = 7.2 Hz, 6H) ppm;
^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 17.00 ppm.

Diethyl (4-carbamoylphenyl) phosphonate (18)

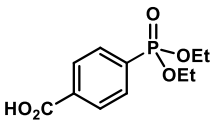


Prepared according to General procedure A using 4-iodobenzamide (61.8 mg, 0.25 mmol) and diethyl *H*-phosphonate (**3**, 66.0 μL, 0.50 mmol). The crude product was purified by pTLC (7% MeOH in CH_2Cl_2) to afford **18** as a colorless crystalline solid (46.0 mg, 72%).

R_f = 0.50 (10% MeOH in CH_2Cl_2). Stain: UV active;

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92–7.83 (m, 4H), 6.50 (br s, 1H), 5.91 (br s, 2H), 4.20–4.04 (m, 4H), 1.32 (t, *J* = 7.2 Hz, 6H) ppm;
^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 16.94 ppm;
^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$/CD_3OD ~10:1): δ 169.2 (d, *J* = 4.0 Hz), 137.2 (d, *J* = 6.0 Hz), 131.8 (d, *J* = 10.1 Hz), 131.3 (d, *J* = 187.0 Hz), 127.6 (d, *J* = 15.2 Hz), 62.6 (d, *J* = 5.1 Hz), 16.1 (d, *J* = 6.1 Hz) ppm;
HRMS (ESI-TOF) calc'd for $C_{11}H_{17}NO_4P$ $[M+H]^+$: 258.08897, found 258.08918; calc'd for $C_{11}H_{16}NO_4PNa$ $[M+Na]^+$: 280.07092, found 280.07111.

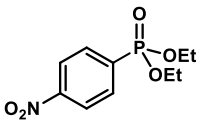
4-(Diethoxyphosphoryl)benzoic acid (19)



Prepared according to modified General procedure A using methyl 4-iodobenzoic acid (62.0 mg, 0.25 mmol), diethyl *H*-phosphonate (**3**, 38.6 µL, 0.275 mmol) and 2,6-lutidine (87.0 µL, 0.75 mmol). The crude product was purified by pTLC (2.5% MeOH + 1% AcOH in CH_2Cl_2) to afford **19** as a white solid (65.0 mg, quantitative).

Spectral data match previously reported results,[42] and ^{1}H/^{31}P NMR data are provided here for convenience.
R_f = 0.15 (2.5% MeOH + 1% AcOH in CH_2Cl_2). Stain: UV active;
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.97 (br s), 8.18–7.97 (m, 2H), 7.89–7.72 (m, 2H), 4.22–4.01 (m, 4H), 1.28 (t, *J* = 6.2 Hz, 6H) ppm;
^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 17.45 ppm.

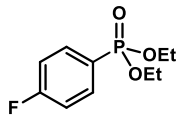
Diethyl (4-nitrophenyl)phosphonate (20)



Prepared according to modified General procedure A using 1-iodo-4-nitrobenzene (62.3 mg, 0.25 mmol), diethyl *H*-phosphonate (**3**, 38.6 µL, 0.275 mmol), $Pd(OAc)_2$ (1.4 mg, 6.25 µmol), XantPhos (3.6 mg, 6.25 µmol), $Ni(phen)_3Cl_2$ (4.2 mg, 6.25 µmol), LiBr (21.7 mg, 0.25 mmol), nano Zn (8.1 mg, 0.125 mmol), 2,6-lutidine (87.0 µL, 0.75 mmol), 2 wt % TPGS-750-M in H_2O (1.0 mL) and EtOAc (0.2 mL). The reaction was performed at 55 °C. The crude product was purified by pTLC (2.5% MeOH in CH_2Cl_2) to afford **20** as a light-yellow oil (56.0 mg, 86%).

Spectral data match previously reported results,[43] and ^{1}H/^{31}P NMR data are provided here for convenience.
R_f = 0.56 (4% MeOH in CH_2Cl_2). Stain: UV active;
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.31–7.28 (m, 2H), 8.02–7.97 (m, 2H), 4.24–4.08 (m, 4H), 1.34 (t, *J* = 7.2 Hz, 6H) ppm;
^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 14.93 ppm.

Diethyl (4-fluorophenyl)phosphonate (21)

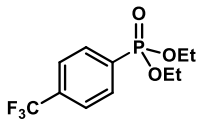


Prepared according to General procedure A using 4-fluoroiodobenzene (28.8 µL, 0.25 mmol) and diethyl *H*-phosphonate (**3**, 66.0 µL, 0.50 mmol). The crude product was purified by pTLC (hexane/EtOAc 1:1) to afford **21** as a light-yellow oil (56.0 mg, 97%).

Spectral data match previously reported results,[36] and ^{1}H/^{31}P/^{19}F NMR data are provided here for convenience.

R_f = 0.36 (hexane/EtOAc 1:1). Stain: UV active;
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85–7.78 (m, 2H), 7.17–7.12 (m, 2H), 4.19–4.02 (m, 4H), 1.32 (t, *J* = 6.8 Hz, 6H) ppm;
^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 17.80 ppm;
^{19}F NMR (376 MHz, $CDCl_3$): δ -106.1 (m) ppm.

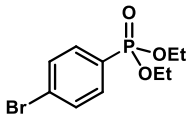
Diethyl (4-(trifluoromethyl)phenyl)phosphonate (22)



Prepared according to General procedure A using 4-iodobenzotrifluoride (36.7 µL, 0.25 mmol) and diethyl *H*-phosphonate (**3**, 66.0 µL, 0.50 mmol). The crude product was purified by pTLC (hexane/EtOAc 1:1) to afford **22** as a light-yellow oil (61.0 mg, 86%).

Spectral data match previously reported results,[36] and ^{1}H/^{31}P/^{19}F NMR data are provided here for convenience.
R_f = 0.47 (hexane/EtOAc 1:1). Stain: UV active;
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 (dd, *J* = 12.8, 8.4 Hz, 2H), 7.72 (dd, *J* = 8.0, 3.2 Hz, 2H), 4.22–4.05 (m, 4H), 1.33 (t, *J* = 6.8 Hz, 6H) ppm;
^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 16.26 ppm;
^{19}F NMR (376 MHz, $CDCl_3$): δ -63.3 (m) ppm.

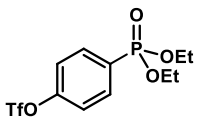
Diethyl (4-(bromo)phenyl)phosphonate (23)



Prepared according to modified General procedure A using 1-bromo-4-iodobenzene (70.7 mg, 0.25 mmol) and diethyl *H*-phosphonate (**3**, 38.6 µL, 0.30 mmol). The reaction was performed at 35 °C. The crude product was purified by pTLC (hexane/EtOAc 1:1) to afford **23** as a yellowish oil (33.2 mg, 45%), and bis-coupling product **47** as a yellow oil (31.0 mg, 36%).

Spectral data of **23** match previously reported results,[44] and ^{1}H/^{31}P NMR data are provided here for convenience.
R_f = 0.37 (hexane/EtOAc 1:1). Stain: UV active;
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70–7.59 (m, 4H), 4.19–4.03 (m, 4H), 1.32 (t, *J* = 6.8 Hz, 6H) ppm;
^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 17.74 ppm.

4-(Diethoxyphosphoryl)phenyl trifluoromethanesulfonate (24)

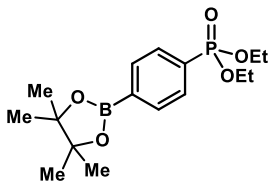


Prepared on 0.50 mmol-scale according to General procedure A using 4-iodophenyl trifluoromethanesulfonate (**SI-1**, 99.6 µL, 0.50 mmol) and diethyl *H*-phosphonate (**3**, 77.2 µL, 0.60 mmol). The crude product was purified by pTLC (EtOAc/CH_2Cl_2 3:2) to afford **24** as a colorless oil (114.0 mg, 63%), and bis-coupling product **47** as a waxy solid (42.0 mg, 24%).

R_f = 0.62 (EtOAc/CH_2Cl_2 3:2). Stain: weakly UV active, $KMnO_4$;
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92 (dd, *J* = 12.8, 8.4 Hz, 2H), 7.38 (dd, *J* = 8.8, 2.8 Hz, 2H), 4.23–4.06 (m, 4H), 1.34 (t, *J* = 7.2 Hz, 6H) ppm;
^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 15.94 ppm;
^{19}F NMR (376 MHz, $CDCl_3$): δ -72.8 (m) ppm;

$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 152.1 (d, *J* = 4.1 Hz), 134.1 (d *J* = 11.0 Hz), 129.6 (d, *J* = 189.0 Hz), 121.5 (d, *J* = 15.9 Hz), 118.6 (q, *J* = 319.0 Hz), 62.5 (d, *J* = 5.7 Hz), 16.2 (d, *J* = 6.1 Hz) ppm;
HRMS (ESI-TOF) calc'd for $C_{11}H_{15}O_6F_3PS$ $[M+H]^+$: 363.02736, found 363.02768; calc'd for $C_{11}H_{14}O_6F_3NaPS$ $[M+Na]^+$: 385.00930, found 385.00952.

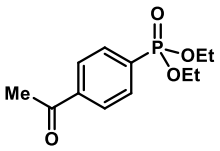
Diethyl (4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)phosphonate (25)



Prepared according to General procedure A using 2-(4-iodophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (82.5 mg, 0.25 mmol) and diethyl *H*-phosphonate (**3**, 66.0 μL, 0.50 mmol). The crude product was purified by pTLC (hexane/EtOAc 1:2) to afford **25** as a white solid (72.0 mg, 85%).

Spectral data match previously reported results,[41] and $^{1}H/^{31}P/^{11}B$ NMR data are provided here for convenience.
R_f = 0.30–0.50 (hexane/EtOAc 1:2). Stain: weakly UV active, $KMnO_4$;
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90–7.87 (m, 2H), 7.82–7.77 (m, 2H), 7.83–7.73 (m, 1H), 4.18–4.00 (m, 4H), 1.34 (s, 12H), 1.30 (t, *J* = 7.2 Hz, 6H) ppm;
$^{31}P\{^{1}H\}$ NMR (162 MHz, $CDCl_3$): δ 18.59 ppm;
^{11}B NMR (128 MHz, $CDCl_3$): 31.03 pm.

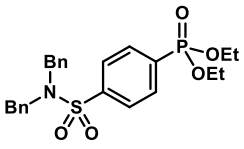
Diethyl (4-acetylphenyl)phosphonate (26)



Prepared according to General procedure B using 4-bromoacetophenone (50.0 mg, 0.25 mmol) and diethyl *H*-phosphonate (**3**, 66.0 μL, 0.50 mmol). The crude product was purified by pTLC (hexane/EtOAc 1:4) to afford **26** as a colorless oil (57.0 mg, 89%).

Spectral data match previously reported results,[38] and $^{1}H/^{31}P$ NMR data are provided here for convenience.
R_f = 0.30 (hexane/EtOAc 1:4). Stain: UV active;
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04–8.01 (m, 2H), 7.94–7.89 (m, 2H), 4.22–4.05 (m, 4H), 2.64 (s, 3H), 1.21 (t, *J* = 6.8 Hz, 6H) ppm;
$^{31}P\{^{1}H\}$ NMR (162 MHz, $CDCl_3$): δ 16.85 ppm.

Diethyl (4-(*N*,*N*-dibenzylsulfamoyl)phenyl)phosphonate (27)

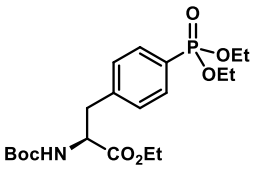


Prepared according to modified General procedure A using *N*,*N*-dibenzyl-4-iodobenzenesulfonamide (**SI-3**, 115.8 mg, 0.25 mmol) and diethyl *H*-phosphonate (**3**, 66.0 μL, 0.50 mmol), 2 wt % TPGS-750-M in H_2O (1.0 mL) and EtOAc (0.2 mL). The crude product was purified by pTLC (hexane/EtOAc 3:7) to afford **27** as a colorless solid (102.0 mg, 86%).

R_f = 0.34 (hexane/EtOAc 1:2). Stain: UV active;
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95–7.86 (m, 4H), 7.24–7.20 (m, 6H), 7.07–7.03 (m, 4H), 4.36 (s, 4H), 4.24–3.07 (m, 4H), 1.35 (t, *J* = 7.2 Hz, 6H) ppm;
$^{31}P\{^{1}H\}$ NMR (162 MHz, $CDCl_3$): δ 15.89 ppm;

$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 144.6 (d, *J* = 3.5 Hz), 135.4, 133.5 (d, *J* = 186.0 Hz), 132.6 (d, *J* = 10.3 Hz), 128.8, 128.7, 128.1, 127.1 (d, *J* = 15.2 Hz), 62.8 (d, *J* = 6.1 Hz), 50.8, 16.6 (d, *J* = 6.1 Hz) ppm;
HRMS (ESI-TOF) calc'd for $C_{24}H_{29}O_5NPS$ $[M+H]^+$: 474.14986, found 474.15015; calc'd for $C_{24}H_{28}O_5NNaPS$ $[M+Na]^+$: 496.13180, found 496.13196.

Ethyl (*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(4-iodophenyl)propanoate (28)

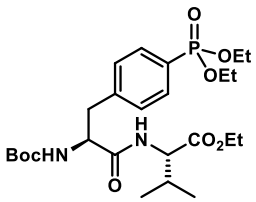


Prepared according to General procedure A using ethyl (*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(4-iodophenyl)propanoate (**SI-4**, 104.8 mg, 0.25 mmol) and diethyl *H*-phosphonate (**3**, 66.0 µL, 0.50 mmol). The crude product was purified by pTLC (EtOAc/CH_2Cl_2 1:1) to afford **28** as a white solid (94.0 mg, 88%).

Spectral data match previously reported results,[45] and $^1H/^{31}P/^{13}C$ NMR data are provided here for convenience.
R_f = 0.60 (EtOAc/CH_2Cl_2 1:1). Stain: weakly UV active;
^1H NMR (400 MHz, $CDCl_3$): δ 7.75–7.70 (m, 2H), 7.25–7.23 (m, 2H), 5.01 (br s, 1H), 4.59 (br s, 1H), 4.18–4.01 (m, 6H), 3.19–3.07 (m, 2H), 1.41 (s, 9H), 1.31 (t, *J* = 7.2 Hz, 6H), 1.22 (t, *J* = 7.2 Hz, 3H) ppm;
$^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$): δ 18.81 ppm;
$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 171.5, 155.0, 141.2, 131.9 (d, *J* = 10.1 Hz), 129.6 (d, *J* = 14.9 Hz), 126.9 (d, *J* = 189.0 Hz), 80.0, 62.1 (d, *J* = 5.4 Hz), 61.5, 54.3, 38.5, 28.3, 16.3 (d, *J* = 6.1 Hz), 14.1 ppm.

Note: C(sp^2)–P cross-coupling of *N*-Boc-4-iodophenylalanine with **3** afforded the corresponding phosphonate product in nearly quantitative yield (^1H NMR using CH_2Br_2 as an internal standard); however, its high polarity caused considerable streaking (R_f = 0.05–0.60), hampering its isolation. For this reason, the carboxylate group was protected and afforded **28** by C(sp^2)–P cross-coupling reaction.

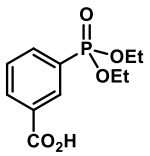
Compounds 29



Prepared on 0.125 mmol-scale according to General procedure A using **SI-5** (64.8 mg, 0.125 mmol) and diethyl *H*-phosphonate (**3**, 33.0 µL, 0.25 mmol). The crude product was purified by pTLC (EtOAc/CH_2Cl_2 1:1) to afford **29** as an off-white solid (55.0 mg, 83%).

R_f = 0.45–0.50 (EtOAc/CH_2Cl_2 1:1). Stain: weakly UV active;
^1H NMR (400 MHz, $CDCl_3$): δ 7.71–7.66 (m, 2H), 7.31–7.28 (m, 2H), 6.60 (br d, 1H), 5.17 (br d, 1H), 4.45–4.35 (m, 2H, overlapped), 4.17–4.00 (m, 6H, overlapped), 3.18–3.01 (m, 2H), 2.10 (m, 1H), 1.36 (s, 9H), 1.28 (t, *J* = 7.2 Hz, 6H), 1.23 (t, *J* = 7.2 Hz, 3H), 0.86 (d, *J* = 7.2 Hz, 3H), 0.83 (d, *J* = 6.8 Hz, 3H) ppm;
$^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$): δ 18.79 ppm;
$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 171.4, 171.0, 155.5, 141.2, 132.1 (d, *J* = 10.1 Hz), 129.6 (d, *J* = 15.2 Hz), 126.8 (d, *J* = 188.0 Hz), 80.3, 62.1 (d, *J* = 5.1 Hz), 61.3, 57.3, 55.5 (br), 38.0 (br), 31.3, 28.3, 18.9, 17.8, 16.4 (d, *J* = 7.1 Hz), 14.3 ppm;
HRMS (ESI-TOF) calc'd for $C_{25}H_{42}O_8N_2P$ $[M+H]^+$: 529.26733, found 529.26692.

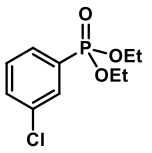
3-(Diethoxyphosphoryl)benzoic acid (30)



Prepared according to General procedure A using 3-iodobenzoic acid (62.0 mg, 0.25 mmol), diethyl *H*-phosphonate (**3**, 66.0 μL, 0.50 mmol) and 2,6-lutidine (87.0 μL, 0.75 mmol). The crude product was purified by pTLC (2.5% MeOH/1% AcOH in CH_2Cl_2) to afford **30** as a white solid (64.0 mg, 99%).

R_f = 0.05–0.15 (2.5% MeOH + 1% AcOH in CH_2Cl_2). Stain: UV active;
^{1}H NMR (400 MHz, CD_3OD): δ 8.42 (dt, *J* = 14.0, 1.2 Hz, 1H), 8.29–8.25 (m, 1H), 8.03–7.95 (m, 1H), 7.67 (td, *J* = 7.6, 4.0 Hz, 1H), 4.21–4.08 (m, 4H), 1.34 (t, *J* = 7.2 Hz, 6H) ppm;
^{31}P{^{1}H} NMR (162 MHz, CD_3OD): δ 17.68 ppm;
^{13}C{^{1}H} NMR (100 MHz, CD_3OD): δ 168.3 (d, *J* = 2.2 Hz), 136.7 (d, *J* = 10.1 Hz), 134.9 (d, *J* = 2.9 Hz), 133.7 (d, *J* = 10.9 Hz), 132.7 (d, *J* = 14.9 Hz), 130.2 (d, *J* = 15.0 Hz), 129.7 (d, *J* = 194.8 Hz), 64.1 (d, *J* = 5.8 Hz), 16.6 (d, *J* = 6.2 Hz) ppm;
HRMS (ESI-TOF) calc'd for $C_{11}H_{16}O_5P$ $[M+H]^+$: 259.07299, found 259.07319; calc'd for $C_{11}H_{15}O_5NaP$ $[M+Na]^+$: 281.05493, found 281.05521.

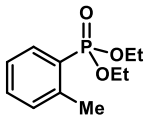
Diethyl (3-chlorophenyl)phosphonate (31)



Prepared according to General procedure A using 1-chloro-3-iodobenzene (31.0 μL, 0.25 mmol) and diethyl *H*-phosphonate (**3**, 38.6 μL, 0.30 mmol). The crude product was purified by pTLC (hexane/EtOAc 1:1) to afford **31** as a colorless oil (50.0 mg, 80%).

Spectral data match previously reported results,[36] and ^{1}H/^{31}P NMR data are provided here for convenience.
R_f = 0.25 (hexane/EtOAc 1:1). Stain: weakly UV active;
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78 (dt, *J* = 13.6, Hz, 1H), 8.20–8.14 (m, 1H), 7.83–7.73 (m, 1H), 7.50–7.41 (m, 1H), 4.10–3.90 (m, 4H), 1.21 (t, *J* = 6.8 Hz, 6H) ppm;
^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 16.55 ppm.

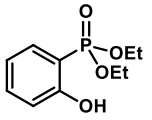
Diethyl 2-tolylphosphonate (32)



Prepared according to General procedure A using 2-iodotoluene (31.8 μL, 0.25 mmol) and diethyl *H*-phosphonate (**3**, 66.0 μL, 0.50 mmol). The crude product was purified by pTLC (hexane/EtOAc 1:1) to afford **32** as a colorless viscous oil (22.0 mg, 39%).

Spectral data match previously reported results,[41] and ^{1}H/^{31}P NMR data are provided here for convenience.
R_f = 0.25 (hexane/EtOAc 1:1). Stain: UV active, $KMnO_4$;
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90 (dd, *J* = 14.4, 7.6 Hz, 1H), 7.42 (t, *J* = 7.6 Hz, 1H), 7.28–7.23 (m, 2H), 4.20–4.03 (m, 4H), 2.57 (s, 3H), 1.32 (t, *J* = 6.8 Hz, 6H) ppm;
^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 19.45 ppm.

Diethyl (2-hydroxyphenyl)phosphonate (33)



Prepared according to General procedure B using (2-iodophenoxy)trimethylsilane (50.5 μL, 0.25 mmol) and diethyl *H*-phosphonate (**3**, 66.0 μL, 0.50 mmol). The crude product was purified by pTLC (hexane/EtOAc 1:4) to afford **33** as a yellow oil (49.0 mg, 85%). Trimethylsilyl group hydrolyzed during the reaction.

Spectral data match previously reported results,[46] and $^{1}H/^{31}P$ NMR data are provided here for convenience.

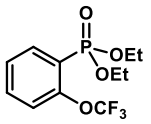
R_f = 0.90 (hexane/EtOAc 1:4). Stain: UV active, visible yellow spot;

^{1}H NMR (400 MHz, $CDCl_3$): δ 10.24 (s, 1H), 7.46 (dt, *J* = 8.4, 1.8 Hz, 1H), 7.90 (dd, *J* = 14.4, 8.0, 2.0 Hz, 1H), 6.98 (t, *J* = 7.6 Hz, 1H), 6.94 (td, *J* = 8.0, 2.4 Hz, 1H), 4.23–4.01 (m, 4H), 1.34 (t, *J* = 7.2 Hz, 6H) ppm;

$^{31}P\{^{1}H\}$ NMR (162 MHz, $CDCl_3$): δ 22.41 ppm.

Note: Cross-coupling of 2-iodophenol with **3** afforded **33** in <10% yield (^{1}H NMR with CH_2Br_2 as an interval standard) regardless of used reaction conditions.

Diethyl (2-(trifluoromethoxy)phenyl)phosphonate (34)



Prepared according to General procedure B using 1-iodo-2-(trifluoromethoxy)benzene (72.0 mg, 38.5 μL, 0.25 mmol) and diethyl *H*-phosphonate (**3**, 66.0 μL, 0.50 mmol). The crude product was purified by pTLC (hexane/EtOAc 1:1) to afford **34** as a colorless oil (53.0 mg, 71%).

Spectral data match previously reported results,[47] and $^{1}H/^{31}P/^{19}F$ NMR data are provided here for convenience.

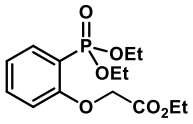
R_f = 0.43 (hexane/EtOAc 1:1). Stain: UV active;

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00 (ddd, *J* = 14.4, 7.6, 1.6 Hz, 1H), 7.58 (br t, *J* = 8.0 Hz, 1H), 7.38–7.32 (m, 2H), 4.26–4.07 (m, 4H), 1.33 (t, *J* = 7.2 Hz, 6H) ppm;

$^{31}P\{^{1}H\}$ NMR (162 MHz, $CDCl_3$): δ 13.56 ppm;

^{19}F NMR (376 MHz, $CDCl_3$): δ -56.2 (d, *J* = 1.5 Hz) ppm.

Ethyl 2-(2-(diethoxyphosphoryl)phenoxy)acetate (35)



Prepared according to General procedure B using ethyl 2-(2-iodophenoxy)acetate (**SI-6**, 55.2 μL, 0.25 mmol) and diethyl *H*-phosphonate (**3**, 66.0 μL, 0.50 mmol). The crude product was purified by pTLC (hexane/EtOAc 5:7) to afford **35** as a light-yellow oil (47.0 mg, 60%).

Spectral data match previously reported results,[48] and $^{1}H/^{31}P/^{13}C$ NMR data are provided here for convenience.

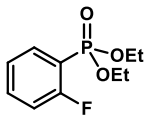
R_f = 0.47 (hexane/EtOAc 5:7). Stain: UV active;

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88 (ddd, *J* = 14.4, 7.2, 1.6 Hz, 1H), 7.47 (t, *J* = 7.6 Hz, 1H), 7.06 (td, *J* = 7.2, 3.2 Hz, 1H), 6.80 (t, *J* = 7.6 Hz, 1H), 4.73 (s, 2H), 4.25 (q, *J* = 7.2 Hz, 2H), 4.27–4.09 (m, 4H, overlappped), 1.33 (t, *J* = 7.2 Hz, 6H), 1.28 (t, *J* = 7.2 Hz, 3H) ppm;

$^{31}P\{^{1}H\}$ NMR (162 MHz, $CDCl_3$): δ 16.32 ppm;

$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 168.3, 159.5 (d, *J* = 2.2 Hz), 136.6 (d, *J* = 6.9 Hz), 134.2 (d, *J* = 2.1 Hz), 121.4 (d, *J* = 14.3 Hz), 117.3 (d, *J* = 185.0 Hz), 112.1 (d, *J* = 9.3 Hz), 65.8, 62.3 (d, *J* = 5.4 Hz), 61.4, 16.4 (d, *J* = 6.7 Hz), 14.2 ppm.

Diethyl (2-fluorophenyl)phosphonate (36)



Prepared according to General procedure A using 2-fluoroiodobenzene (29.2 µL, 0.25 mmol) and diethyl *H*-phosphonate (**3**, 66.0 µL, 0.50 mmol). The crude product was purified by pTLC (hexane/EtOAc 1:1) to afford **36** as a yellowish oil (26.0 mg, 44%).

Spectral data match previously reported results,[36] and $^{1}H/^{31}P/^{19}F$ NMR data are provided here for convenience.

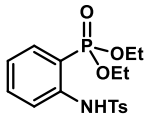
R_f = 0.35 (hexane/EtOAc 1:1). Stain: UV active;

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90–7.82 (m, 1H), 7.57–7.51 (m, 1H), 7.26–7.21 (m, 1H), 7.15–7.09 (m, 1H), 4.25–4.09 (m, 4H), 1.34 (t, *J* = 6.8 Hz, 6H) ppm;

^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 13.65 ppm;

^{19}F NMR (376 MHz, $CDCl_3$): δ -103.73 (m) ppm.

Diethyl (2-((4-methylphenyl)sulfonamido)phenyl)phosphonate (37)



Prepared according to General procedure B using *N*-(2-iodophenyl)-toluenesulfonamide (**SI-8**, 93.3 mg, 0.25 mmol) and diethyl *H*-phosphonate (**3**, 66.0 µL, 0.50 mmol). The crude product was purified by pTLC (hexane/EtOAc 3:2) to afford **37** as a light-yellow solid (34.0 mg, 35%).

R_f = 0.30 (hexane/EtOAc 3:2). Stain: UV active;

^{1}H NMR (400 MHz, $CDCl_3$): δ 10.26 (s, 1H), 7.80–7.76 (m, 1H, overlapped), 7.76 (d, *J* = 8.4 Hz, 2H), 7.48–7.42 (m, 2H), 7.21 (d, *J* = 8.0 Hz, 2H), 7.10–7.05 (m, 1H), 4.01–3.92 (m, 2H), 3.86–3.76 (m, 2H) 2.35 (s, 3H), 1.22 (t, *J* = 7.2 Hz, 6H) ppm;

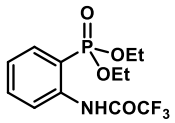
^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 19.15 ppm;

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 143.7, 142.2 (d, *J* = 7.9 Hz), 136.9, 134.1 (d, *J* = 2.3 Hz), 132.9 (d, *J* = 5.9 Hz), 129.6, 127.5, 123.5 (d, *J* = 13.3 Hz), 119.9 (d, *J* = 11.6 Hz), 114.7 (d, *J* = 178.0 Hz), 62.6 (d, *J* = 4.9 Hz), 21.6, 16.2 (d, *J* = 6.7 Hz) ppm;

HRMS (ESI-TOF) calc'd for $C_{17}H_{23}O_5NPS$ $[M+H]^+$: 384.10291, found 384.10265.

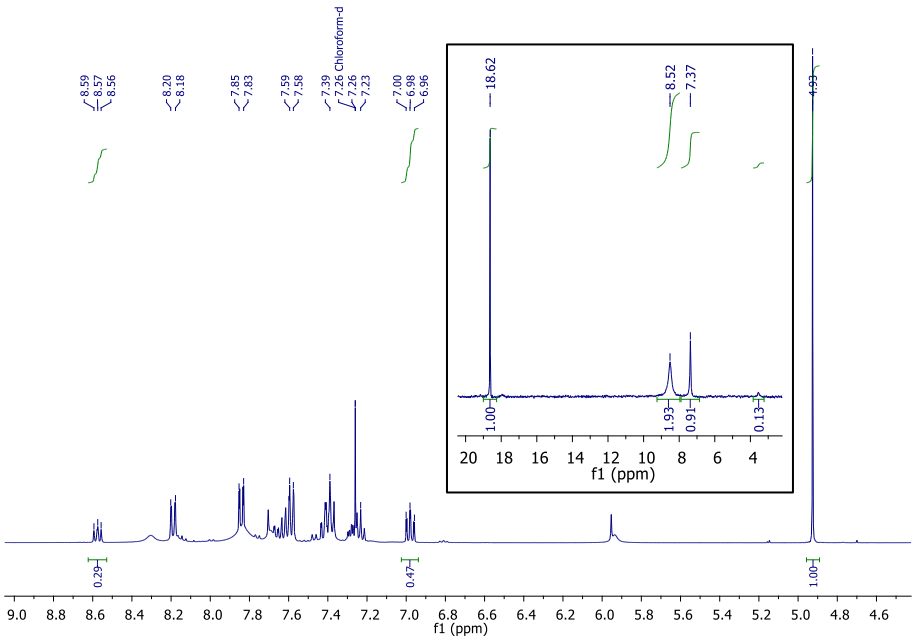
Note: Cross-coupling of **SI-8** with **3** following General procedure A (performed at 55 °C) afforded **37** in 30% yield.

Diethyl (2-(2,2,2-trifluoroacetamido)phenyl)phosphonate (38)



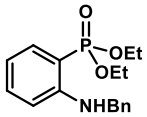
Prepared according to General procedure A using 2,2,2-trifluoro-*N*-(2-iodophenyl)acetamide (**SI-9**, 78.8 mg, 0.25 mmol) and diethyl *H*-phosphonate (**3**, 66.0 µL, 0.50 mmol). The crude reaction mixture was analyzed by ^{31}P and by ^{1}H NMR spectroscopy with CH_2Br_2 as an internal standard (18.2 mg, spectrum shown below). The yield of **38** was determined to be 24%.

^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 18.62 ppm.



^{1}H NMR (400 MHz, $CDCl_3$) of the crude reaction mixture using CH_2Br_2 as an internal standard (δ 4.93 ppm, 18.2 mg). The signal at δ 8.57 ppm was assigned to **38**, and the signal at δ 6.98 ppm corresponds to the starting compound **SI-9**. ^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$) spectrum is shown in the black box, the signal at δ 18.62 ppm corresponds to **38**.

Diethyl (2-(benzylamino)phenyl)phosphonate (39)

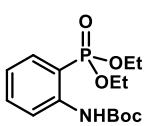


Prepared according to General procedure B using *N*-benzyl-2-iodoaniline (**SI-10**, 48.3 µL, 0.25 mmol) and diethyl *H*-phosphonate (**3**, 66.0 µL, 0.50 mmol). The reaction was performed at 55 °C. The crude product was purified by pTLC (hexane/EtOAc 2:1) to afford **39** as a light-yellow oil (36.0 mg, 45%).

$\mathbf{R}_f$ = 0.55 (hexane/EtOAc 2:1). Stain: UV active, $KMnO_4$ stain;
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48 (ddd, *J* = 14.8, 7.6, 1.6 Hz, 1H), 7.37–7.22 (m, 6H, overlapped with $CHCl_3$), 7.13 (t, *J* = 5.2 Hz, 1H), 6.65 (ddd, *J* = 7.6, 3.2, 0.8 Hz, 1H), 6.57 (t, *J* = 7.6 Hz, 1H), 4.40 (d, *J* = 5.6 Hz, 2H), 4.17–4.01 (m, 4H), 1.33 (t, *J* = 7.2 Hz, 6H) ppm;
^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 21.76 ppm;
^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 151.8 (d, *J* = 8.9 Hz), 139.1, 134.3 (d, *J* = 2.2 Hz), 133.6 (d, *J* = 7.2 Hz), 128.7, 127.1, 127.0, 115.7 (d, *J* = 14.2 Hz), 111.5 (d, *J* = 12.2 Hz), 108.0 (d, *J* = 182.0 Hz), 62.1 (d, *J* = 5.1 Hz), 47.3, 16.4 (d, *J* = 6.7 Hz) ppm;
HRMS (ESI-TOF) calc'd for $C_{17}H_{23}O_3NP$ $[M+H]^+$: 320.14101, found 320.14079.

Note: Cross-coupling of **SI-10** with **3** following General procedure A afforded **39** in 35% yield.

***tert*-Butyl (2-(diethoxyphosphoryl)phenyl)carbamate (40)**

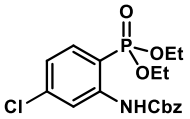


Prepared according to General procedure B using *tert*-butyl (2-iodophenyl)carbamate (**SI-11**, 79.8 mg, 0.25 mmol) and diethyl *H*-phosphonate (**3**, 66.0 µL, 0.50 mmol). The reaction was performed at 55 °C. The crude product was purified by pTLC (hexane/EtOAc 7:2) to afford **40** as a viscous colorless oil (62.0 mg, 75%).

Spectral data match previously reported results,[49] and $^{1}H/^{31}P$ NMR data are provided here for convenience.
R_f = 0.50 (hexane/EtOAc 7:2). Stain: UV active;
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.64 (s, 1H), 8.24 (t, *J* = 7.6 Hz, 1H), 7.56–7.46 (m, 2H), 7.03 (td, *J* = 7.6, 2.8 Hz, 1H), 4.19–3.99 (m, 4H), 1.51 (s, 9H), 1.31 (t, *J* = 7.2 Hz, 6H) ppm;
$^{31}P\{^{1}H\}$ NMR (162 MHz, $CDCl_3$): δ 19.54 ppm.

Note: Cross-coupling of **SI-11** with **3** following General procedure A afforded **40** in 43% yield.

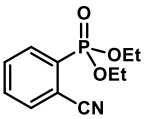
Benzyl (5-chloro-2-(diethoxyphosphoryl)phenyl)carbamate (41)



Prepared according to modified General procedure A using benzyl (5-chloro-2-iodophenyl)carbamate (**SI-12**, 96.9 mg, 0.25 mmol), diethyl *H*-phosphonate (**3**, 66.0 µL, 0.50 mmol), 2 wt % TPGS-750-M in H_2O (1.0 mL) and EtOAc (0.2 mL). The crude product was purified by pTLC (hexane/EtOAc 2:1) to afford **41** as an off-white solid (84.0 mg, 85%).

R_f = 0.50 (hexane/EtOAc 2:1). Stain: UV active, $KMnO_4$ stain;
^{1}H NMR (400 MHz, $CDCl_3$): δ 10.15 (s, 1H), 8.48 (dd, *J* = 5.6, 2.0 Hz, 1H), 7.49–7.32 (m, 6H), 7.05 (dt, *J* = 8.0, 2.0 Hz, 1H), 5.21 (s, 2H), 4.19–3.98 (m, 4H), 1.31 (dt, *J* = 7.2, 0.8 Hz, 6H) ppm;
$^{31}P\{^{1}H\}$ NMR (162 MHz, $CDCl_3$): δ 18.65 ppm;
$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 153.3, 144.0 (d, *J* = 8.5 Hz), 140.5 (d, *J* = 3.4 Hz), 136.1, 133.7 (d, *J* = 6.7 Hz), 128.6, 128.3, 128.2, 122.5 (d, *J* = 14.3 Hz), 119.2 (d, *J* = 12.1 Hz), 111.4 (d, *J* = 181.0 Hz), 67.1, 62.8 (d, *J* = 5.3 Hz), 16.4 (d, *J* = 6.6 Hz) ppm;
HRMS (ESI-TOF) calc'd for $C_{18}H_{22}O_5NClP$ $[M+H]^+$: 398.09186, found 398.09162.

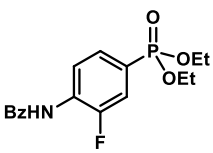
Diethyl (2-cyanophenyl)phosphonate (42)



Prepared according to modified General procedure A using 2-iodobenzonitrile (57.3 mg, 0.25 mmol), diethyl *H*-phosphonate (**3**, 66.0 µL, 0.50 mmol), 2 wt % TPGS-750-M in H_2O (1.0 mL) and EtOAc (0.2 mL). The reaction was performed at 55 °C. The crude product was purified by pTLC (hexane/EtOAc 2:3) to afford **42** as a beige solid (19.0 mg, 32%).

Spectral data match previously reported results,[50] and $^{1}H/^{31}P$ NMR data are provided here for convenience.
R_f = 0.35 (hexane/EtOAc 2:3). Stain: UV active;
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.11 (ddd, *J* = 14.4, 7.6, 1.6 Hz, 1H), 7.82–7.79 (m, 1H), 7.56–7.46 (m, 2H), 4.32–4.15 (m, 4H), 1.38 (t, *J* = 6.8 Hz, 6H) ppm;
$^{31}P\{^{1}H\}$ NMR (162 MHz, $CDCl_3$): δ 12.60 ppm.

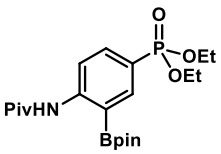
Diethyl (4-benzamido-3-fluorophenyl)phosphonate (43)



Prepared according to modified General procedure A using *N*-(2-fluoro-4-iodophenyl)benzamide (**SI-13**, 85.3 mg, 0.25 mmol), diethyl *H*-phosphonate (**3**, 38.6 µL, 0.30 mmol), 2 wt % TPGS-750-M in H_2O (1.0 mL) and EtOAc (0.2 mL). The crude product was purified by pTLC (hexane/EtOAc 1:1) to afford **43** as a colorless crystalline solid (72.0 mg, 82%).

$\mathbf{R}_f$ = 0.41 (hexane/EtOAc 1:1). Stain: UV active;
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.66 (td, *J* = 8.0, 4.8 Hz, 1H), 8.24 (br d, *J* = 2.8 Hz, 1H), 7.91–7.88 (m, 2H), 7.65–7.50 (m, 5H), 4.20–4.04 (m, 4H), 1.33 (t, *J* = 7.2 Hz, 6H) ppm;
^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 16.69 (d, *J* = 7.9 Hz) ppm;
^{19}F NMR (376 MHz, $CDCl_3$): δ -130.6 (m) ppm;
^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 165.7, 152.0 (dd, *J* = 244.7, 24.1 Hz), 134.1, 132.6, 130.5 (dd, *J* = 9.8, 3.4 Hz), 129.0, 128.7 (dd, *J* = 9.2, 3.1 Hz), 127.3, 124.3 (dd, *J* = 193.0, 6.1 Hz), 121.5 (d, *J* = 16.2 Hz, broadened), 118.3 (dd, *J* = 20.7, 11.4 Hz), 62.4 (d, *J* = 5.5 Hz), 16.4 (d, *J* = 6.5 Hz) ppm;
HRMS (ESI-TOF) calc'd for $C_{17}H_{20}O_4NFP$ $[M+H]^+$: 352.11085, found 352.11064.

Diethyl (4-pivalamido-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)phosphonate (44)

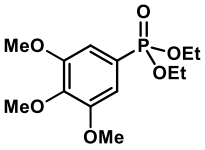


Prepared according to modified General procedure A using *N*-(4-iodo-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)pivalamide (**SI-14**, 107.3 mg, 0.25 mmol), diethyl *H*-phosphonate (**3**, 66.0 µL, 0.30 mmol), 2 wt % TPGS-750-M in H_2O (1.0 mL) and EtOAc (0.2 mL). The crude product was purified by pTLC (2.5% MeOH in EtOAc/CH_2Cl_2 1:1) to afford **44** as an off-white solid (83.0 mg, 76%).

$\mathbf{R}_f$ = 0.56 (2.5% MeOH in EtOAc/CH_2Cl_2 1:1). Stain: UV active;
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.70 (s, 1H), 8.68 (dd, *J* = 8.8, 3.6 Hz, 1H), 8.27 (dd, *J* = 13.2, 2.0 Hz, 1H), 7.84 (ddd, *J* = 12.8, 8.8, 2.0 Hz, 1H), 4.17–3.99 (m, 4H), 1.38 (s, 9H), 1.33 (s, 12H, overlapped), 1.31 (t, *J* = 6.8 Hz, 6H, overlapped) ppm;
^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 19.16 ppm;
^{11}B NMR (128 MHz, $CDCl_3$): δ 29.94 pm;
^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 177.7, 148.5 (d, *J* = 2.8 Hz), 140.6 (d, *J* = 11.1 Hz), 136.3 (d, *J* = 10.8 Hz), 121.6 (d, *J* = 191.0 Hz), 118.7 (d, *J* = 14.0 Hz), 84.7, 62.1 (d, *J* = 5.3 Hz), 40.4, 27.6, 25.1, 16.4 (d, *J* = 6.6 Hz) ppm;*
HRMS (ESI-TOF) calc'd for $C_{21}H_{36}O_6NBP$ $[M+H]^+$: 440.23678, found 440.23701.

Note: *One carbon (C_{Ar}–B) signal is missing in the ^{13}C NRM spectrum due to quadrupolar relaxation.

Diethyl (3,4,5-trimethoxyphenyl)phosphonate (45)



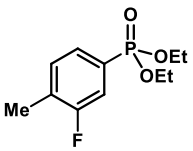
Prepared according to General procedure B using 5-iodo-1,2,3-trimethoxybenzene (73.5 mg, 0.25 mmol) and diethyl *H*-phosphonate (**3**, 66.0 µL, 0.50 mmol). The crude product was purified by pTLC (EtOAc) to afford **45** as a viscous light-yellow oil (73.0 mg, 96%).

Spectral data partially match previously reported results,[51] and the ^{1}H/^{31}P/^{13}C NMR data are provided here for convenience. In the previous report, the ^{31}P NMR chemical shift of –7.84 ppm does not match our value of +19.28 ppm. Moreover, other ^{31}P NMR shifts reported in the previous study do not match typical ^{31}P NMR shifts of dialkyl arylphosphonates (25–10 ppm).

$\mathbf{R}_f$ = 0.36 (EtOAc). Stain: UV active;
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.02 (d, *J* = 14.8 Hz, 2H), 4.20–4.02 (m, 4H), 3.90 (s, 6H), 3.89 (s, 3H), 1.34 (t, *J* = 6.8 Hz, 12H) ppm;
^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 19.28 ppm;

$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 153.4 (d, *J* = 22.1 Hz), 141.5 (d, *J* = 3.7 Hz), 122.9 (d, *J* = 190.0 Hz), 108.8 (d, *J* = 11.3 Hz), 62.1 (d, *J* = 5.4 Hz), 60.8, 56.3, 16.3 (d, *J* = 6.6 Hz) ppm.

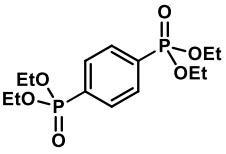
Diethyl (3-fluoro-4-methylphenyl)phosphonate (46)



Prepared according to General procedure A using 2-fluoro-4-iodotoluene (33.7 μL, 0.25 mmol) and diethyl *H*-phosphonate (**3**, 66.0 μL, 0.50 mmol). The crude product was purified by pTLC (hexane/EtOAc 3:2) to afford **46** as a clear oil (50.0 mg, 81%).

R_f = 0.30 (hexane/EtOAc 3:2). Stain: UV active;
^1H NMR (400 MHz, $CDCl_3$): δ 7.47–7.36 (m, 2H), 7.28–7.23 (m, 1H), 4.15–3.99 (m, 4H), 2.28 (s, 3H), 1.28 (t, *J* = 7.2 Hz, 6H) ppm;
$^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$): δ 17.26 (d, *J* = 7.9 Hz) ppm;
^{19}F NMR (376 MHz, $CDCl_3$): δ -116.2 (m) ppm;
$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 161.0 (dd, *J* = 248.8, 21.7 Hz), 131.9 (dd, *J* = 17.6, 4.7 Hz), 130.1 (dd, *J* = 17.2, 3.1 Hz), 127.9 (dd, *J* = 189.7, 6.4 Hz), 127.4 (dd, *J* = 9.3, 3.7 Hz), 118.2 (dd, *J* = 23.3, 10.8 Hz), 62.3 (d, *J* = 5.4 Hz), 16.4 (d, *J* = 6.6 Hz), 14.8 (d, *J* = 3.6 Hz) ppm;
HRMS (ESI-TOF) calc'd for $C_{11}H_{17}O_3FP$ $[M+H]^+$: 247.08939, found 247.08958; calc'd for $C_{11}H_{16}O_3FNaP$ $[M+Na]^+$: 269.07133, found 269.07149.

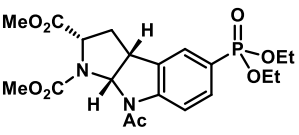
Tetraethyl 1,4-phenylenebis(phosphonate) (47)



Prepared according to General procedure A using 1,4-diiodobenzene (82.5 mg, 0.25 mmol) and diethyl *H*-phosphonate (**3**, 99.0 μL, 0.75 mmol) and 2,6-lutidine (87.0 μL, 0.75 mmol). The crude product was purified by pTLC (5% MeOH + 1% AcOH in EtOAc) to afford **47** as a waxy solid (86.0 mg, 98%).

Spectral data match previously reported results,[52] and $^1H/^{31}P$ NMR data are provided here for convenience.
R_f = 0.30–0.45 (5% MeOH + 1% AcOH in EtOAc). Stain: weakly UV active;
^1H NMR (400 MHz, $CDCl_3$): δ 7.92–7.88 (m, 4H), 4.22–4.05 (m, 8H), 1.33 (t, *J* = 6.8 Hz, 12H) ppm;
$^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$): δ 16.82 ppm.

Compound 48

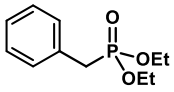


Prepared on 0.125 mmol-scale according to modified General procedure A using iodide **SI-15** (55.5 mg, 0.125 mmol), diethyl *H*-phosphonate (**3**, 33.0 μL, 0.25 mmol), 2 wt % TPGS-750-M in H_2O (0.5 mL) and EtOAc (0.1 mL). The crude product was purified by pTLC (5% MeOH in EtOAc/CH_2Cl_2 1:1) to afford **48** as a white solid (51.0 mg, 90%).

R_f = 0.55 (5% MeOH in EtOAc/CH_2Cl_2 1:1). Stain: UV active;
^1H NMR (400 MHz, $CDCl_3$): δ 8.02 (br s, 1H), 7.64 (dd, *J* = 12.8, 8.4 Hz, 1H), 7.56 (d, *J* = 12.8 Hz, 1H), 6.25 (d, *J* = 6.0 Hz, 1H), 4.58 (br d, *J* = 7.2 Hz, 1H), 4.12–3.95 (m, 5H, overlapped), 3.68 (s, 3H), 3.12 (s, 3H), 2.71–2.51 (m, 5H, overlapped), 1.27 (dt, *J* = 6.8, 6.4 Hz, 6H) ppm;
$^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$): δ 18.64 ppm;
$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 171.0, 155.1, 146.7, 133.0 (d, *J* = 10.8 Hz), 131.7 (d, *J* = 15.8 Hz), 127.6 (d, *J* = 11.3 Hz), 123.7 (d, *J* = 189.5 Hz), 118.5 (d, *J* = 15.6 Hz), 78.7 (br), 62.1

(d, J = 5.4 Hz), 62.0 (d, J = 5.6 Hz), 59.6 (br), 53.2, 52.1, 45.2 (br), 33.6 (br), 23.7 (br), 16.4 (d, J = 6.7 Hz) ppm;
HRMS (ESI-TOF) calc'd for $C_{20}H_{28}O_8N_2P$ $[M+H]^+$: 455.15778, found 455.15810.

Diethyl benzylphosphonate (49)

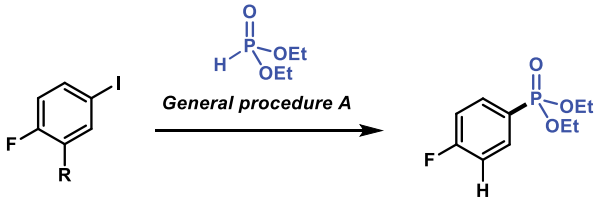


Prepared according to modified General procedure A using benzyl bromide (29.7 µL, 0.25 mmol), diethyl *H*-phosphonate (**3**, 38.6 µL, 0.30 mmol), $Pd(OAc)_2$ (0.6 mg, 2.50 µmol), XantPhos (1.4 mg, 2.50 µmol), LiCl (10.7 mg, 0.25 mmol), 2,6-lutidine (58.0 µL, 0.50 mmol), 2 wt % TPGS-750-M in H_2O (0.5 mL) and deoxygenated THF (50 µL). The crude product was purified by pTLC (hexane/EtOAc 1:1) to afford **49** as a yellowish oil (56.0 mg, 98%).

Spectral data match previously reported results,[53] and $^1H/^{31}P$ NMR data are provided here for convenience.
$\mathbf{R_f}$ = 0.4 (hexane/EtOAc 1:1). Stain: UV active, $KMnO_4$;
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30–7.22 (m, 5H), 4.06–3.93 (m, 4H), 3.14 (d, J = 21.6 Hz, 2H), 1.23 (t, J = 7.2 Hz, 6H) ppm;
^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 26.44 ppm.

Note: Control experiment with no Pd catalyst afforded no product, thus excluding S_N2 reaction pathway. Cross-coupling with benzyl chloride afforded **49** in 24% yield (^{1}H NMR with CH_2Br_2 as an internal standard).

Cross-coupling with boronic acid 50 and pinacol boronate 51

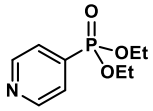


50 (R = $B(OH)_2$)
51 (R = Bpin)

21: 90% (from **50**)
67% (from **51**)

C(sp^2)–P cross-coupling reactions **50** and **51** afforded protodeborylation product **21** instead of the expected product containing intact boronic acid and pinacol boronate, respectively.
Representative procedure: Performed according to General procedure A using pinacol boronate **51** (87.0 mg, 0.25 mmol), diethyl *H*-phosphonate (**3**, 39.6 µL, 0.30 mmol), $Pd(OAc)_2$ (1.4 mg, 6.25 µmol), XantPhos (3.6 mg, 6.25 µmol), $Ni(phen)_3Cl_2$ (1.7 mg, 2.50 µmol), LiBr (21.7 mg, 0.25 mmol), nano Zn (8.1 mg, 0.125 mmol), 2,6-lutidine (34.8 µL, 0.30 mmol), 2 wt % TPGS-750-M in H_2O (1.0 mL) and EtOAc (0.2 mL). The reaction was performed at 45 °C. Analysis of the crude reaction mixture by ^{1}H NMR with CH_2Br_2 as an internal standard revealed the formation of **21** in 67% yield (90% yield from **50**).

Diethyl pyridin-4-ylphosphonate (52)

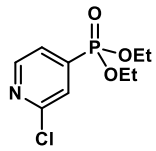


Prepared according to modified General procedure A using 4-iodopyridine (51.3 mg, 0.25 mmol), diethyl *H*-phosphonate (**3**, 66.0 µL, 0.50 mmol), $Pd(OAc)_2$ (1.4 mg, 6.25 µmol), XantPhos (3.6 mg, 6.25 µmol), $Ni(phen)_3Cl_2$ (8.2 mg, 12.50 µmol), LiBr (21.7 mg, 0.25 mmol), nano Zn (8.1 mg, 0.125 mmol), 2,6-lutidine (87.0 µL, 0.75 mmol), 2 wt %

TPGS-750-M in H_2O (1.0 mL) and EtOAc (0.2 mL). The reaction was performed at 55 °C. The crude product was purified by pTLC (4% MeOH on CH_2Cl_2) to afford **52** as a light-yellow oil (48.0 mg, 89%).

Spectral data match previously reported results,[54] and $^{1}H/^{31}P$ NMR data are provided here for convenience.
R_f = 0.22 (4% MeOH on CH_2Cl_2). Stain: UV active;
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.77–8.74 (m, 2H), 7.66–7.62 (m, 2H), 4.23–4.07 (m, 4H), 1.33 (t, *J* = 7.2 Hz, 6H) ppm;
$^{31}P\{^{1}H\}$ NMR (162 MHz, $CDCl_3$): δ 14.61 ppm.

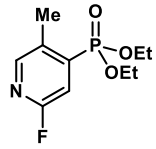
Diethyl (2-chloropyridin-4-yl)phosphonate (53)



Prepared according to General procedure A using 2-chloro-4-iodopyridine (59.9 mg, 0.25 mmol), diethyl *H*-phosphonate (**3**, 66.0 μL, 0.50 mmol), $Pd(OAc)_2$ (1.4 mg, 6.25 μmol), XantPhos (3.6 mg, 6.25 μmol), $Ni(phen)_3Cl_2$ (4.2 mg, 6.25 μmol), LiBr (21.7 mg, 0.25 mmol), nano Zn (8.1 mg, 0.125 mmol), 2,6-lutidine (87.0 μL, 0.75 mmol), 2 wt % TPGS-750-M in H_2O (1.0 mL) and EtOAc (0.2 mL). The reaction was performed at 55 °C. The crude product was purified by pTLC (EtOAc/CH_2Cl_2 1:1) to afford **53** as a light-yellow oil (47.0 mg, 76%).

Spectral data match previously reported results,[55] and $^{1}H/^{31}P/^{13}C$ NMR data are provided here for convenience.
R_f = 0.44 (EtOAc/CH_2Cl_2 1:1). Stain: UV active;
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.54–8.52 (m, 1H), 7.69 (dt, *J* =13.6, 0.8 Hz, 1H), 7.78 (ddd, *J* = 12.8, 4.8, 1.2 Hz, 1H), 4.25–4.09 (m, 4H), 1.35 (dt, *J* = 6.8, 0.4 Hz, 6H) ppm;
$^{31}P\{^{1}H\}$ NMR (162 MHz, $CDCl_3$): δ 12.55 ppm;
$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 152.2 (d, *J* = 18.3 Hz), 150.2 (d, *J* = 13.8 Hz), 141.2 (d, *J* = 184.1 Hz), 126.3 (d, *J* = 9.4 Hz), 123.8 (d, *J* = 8.0 Hz), 63.1 (d, *J* = 5.7 Hz), 16.4 (d, *J* = 6.2 Hz) ppm.

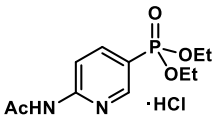
Diethyl (2-fluoro-5-methylpyridin-4-yl)phosphonate (54)



Prepared according to modified General procedure A using 2-fluoro-4-iodo-5-methylpyridine (59.3 mg, 0.25 mmol), diethyl *H*-phosphonate (**3**, 66.0 μL, 0.50 mmol), 2,6-lutidine (87.0 μL, 0.75 mmol), 2 wt % TPGS-750-M in H_2O (1.0 mL) and EtOAc (0.2 mL). The reaction was performed at 55 °C. The crude product was purified by pTLC (hexane/EtOAc 1:1) to afford **54** as a colorless oil (26.0 mg, 42%).

R_f = 0.47 (hexane/EtOAc 1:1). Stain: UV active;
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10 (d, *J* = 6.8 Hz, 1H), 7.37 (d, *J* = 15.2, 3.2 Hz, 1H), 4.24–4.08 (m, 4H), 2.49 (s, 3H), 1.34 (t, *J* = 7.2 Hz, 6H) ppm;
$^{31}P\{^{1}H\}$ NMR (162 MHz, $CDCl_3$): δ 13.1 (d, *J* = 12.3 Hz) ppm;
^{19}F NMR (376 MHz, $CDCl_3$): δ -71.4 (d, *J* = 12.4 Hz) ppm;
$^{13}C\{^{1}H\}$ NMR (151 MHz, $CDCl_3$): δ 162.2 (dd, *J* = 240.2, 20.4 Hz), 149.5 (dd, *J* = 14.5, 13.4 Hz), 141.8 (dd, *J* = 182.6, 6.0 Hz), 133.0 (dd, *J* = 8.5, 5.1 Hz), 113.2 (dd, *J* = 38.7, 10.0 Hz), 63.0 (d, *J* = 5.7 Hz), 17.2 (d, *J* = 2.0 Hz), 16.4 (d, *J* = 6.2 Hz) ppm;
HRMS (ESI-TOF) calc'd for $C_{10}H_{16}O_3NFP$ $[M+H]^+$: 248.08463, found 248.08488.

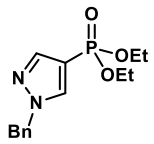
Diethyl (6-acetamidopyridin-3-yl)phosphonate hydrochloride (55·HCl)



Prepared according to modified General procedure A using *N*-(5-iodopyridin-2-yl)acetamide **SI-16** (65.5 mg, 0.25 mmol), diethyl *H*-phosphonate (**3**, 66.0 μL, 0.50 mmol), 2,6-lutidine (87.0 μL, 0.75 mmol), 2 wt % TPGS-750-M in H_2O (1.0 mL) and EtOAc (0.2 mL). The reaction was performed at 55 °C. The crude product was purified by pTLC (5% MeOH in EtOAc/CH_2Cl_2 1:1) to afford **55** as a yellow oil (57.0 mg, 84%), containing trace amounts of TPGS-750-M surfactant. Analytically pure product was obtained by dissolving the oil in 1,4-dioxane (2 mL) and adding ~3M HCl in dioxane (200 μL). After adding Et_2O (2 mL) a white precipitate formed and the mixture was centrifuged (6000 rpm, 6 minutes), filtered and the precipitate was washed with 1,4-dioxane/Et_2O (1:1, 2 × 2 mL). The precipitate was dried to afford **55·HCl** as a white amorphous solid.

R_f (free base) = 0.36 (5% MeOH in EtOAc/CH_2Cl_2 1:1). Stain: UV active;
^{1}H NMR (55·HCl, 600 MHz, $CDCl_3$): δ 10.49 (br s, 1H), 8.63–8.58 (m, *2*H, overlapped), 8.32 (d, *J* = 10.2 Hz, 1H), 4.24–4.12 (m, 4H), 2.37 (s, 3H), 1.35 (t, *J* = 6.6 Hz, 6H) ppm;
^{31}P{^{1}H} NMR (55·HCl, 162 MHz, $CDCl_3$): δ 11.55 ppm;
^{13}C{^{1}H} NMR (55·HCl, 151 MHz, $CDCl_3$): δ 170.7, 151.9, 146.4 (d, *J* = 7.8 Hz), 143.8 (d, *J* = 15.9 Hz), 121.6 (d, *J* = 199.0 Hz), 116.0 (d, *J* = 11.6 Hz), 63.4 (d, *J* = 5.6 Hz), 25.1, 16.5 (d, *J* = 6.0 Hz) ppm;
HRMS (ESI-TOF) calc'd for $C_{11}H_{18}O_4N_2P$ $[M–Cl+H]^+$: 273.09987, found 273.09974.

Diethyl (1-benzyl-1*H*-pyrazol-4-yl)phosphonate (56)

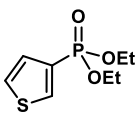


Prepared according to modified General procedure A using 1-benzyl-4-iodo-1*H*-pyrazole (71.0 mg, 0.25 mmol), diethyl *H*-phosphonate (**3**, 66.0 μL, 0.50 mmol), $Pd(OAc)_2$ (1.4 mg, 6.25 μmol), XantPhos (3.6 mg, 6.25 μmol), $Ni(phen)_3Cl_2$ (4.2 mg, 6.25 μmol), LiBr (21.7 mg, 0.25 mmol), nano Zn (8.1 mg, 0.125 mmol), 2,6-lutidine (87.0 μL, 0.75 mmol), 2 wt % TPGS-750-M in H_2O (0.5 mL) and EtOAc (0.1 mL). The crude product was purified by pTLC (5% MeOH in CH_2Cl_2) to afford **56** as a viscous light-yellow oil (55.0 mg, 75%).

Spectral data match previously reported results,[33] and ^{1}H/^{31}P NMR data are provided here for convenience.
R_f = 0.35 (5% MeOH in CH_2Cl_2). Stain: UV active, $KMnO_4$ stain;
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75 (s, 1H), 7.72 (d, *J* = 2.0 Hz, 1H), 7.39–7.33 (m, 3H), 7.29–7.24 (m, 2H), 5.31 (s, 2H), 4.15–4.00 (m, 4H), 1.31 (t, *J* = 7.2 Hz, 6H) ppm;
^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 13.77 ppm.

Note: Cross-coupling of unprotected 4-iodo-1*H*-pyrazole with **3** afforded no detectable phosphonate product.

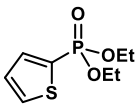
Diethyl thiophen-3-ylphosphonate (57)



Prepared according to General procedure A using 3-iodothiophene (25.4 μL, 0.25 mmol) and diethyl *H*-phosphonate (**3**, 66.0 μL, 0.50 mmol). The crude product was purified by pTLC (hexane/EtOAc 2:3) to afford **57** as a yellow oil (47.0 mg, 85%).

Spectral data match previously reported results,[41] and $^{1}H/^{31}P$ NMR data are provided here for convenience.
R_f = 0.46 (hexane/EtOAc 2:3). Stain: UV active;
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98 (dddd, *J* = 11.2, 8.4, 2.8, 1.2 Hz, 1H), 7.44–7.41 (m, 1H), 7.34–7.32 (m, 1H), 4.19–4.03 (m, 4H), 1.32 (t, *J* = 7.2 Hz, 6H) ppm;
$^{31}P\{^{1}H\}$ NMR (162 MHz, $CDCl_3$): δ 13.20 ppm.

Diethyl thiophen-2-ylphosphonate (58)

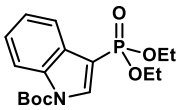


Prepared according to General procedure A using 2-iodothiophene (27.6 μL, 0.25 mmol) and diethyl *H*-phosphonate (**3**, 66.0 μL, 0.50 mmol). The crude product was purified by pTLC (hexane/EtOAc 2:3) to afford **58** as a yellow oil (50.0 mg, 91%).

Spectral data match previously reported results,[36] and $^{1}H/^{31}P$ NMR data are provided here for convenience.
R_f = 0.63 (hexane/EtOAc 2:3). Stain: UV active;
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70–7.64 (m, 2H), 7.19–7.16 (m, 1H), 4.22–4.05 (m, 4H), 1.33 (t, *J* = 7.2 Hz, 6H) ppm;
$^{31}P\{^{1}H\}$ NMR (162 MHz, $CDCl_3$): δ 11.90 ppm.

Note: **58** was also prepared according to General procedure B using 2-bromothiophene (24.2 μL, 0.25 mmol) and diethyl *H*-phosphonate (**3**, 66.0 μL, 0.50 mmol). The reaction was performed at 55 °C. The crude product was purified by pTLC (hexane/EtOAc 2:3) to afford **58** as a yellow oil (21.0 mg, 38%).

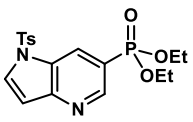
***tert*-Butyl 3-(diethoxyphosphoryl)-1*H*-indole-1-carboxylate (59)**



Prepared according to General procedure A using *tert*-butyl 3-iodo-1*H*-indole-1-carboxylate (**SI-17**, 85.8 mg, 0.25 mmol) and diethyl *H*-phosphonate (**3**, 66.0 μL, 0.50 mmol). The crude product was purified by pTLC (hexane/EtOAc 1:1) to afford **59** as a light-yellow oil (62.0 mg, 70%).

R_f = 0.39 (hexane/EtOAc 1:1). Stain: UV active;
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.21 (br d, *J* = 8.0 Hz, 1H), 8.16 (d, *J* = 5.2 Hz, 1H), 7.78 (d, *J* = 8.0 Hz, 1H), 7.38 (dt, *J* = 7.2, 1.2 Hz, 1H), 7.31 (dt, *J* = 8.0, 1.2 Hz, 1H), 4.24–4.02 (m, 4H), 1.67 (s, 9H), 1.32 (t, *J* = 7.2 Hz, 6H) ppm;
$^{31}P\{^{1}H\}$ NMR (162 MHz, $CDCl_3$): δ 14.67 ppm;
$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 148.9, 136.1 (d, *J* = 9.6 Hz), 135.0 (d, *J* = 23.9 Hz), 129.1 (d, *J* = 11.0 Hz), 125.3, 123.8, 121.2, 115.5, 107.1 (d, *J* = 211.6 Hz), 85.1, 62.1 (d, *J* = 4.9 Hz), 28.2, 16.5 (d, *J* = 6.8 Hz) ppm;
HRMS (ESI-TOF) calc'd for $C_{17}H_{25}O_5NP$ $[M+H]^+$: 354.14649, found 354.14634.

Diethyl (1-tosyl-1*H*-pyrrolo[3,2-*b*]pyridin-6-yl)phosphonate (60)

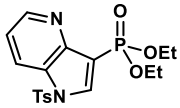


Prepared on 0.125-mmol scale according to General procedure A using 6-iodo-1-tosyl-1*H*-pyrrolo[3,2-*b*]pyridine (**SI-19**, 49.8 mg, 0.125 mmol) and diethyl *H*-phosphonate (**3**, 33.0 μL, 0.25 mmol). The reaction was performed at 55 °C. The crude product was purified by pTLC (100% EtOAc) to afford **60** as an off-white wax (29.0 mg, 57%).

R_f = 0.39 (hexane/EtOAc 1:1), 0.55 (100% EtOAc). Stain: UV active, $KMnO_4$;
^{1}H NMR (600 MHz, C_6D_6): δ 9.22 (d, *J* = 5.4 Hz, 1H), 9.11 (d, *J* = 15.6 Hz, 1H), 7.60–7.56 (m, 3H), 6.63 (d, *J* = 3.6 Hz, 1H), 6.48 (d, *J* = 7.8 Hz, 2H), 3.98–3.91 (m, 2H), 3.87–3.80 (m, 2H), 1.66 (s, 3H), 0.97 (t, *J* = 7.2 Hz, 6H) ppm;
^{31}P{^{1}H} NMR (162 MHz, C_6D_6): δ 17.02 ppm;
^{13}C{^{1}H} NMR (151 MHz, C_6D_6): δ 151.8, 149.0 (d, *J* = 12.4 Hz), 145.4, 135.3, 132.0, 130.2, 128.4, 127.1, 124.6 (d, *J* = 10.9 Hz), 121.0 (d, *J* = 188.9 Hz), 110.2, 62.3 (d, *J* = 5.1 Hz), 21.1, 16.3 (d, *J* = 6.0 Hz) ppm;
HRMS (ESI-TOF) calc'd for $C_{18}H_{22}O_5N_2PS$ $[M+H]^+$: 409.09816, found 409.09792.

Note: Cross-coupling of **SI-19** with **3** following General procedure B afforded no detectable amounts of **60**.

Diethyl (1-tosyl-1*H*-pyrrolo[3,2-b]pyridin-3-yl)phosphonate (61)

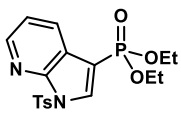


Prepared on 0.125-mmol scale according to General procedure B using 3-iodo-1-tosyl-1*H*-pyrrolo[3,2-*b*]pyridine (**SI-20**, 49.8 mg, 0.125 mmol), diethyl *H*-phosphonate (**3**, 66.0 µL, 0.50 mmol), Pd[P(*t*-Bu)$_3$]$_2$ (1.7 mg, 3.125 µmmol), Pd(OAc)$_2$ (0.7 mg, 3.125 µmmol), XantPhos (1.8 mg, 3.125 µmmol), LiBr (10.9 mg, 0.125 mmol), 2,6-lutidine (43.5 µL, 0.375 mmol), 2 wt % TPGS-750-M in H_2O (0.5 mL) and EtOAc (0.1 mL). The reaction was performed at 55 °C. The crude product was purified by pTLC (3% MeOH in EtOAc/CH_2Cl_2 1:1) to afford **61** as a white solid (47.0 mg, 92%).

R_f = 0.54 (3% MeOH in EtOAc/CH_2Cl_2 1:1). Stain: UV active;
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.65 (dd, *J* = 4.8, 1.6 Hz, 1H), 8.33 (d, *J* = 5.2 Hz, 1H), 8.26 (dt, *J* = 8.4, 2.0 Hz, 1H), 7.83 (d, *J* = 8.4 Hz, 2H), 7.30 (d, *J* = 8.4 Hz, 2H, overlapped), 7.28 (d, *J* = 8.4 Hz, 1H, overlapped), 4.31–4.14 (m, 4H), 2.39 (s, 3H), 1.32 (t, *J* = 7.2 Hz, 6H) ppm;
^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 11.50 ppm;
^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 147.3, 146.9 (d, *J* = 8.3 Hz), 146.4, 137.0 (d, *J* = 21.8 Hz), 134.4, 130.4, 128.9 (d, *J* = 11.9 Hz), 127.3, 121.0, 119.8, 110.5 (d, *J* = 208.7 Hz), 62.7 (d, *J* = 5.3 Hz), 21.7, 16.4 (d, *J* = 6.5 Hz) ppm;
HRMS (ESI-TOF) calc'd for $C_{18}H_{22}O_5N_2PS$ $[M+H]^+$: 409.09816, found 409.09848

Note: Cross-coupling of **SI-20** with **3** following General procedure A (performed at 55 °C) afforded **61** in 42% yield.

Diethyl (1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)phosphonate (62)

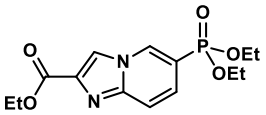


Prepared according to modified General procedure A using 3-iodo-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridine (**SI-21**, 99.6 mg, 0.25 mmol), diethyl *H*-phosphonate (**3**, 66.0 µL, 0.50 mmol), 2,6-lutidine (87.0 µL, 0.75 mmol), 2 wt % TPGS-750-M in H_2O (1.0 mL) and EtOAc (0.2 mL). The crude product was purified by pTLC (hexane/EtOAc 1:2) to afford **62** as an off-white solid (92.0 mg, 90%).

R_f = 0.30 (hexane/EtOAc 1:2). Stain: UV active;
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.48 (dd, *J* = 4.8, 1.6 Hz, 1H), 8.25 (d, *J* = 5.6 Hz, 1H), 8.13 (d, *J* = 8.4 Hz, 2H), 8.08 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.31 (d, *J* = 8.4 Hz, 2H), 7.26 (dd, *J* = 8.0, 4.8 Hz, 1H, overlapped with $CHCl_3$), 4.23–4.04 (m, 4H), 2.39 (s, 3H), 1.32 (t, *J* = 7.2 Hz, 6H) ppm;
^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 12.55 ppm;

$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 147.4 (d, *J* = 13.6 Hz), 146.0, 145.9, 134.6, 134.0 (d, *J* = 22.5 Hz), 130.2, 129.9, 128.6, 122.1 (d, *J* = 11.1 Hz), 119.8, 105.7 (d, *J* = 213.7 Hz), 62.4 (d, *J* = 5.3 Hz), 21.8, 16.4 (d, *J* = 6.5 Hz) ppm;
HRMS (ESI-TOF) calc'd for $C_{18}H_{22}O_5N_2PS$ $[M+H]^+$: 409.09816, found 409.09797.

Ethyl 6-(diethoxyphosphoryl)imidazo[1,2-*a*]pyridine-2-carboxylate (63)

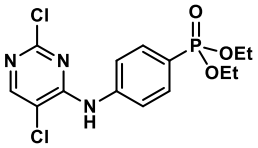


Prepared on 0.125-mmol scale according to modified General procedure A using ethyl 6-iodoimidazo[1,2-*a*]pyridine-2-carboxylate (**SI-22,** 39.5 mg, 0.125 mmol), diethyl *H*-phosphonate (**3**, 66.0 μL, 0.50 mmol), 2,6-lutidine (43.5 μL, 0.375 mmol), 2 wt % TPGS-750-M in H_2O (0.5 mL) and EtOAc (0.1 mL). The reaction was performed at 55 °C. The crude product was purified by pTLC (4% EtOH in EtOAc/CH_2Cl_2 1:1) to afford **63** as a white solid (26.0 mg, 64%).

R_f = 0.43 (4% EtOH in EtOAc/CH_2Cl_2 1:1). Stain: UV active;
^1H NMR (400 MHz, $CDCl_3$): δ 8.70 (dt, *J* = 11.6, 1.2 Hz, 1H), 8.23 (s, 1H),7.73 (dd, *J* = 9.6, 3.6 Hz, 1H), 7.40 (td, *J* = 10.0, 1.6 Hz, 1H), 4.47 (q, *J* = 7.2 Hz, 2H), 4.26–4.08 (m, 4H), 1.44 (t, *J* = 7.2 Hz, 3H),1.36 (t, *J* = 7.2 Hz, 6H) ppm;
$^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$): δ 15.25 ppm;
$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 162.9, 145.2 (d, *J* = 1.5 Hz), 138.3, 132.5 (d, *J* = 11.1 Hz), 126.1 (d, *J* = 7.1 Hz), 119.3 (d, *J* = 13.6 Hz), 117.8, 115.4 (d, *J* = 196.2 Hz), 62.8 (d, *J* = 5.4 Hz), 61.5, 16.4 (d, *J* = 6.4 Hz), 14.5 ppm;
HRMS (ESI-TOF) calc'd for $C_{14}H_{20}O_5N_2P$ $[M+H]^+$: 327.11043, found 327.11038.

Note: Carboxylate in **63** is prone to transesterification with alcohols (*e.g.*, MeOH) during chromatography separation using silica gel. Thus, we used mobile phase containing EtOH.

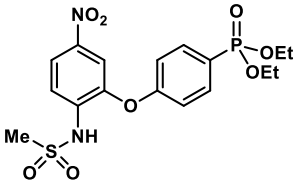
Diethyl (4-((2,5-dichloropyrimidin-4-yl)amino)phenyl)phosphonate (64)



Prepared on 0.125-mmol scale according to modified General procedure A using 2,5-dichloro-*N*-(4-iodophenyl)pyrimidin-4-amine (**SI-23**, 45.8 mg, 0.125 mmol), diethyl *H*-phosphonate (**3**, 33.0 μL, 0.25 mmol), 2 wt % TPGS-750-M in H_2O (0.5 mL) and EtOAc (0.1 mL). The crude product was purified by pTLC (EtOAc/CH_2Cl_2 5:4) to afford **64** as a white solid (31.0 mg, 66%).

R_f = 0.22 (EtOAc/CH_2Cl_2 5:4). Stain: UV active;
^1H NMR (400 MHz, $CDCl_3$): δ 8.24 (s, 1H), 7.84–7.76 (m, 4H), 7.58 (br s, 1H), 4.18–4.02 (m, 4H), 1.31 (t, *J* = 7.2 Hz, 6H) ppm;
$^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$): δ 18.12 ppm;
$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 158.2, 156.3, 155.3, 140.8 (d, *J* = 3.5 Hz), 133.1 (d, *J* = 10.6 Hz), 124.2 (d, *J* = 191.6 Hz), 120.4 (d, *J* = 15.2 Hz), 114.3, 62.2 (d, *J* = 5.4 Hz), 16.4 (d, *J* = 6.5 Hz) ppm;
HRMS (ESI-TOF) calc'd for $C_{14}H_{17}O_3N_3Cl_2P$ $[M+H]^+$: 376.03791, found 376.03775.

Diethyl (4-(2-(methylsulfonamido)-5-nitrophenoxy)phenyl)phosphonate (65)

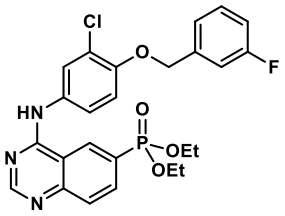


Prepared on 0.125 mmol-scale according to General procedure B using iodonimesulide **SI-24** (54.3 mg, 0.125 mmol) and diethyl *H*-phosphonate (**3**, 33.0 µL, 0.25 mmol), 2 wt % TPGS-750-M in H_2O (1.0 mL) and EtOAc (0.2 mL). The reaction was performed at 55 °C. The crude product was purified by pTLC (EtOAc/CH_2Cl_2 3:2), followed by second pTLC (2% MeOH in EtOAc/CH_2Cl_2 1:1) to afford **65** as a yellow solid (52.0 mg, 94%).

R_f = 0.28–0.44 (EtOAc/CH_2Cl_2 1:1). Stain: UV active, visible yellow spot;
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.74 (dd, *J* = 12.8, 8.8 Hz, 2H), 7.69–7.67 (m, 2H, overlapped), 7.05 (dd, *J* = 8.8, 3.2 Hz, 2H), 4.12–3.97 (m, 4H), 3.01 (s, 3H), 1.26 (t, *J* = 6.8 Hz, 6H) ppm;
^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 17.23 ppm;
^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$/CD_3OD ~10:1): δ 159.1 (d, *J* = 3.7 Hz), 145.2, 142.6, 137.9, 134.2 (d, *J* = 11.4 Hz), 123.9 (d, *J* = 193.0 Hz), 120.8, 118.7, 118.5 (d, *J* = 16.2 Hz), 114.5, 62.5 (d, *J* = 5.7 Hz), 40.2, 16.2 (d, *J* = 6.6 Hz) ppm;
HRMS (ESI-TOF) calc'd for $C_{17}H_{22}O_8N_2PS$ $[M+H]^+$: 445.08290, found 445.08267.

Note: ^{1}H NMR signals of **65** were significantly broadened when the concentration of **65** in $CDCl_3$ exceeded ca. 10 mg/1 mL. Cross-coupling of **SI-24** with **3** following General procedure A afforded **65** in <5% yield (^{1}H NMR with CH_2Br_2 as an internal standard).

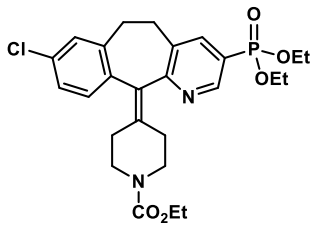
Compound 66



Prepared on 0.125-mmol scale according to modified General procedure A using 4-[3-chloro-4-(3-fluorobenzyloxy)phenylamino]-6-iodoquinazoline (63.1 mg, 0.125 mmol), diethyl *H*-phosphonate (**3**, 33.0 µL, 0.25 mmol), $Pd(OAc)_2$ (0.7 mg, 3.13 µmol), XantPhos (1.8 mg, 3.13 µmol), $Ni(phen)_3Cl_2$ (2.1 mg, 3.13 µmol), LiBr (10.9 mg, 0.125 mmol), nano Zn (4.1 mg, 62.50 µmol), 2,6-lutidine (43.5 µL, 0.375 mmol), 2 wt % TPGS-750-M in H_2O (1.0 mL) and EtOAc (0.2 mL). The reaction was performed at 55 °C. The crude product was purified by pTLC (5% MeOH in CH_2Cl_2, then EtOAc/CH_2Cl_2 1:1) to afford **66** as a beige solid (56.0 mg, 87%).

R_f = 0.40–0.50 (5% MeOH in CH_2Cl_2), 0.25 (EtOAc/CH_2Cl_2 1:1). Stain: UV active;
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.00 and 8.97 (2 × s, 2H), 8.78 (s, 1H), 8.00–7.90 (m, 2H), 7.88 (d, *J* = 2.4 Hz, 1H), 7.60 (dd, *J* = 8.8, 2.8 Hz, 1H), 7.36 (td, *J* = 8.0, 6.0 Hz, 1H), 7.24 (t, *J* = 11.6 Hz, 2H, overlapped with $CHCl_3$), 7.05–6.99 (m, 2H, overlapped), 5.18 (s, 2H), 4.12–3.94 (m, 4H), 1.23 (t, *J* = 7.2 Hz, 3H) ppm;
^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 17.30 ppm;
^{19}F NMR (376 MHz, $CDCl_3$): δ -112.57 (m) ppm;
^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 164.1 (d, *J* = 244.9 Hz), 158.9, 157.3, 152.4 (d, *J* = 2.9 Hz), 151.4, 139.2 (d, *J* = 7.3 Hz), 133.6 (d, *J* = 9.2 Hz), 132.5, 130.3 (d, *J* = 8.2 Hz), 129.4 (d, *J* = 13.0 Hz), 129.0 (d, *J* = 13.6 Hz), 126.0, 125.2 (d, *J* = 189.4 Hz), 123.5, 123.3, 122.5 (d, *J* = 3.0 Hz), 115.2 (d, *J* = 17.2 Hz), 115.0 (d, *J* = 21.0 Hz), 114.3, 114.0 (d, *J* = 22.2 Hz), 70.5 (d, *J* = 1.8 Hz), 62.7 (d, *J* = 5.3 Hz), 16.3 (d, *J* = 6.7 Hz) ppm;
HRMS (ESI-TOF) calc'd for $C_{25}H_{25}O_4N_3ClFP$ $[M+H]^+$: 516.12498, found 516.12460.

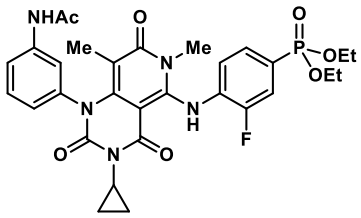
Compound 67



Prepared on 0.125-mmol scale according to modified General procedure A using iodo-loratadine **SI-25** (63.5 mg, 0.125 mmol), diethyl *H*-phosphonate (**3**, 33.0 μL, 0.25 mmol), $Pd(OAc)_2$ (0.7 mg, 3.13 μmol), XantPhos (1.8 mg, 3.13 μmol), $Ni(phen)_3Cl_2$ (2.1 mg, 3.13 μmol), LiBr (10.9 mg, 0.125 mmol), nano Zn (4.1 mg, 0.063 mmol), 2,6-lutidine (43.5 μL, 0.375 mmol), 2 wt % TPGS-750-M in H_2O (1.0 mL) and EtOAc (0.2 mL). The reaction was performed at 55 °C. The crude product was purified by pTLC (1% MeOH + 0.5% Et_3N in EtOAc) to afford **67** as a colorless film (57.0 mg, 88%).

R_f = 0.38 (1% MeOH in EtOAc). Stain: UV active, $KMnO_4$;
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.69 (d, *J* = 6.0 Hz, 1H), 7.84 (d, *J* = 13.6 Hz, 1H), 7.15–7.07 (m, 3H), 4.21–4.01 (m, 4H), 3.77 (br s, 2H), 3.40–3.32 (m, 2H), 3.18–3.11 (m, 2H), 2.92–2.75 (m, 2H), 2.49–2.44 (m, 1H), 2.37–2.23 (m, 2H), 1.31 (m, 6H), 1.22 (t, *J* = 7.2 Hz, 3H) ppm;
^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 16.19 ppm;
^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 160.6, 155.5, 149.1 (d, *J* = 12.0 Hz), 141.1 (d, *J* = 8.8 Hz), 139.4, 139.0, 137.1, 133.6 (d, *J* = 1.3 Hz), 133.5, 133.4, 130.7, 129.1, 126.5, 123.2 (d, *J* = 189.0 Hz), 62.6 (d, *J* = 5.7 Hz), 61.4, 44.8, 44.8, 31.5, 31.5, 30.9, 30.7, 16.4 (d, *J* = 6.1 Hz), 14.8 ppm;
HRMS (ESI-TOF) calc'd for $C_{26}H_{33}O_5N_2ClP$ $[M+H]^+$: 519.18101, found 519.18091.

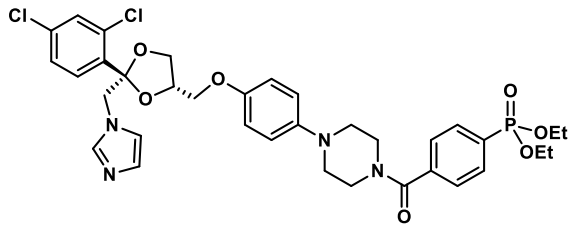
Compound 68



Prepared on 0.125-mmol scale according to modified General procedure A using trametinib (76.9 mg, 0.125 mmol), diethyl *H*-phosphonate (**3**, 33.0 μL, 0.25 mmol), 2,6-lutidine (43.5 μL, 0.375 mmol), 2 wt % TPGS-750-M in H_2O (1.0 mL) and EtOAc (0.2 mL). The crude reaction mixture was centrifuged (6 min at 6000 rpm), the precipitate was filtered, washed with dist. H_2O (3 × 1 mL), and purified by pTLC (5% MeOH in EtOAc/CH_2Cl_2 1:1) to afford **68** as a white solid (68.7 mg, 88%).

R_f = 0.34 (5% MeOH in EtOAc/CH_2Cl_2 1:1). Stain: UV active;
^{1}H NMR (400 MHz, $CDCl_3$): δ 11.28 (s, 1H), 8.36 (br s, 1H), 7.83 (s, 1H), 7.60–7.51 (m, 2H), 7.23–7.19 (m, 2H), 6.96–6.91 (m, 2H), 4.18–4.06 (m, 4H), 3.21 (s, 3H), 2.72 (m, 1H), 2.08 (s, 3H), 1.40 (s, 3H), 1.32 (t, *J* = 7.2 Hz, 6H), 1.11–1.06 (m, 2H), 0.78–0.75 (m, 2H) ppm;
^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 15.91 (d, *J* = 6.5 Hz) ppm;
^{19}F NMR (376 MHz, $CDCl_3$): δ -124.21 (m) ppm;
^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 168.9, 164.8, 163.9, 154.5 (dd, *J* = 250.0, 22.0 Hz), 151.8, 151.2, 144.8, 140.1, 139.4, 132.2 (dd, *J* = 11.6, 3.3 Hz), 129.1, 128.5 (dd, *J* = 9.6, 3.6 Hz), 126.3 (dd, *J* = 192.0 Hz, 5.5 Hz), 124.0, 122.5 (d, *J* = 17.7 Hz), 120.5, 119.8 (dd, *J* = 20.3, 11.1 Hz), 119.0, 104.5, 90.7, 62.6 (d, *J* = 6.1 Hz), 34.8, 25.4, 24.5, 16.4 (d, *J* = 6.1 Hz), 13.5, 8.5 ppm;
HRMS (ESI-TOF) calc'd for $C_{30}H_{34}O_7N_5FP$ $[M+H]^+$: 648.19938, found 648.19891; calc'd for $C_{30}H_{33}O_7N_5FNaP$ $[M+Na]^+$: 648.19938, found 648.19891.

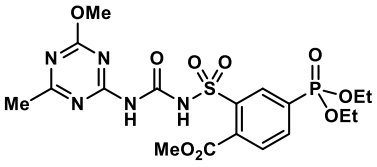
Compound 69



Prepared according to General procedure A using **SI-26** (178.8 mg, 0.25 mmol), diethyl *H*-phosphonate (**3**, 66.0 μL, 0.50 mmol), 2 wt % TPGS-750-M in H_2O (1.0 mL) and EtOAc (0.2 mL). The crude product was suspended in 1,4-dioxane (3 mL), centrifuged (6 min, 6000 rpm) and decanted. This procedure was repeated twice to remove traces of surfactant, which are difficult to remove by chromatography. Then the solids were suspended in Et_2O (2 mL), centrifuged (6 min, 6000 rpm), decanted, and redissolved in $CHCl_3$ (3 mL). Sat. aq. $NaHCO_3$ (4 mL) was added and the mixture was vigorously stirred for 10 minutes. The organic phase was separated and the aqueous phase was extracted with $CHCl_3$ (3 × 2 mL). Combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash column chromatography (1% MeOH in CH_2Cl_2 → 10% MeOH in CH_2Cl_2) to afford **69** as a viscous colorless oil (173.0 mg, 95%).

$\mathbf{R}_f$ = 0.50 (10% MeOH in CH_2Cl_2). Stain: UV active, $KMnO_4$;
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89 (dd, *J* = 13.2, 8.4 Hz, 2H), 7.58 (d, *J* = 8.4 Hz, 1H), 7.53–7.50 (m, 3H), 7.47 (d, *J* = 2.0 Hz, 1H), 7.26 (dd, *J* = 8.4, 2.4 Hz, 1H, overlapped with $CHCl_3$), 6.98 (d, *J* = 11.2 Hz, 2H), 6.88 (d, *J* = 9.2 Hz, 2H), 6.77 (d, *J* = 9.2 Hz, 2H), 4.51 (d, *J* = 14.8 Hz, 1H), 4.41 (d, *J* = 14.8 Hz, 1H), 4.37–4.31 (m, 1H), 4.20–4.05 (m, 4H), 3.94 (br s, 2H), 3.87 (dd, *J* = 8.4, 6.4 Hz, 1H), 3.72 (td, *J* = 8.4, 4.8 Hz, 2H), 3.53 (br s, 2H), 3.28 (dd, *J* = 9.6, 6.8 Hz, 1H), 3.15 (br s, 2H), 2.99 (br s, 2H), 1.34 (t, *J* = 6.8 Hz, 6H) ppm;
^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 17.29 ppm;
^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 169.1, 152.9, 145.5, 139.4 (d, *J* = 3.2 Hz), 138.7, 135.7, 134.5, 132.9, 132.0 (d, *J* = 10.0 Hz), 131.2, 130.1 (d, *J* = 187.1 Hz), 129.5, 128.4, 127.1 (d, *J* = 14.1 Hz), 126.9, 121.1, 118.8, 115.2, 107.9, 77.4, 74.7, 67.5, 67.4, 62.2 (d, *J* = 5.5 Hz), 51.1, 50.7 (br), 47.6 (br), 42.1 (br), 16.3 (d, *J* = 6.4 Hz) ppm;
HRMS (ESI-TOF) calc'd for $C_{35}H_{40}Cl_2N_4O_7P$ $[M+H]^+$: 729.20062, found 729.19939.

Compound 70

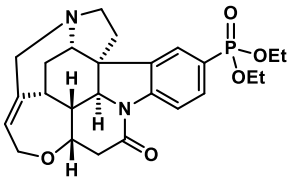


Prepared according to modified General procedure B using iodosulfuron-methyl sodium salt (132.4 mg, 0.25 mmol), diethyl *H*-phosphonate (**3**, 66.0 μL, 0.50 mmol), 2 wt % TPGS-750-M in H_2O (1.0 mL) and EtOAc (0.2 mL). The crude product was triturated with Et_2O (3 × 1.5 mL, the mixture was briefly sonicated each time) and the solid residue was then purified by pTLC (8% MeOH in EtOAc/CH_2Cl_2 1:1) to afford **70** as a white powder (100.0 mg, 79%).

$\mathbf{R}_f$ = 0.29 (8% MeOH in EtOAc/CH_2Cl_2 1:1). Stain: UV active;
^{1}H NMR (600 MHz, CD_3OD): δ 8.50 (dd, *J* = 13.8, 1.2 Hz, 1H), 7.93 (ddd, *J* = 13.2, 7.8, 1.8 Hz, 1H), 7.64 (dd, *J* = 7.8 ,4.2, 1H), 4.20–4.10 (m, 4H), 3.95 (s, 3H), 3.94 (s, 3H), 2.37 (s, 3H), 1.32 (t, *J* = 6.6 Hz, 3H) ppm;
^{31}P{^{1}H} NMR (162 MHz, CD_3OD): δ 16.07 ppm;
^{13}C{^{1}H} NMR (151 MHz, CD_3OD): δ 180.1, 172.3, 170.0, 167.0, 158.4, 143.7 (d, *J* = 15.1 Hz), 137.1 (d, *J* = 2.9 Hz), 134.9 (d, *J* = 10.1 Hz), 133.3 (overlapped signals), 131.2 (d, *J* = 190.4 Hz), 129.6 (d, *J* = 14.8), 64.3 (d, *J* = 5.7 Hz), 55.5, 53.7, 25.1, 16.6 (d, *J* = 6.2 Hz) ppm;

HRMS (ESI-TOF) calc'd for $C_{18}H_{25}O_9N_5PS$ $[M+H]^+$: 518.11051, found 518.11043.

Compound 71

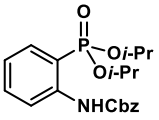


Prepared on 0.125-mmol scale according to General procedure A using iodostrychnine **SI-27** (57.5 mg, 0.125 mmol) and diethyl *H*-phosphonate (**3**, 33.0 µL, 0.25 mmol). The crude product was purified by pTLC (10% MeOH in CH_2Cl_2) to afford **71** as a beige solid (38.0 mg, 65%).

$\mathbf{R}_f$ = 0.48 (10% MeOH in CH_2Cl_2). Stain: UV active, $KMnO_4$;
^{1}H NMR (600 MHz, $CDCl_3$): δ 8.16 (dd, *J* = 7.8, 3.0 Hz, 1H), 7.68 (ddd, *J* = 12.6, 7.8, 1.2 Hz, 1H), 7.63 (d, *J* = 12.6, 1H), 5.93 (br t, 1H), 4.28 (dt, *J* = 8.4, 3.6 Hz, 1H), 4.17–4.03 (m, 7H, overlapped signals), 3.92 (d, *J* = 10.2 Hz, 1H), 3.73 (d, *J* = 15.0 Hz, 1H), 3.28–3.25 (m, 1H), 3.17–3.12 (m, 2H, overlapped signals), 2.88 (q, *J* = 10.2 Hz, 1H), 2.75 (d, *J* = 14.4 Hz, 1H), 2.68 (dd, *J* = 17.4, 3.0 Hz, 1H), 2.37 (dt, *J* = 14.4, 4.2 Hz, 1H), 1.92–1.90 (m, 2H), 1.46 (d, *J* = 14.4 Hz, 1H), 1.32 (t, 7.2 Hz, 6H), 1.27 (dt, *J* = 10.8, 3.0 Hz, 1H) ppm;
^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 19.10 ppm;
^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 169.8, 145.7 (d, *J* = 3.3 Hz), 139.9, 133.1 (d, *J* = 11.0 Hz), 128.2, 126.3 (d, *J* = 11.6 Hz), 123.8 (d, *J* = 192.8 Hz), 116.1 (d, *J* = 15.9 Hz), 77.4, 64.8, 62.3 (d, *J* = 5.3 Hz), 60.6, 60.3, 52.7, 52.0, 50.4, 48.2, 42.9, 42.6, 31.6, 26.9, 16.5 (d, *J* = 6.3 Hz) ppm;*
HRMS (ESI-TOF) calc'd for $C_{25}H_{32}O_5N_2P$ $[M+H]^+$: 471.20434, found 471.20398.

Note: *One carbon signal is missing in the ^{13}C NMR spectrum.

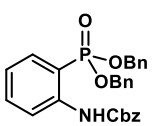
Benzyl (2-(diisopropoxyphosphoryl)phenyl)carbamate (75)



Prepared according to General procedure A using benzyl (2-iodophenyl)carbamate (**6**, 88.3 mg, 0.25 mmol) and di-*iso*-propyl *H*-phosphonate (**72**, 49.8 µL, 0.30 mmol). The crude product was purified by pTLC (hexane/EtOAc 3:1) to afford **75** as a viscous light-yellow oil (79.0 mg, 81%).

$\mathbf{R}_f$ = 0.46 (hexane/EtOAc 3:1). Stain: UV active, $KMnO_4$;
^{1}H NMR (400 MHz, $CDCl_3$): δ 10.10 (s, 1H), 8.35 (t, *J* = 11.4 Hz, 1H), 7.57 (ddd, *J* = 14.4, 7.6, 1.6 Hz, 1H), 7.52–7.47 (m, 1H), 7.43–7.40 (m, 2H), 7.38–7.28 (m, 3H), 7.06 (ddd, *J* = 7.6, 2.8, 0.8 Hz, 1H), 5.21 (s, 2H), 4.70–4.59 (m, 2H), 1.36 (d, *J* = 6.4 Hz, 6H), 1.20 (d, *J* = 6.0 Hz, 6H) ppm;
^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 19.46 ppm;
^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 153.6, 142.5 (d, *J* = 7.2 Hz), 136.4, 133.8 (d, *J* = 2.4 Hz), 132.8 (d, *J* = 5.8 Hz), 128.5, 128.2, 128.1, 122.1 (d, *J* = 13.5 Hz), 119.2 (d, *J* = 11.3 Hz), 114.9 (d, *J* = 179.7 Hz), 71.5 (d, *J* = 5.3 Hz), 66.7, 24.1 (d, *J* = 3.9 Hz), 23.7 (d, *J* = 5.0 Hz) ppm;
HRMS (ESI-TOF) calc'd for $C_{20}H_{27}O_5NP$ $[M+H]^+$: 392.16214, found 392.16209.

Benzyl (2-(bis(benzyloxy)phosphoryl)phenyl)carbamate (76)

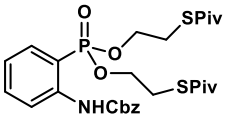


Prepared according to General procedure B using benzyl (2-iodophenyl)carbamate (**6**, 88.3 mg, 0.25 mmol) and dibenzyl *H*-phosphonate (**73**, 110.5 µL, 0.50 mmol, technical grade). The crude product was purified by pTLC (hexane/EtOAc 3:1) to afford **76** as a viscous light-yellow oil (59.0 mg, 48%).

$\mathbf{R}_f$ = 0.57 (hexane/EtOAc 2:1). Stain: UV active, $KMnO_4$;

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.95 (s, 1H), 8.37 (t, *J* = 7.6 Hz, 1H), 7.58 (ddd, *J* = 14.8, 8.0, 1.6 Hz, 1H), 7.54–7.50 (m, 1H), 7.47–7.43 (m, 2H), 7.41–7.28 (m, 13H), 7.04 (ddd, *J* = 7.6, 3.2, 0.8 Hz, 1H), 5.23 (s, 2H), 5.15–4.99 (m, 4H) ppm;
^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 20.25 ppm;
^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 153.5, 142.8 (d, *J* = 7.3 Hz), 136.3, 135.6 (d, *J* = 6.9 Hz), 134.3 (d, *J* = 2.3 Hz), 132.8 (d, *J* = 5.9 Hz), 128.6, 128.6, 128.5, 128.3, 128.2, 128.1, 127.6, 127.0, 122.3 (d, *J* = 13.7 Hz), 119.4 (d, *J* = 11.4 Hz), 112.9 (d, *J* = 180.5 Hz), 68.1 (d, *J* = 5.1 Hz), 66.9 ppm;
HRMS (ESI-TOF) calc'd for $C_{28}H_{27}O_5NP$ $[M+H]^+$: 488.16214, found 488.16201.

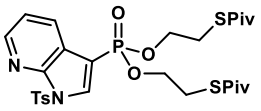
Bis-SATE carbamate 77



Prepared according to General procedure B using benzyl (2-iodophenyl)carbamate (**6**, 88.3 mg, 0.25 mmol) and bis-SATE *H*-phosphonate **74** (111.0 µL, 0.30 mmol). The crude product was purified by pTLC (hexane/EtOAc/CH_2Cl_2 4:1:1) to afford **77** as a colorless oil (131.0 mg, 88%).

R_f = 0.61 (hexane/EtOAc/CH_2Cl_2 4:1:1). Stain: UV active, $KMnO_4$;
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.89 (s, 1H), 8.37 (t, *J* = 8.0 Hz, 1H), 7.59–7.50 (m, 2H, overlapped signals), 7.43–7.41 (m, 2H), 7.38–7.31 (m, 3H), 7.04 (ddd, *J* = 8.0, 3.2, 0.8 Hz, 1H), 5.20 (s, 2H), 4.19–4.12 (m, 2H), 4.08–4.00 (m, 2H), 3.12 (t, *J* = 6.8 Hz, 4H), 1.20 (s, 18H) ppm;
^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 19.74 ppm;
^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 205.4, 153.4, 142.9 (d, *J* = 7.4 Hz), 136.2, 134.4 (d, *J* = 2.2 Hz), 132.7 (d, *J* = 5.9 Hz), 128.5, 128.2, 128.1, 122.2 (d, *J* = 13.7 Hz), 119.3 (d, *J* = 11.5 Hz), 112.2 (d, *J* = 181.0 Hz), 66.8, 64.8 (d, *J* = 5.2 Hz), 46.4, 28.7 (d, *J* = 7.1 Hz), 27.3 ppm;
HRMS (ESI-TOF) calc'd for $C_{28}H_{39}O_7NPS_2$ $[M+H]^+$: 596.19001, found 596.18993.

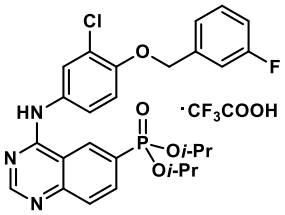
Bis-SATE phosphonate 78



Prepared according to modified General procedure B using 3-iodo-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridine **SI-21** (99.6 mg, 0.25 mmol), bis-SATE *H*-phosphonate **74** (138.8 µL, 0.38 mmol), 2 wt % TPGS-750-M in H_2O (1.0 mL) and EtOAc (0.2 mL). The crude product was purified by pTLC (hexane/EtOAc/CH_2Cl_2 2:1:1) and then by second pTLC (3% MeOH in CH_2Cl_2) to afford **78** as a colorless waxy solid (156.0 mg, 97%).

R_f = 0.43 (hexane/EtOAc/CH_2Cl_2 2:1:1). Stain: UV active, $KMnO_4$;
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.48 (dd, *J* = 4.8, 1.6 Hz, 1H), 8.29 (d, *J* = 5.6 Hz, 1H), 8.14 (d, *J* = 8.4 Hz, 2H), 8.10 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.31 (d, *J* = 8.0 Hz, 2H), 7.26 (dd, *J* = 8.0, 4.8 Hz, 1H, overlapped with $CHCl_3$), 4.24–4.05 (m, 4H), 3.13 (t, *J* = 6.4 Hz, 4H), 2.39 (s, 3H), 1.17 (s, 18H) ppm;
^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 13.16 ppm;
^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 205.4, 147.2 (d, *J* = 13.9 Hz), 146.0, 145.9, 134.4, 134.2 (d, *J* = 23.2 Hz), 130.3, 129.8, 128.5, 122.1 (d, *J* = 11.3 Hz), 119.7, 104.6 (d, *J* = 216.3 Hz), 64.6 (d, *J* = 5.2 Hz), 46.4, 28.8 (d, *J* = 7.2 Hz), 27.2, 21.7 ppm;
HRMS (ESI-TOF) calc'd for $C_{28}H_{38}O_7N_2PS_3$ $[M+H]^+$: 641.15733, found 641.15723.

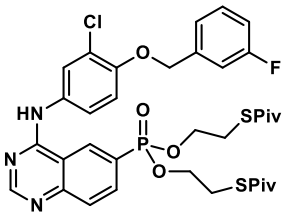
Compound 79·TFA



Prepared on 0.125-mmol scale according to modified General procedure A using 4-[3-chloro-4-(3-fluorobenzyloxy)phenylamino]-6-iodoquinazoline (63.1 mg, 0.125 mmol), di-*iso*-propyl *H*-phosphonate (**72**, 41.5 μL, 0.25 mmol), 2 wt % TPGS-750-M in H_2O (1.0 mL) and EtOAc (0.2 mL). The reaction was performed at 55 °C. Analysis of the crude reaction mixture revealed 80% conversion of starting aryl iodide and 75% yield of **79** (determined by ^{1}H NMR with CH_2Br_2 as an internal standard). The crude product was purified by pTLC (5% MeOH in CH_2Cl_2) and then by preparative HPLC (gradient H_2O + 0.1% TFA → CH_3OH over 25 min) to afford **79·TFA** as a bright yellow solid (62.0 mg, 75%), partially soluble in $CHCl_3$ and well-soluble in CH_3OH.

R_f (free base) = 0.29 (5% MeOH in CH_2Cl_2). Stain: UV active, visible yellow spot;
^{1}H NMR (600 MHz, $CDCl_3$, TFA salt): δ 11.00 (br s, 1H), 9.26 (d, *J* = 15.6 Hz, 1H), 8.77 (s, 1H), 8.20 (d, *J* = 7.2 Hz, 1H), 8.05 (d, *J* = 10.2 Hz, 1H), 7.80 (s, 1H), 7.58 (d, *J* = 9.0 Hz, 1H), 7.39–7.36 (m, 1H), 7.26–7.20 (m, 2H, overlapped with $CHCl_3$), 7.05–7.02 (m, 2H, overlapped signals), 5.20 (s, 2H), 4.58–4.53 (m, 2H), 1.23 (d, *J* = 6.0 Hz, 6H), 1.13 (d, *J* = 6.0 Hz, 6H) ppm;
^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$, TFA salt): δ 12.56 ppm;
^{19}F NMR (376 MHz, $CDCl_3$, TFA salt): δ -75.61, -112.57 (m) ppm;
^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$/CD_3OD ~10:1, TFA salt): δ 163.0 (d, *J* = 244.7 Hz), 161.8, 159.6, 153.3, 152.7, 143.9, 138.8 (d, *J* = 7.3 Hz), 136.6 (d, *J* = 8.8 Hz), 130.3, 130.2, 129.9 (d, *J* = 192.1 Hz), 128.4 (d, *J* = 13.2 Hz), 126.3, 123.6, 123.5, 123.2 (d, *J* = 13.5 Hz), 122.5 (d, *J* = 3.0 Hz), 115.0 (d, *J* = 21.0 Hz), 114.0 (d, *J* = 22.2 Hz), 113.9, 113.4 (d, *J* = 17.1 Hz), 72.5 (d, *J* = 5.9 Hz), 70.3 (d, *J* = 1.8 Hz), 23.9 (d, *J* = 4.1 Hz), 23.7 (d, *J* = 4.7 Hz) ppm;
HRMS (ESI-TOF) calc'd for $C_{27}H_{29}O_4N_3ClFP$ $[M–TFA+H]^+$: 544.15628, found 544.15588.

Bis-SATE phosphonate 80



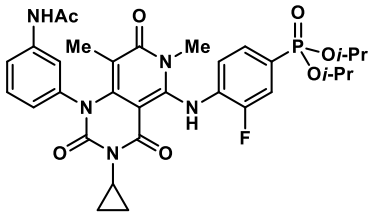
Prepared according to modified General procedure B using 4-[3-chloro-4-(3-fluorobenzyloxy)phenylamino]-6-iodoquinazoline (63.1 mg, 0.125 mmol), bis-SATE *H*-phosphonate **74** (69.4 μL, 0.188 mmol), 2 wt % TPGS-750-M in H_2O (1.0 mL) and EtOAc (0.2 mL). The reaction was performed at 55 °C. Analysis of the crude reaction mixture revealed full conversion of starting aryl iodide and quantitative yield of **80** (determined by ^{1}H NMR with CH_2Br_2 as an internal standard). The crude product was purified by pTLC (EtOAc/CH_2Cl_2 1:1) to afford **80** as a light-yellow solid (93.0 mg, 99%).

R_f = 0.50 (EtOAc/CH_2Cl_2 1:1). Stain: UV active;
^{1}H NMR (600 MHz, $CDCl_3$): δ 9.45 (s, 1H), 9.02 (d, *J* = 15.6 Hz, 1H), 8.74 (s, 1H), 7.99 (td, *J* = 9.6, 1.2 Hz, 1H), 7.90–7.89 (m, 1H), 7.86 (d, *J* = 2.4 Hz, 1H), 7.62 (dd, *J* = 9.0, 2.4 Hz, 1H), 7.35–7.32 (m, 1H), 7.23–7.19 (m, 2H), 7.01–6.98 (m, 2H), 5.15 (s, 2H), 4.05–3.95 (m, 4H), 3.06–2.97 (m, 4H), 1.12 (s, 18H) ppm;
^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 17.28 ppm;
^{19}F NMR (376 MHz, $CDCl_3$): δ -112.60 (m) ppm;
^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 205.9, 163.1* (d, *J* = 246.4 Hz), 158.7, 157.4, 152.5 (d, *J* = 2.3 Hz), 151.5, 139.1 (d, *J* = 7.4 Hz), 133.7 (d, *J* = 9.7 Hz), 132.4, 130.3 (d, *J* = 8.2 Hz), 129.1 (d, *J* = 14.0 Hz), 129.1 (d, *J* = 12.7 Hz), 125.9, 124.3 (d, *J* = 192.8 Hz), 123.4, 123.1, 122.5

(d, J = 2.9 Hz), 115.1, 115.0, 114.9, 114.2, 114.0 (d, J = 22.2 Hz), 70.4, 65.0 (d, J = 5.3 Hz), 46.6, 28.6 (d, J = 7.4 Hz), 27.3 ppm;
HRMS (ESI-TOF) calc'd for $C_{35}H_{41}O_6N_3ClFPS_2$ $[M+H]^+$: 748.18415, found 748.18427.

Note *The C–F signal was assigned based on comparison with the 100 MHz $^{13}C\{^1H\}$ spectrum.

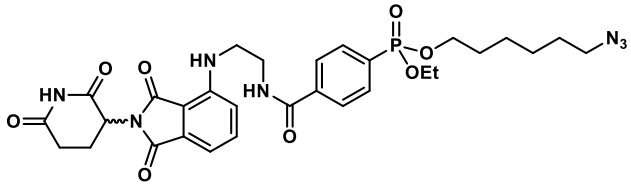
Compound 81



Prepared according to modified General procedure A using trametinib (76.9 mg, 0.125 mmol), di-*iso*-propyl *H*-phosphonate (**72**, 41.5 µL, 0.25 mmol), 2 wt % TPGS-750-M in H_2O (1.0 mL) and EtOAc (0.2 mL). The crude product was purified by pTLC (5% MeOH in EtOAc/CH_2Cl_2 1:1) and then by second pTLC (5% MeOH in EtOAc/CH_2Cl_2 10:1) to afford **81** as a white solid (43.0 mg, 53%).

$\mathbf{R_f}$ = 0.30 (5% MeOH in EtOAc). Stain: UV active;
^{1}H NMR (600 MHz, $CDCl_3$): δ 11.29 (s, 1H), 8.36 (br d, J = 13.8 Hz, 1H), 7.83 (s, 1H), 7.58–7.52 (m, 2H), 7.23 (t, J = 8.4 Hz, 1H), 7.18 (d, J = 7.8 Hz, 1H), 6.95–6.91 (m, 2H), 4.70 (m, 2H), 3.20 (s, 3H), 2.72 (m, 1H), 2.08 (s, 3H), 1.40 (s, 3H), 1.36 (d, J = 6.0 Hz, 6H), 1.24 (d, J = 6.0 Hz, 6H), 1.11 (d, J = 7.2 Hz, 2H), 0.76 (d, J = 3.6 Hz, 2H) ppm;
^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 13.56 (d, J = 6.8 Hz) ppm;
^{19}F NMR (376 MHz, $CDCl_3$): δ -124.25 (m) ppm;
^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 168.9, 164.8, 163.9, 154.5 (dd, J = 251.4, 21.7 Hz), 151.8, 151.4, 144.8, 140.1, 139.4, 131.8 (dd, J = 11.3, 2.6 Hz), 129.1, 128.4 (dd, J = 9.2, 2.9 Hz), 128.1 (dd, J = 194.5, 5.1 Hz), 124.0, 122.5 (d, J = 17.4 Hz), 120.5, 119.8 (dd, J = 20.1, 11.0 Hz), 119.0, 104.4, 90.6, 71.5 (d, J = 5.6 Hz), 34.8, 25.4, 24.5, 24.1 (d, J = 3.9 Hz), 23.9 (d, J = 4.5 Hz), 13.5, 8.5 ppm;
HRMS (ESI-TOF) calc'd for $C_{32}H_{38}O_7N_5FP$ $[M+H]^+$: 654.24874, found 654.24864.

Compound 82



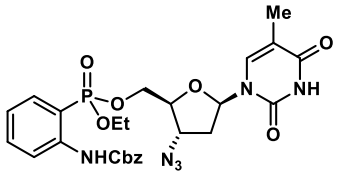
Prepared on 0.125-mmol scale according to modified General procedure B using iodide **SI-29** (68.3 mg, 0.125 mmol), *H*-phosphonate **83** (58.8 mg, 0.25 mmol), 2 wt % TPGS-750-M in H_2O (0.5 mL) and EtOAc (0.1 mL). The crude product was purified by pTLC (acetone/EtOAc 1:8) to afford **82** as yellow foamy solid (39.0 mg, 48%, 63% brsm) and **SI-29** (16.9 mg, 25% recovery). Heating above 35 °C during concentration under reduced pressure as well as using alcohols for chromatography isolation were avoided.

$\mathbf{R_f}$ = 0.29 (acetone/EtOAc 1:8). Stain: UV active (both long- and short-wave), $KMnO_4$, visible yellow spot;
^{1}H NMR (600 MHz, $CDCl_3$): δ 8.88 (s, 1H), 7.84–7.77 (m, 4H), 7.47–7.43 (m, 2H, overlapped signals), 7.04 (d, J = 7.2 Hz, 2H), 6.97 (d, J = 8.4 Hz, 1H), 4.91–4.88 (m, 1H), 4.17–3.96 (m, 4H), 3.67–3.65 (m, 2H), 3.55–3.53 (m, 2H), 3.23 (t, J = 6.6 Hz, 2H), 2.88–2.66 (m, 3H), 2.11–2.07 (m, 1H), 1.69–1.65 (m, 2H), 1.58–1.53 (m, 2H), 1.39–1.32 (m, 4H), 1.31 (dt, J = 7.2, 2.4 Hz, 3H) ppm;
^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 17.19 ppm;
^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 171.6, 169.6, 169.2, 167.6, 167.5, 146.8, 137.8 (d, J = 1.5 Hz), 136.5, 132.5, 132.0 (d, J = 10.1 Hz), 131.4* (d, J = 189.1 Hz, partially overlapped), 127.4

(d, J = 15.3 Hz), 117.0, 112.2, 110.5, 66.4 (d, J = 5.7 Hz), 62.8 (d, J = 5.4 Hz), 51.4, 49.1, 42.1, 39.8, 31.6, 30.3 (d, J = 6.3 Hz), 28.8, 26.3, 25.2, 22.9, 16.4 (d, J = 6.2 Hz) ppm;
HRMS (ESI-TOF) calc'd for $C_{30}H_{37}O_8N_7P$ $[M+H]^+$: 654.24357, found 654.24321.

Notes: *The C(sp^2)–P signal was assigned based on the comparison with the 100 MHz ^{13}C NMR spectrum. Cross-coupling of **SI-28** with **83** following General procedure A afforded **82** in virtually the same yield. Higher concentrations of **82** in $CDCl_3$ (ca. >8 mg/mL) caused significant peak broadening in ^1H NMR spectra due to molecular interactions and increased solution viscosity.

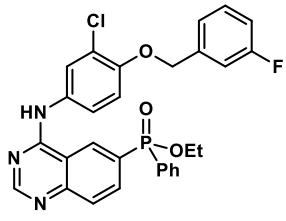
Azidothymidyl phosphonate 84



Prepared on 0.125-mmol scale according to modified General procedure B using AZT H-phosphonate **85** (44.9 mg, 0.125 mmol), benzyl (2-iodophenyl)carbamate (**6**, 53.0 mg, 0.15 mmol), 2 wt % TPGS-750-M in H_2O (0.5 mL) and EtOAc (0.1 mL). After 15 hours, $^1H/^{31}P$ NMR analysis with CH_2Br_2 as an internal standard showed full conversion of **85**, 55% ^1H NMR yield of **84**, and 30% unreacted **6**. The crude product was purified by pTLC (EtOAc/CH_2Cl_2 2:1) and then by second pTLC (5% acetone in EtOAc/$CHCl_3$ 1:1) to afford **84** as a white solid (41.0 mg, 56%), mixture of two diastereomers in 1:1.1 ratio (determined by ^{31}P NMR).

$\mathbf{R}_f$ = 0.43 (EtOAc/CH_2Cl_2 2:1). Stain: UV active, $KMnO_4$;
^{1}H NMR (two diastereomers, 600 MHz, $CDCl_3$): δ 9.91 (d, J = 21.6, 1H), 9.28 (s, 1H), 8.41 (dd, J = 7.8, 7.8 Hz, 2H), 7.57–7.54 (m, 2H), 7.41 (d, J = 7.8 Hz, 2H), 7.35 (t, J = 7.8 Hz, 2H), 7.31 (m, 1H), 7.10–7.07 (m, 1H), 6.19* and 6.11 (2 × t, 2 × J = 6.6 Hz, 2 × 0.5H), 5.20 (s, 2H), 4.32–4.15 (m, 4H), 4.10–4.05 (m, 1H), 4.00 (br d, J = 3.0 Hz, 1H), 2.41–2.33 (m, 1H), 2.29–2.16 (m, 1H), 1.80 (d, J = 13.2 Hz, 3H), 1.32 (q, J = 6.6 Hz, 3H) ppm;
^{31}P{^{1}H} NMR (two diastereomers, 162 MHz, $CDCl_3$): δ 20.83* and 20.65* (1:1.1 integral ratio) ppm;
^{13}C{^{1}H} NMR (two diastereomers, 100 MHz, $CDCl_3$): δ 163.7 (d, J = 3.5 Hz), 153.4, 150.3 (d, J = 13.9 Hz), 143.26* (d, J = 6.5 Hz) and 143.22* (d, J = 6.3 Hz), 136.1, 135.3* (d, J = 13.0 Hz), 134.9, 132.35* (d, J = 6.2 Hz) and 132.28* (d, J = 5.9 Hz), 128.6, 128.4, 122.61* (d, J = 6.0 Hz) and 122.52* (d, J = 6.0 Hz), 119.8 (d, J = 10.0 Hz), 111.86* (d, J = 180.1 Hz) and 111.80* (d, J =180.0 Hz), 111.6, 111.5, 85.2, 84.9, 82.39* (d, J = 7.4 Hz) and 82.35* (d, J = 6.9 Hz), 67.1, 65.05* (d, J = 4.8 Hz) and 65.98* (d, J = 4.7 Hz), 63.58* (d, J = 5.4 Hz) and 63.54* (d, J = 6.2 Hz), 60.3 (d, J = 12.7 Hz), 37.6, 16.29 (d, J = 6.2 Hz), 12.45 (d, J = 10.7 Hz) ppm;
HRMS (ESI-TOF) calc'd for $C_{26}H_{30}O_8N_6P$ $[M+H]^+$: 585.18572, found 585.18530.

Compound 88

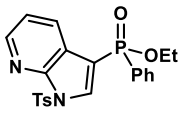


Prepared on 0.125-mmol scale according to modified General procedure A using 4-[3-chloro-4-(3-fluorobenzyloxy)phenylamino]-6-iodoquinazoline (63.1 mg, 0.125 mmol), ethyl phenyl-H-phosphinate (**86**, 40.1 μL, 0.25 mmol), 2 wt % TPGS-750-M in H_2O (1.0 mL) and EtOAc (0.2 mL). The reaction was performed at 45 °C. Analysis of the crude reaction mixture revealed full conversion of starting aryl iodide and 84% yield of **88** (determined by ^1H NMR with CH_2Br_2 as an internal standard). The crude product was purified by pTLC (1% MeOH in EtOAc/CH_2Cl_2 1:1) and then by preparative HPLC (gradient H_2O + 0.1% TFA → CH_3OH over 25 min) to afford **88·TFA** as a bright yellow solid. **88·TFA** was dissolved in CH_2Cl_2 (10 mL) and washed sat. aq. $NaHCO_3$ (5 mL), organic phase was dried over Na_2SO_4 and concentrated under reduced

pressure and the residue was purified by pTLC (5% MeOH in CH_2Cl_2) to afford **88** as a light-yellow solid (52.0 mg, 76%).

$\mathbf{R}_f$ = 0.35 (1% MeOH in EtOAc/CH_2Cl_2 1:1). Stain: UV active, $KMnO_4$, visible yellow spot;
^{1}H NMR (600 MHz, $CDCl_3$): δ 10.21 (br s, 1H), 9.53 (d, *J* = 13.2 Hz, 1H), 8.69 (s, 1H), 7.91 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.83 (t, *J* = 6.8 Hz, 1H), 7.67 (dd, *J* = 12.6, 7.2 Hz, 2H), 7.63 (d, *J* = 2.4 Hz, 1H), 7.46 (t, *J* = 7.8 Hz, 1H), 7.40–7.35 (m, 2H), 7.31 (td, *J* = 7.8, 3.6 Hz, 2H), 7.24 (d, *J* = 7.2 Hz, 1H), 7.21 (d, *J* = 9.6 Hz, 1H), 7.04 (td, *J* = 8.4, 2.4 Hz, 1H), 6.85 (d, *J* = 8.4 Hz, 1H), 5.14 (s, 2H), 4.01–3.86 (m, 2H),
1.22 (t, *J* = 7.2 Hz, 1H) ppm;
^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 30.92 ppm;
^{19}F NMR (376 MHz, $CDCl_3$): δ -112.53 (m) ppm;
^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 163.2 (d, *J* = 246.6 Hz), 159.2, 157.0, 151.7, 151.6, 139.2 (d, *J* = 7.4 Hz), 133.8 (d, *J* = 11.2 Hz), 132.7 (d, *J* = 2.1 Hz), 132.1, 131.3 (d, *J* = 10.3 Hz), 130.7 (d, *J* = 141.9 Hz), 130.3 (d, *J* = 8.3 Hz), 129.7 (d, *J* = 11.2 Hz), 128.8 (d, *J* = 13.4 Hz), 128.6 (d, *J* = 136.8 Hz), 128.5 (d, *J* = 12.2 Hz), 126.7, 123.9, 123.4, 122.5 (d, *J* = 2.7 Hz), 115.3 (d, *J* = 14.6 Hz), 115.1 (d, *J* = 21.1 Hz), 114.09, 114.06 (d, *J* = 22.2 Hz), 70.5, 61.8 (d, *J* = 5.9 Hz), 16.4 (d, *J* = 6.9 Hz) ppm;
HRMS (ESI-TOF) calc'd for $C_{29}H_{25}O_3N_3ClFP$ $[M+H]^+$: 548.13006, found 548.12958.

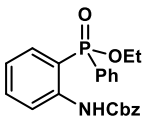
Ethyl phenyl(1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)phosphinate (89)



Prepared according to modified General procedure A using 3-iodo-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridine (**SI-21**, 99.6 mg, 0.25 mmol), ethyl phenyl-*H*-phosphinate (**88**, 80.2 µL, 0.50 mmol), 2 wt % TPGS-750-M in H_2O (1.0 mL) and EtOAc (0.2 mL). The crude product was purified by pTLC (EtOAc/CH_2Cl_2 2:1) and then by second pTLC (2% MeOH in EtOAc/CH_2Cl_2 2:3) to afford **89** as a white solid (89.0 mg, 81%).

$\mathbf{R}_f$ = 0.55 (2% MeOH in EtOAc/CH_2Cl_2 2:3). Stain: UV active, $KMnO_4$;
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.45 (dd, *J* = 4.8, 1.6 Hz, 1H), 8.20 (d, *J* = 5.6 Hz, 1H), 8.12 (d, *J* = 8.4 Hz, 2H), 8.02 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.87–7.82 (m, 2H), 7.57–7.44 (m, 3H), 7.30 (d, *J* = 8.0 Hz, 2H), 7.20 (dd, *J* = 8.0, 4.8 Hz, 1H), 4.17–4.10 (m, 2H), 2.39 (s, 3H), 1.38 (t, *J* = 6.8 Hz, 3H) ppm;
^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 25.55 ppm;
^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 147.5 (d, *J* = 11.6 Hz), 146.0, 145.8, 134.5, 133.4 (d, *J* = 19.2 Hz), 132.6 (d, *J* = 2.9 Hz), 131.2 (d, *J* = 10.6 Hz), 131.3 (d, *J* = 143.1 Hz), 130.1, 129.8, 128.8 (d, *J* = 13.5 Hz), 128.5, 122.0 (d, *J* = 10.8 Hz), 119.8, 109.2 (d, *J* = 156.0 Hz), 61.4 (d, *J* = 5.6 Hz), 21.7, 16.5 (d, *J* = 6.7 Hz) ppm;
HRMS (ESI-TOF) calc'd for $C_{22}H_{22}O_4N_2PS$ $[M+H]^+$: 441.10324, found 441.10314.

Benzyl (2-(ethoxy(phenyl)phosphoryl)phenyl)carbamate (90)

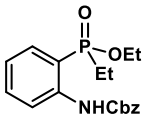


Prepared according to General procedure A using benzyl (2-iodophenyl)carbamate (**6**, 88.3 mg, 0.25 mmol) and ethyl phenyl-*H*-phosphinate (**86**, 80.2 µL, 0.50 mmol). The crude product was purified by pTLC (hexane/EtOAc 5:2) to afford **90** as a light-brown oil (74.0 mg, 75%).

$\mathbf{R}_f$ = 0.50 (hexane/EtOAc 2:1). Stain: UV active;

^{1}H NMR (400 MHz, $CDCl_3$): δ 10.57 (s, 1H), 8.36 (dd, *J* = 8.4, 5.2 Hz, 1H), 7.80–7.75 (m, 2H), 7.55–7.29 (m, 10H), 7.02 (ddd, *J* = 7.6, 2.4, 0.8 Hz, 1H), 5.21 (s, 2H), 4.26–4.03 (m, 2H), 1.39 (t, *J* = 7.2 Hz, 3H) ppm;
^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 35.38 ppm;
^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 153.6, 143.6 (d, *J* = 5.7 Hz), 136.4, 133.8 (d, *J* = 2.1 Hz), 132.6–132.5 (m, overlapped signals), 131.5 (d, *J* = 142.4 Hz), 131.2 (d, *J* = 10.2 Hz), 128.8, 128.6, 128.5, 128.2, 128.1, 122.2 (d, *J* = 12.3 Hz), 119.6 (d, *J* = 9.1 Hz), 115.8 (d, *J* = 127.9 Hz), 66.7, 61.7 (d, *J* = 5.9 Hz), 16.4 (d, *J* = 6.7 Hz) ppm;
HRMS (ESI-TOF) calc'd for $C_{22}H_{23}O_4NP$ $[M+H]^+$: 396.13592, found 396.13580.

Benzyl (2-(ethoxy(ethyl)phosphoryl)phenyl)carbamate (91)

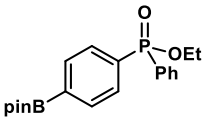


Prepared according to modified General procedure A using benzyl (2-iodophenyl)carbamate (**6**, 88.3 mg, 0.25 mmol), ethyl ethyl-*H*-phosphinate (**87**, 89.9 μL, 0.50 mmol), $Pd(OAc)_2$ (1.4 mg, 6.25 μmol), XantPhos (3.6 mg, 6.25 μmol), $Ni(phen)_3Cl_2$ (4.2 mg, 6.25 μmol), KOAc (25.0 mg, 0.25 mmol), nano Zn (8.1 mg, 0.125 mmol), 2,6-lutidine (87.0 μL, 0.75 mmol), 2 wt % TPGS-750-M in H_2O (0.5 mL) and EtOAc (0.1 mL). The reaction was performed at 55 °C. The analysis of the crude reaction mixture by ^{1}H NMR with CH_2Br_2 as an internal standard showed 47% yield of **91** and 39% RSM. The crude product was purified by pTLC (hexane/EtOAc 3:1) to afford **91** as a light-yellow oil (35.0 mg, 40%).

R_f = 0.32 (hexane/EtOAc 3:1). Stain: UV active, weakly stains with $KMnO_4$;
^{1}H NMR (400 MHz, $CDCl_3$): δ 10.70 (s, 1H), 8.41 (dd, *J* = 8.4, 5.2 Hz, 1H), 7.53–7.47 (m, 2H), 7.44–7.29 (m, 6H), 7.08–7.03 (m, 1H), 5.20 (dd, *J* = 12.4, 15.6 Hz, 2H, strong roofing effect), 4.17–4.07 (m, 1H), 3.92–3.82 (m, 1H), 1.98–1.82 (m, 2H), 1.30 (t, *J* = 7.2 Hz, 3H), 1.10 (dt, *J* = 19.4, 7.6 Hz, 3H) ppm;
^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 51.36 ppm;
^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 153.7, 144.2 (d, *J* = 5.1 Hz), 136.4, 133.9 (d, *J* = 2.2 Hz), 131.8 (d, *J* = 8.5 Hz), 128.5, 128.2, 128.1, 122.1 (d, *J* = 11.8 Hz), 119.3 (d, *J* = 8.4 Hz), 114.6 (d, *J* = 114.6 Hz), 66.7, 61.2 (d, *J* = 6.2 Hz), 23.5 (d, *J* = 103.8 Hz), 16.4 (d, *J* = 6.5 Hz), 5.5 (d, *J* = 4.7 Hz) ppm;
HRMS (ESI-TOF) calc'd for $C_{18}H_{23}O_4NP$ $[M+H]^+$: 348.13592, found 348.13626.

Note: Cross-coupling of **6** with **87** following General procedure B afforded **91** in 17% yield (^{1}H NMR with CH_2Br_2 as an internal standard). Variations in base (*N*-methylmorpholine instead of 2,6-lutidine) and ligand (dppf or DPEphos instead of XantPhos) afforded **91** in <10% yield (^{1}H NMR with CH_2Br_2 as an internal standard).

Ethyl phenyl(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)phosphinate (92)



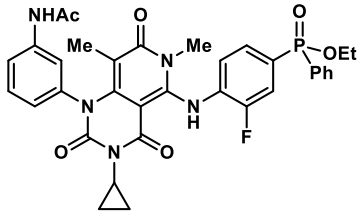
Prepared according to General procedure B using 2-(4-iodophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (82.5 mg, 0.25 mmol) and ethyl phenyl-*H*-phosphinate (**86**, 80.2 μL, 0.50 mmol). The crude product was purified by pTLC (hexane/EtOAc 1:2) and then by second pTLC (EtOAc/CH_2Cl_2 1:1) to afford **92** as a colorless oil (60.0 mg, 65%).

R_f = 0.45 (hexane/EtOAc 1:2). Stain: UV active;
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91–7.79 (m, 6H), 7.54–7.42 (m, 3H), 4.18–4.08 (m, 2H), 1.38 (t, *J* = 6.8 Hz, 3H, overlapped), 1.35 (s, 12H, overlapped) ppm;
^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 31.14 ppm;

^{11}B NMR (128 MHz, $CDCl_3$): δ 31.05 ppm;
^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 134.7 (d, *J* = 12.4 Hz), 134.3 (d, *J* = 133.3 Hz), 132.1 (d, *J* = 1.7 Hz), 131.7 (d, *J* = 136.3 Hz), 131.6 (d, *J* = 10.0 Hz), 130.8 (d, *J* = 9.6 Hz), 128.5 (d, *J* = 13.0 Hz), 84.2, 61.2 (d, *J* = 5.6 Hz), 24.9, 16.5 (d, *J* = 6.6 Hz) ppm;
HRMS (ESI-TOF) calc'd for $C_{20}H_{27}O_4BP$ $[M+H]^+$: 373.17345, found 373.17375.

Note: *One carbon (C_{Ar}–B) signal is missing in the ^{13}C NRM spectrum due to quadrupolar relaxation.

Compound 93

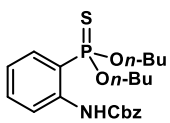


Prepared on 0.125-mmol scale according to modified General procedure A using trametinib (76.9 mg, 0.125 mmol), ethyl phenyl-*H*-phosphinate (**86**, 40.1 μL, 0.25 mmol), 2,6-lutidine (43.5 μL, 0.375 mmol), 2 wt % TPGS-750-M in H_2O (1.0 mL) and EtOAc (0.2 mL). The crude product was purified by pTLC (5% MeOH in EtOAc/CH_2Cl_2 1:1) to afford **93** as a white solid (63.0 mg, 77%).

R_f = 0.27 (5% MeOH in EtOAc/CH_2Cl_2 1:1). Stain: UV active;
^{1}H NMR (600 MHz, $CDCl_3$): δ 11.26 (s, 1H), 8.52 (s, 1H), 7.82 (s, 1H), 7.78 (dd, *J* = 12.6, 7.8 Hz, 2H), 7.59–7.51 (m, 3H), 7.48–7.45 (m, 2H), 7.23–7.19 (m, 2H), 6.93–6.90 (m, 2H), 4.15–4.07 (m, 2H), 3.17 (s, 3H), 2.70 (m, 1H), 2.07 (s, 3H), 1.38 (s, 3H), 1.37 (t, *J* = 7.2 Hz, 3H), 1.09–1.05 (m, 2H), 0.77–0.73 (m, 2H) ppm;
^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 28.92 (d, *J* = 5.4 Hz) ppm;
^{19}F NMR (376 MHz, $CDCl_3$): δ -124.04 (m) ppm;
^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 168.9, 164.7, 163.9, 154.5 (dd, *J* = 251.9, 18.7 Hz), 151.8, 151.2, 144.7, 140.1, 139.4, 132.7, 131.9 (d, *J* = 11.3 Hz), 131.6 (d, *J* = 10.1 Hz), 130.7* (d, *J* = 139.7 Hz, partially overlapped), 129.8* (dd, *J* = 142.4, 2.9 Hz, partially overlapped), 129.0, 128.9 (d, *J* = 13.1 Hz), 128.2 (d, *J* = 8.0 Hz), 124.0, 122.5 (d, *J* = 15.3 Hz), 120.4, 119.8 (dd, *J* = 19.8, 11.3 Hz), 119.0, 104.5, 90.7, 61.6 (d, *J* = 5.6 Hz), 34.8, 25.4, 24.5, 16.4 (d, *J* = 6.3 Hz), 13.4, 8.5 ppm;
HRMS (ESI-TOF) calc'd for $C_{34}H_{34}O_6N_5FP$ $[M+H]^+$: 658.22252, found 658.22242.

Note: *C(sp^2)–P signals were assigned based on comparison with the 100 MHz ^{13}C NMR spectrum. The splitting pattern of some of the ^{13}C signals was not fully resolved and assigned, please refer to the comparison of 151 and 100 MHz ^{13}C NMR spectra in the "NMR Data" section.

Benzyl (2-(dibutoxyphosphorothioyl)phenyl)carbamate (95)



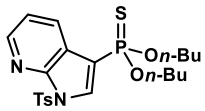
Prepared according to modified General procedure A using benzyl (2-iodophenyl)carbamate (**6**, 88.3 mg, 0.25 mmol) and di-*n*-butyl *H*-thiophosphonate (**94**, 52.6 μL, 0.30 mmol), which was added in two portions (0.15 mmol at the beginning, and 0.15 mmol after 7.5 hours). The crude product was purified by preparative reverse-phase C18 HPLC (gradient H_2O + 0.1% TFA → CH_3CN over 20 min) to afford **95** as a colorless oil (67.0 mg, 56%, 71% brsm) and starting **6** (18.3 mg, 21% RSM). Attempted isolation of **95** using normal-phase pTLC failed due to co-elution of **95** with **6**.

R_f = 0.2 (hexane/EtOAc 3:1). Stain: UV active, $KMnO_4$;
^{1}H NMR (600 MHz, $CDCl_3$): δ 8.71 (br s, 1H), 8.16 (br t, *J* = 7.2 Hz, 1H), 7.92 (dd, *J* = 17.4, 7.8 Hz, 1H), 7.52 (t, *J* = 7.8 Hz, 1H), 7.42–7.33 (m, 5H), 7.13 (td, *J* = 7.2, 2.4 Hz, 1H), 6.98–6.93 (m, 2H), 5.23

(s, 2H), 4.13–4.02 (m, 2H), 1.63 (quintet, J = 6.6 Hz, 4H), 1.37 (sextet, J = 7.8 Hz, 4H), 0.87 (t, J = 7.2 Hz, 6H) ppm;
^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 83.98 ppm;
^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 153.4, 139.8 (d, J = 4.2 Hz), 136.3, 133.7, 133.3 (d, J = 11.0 Hz), 128.6, 128.3, 128.2, 122.8 (d, J = 14.8 Hz), 121.0 (d, J = 8.6 Hz), 120.5* (d, J = 146.9 Hz), 67.04, 67.00, 32.2 (d, J = 7.4 Hz), 18.9, 13.6 ppm;
HRMS (ESI-TOF) calc'd for $C_{22}H_{31}O_4NPS$ $[M+H]^+$: 436.17059, found 436.17099; calc'd for $C_{22}H_{30}O_4NNaPS$ $[M+Na]^+$: 458.15254, found 458.15276.

Note: *The C–P signal was assigned based on analysis of the 100 MHz ^{13}C{^{1}H} NMR spectrum.

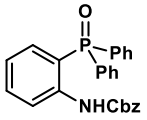
_O_,_O_-Di-_n_-butyl (1-tosyl-1_H_-pyrrolo[2,3-_b_]pyridin-3-yl)phosphonothioate (96)



Prepared according to modified General procedure A using 3-iodo-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridine (**SI-21**, 99.6 mg, 0.25 mmol) and di-*n*-butyl *H*-thiophosphonate (**94**, 92.1 μL, 0.525 mmol), which was added in three portions (0.175 mmol at the beginning, 0.175 mmol after 3 hours, and 0.175 mmol after 3 hours). The crude product was purified by pTLC (hexane/EtOAc 3:1) to afford **96** as a viscous light-yellow oil (82.0 mg, 68%).

R_f = 0.50 (hexane/EtOAc 3:1). Stain: UV active, $KMnO_4$;
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.47 (dd, J = 4.8, 1.6 Hz, 1H), 8.25 (d, J = 6.4 Hz, 1H), 8.17–8.14 (m, 3H), 7.31 (d, J = 8.4 Hz, 2H), 7.26 (dd, J = 8.0, 4.8 Hz, 1H, overlapped with $CHCl_3$), 4.15–3.99 (m, 4H), 2.39 (s, 3H), 1.63 (quint, J = 6.8 Hz, 4H), 1.36 (sextet, J = 7.2 Hz, 4H), 0.88 (t, J = 6.8 Hz, 6H) ppm;
^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 76.11 ppm;
^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 147.5 (d, J = 12.7 Hz), 146.0, 145.8, 134.6, 134.1 (d, J = 26.1 Hz), 130.3, 129.8, 128.6, 121.2 (d, J = 9.6 Hz), 119.7, 111.6 (d, J = 175.2 Hz), 66.6 (d, J = 5.7 Hz), 32.2 (d, J = 7.6 Hz), 21.8, 18.9, 13.6 ppm;
HRMS (ESI-TOF) calc'd for $C_{22}H_{30}O_4N_2PS_2$ $[M+H]^+$: 481.13791, found 481.13773.

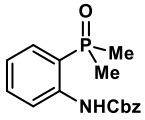
Benzyl (2-(diphenylphosphoryl)phenyl)carbamate (99)



Prepared according to General procedure A using benzyl (2-iodophenyl)carbamate (**6**, 88.3 mg, 0.25 mmol) and diphenylphosphine oxide (**97**, 101.1 mg, 0.50 mmol). The reaction was performed at 55 °C. The crude product was purified by pTLC (hexane/EtOAc 2:1) to afford **99** as a colorless semi-solid (67.0 mg, 63%).

R_f = 0.35 (hexane/EtOAc 2:1). Stain: UV active;
^{1}H NMR (400 MHz, $CDCl_3$): δ 10.54 (s, 1H), 8.37 (dd, J = 8.4, 4.8 Hz, 1H), 7.65–7.55 (m, 6H), 7.52–7.45 (m, 5H), 7.35–7.28 (m, 5H), 6.98–6.93 (m, 2H), 5.13 (s, 2H) ppm;
^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 36.61 ppm;
^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 153.7, 144.7 (d, J = 3.0 Hz), 136.4, 133.4 (d, J = 2.2 Hz), 132.8 (d, J = 10.6 Hz), 132.4 (d, J = 2.7 Hz), 132.1 (d, J = 10.0 Hz), 131.7 (d, J = 104.8 Hz), 128.7 (d, J = 12.3 Hz), 128.4, 127.97, 127.96, 122.8 (d, J = 12.6 Hz), 120.4 (d, J = 7.3 Hz), 116.5 (d, J = 100.3 Hz), 66.6 ppm;
HRMS (ESI-TOF) calc'd for $C_{26}H_{23}O_3NP$ $[M+H]^+$: 428.14101, found 428.14084.

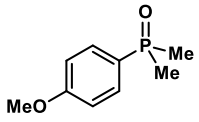
Benzyl (2-(dimethylphosphoryl)phenyl)carbamate (100)



Prepared according to modified General procedure B using benzyl (2-iodophenyl)carbamate (**6**, 88.3 mg, 0.25 mmol), dimethylphosphine oxide (**98**, 60.0 µL, 0.75 mmol), Pd[P(*t*-Bu)$_3$]$_2$ (3.2 mg, 6.25 µmol), Pd(OAc)$_2$ (0.6 mg, 2.50 µmol), XantPhos (1.4 mg, 2.50 µmol), LiBr (21.7 mg, 0.25 mmol), *N*-methylmorpholine (82.5 µL, 0.75 mmol), 2 wt % TPGS-750-M in H_2O (0.5 mL) and EtOAc (0.1 mL). The reaction was performed at 55 °C. The crude product was purified by pTLC (EtOAc/CH_2Cl_2 1:1) to afford **100** as an off-white solid (65.0 mg, 86%).

$\mathbf{R}_f$ = 0.40 (EtOAc/CH_2Cl_2 1:1). Stain: UV active, $KMnO_4$;
^{1}H NMR (400 MHz, $CDCl_3$): δ 10.86 (s, 1H), 8.40 (dd, *J* = 8.4, 4.4 Hz, 1H), 7.50–7.27 (m, 6H), 7.17 (ddd, *J* = 14.0, 7.6, 1.6 Hz, 1H), 7.07–7.02 (m, 1H), 5.20 (s, 2H), 1.79 (d, *J* = 13.2 Hz, 6H) ppm;
^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 44.93 ppm;
^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 153.7, 144.0 (d, *J* = 2.5 Hz), 136.4, 133.2 (d, *J* = 2.2 Hz), 129.6 (d, *J* = 11.0 Hz), 128.5, 128.1, 128.0, 122.1 (d, *J* = 12.2 Hz), 119.8 (d, *J* = 7.1 Hz), 117.7 (d, *J* = 94.4 Hz), 66.6, 19.0 (d, *J* = 71.3 Hz) ppm;
HRMS (ESI-TOF) calc'd for $C_{16}H_{19}O_3NP$ $[M+H]^+$: 304.10971, found 304.10947.

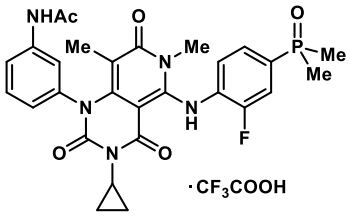
(4-Methoxyphenyl)dimethylphosphine oxide (101)



Prepared according to modified General procedure B using 4-iodoanisole (58.5 mg, 0.25 mmol), dimethylphosphine oxide (**98**, 40.0 µL, 0.50 mmol), Pd[P(*t*-Bu)$_3$]$_2$ (6.6 mg, 12.50 µmol), LiBr (21.7 mg, 0.25 mmol), KOAc (12.5 mg, 0.125 mmol), *N*-methylmorpholine (82.5 µL, 0.75 mmol), 2 wt % TPGS-750-M in H_2O (0.5 mL) and EtOAc (0.1 mL). The reaction was performed at 60 °C. The crude product was purified by pTLC (EtOAc/MeOH 5:1) to afford **101** as a light-yellow solid (31.0 mg, 67%).

Spectral data match previously reported results,[56] and ^{1}H/^{31}P/^{13}C NMR and HRMS data are provided here for convenience.
$\mathbf{R}_f$ = 0.29 (EtOAc/MeOH 5:1). Stain: UV active;
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62 (dd, *J* = 11.2, 8.4 Hz, 2H), 6.95 (dd, *J* = 8.8, 2.0 Hz, 2H), 3.81 (s, 3H), 1.67 (d, *J* = 13.2 Hz, 6H) ppm;
^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 34.12 ppm;
^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 162.3 (d, *J* = 2.7 Hz), 131.5 (d, *J* = 10.7 Hz), 125.8 (d, *J* = 104.2 Hz), 114.3 (d, *J* = 9.6 Hz), 55.4, 18.4 (d, *J* = 71.3 Hz) ppm;
HRMS (ESI-TOF) calc'd for $C_9H_{14}O_2P$ $[M+H]^+$: 185.07259, found 185.07280.

Compound 102·TFA

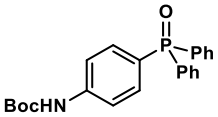


Prepared on 0.125-mmol scale according to modified General procedure B using trametinib (76.9 mg, 0.125 mmol), dimethylphosphine oxide (**98**, 30.0 µL, 0.375 mmol), Pd[P(*t*-Bu)$_3$]$_2$ (1.6 mg, 3.125 µmol), Pd(OAc)$_2$ (0.3 mg, 1.25 µmol), XantPhos (0.7 mg, 1.25 µmol), LiBr (10.9 mg, 0.125 mmol), *N*-methylmorpholine (41.2 µL, 0.375 mmol), 2 wt % TPGS-750-M in H_2O (1.5 mL) and EtOAc (0.4 mL). The reaction was performed at 55 °C. The crude reaction mixture was concentrated under reduced pressure to remove EtOAc and then directly subjected to preparative C8 HPLC (gradient H_2O + 0.1% TFA → CH_3OH over 25 min) to afford **102·TFA** as an off-white solid (79.9 mg, 81%).

$\mathbf{R}_f$ = 0.50 (EtOAc/CH_2Cl_2/MeOH 4:1:1). Stain: UV active, $KMnO_4$;
^{1}H NMR (TFA salt, 600 MHz, $CDCl_3$): δ 11.31 (s, 1H), 8.24 (s, 1H), 7.79 (s, 1H), 7.53 (t, *J* = 10.2 Hz, 1H), 7.46 (t, *J* = 9.6 Hz, 1H), 7.28–7.25 (m, 1H, overlapped with $CHCl_3$), 7.00–6.95 (m, 2H), 3.22 (s, 3H), 2.72 (m, 1H), 2.11 (s, 3H), 1.75 (d, *J* = 13.2 Hz, 6H), 1.41 (s, 3H), 1.11–1.08 (m, 2H), 0.77–0.75 (m, 2H) ppm;
^{31}P{^{1}H} NMR (TFA salt, 162 MHz, $CDCl_3$): δ 33.67 ppm;
^{19}F NMR (TFA salt, 376 MHz, $CDCl_3$): δ -76.14, -123.55 (m) ppm;
^{13}C{^{1}H} NMR (TFA salt, 151 MHz, $CDCl_3$): δ 168.8, 164.8, 163.9, 154.8 (dd, *J* = 252.3, 16.3 Hz), 151.8, 151.3, 144.8, 140.2, 139.3, 132.6 (dd, *J* = 98.6, 1.8 Hz), 131.6 (d, *J* = 11.6 Hz), 129.2, 126.3 (dd, *J* = 9.2, 3.0 Hz), 124.2, 123.0 (d, *J* = 13.5 Hz), 120.5, 119.1, 118.0 (dd, *J* = 20.1, 11.0 Hz), 104.5, 90.7, 34.8, 25.4, 24.6, 18.2 (d, *J* = 72.2 Hz), 13.5, 8.5 ppm;
HRMS (ESI-TOF) calc'd for $C_{28}H_{30}O_5N_5FP$ $[M+H]^+$: 566.19631, found 566.19624.

Notes: Larger volumes of aq. TPGS-750-M solution and EtOAc were used to form an emulsion stable throughout the reaction progress and to avoid clumping of the reaction mixture. The P(=O)Me_2 group makes **102** considerably soluble in H_2O; therefore, we suggest subjecting the crude reaction mixture directly to preparative HPLC to avoid significant material losses during extraction work-up.

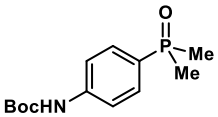
***tert*-Butyl (4-(diphenylphosphoryl)phenyl)carbamate (103)**



Prepared according to General procedure A using *tert*-butyl (4-iodophenyl)carbamate (79.8 mg, 0.25 mmol) and diphenylphosphine oxide (**97**, 101.2 mg, 0.50 mmol). The reaction was performed at 55 °C. The crude product was purified by pTLC (2.5% MeOH in CH_2Cl_2), and then by second pTLC (5% MeOH in CH_2Cl_2) to afford **103** as an off-white foam (47.3 mg, 48%).

Spectral data match previously reported results,[57] and ^{1}H/^{31}P NMR data are provided here for convenience.
$\mathbf{R}_f$ = 0.24 (2.5% MeOH in CH_2Cl_2). Stain: UV active;
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64–7.61 (m, 4H), 7.57–7.41 (m, 10H), 7.05 (br s, 1H), 1.49 (s, 9H) ppm;
^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 28.96 ppm.

***tert*-Butyl (4-(dimethylphosphoryl)phenyl)carbamate (104)**

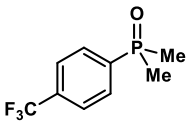


Prepared according to modified General procedure B using *tert*-butyl (4-iodophenyl)carbamate (79.8 mg, 0.25 mmol), dimethylphosphine oxide (**98**, 40.0 μL, 0.50 mmol), Pd[P(*t*-Bu)$_3$]$_2$ (3.2 mg, 6.25 μmol), $Pd(OAc)_2$ (0.6 mg, 2.50 μmol), XantPhos (1.4 mg, 2.50 μmol), LiBr (21.7 mg, 0.25 mmol), KOAc (12.5 mg, 0.125 mmol), *N*-methylmorpholine (82.5 μL, 0.75 mmol), 2 wt % TPGS-750-M in H_2O (0.5 mL) and EtOAc (0.1 mL). The reaction was performed at 60 °C. The crude product was purified by pTLC (1% MeOH in EtOAc), and then by second pTLC (5% MeOH in EtOAc) to afford **104** as a light-yellow solid (29.0 mg, 43%).

$\mathbf{R}_f$ = 0.49 (2.5% MeOH in EtOAc). Stain: UV active, $KMnO_4$;
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64 (dd, *J* = 11.2, 8.8 Hz, 2H), 7.50 (dd, *J* = 8.4, 2.0 Hz, 2H), 6.77 (br s, 1H), 1.71 (d, *J* = 12.8 Hz, 6H), 1.52 (s, 9H) ppm;
^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 34.27 ppm;

$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 152.6, 142.1 (d, *J* = 3.0 Hz), 130.8 (d, *J* = 10.5 Hz), 127.9 (d, *J* = 103.0 Hz), 118.3 (d, *J* = 12.1 Hz), 81.1, 28.4, 18.3 (d, *J* = 71.4 Hz) ppm;
HRMS (ESI-TOF) calc'd for $C_{13}H_{21}O_3NP$ $[M+H]^+$: 270.12536, found 270.12553; calc'd for $C_{13}H_{20}O_3NNaP$ $[M+Na]^+$: 292.10730, found 292.10749.

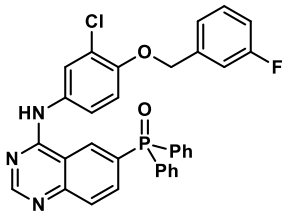
Dimethyl(4-(trifluoromethyl)phenyl)phosphine oxide (105)



Prepared according to modified General procedure B using 4-iodobenzotrifluoride (36.7 μL, 0.25 mmol), dimethylphosphine oxide (**98**, 40.0 μL, 0.50 mmol), $Pd[P(t\text{-}Bu)_3]_2$ (3.2 mg, 6.25 μmol), $Pd(OAc)_2$ (0.6 mg, 2.50 μmol), XantPhos (1.4 mg, 2.50 μmol), LiBr (21.7 mg, 0.25 mmol), KOAc (12.5 mg, 0.125 mmol), *N*-methylmorpholine (82.5 μL, 0.75 mmol), 2 wt % TPGS-750-M in H_2O (0.5 mL) and EtOAc (0.1 mL). The reaction was performed at 60 °C. The crude product was purified by pTLC (10% MeOH in EtOAc) to afford **105** as a yellow oil (34.0 mg, 61%).

Spectral data match previously reported results,[58] and $^1H/^{31}P/^{19}F$ NMR data are provided here for convenience.
R_f = 0.20 (10% MeOH in EtOAc). Stain: UV active, $KMnO_4$;
^1H NMR (400 MHz, $CDCl_3$): δ 7.88–7.83 (m, 2H), 7.74–7.71 (m, 2H), 1.67 (d, *J* = 13.2 Hz, 6H) ppm;
$^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$): δ 33.38 ppm;
^{19}F NMR (376 MHz, $CDCl_3$): δ -63.2 ppm.

Compound 106



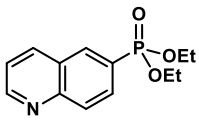
Prepared on 0.125-mmol scale according to modified General procedure A using 4-[3-chloro-4-(3-fluorobenzyloxy)phenylamino]-6-iodoquinazoline (63.1 mg, 0.125 mmol), diphenylphosphine oxide (**97**, 50.6 mg, 0.25 mmol), 2 wt % TPGS-750-M in H_2O (1.0 mL) and EtOAc (0.2 mL). The reaction was performed at 55 °C. Analysis of the crude reaction mixture revealed >90% conversion of starting aryl iodide and 74% yield of **106** (determined by ^1H NMR with CH_2Br_2 as an internal standard). The crude product was purified by pTLC (5% MeOH in CH_2Cl_2) and then by preparative HPLC (gradient H_2O + 0.1% TFA → CH_3OH over 25 min) to afford **106·TFA** as a bright yellow solid. **106·TFA** was dissolved in CH_2Cl_2 (10 mL) and washed sat. aq. $NaHCO_3$ (5 mL), organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by pTLC (3.5% MeOH in EtOAc/CH_2Cl_2 2:3) to afford **106** as a light-yellow solid (52.0 mg, 72%).

R_f = 0.25 (5% MeOH in CH_2Cl_2), 0.29 (3.5% MeOH in EtOAc/CH_2Cl_2 2:3). Stain: UV active, visible yellow spot;
^1H NMR (600 MHz, $CDCl_3$): δ 10.64 (br s, 1H), 9.75 (d, *J* = 13.2 Hz, 1H), 8.67 (s, 1H), 7.79 (dd, *J* = 8.4, 3.0 Hz, 1H), 7.65 (s, 1H), 7.45–7.33 (m, 9H), 7.26–7.18 (m, 6H, overlapped with $CHCl_3$), 7.02 (td, *J* = 8.4, 2.4 Hz, 1H), 6.66 (d, *J* = 8.4 Hz, 1H), 5.07 (s, 1H) ppm;
$^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$): δ 29.92 ppm;
^{19}F NMR (376 MHz, $CDCl_3$): δ -112.54 (m) ppm;
$^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$): δ 163.1 (d, *J* = 246.4 Hz), 159.1, 157.0, 151.5, 151.3, 139.3 (d, *J* = 7.2 Hz), 133.9 (d, *J* = 13.0 Hz), 132.4, 131.9 (d, *J* = 10.1 Hz), 131.4 (d, *J* = 105.1 Hz), 130.3 (d, *J* = 8.2 Hz), 130.1 (d, *J* = 8.2 Hz), 129.0* (d, *J* = 160.7 Hz), 128.7 (d, *J* = 12.2 Hz), 127.8 (d, *J* = 11.6 Hz), 126.4, 123.5, 123.2, 122.5 (d, *J* = 2.6 Hz), 115.7 (d, *J* = 12.7 Hz), 115.0 (d, *J* = 21.1 Hz), 114.1, 113.9, 70.4 ppm;

HRMS (ESI-TOF) calc'd for $C_{33}H_{25}O_2N_3ClFP$ $[M+H]^+$: 580.13515, found 580.13483.

Note: *One of the C–P signals was assigned based on the 100 MHz $^{13}C\{^1H\}$ NMR spectrum and ^{13}C APT spectra, please refer to the "NMR data" section.

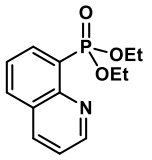
Diethyl quinolin-6-ylphosphonate (126)



Prepared according to modified General procedure A using quinolin-6-yl trifluoromethanesulfonate (**SI-30**, 69.3 mg, 0.25 mmol), diethyl *H*-phosphonate (**3**, 82.5 µL, 0.625 mmol), $Pd(OAc)_2$ (2.8 mg, 12.50 µmol), dppf (7.0 mg, 12.50 µmol), $NiCl_2$.glyme (1.4 mg, 6.25 µmol), 1,10-phenanthroline (2.3 mg, 12.5 µmol), nano Zn (8.1 mg, 0.125 mmol), LiBr (21.7 mg, 0.25 mmol), 2,6-lutidine (87.0 µL, 0.75 mmol), 2 wt % TPGS-750-M in H_2O (0.5 mL) and deoxygenated THF (0.05 mL). The reaction was performed at 45 °C. The crude product was purified by pTLC (hexane/EtOAc 1:1) to afford **126** as a viscous light-yellow oil (51.0 mg, 77%).

Spectral data match previously reported results,[59] and $^1H/^{31}P$ NMR data are provided here for convenience.
R_f = 0.10 (hexane/EtOAc 1:1). Stain: UV active;
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.03 (dd, *J* = 4.0, 1.6 Hz, 1H), 8.44 (dd, *J* = 15.2, 1.2 Hz, 1H), 8.25 (d, *J* = 8.4 Hz, 1H), 8.19 (dd, *J* = 8.4, 3.6 Hz, 1H), 8.06–7.97 (m, 1H), 7.50 (dd, *J* = 8.4, 4.4 Hz, 1H), 4.26–4.08 (m, 4H), 1.35 (t, *J* = 6.8 Hz, 6H) ppm;
$^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$): δ 17.75 ppm.

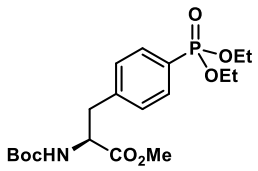
Diethyl quinolin-8-ylphosphonate (127)



Prepared according to modified General procedure A using quinolin-8-yl trifluoromethanesulfonate (**SI-31**, 69.3 mg, 0.25 mmol), diethyl *H*-phosphonate (**3**, 82.5 µL, 0.625 mmol), $Pd(OAc)_2$ (1.4 mg, 6.25 µmol), dppf (3.5 mg, 6.25 µmol), $Ni(phen)_3Cl_2$ (1.7 mg, 2.50 µmol), nano Zn (8.1 mg, 0.125 mmol), LiBr (21.7 mg, 0.25 mmol), 2,6-lutidine (87.0 µL, 0.75 mmol), 2 wt % TPGS-750-M in H_2O (1.0 mL) and EtOAc (0.1 mL). The reaction was performed at 55 °C. The crude product was purified by pTLC (1% MeOH in hexane/EtOAc 3:7) to afford **127** as a viscous light-yellow oil (44.0 mg, 66%).

Spectral data match previously reported results,[60] and $^1H/^{31}P$ NMR data are provided here for convenience.
R_f = 0.15 (1% MeOH in hexane/EtOAc 3:7). Stain: UV active;
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.06 (dd, *J* = 4.0, 1.6 Hz, 1H), 8.37 (ddd, *J* = 16.0, 7.2, 1.6 Hz, 1H), 8.18 (dt, *J* = 8.4, 1.6 Hz, 1H), 7.99 (d, *J* = 8.0 Hz, 1H), 7.58 (ddd, *J* = 10.4, 7.2, 3.2 Hz, 1H), 7.46 (dd, *J* = 8.4, 4.4 Hz, 1H), 4.38–4.22 (m, 4H), 1.34 (t, *J* = 7.2 Hz, 6H) ppm;
$^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$): δ 17.30 ppm.

Compound 128



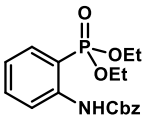
Prepared on 0.125-mmol scale according to modified General procedure A using aryl triflate **SI-32** (53.4 mg, 0.125 mmol), diethyl *H*-phosphonate (**3**, 41.3 µL, 0.313 mmol), $Pd(OAc)_2$ (0.7 mg, 3.125 µmol), dppf (1.8 mg, 3.125 µmol), $Ni(phen)_3Cl_2$ (0.8 mg, 1.250 µmol), nano Zn (4.1 mg, 62.5 µmol), LiBr (10.8 mg, 0.125 mmol), 2,6-lutidine (43.5 µL, 0.375 mmol), 2 wt %

TPGS-750-M in H_2O (0.5 mL) and THF (0.05 mL). The reaction was performed at 45 °C. The crude product was purified by pTLC (EtOAc/CH_2Cl_2 1:1) to afford **128** as a viscous light-yellow oil (29.0 mg, 56%) which solidified upon standing.

Spectral data match previously reported results,[61] and $^{1}H/^{31}P$ NMR data are provided here for convenience.
R_f = 0.50 (EtOAc/CH_2Cl_2 1:1). Stain: weakly UV active, $KMnO_4$;
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72 (dd, *J* = 13.2, 8.0 Hz, 2H), 7.23 (dd, *J* = 8.0, 4.0 Hz, 2H), 5.01 (d, *J* = 8.0 Hz, 1H), 4.62–4.57 (m, 1H), 4.17–4.00 (m, 4H), 3.70 (s, 3H), 3.19–3.02 (m, 2H), 1.39 (s, 9H), 1.30 (t, *J* = 7.2 Hz, 6H) ppm;
^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 18.76 ppm.

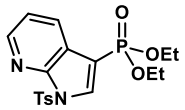
Scale-up experiments

Benzyl (2-(diethoxyphosphoryl)phenyl)carbamate (7)



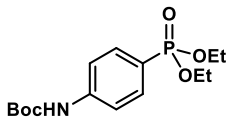
Prepared on 2.50-mmol scale according to modified General procedure A using benzyl (2-iodophenyl)carbamate (**6**, 883.0 mg, 2.50 mmol), diethyl *H*-phosphonate (**3**, 386.0 µL, 3.00 mmol), $Pd(OAc)_2$ (7.0 mg, 31.25 µmol), XantPhos (18.1 mg, 31.25 µmol), $Ni(phen)_3Cl_2$ (8.4 mg, 12.50 µmol), nano Zn (81.0 mg, 1.25 mmol), LiBr (217.0 mg, 2.50 mmol), 2,6-lutidine (580.0 µL, 5.00 mmol), 2 wt % TPGS-750-M in H_2O (5.0 mL) and EtOAc (1.0 mL). The reaction was performed at 45 °C over 19 hours. The crude product was purified by flash column chromatography (hexane/EtOAc 2:1) to afford **7** as a viscous light-yellow oil (754.0 mg, 83%).

Diethyl (1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)phosphonate (62)



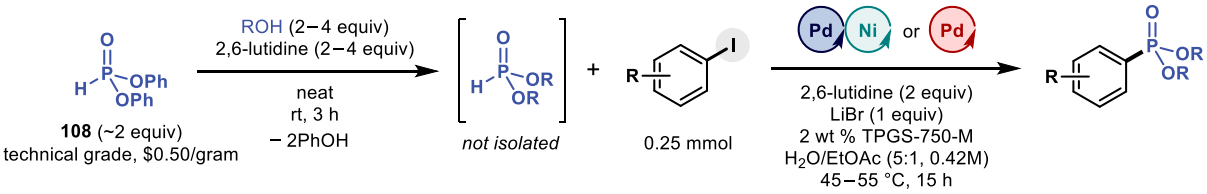
Prepared on 1.50-mmol scale according to modified General procedure A using 3-iodo-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridine (**SI-21**, 597.3 mg, 1.50 mmol), diethyl *H*-phosphonate (**3**, 386.0 µL, 3.00 mmol), $Pd(OAc)_2$ (8.4 mg, 37.50 µmol), XantPhos (21.7 mg, 37.50 µmol), $Ni(phen)_3Cl_2$ (10.2 mg, 15.00 µmol), nano Zn (48.6 mg, 0.75 mmol), LiBr (130.2 mg, 1.50 mmol), 2,6-lutidine (580.0 µL, 5.00 mmol), 2 wt % TPGS-750-M in H_2O (6.0 mL) and EtOAc (1.2 mL). The reaction was performed at 45 °C over 15 hours. The crude product was purified by flash column chromatography (hexane/EtOAc 1:1 → 1:3) to afford **62** as a beige solid (546.0 mg, 89%).

tert-Butyl (4-(diethoxyphosphoryl)phenyl)carbamate (15)



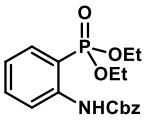
Prepared on 2.50-mmol scale according to modified General procedure A using *tert*-butyl (4-iodophenyl)carbamate (798.0 mg, 2.50 mmol), diethyl *H*-phosphonate (**3**, 650.0 µL, 5.00 mmol), $Pd(OAc)_2$ (14.1 mg, 62.50 µmol), XantPhos (36.2 mg, 62.50 µmol), $Ni(phen)_3Cl_2$ (17.0 mg, 25.00 µmol), nano Zn (81.0 mg, 1.25 mmol), LiBr (217.0 mg, 2.50 mmol), 2,6-lutidine (870.0 µL, 7.50 mmol), 2 wt % TPGS-750-M in H_2O (5.0 mL) and deoxygenated THF (0.5 mL). The reaction was performed at 45 °C over 19 hours. The crude product was purified by flash column chromatography (hexane/EtOAc 3:1 → 1:1) to afford **15** as a tan powder (680.0 mg, 83%).

General procedure C (One-pot *H*-phosphonate synthesis and C(sp^2)–P coupling)



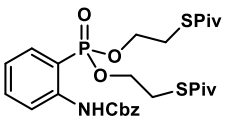
Step 1. A test tube or a small vial containing a magnetic stirring bar was charged with **108** (2 equiv), alcohol (2-4 equiv) and 2,6-lutidine (2-4 equiv) under argon. The reaction mixture was stirred at laboratory temperature for 3 hours under argon.
Step 2. General procedure A or B was then followed.

Benzyl (2-(diethoxyphosphoryl)phenyl)carbamate (7)



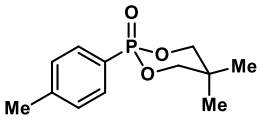
The first step was done according to General procedure C using diphenyl *H*-phosphonate (**108**, 106.6 µL, 0.50 mmol, assumed 90% purity), ethanol (99.3 µL, 1.00 mmol) and 2,6-lutidine (116.0 µL, 1.00 mmol). The second step was done according to General procedure A using benzyl (2-iodophenyl)carbamate (**6**, 88.3 mg, 0.25 mmol). The crude product was purified by pTLC (hexane/EtOAc 2:1) to afford **7** as a viscous light-yellow oil (72.7 mg, 80%).

Bis-SATE carbamate 77



The first step was done according to General procedure C using diphenyl *H*-phosphonate (**108**, 64.0 µL, 0.30 mmol, assumed 90% purity), *S*-(2-hydroxyethyl) 2,2-dimethylpropanethioate (97.4 mg, 0.60 mmol) and 2,6-lutidine (69.6 µL, 0.60 mmol). The second step was done according to General procedure B using benzyl (2-iodophenyl)carbamate (**6**, 88.3 mg, 0.25 mmol). The crude product was purified by pTLC (hexane/EtOAc/CH_2Cl_2 4:1:1) to afford **77** as a viscous light-yellow oil (72.7 mg, 80%).

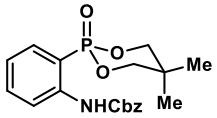
5,5-Dimethyl-2-(*p*-tolyl)-1,3,2-dioxaphosphinane 2-oxide (111)



The first step was done according to General procedure C using diphenyl *H*-phosphonate (**108**, 80.0 µL, 0.375 mmol, assumed 90% purity), 2,2-dimethylpropane-1,3-diol (**110**, 78.1 mg, 0.75 mmol) and 2,6-lutidine (87.0 µL, 0.75 mmol). The second step was done according to General procedure A using 4-iodotoluene (**2**, 58.5 mg, 0.25 mmol). The crude product was purified by pTLC (EtOAc/CH_2Cl_2 1:1) to afford **111** as an off-white solid (45.0 mg, 75%).

R_f = 0.40 (EtOAc/CH_2Cl_2 1:1). Stain: UV active, $KMnO_4$;
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69 (dd, *J* = 13.6, 8.4 Hz, 2H), 7.26 (dd, *J* = 8.0, 4.0 Hz, 2H), 4.23 (t, *J* = 10.4 Hz, 2H), 3.82 (dd, *J* = 13.2, 11.2 Hz, 2H), 2.36 (s, 3H), 1.09 (s, 3H), 1.06 (s, 3H) ppm;
^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 16.04 ppm;
^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 143.7 (d, *J* = 2.5 Hz), 131.7 (d, *J* = 10.6 Hz), 129.5 (d, *J* = 15.7 Hz), 123.0 (d, *J* = 190.7 Hz), 75.6 (d, *J* = 5.9 Hz), 32.6 (d, *J* = 5.7 Hz), 21.7 (d, *J* = 1.3 Hz), 21.6 (d, *J* = 6.7 Hz) ppm;
HRMS (ESI-TOF) calc'd for $C_{12}H_{18}O_3P$ $[M+H]^+$: 241.09881, found 241.09875.

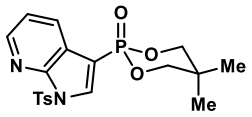
Benzyl (2-(5,5-dimethyl-2-oxido-1,3,2-dioxaphosphinan-2-yl)phenyl)carbamate (112)



The first step was done according to General procedure C using diphenyl *H*-phosphonate (**108**, 106.6 µL, 0.50 mmol, assumed 90% purity), 2,2-dimethylpropane-1,3-diol (**110**, 52.1 mg, 0.50 mmol) and 2,6-lutidine (72.5 µL, 0.625 mmol). The second step was done using according to General procedure B using benzyl (2-iodophenyl)carbamate (**6**, 88.3 mg, 0.25 mmol), Pd[P(*t*-Bu)$_3$]$_2$ (3.2 mg, 6.25 µmol), Pd(OAc)$_2$ (0.6 mg, 2.50 µmol), XantPhos (1.4 mg, 2.50 µmol), LiBr (21.7 mg, 0.25 mmol), 2,6-lutidine (58.0 µL, 0.50 mmol), 2 wt % TPGS-750-M in H_2O (0.5 mL) and EtOAc (0.1 mL). The crude product was purified by pTLC (hexane/EtOAc 1:2) to afford **112** as a beige solid (54.0 mg, 58%).

R$_f$ = 0.28 (hexane/EtOAc 1:2). Stain: UV active, $KMnO_4$;
^{1}H NMR (400 MHz, CDCl$_3$): δ 9.91 (s, 1H), 8.38 (t, *J* = 8.0 Hz, 1H), 7.64 (ddd, *J* = 14.8, 7.6, 1.6 Hz, 1H), 7.55 (t, *J* = 7.6 Hz, 1H), 7.42–7.39 (m, 2H), 7.36–7.28 (m, 3H), 7.08 (tdd, *J* = 7.6, 3.2, 1.2 Hz, 1H), 5.19 (s, 2H), 4.40 (dd, *J* = 11.2, 5.2 Hz, 2H), 3.88 (dd, *J* = 11.6, 17.6 Hz, 2H), 1.28 (s, 3H), 0.98 (s, 3H) ppm;
^{31}P{^{1}H} NMR (162 MHz, CDCl$_3$): δ 17.70 ppm;
^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$): δ 153.4, 143.3 (d, *J* = 7.7 Hz), 136.2, 134.8 (d, *J* = 2.2 Hz), 132.5 (d, *J* = 6.0 Hz), 128.5, 128.2, 128.1, 122.2 (d, *J* = 14.0 Hz), 119.6 (d, *J* = 11.7 Hz), 111.4 (d, *J* = 188.5 Hz), 75.4 (d, *J* = 5.9 Hz), 66.9, 32.8 (d, *J* = 5.8 Hz), 22.3, 21.4 ppm;
HRMS (ESI-TOF) calc'd for $C_{19}H_{23}O_5NP$ $[M+H]^+$: 376.13084, found 376.13076.

5,5-Dimethyl-2-(1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-1,3,2-dioxaphosphinane 2-oxide (113)

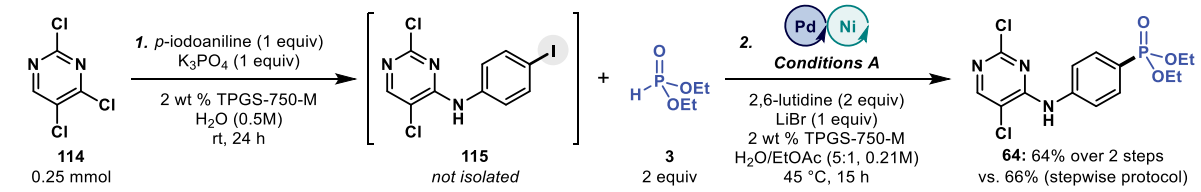


The first step was done according to General procedure C using diphenyl *H*-phosphonate (**108**, 106.6 µL, 0.50 mmol, assumed 90% purity), 2,2-dimethylpropane-1,3-diol (**110**, 52.1 mg, 0.50 mmol) and 2,6-lutidine (72.5 µL, 0.625 mmol). The second step was done according to General procedure B using 3-iodo-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridine (**SI-21**, 99.6 mg, 0.25 mmol), Pd[P(*t*-Bu)$_3$]$_2$ (3.2 mg, 6.25 µmol), Pd(OAc)$_2$ (0.6 mg, 2.50 µmol), XantPhos (1.4 mg, 2.50 µmol), LiBr (21.7 mg, 0.25 mmol), 2,6-lutidine (58.0 µL, 0.50 mmol), 2 wt % TPGS-750-M in H_2O (1.0 mL) and EtOAc (0.2 mL). The crude product was purified by pTLC (EtOAc/CH_2Cl_2 1:1) to afford **113** as a colorless oil (104.0 mg, 99%).

R$_f$ = 0.21 (hexane/EtOAc 1:2), 0.45 (EtOAc/CH_2Cl_2 3:2). Stain: UV active, $KMnO_4$;
^{1}H NMR (400 MHz, CDCl$_3$): δ 8.49 (dd, *J* = 4.8, 1.6 Hz, 1H), 8.22 (d, *J* = 6.0 Hz, 1H), 8.15–8.11 (m, 3H, overlapped signals), 7.50–7.27 (m, 6H), 7.31 (d, *J* = 8.0 Hz, 2H), 7.27 (dd, *J* = 8.0, 4.8 Hz, 1H), 4.25 (dd, *J* = 13.6, 11.2 Hz, 2H), 3.94 (t, *J* = 10.4 Hz, 2H), 2.39 (s, 3H), 1.22 (s, 3H), 1.08 (s, 3H) ppm;
^{31}P{^{1}H} NMR (162 MHz, CDCl$_3$): δ 7.93 ppm;
^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$): δ 147.1 (d, *J* = 13.9 Hz), 146.15, 146.13, 134.2, 133.2 (d, *J* = 22.1 Hz), 130.2, 129.8, 128.5, 121.7 (d, *J* = 11.8 Hz), 119.9, 103.8 (d, *J* = 211.8 Hz), 76.5 (d, *J* = 6.1 Hz), 32.6 (d, *J* = 6.3 Hz), 21.6 (d, *J* = 6.8 Hz), 21.4 ppm;
HRMS (ESI-TOF) calc'd for $C_{19}H_{22}O_5N_2PS$ $[M+H]^+$: 421.09816, found 421.09811.

Tandem processes involving C(sp^2)–P cross-coupling

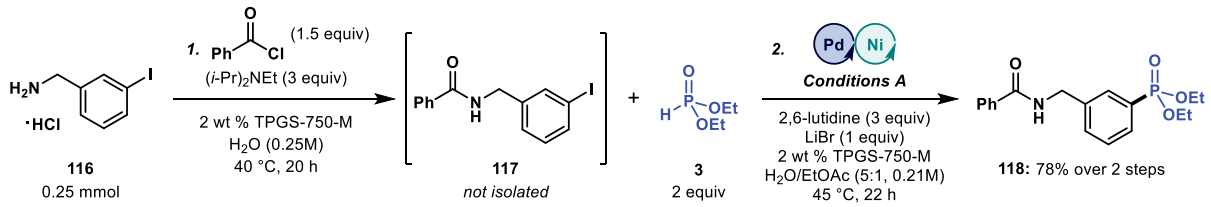
One-pot S_NAr and C(sp^2)–P cross-coupling



Step 1. A small vial was charged with 2,4,5-trichloropyrimidine (**114**, 45.9 mg, 0.25 mmol), 4-iodoaniline (54.8 mg, 0.25 mmol), $K_3PO_4 \cdot H_2O$ (58.0 mg, 0.25 mmol) and a magnetic stir bar. The vial was capped with a rubber septum and evacuated/back-filled with argon 3 times. Then 2 wt % TPGS-750-M in H_2O (0.5 mL) was added and the reaction mixture was stirred at laboratory temperature for 24 hours.

Step 2. To this reaction mixture was then added $Pd(OAc)_2$ (1.4 mg, 6.25 µmol), XantPhos (3.6 mg, 6.25 µmol), $Ni(phen)_3Cl_2$ (1.7 mg, 2.50 µmol), nano Zn (8.1 mg, 0.125 mmol), LiBr (21.7 mg, 0.25 mmol), 2,6-lutidine (58.0 µL, 0.50 mmol), diethyl *H*-phosphonate (**3**, 66.0 µL, 0.50 mmol) and degassed EtOAc (0.1 mL). The reaction mixture was heated at 45 °C under argon for 15 hours. The reaction mixture was extracted with EtOAc (3 × 2 mL) and combined organic extracts were concentrated under reduced pressure. The residue was purified by pTLC (EtOAc/CH_2Cl_2 5:4) to afford **64** as a light-yellow oil (60.0 mg, 64%) which solidified upon standing.

One-pot amide-bond formation and C(sp^2)–P cross-coupling



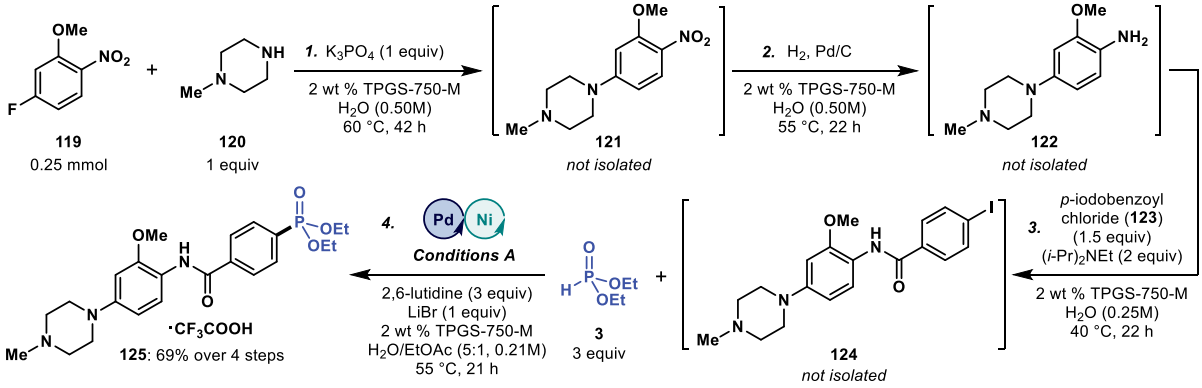
Step 1. A small vial was charged with 3-iodobenzylamine hydrochloride (67.4 mg, 0.25 mmol) and a magnetic stir bar. The vial was capped with a rubber septum and evacuated/back-filled with argon 3 times. Then 2 wt % TPGS-750-M in H_2O (1.0 mL) was added, followed $(i\text{-Pr})_2NEt$ (131.0 µL, 0.75 mmol) and benzoyl chloride (43.6 µL, 0.38 mmol) The reaction mixture was vigorously stirred at 40 °C for 20 hours under argon.

Step 2. To this reaction mixture was then added $Pd(OAc)_2$ (1.4 mg, 6.25 µmol), XantPhos (3.6 mg, 6.25 µmol), $Ni(phen)_3Cl_2$ (1.7 mg, 2.50 µmol), nano Zn (8.1 mg, 0.125 mmol), LiBr (21.7 mg, 0.25 mmol), 2,6-lutidine (58.0 µL, 0.50 mmol), diethyl *H*-phosphonate (**3**, 66.0 µL, 0.50 mmol) and degassed EtOAc (0.2 mL). The reaction mixture was heated at 45 °C for 22 hours under argon. The reaction mixture was extracted with EtOAc (3 × 2 mL), combined organic phases were washed with 1M aq. HCl (5 mL) and sat. aq. K_2CO_3 (5 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by pTLC (EtOAc) to afford **118** as a light-yellow solid (68.0 mg, 78%).

R_f = 0.39 (EtOAc). Stain: UV active, $KMnO_4$;

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82–7.77 (m, 3H), 7.71 (dd, *J* = 13.2, 7.6 Hz, 1H), 7.58 (d, *J* = 7.6 Hz, 1H), 7.53–7.41 (m, 4H), 6.68 (br s, 1H), 4.69 (d, *J* = 6.0 Hz, 2H), 4.18–4.02 (m, 4H), 1.31 (t, *J* = 6.8 Hz, 6H) ppm;
^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 18.35 ppm;
^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 167.7, 139.4 (d, *J* = 14.7 Hz), 134.2, 132.0 (d, *J* = 3.0 Hz), 131.6, 130.9 (d, *J* = 10.3 Hz), 130.5 (d, *J* = 9.6 Hz), 128.9 (d, *J* = 15.4 Hz), 128.54 (d, *J* = 186.7 Hz), 128.50, 127.2, 62.2 (d, *J* = 5.5 Hz), 43.5, 16.3 (d, *J* = 6.5 Hz) ppm;
HRMS (ESI-TOF) calc'd for $C_{18}H_{23}O_4NP$ $[M+H]^+$: 348.13592, found 348.13586.

One-pot S_NAr, NO_2 reduction, amide-bond formation and C(sp^2)–P cross-coupling



In *Steps 1-3,* modified literature procedures were followed (micellar S_NAr reaction,[23] micellar nitro reduction,[62] amine acylation[63]) and performed with no optimization, except for the S_NAr step which required increased temperature (60 °C) and reaction time (42 hours) to reach high conversion. General procedure B was followed in *Step 4*. Vigorous stirring was crucial for all reactions but, simultaneously, splashing and depositing of solids on walls were minimized to avoid diminished conversion.

Step 1. A small vial was charged with 5-fluoro-2-nitroanisole (**119**, 42.8 mg, 0.25 mmol), $K_3PO_4 \cdot H_2O$ (58.0 mg, 0.25 mmol) and a magnetic stir bar. The vial was capped with a rubber septum and evacuated/back-filled with argon 3 times. Then 1-methylpiperazine (**120**, 27.7 µL, 0.25 mmol) and 2 wt % TPGS-750-M in H_2O (0.5 mL) were added and the reaction mixture was vigorously stirred at 60 °C for 42 hours. The progress of the reaction was monitored by LC-MS analysis.

Step 2. To the reaction mixture was then added Pd/C (10 wt %, 2.7 mg, 2.5 µmol). The reaction mixture was flushed with H_2 and vigorously stirred at 55 °C for 22 hours under H_2 (two H_2 balloons). The progress of the reaction was monitored by LC-MS analysis, which revealed >95% conversion after 22 hours.

Step 3. To the reaction mixture was then added *p*-iodobenzoyl chloride (**123**, 99.9 mg, 0.375 mmol), 2 wt % TPGS-750-M in H_2O (0.5 mL) and $(i\text{-Pr})_2NEt$ (87.3 µL, 0.50 mmol). The reaction mixture was vigorously stirred at 40 °C for 22 hours. The progress of the reaction was monitored by LC-MS analysis, which revealed >90% conversion after 22 hours.

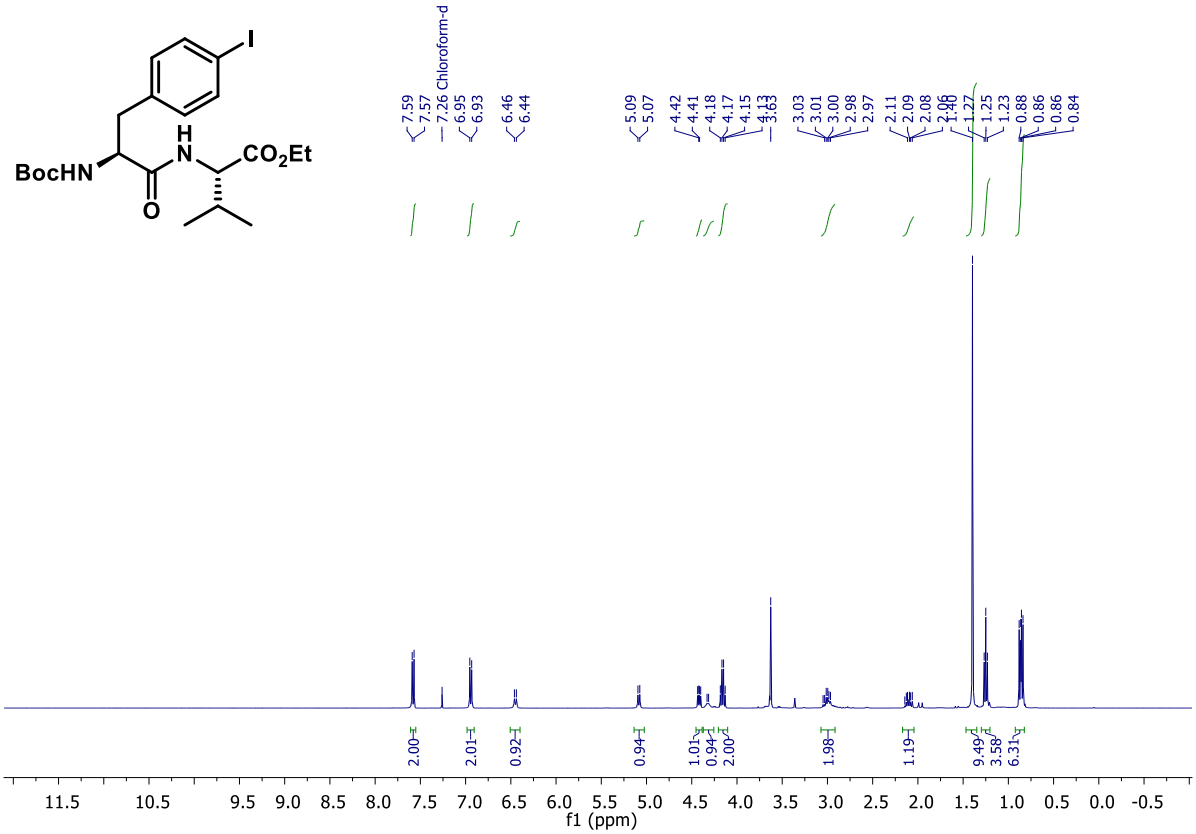
Step 4. The reaction mixture was then flushed with Ar for ~30 min. Then $Pd(OAc)_2$ (1.4 mg, 6.25 µmol), XantPhos (3.6 mg, 6.25 µmol), $Ni(phen)_3Cl_2$ (1.7 mg, 2.50 µmol), nano Zn (8.1 mg, 0.125 mmol), LiBr (21.7 mg, 0.25 mmol), 2,6-lutidine (87.0 µL, 0.75 mmol), diethyl *H*-phosphonate (**3**, 99.0 µL, 0.75 mmol) and degassed EtOAc (0.2 mL) were added. The reaction mixture was heated at 55 °C under

Ar for 21 hours and the reaction progress was monitored by LC-MS analysis. Upon completion, the reaction mixture was then extracted with EtOAc (6 × 2 mL), combined organic extracts were washed with sat. aq. $NaHCO_3$ (10 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by pTLC (7.5% MeOH in CH_2Cl_2) to afford **125** as a bright-yellow oil (107.0 mg) containing impurities. Crude **125** was purified by preparative reverse-phase C8 HPLC (gradient H_2O + 0.1% TFA → CH_3CN over 20 min) to afford **125·TFA** as a bright-yellow solid (99.5 mg, 69%).

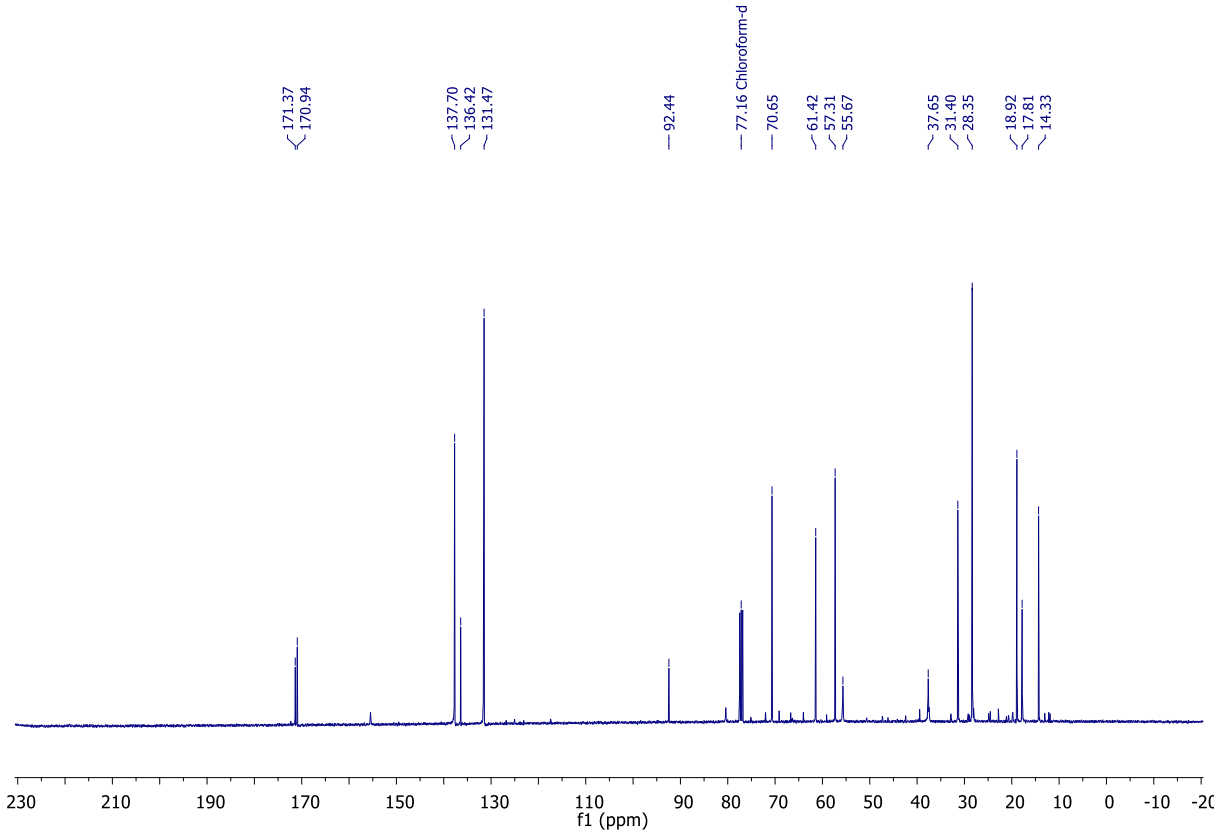
R_f (free base) = 0.51 (10% MeOH in CH_2Cl_2). Stain: UV active, anisaldehyde (pale-yellow spot);
^{1}H NMR (TFA salt, 400 MHz, CD_3OD): δ 8.06 (dd, *J* = 8.0, 4.0 Hz, 2H), 7.95–7.90 (m, 2H), 7.78 (d, *J* = 8.8 Hz, 1H), 6.76 (d, *J* = 2.4 Hz, 1H), 6.64 (dd, *J* = 8.8, 2.8 Hz, 1H), 4.21–4.12 (m, 4H), 3.91 (s, 3H, overlapped), 3.87 (br s, 2H, overlapped), 3.63 (d, *J* = 12.8 Hz, 2H, broad), 3.30–3.26 (m, 2H, overlapped), 3.08 (t, *J* = 12.4 Hz, 2H, broad), 2.99 (s, 3H), 1.31 (t, *J* = 6.8 Hz, 6H) ppm;
^{31}P{^{1}H} NMR (TFA salt, 162 MHz, CD_3OD): δ 17.58 ppm;
^{19}F NMR (TFA salt, 376 MHz, CD_3OD): δ -77.28 ppm;
^{13}C{^{1}H} NMR (TFA salt, 100 MHz, CD_3OD): δ 167.3, 154.0, 150.0, 140.1 (d, *J* = 3.3 Hz), 133.0 (d, *J* = 10.2 Hz), 132.3 (d, *J* = 188.2 Hz), 125.9, 121.5, 109.3, 102.2, 64.1 (d, *J* = 5.8 Hz), 56.4, 54.7, 48.3, 43.6, 16.6 (d, *J* = 6.2 Hz) ppm;
HRMS (ESI-TOF) calc'd for $C_{23}H_{33}O_5N_3P$ $[M–TFA+H]^+$: 462.21523, found 462.21517.

NMR data

Compound SI-5

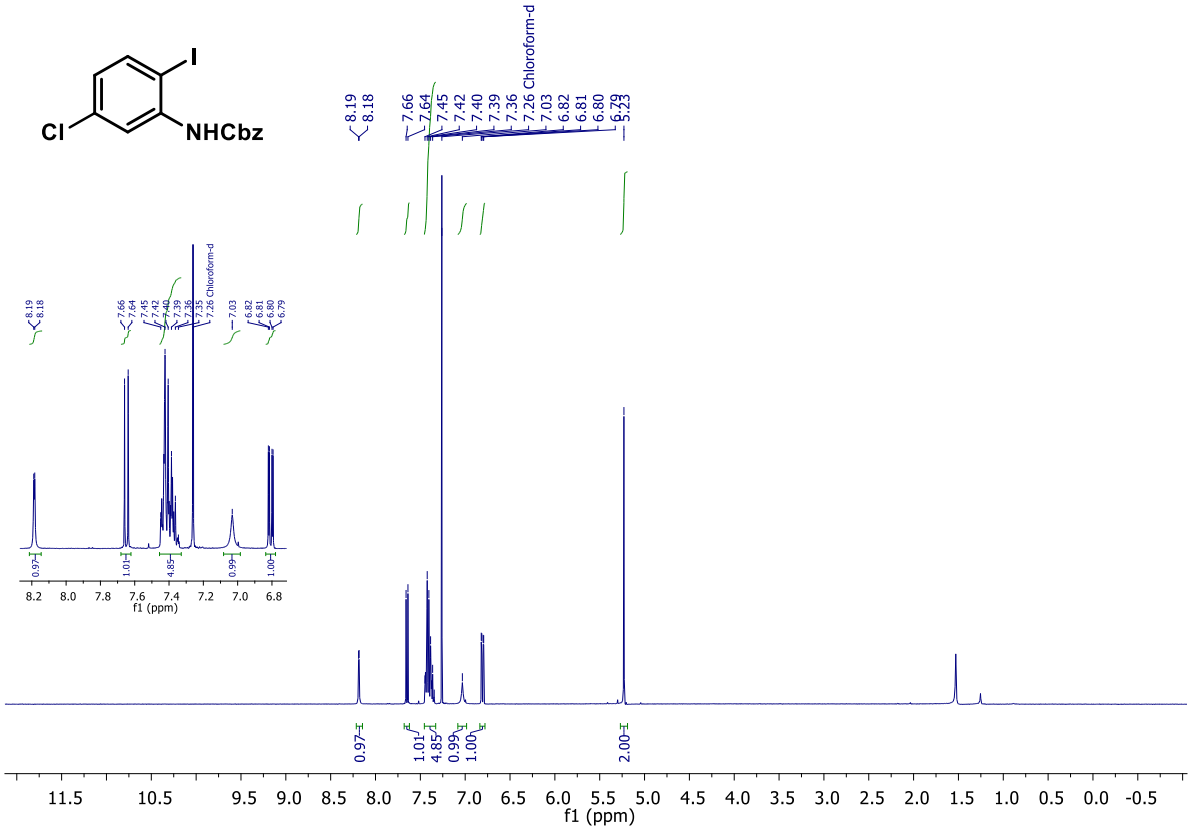


^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **SI-5**. The signal at δ = 3.63 ppm corresponds to TPGS-750-M impurity.

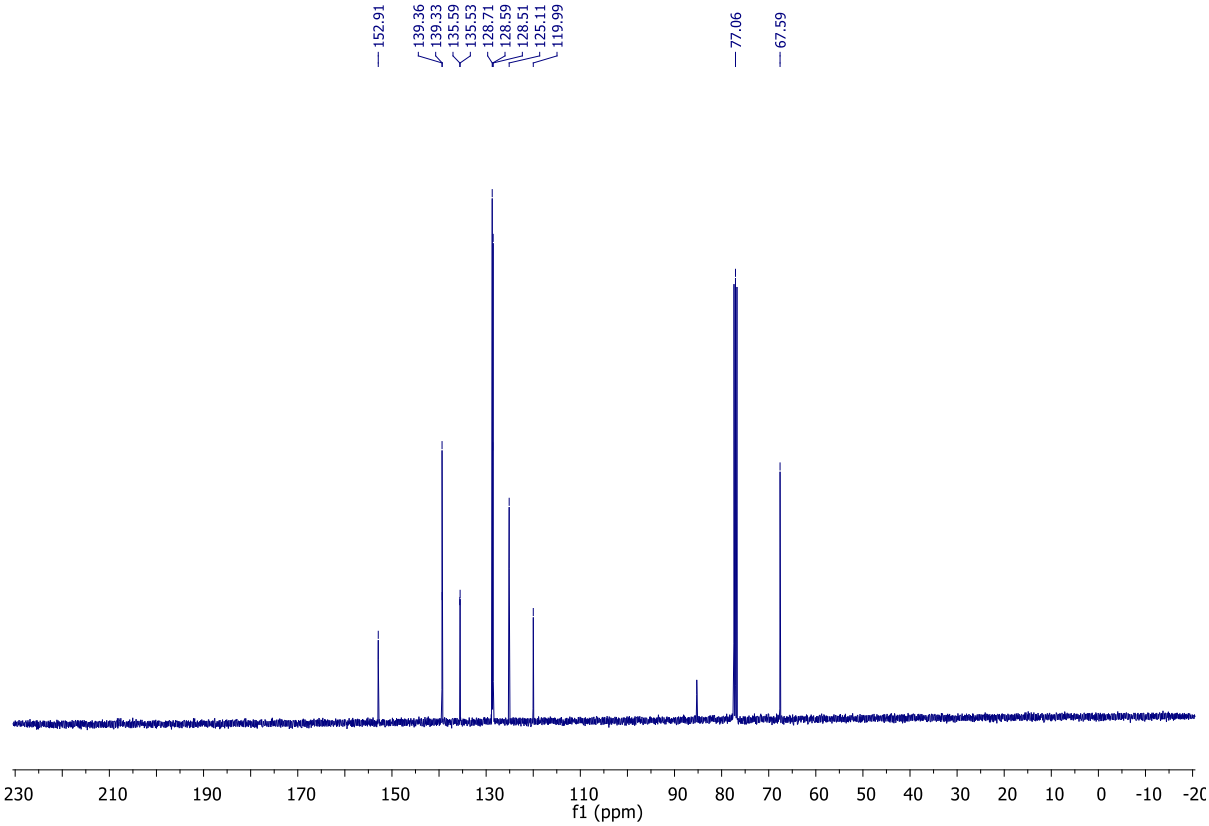


^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) spectrum of **SI-5**. Low-intensity signals correspond to TPGS-750-M impurity.

Compound SI-12

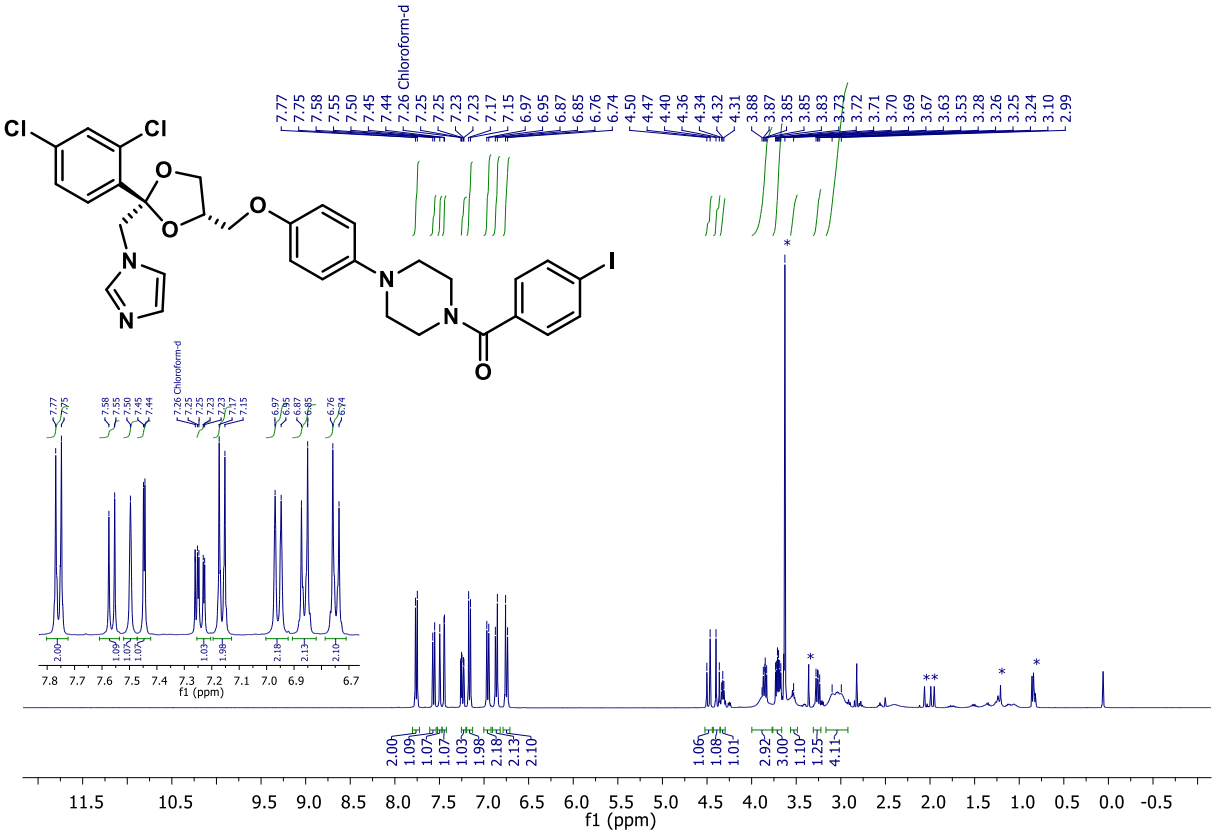


^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **SI-12**.

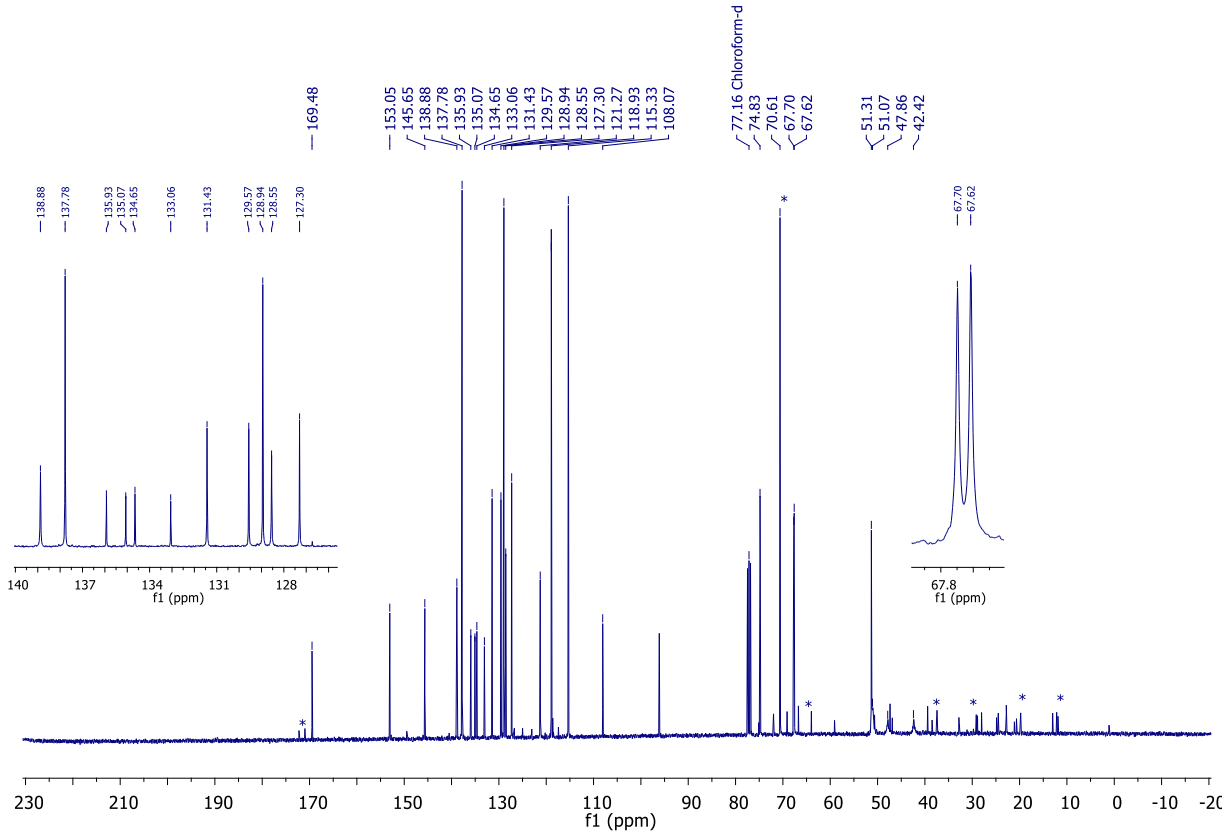


^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) spectrum of **SI-12**.

Compound SI-26

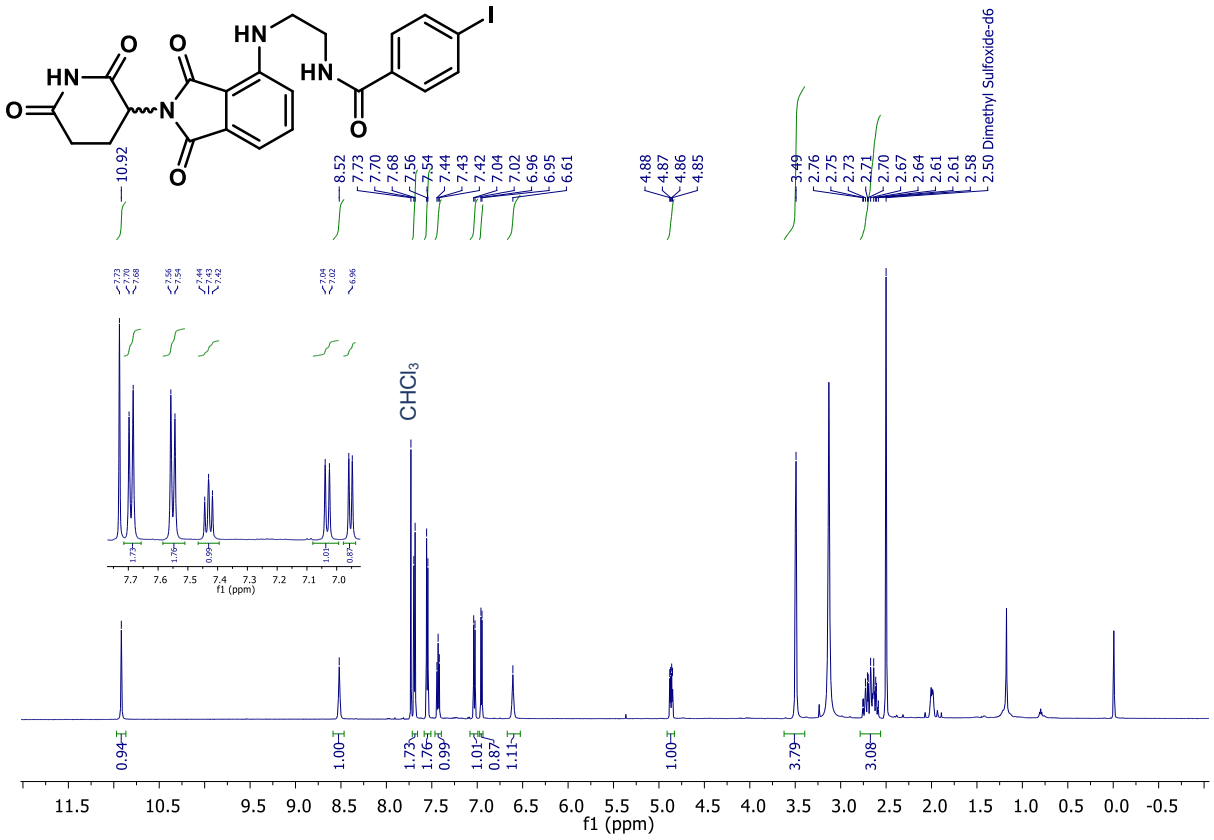


^{1}H NMR (400 MHz, CDCl$_3$) spectrum of **SI-26**. Asterisks denote TPGS-750-M impurity.

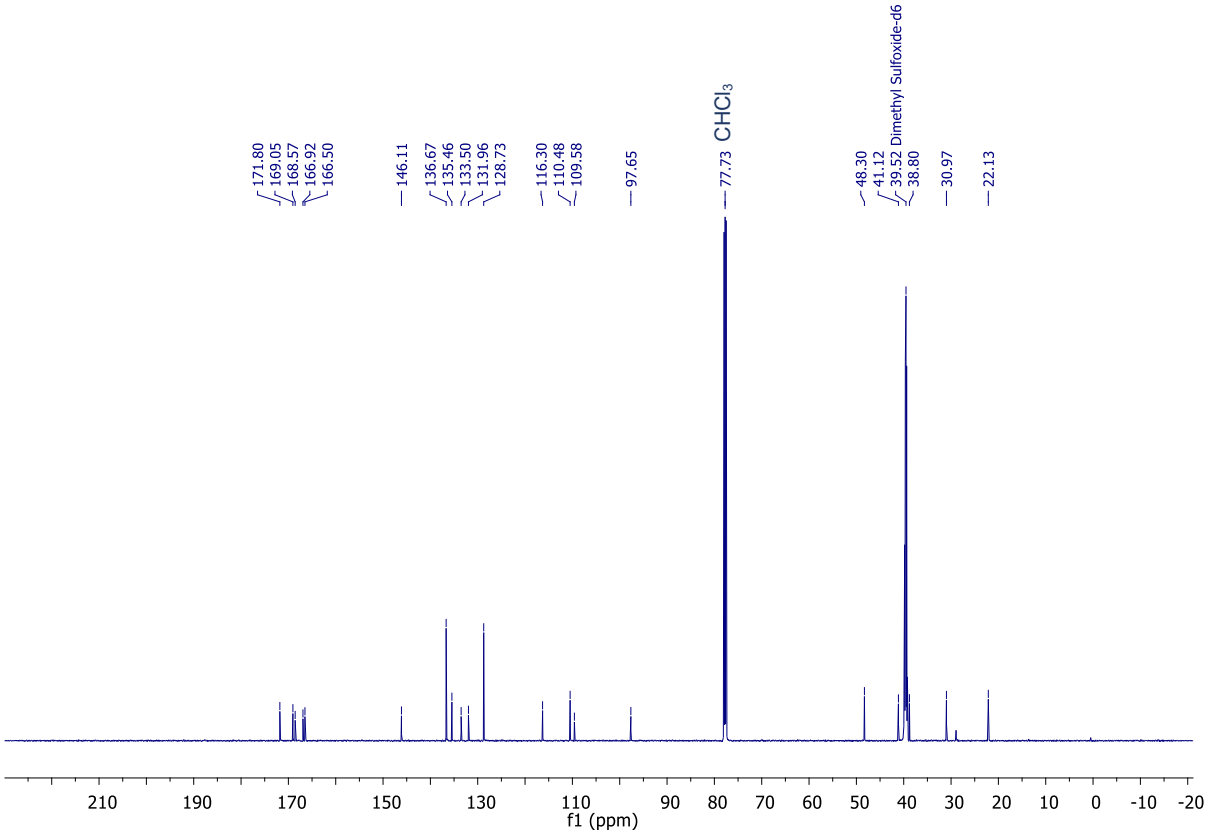


^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$) spectrum of **SI-26**. Asterisks denote TPGS-750-M impurity.

Compound SI-29

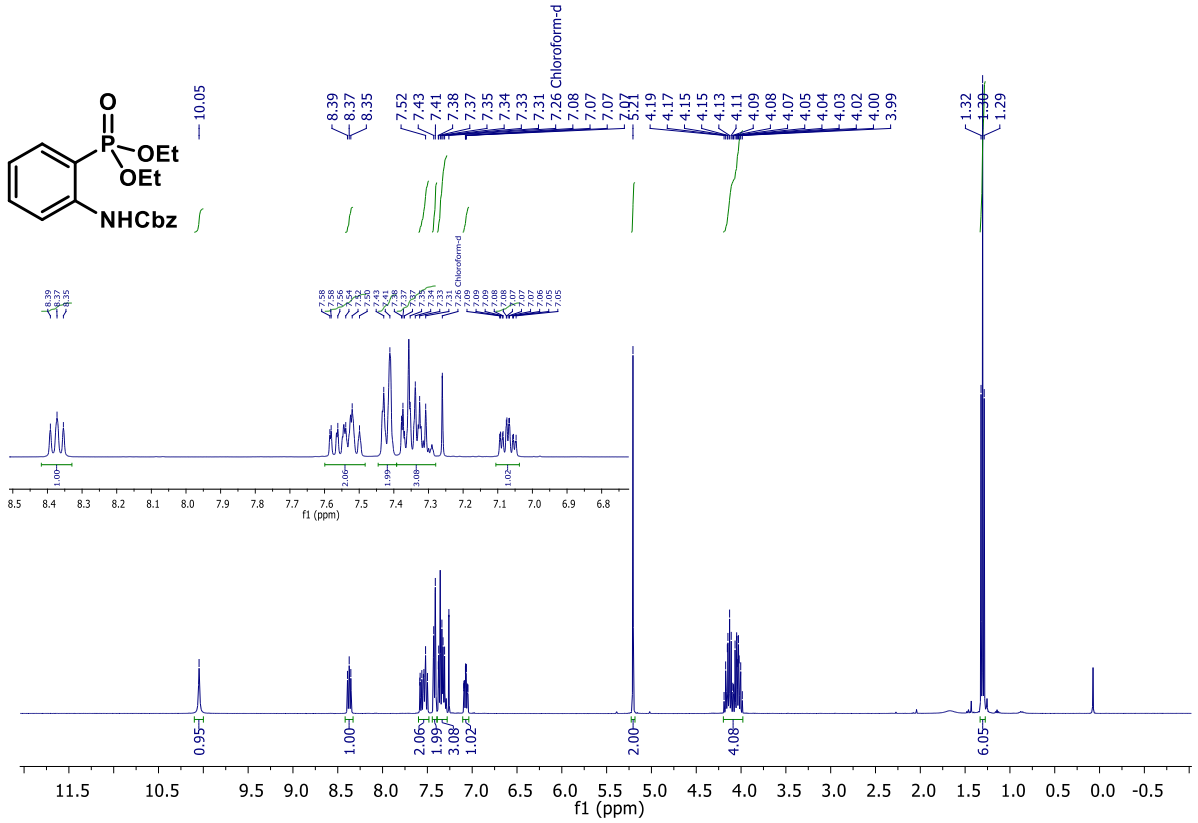


^{1}H NMR (600 MHz, CDCl$_3$/DMSO-*d*$_6$ ~5:1) spectrum of **SI-29**.

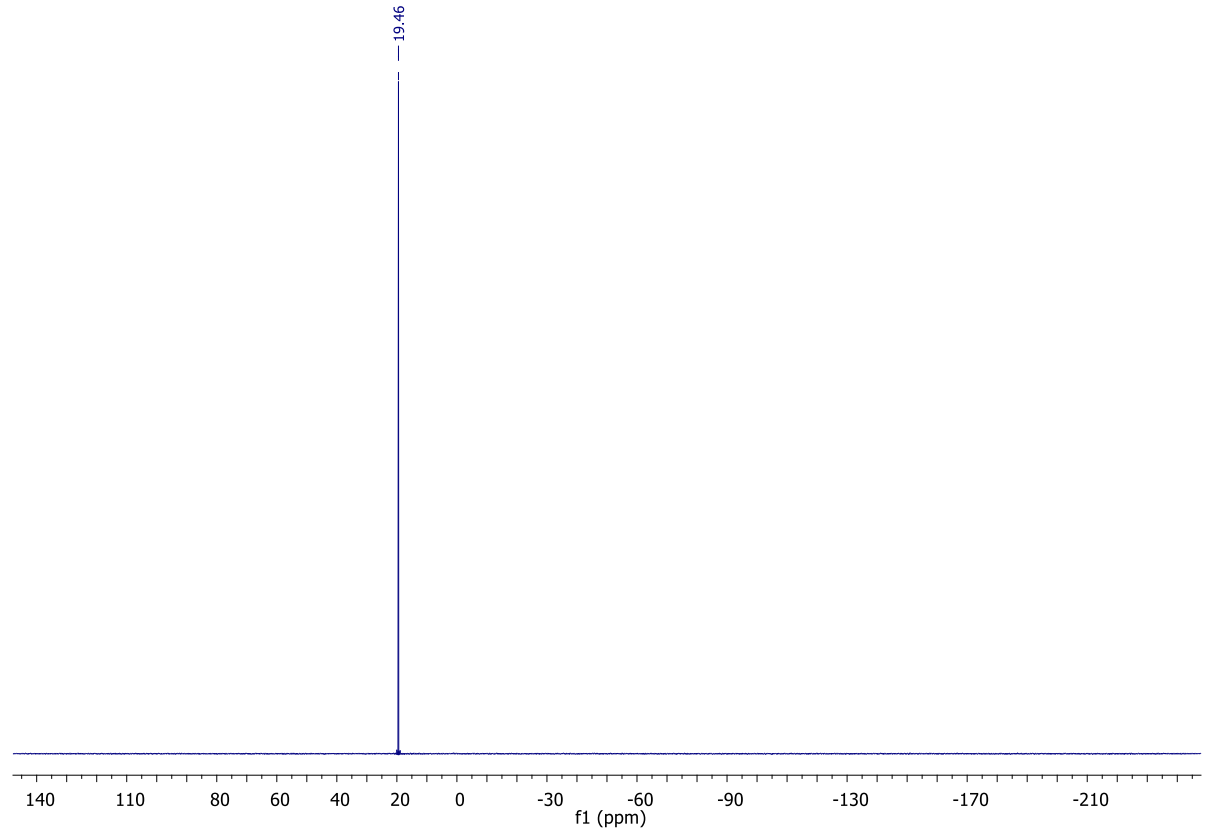


^{13}C{^{1}H} NMR (151 MHz, CDCl$_3$/DMSO-*d*$_6$ ~5:1) spectrum of **SI-29**.

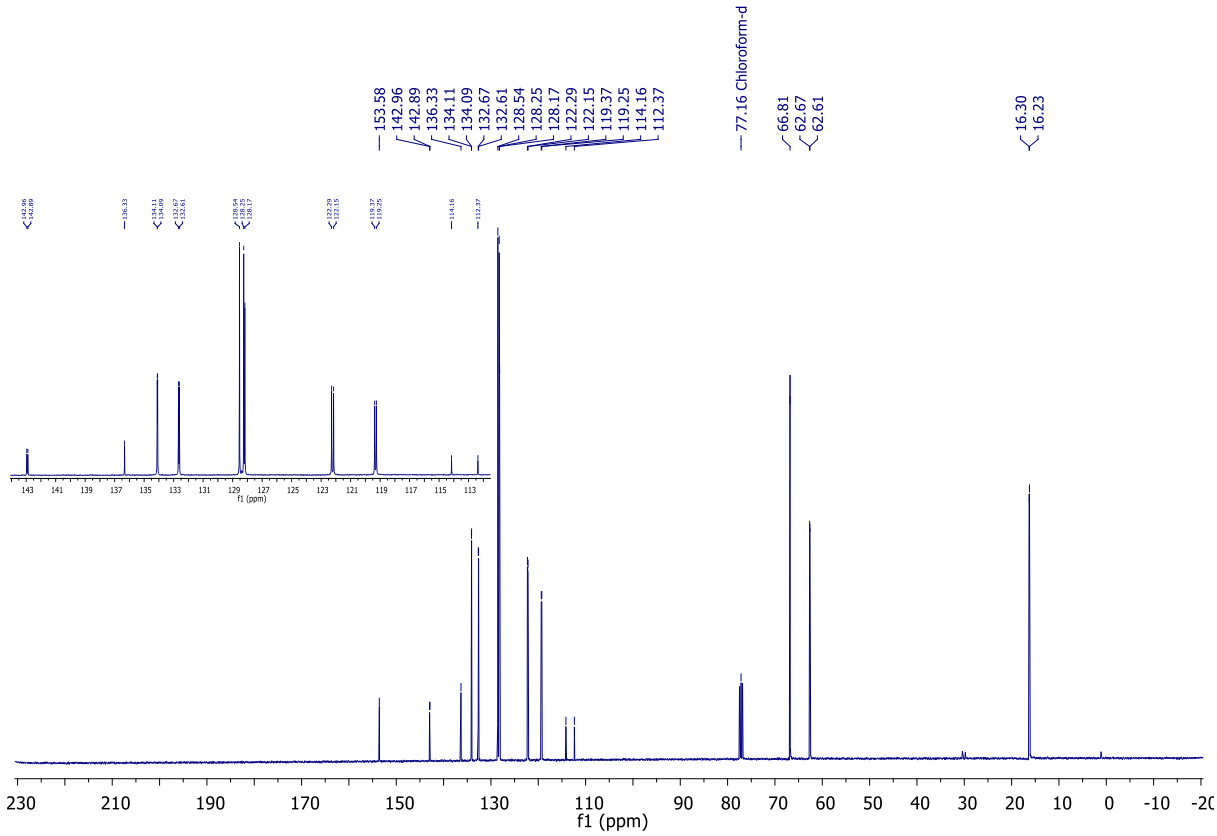
Compound 7



^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **7**.

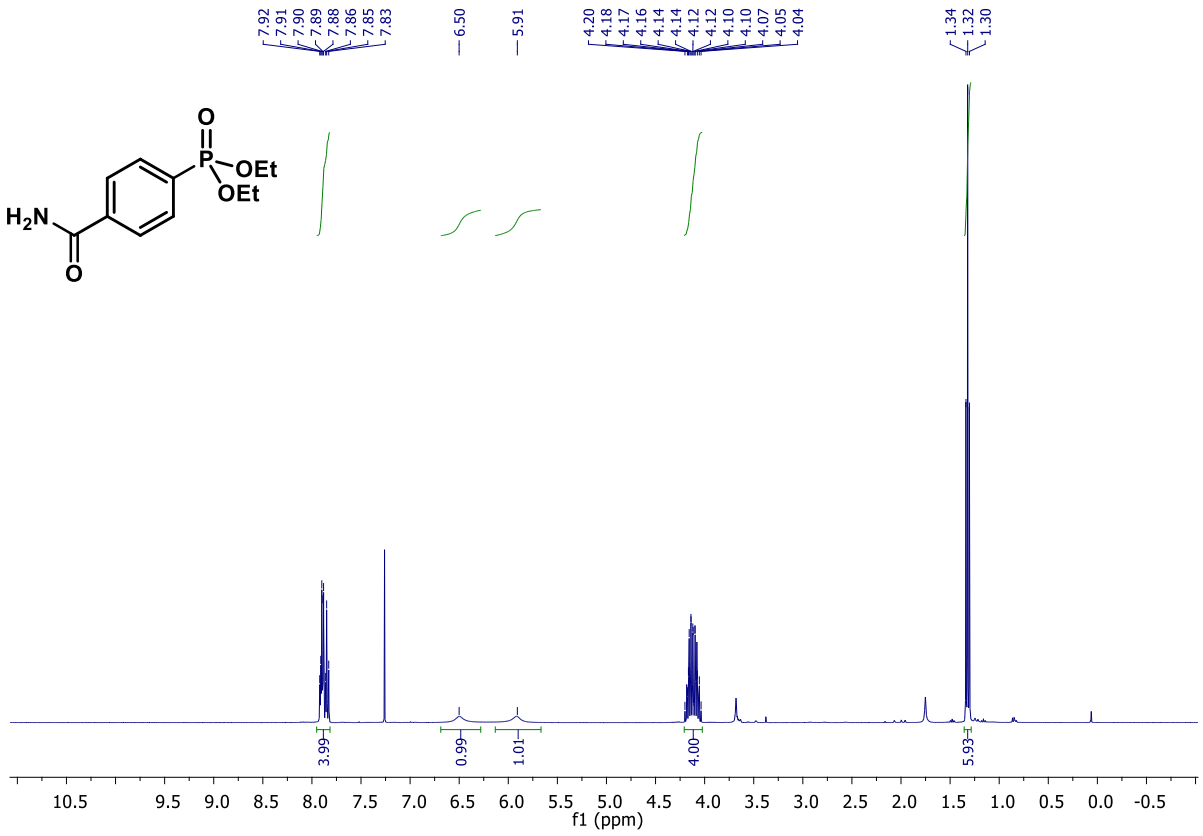


^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$) spectrum of **7**.

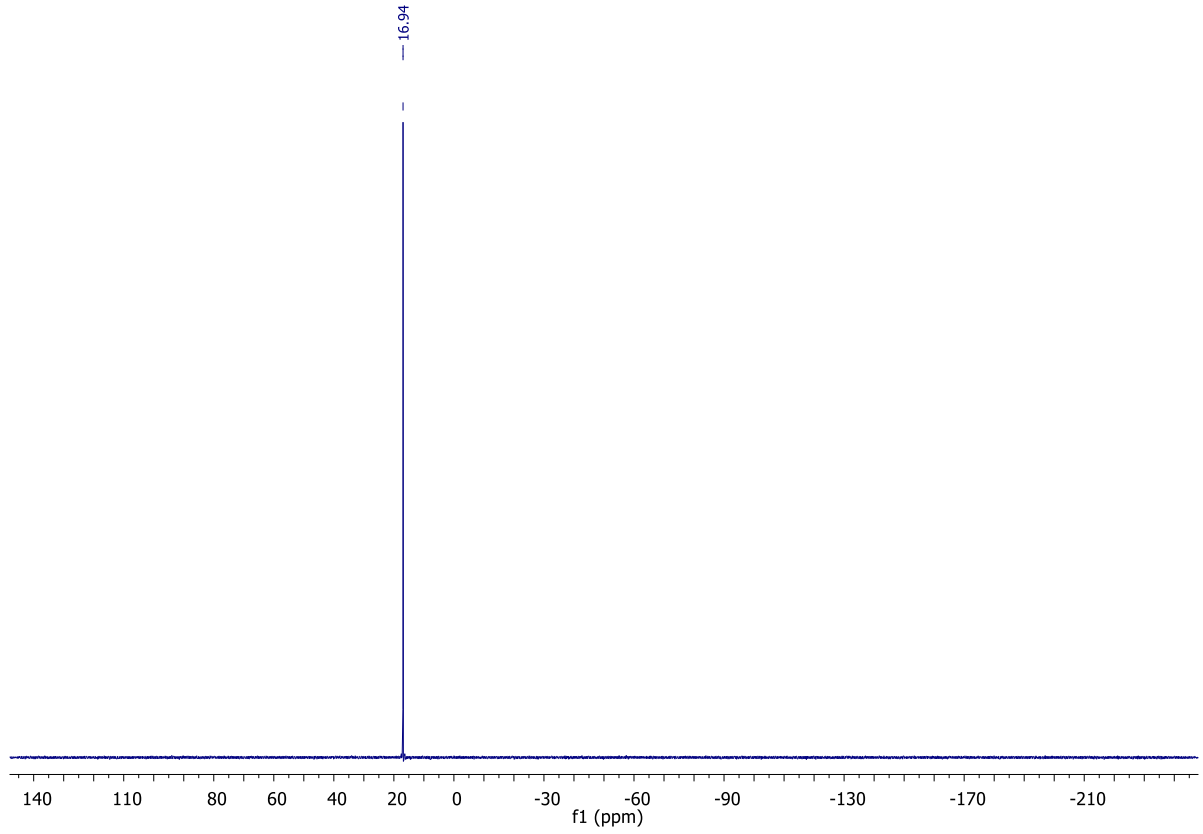


$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) spectrum of **7**.

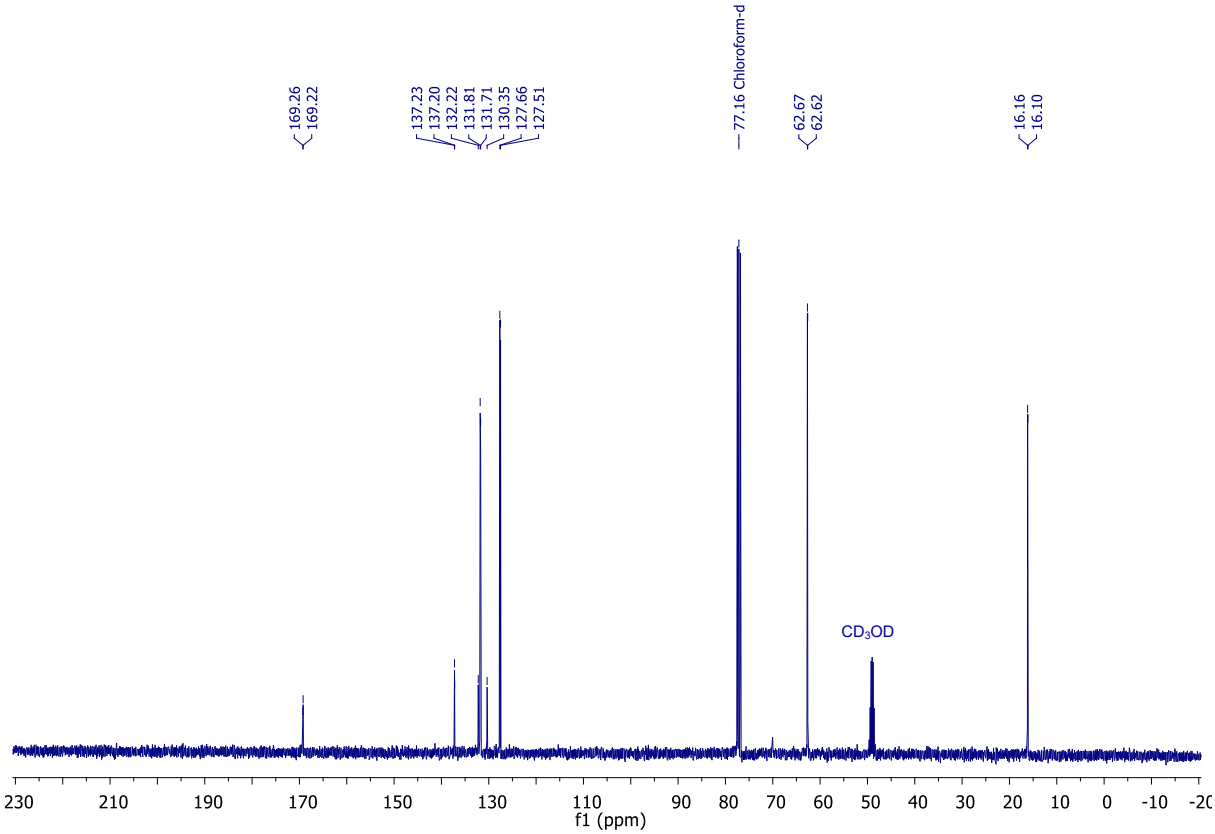
Compound 18



^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **18**.

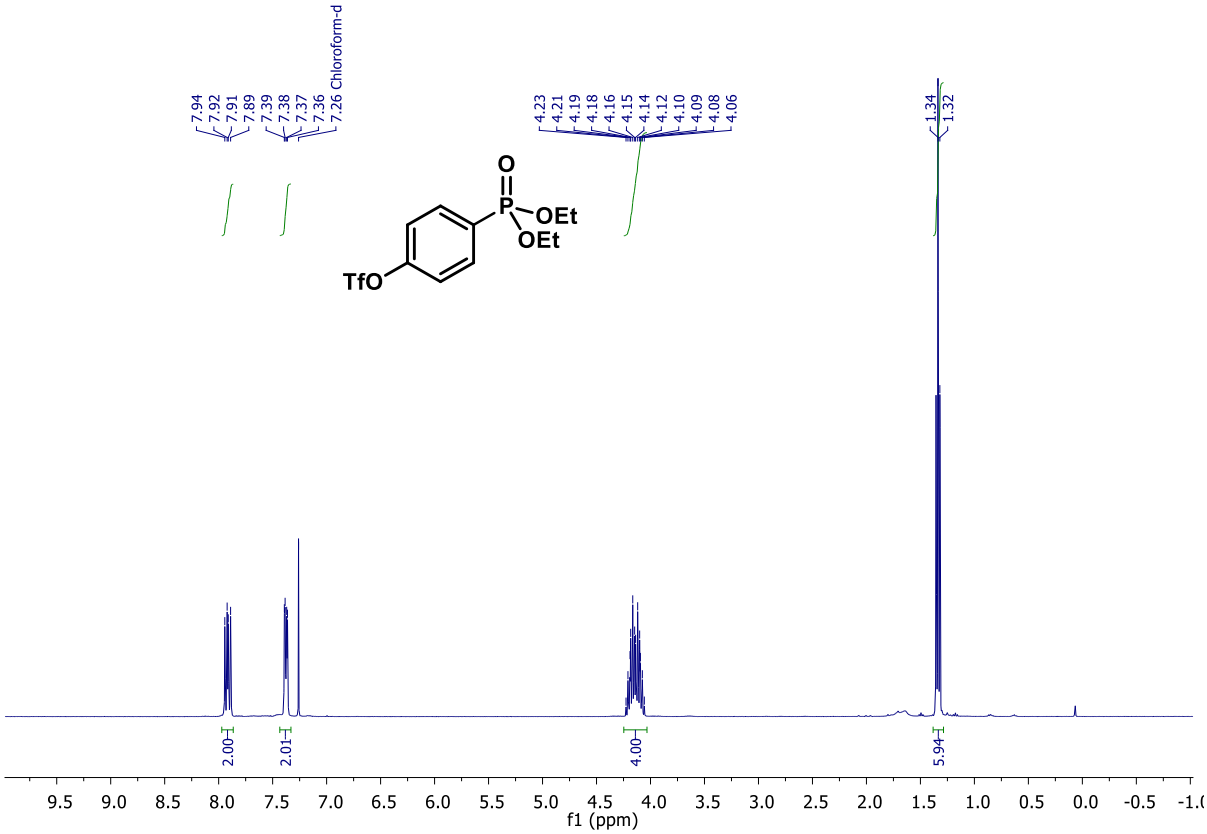


^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$) spectrum of **18**.

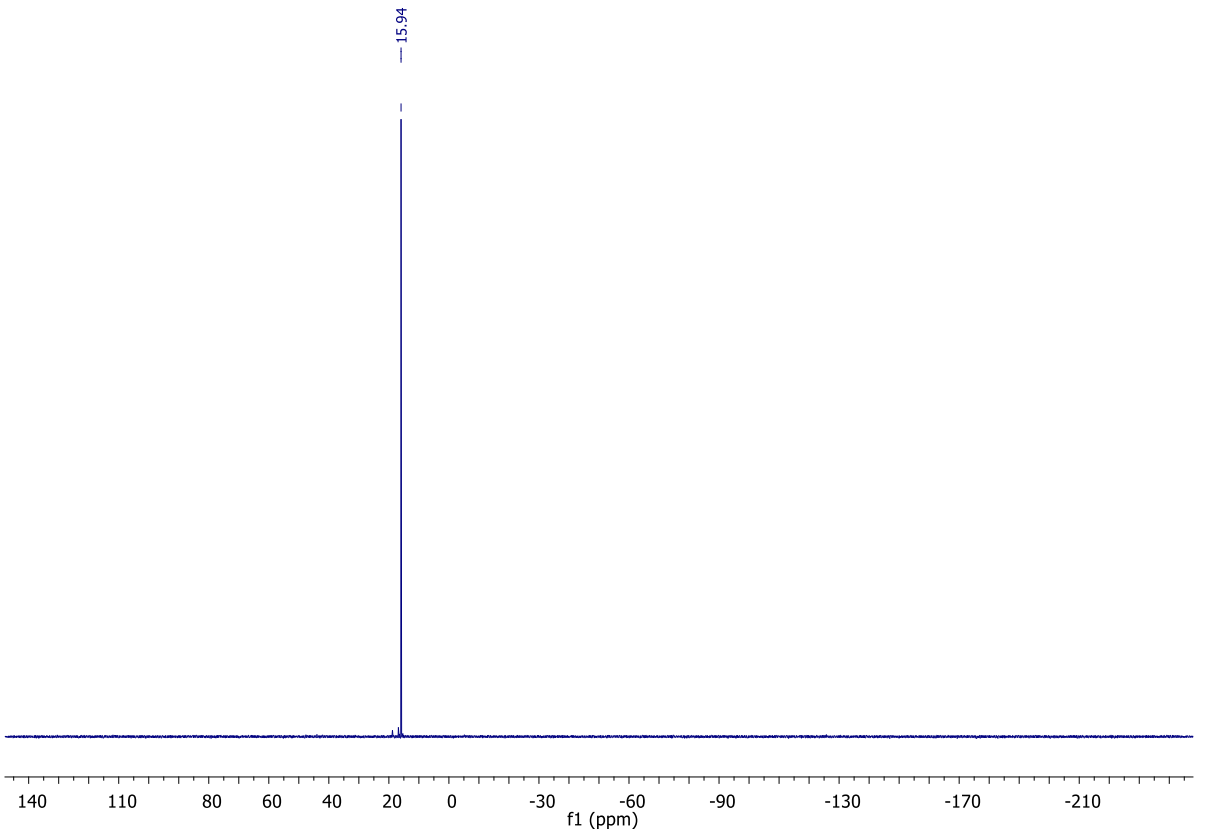


$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) spectrum of **18**.

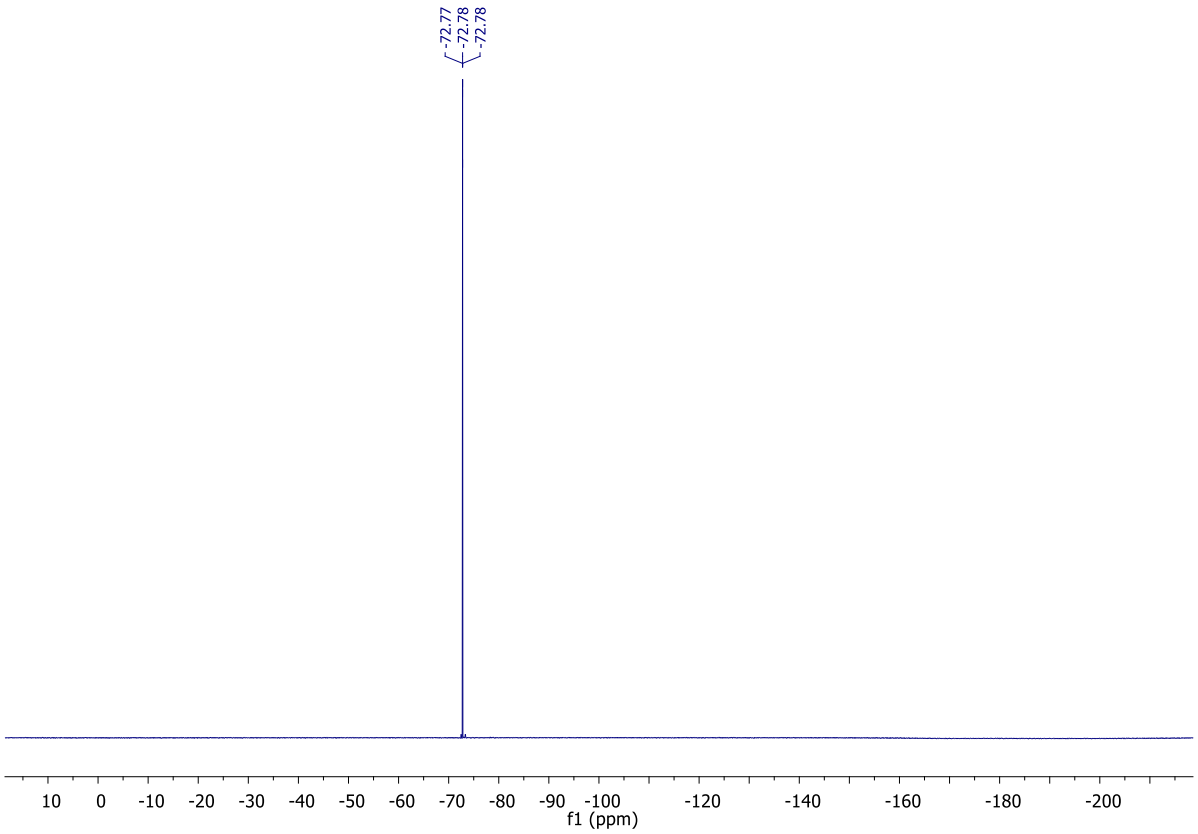
Compound 24



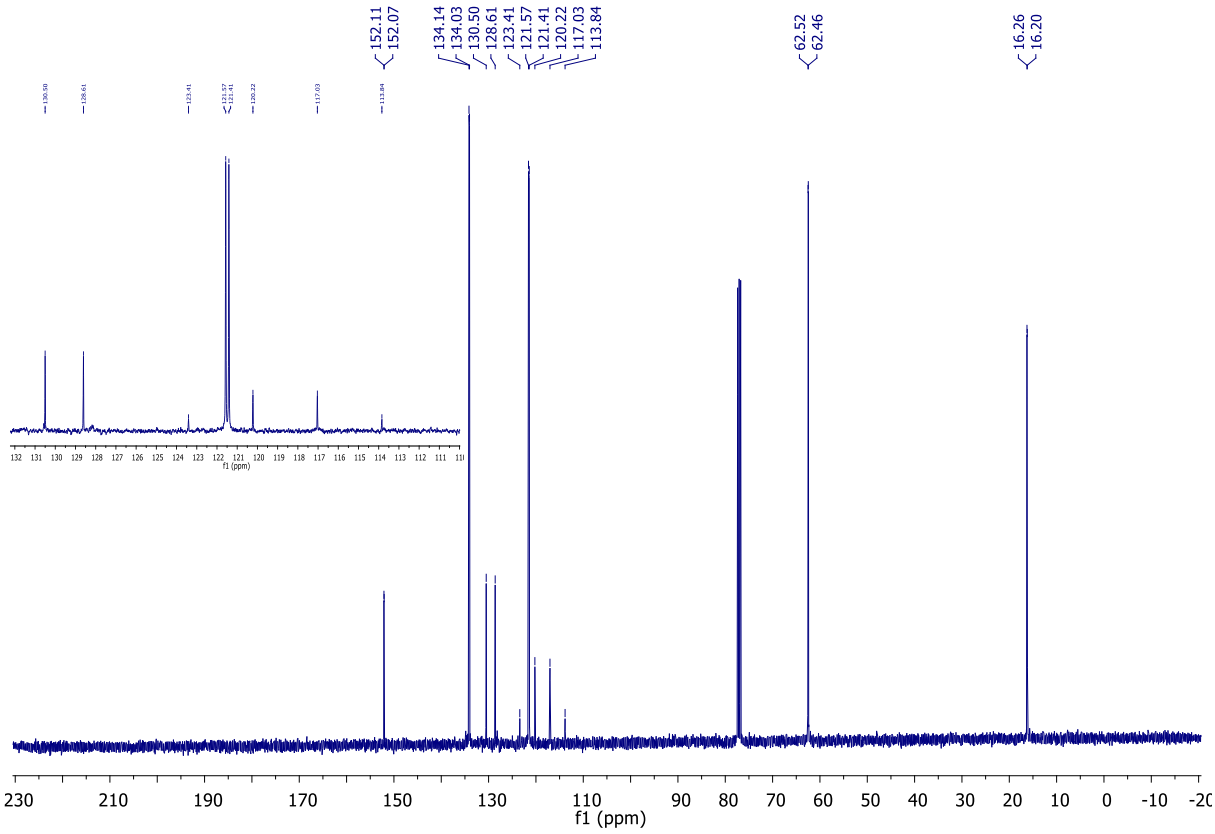
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **24**.



^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$) spectrum of **24**.

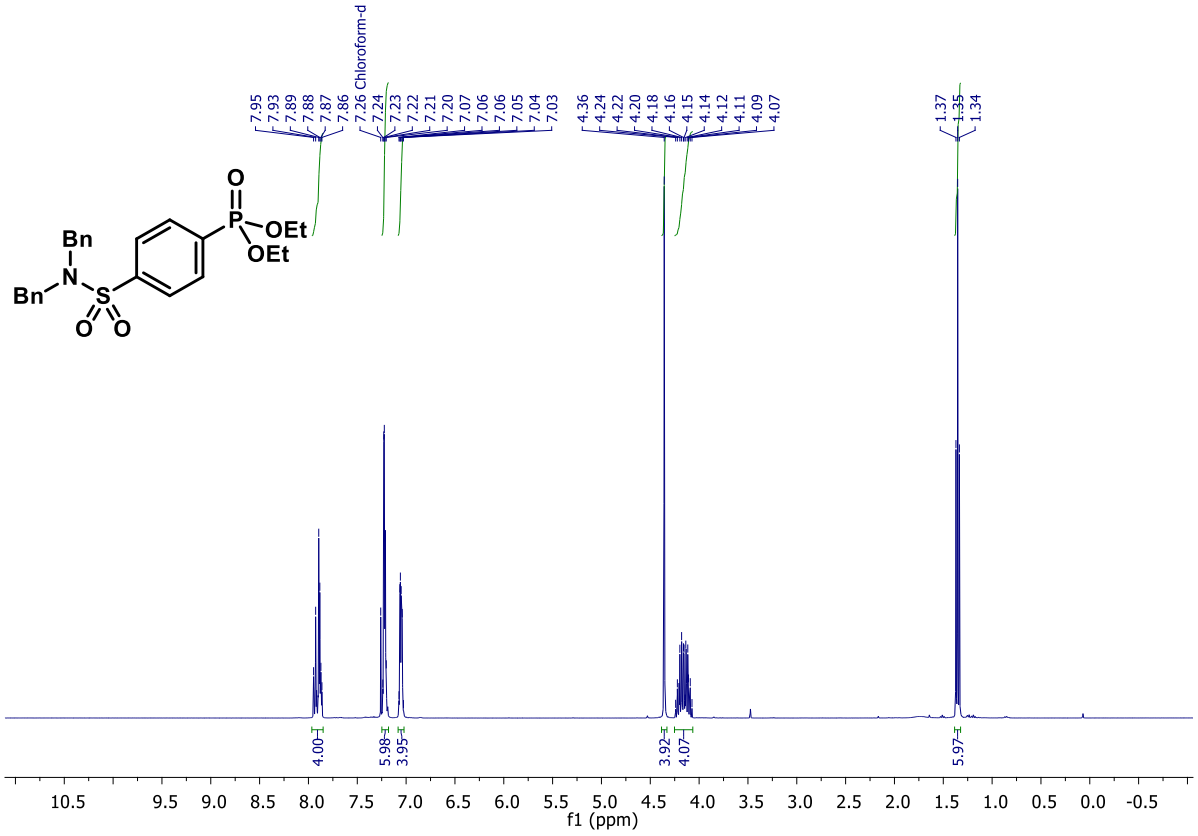


^{19}F NMR (376 MHz, $CDCl_3$) spectrum of **24**.

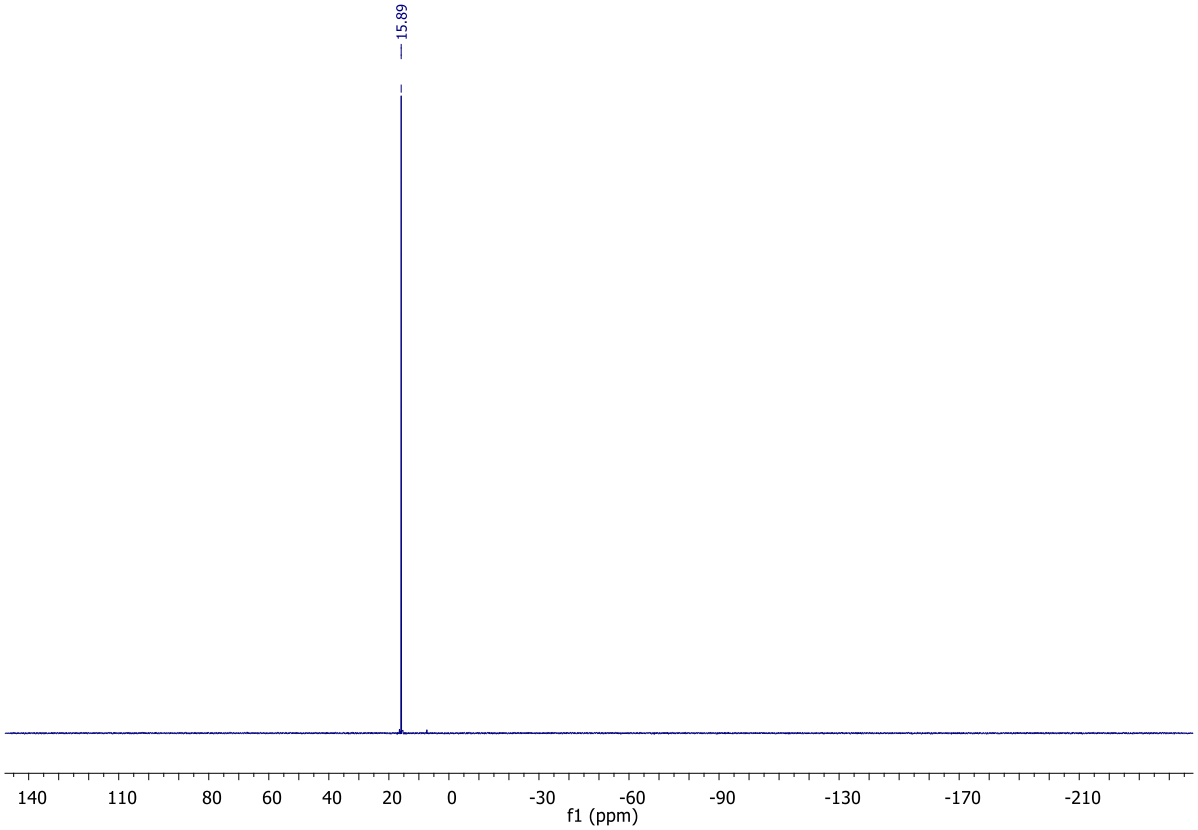


^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) spectrum of **24**.

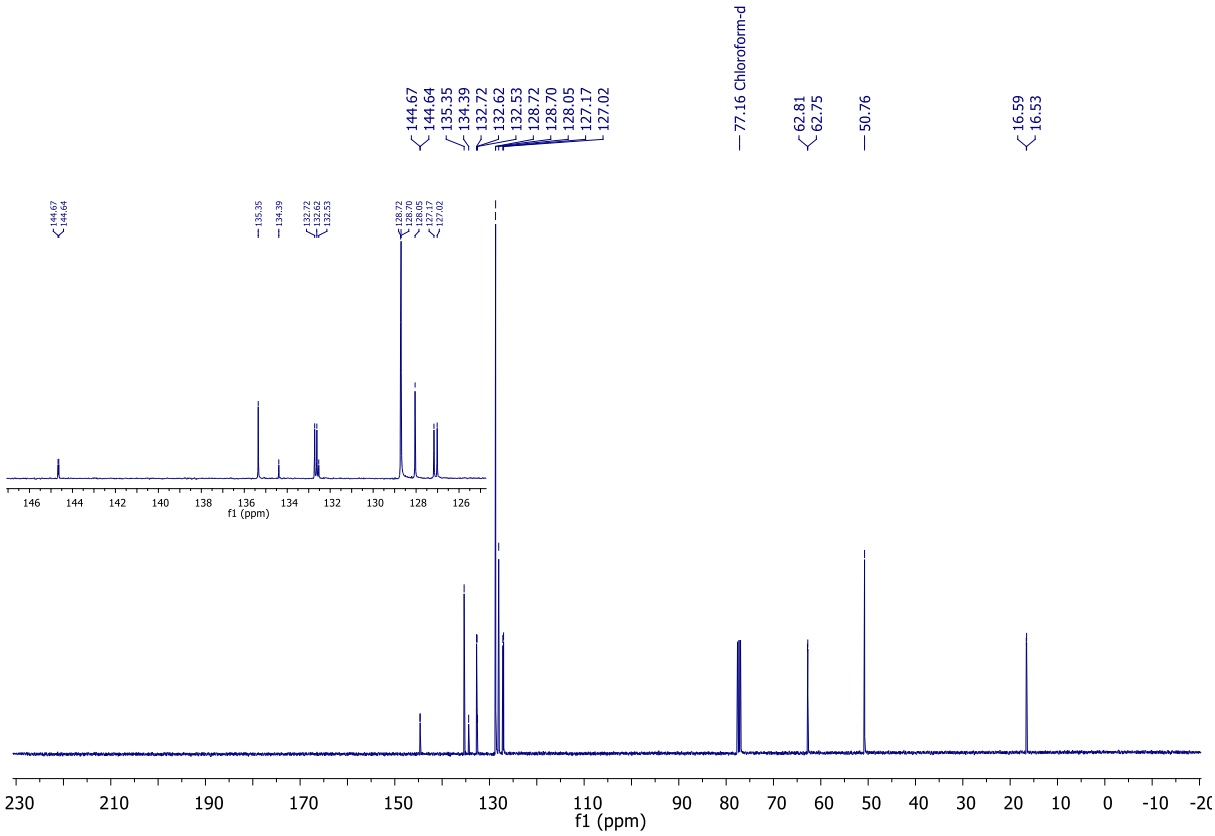
Compound 27



^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **27**.

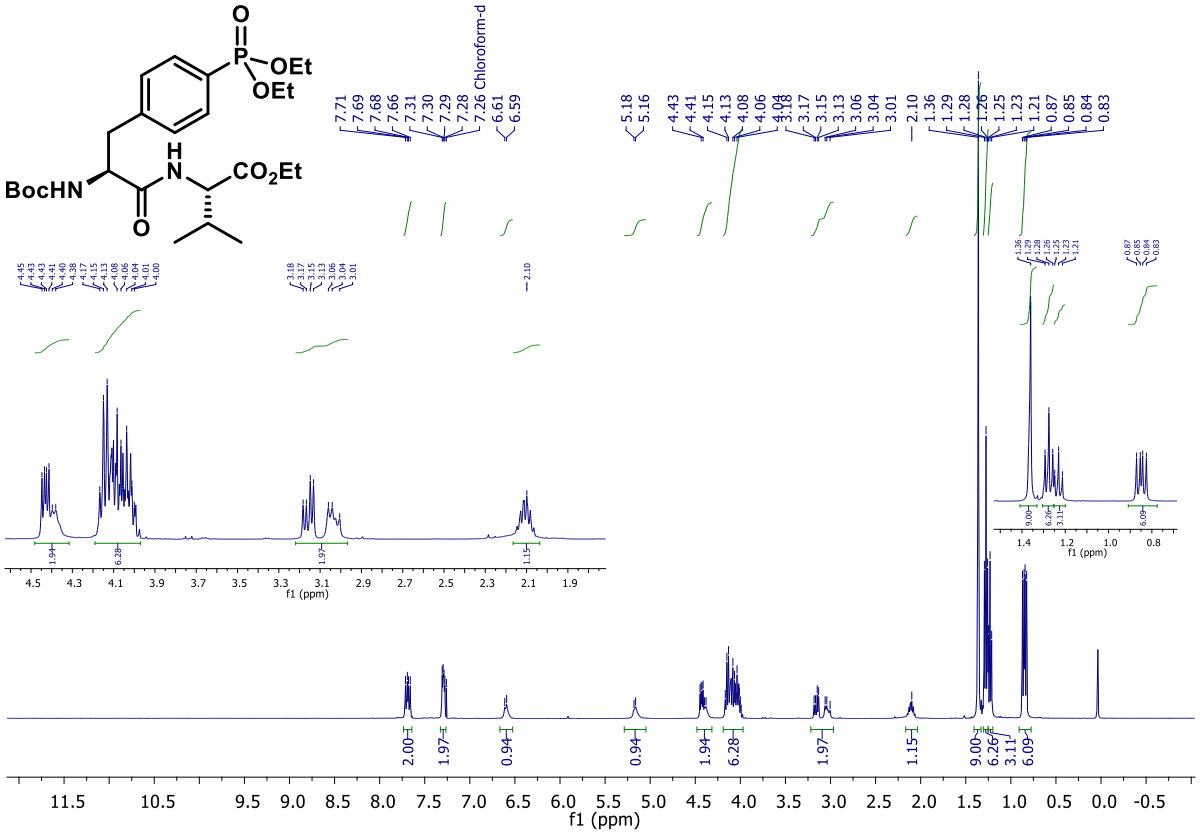


^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$) spectrum of **27**.

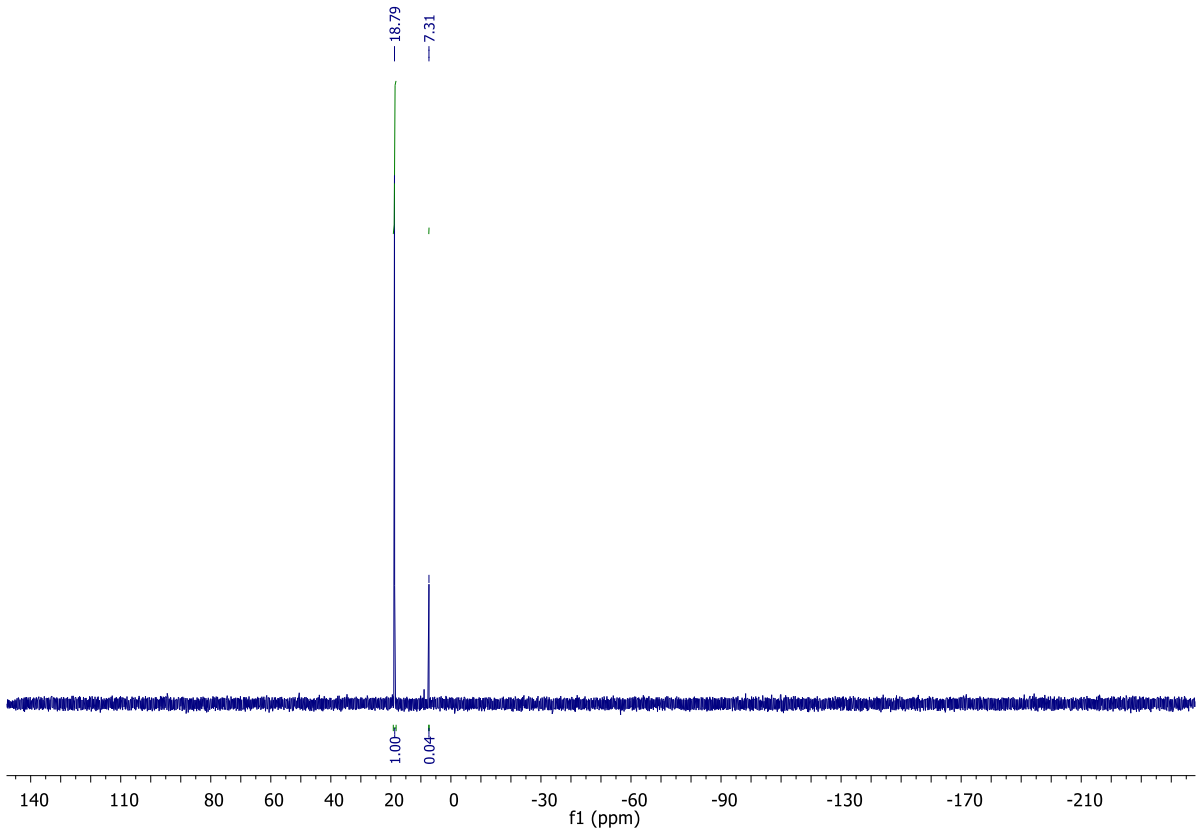


$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) spectrum of **27**.

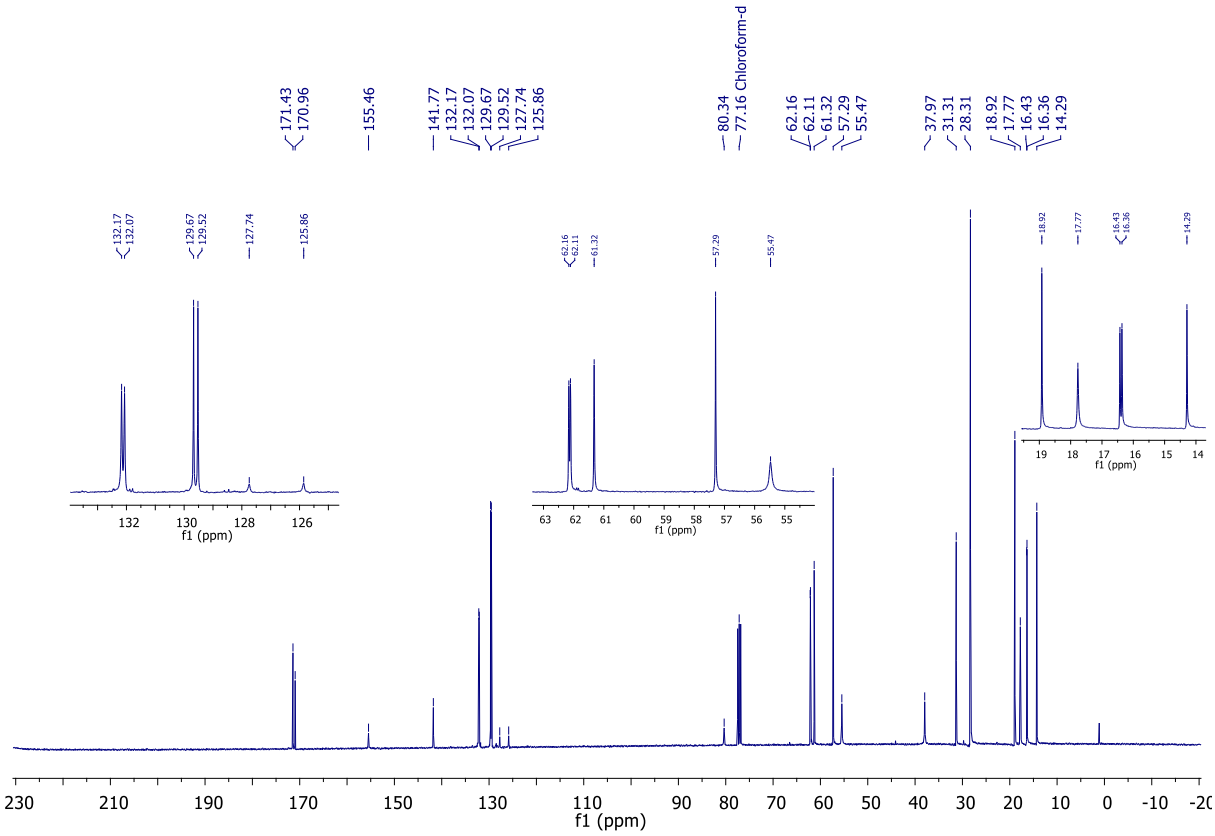
Compound 29



^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **29**.

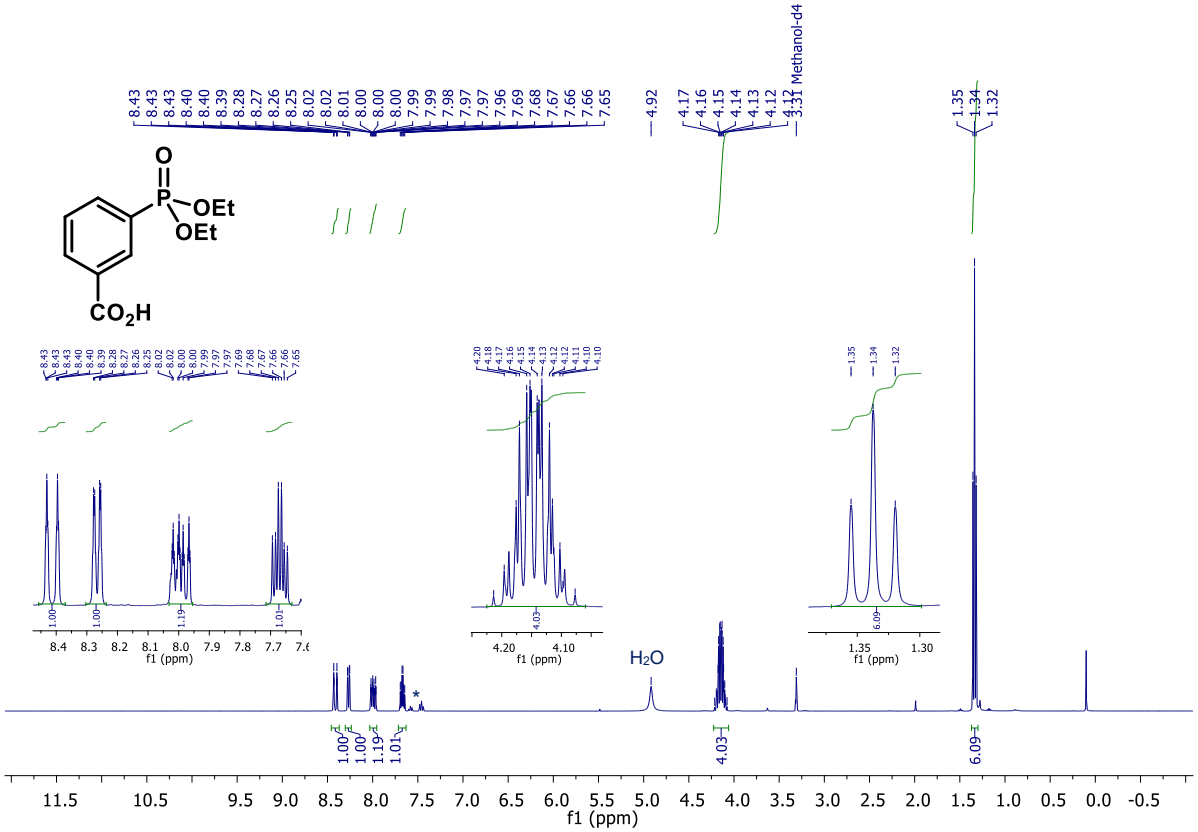


^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$) spectrum of **29**. The signal at 7.31 ppm corresponds to ca. 4% of *H*-phosphonate impurity.

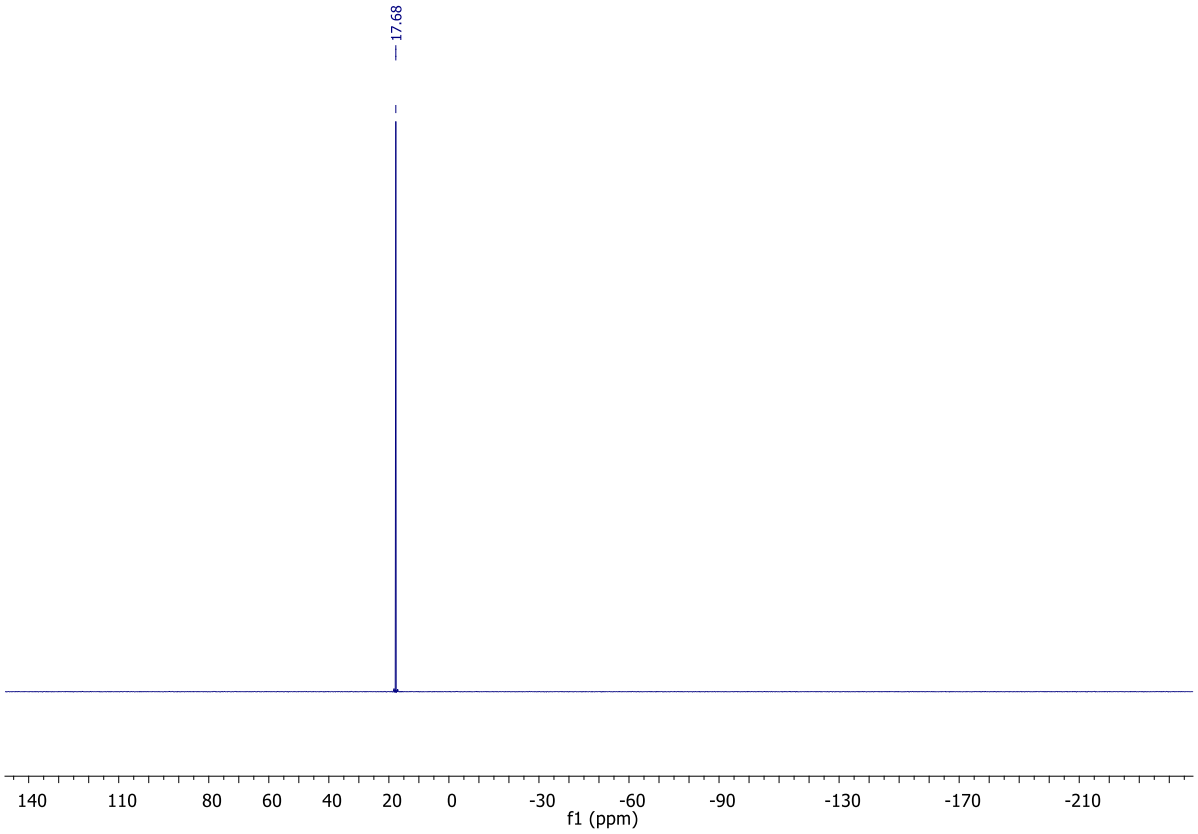


$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) spectrum of **29**.

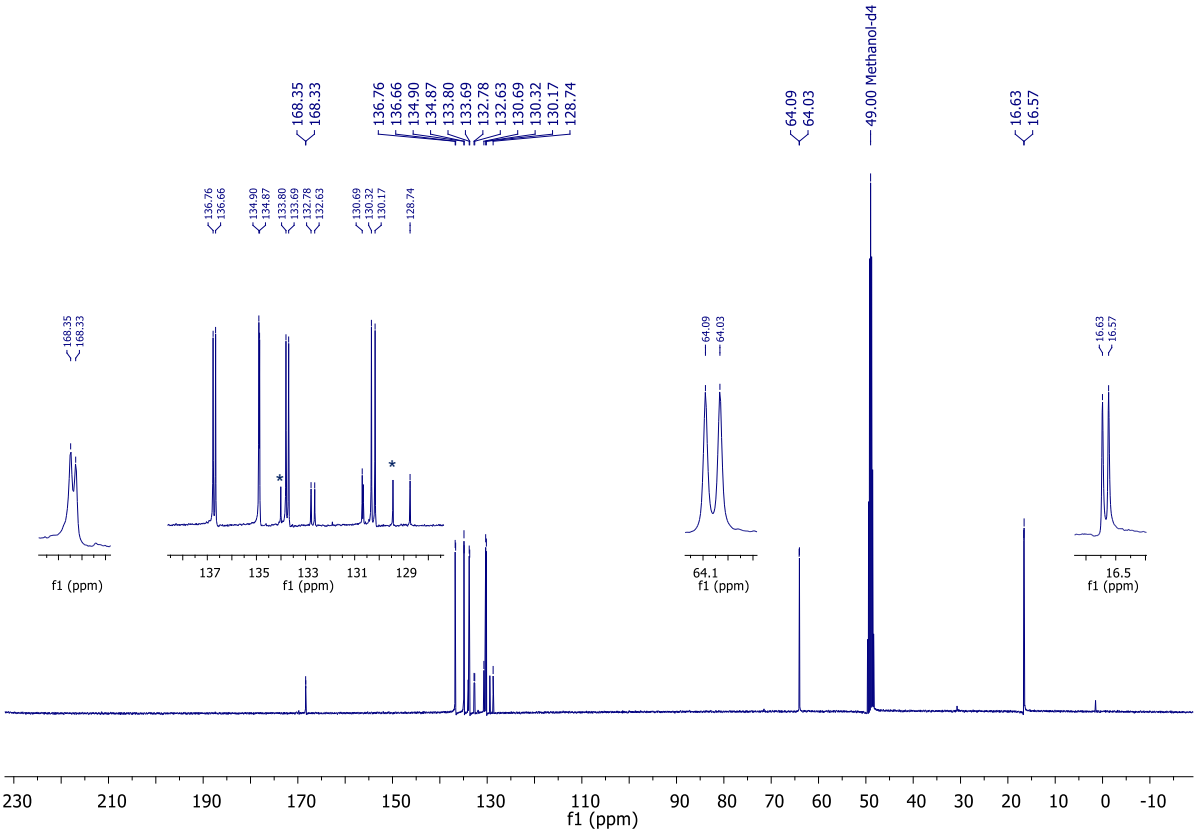
Compound 30



^{1}H NMR (400 MHz, CD_3OD) spectrum of **30**. Asterisk denotes signal of polar impurity which was difficult to remove.

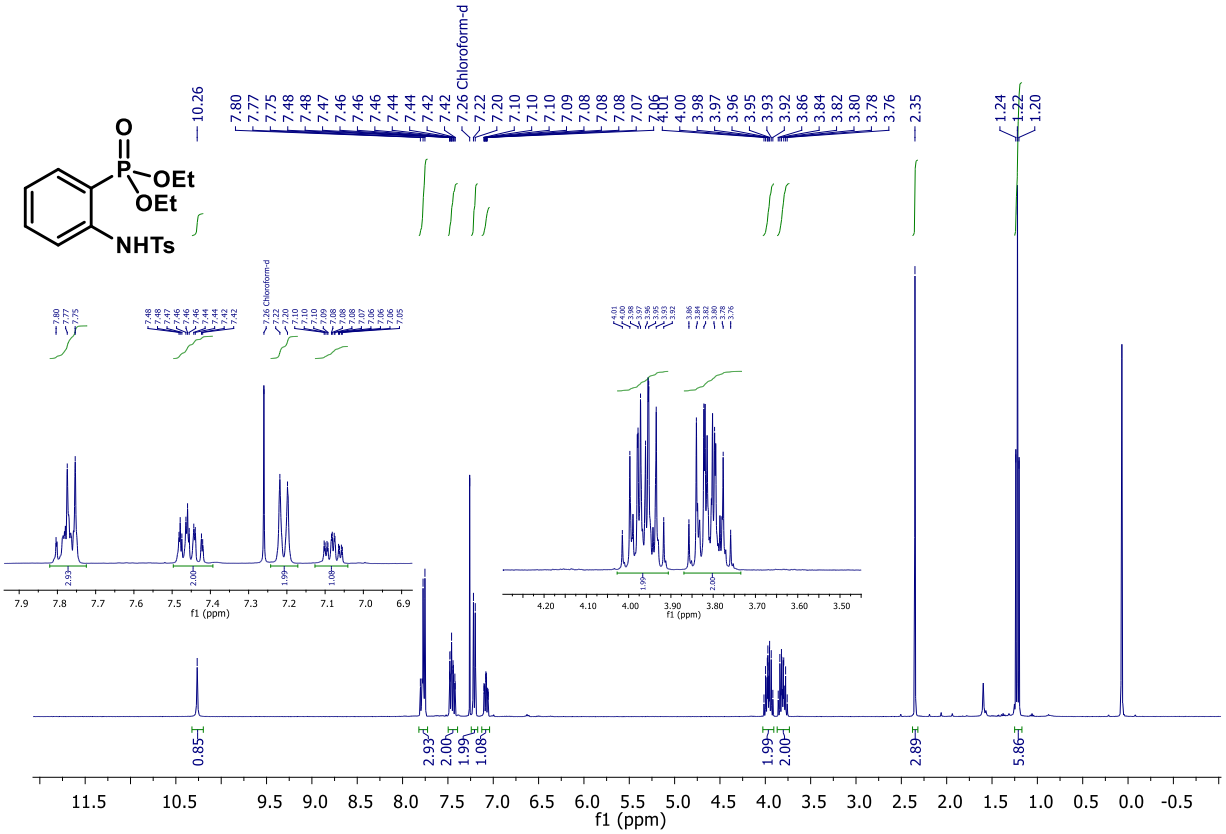


^{31}P{^{1}H} NMR (162 MHz, CD_3OD) spectrum of **30**.

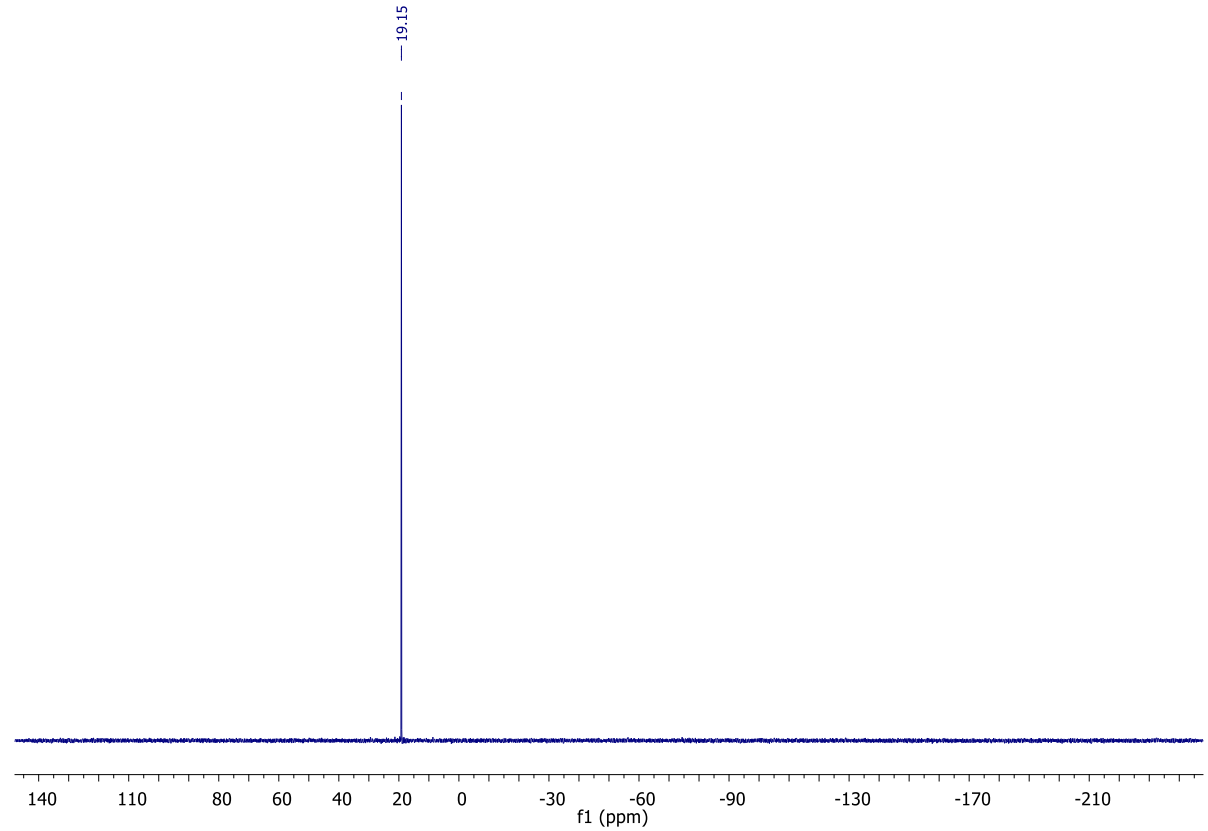


$^{13}C\{^{1}H\}$ NMR (100 MHz, CD_3OD) spectrum of **30**. Asterisks denote signal of polar impurity which was difficult to remove.

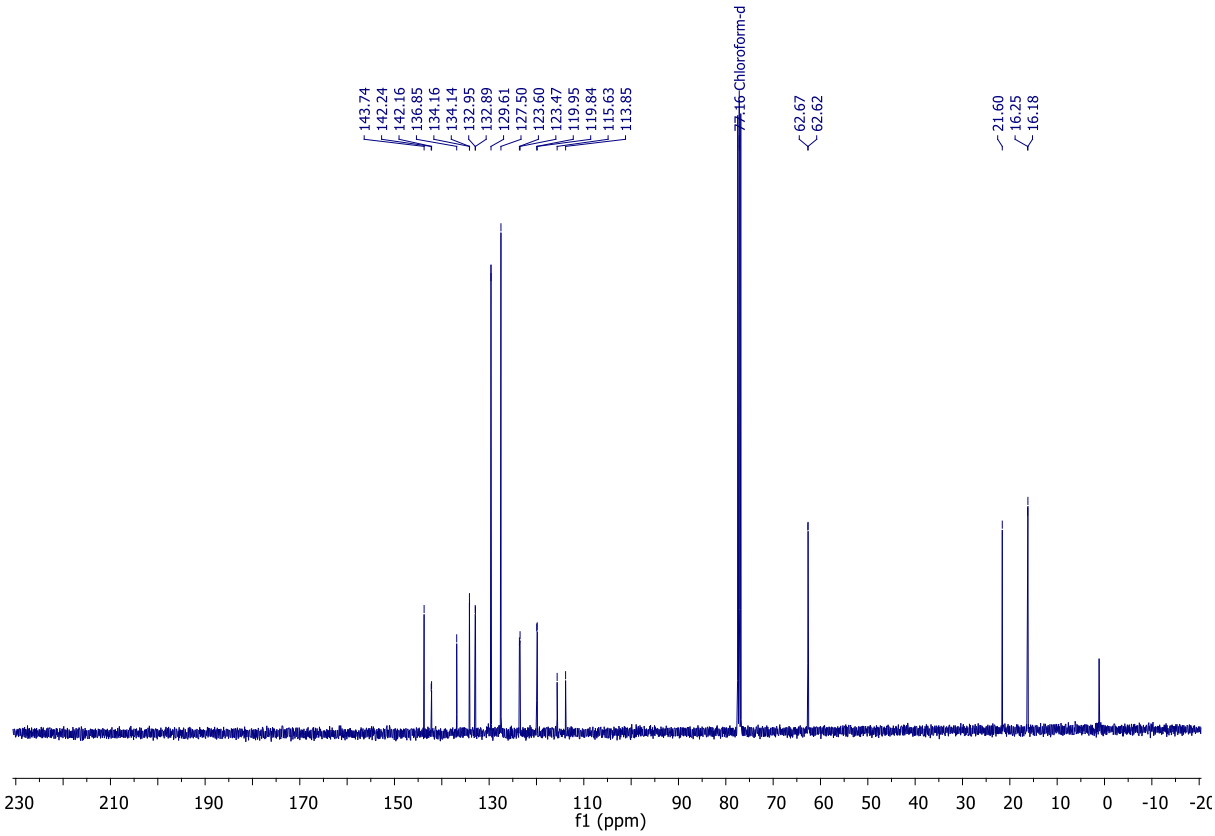
Compound 37



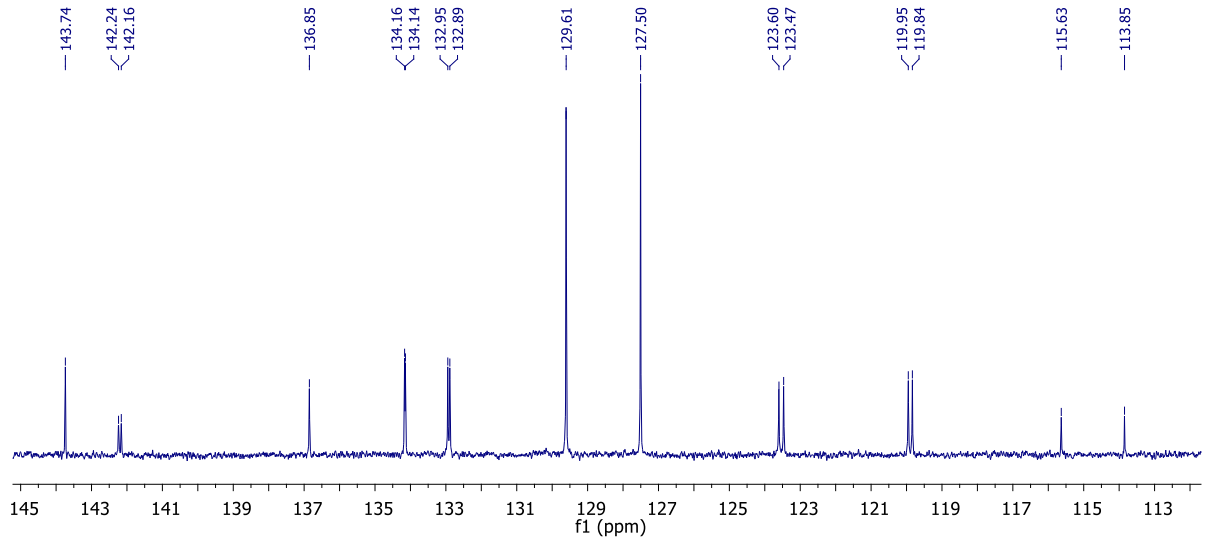
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **37**.



$^{31}P\{^{1}H\}$ NMR (162 MHz, $CDCl_3$) spectrum of **37**.

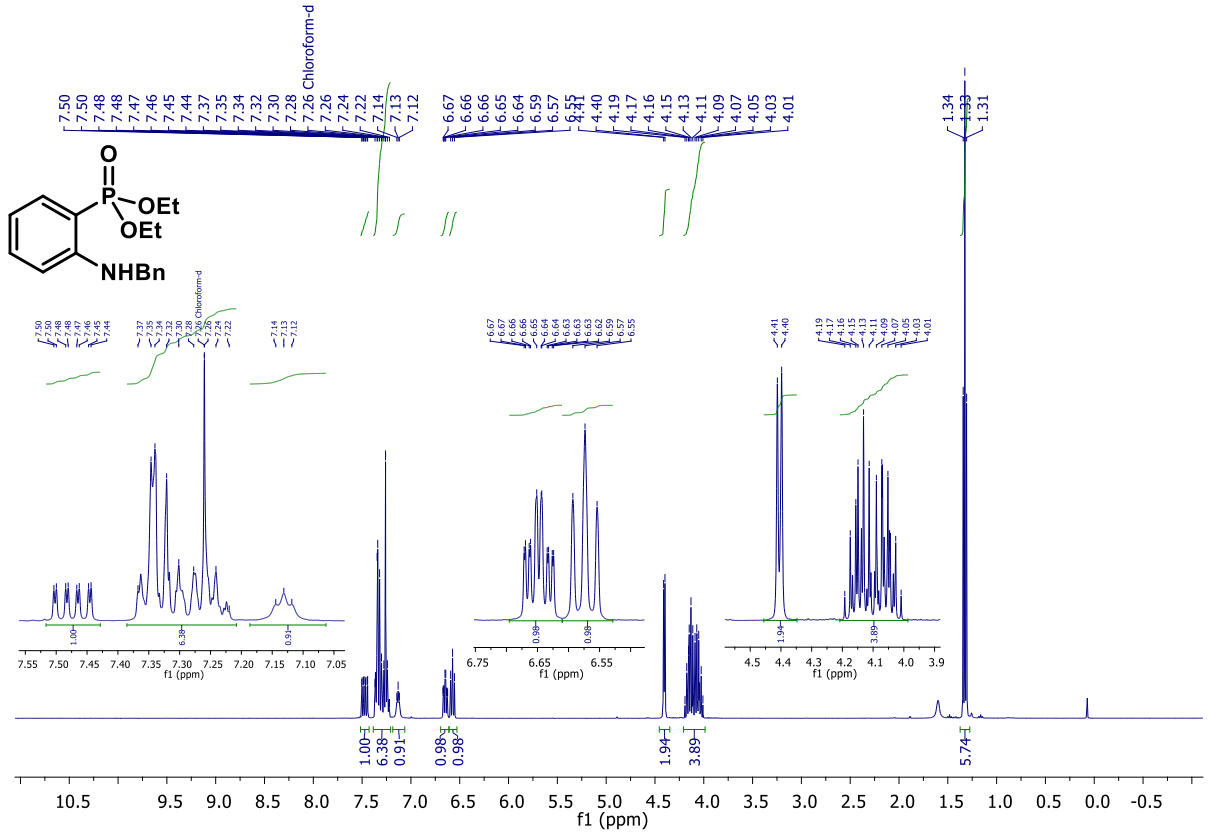


$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) spectrum of **37**.

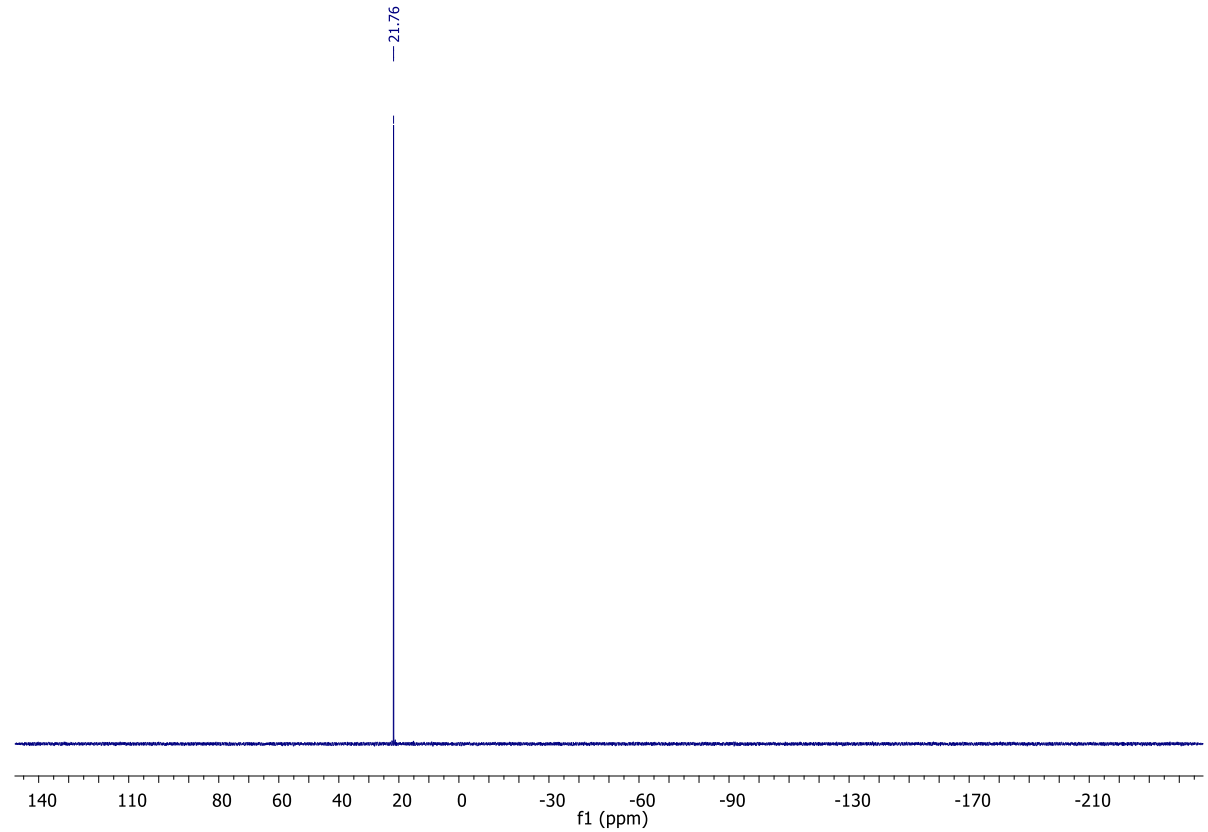


Detail of **$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$)** spectrum of **37**.

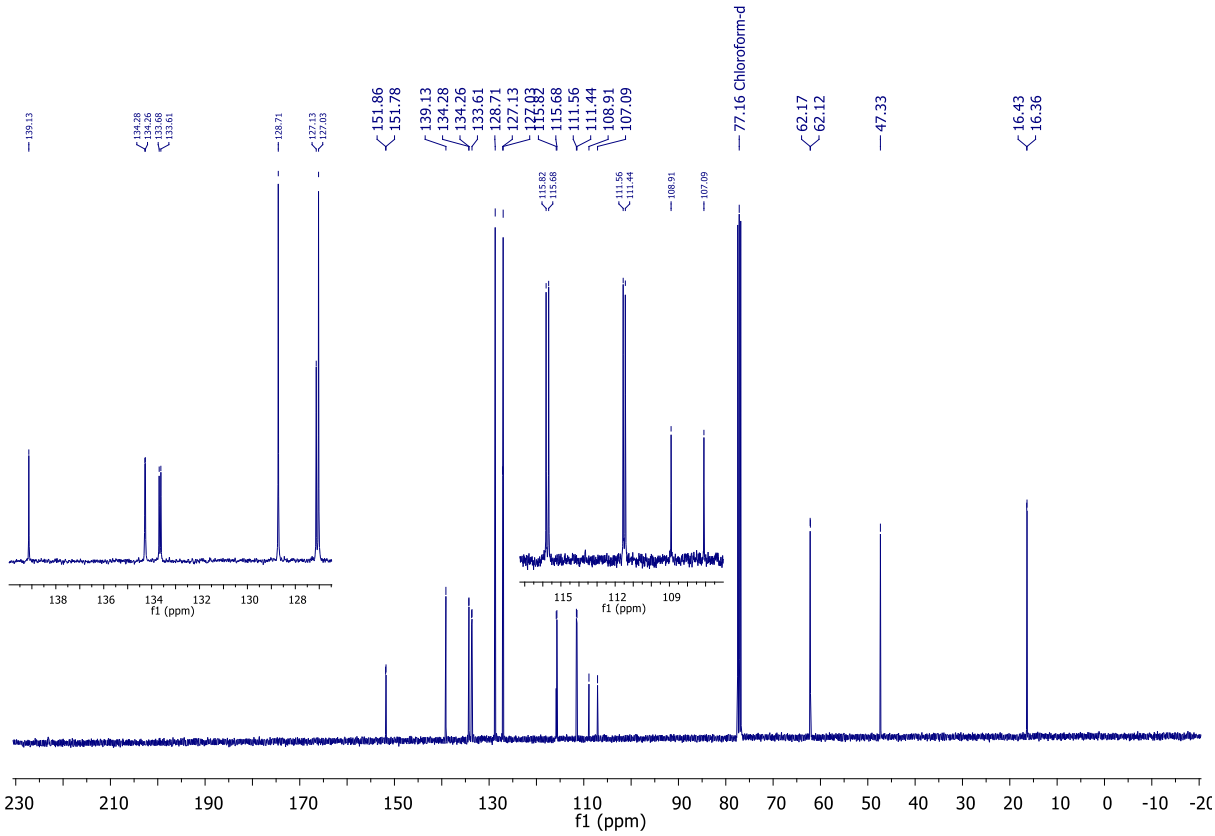
Compound 39



^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **39**.

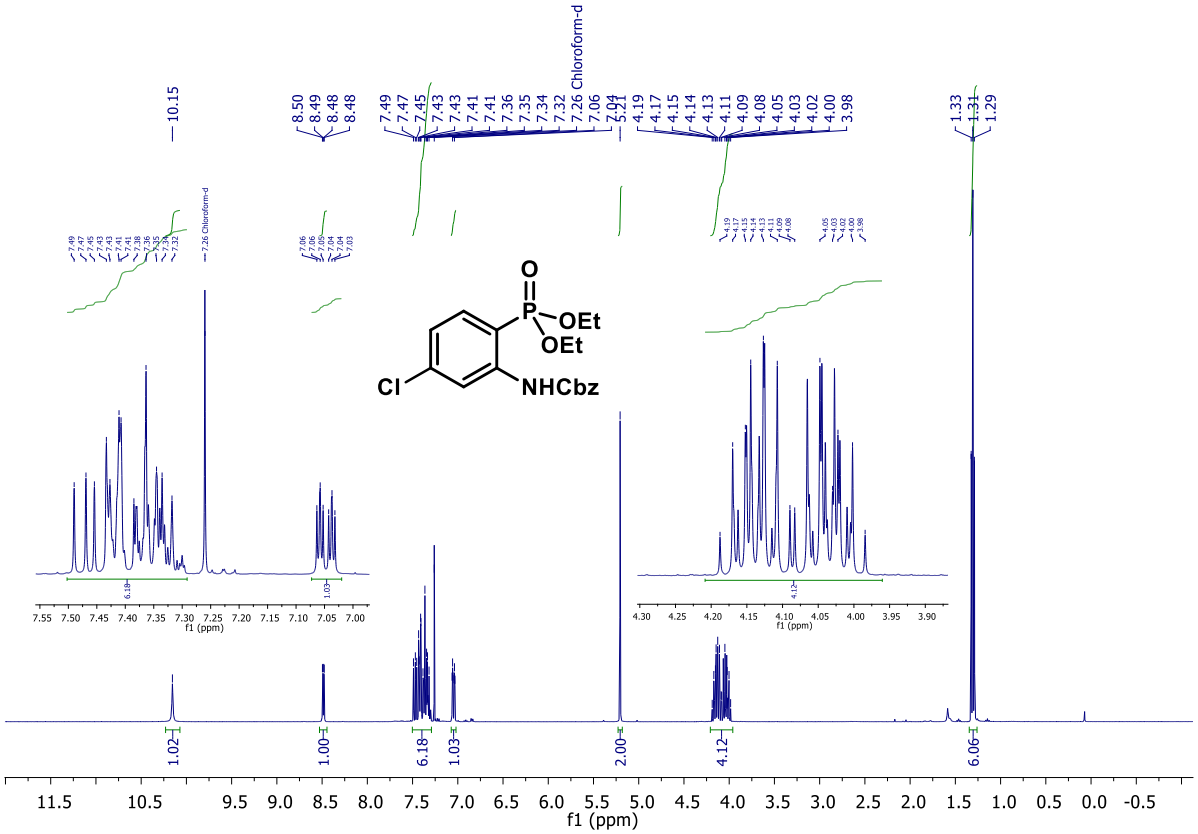


$^{31}P\{^{1}H\}$ NMR (162 MHz, $CDCl_3$) spectrum of **39**.

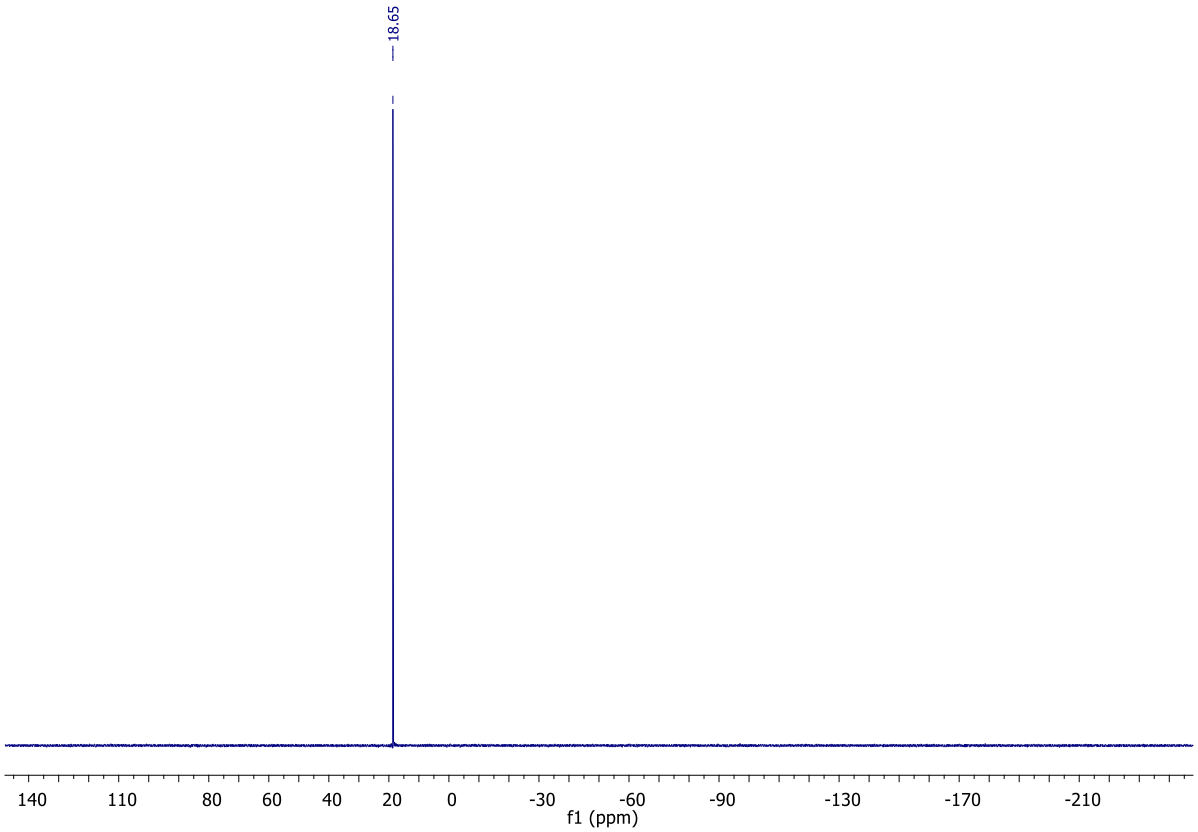


$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) spectrum of **39**.

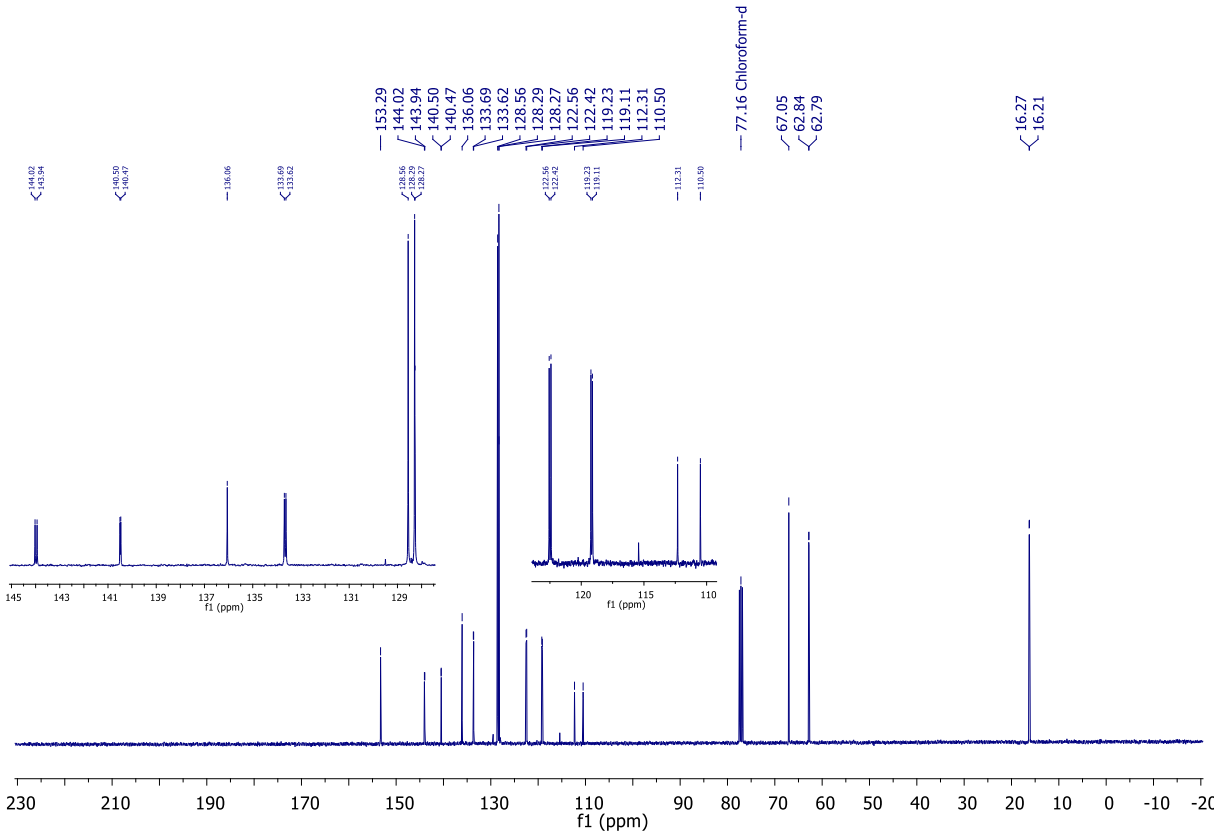
Compound 41



^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **41**.

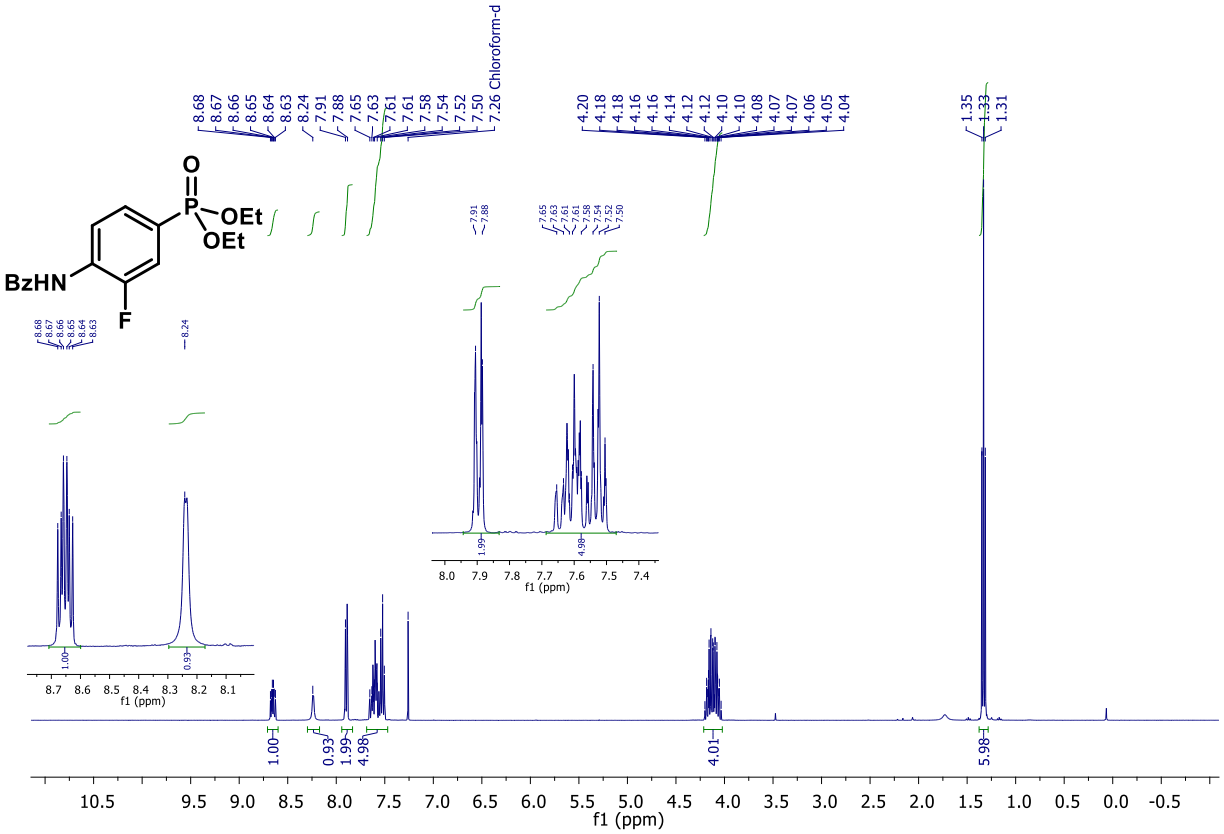


^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$) spectrum of **41**.

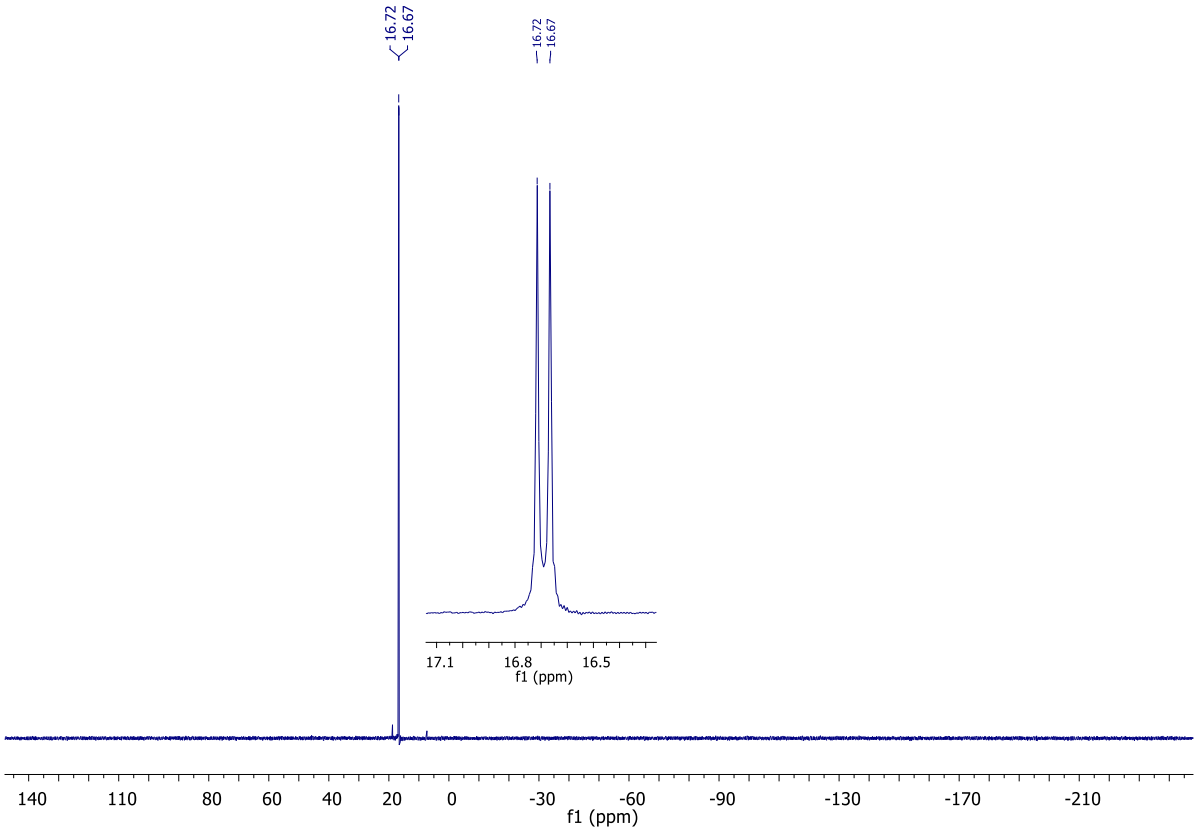


$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) spectrum of **39**.

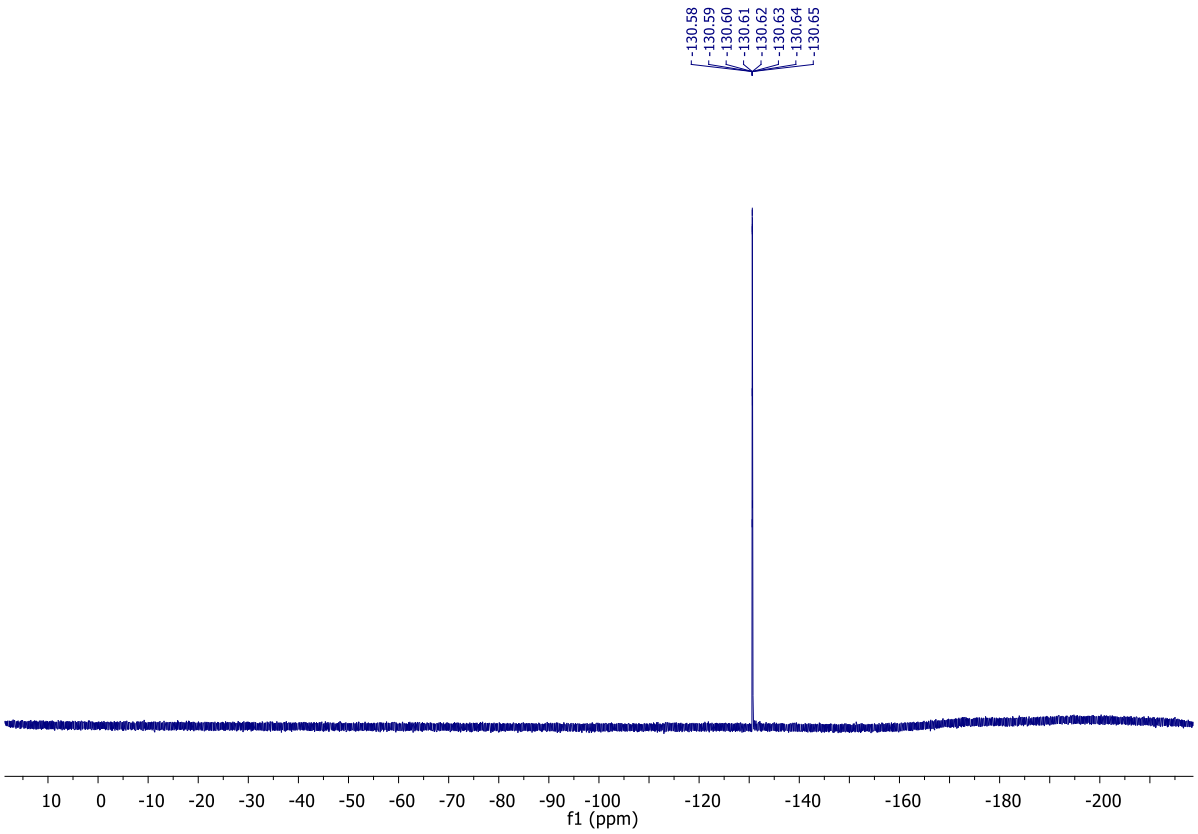
Compound 43



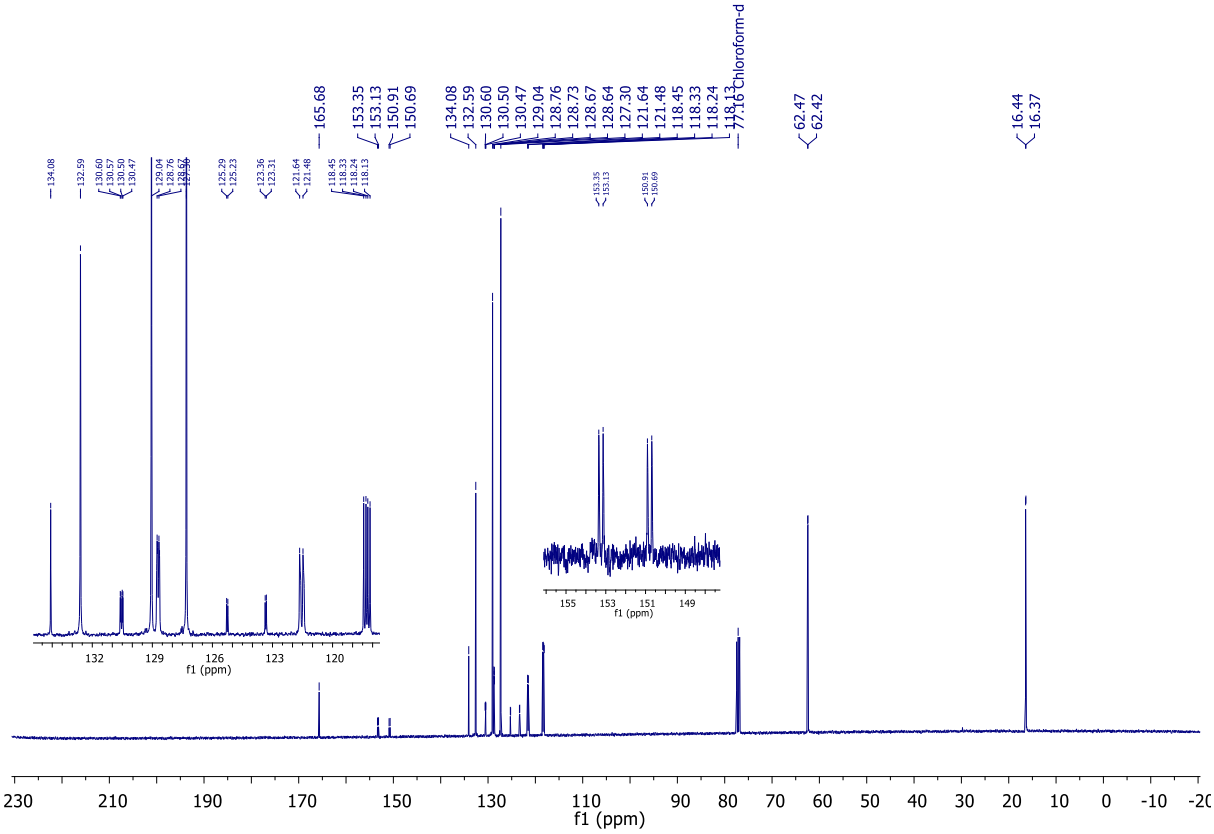
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **43**.



^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$) spectrum of **43**.

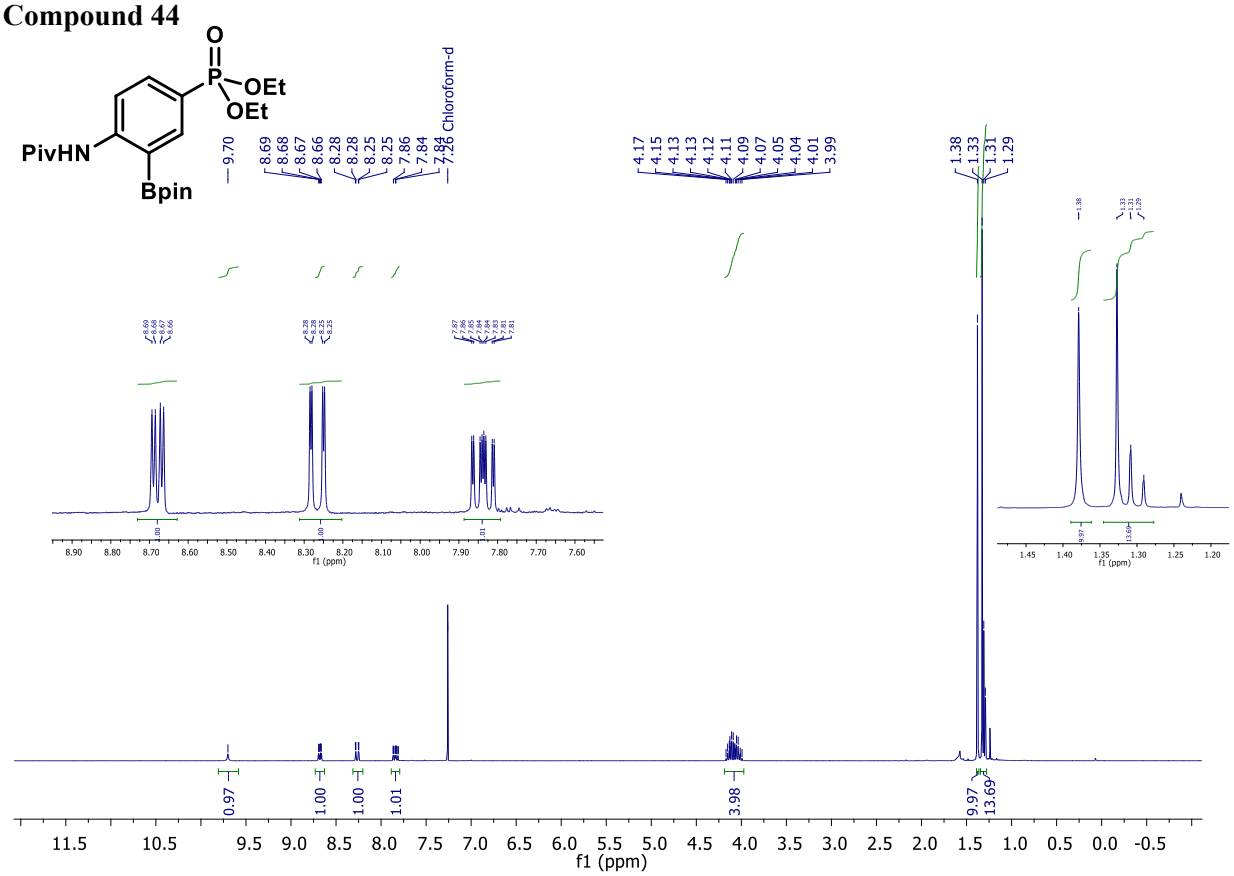


^{19}F NMR (376 MHz, $CDCl_3$) spectrum of **43**.

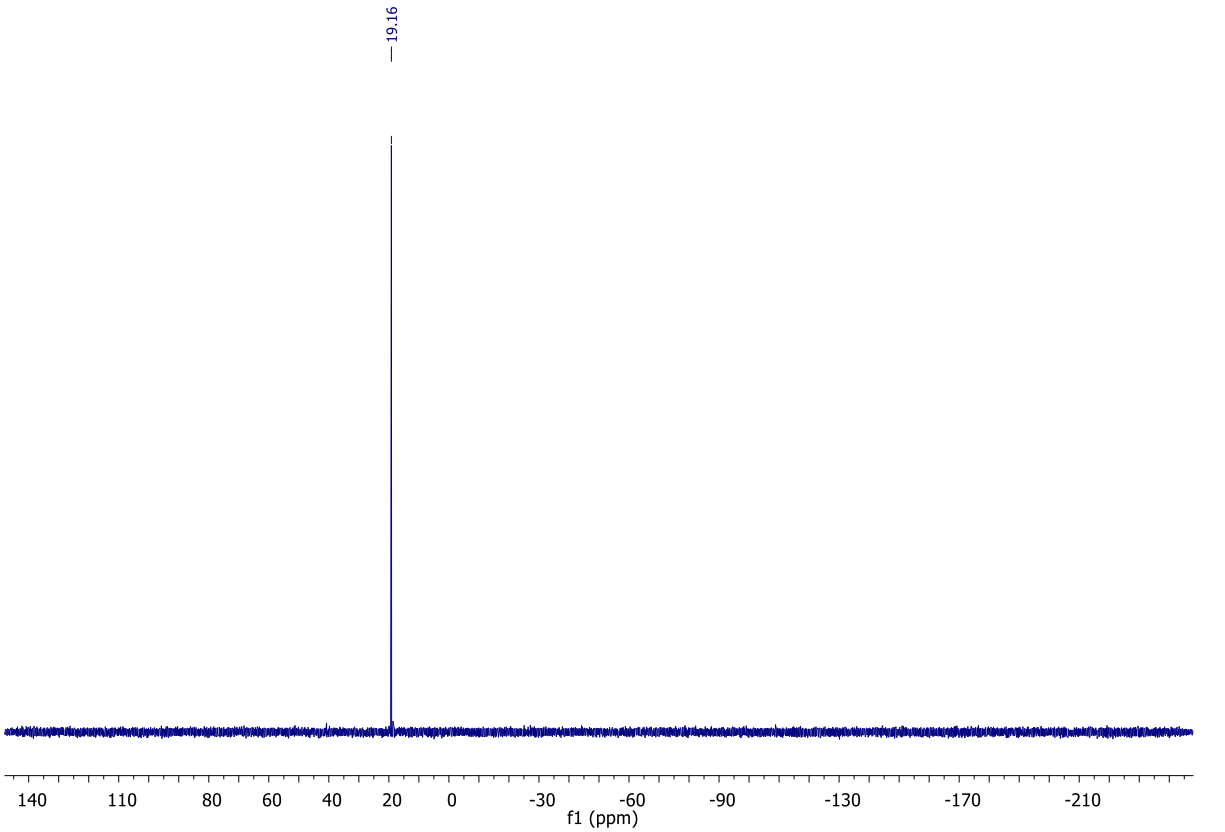


^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) spectrum of **43**.

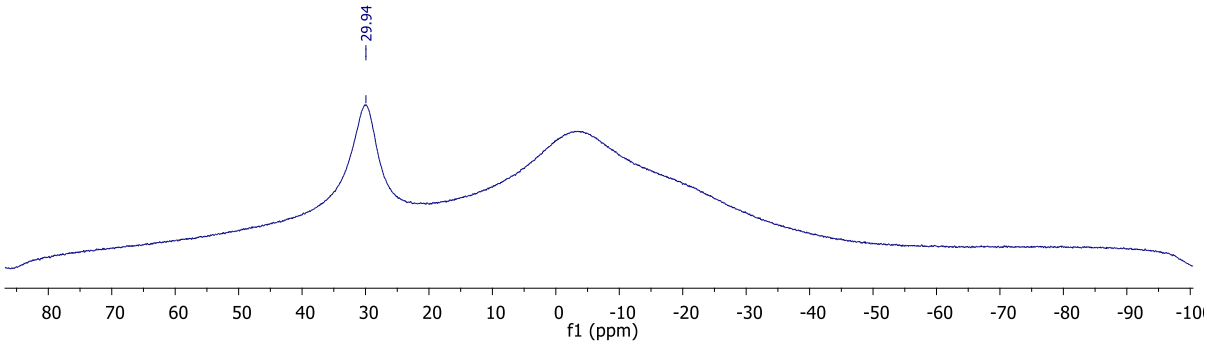
Compound 44



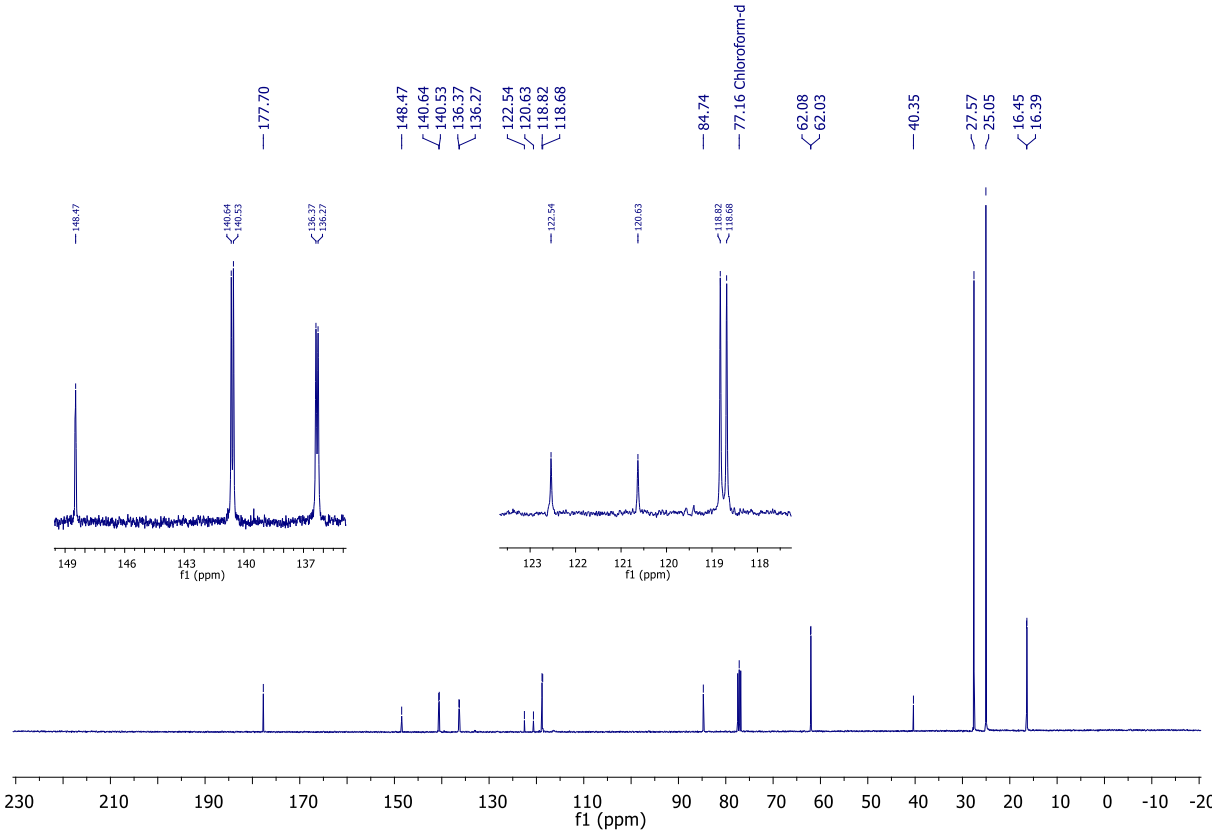
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **44**.



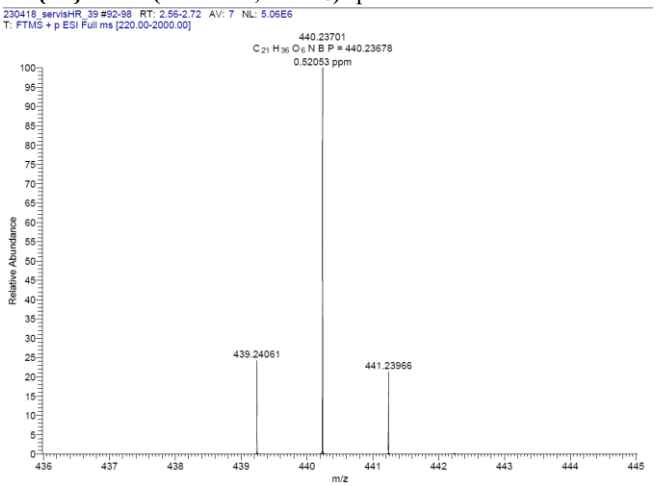
^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$) spectrum of **44**.



^{11}B NMR (128 MHz, $CDCl_3$) spectrum of **44**.

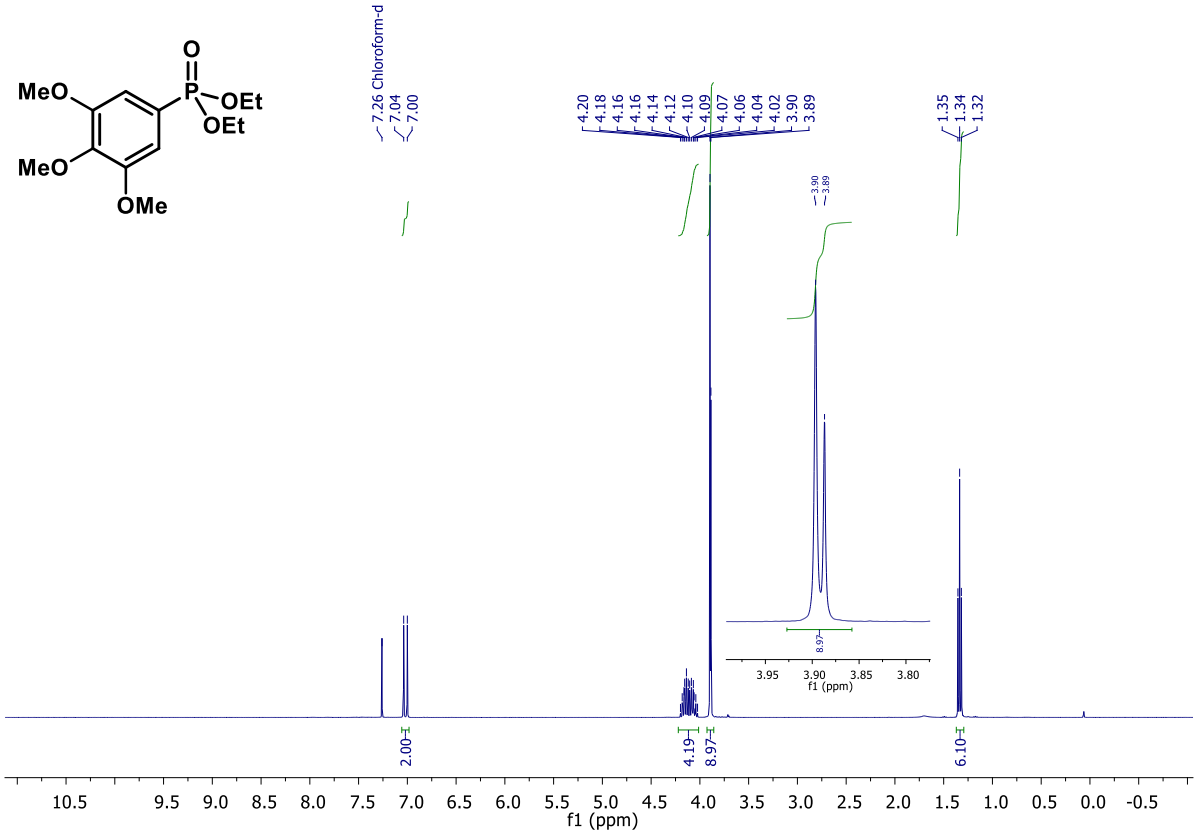


^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) spectrum of **44**.

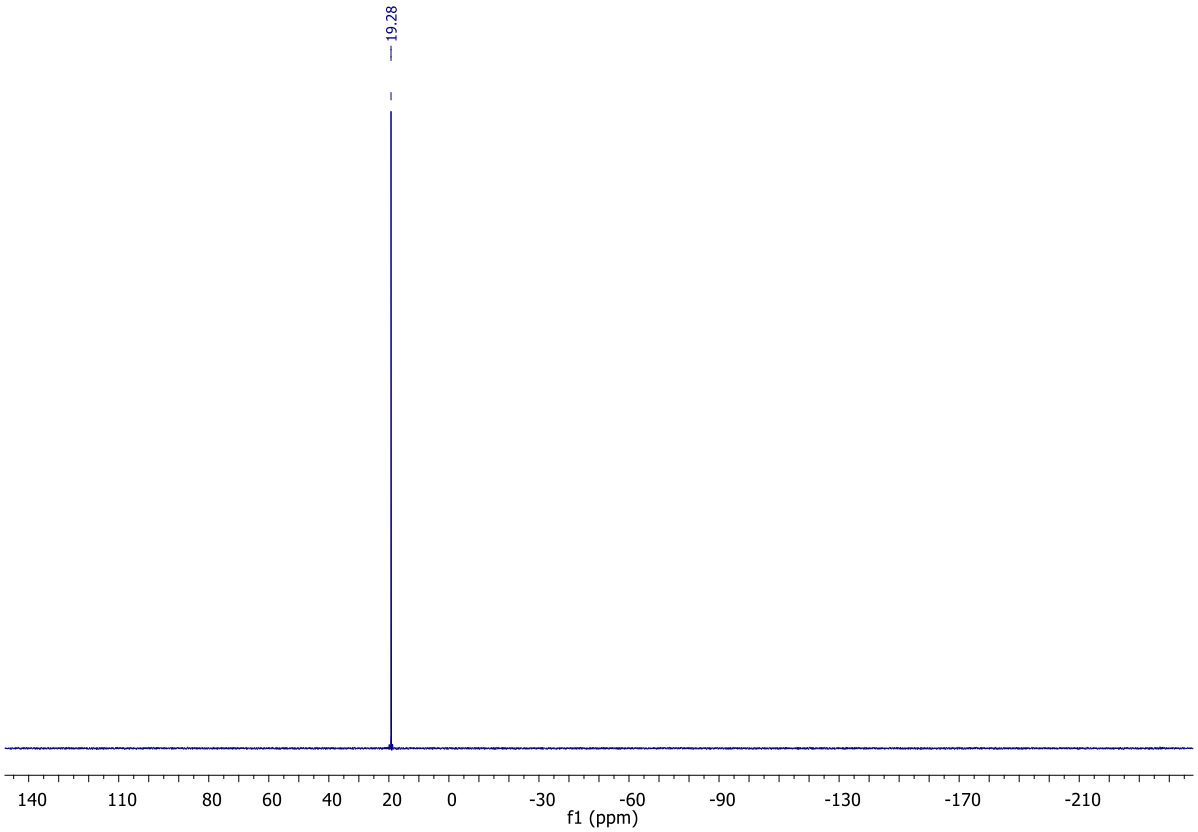


HRMS (ESI-TOF) spectrum of compound **44**. The signal at *m*/*z* 440.23701 corresponds to the most abundant ^{11}B isotopomer.

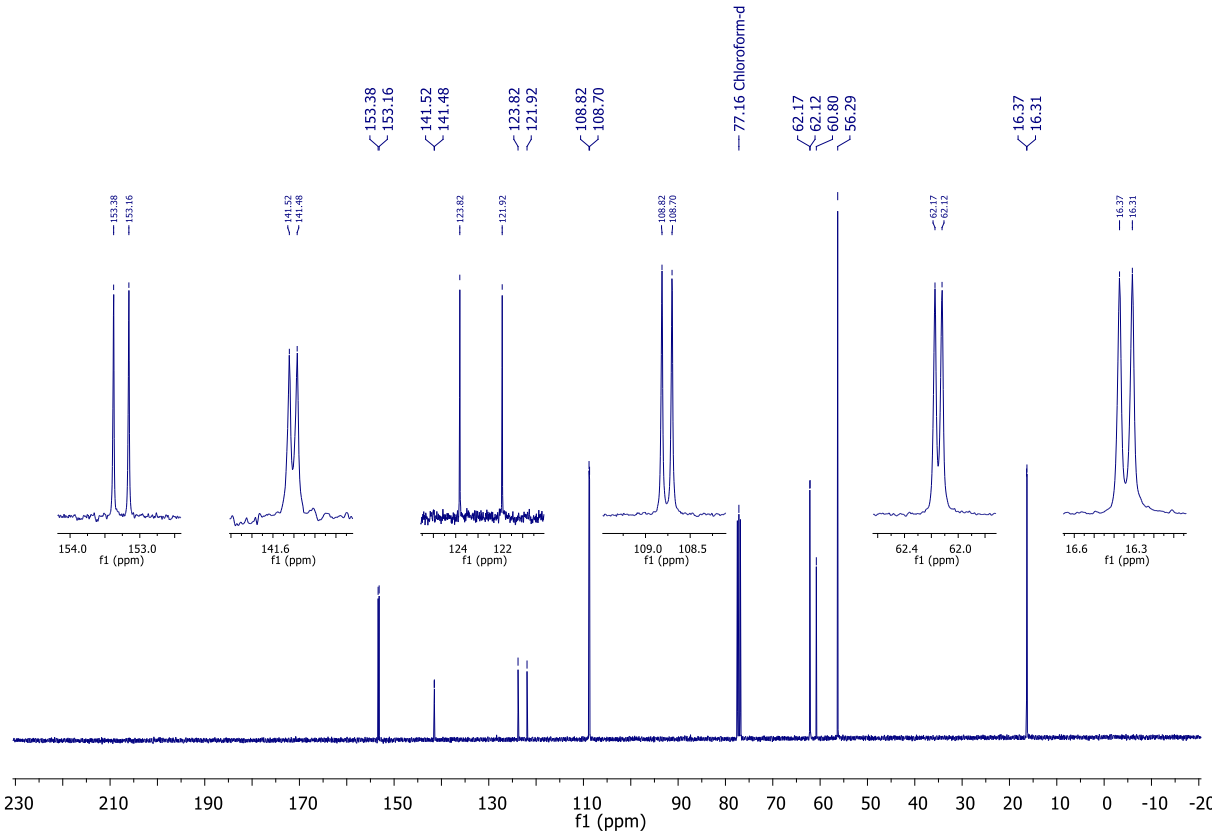
Compound 45



^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **45**.

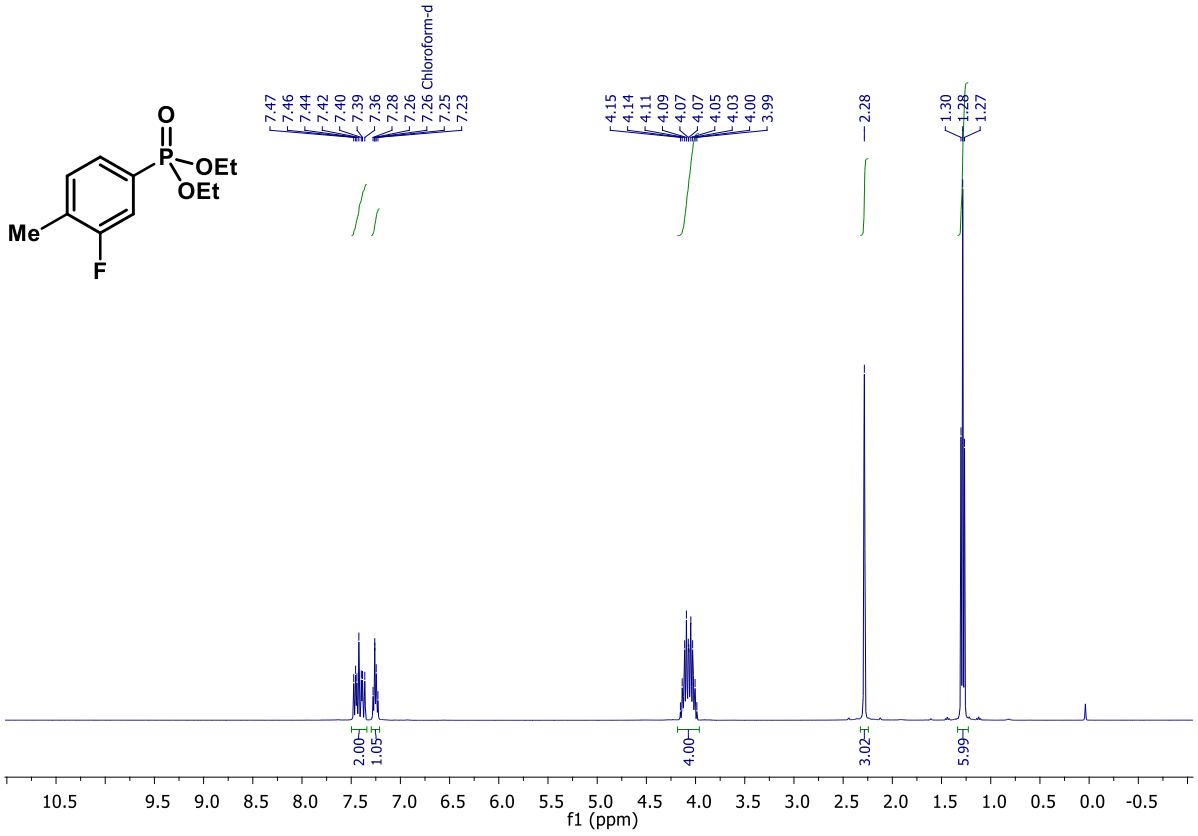


^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$) spectrum of **45**.

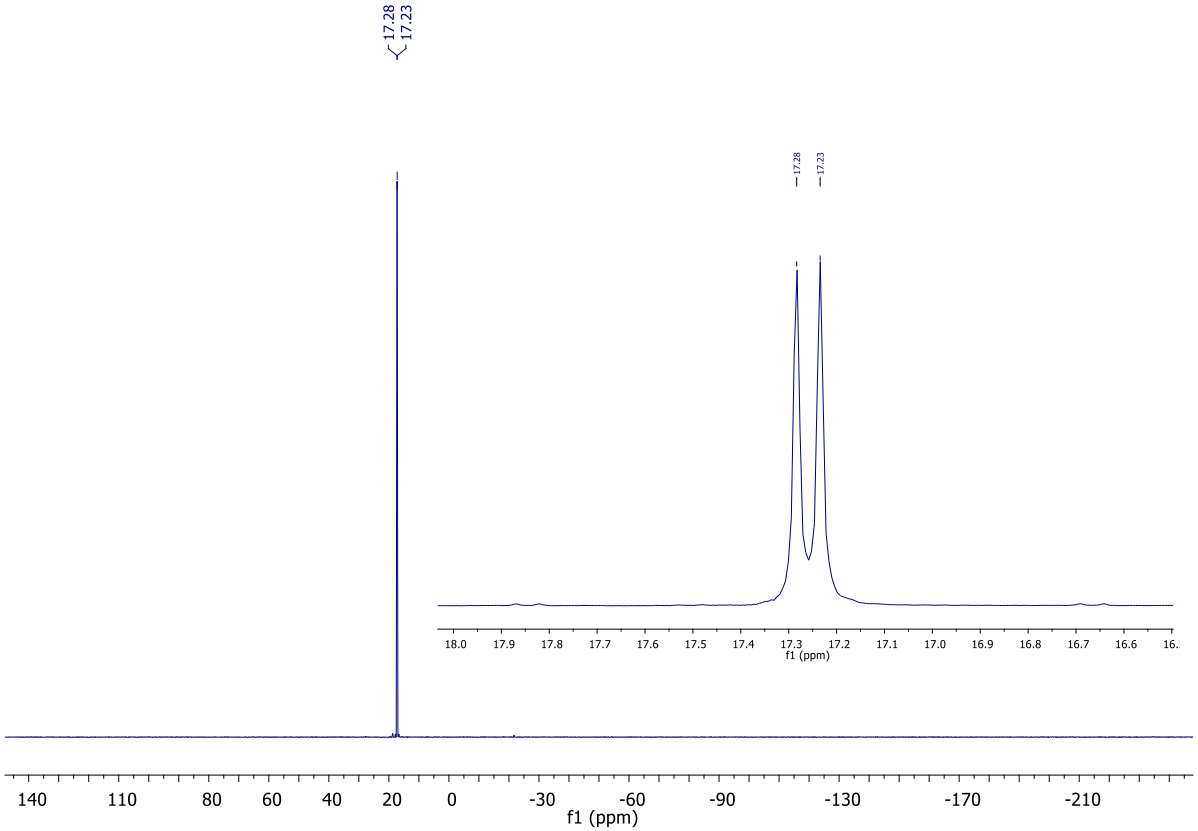


$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) spectrum of **45**.

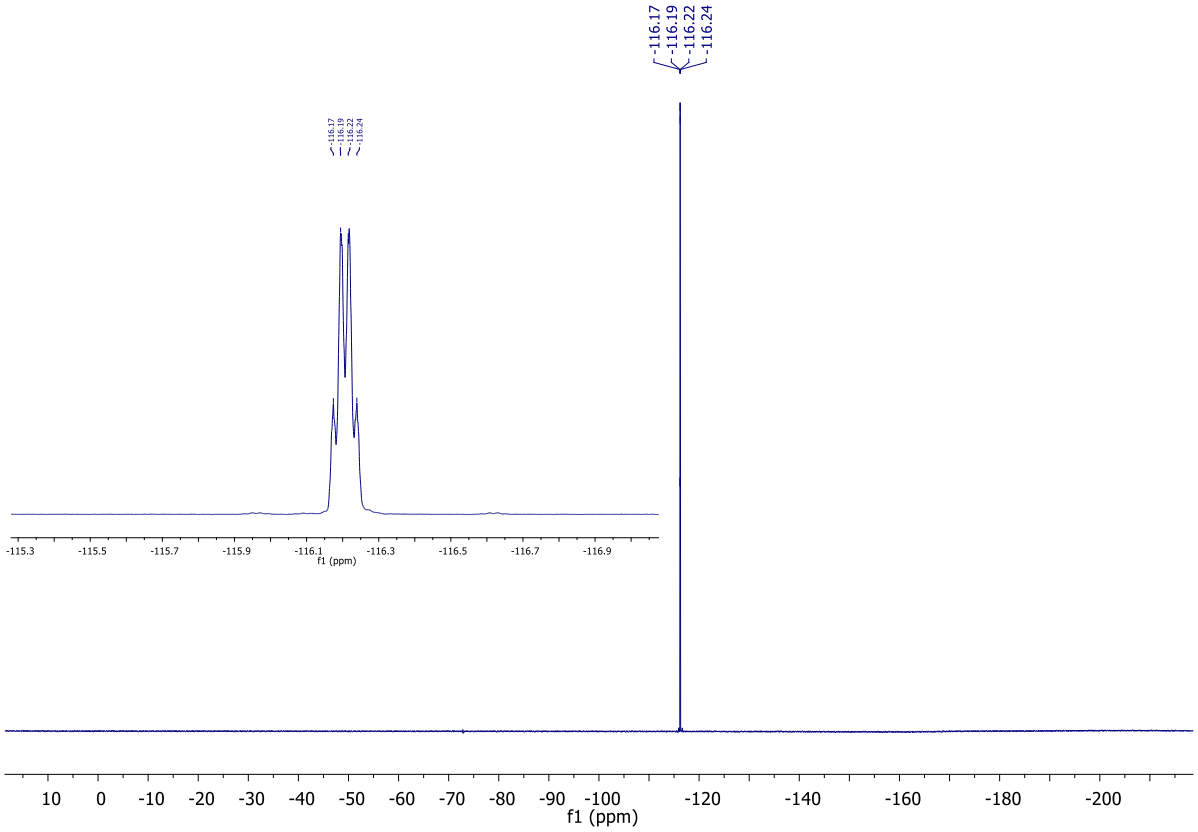
Compound 46



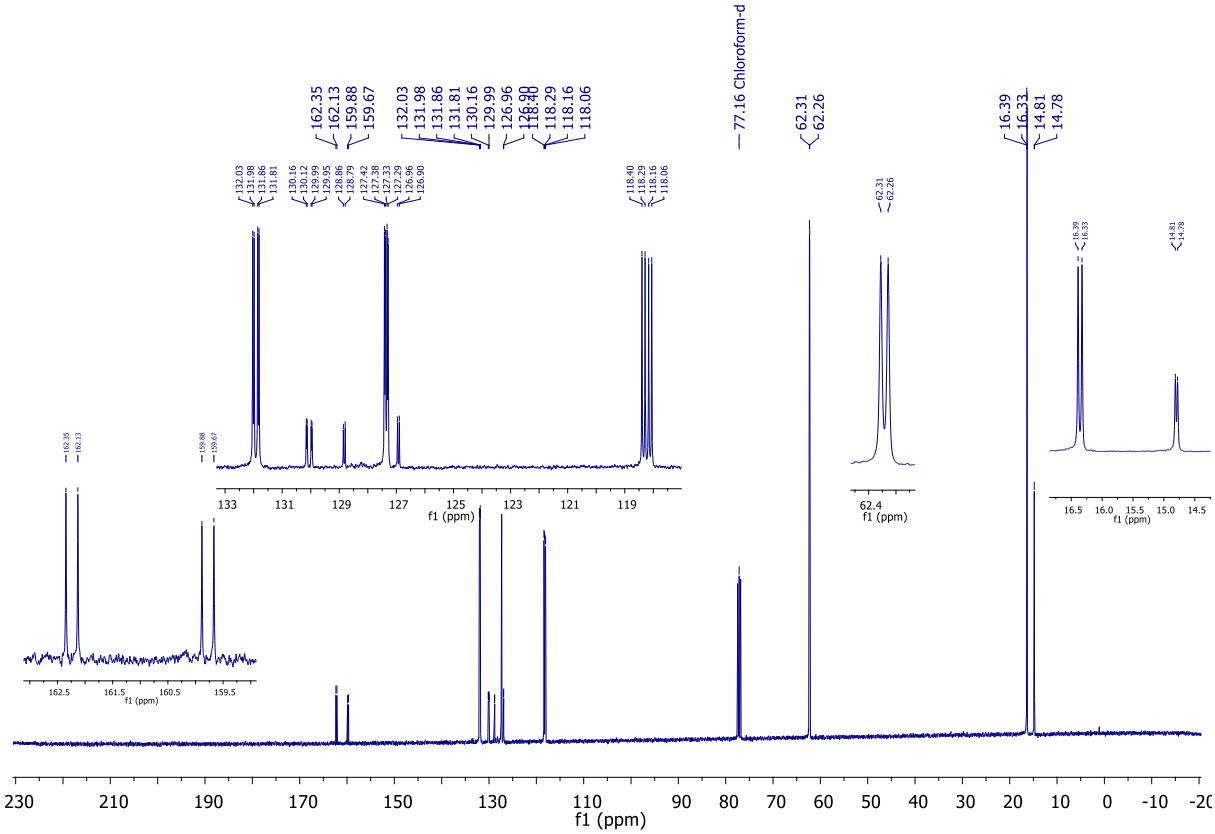
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **46**.



^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$) spectrum of **46**.

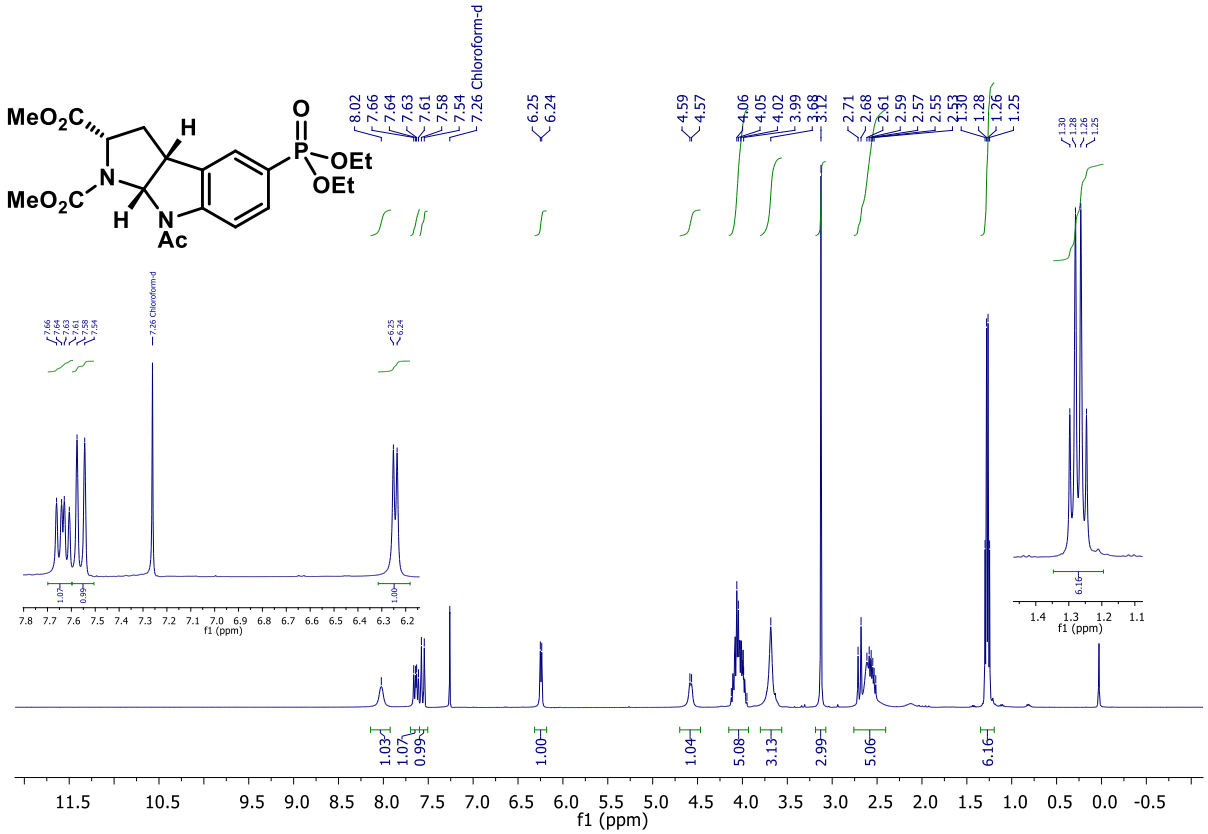


^{19}F NMR (376 MHz, $CDCl_3$) spectrum of **46**.

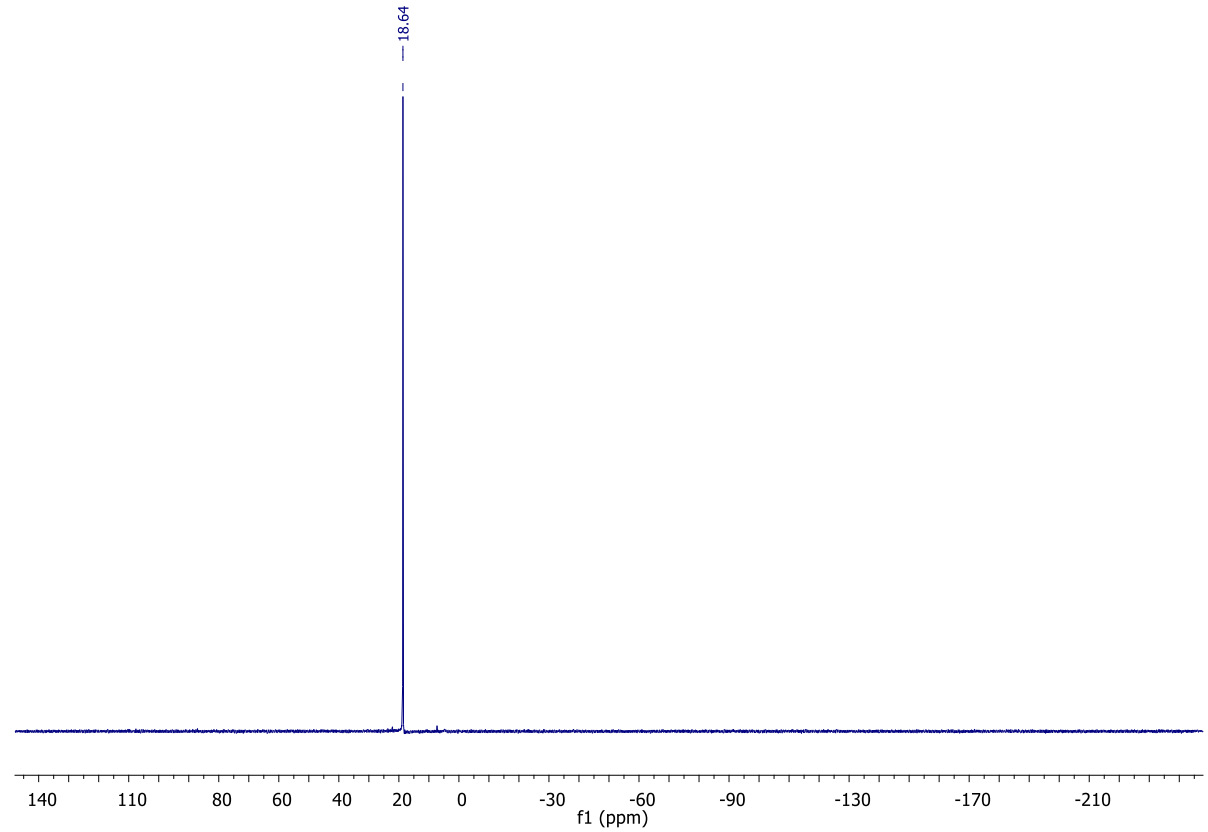


^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) spectrum of **46**.

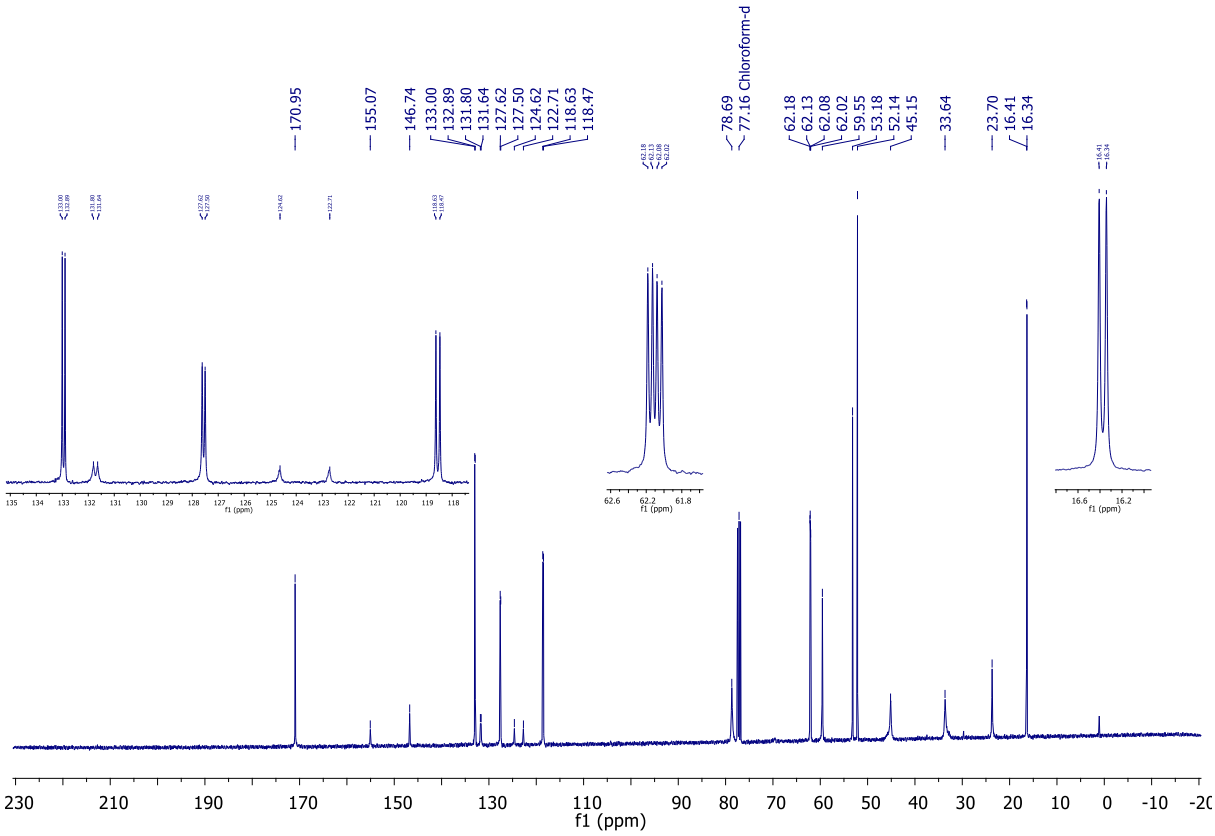
Compound 48



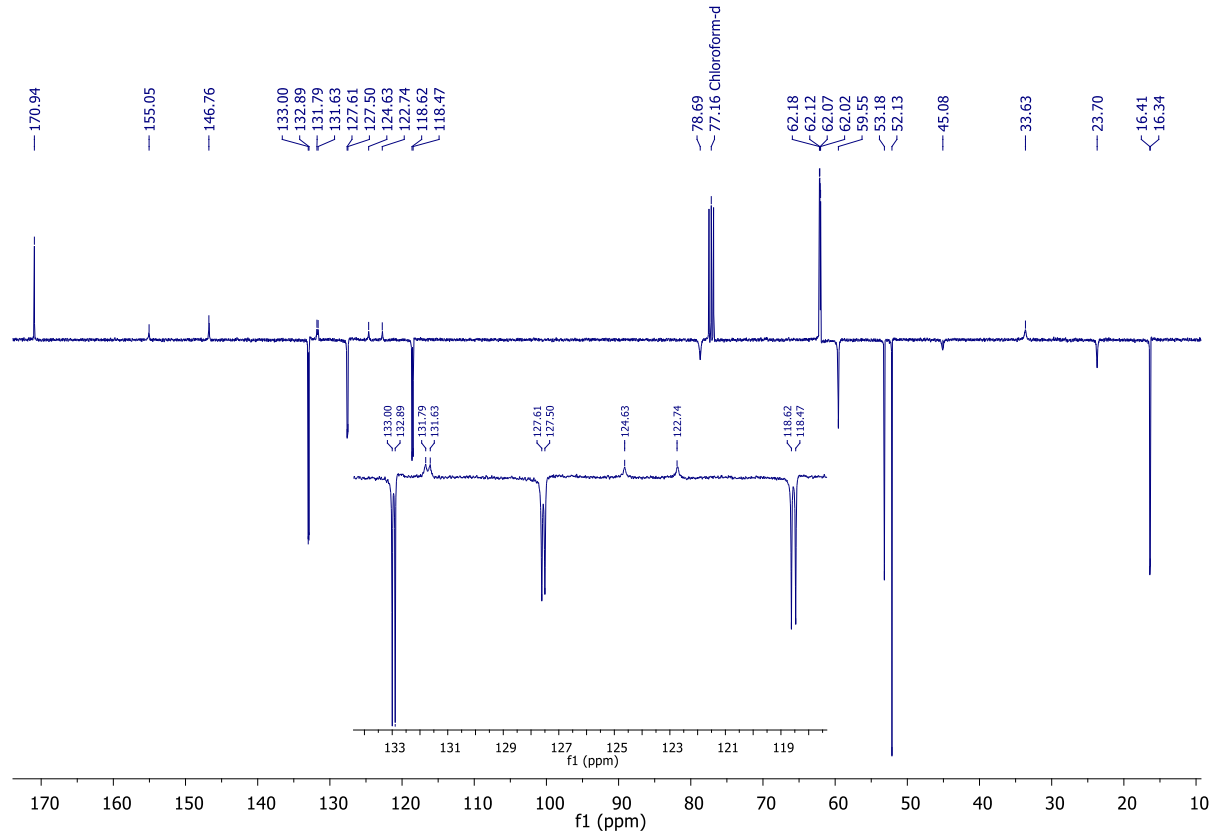
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **48**.



^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$) spectrum of **48**.

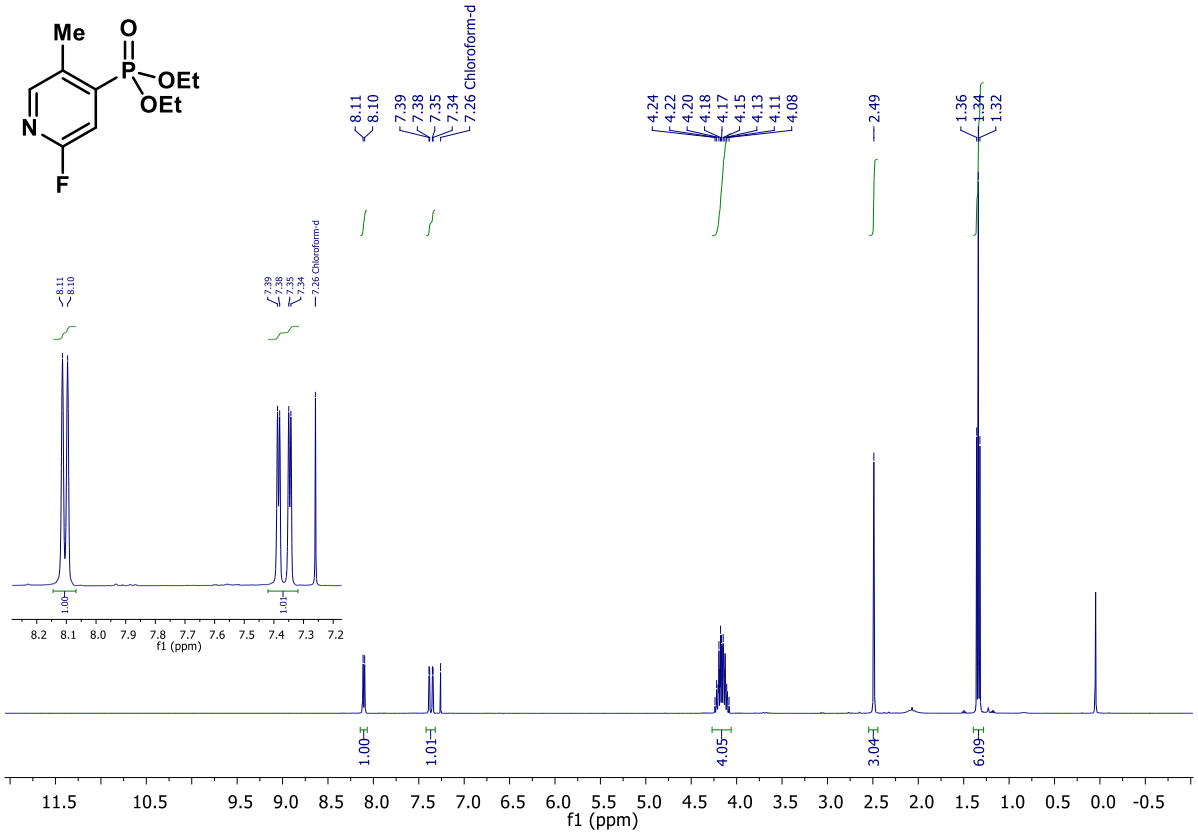


$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) spectrum of **48**.

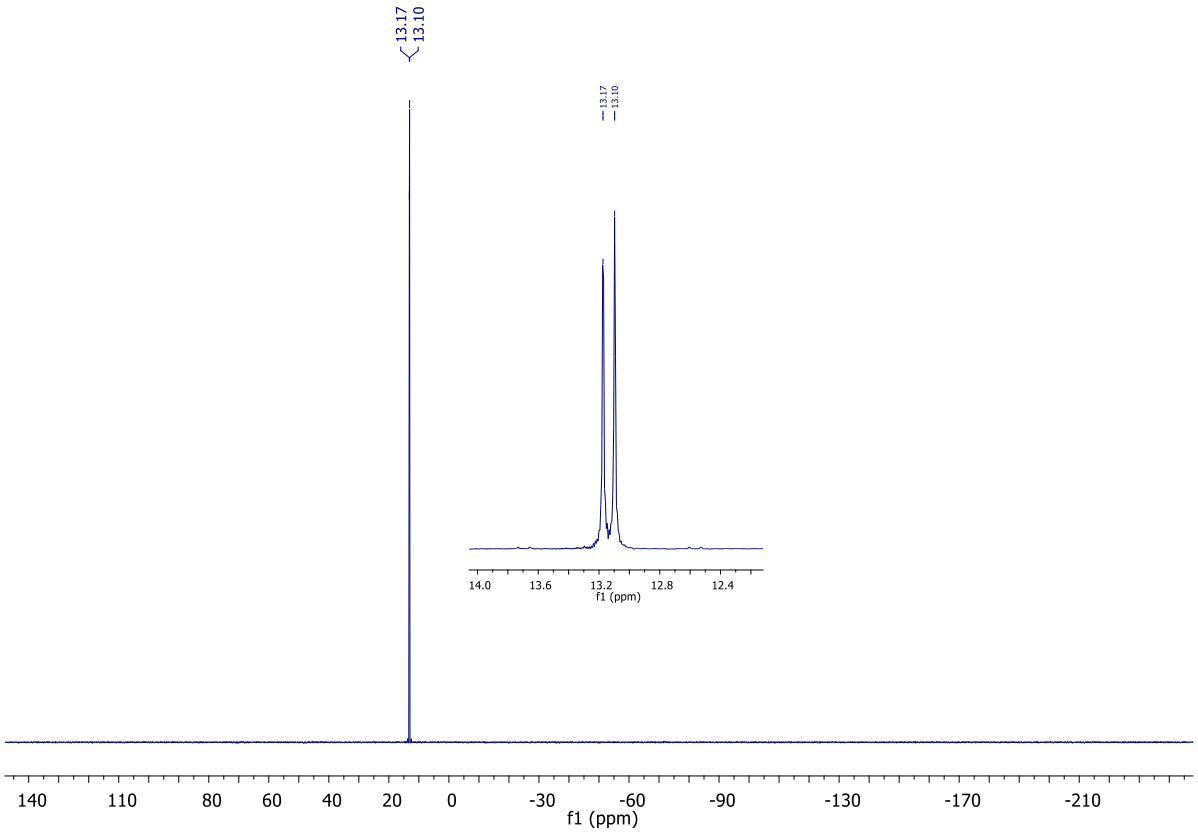


$^{13}C\{^{1}H\}$ APT NMR (100 MHz, $CDCl_3$) spectrum of **48**.

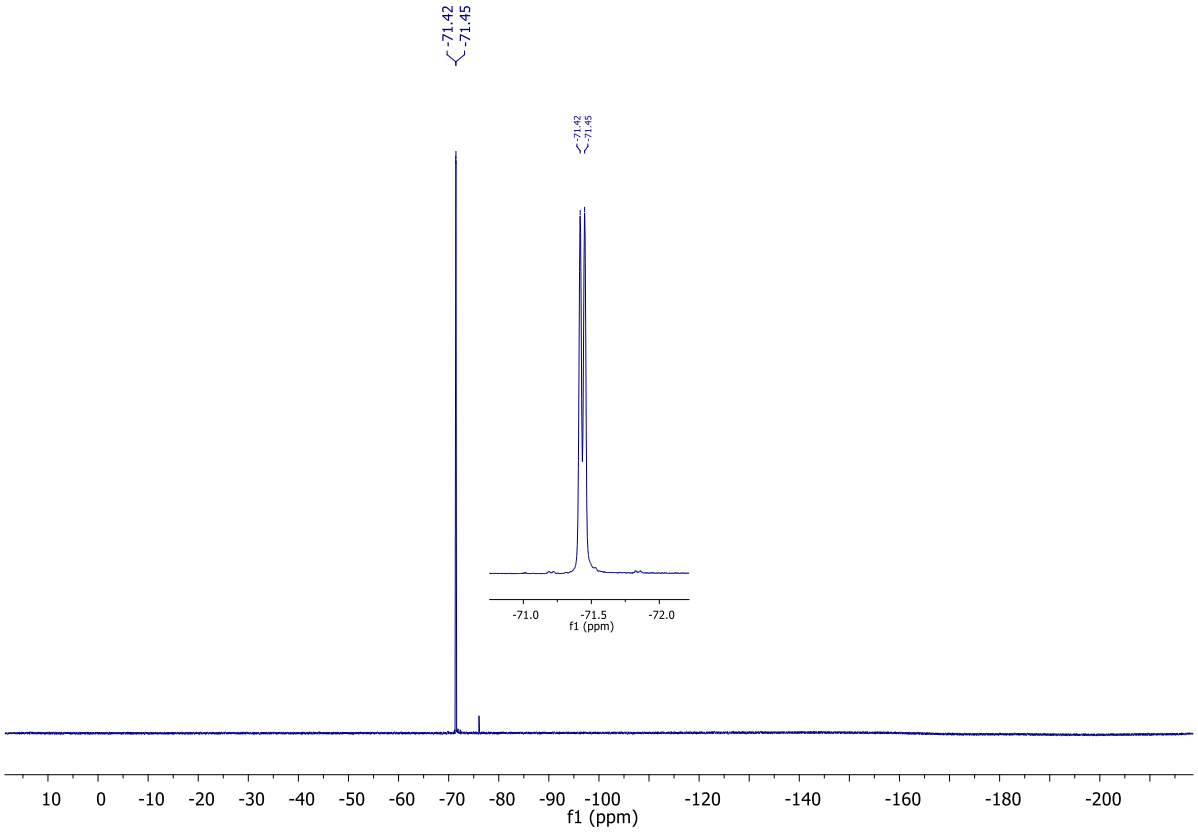
Compound 54



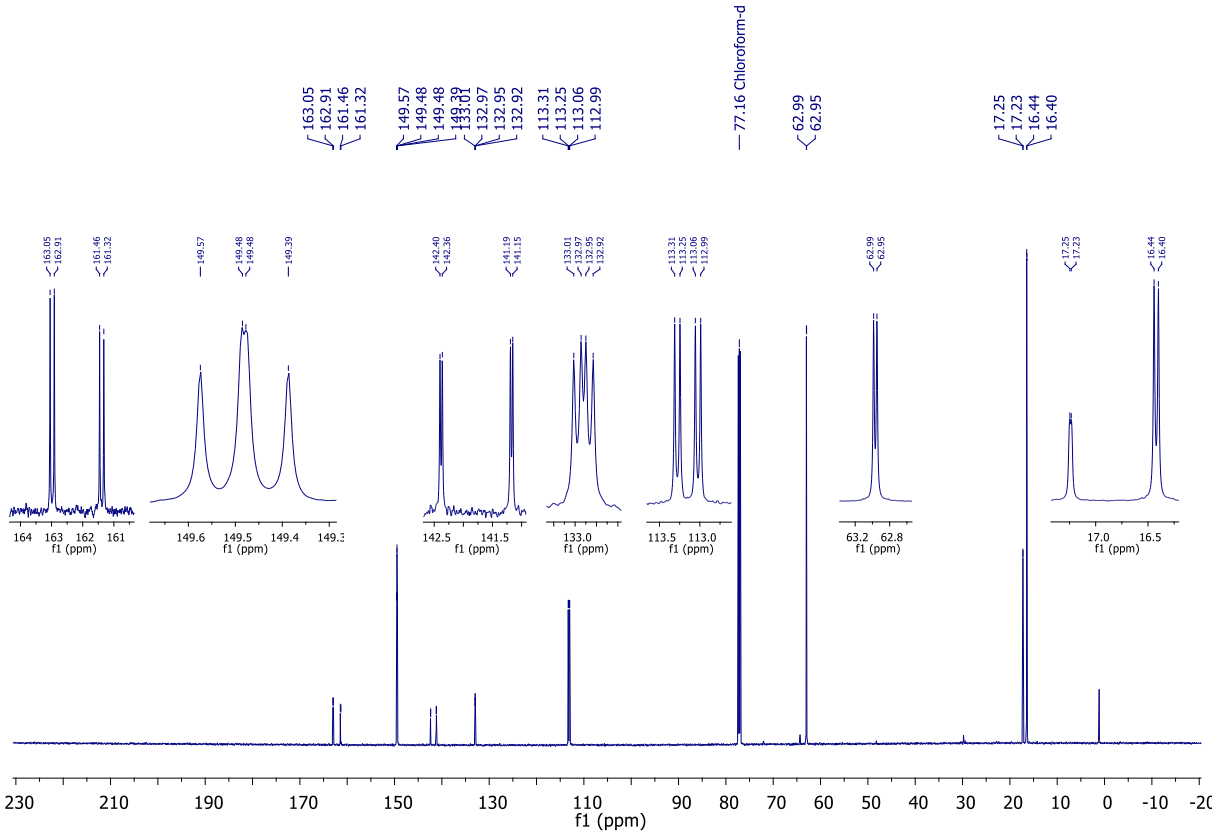
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **54**.



^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$) spectrum of **54**.

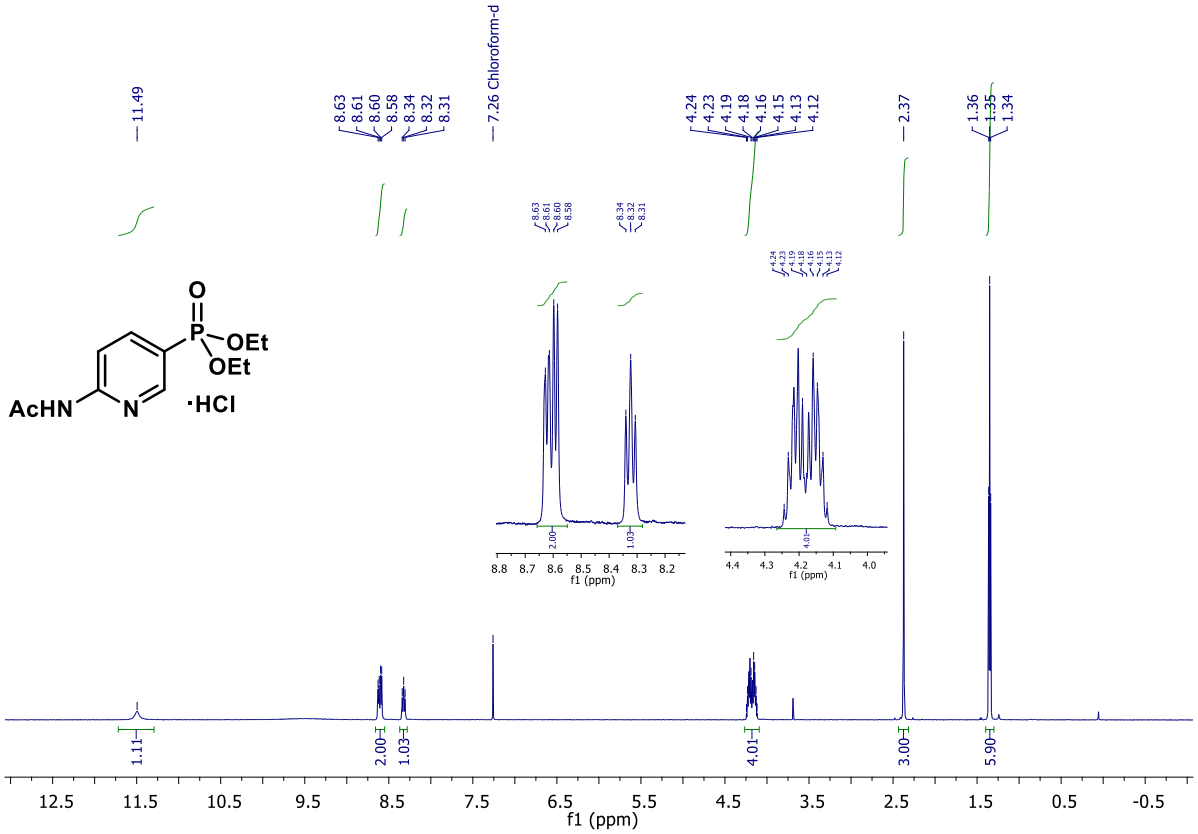


^{19}F NMR (376 MHz, $CDCl_3$) spectrum of **54**.

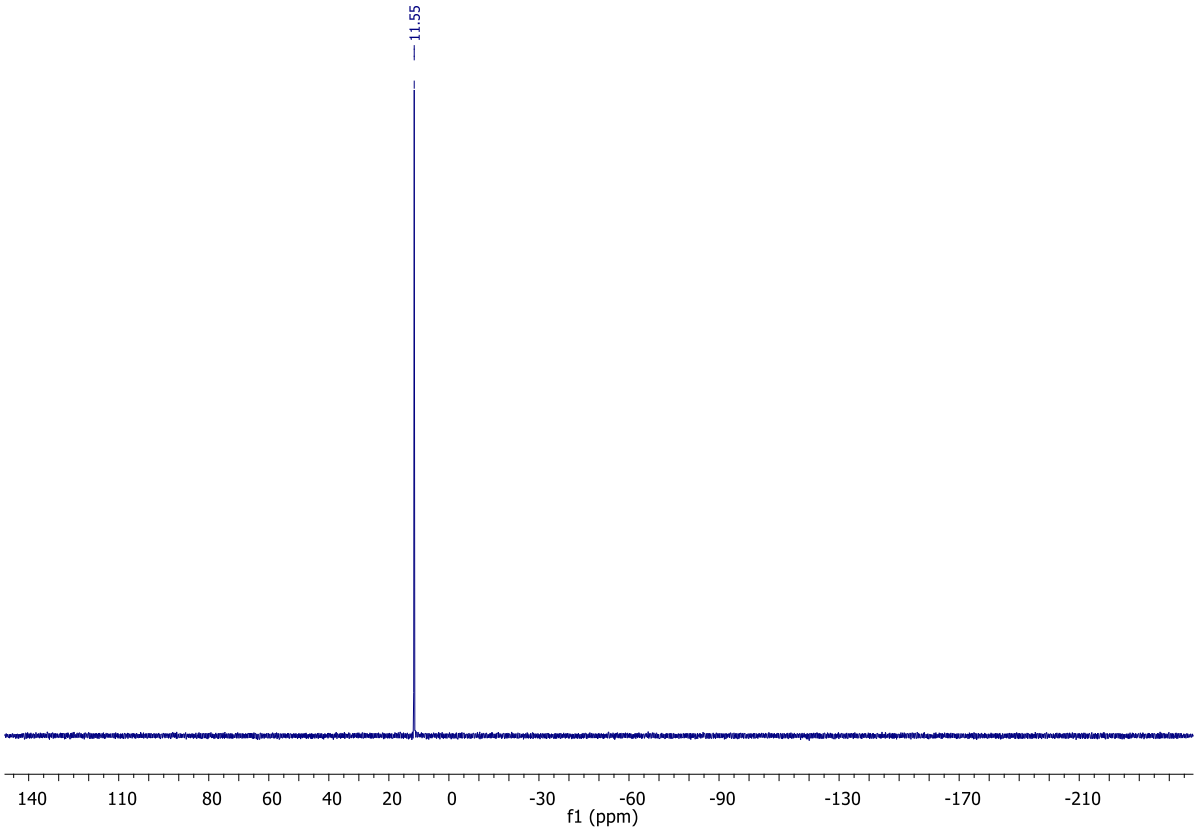


^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) spectrum of **54**.

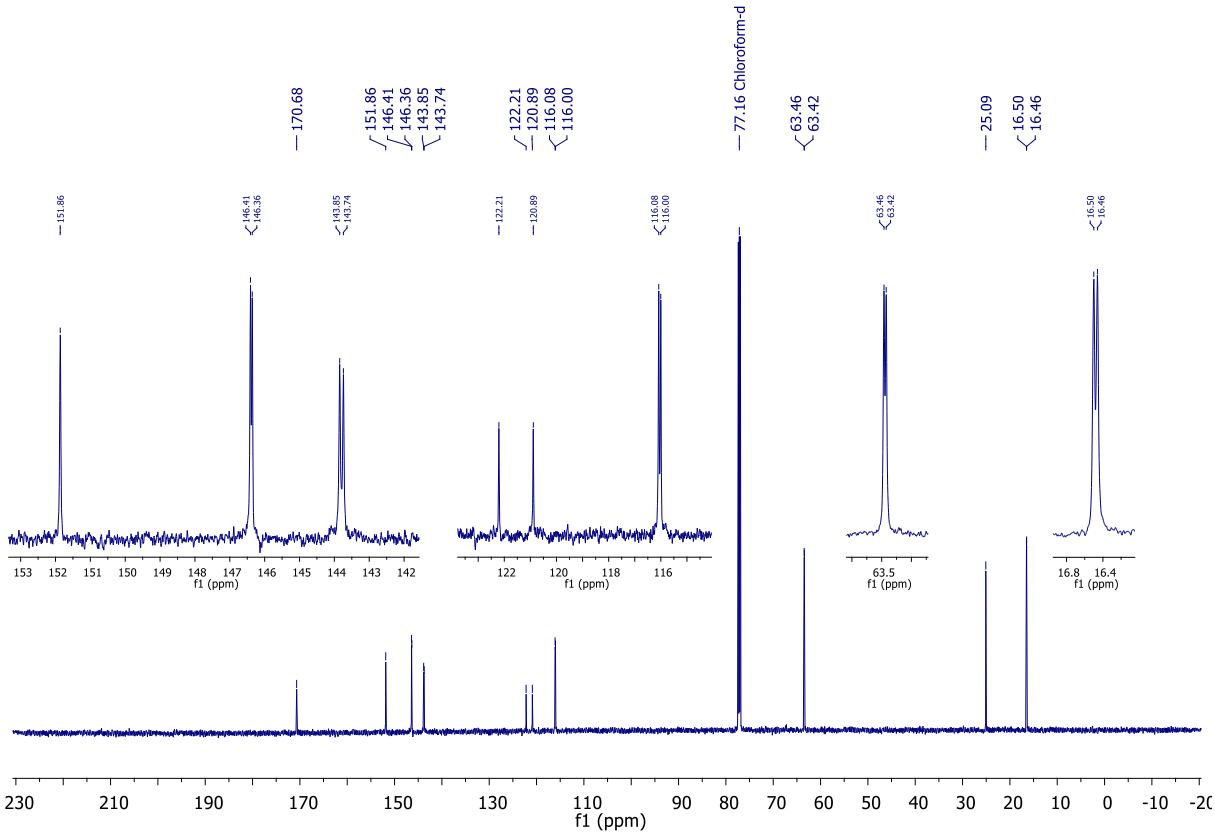
Compound 55·HCl



^{1}H NMR (600 MHz, $CDCl_3$) spectrum of **55·HCl**.

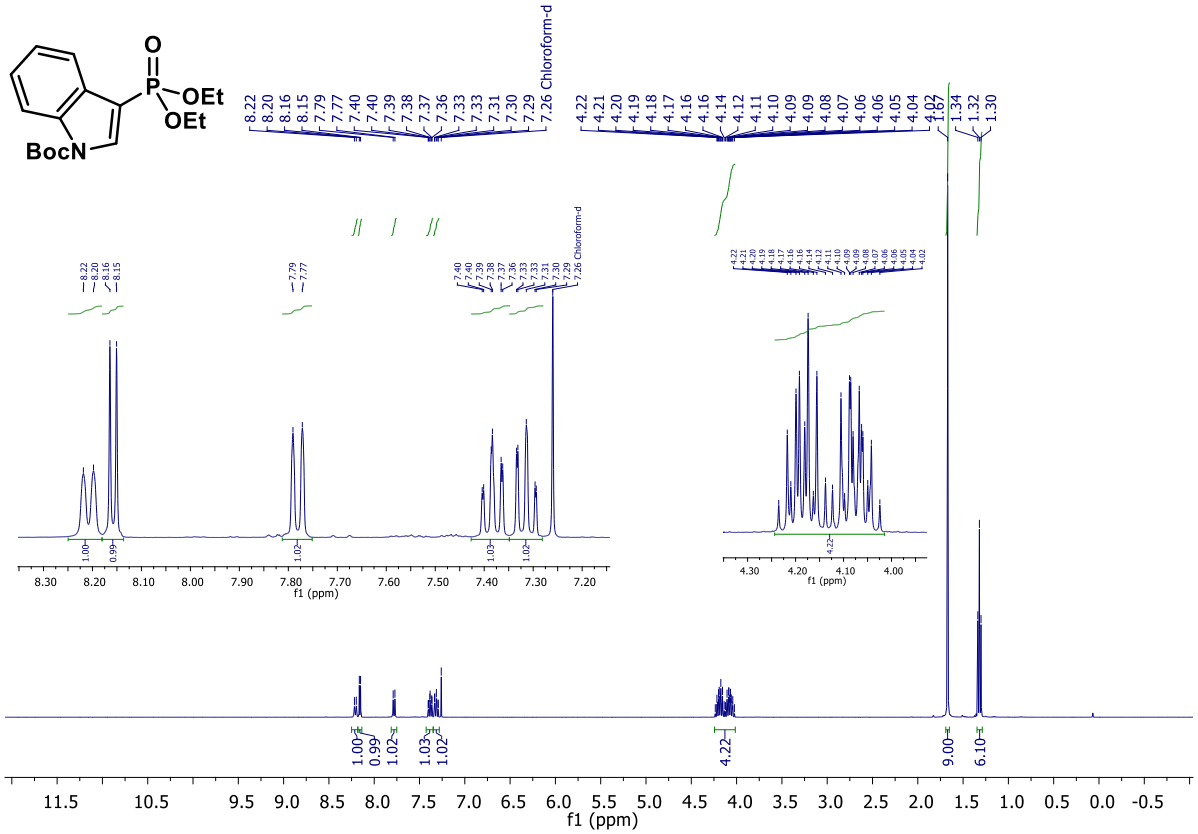


^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$) spectrum of **55·HCl**.

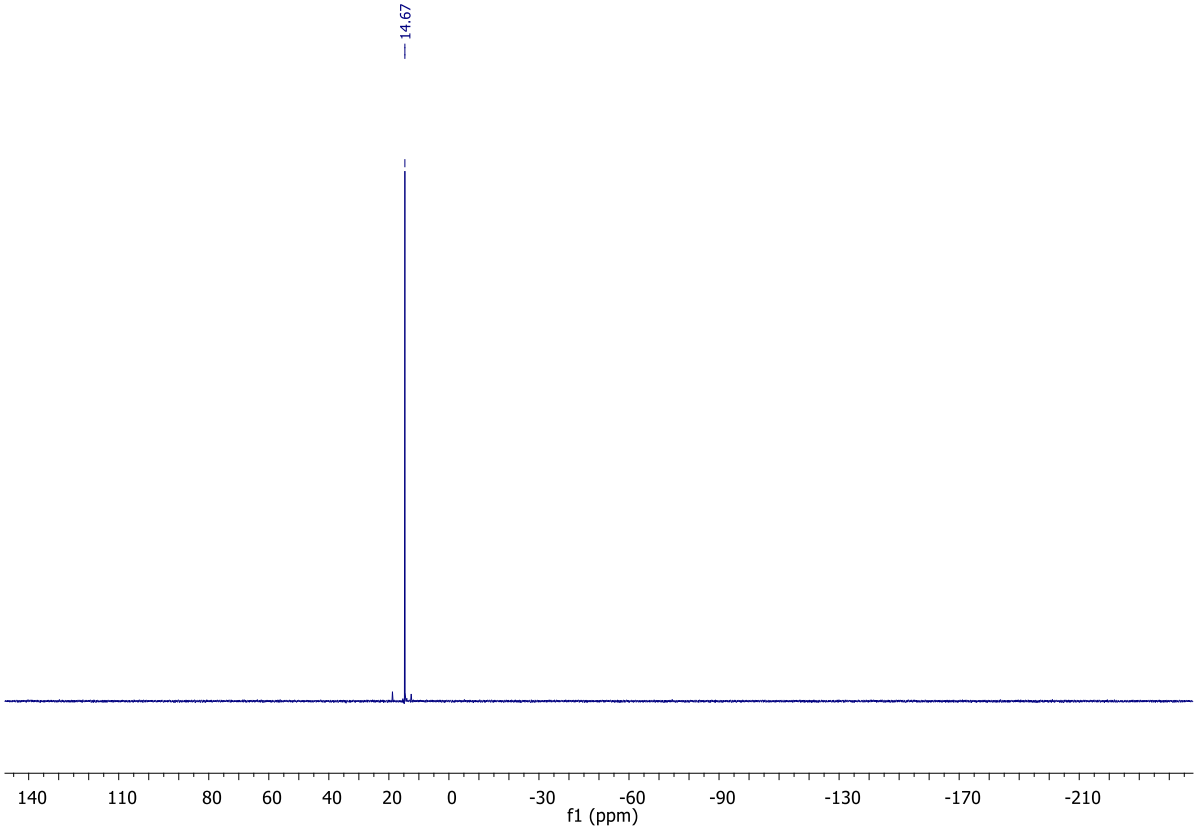


$^{13}C\{^{1}H\}$ NMR (151 MHz, $CDCl_3$) spectrum of **55·HCl**.

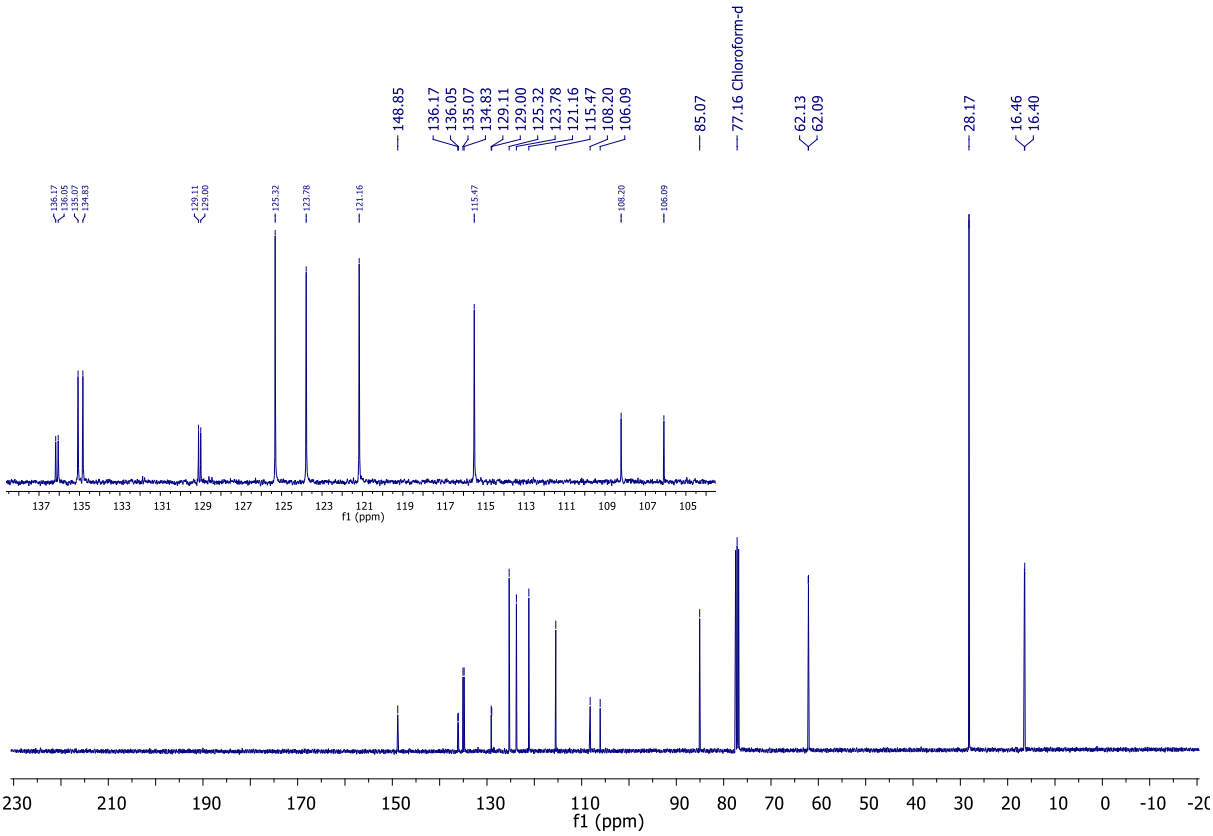
Compound 59



^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **59**.

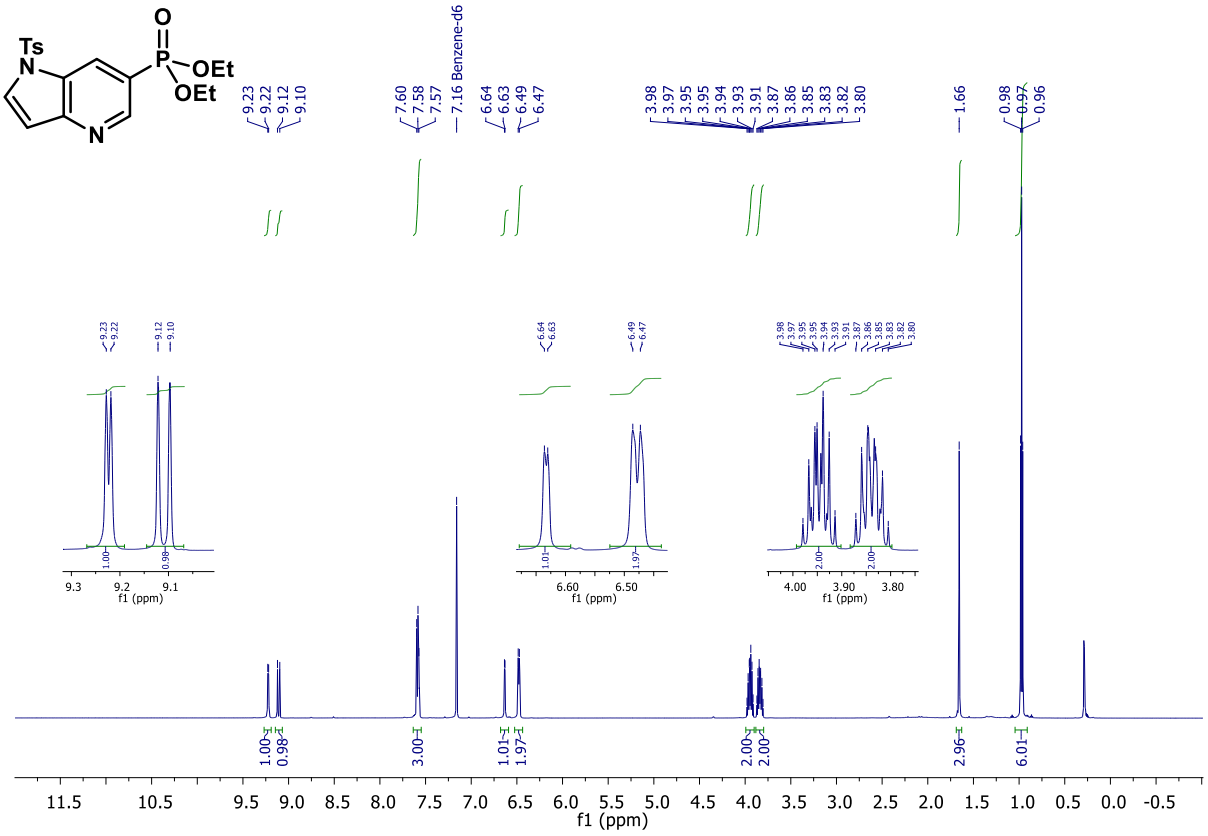


^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$) spectrum of **59**.

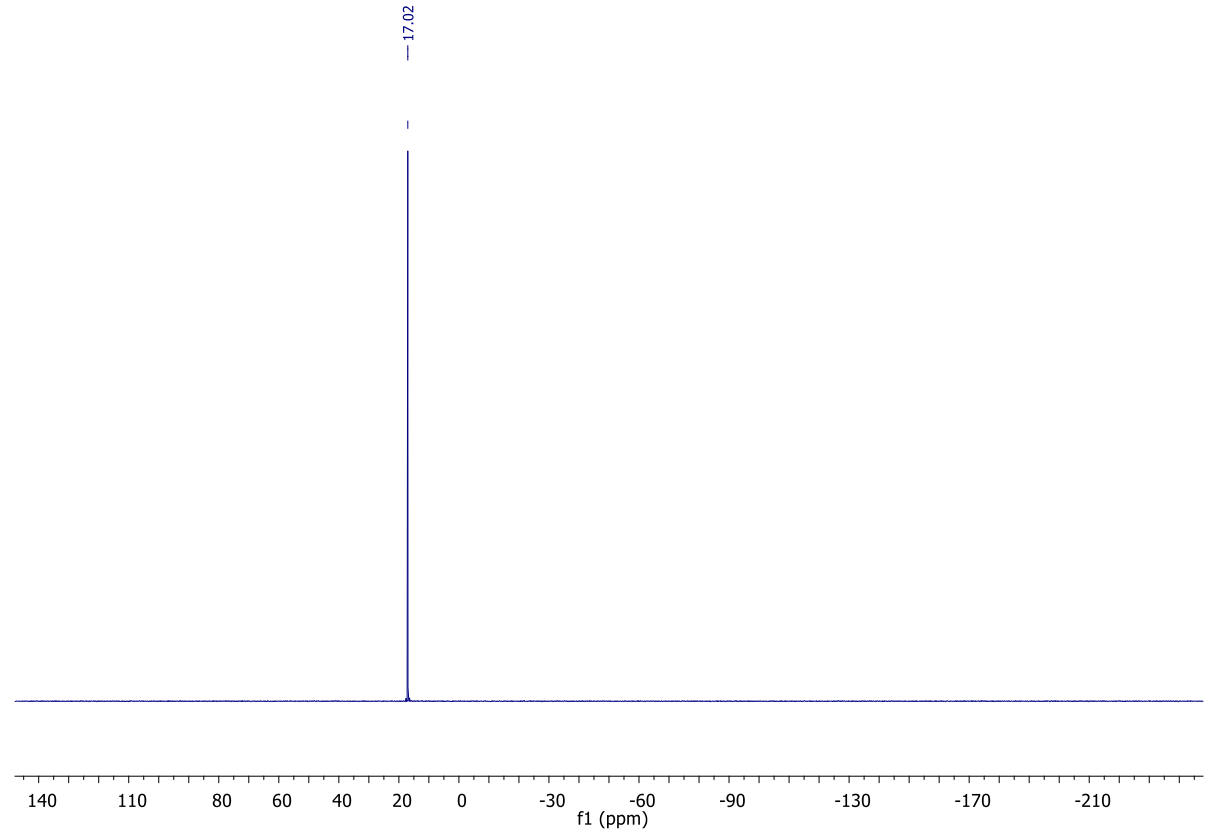


$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) spectrum of **59**.

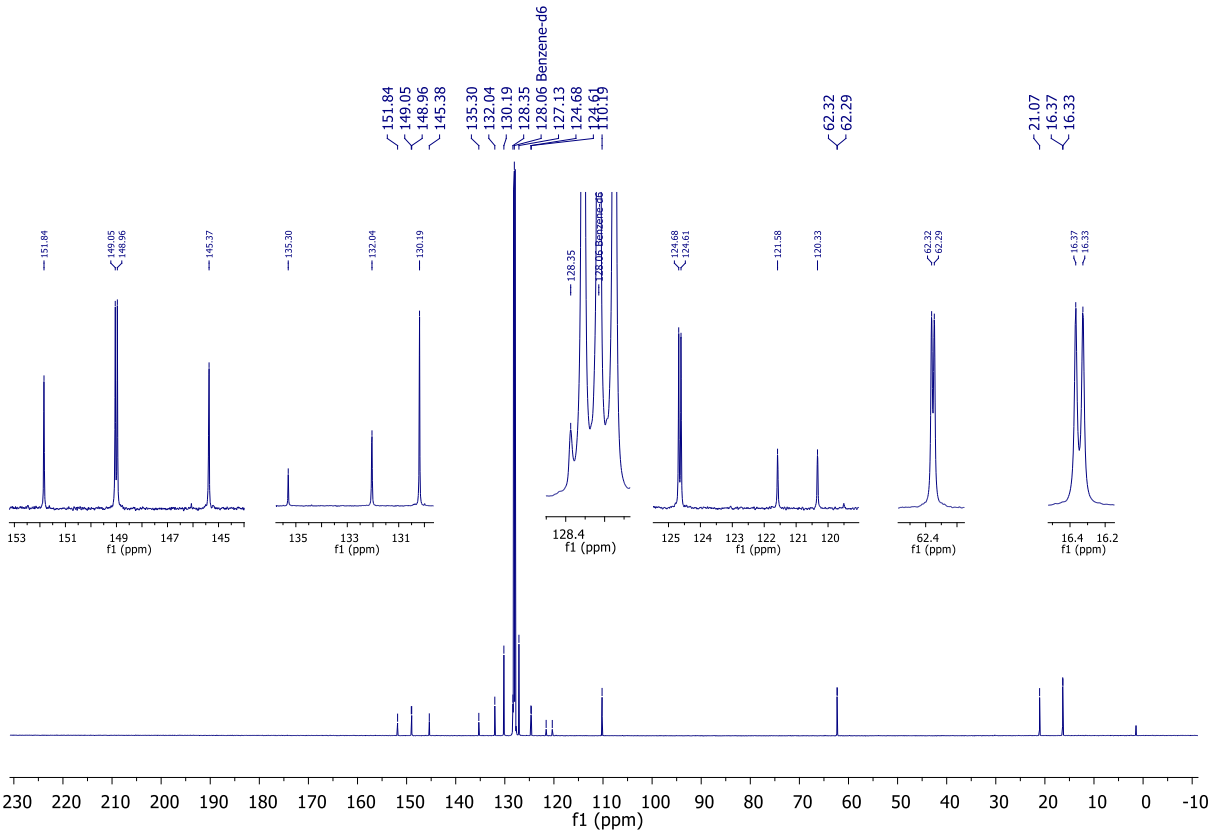
Compound 60



^{1}H NMR (600 MHz, C_6D_6) spectrum of **60**.

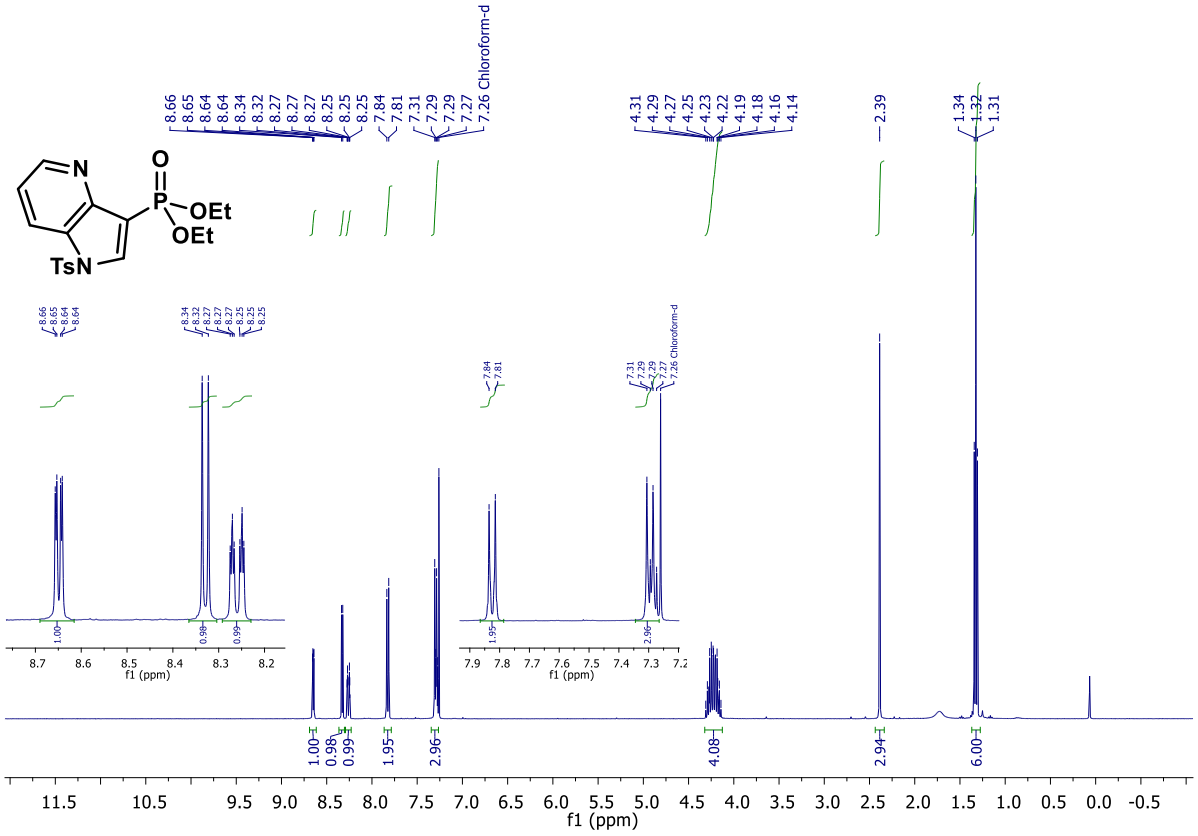


^{31}P{^{1}H} NMR (162 MHz, C_6D_6) spectrum of **60**.

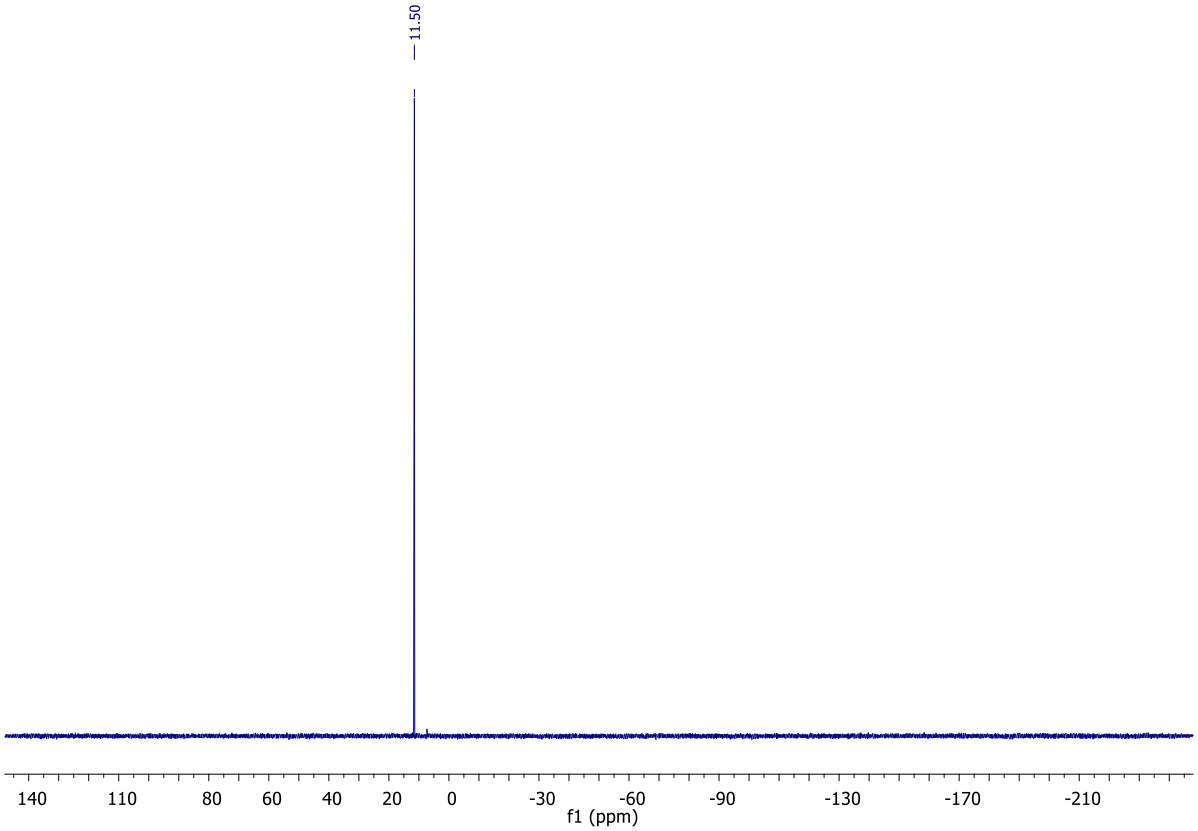


$^{13}C\{^{1}H\}$ NMR (151 MHz, C_6D_6) spectrum of **60**.

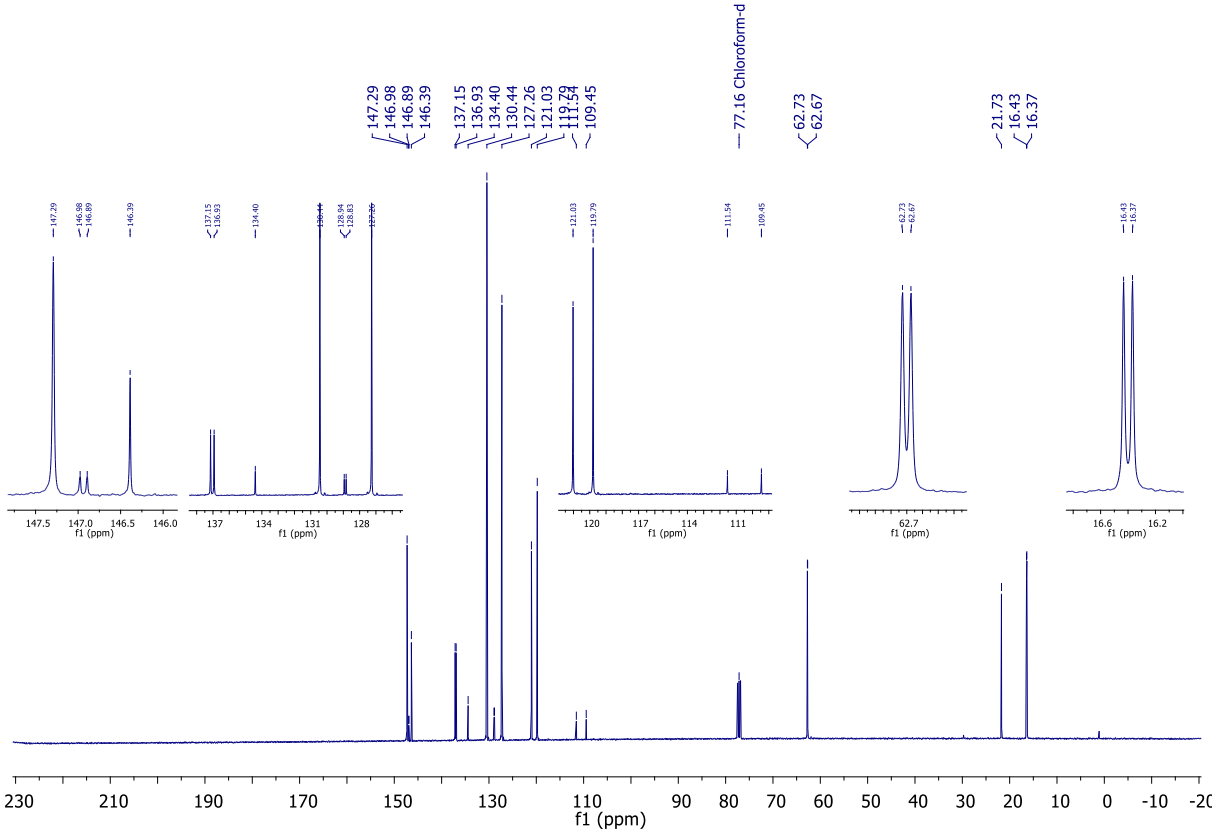
Compound 61



^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **61**.

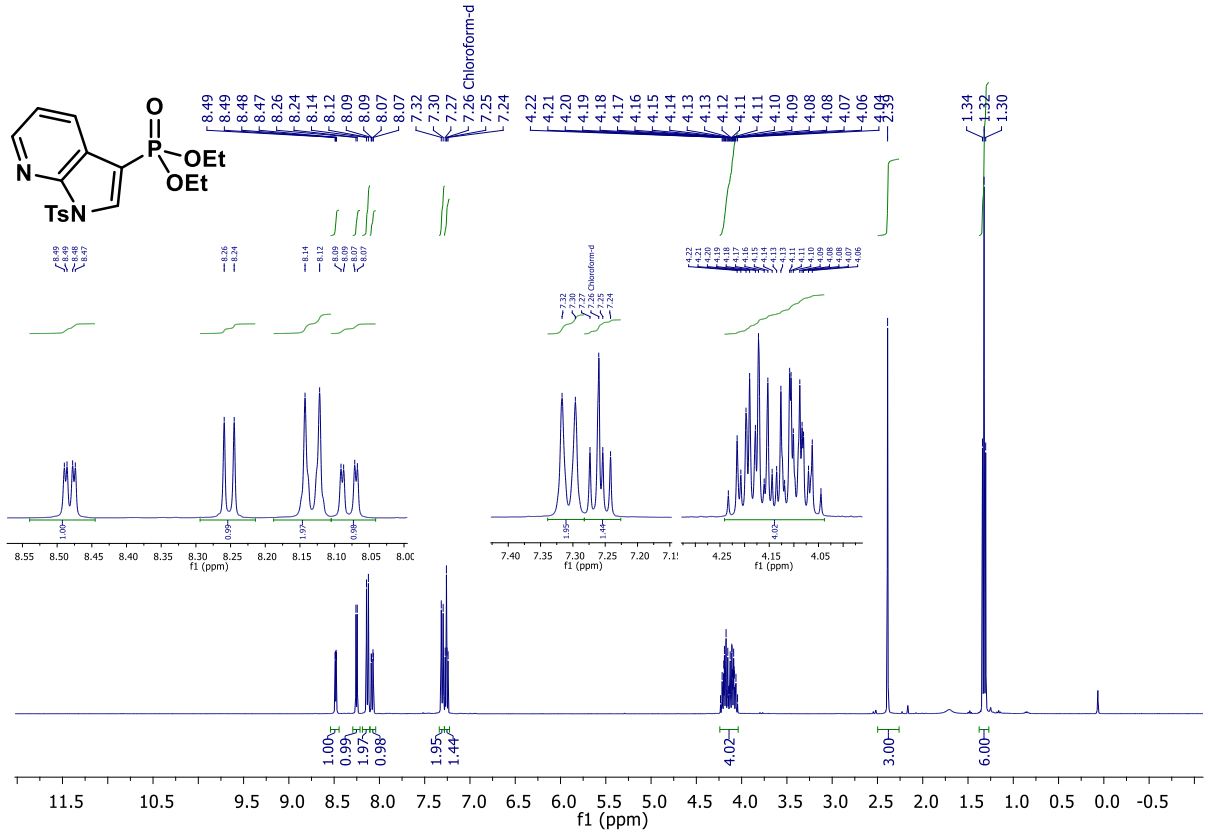


^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$) spectrum of **61**.

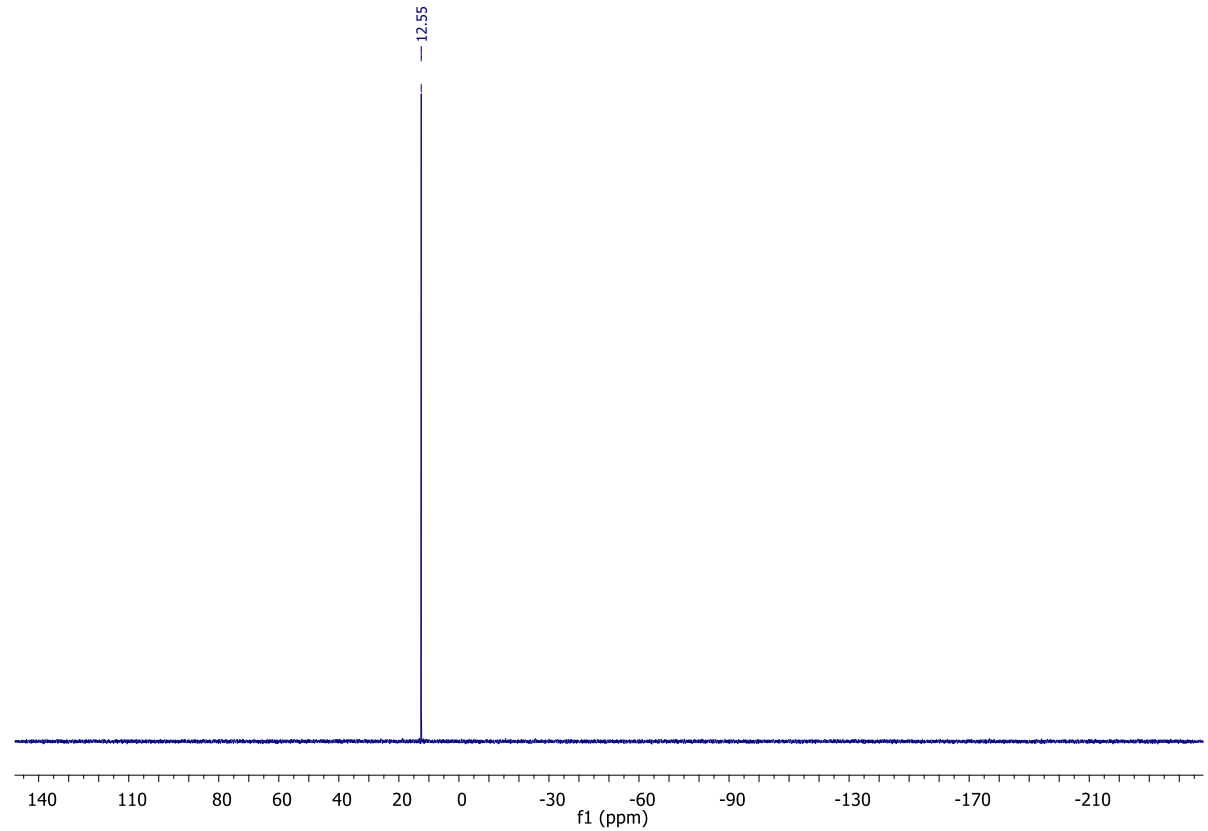


$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) spectrum of **61**.

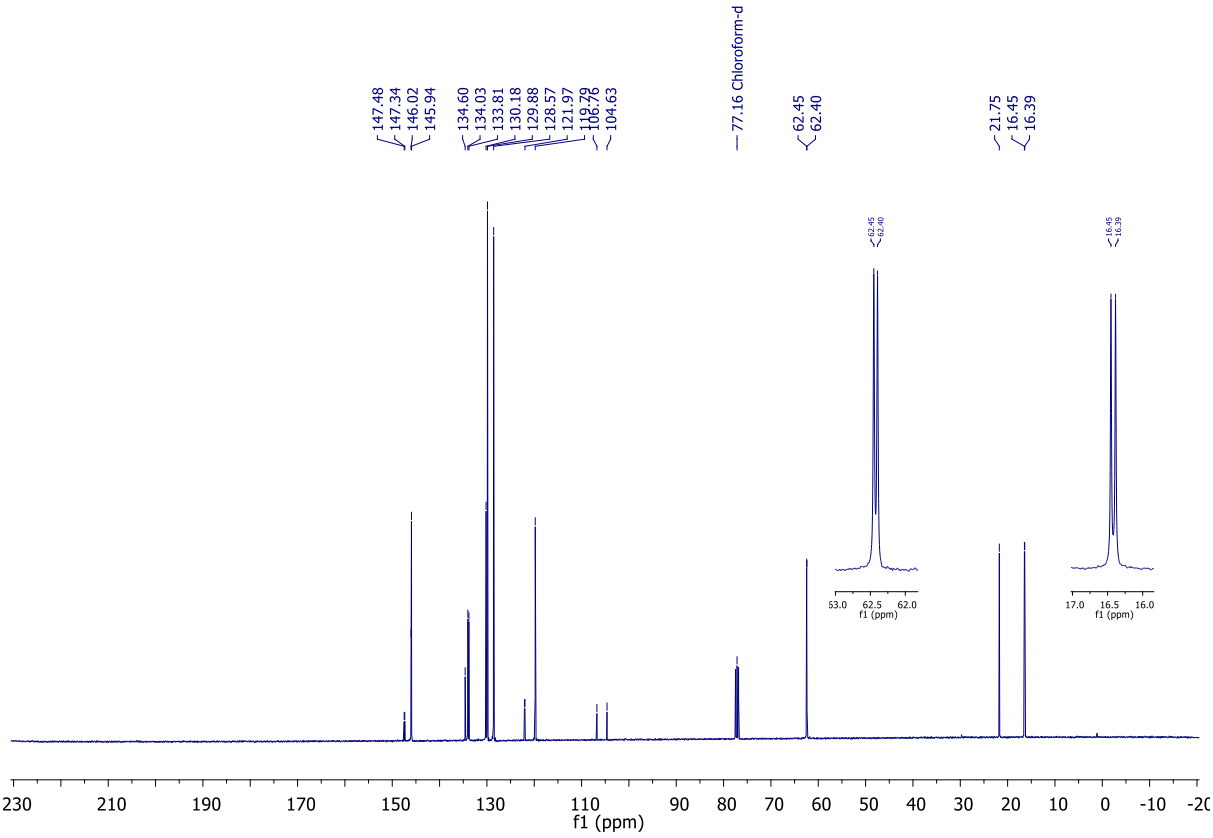
Compound 62



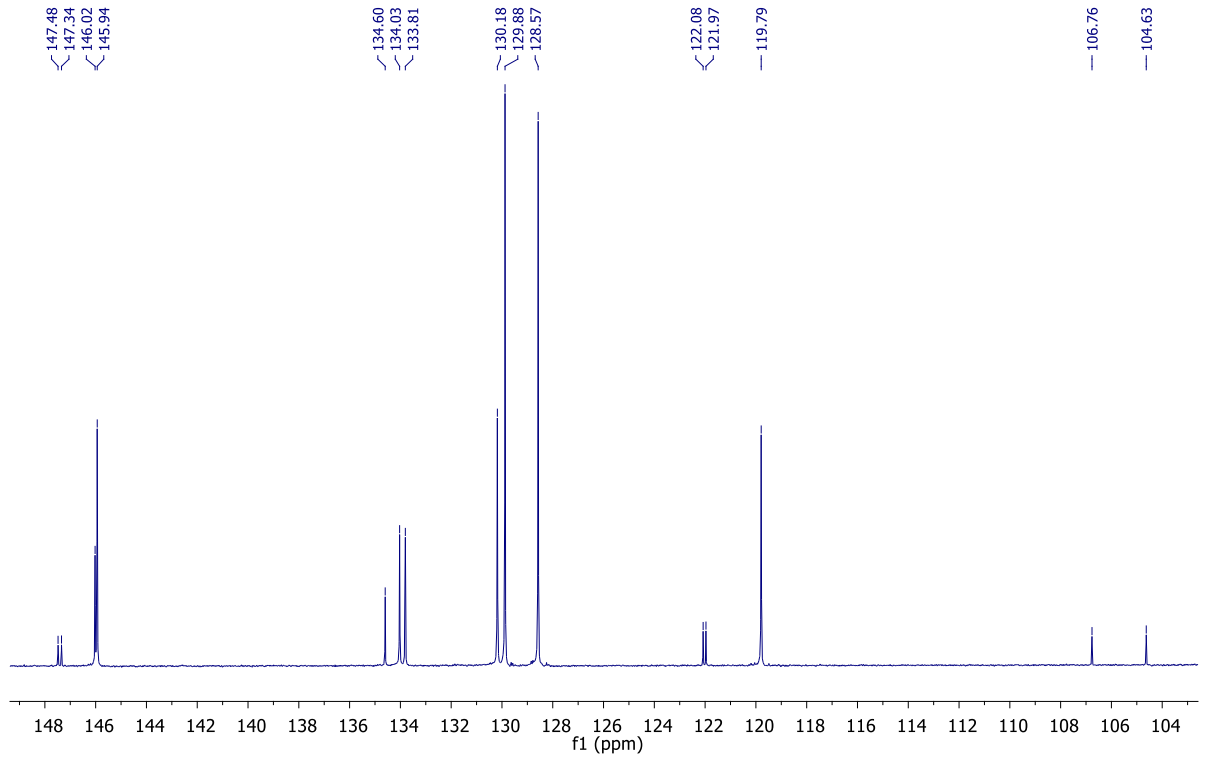
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **62**.



^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$) spectrum of **62**.

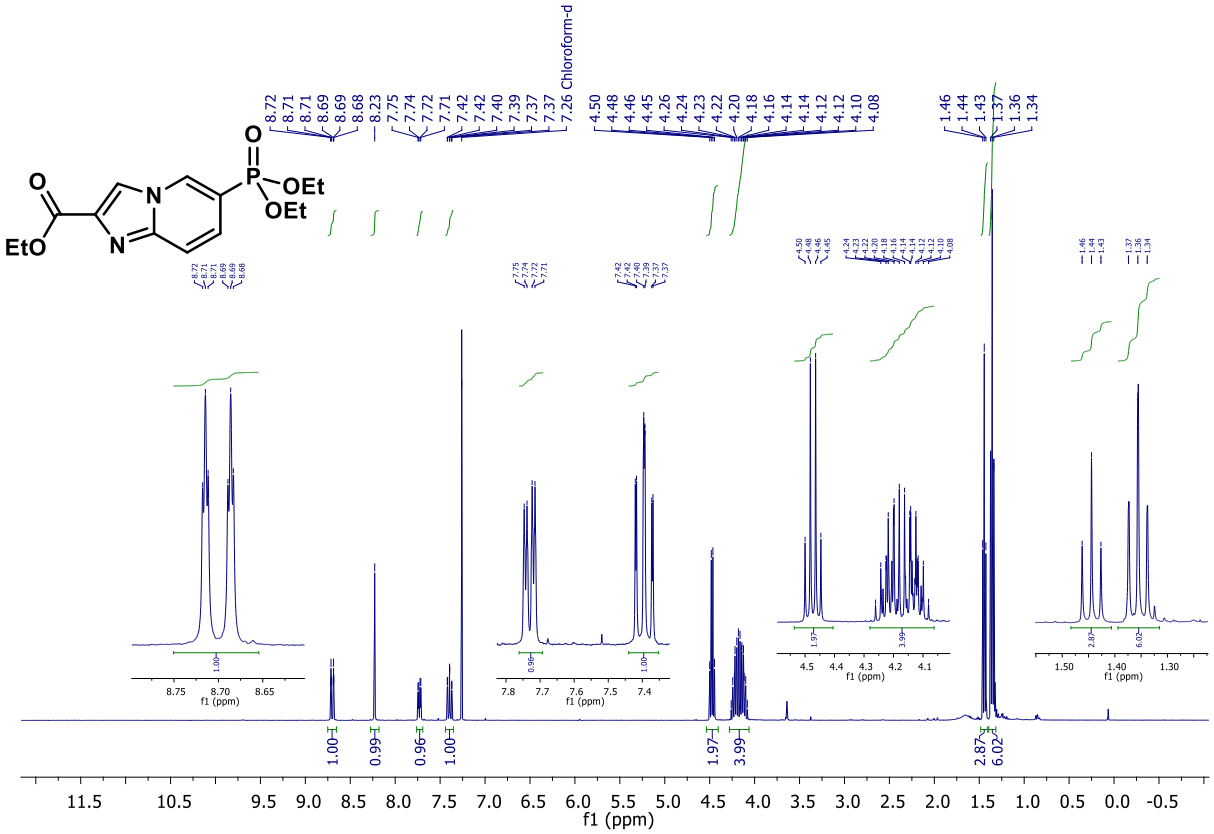


$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) spectrum of **62**.

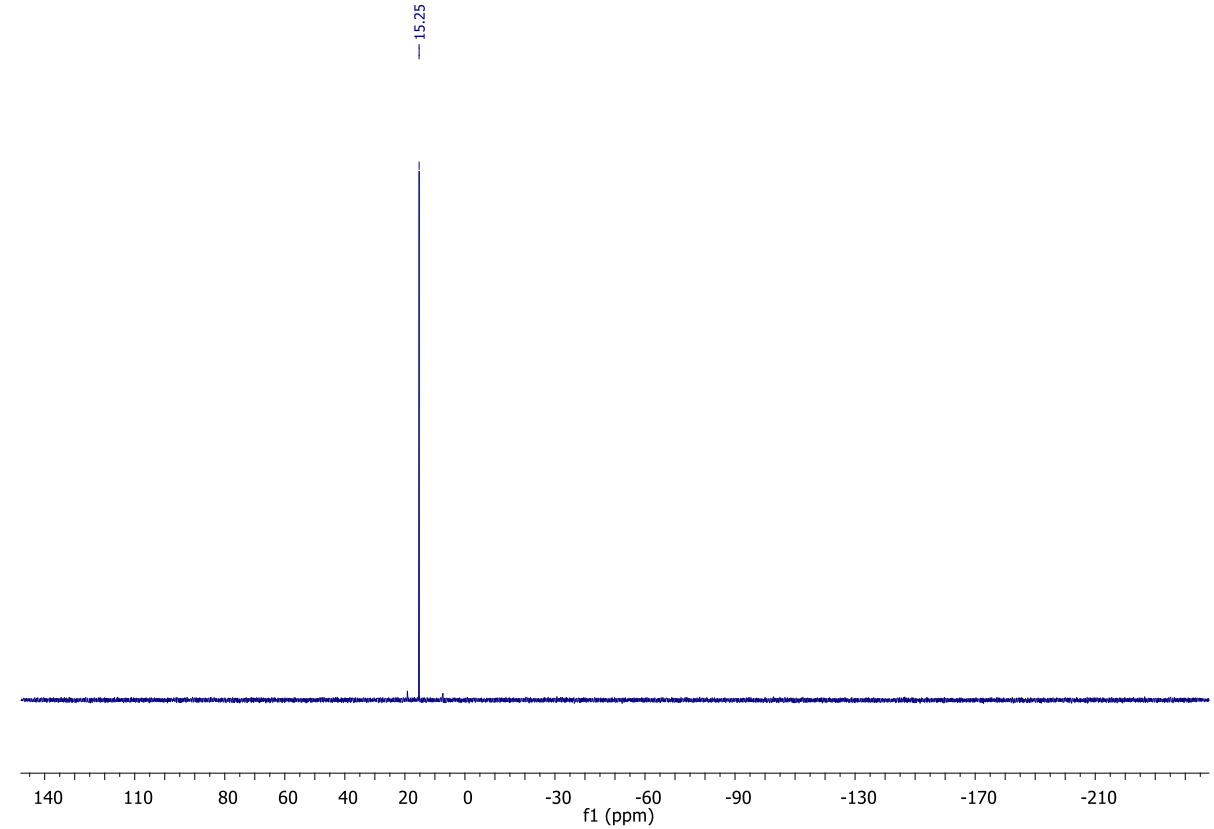


$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) spectrum of **62** in more detail.

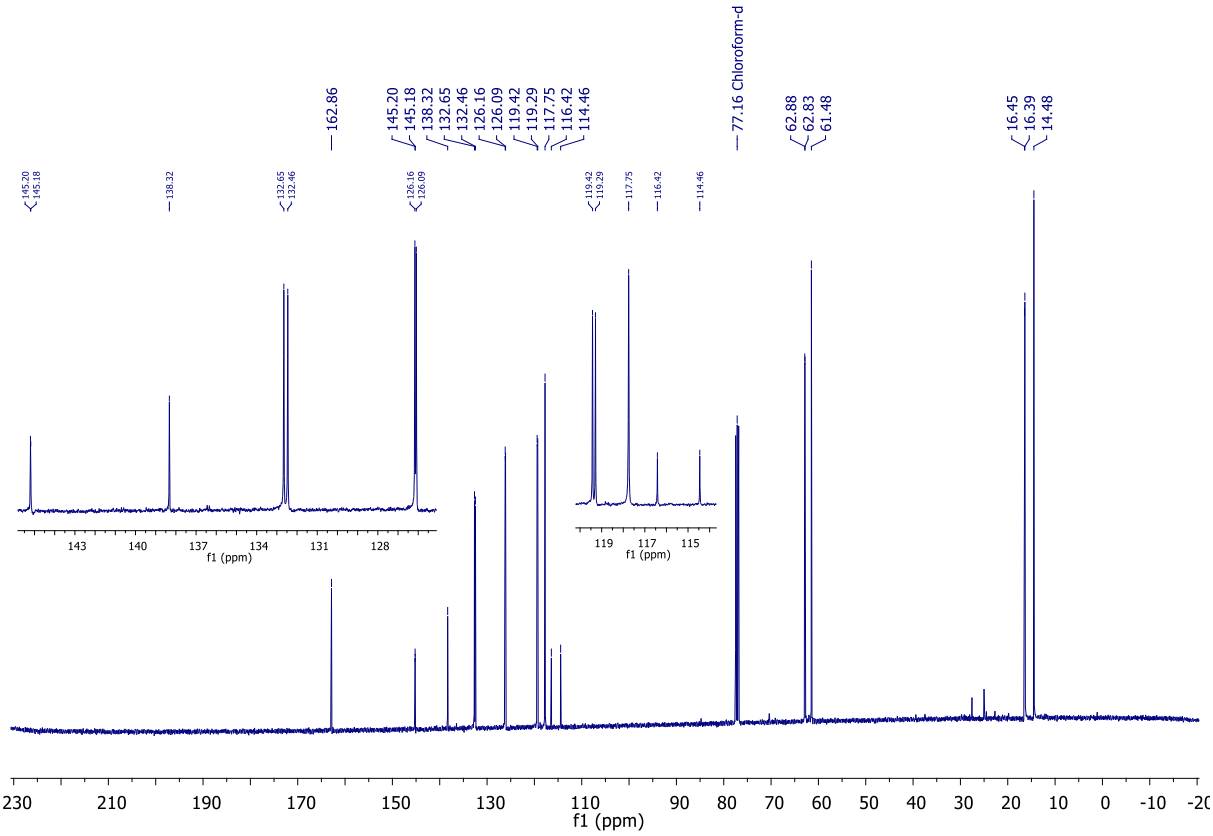
Compound 63



^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **63**

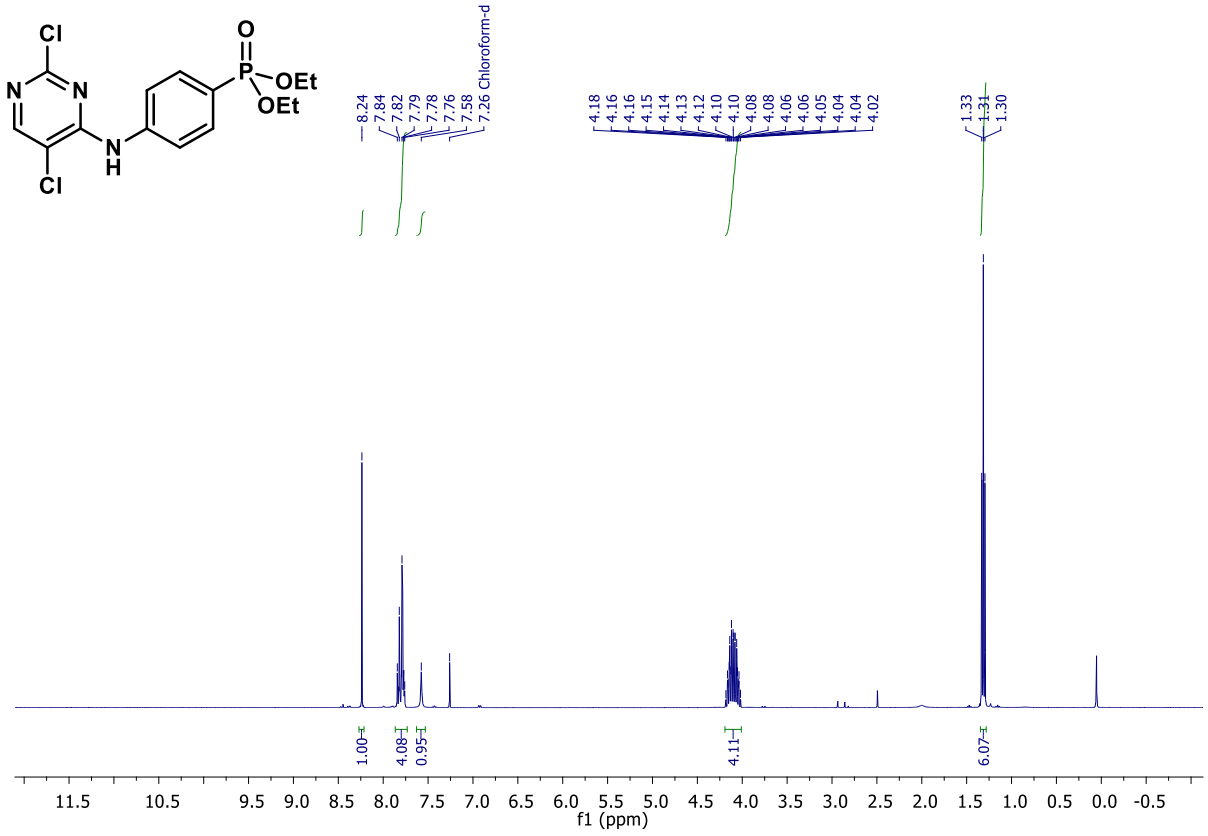


^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$) spectrum of **63**.

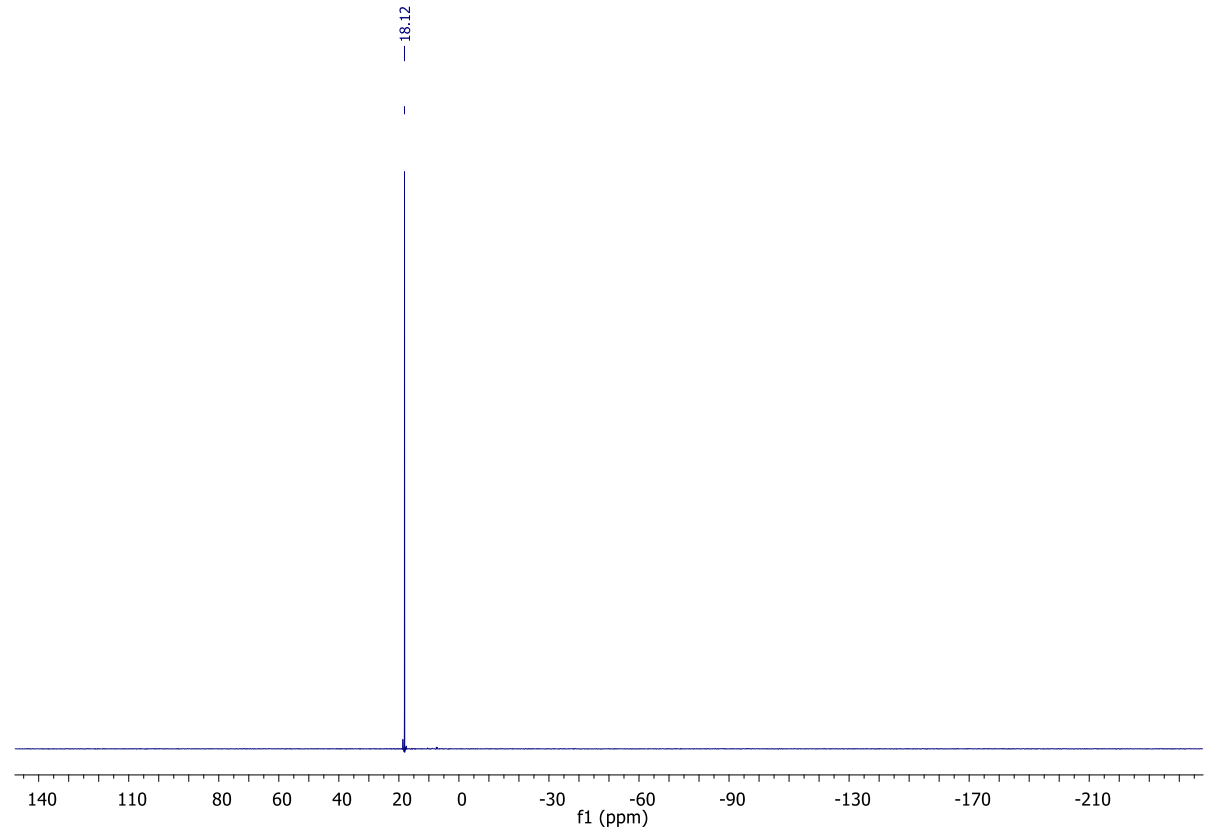


$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) spectrum of **63**.

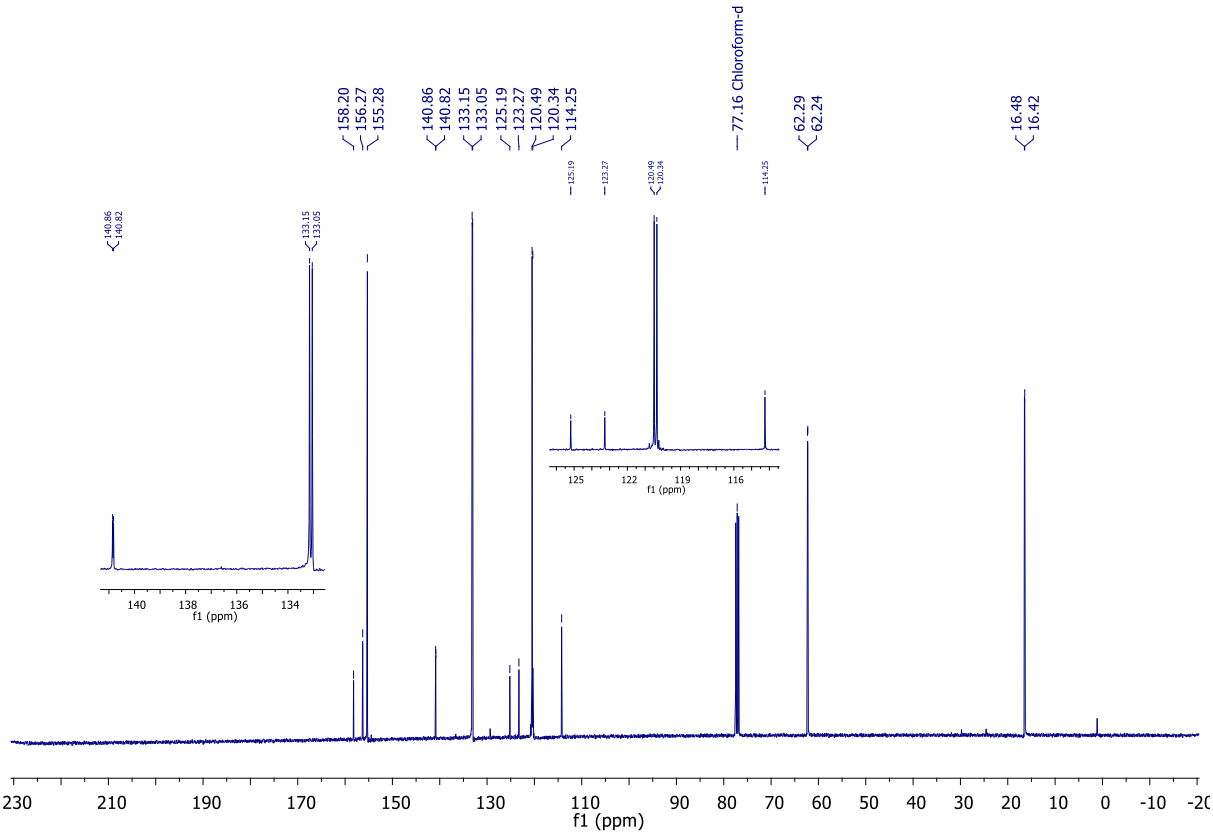
Compound 64



^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **64**.

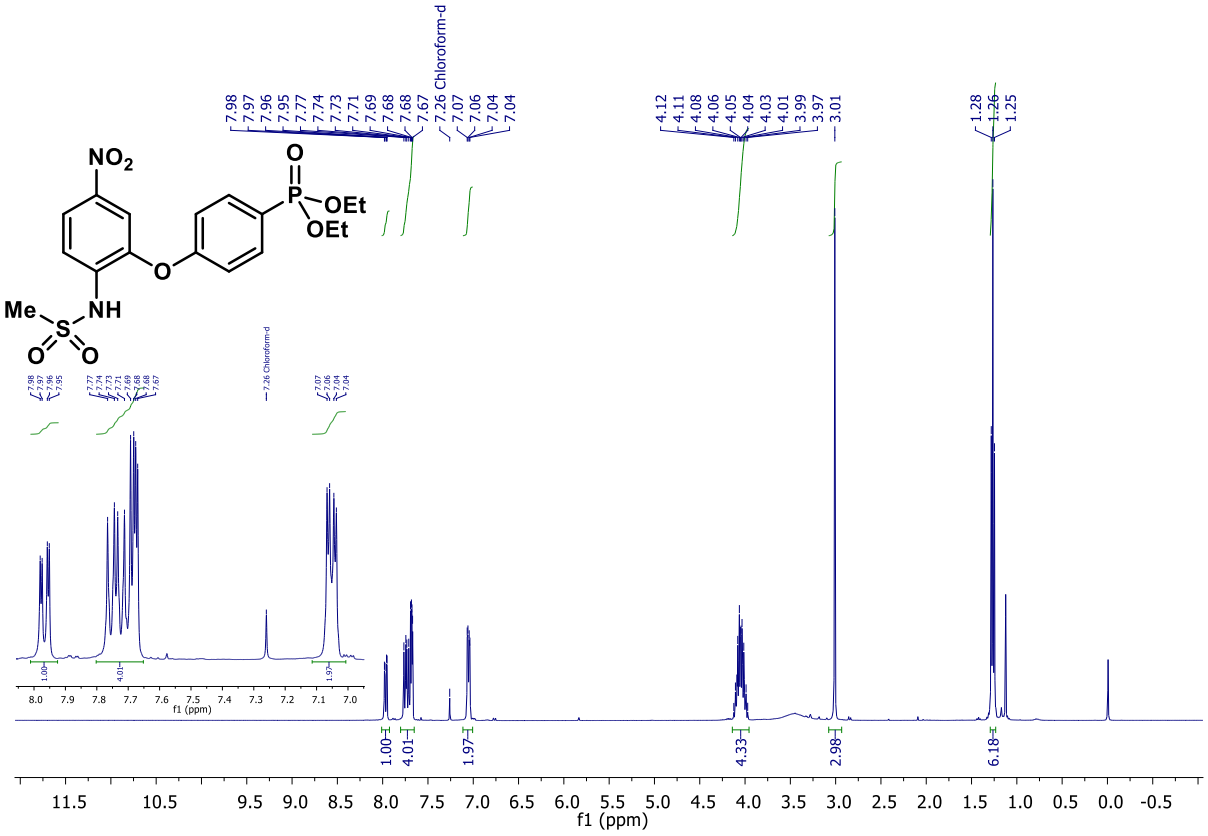


^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$) spectrum of **64**.

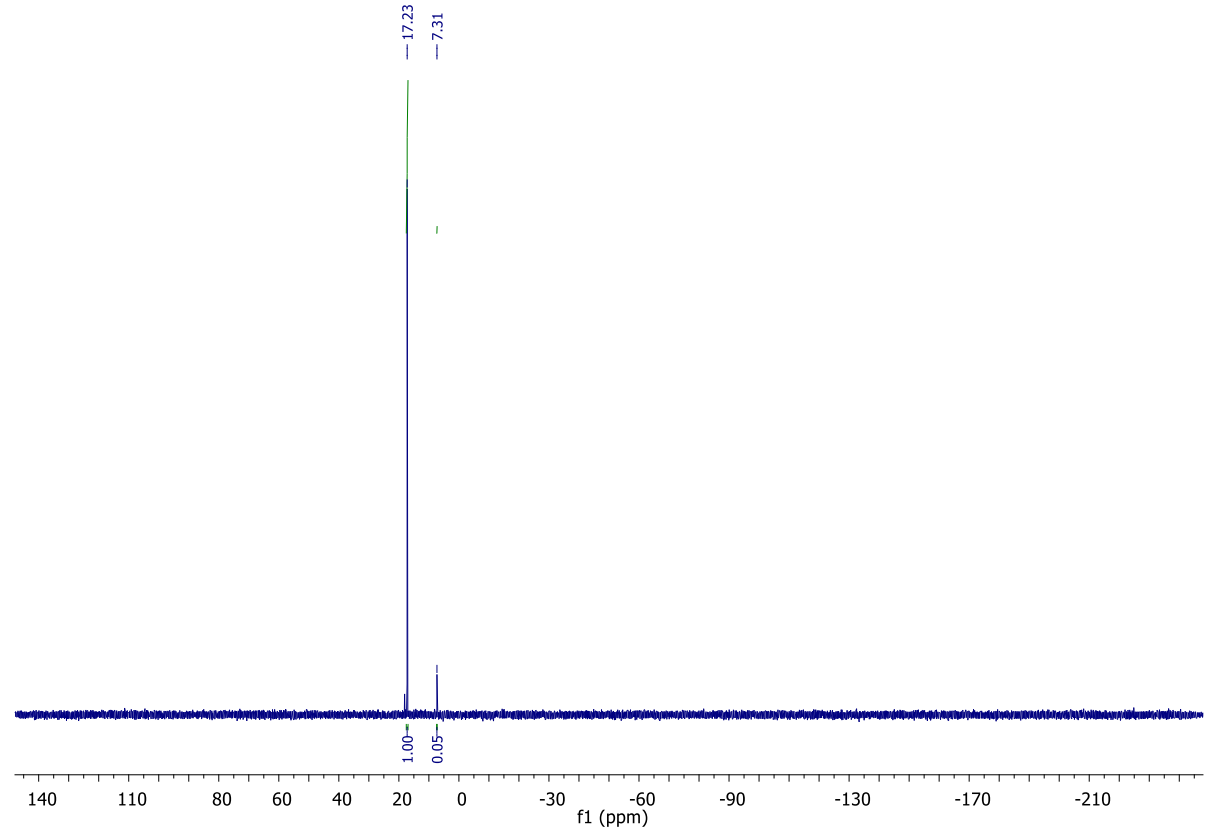


$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) spectrum of **64**.

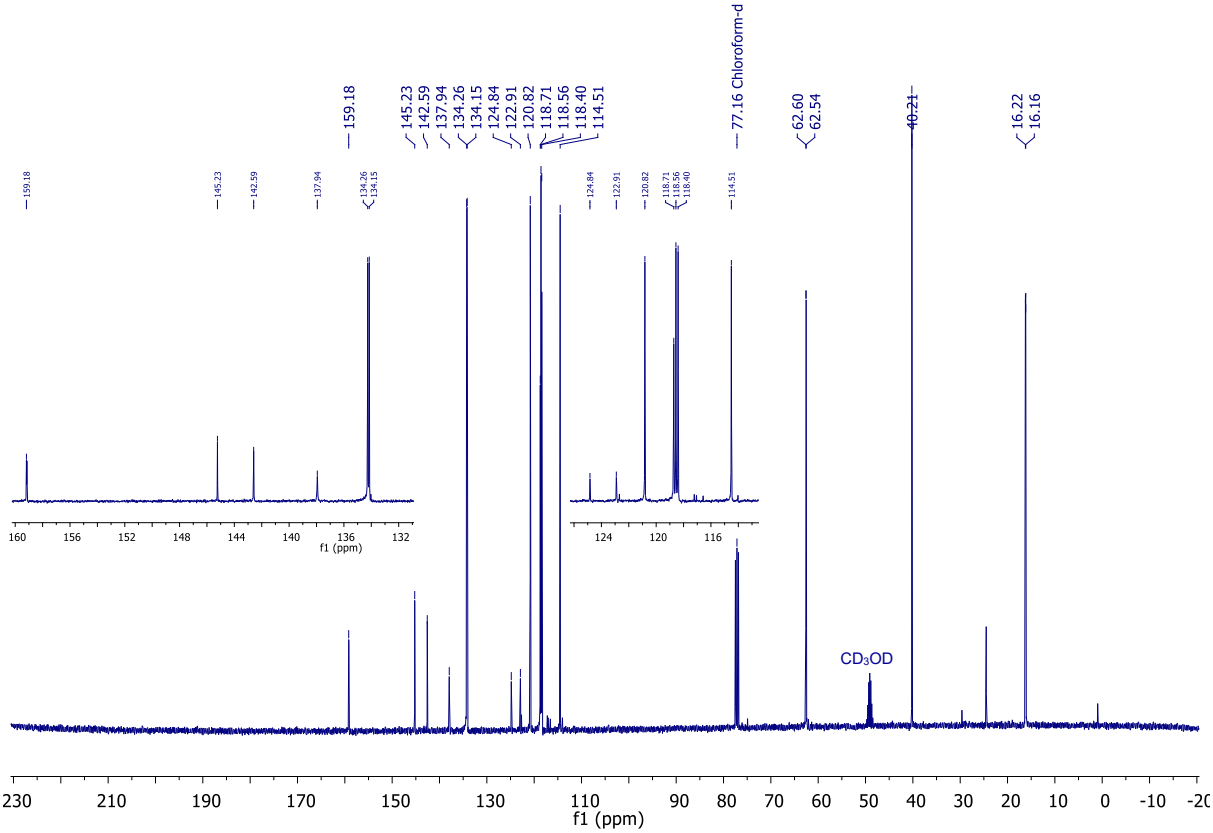
Compound 65



^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **65**.

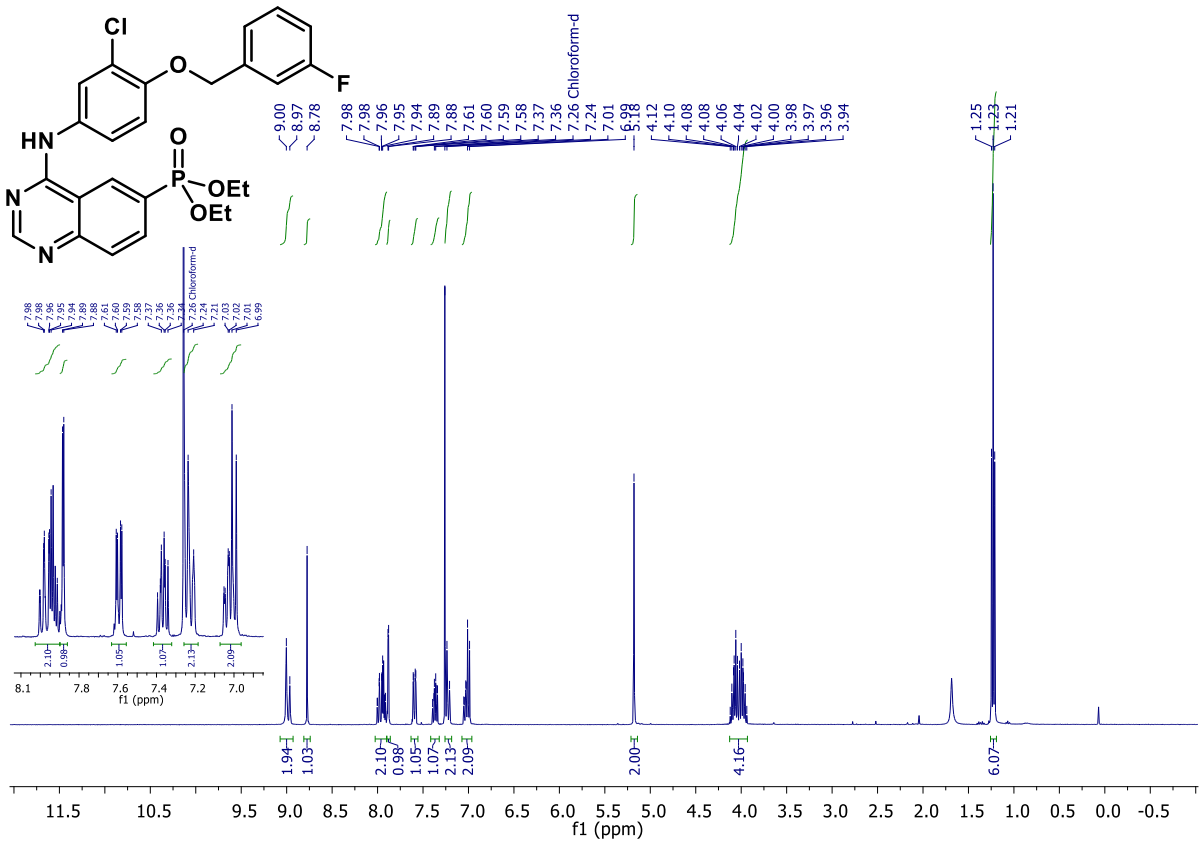


^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$) spectrum of **65**. The signal at 7.31 ppm corresponds to ca. 5% of *H*-phosphonate impurity.

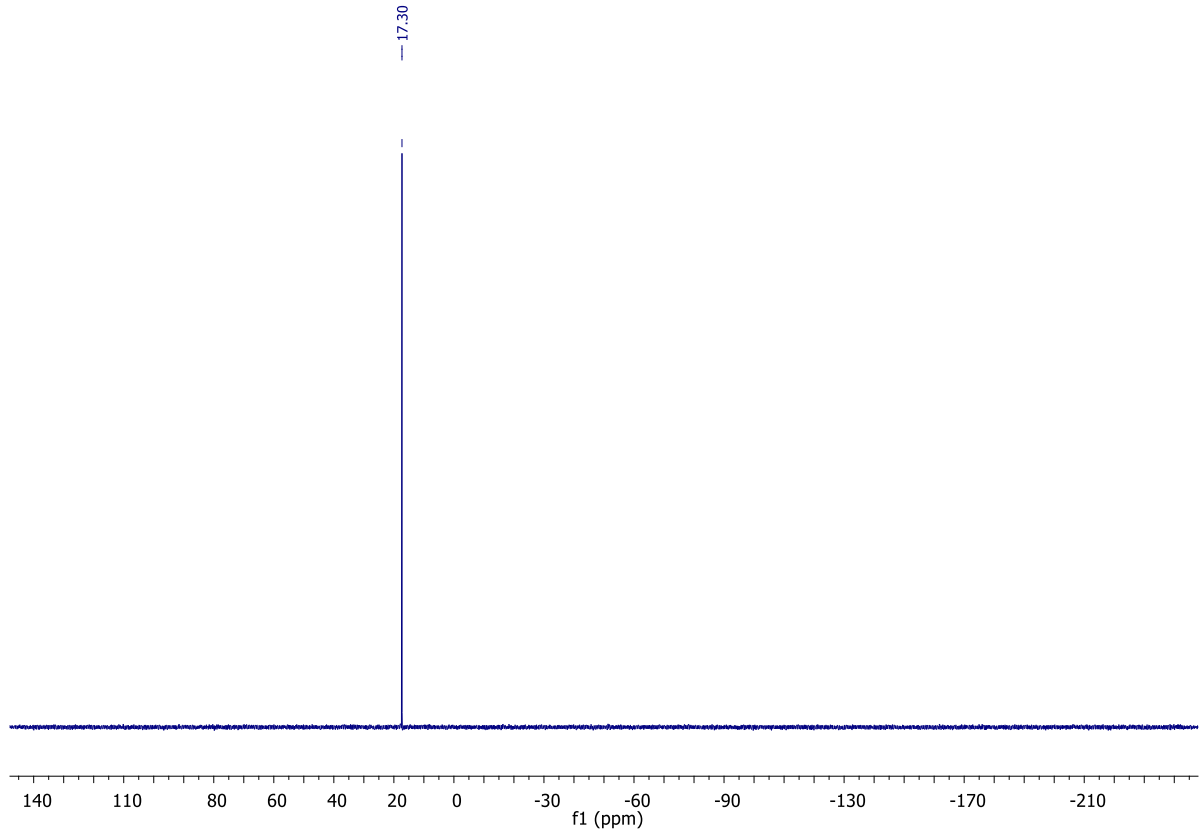


$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3/CD_3OD$ ~10:1) spectrum of **65**.

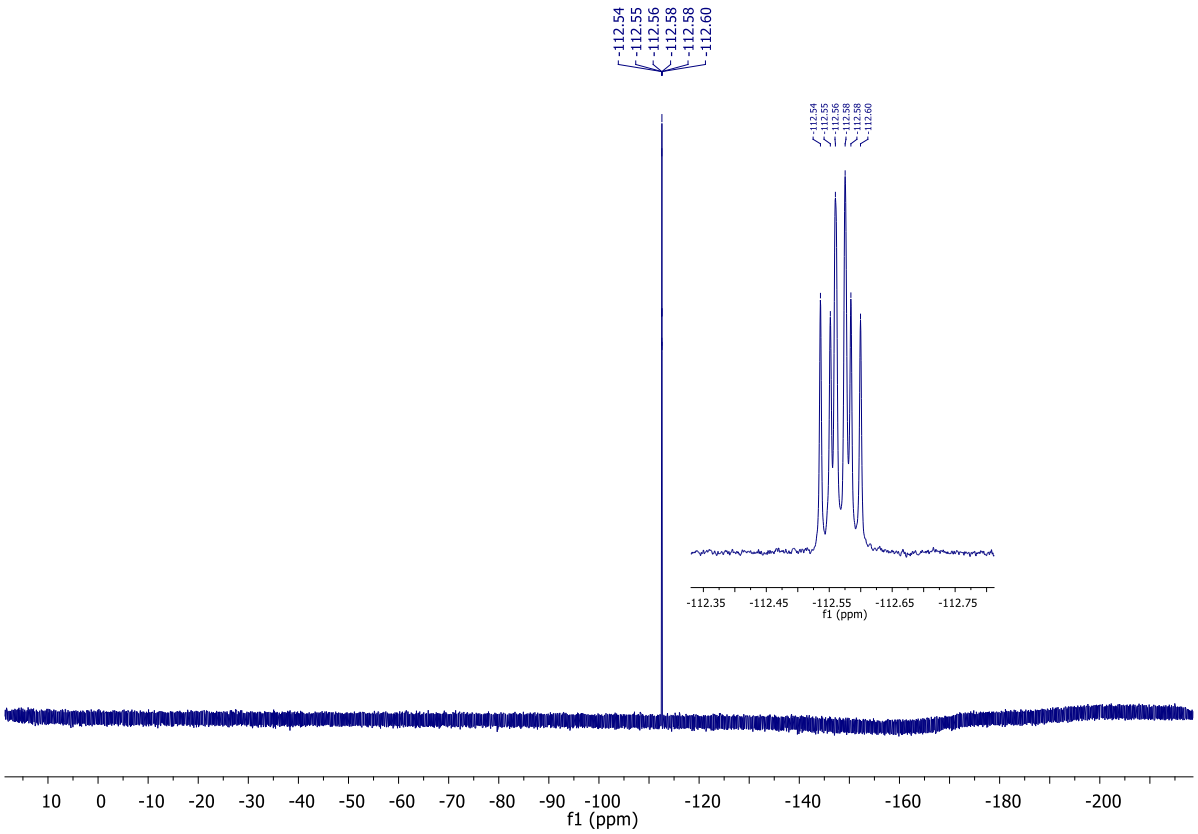
Compound 66



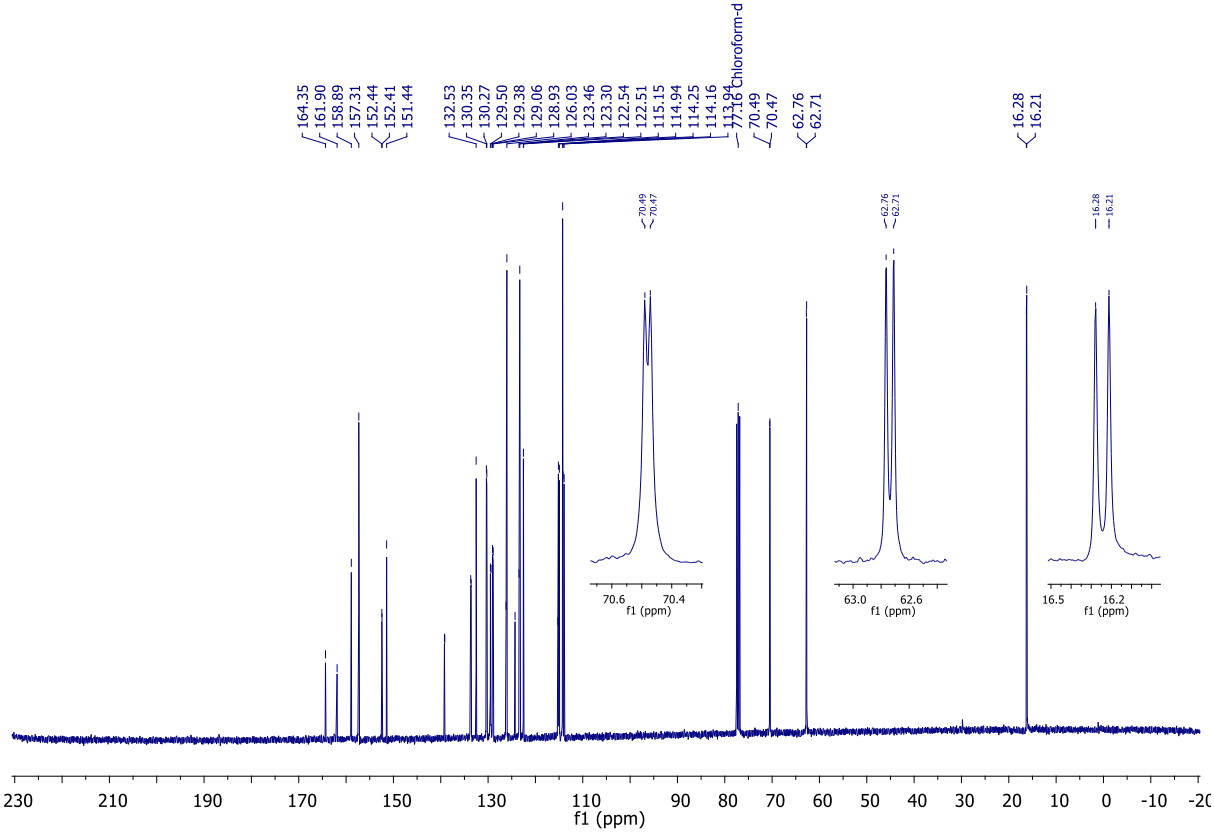
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **66**.



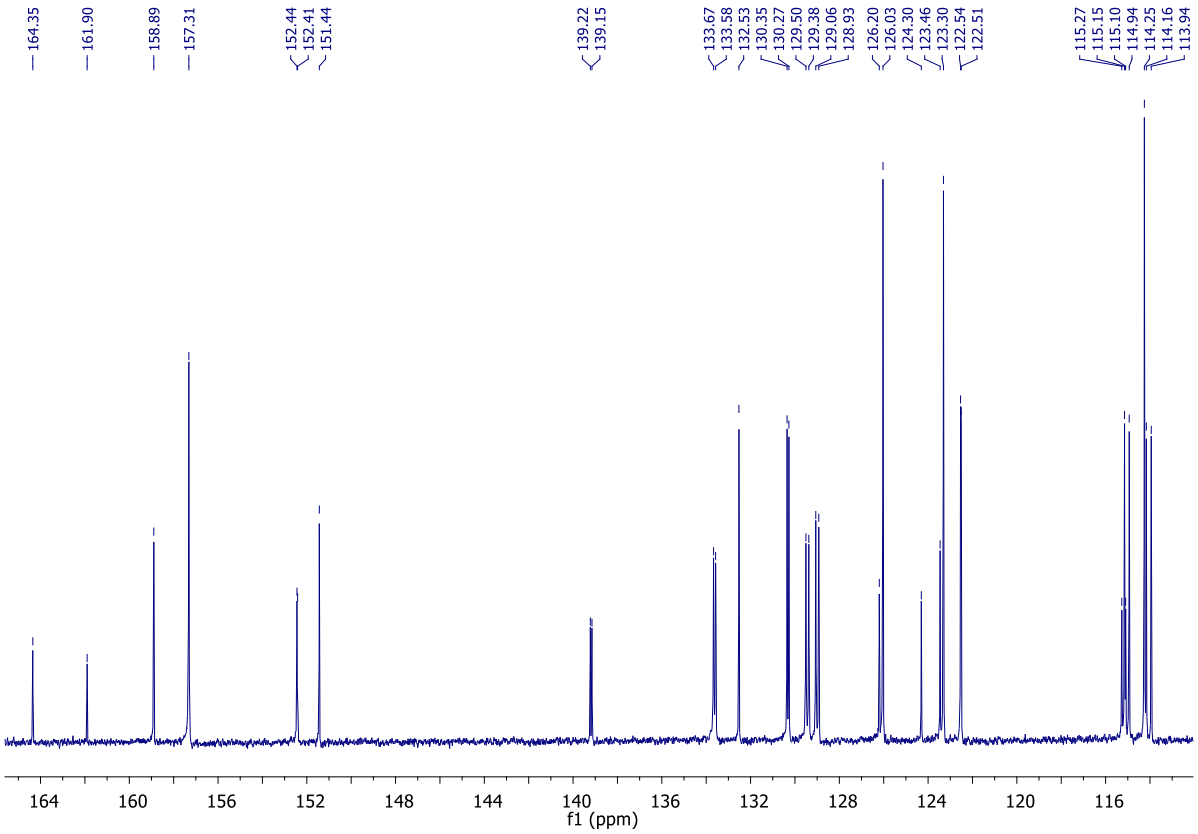
^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$) spectrum of **66**.



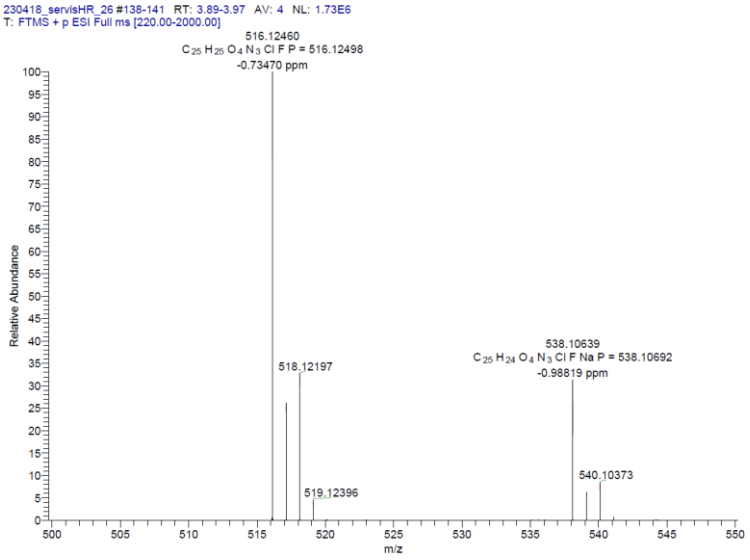
^{19}F NMR (376 MHz, $CDCl_3$) spectrum of **66**.



^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) spectrum of **66**.

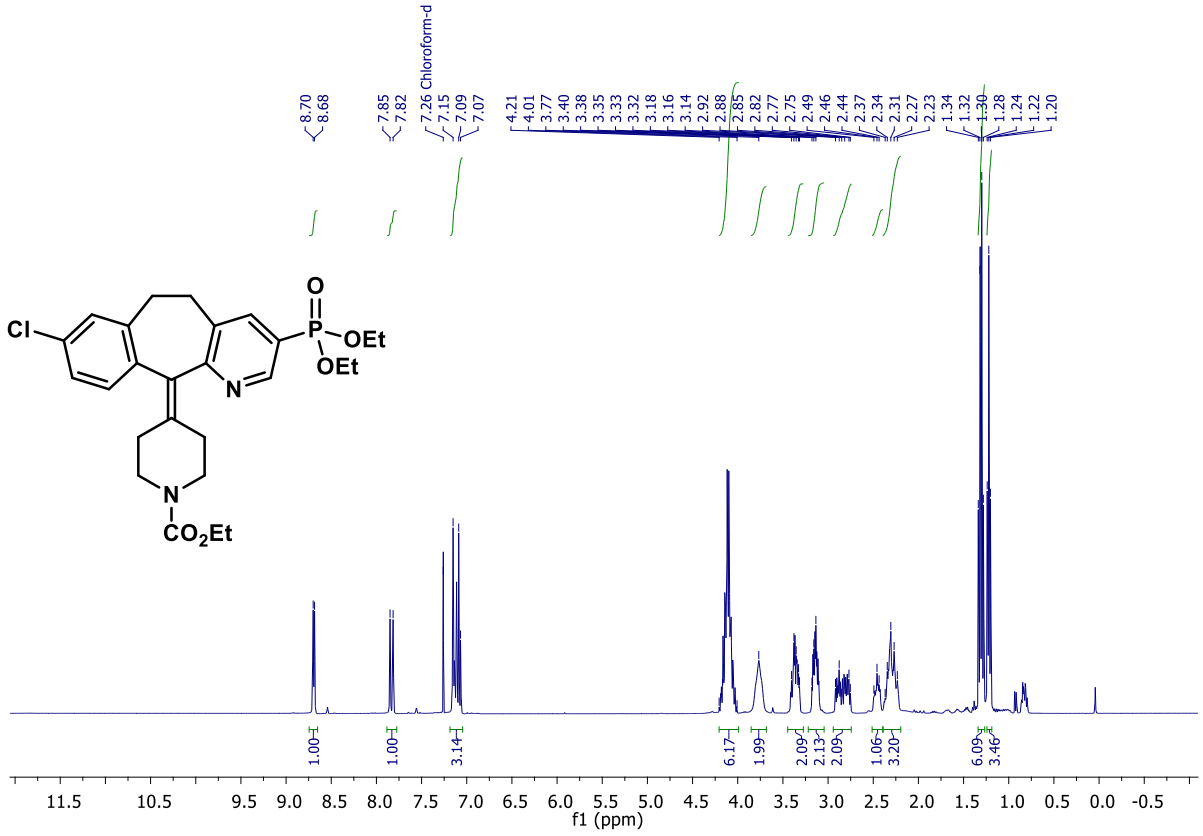


$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) spectrum of **66** in more detail.

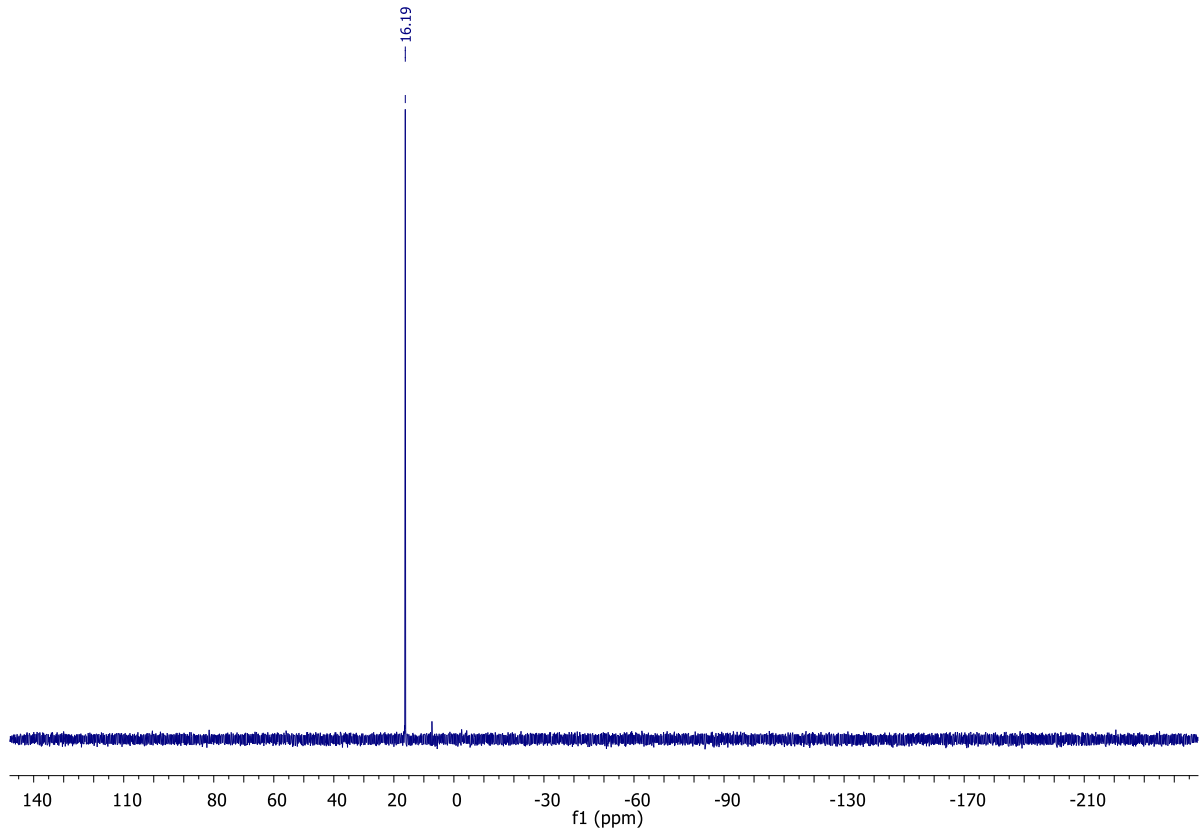


HRMS (ESI-TOF) spectrum of compound **66**.

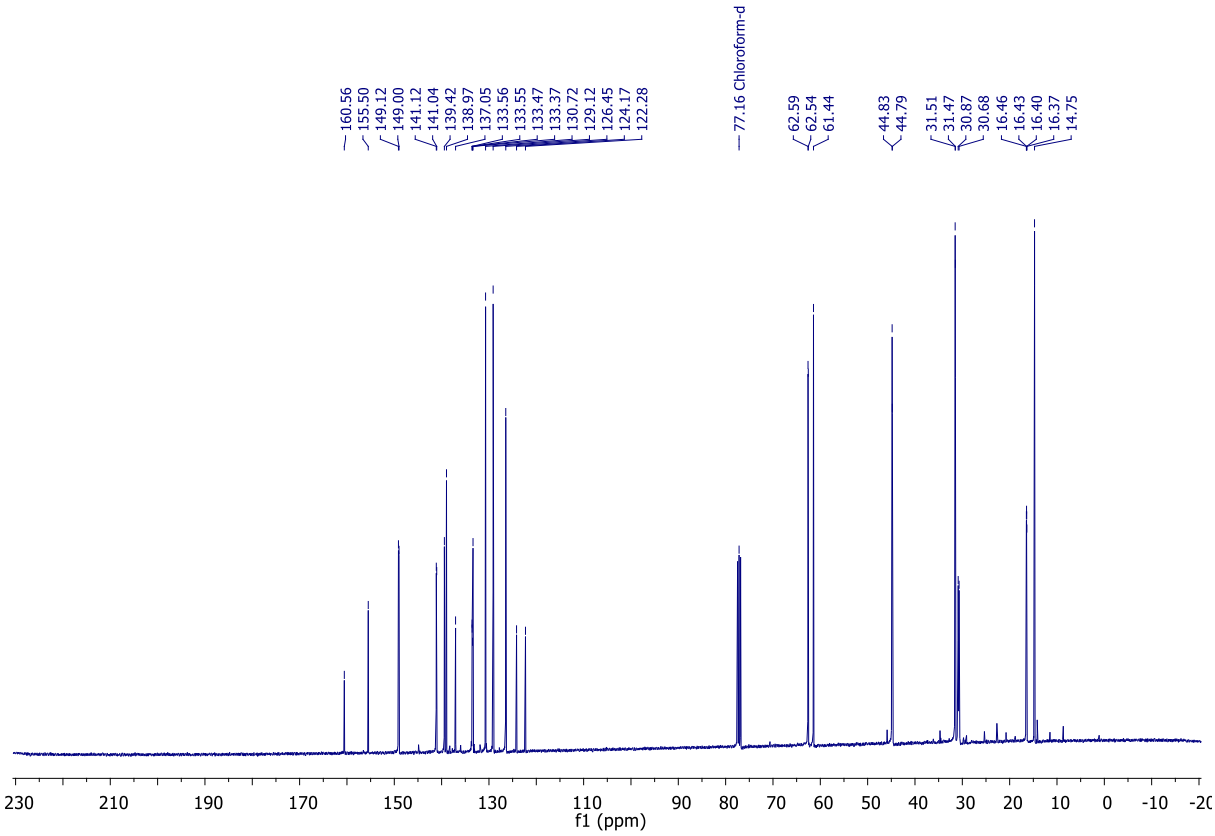
Compound 67



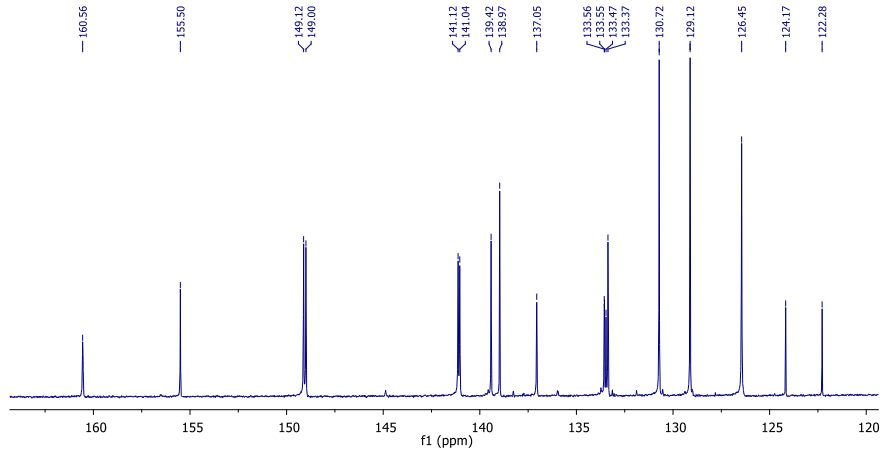
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **67**.



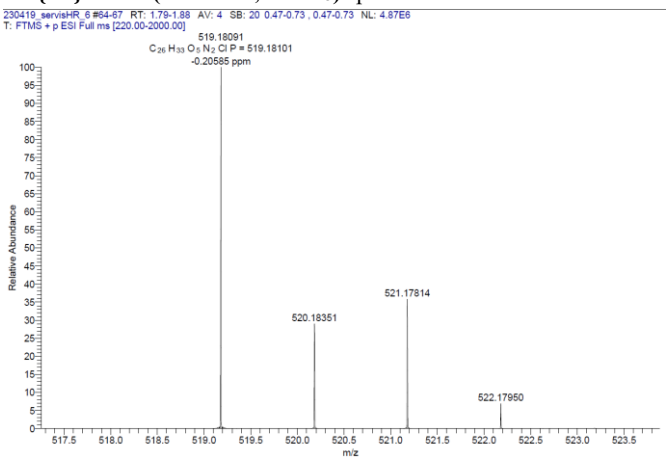
^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$) spectrum of **67**.



$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) spectrum of **67**.

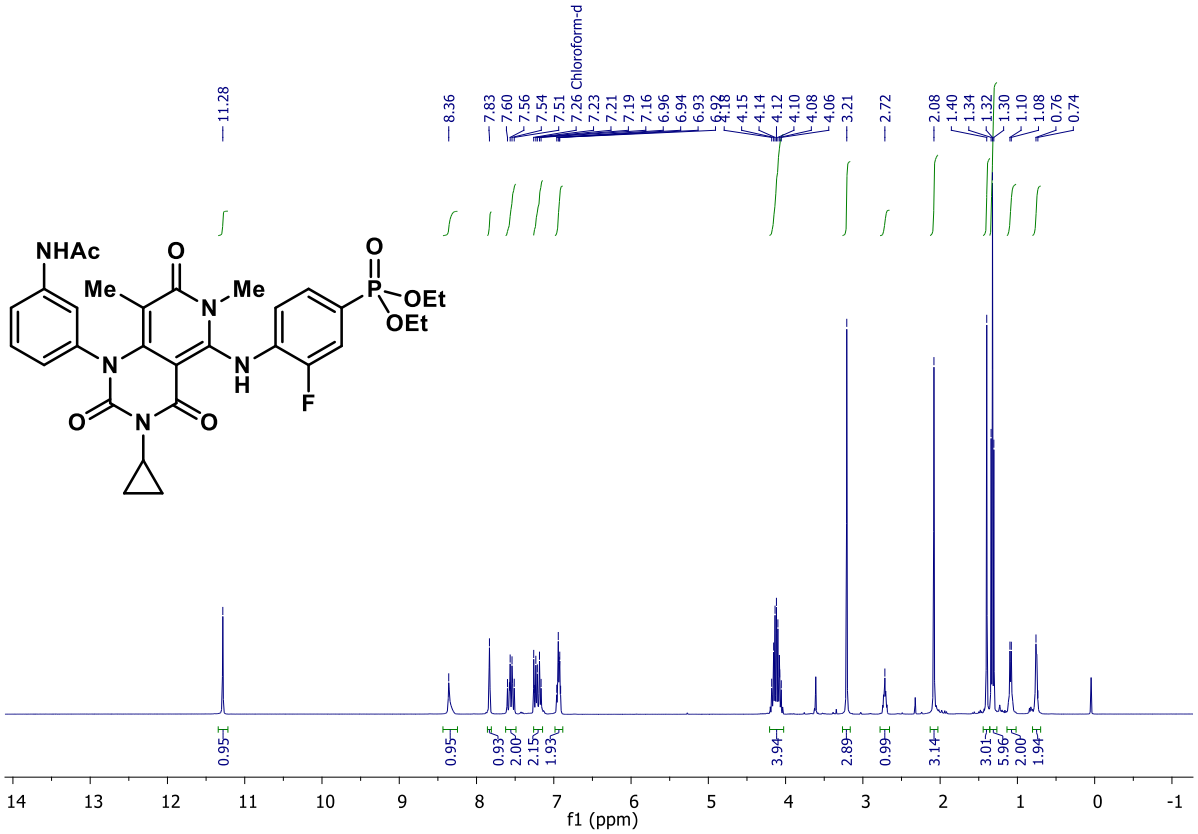


$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) spectrum of **67** in more detail.

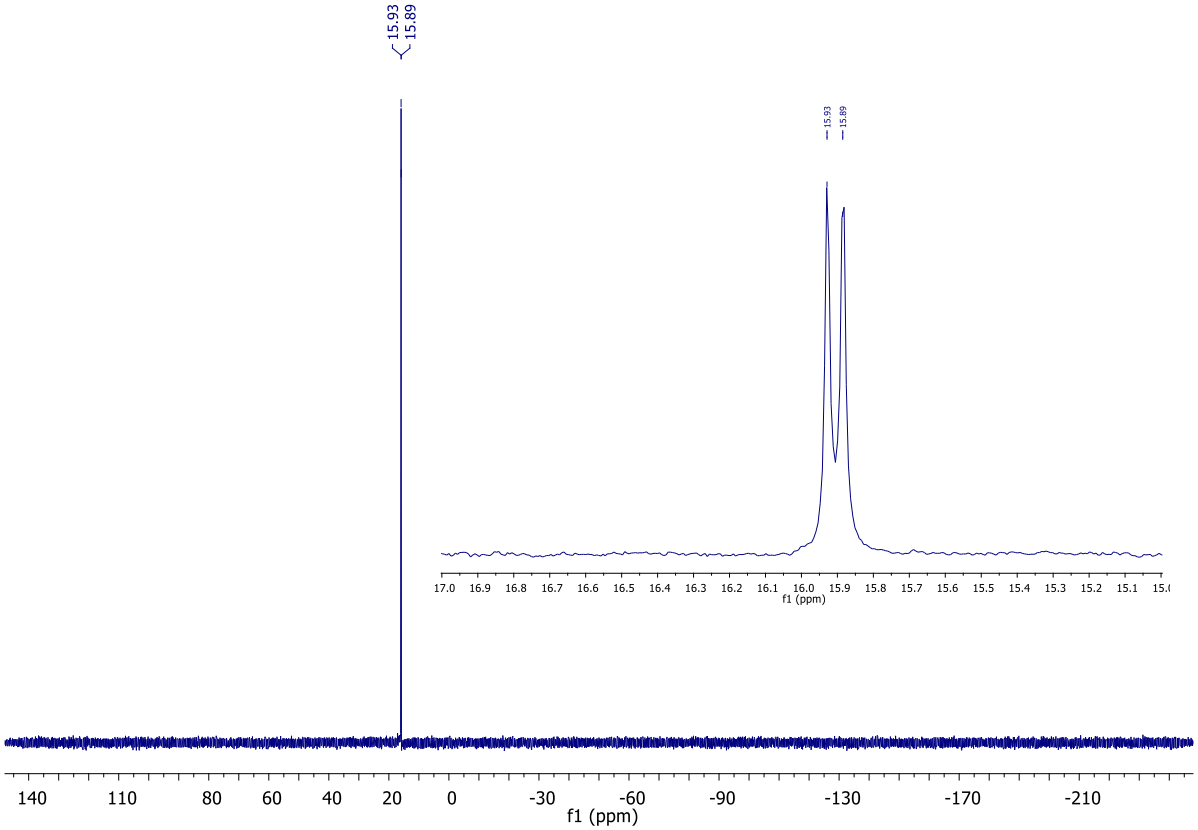


HRMS (ESI-TOF) spectrum of compound **67**.

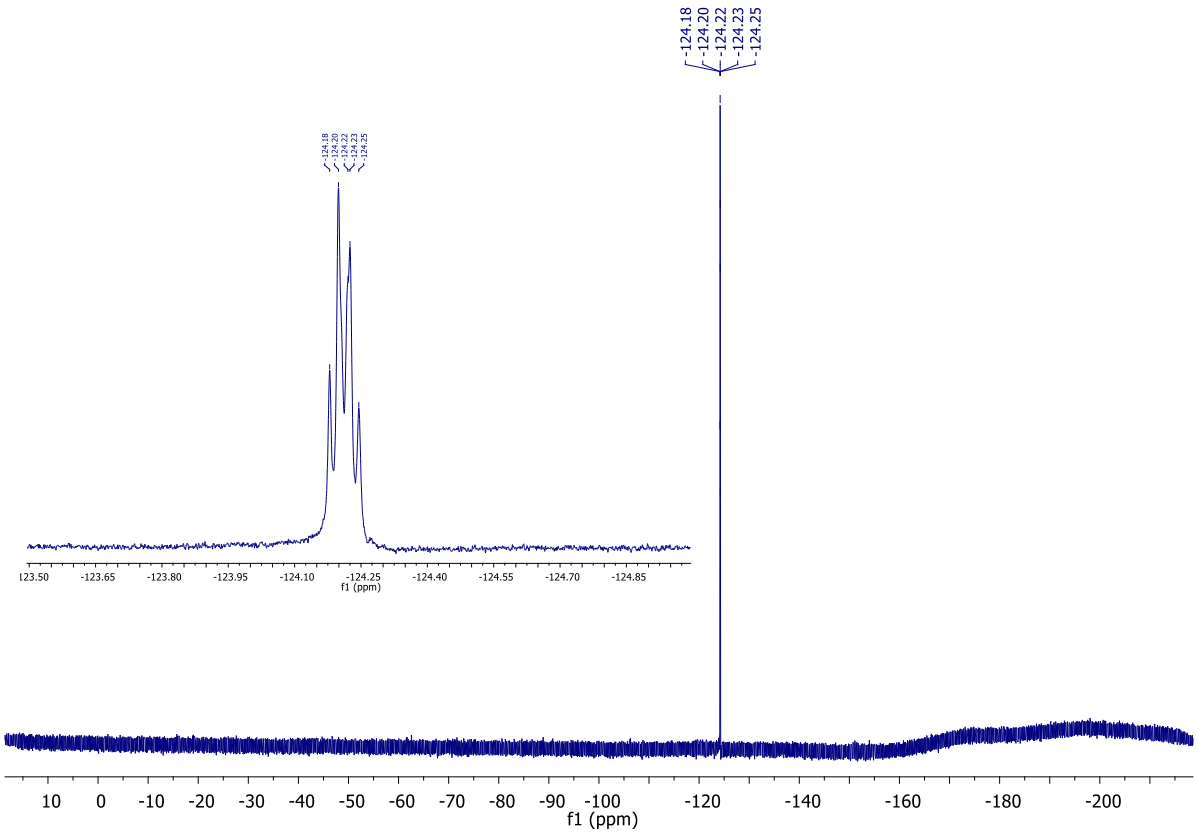
Compound 68



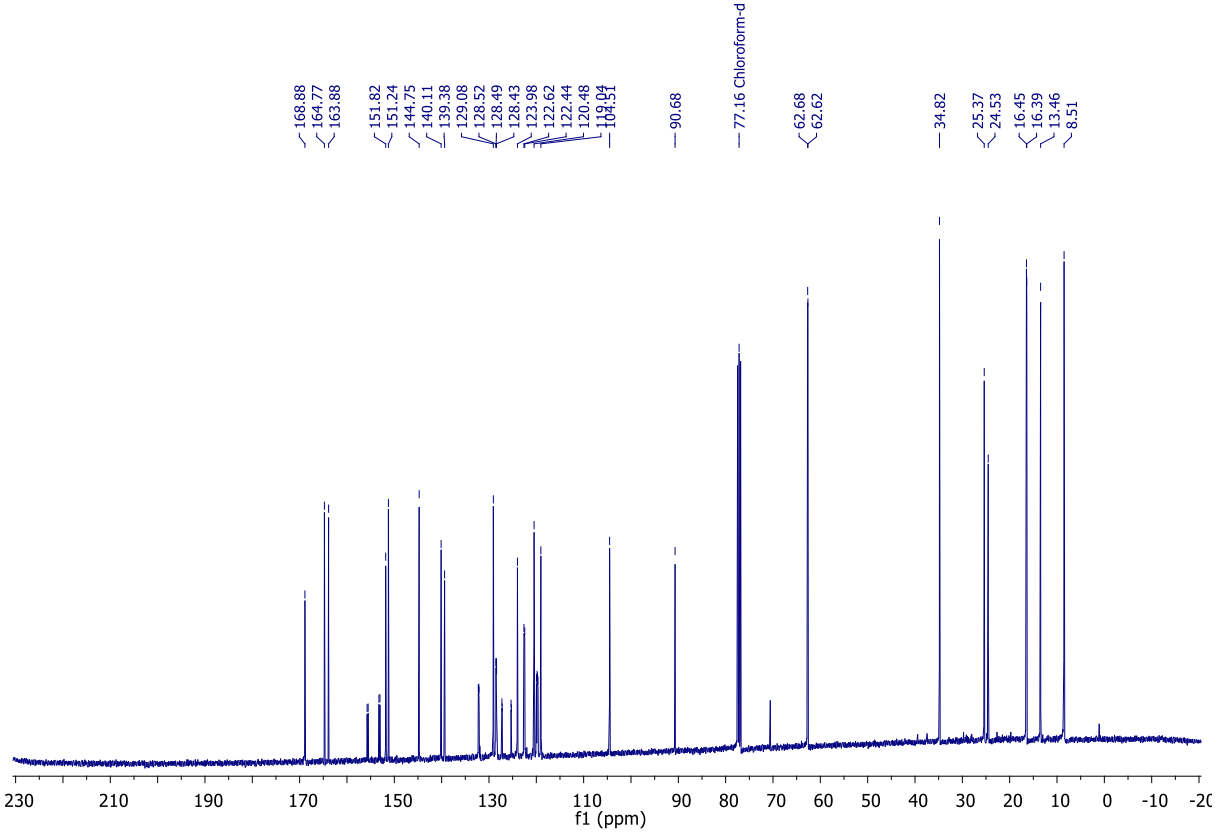
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **68**.



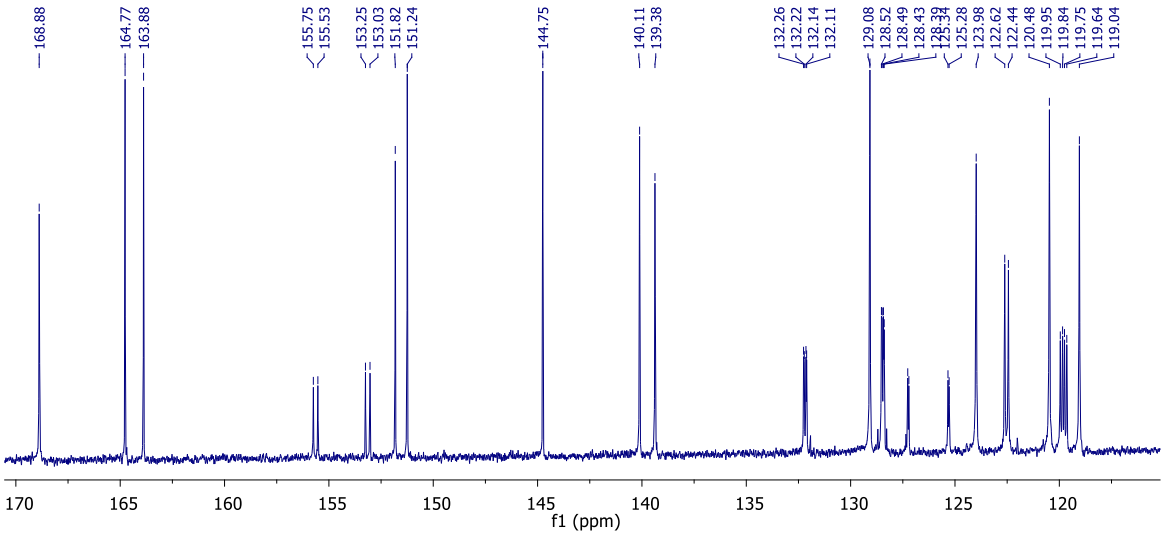
^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$) spectrum of **68**.



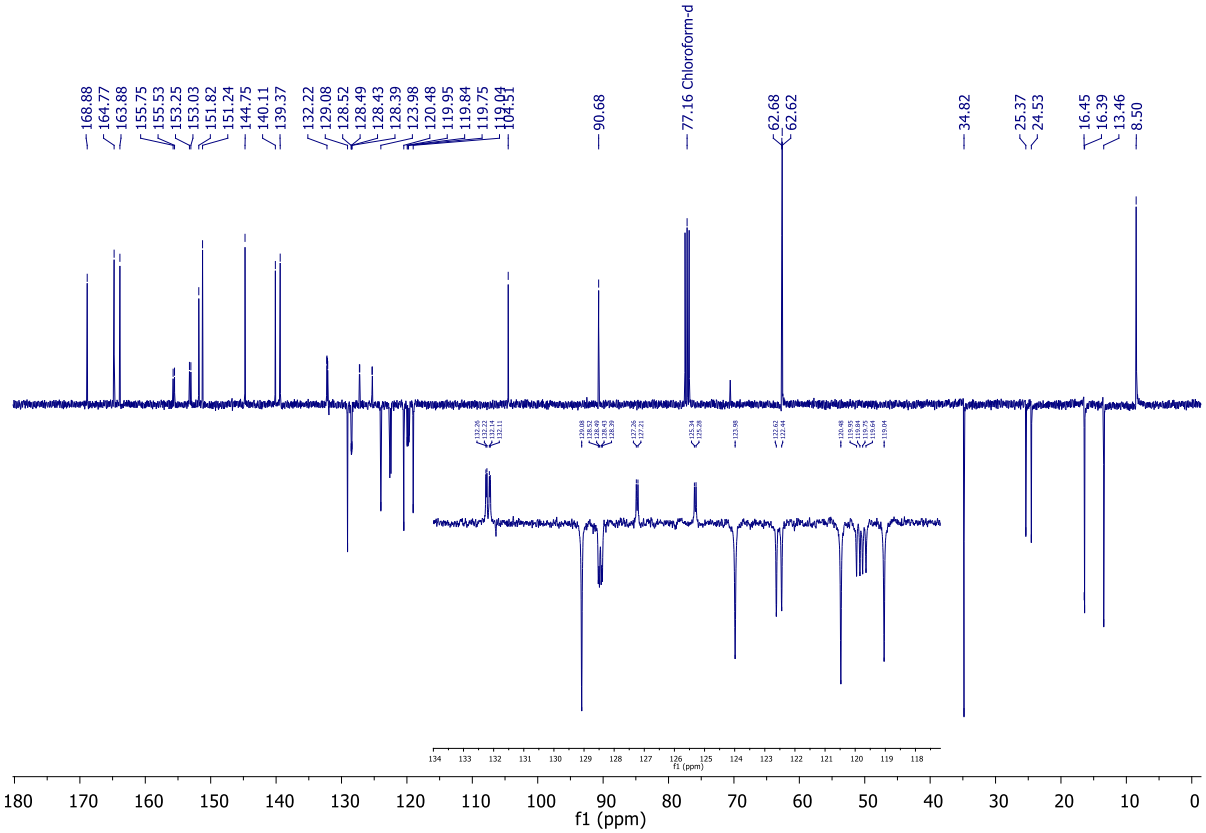
^{19}F NMR (376 MHz, $CDCl_3$) spectrum of **68**.



^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) spectrum of **68**.

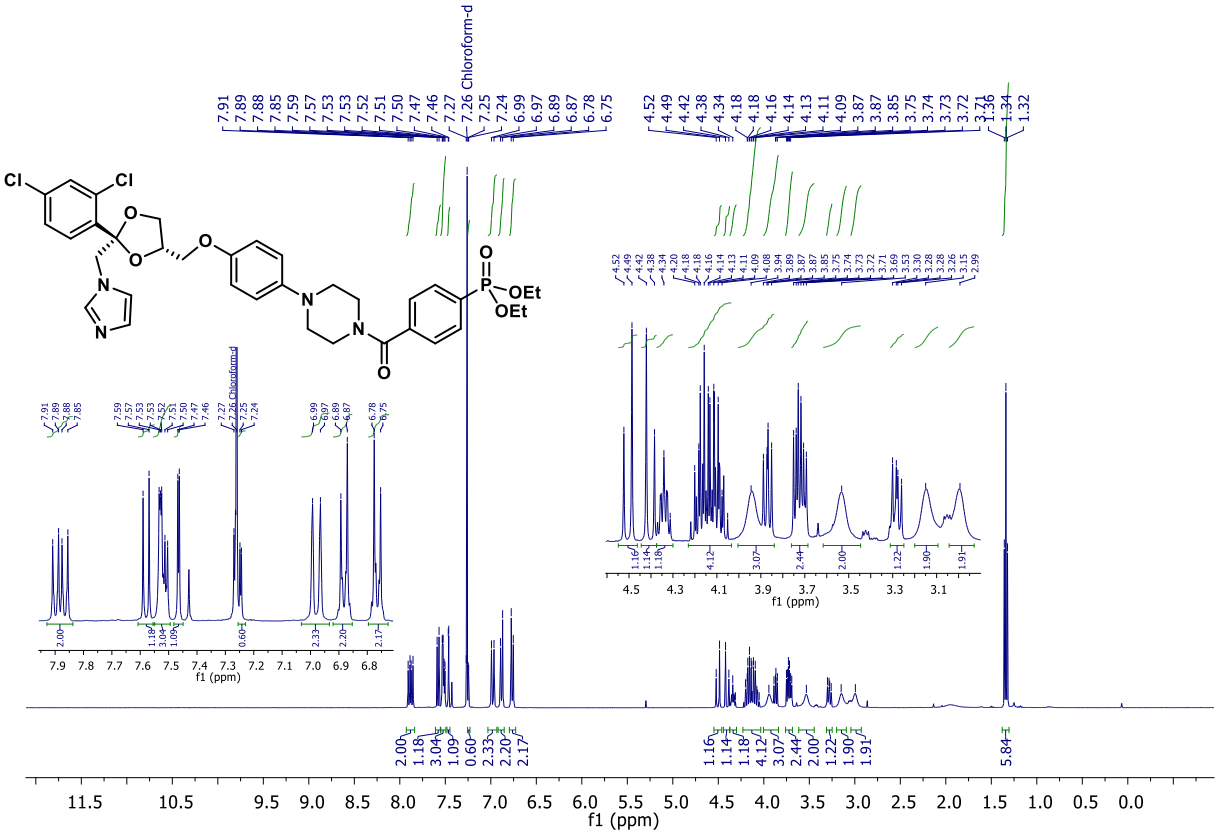


$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) spectrum of **68** in more detail.

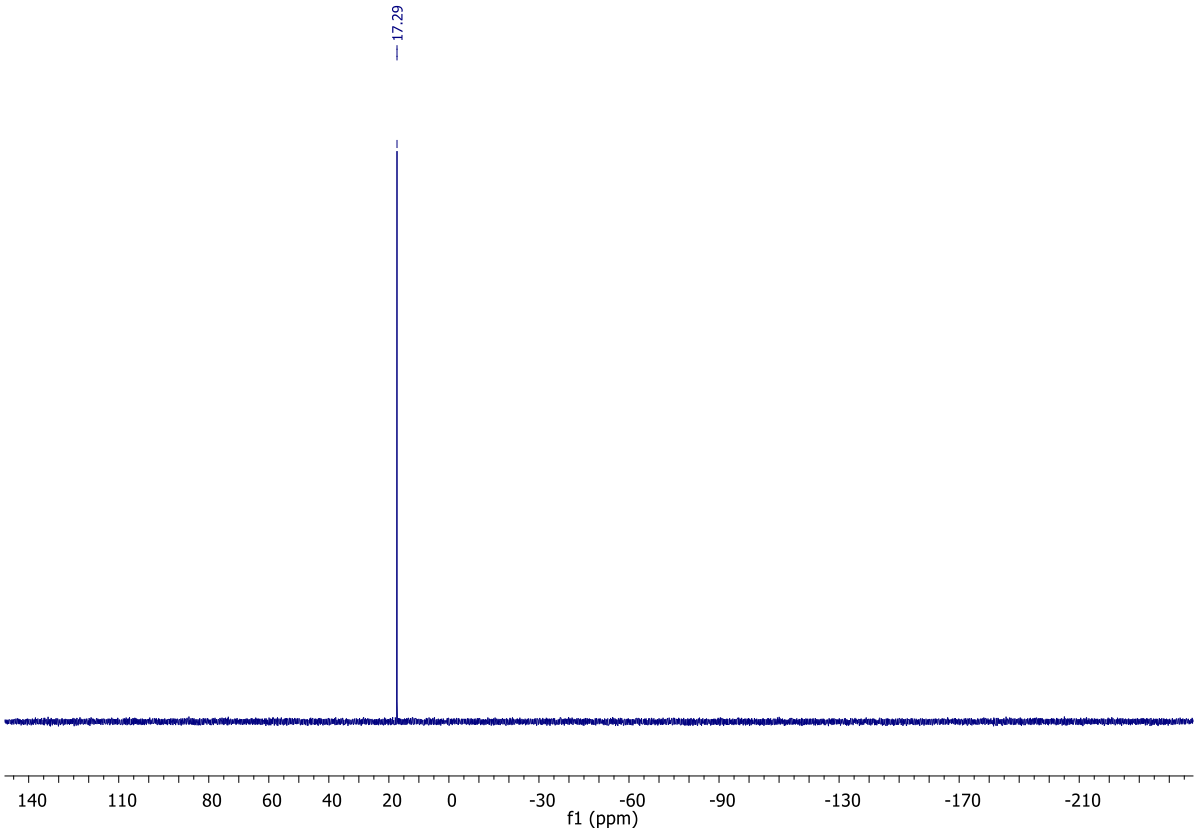


$^{13}C\{^{1}H\}$ APT NMR (100 MHz, $CDCl_3$) spectrum of **68**.

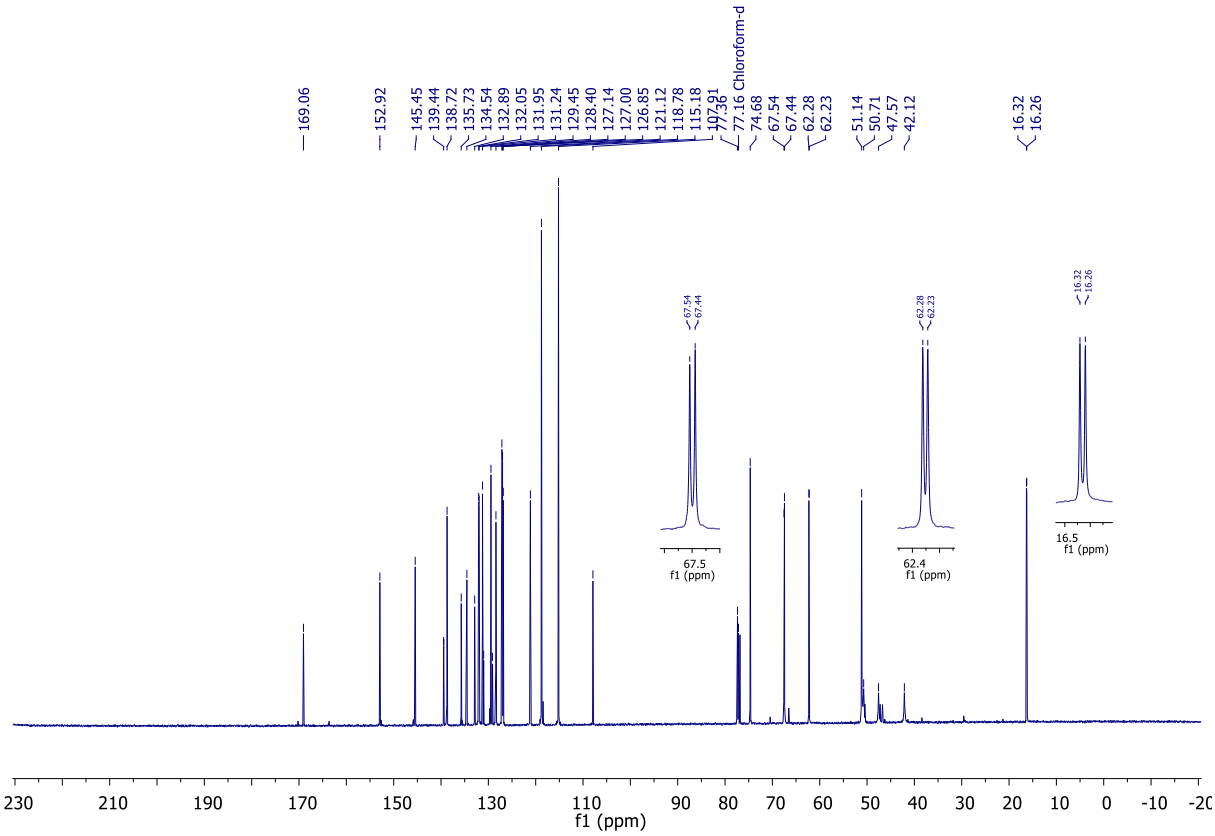
Compound 69



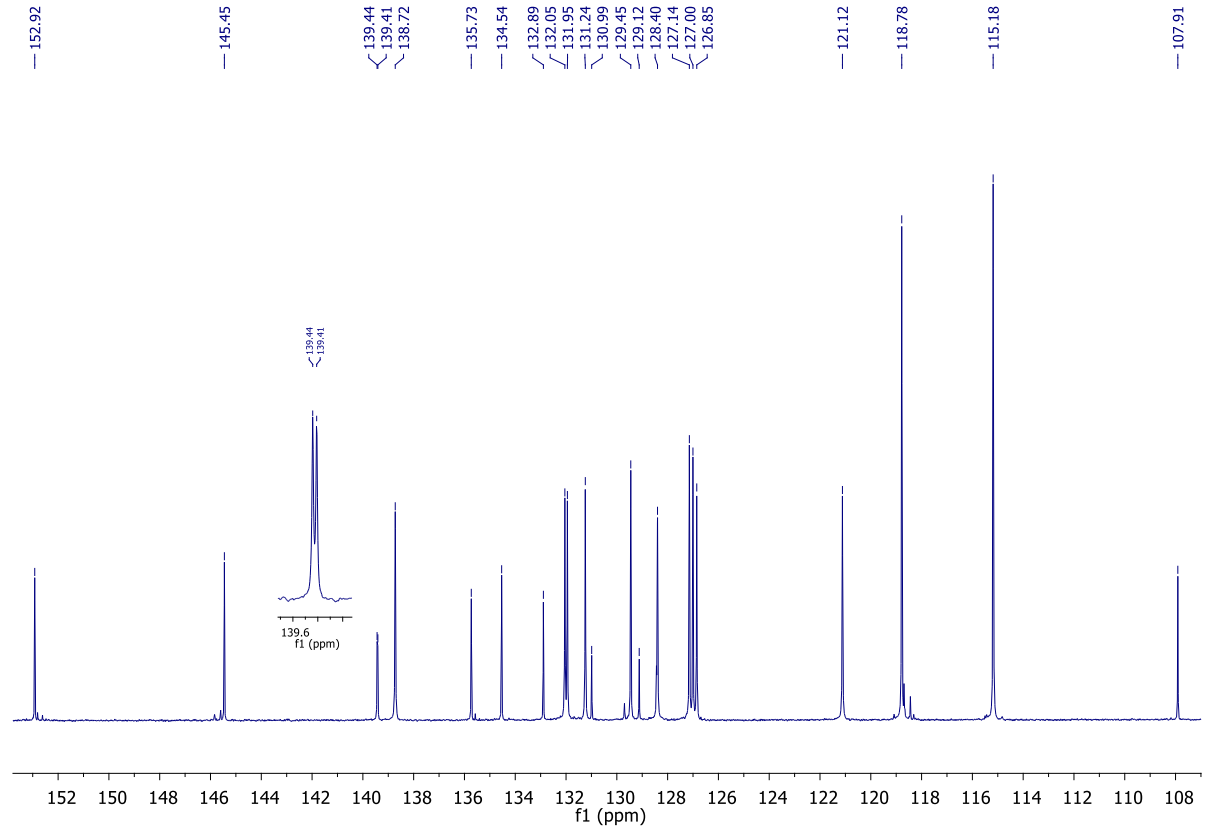
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **69**.



^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$) spectrum of **69**.

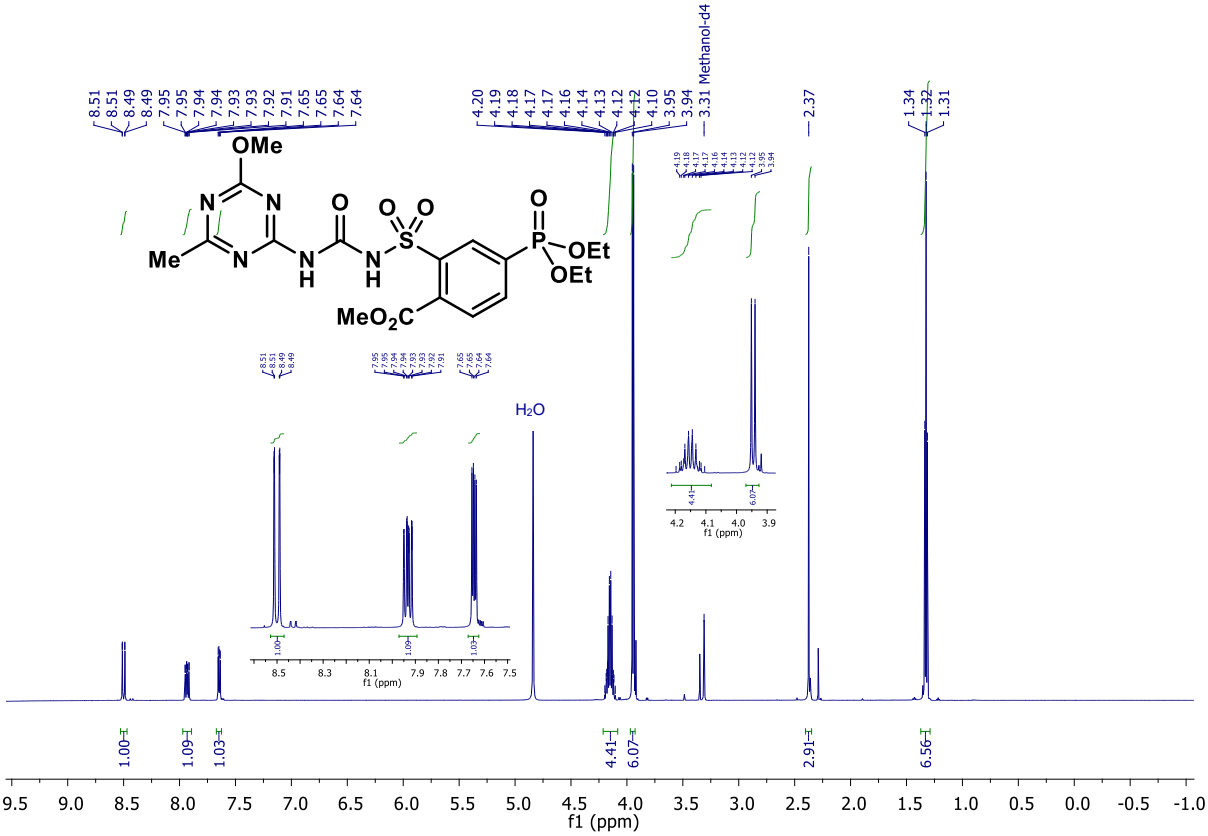


$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) spectrum of **69**.

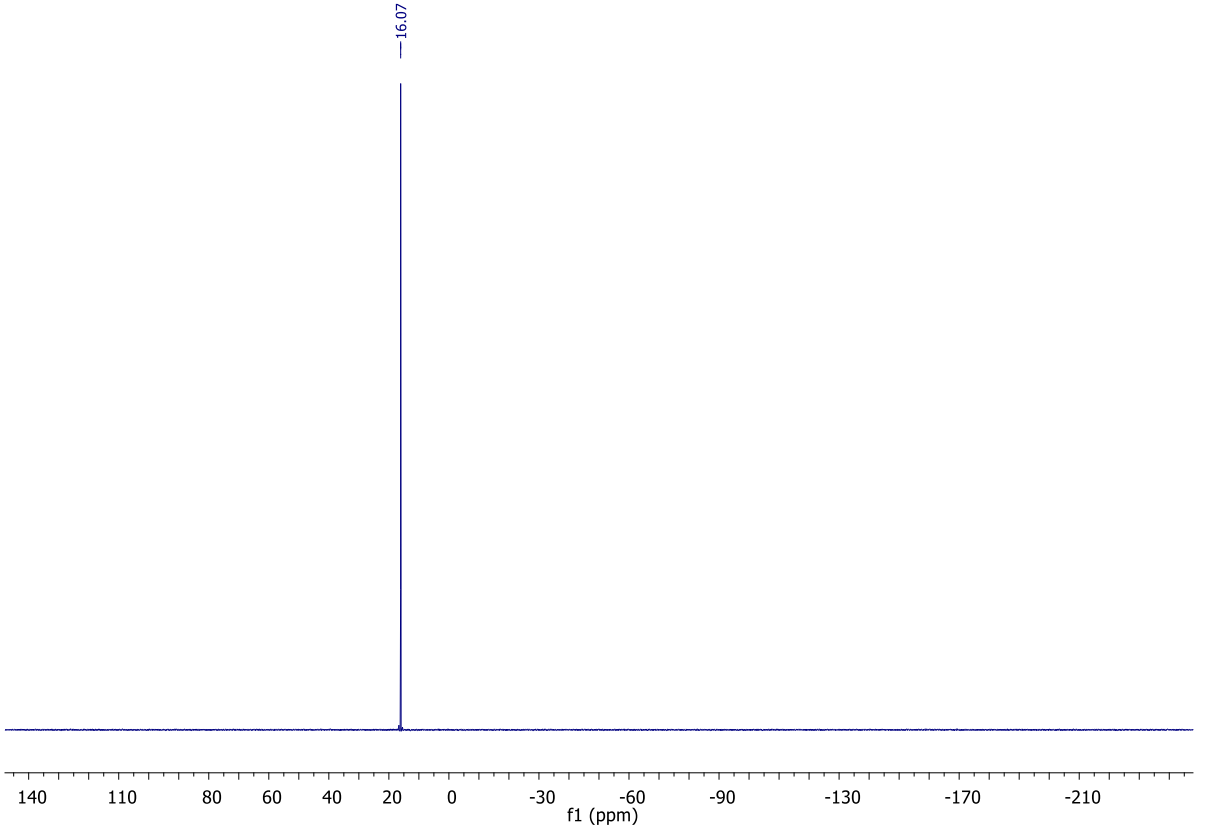


$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) spectrum of **69** in more detail.

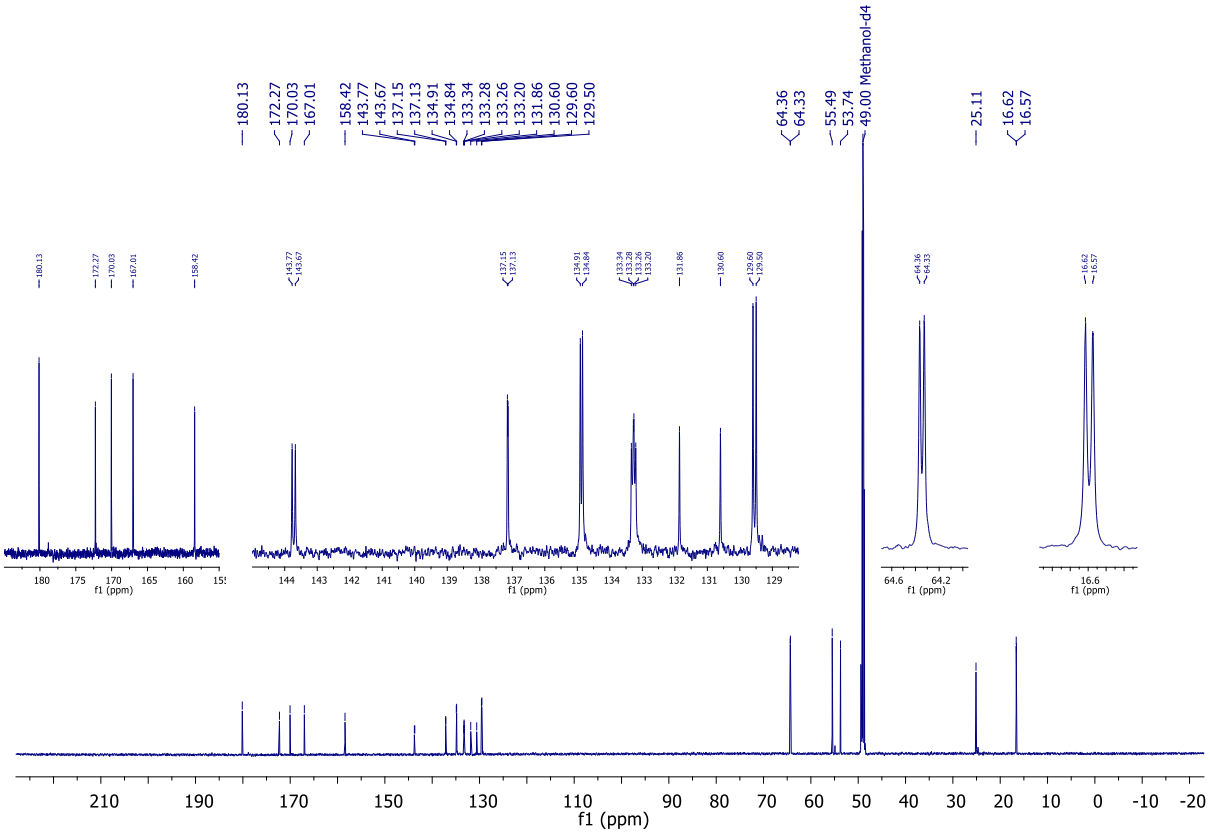
Compound 70



^{1}H NMR (600 MHz, CD_3OD) spectrum of **70**.

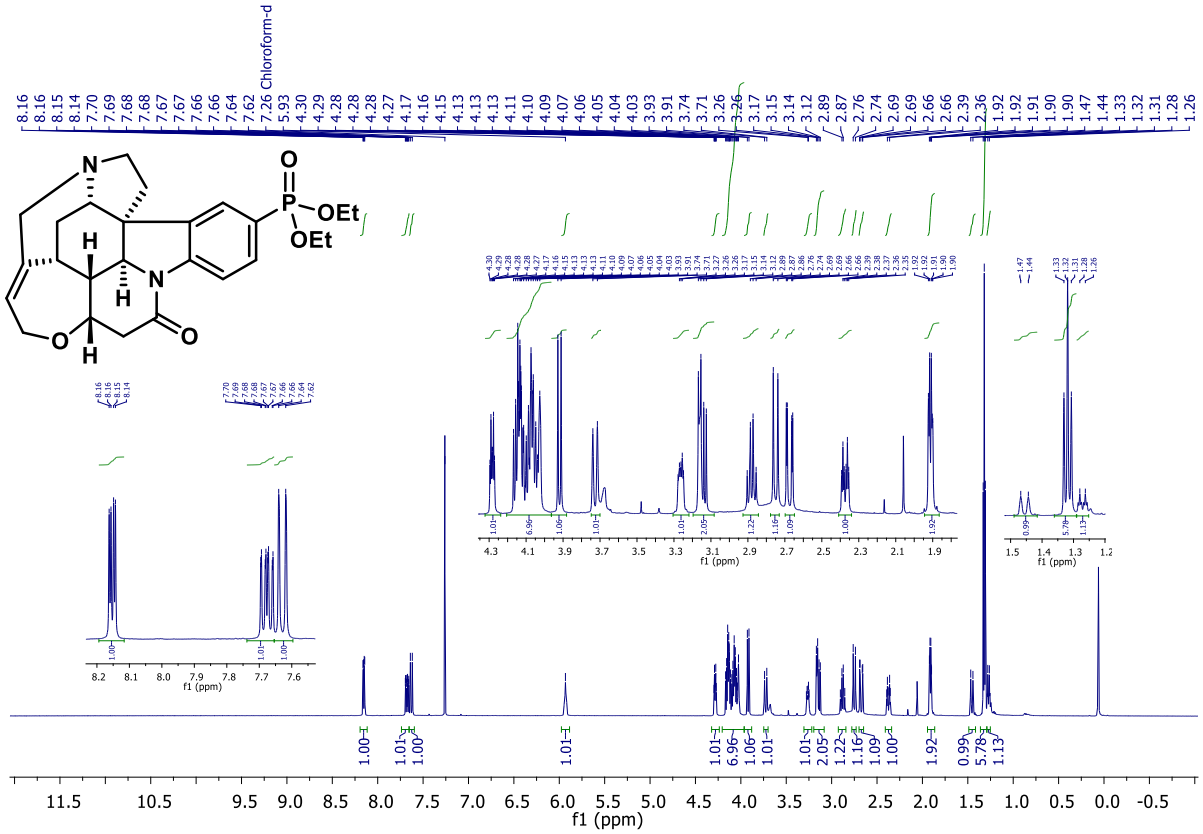


^{31}P{^{1}H} NMR (162 MHz, CD_3OD) spectrum of **70**.

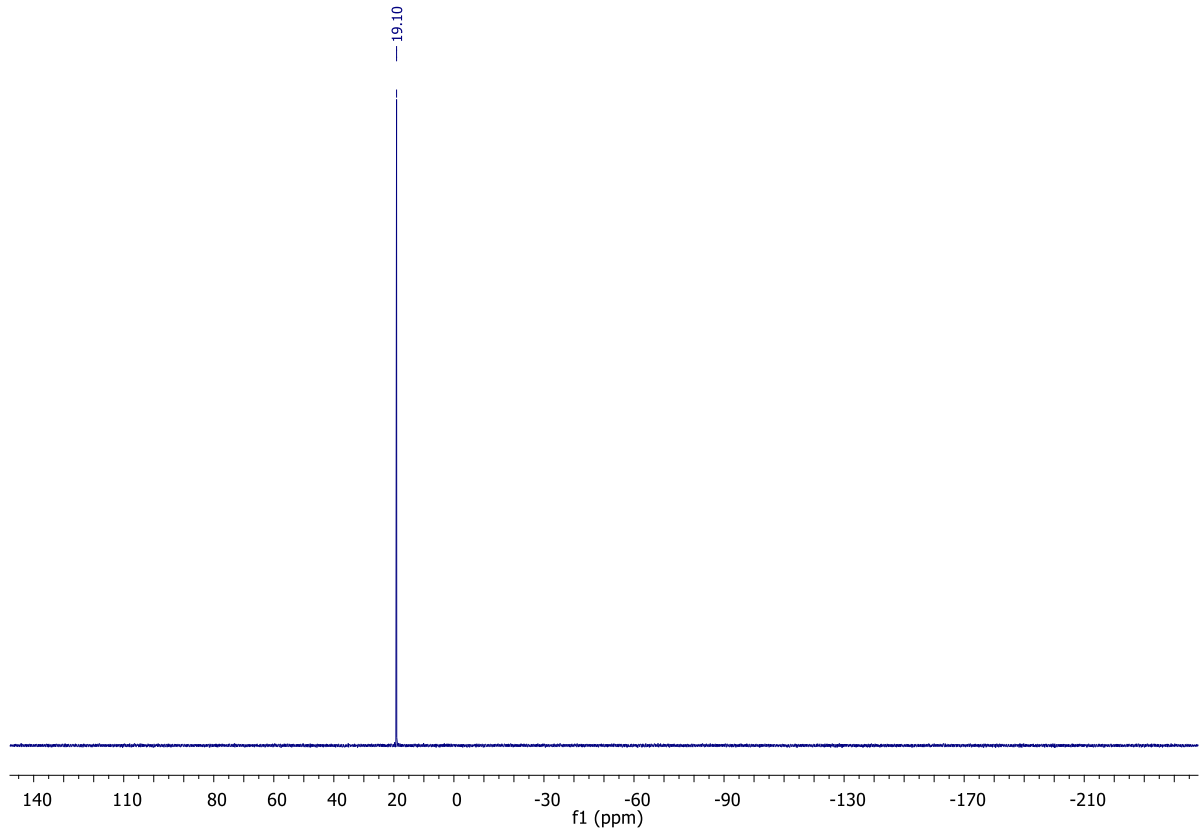


$^{13}C\{^{1}H\}$ NMR (151 MHz, CD_3OD) spectrum of **70**.

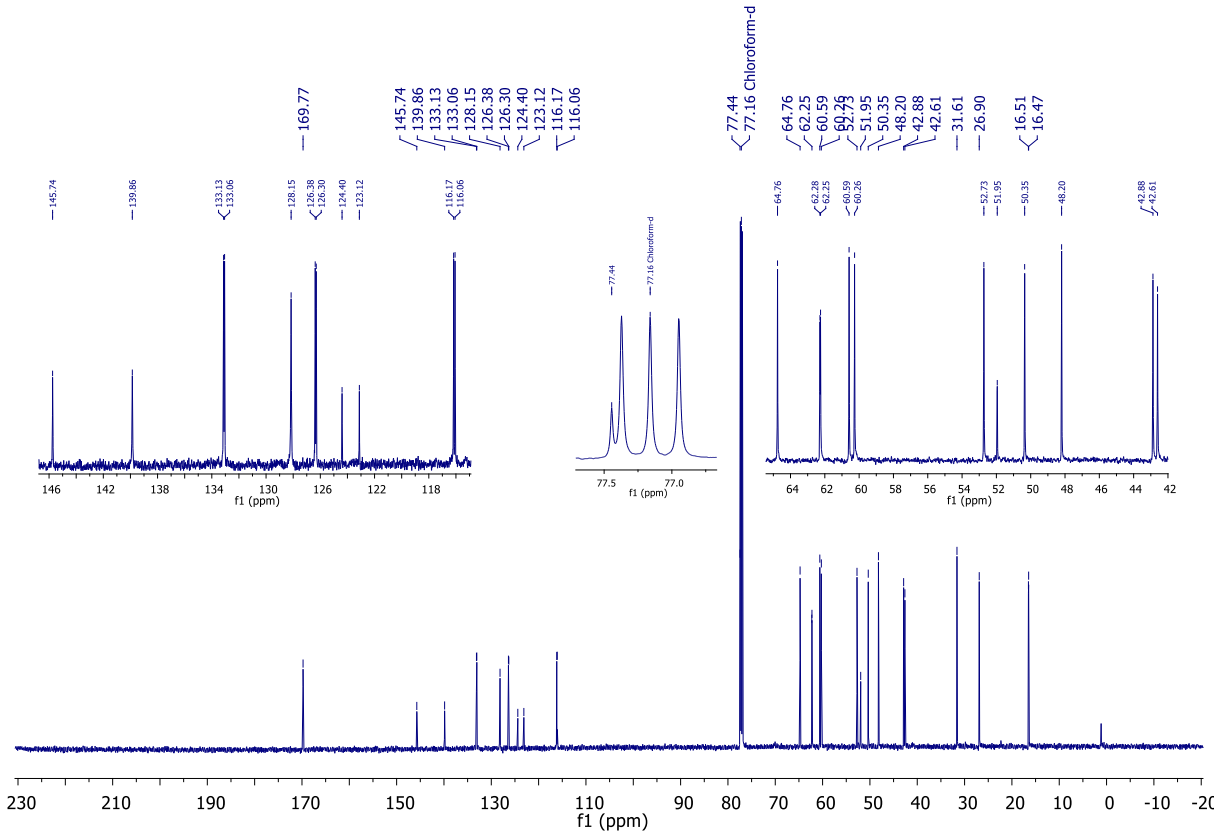
Compound 71



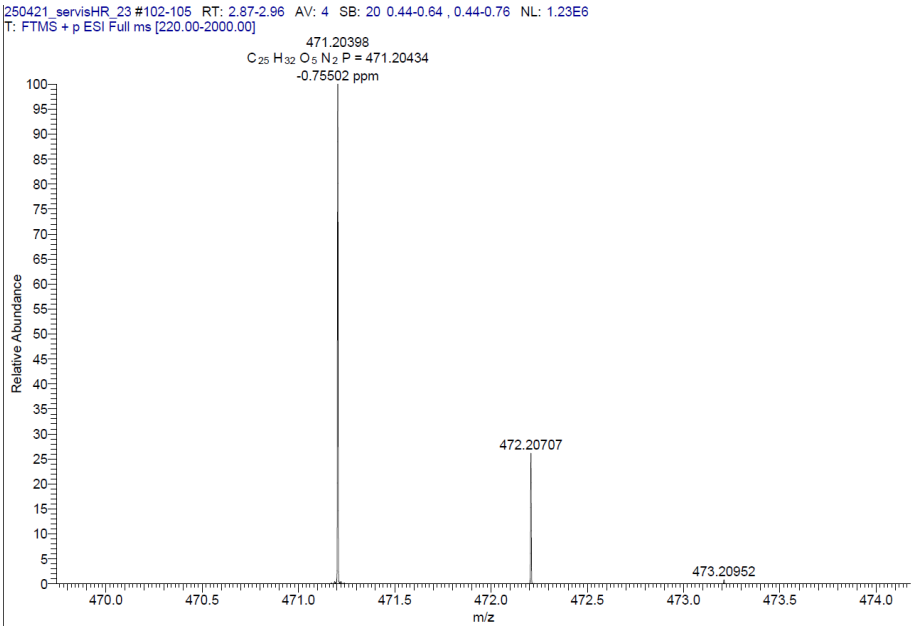
^{1}H NMR (600 MHz, $CDCl_3$) spectrum of **71**.



^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$) spectrum of **71**.

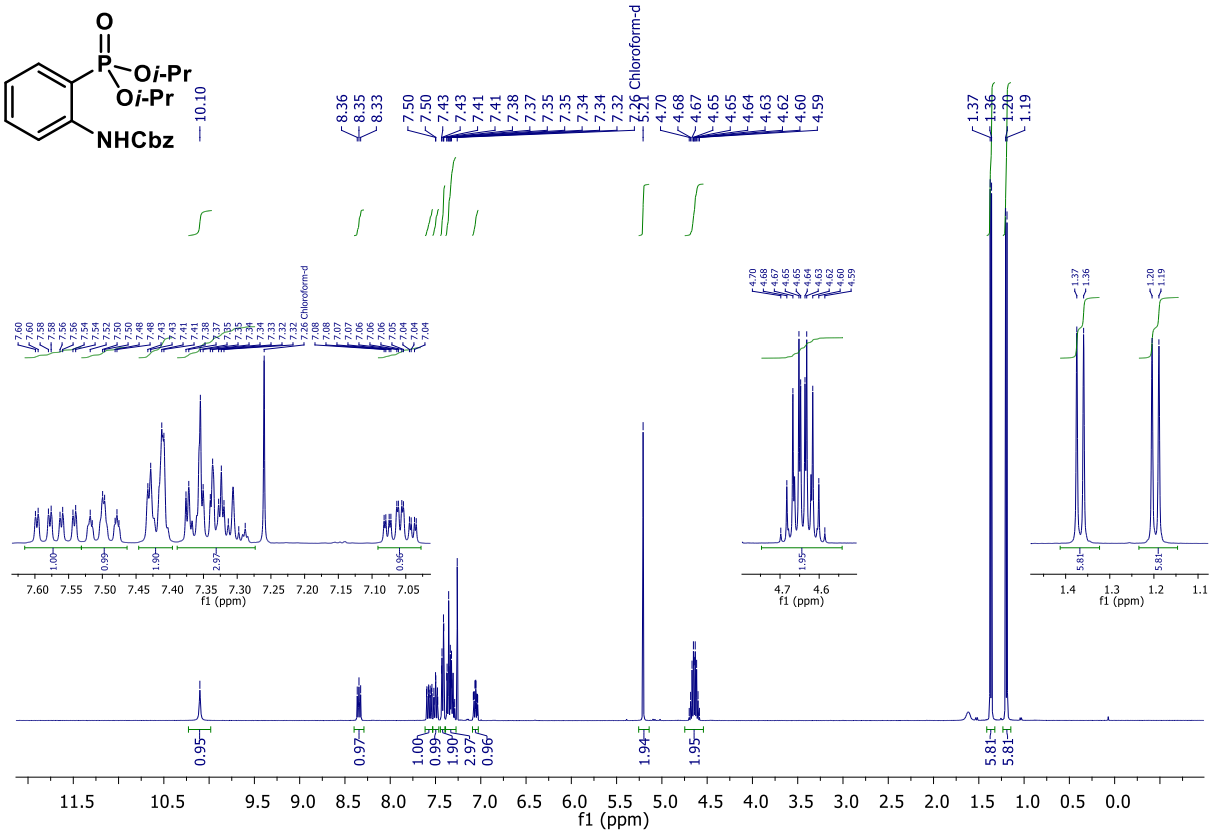


$^{13}C\{^{1}H\}$ NMR (151 MHz, $CDCl_3$) spectrum of **71**.

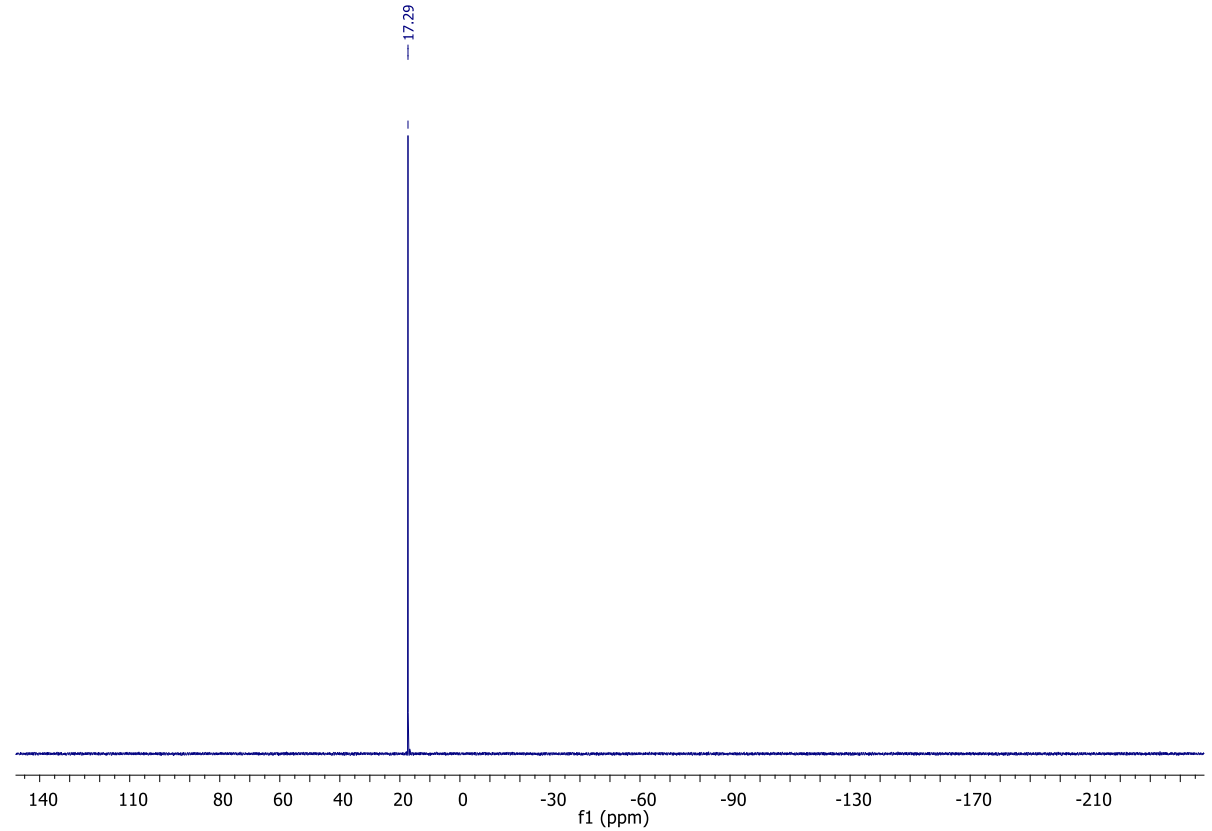


HRMS (ESI-TOF) spectrum of compound **71**.

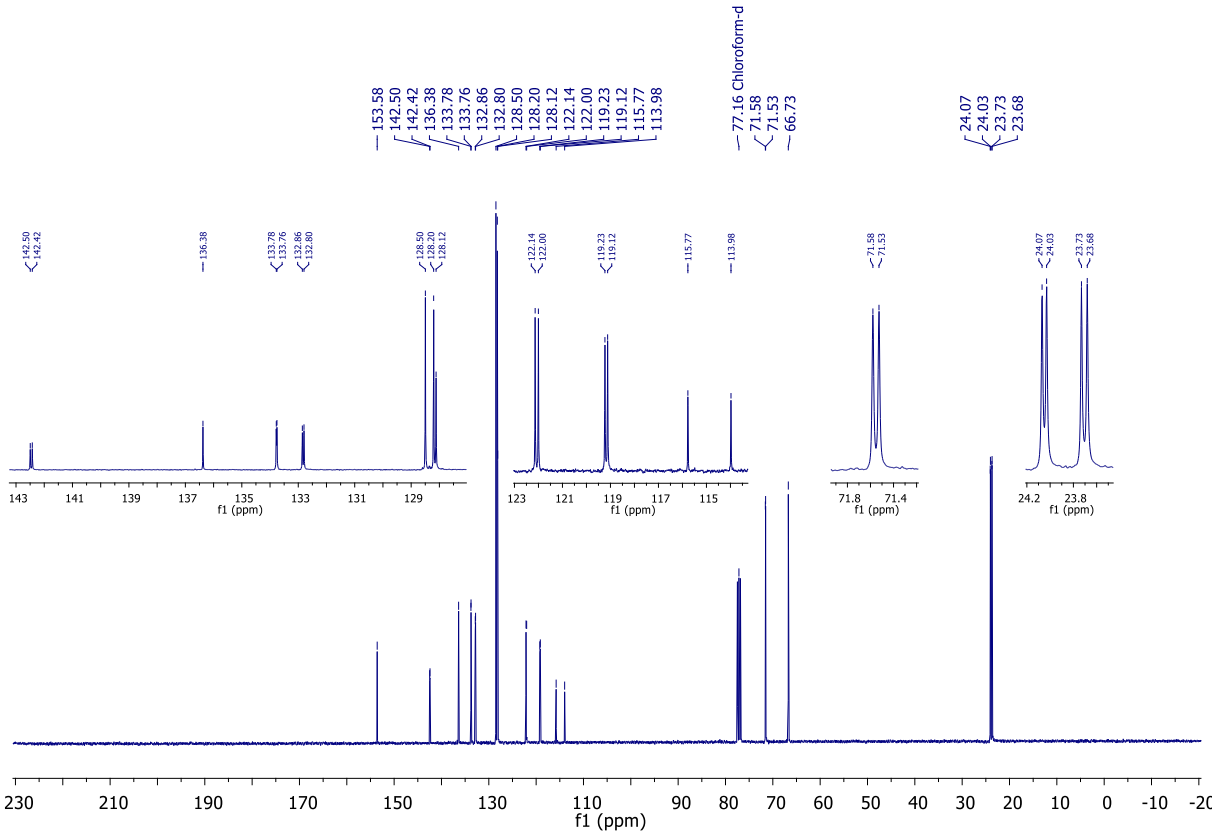
Compound 75



^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **75**.

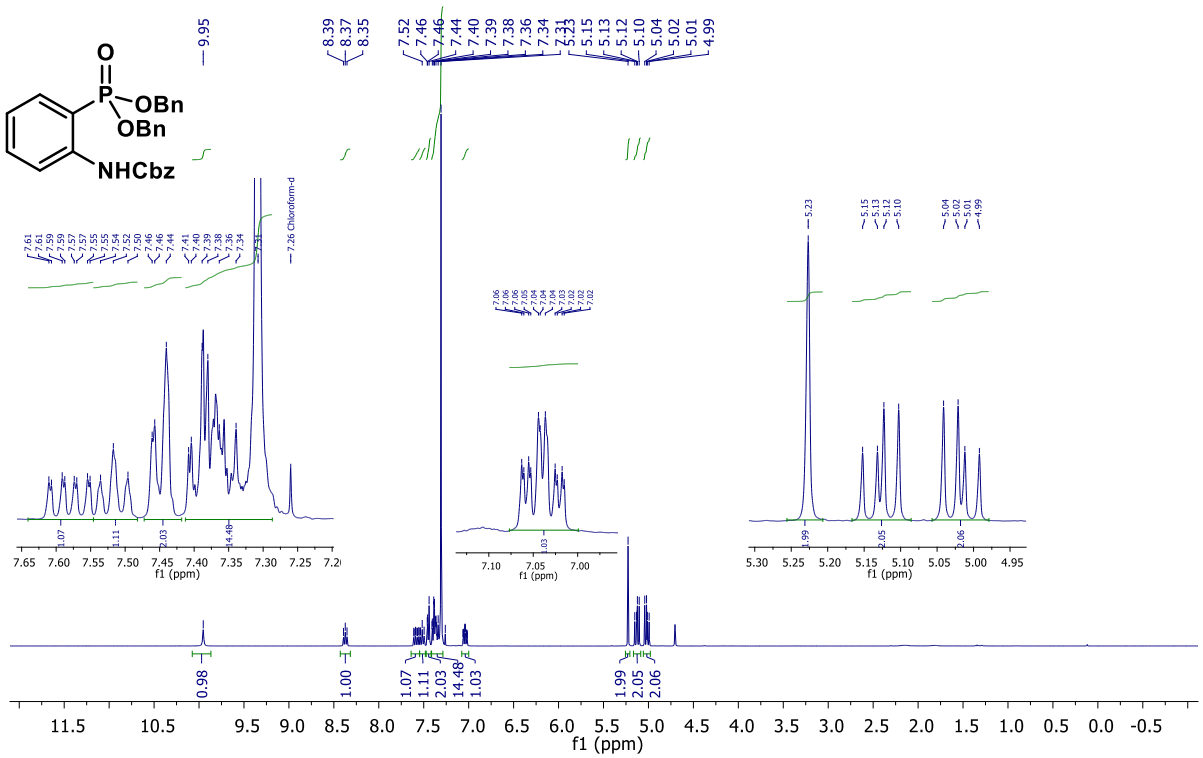


^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$) spectrum of **75**.

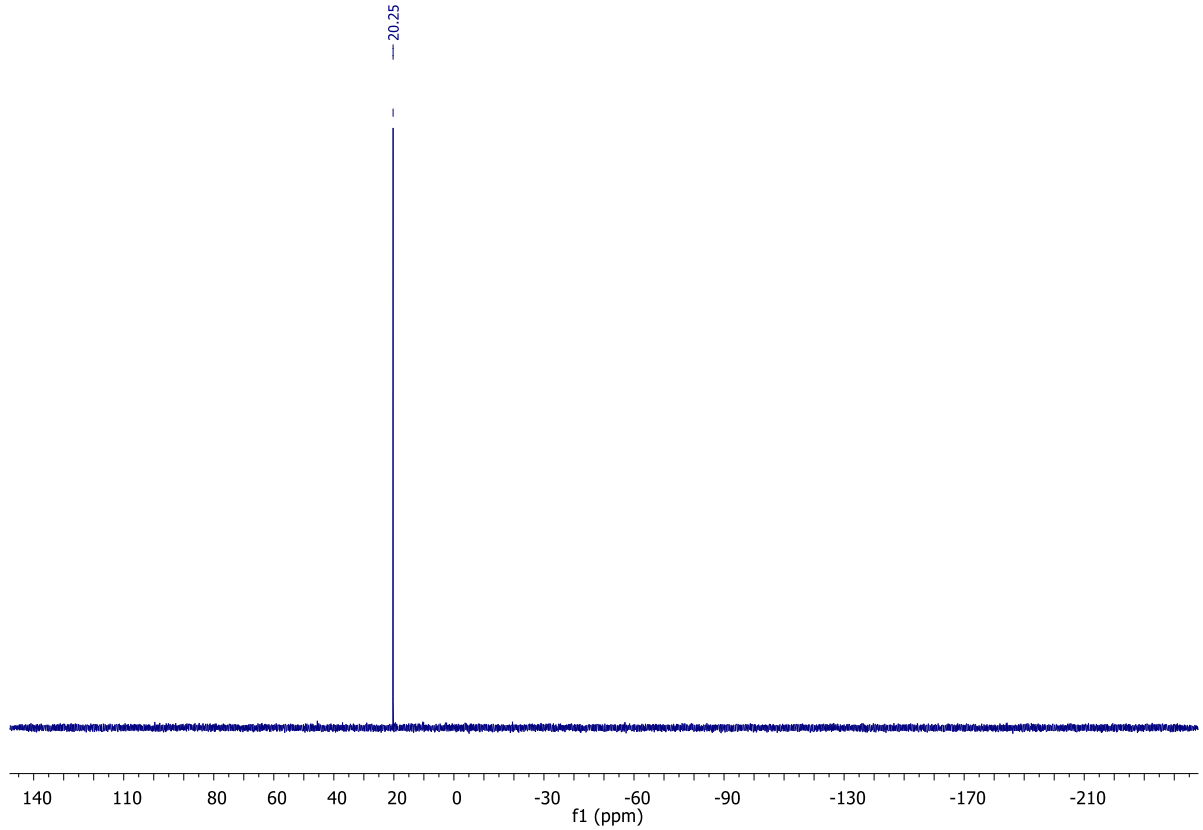


$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) spectrum of **75**.

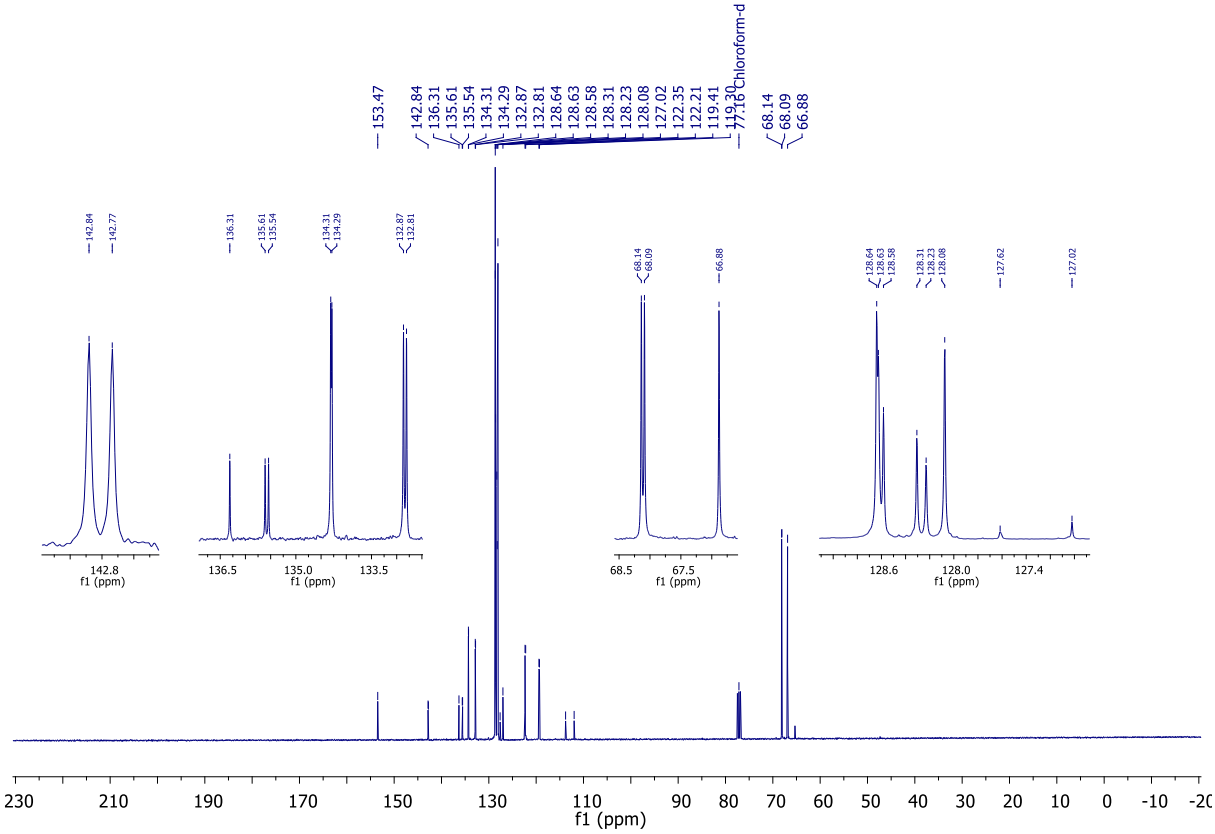
Compound 76



^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **76**.

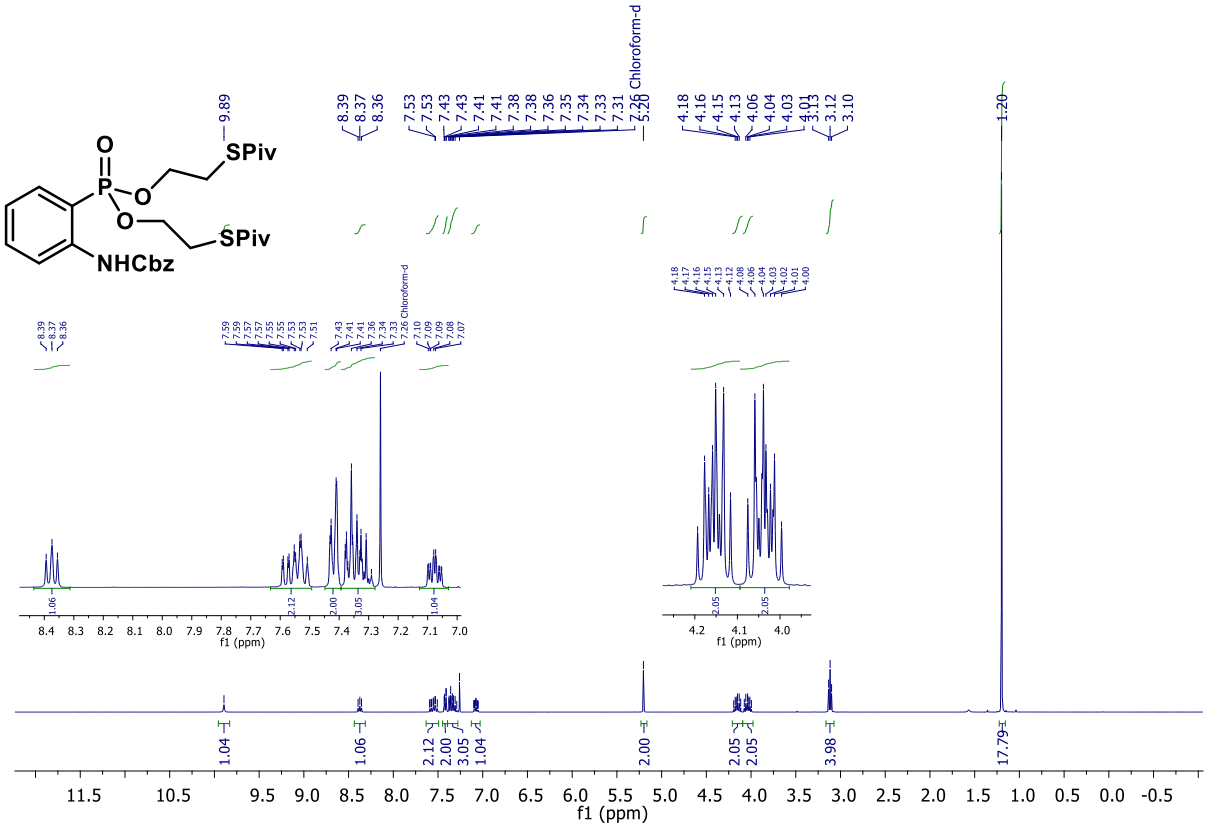


^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$) spectrum of **76**.

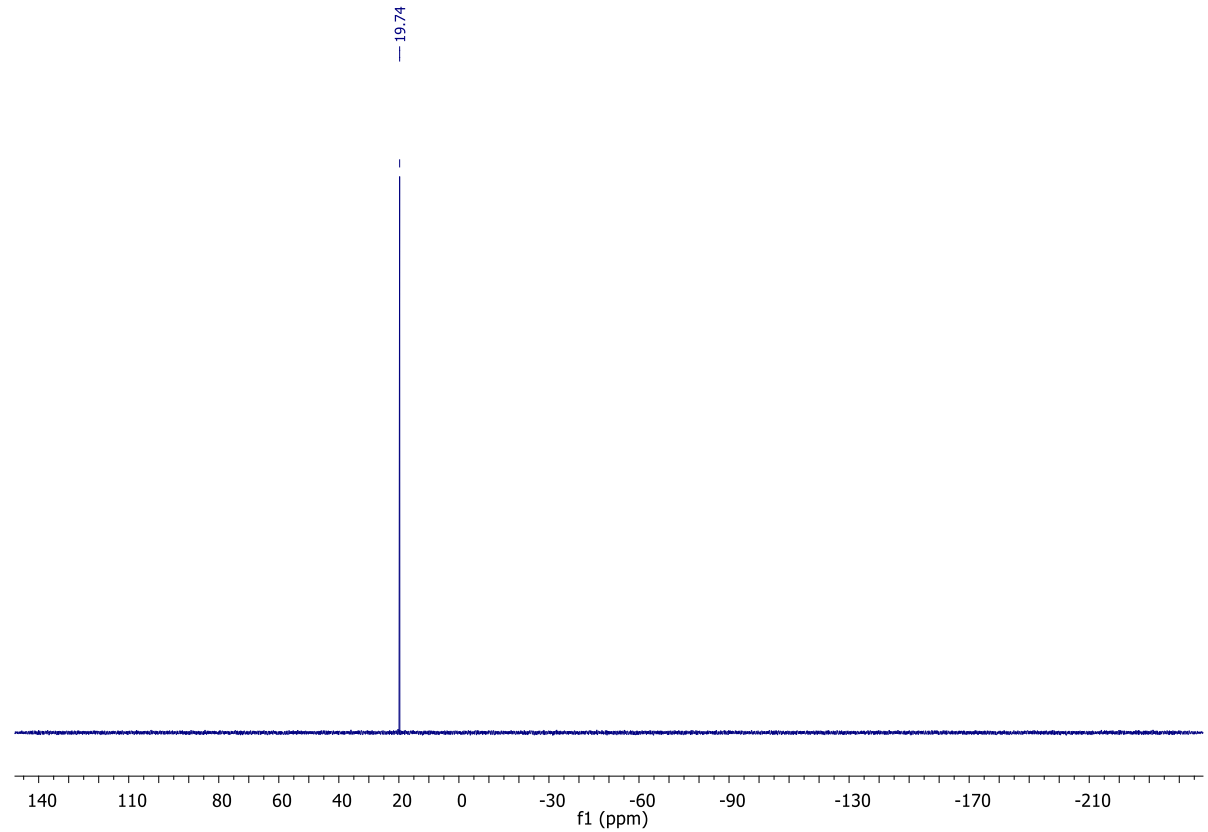


$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) spectrum of **76**.

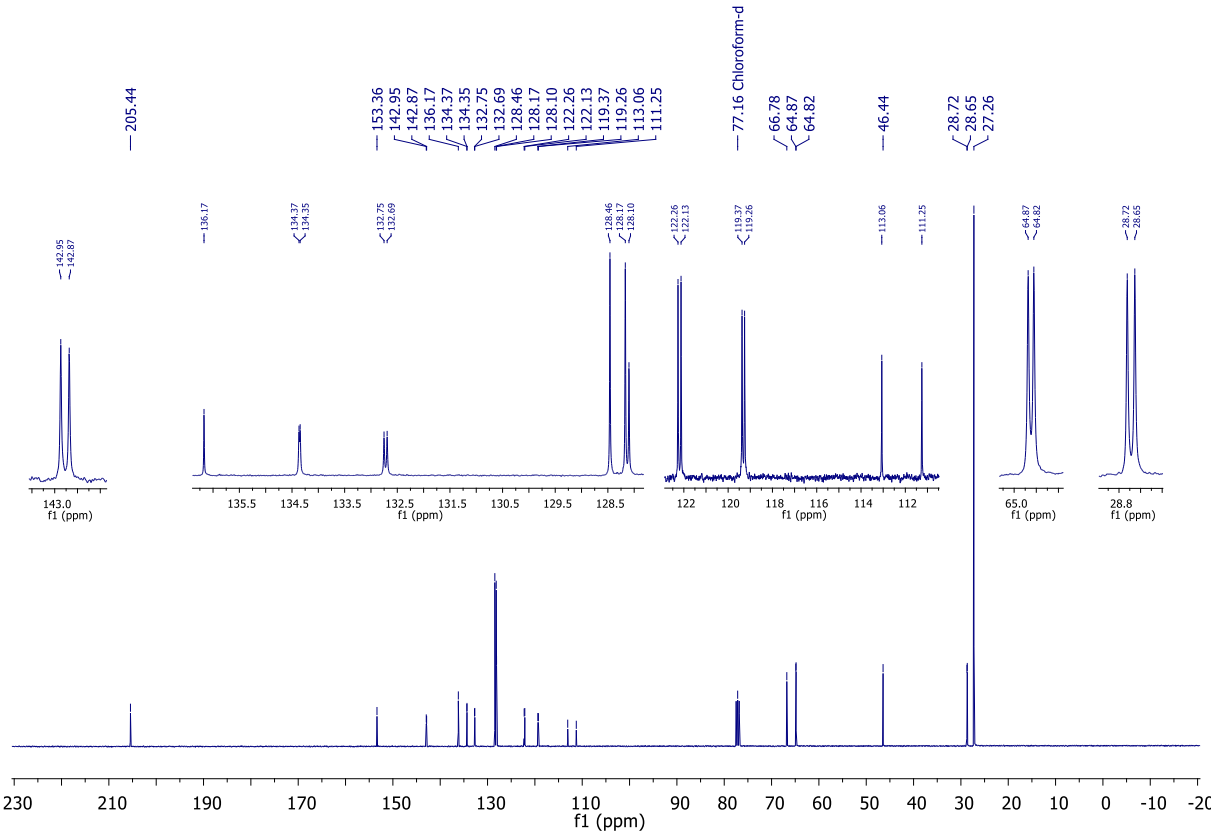
Compound 77



^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **77**.

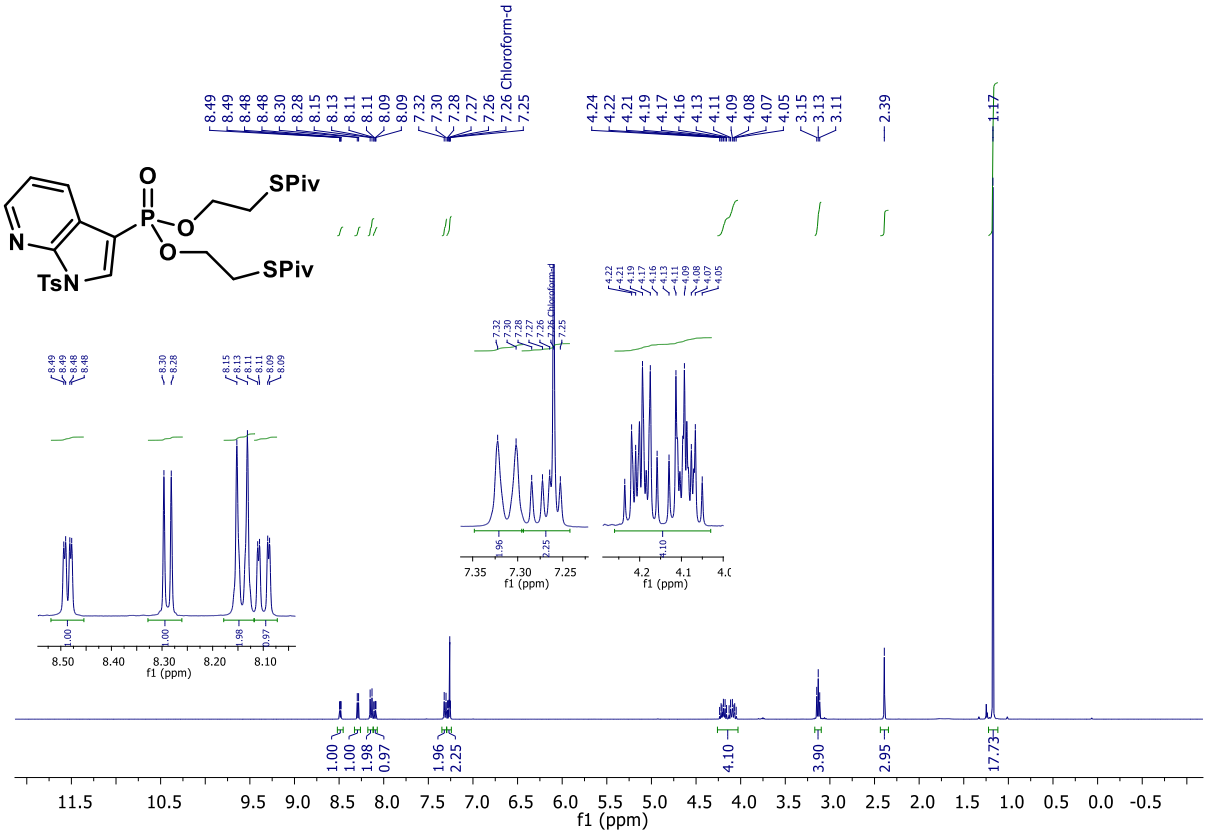


^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$) spectrum of **77**.

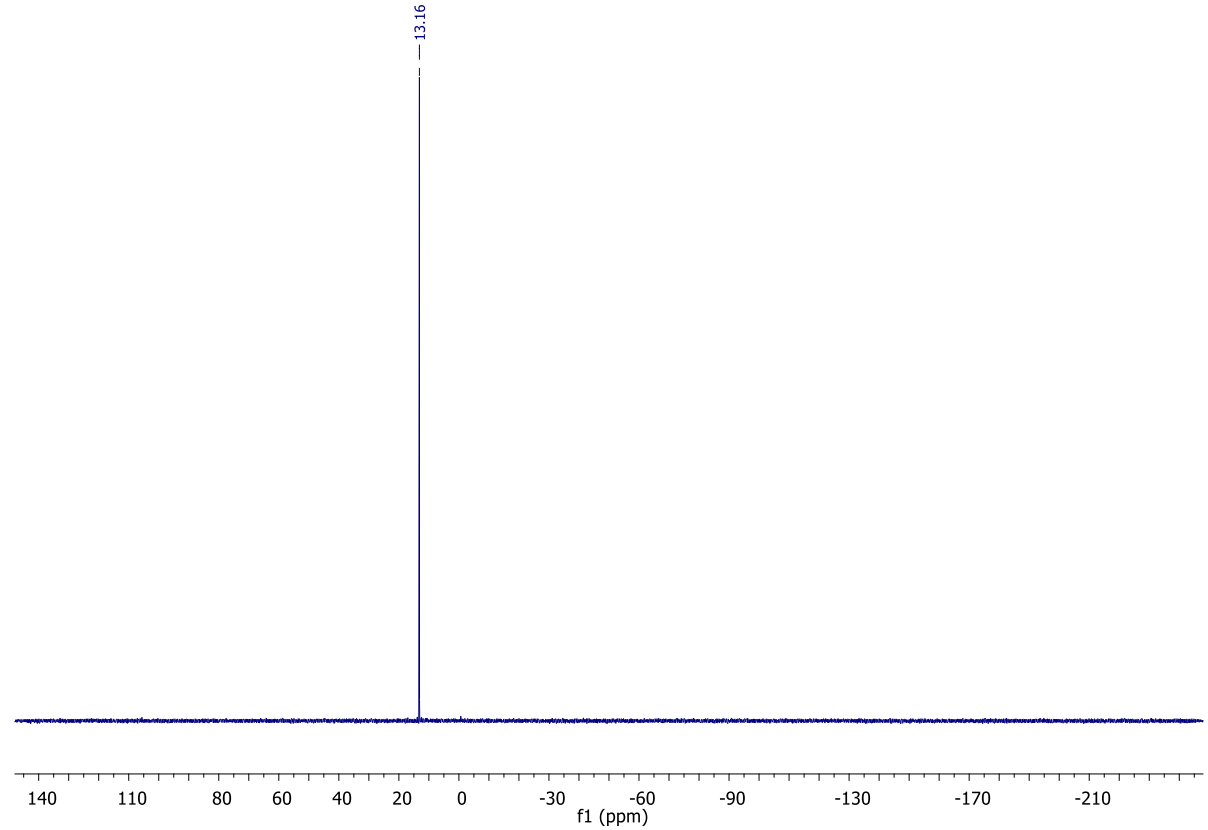


$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) spectrum of **77**.

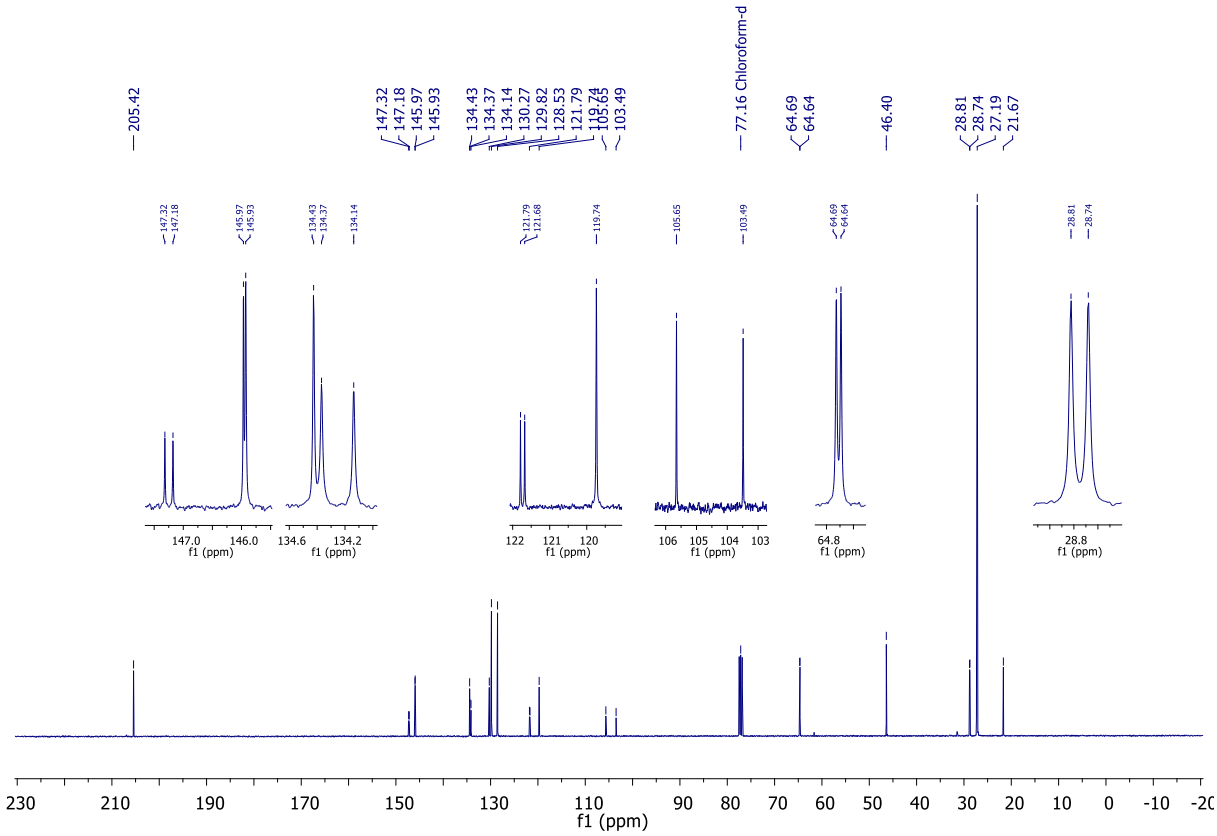
Compound 78



^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **78**.

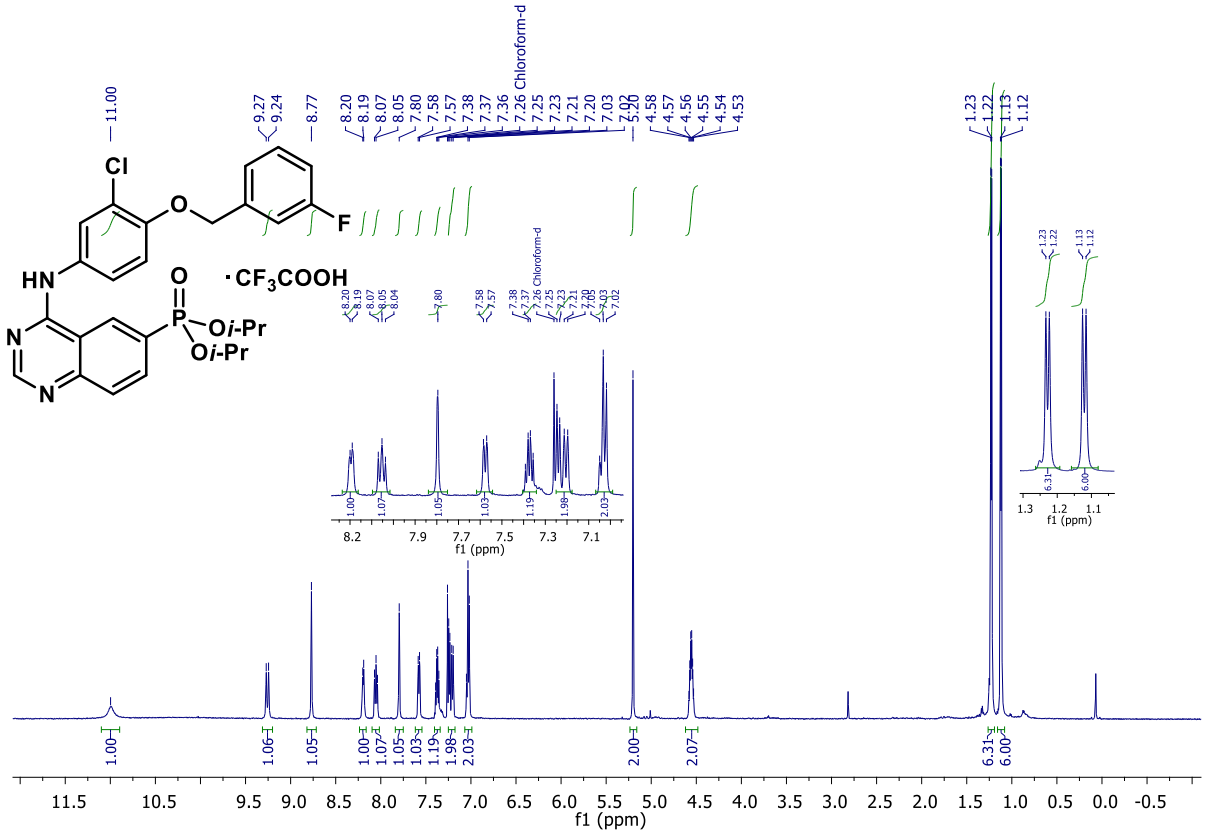


^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$) spectrum of **78**.

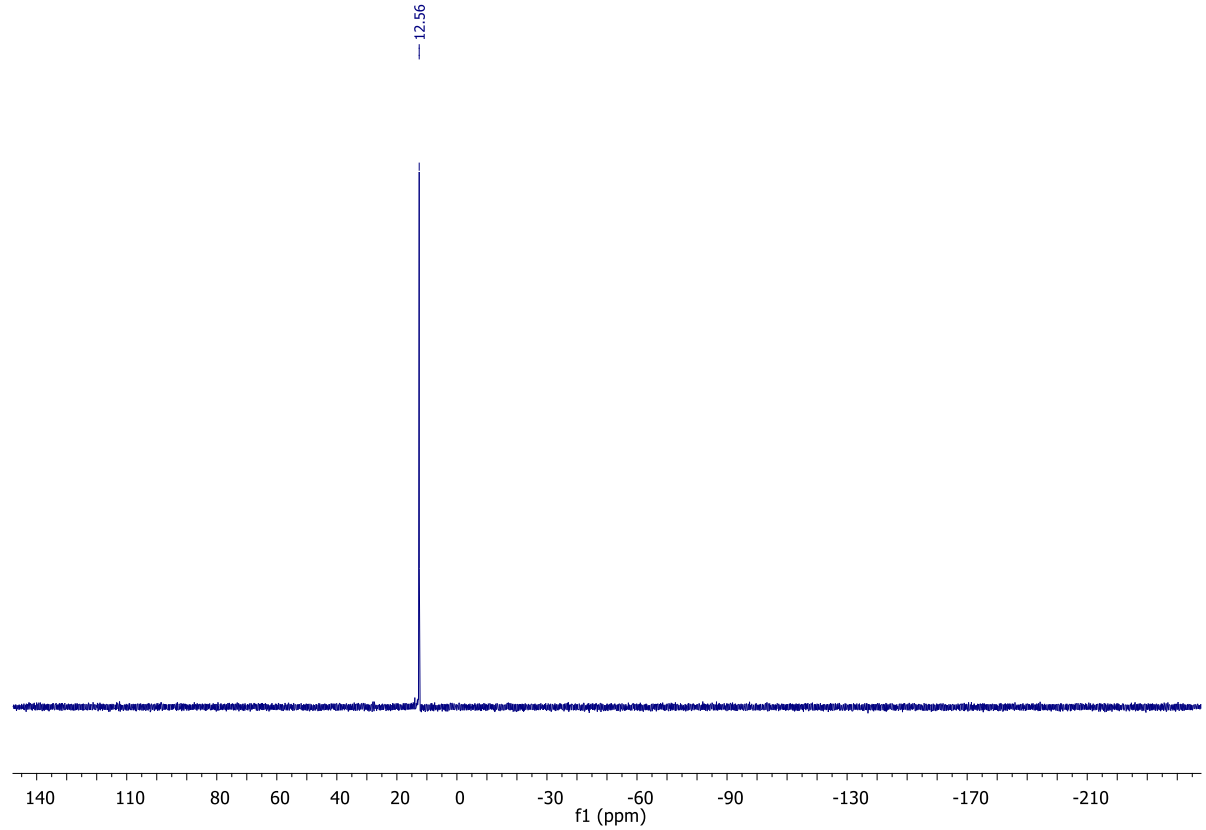


$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) spectrum of **78**.

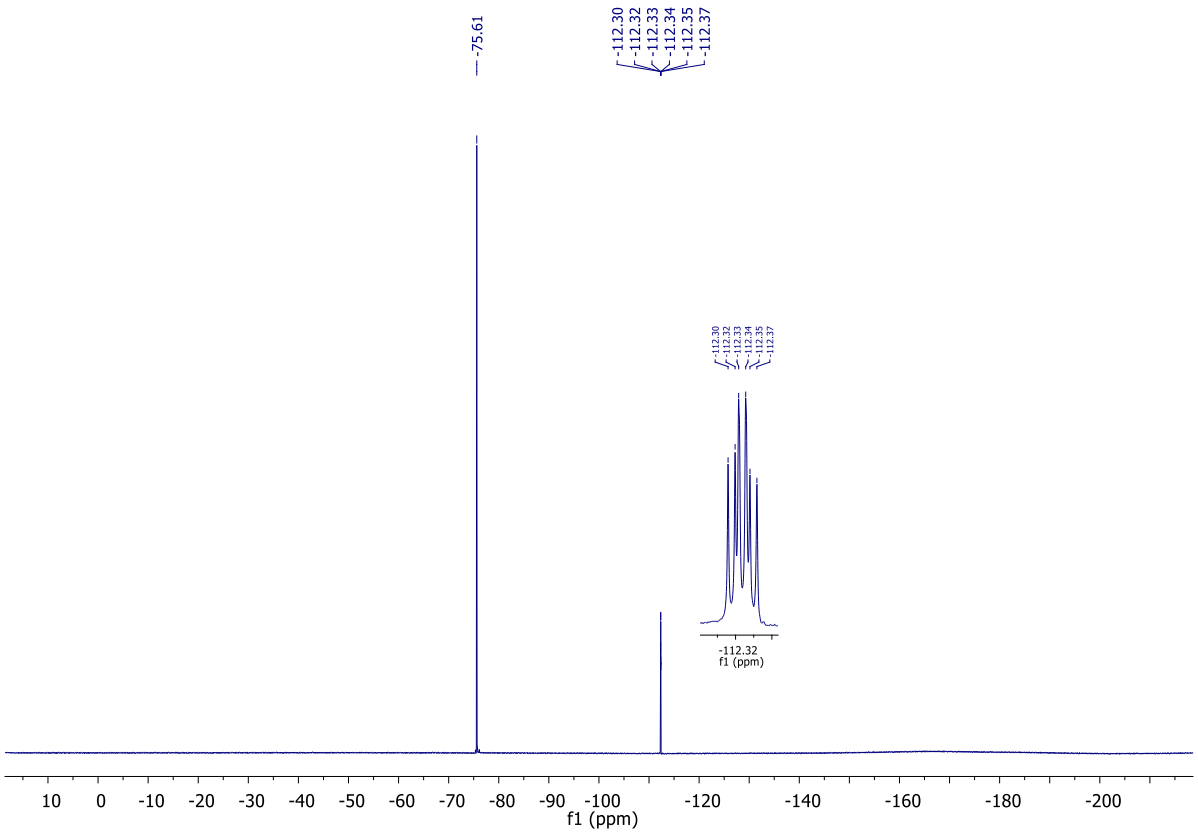
Compound 79·TFA



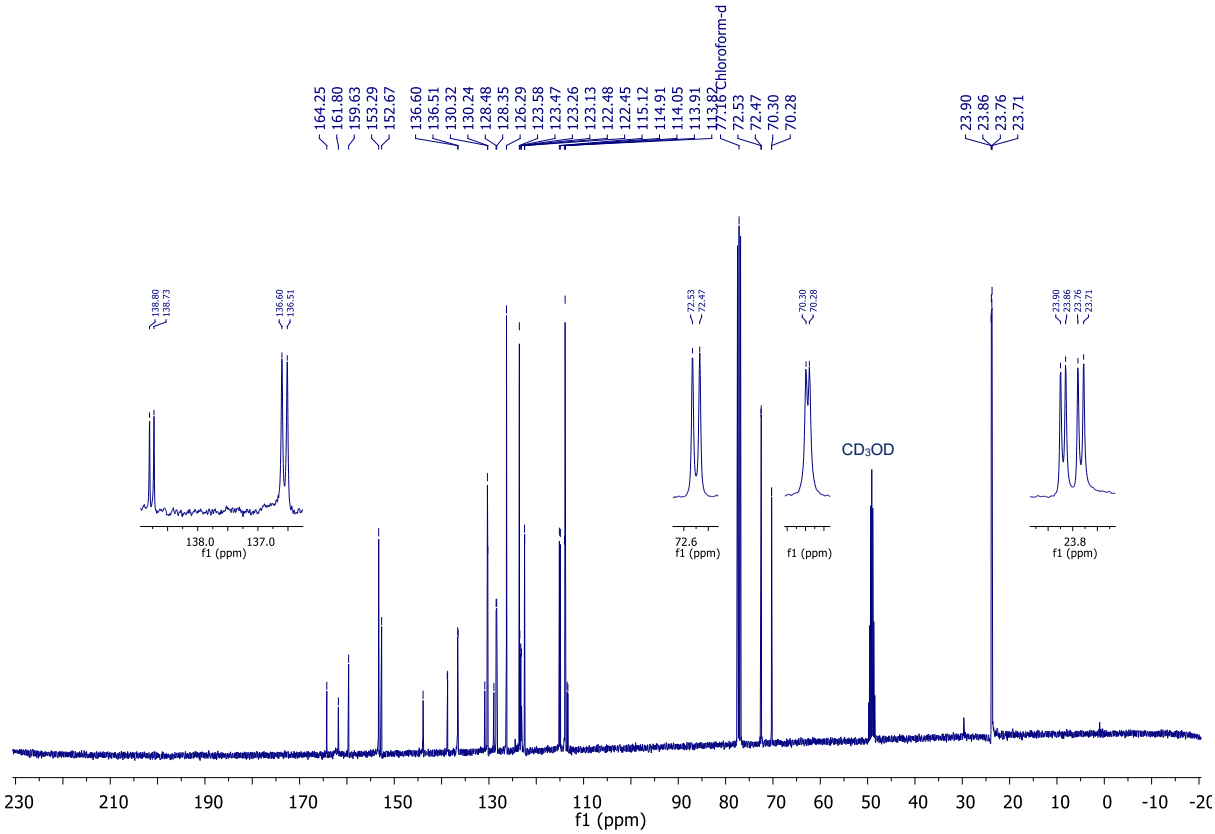
^{1}H NMR (600 MHz, $CDCl_3$) spectrum of **79·TFA**.



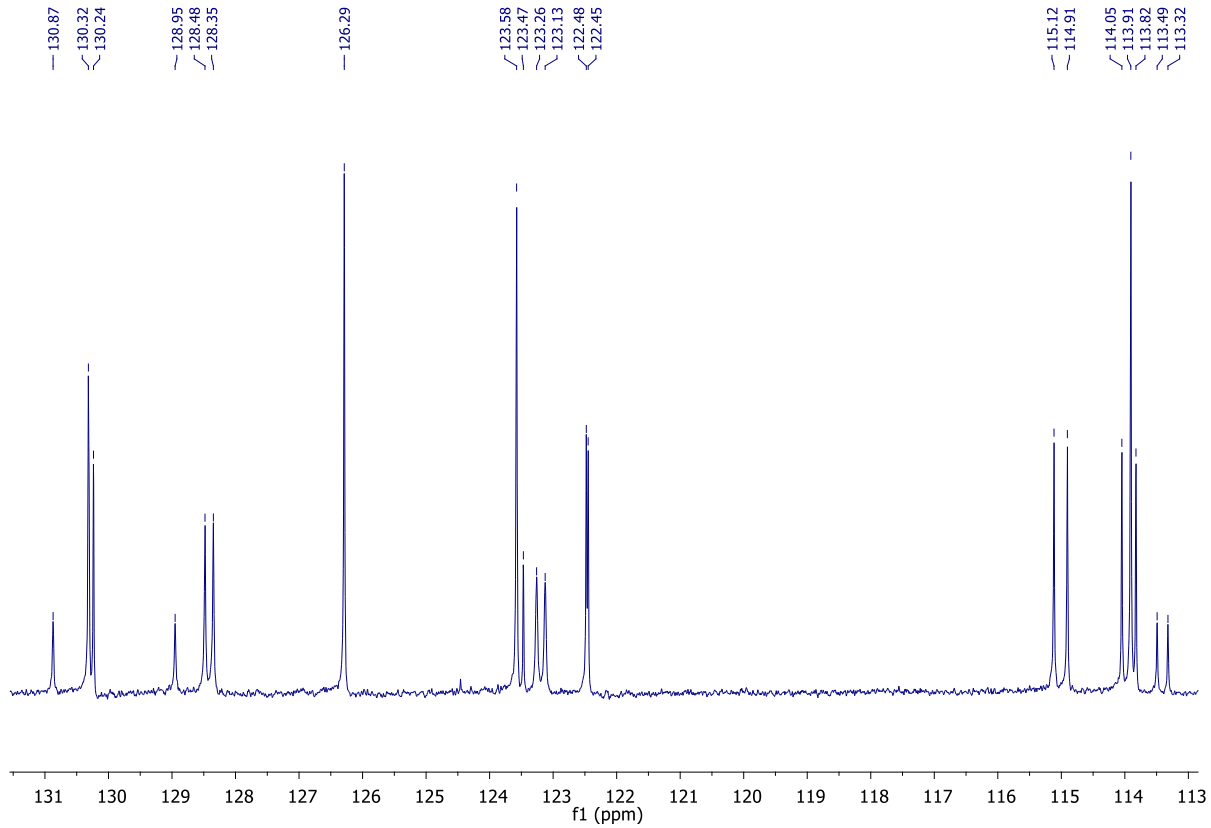
^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$) spectrum of **79·TFA**.



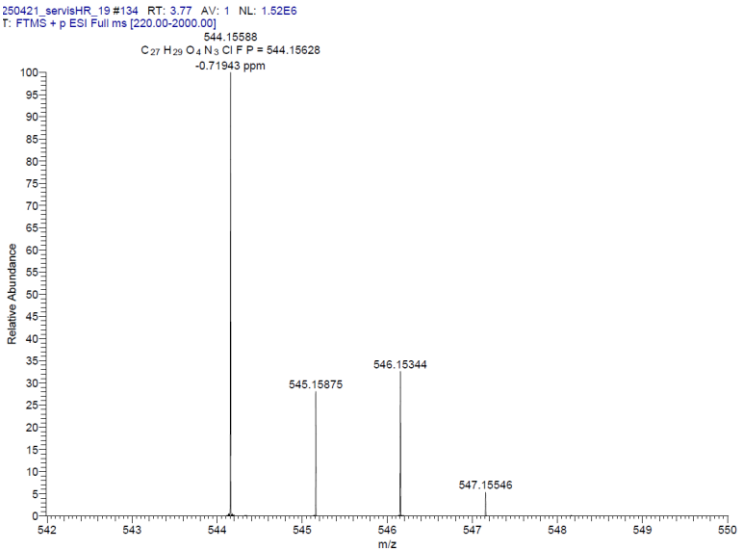
^{19}F NMR (376 MHz, $CDCl_3$) spectrum of **79·TFA**.



^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$/CD_3OD ~10:1) spectrum of **79·TFA**.

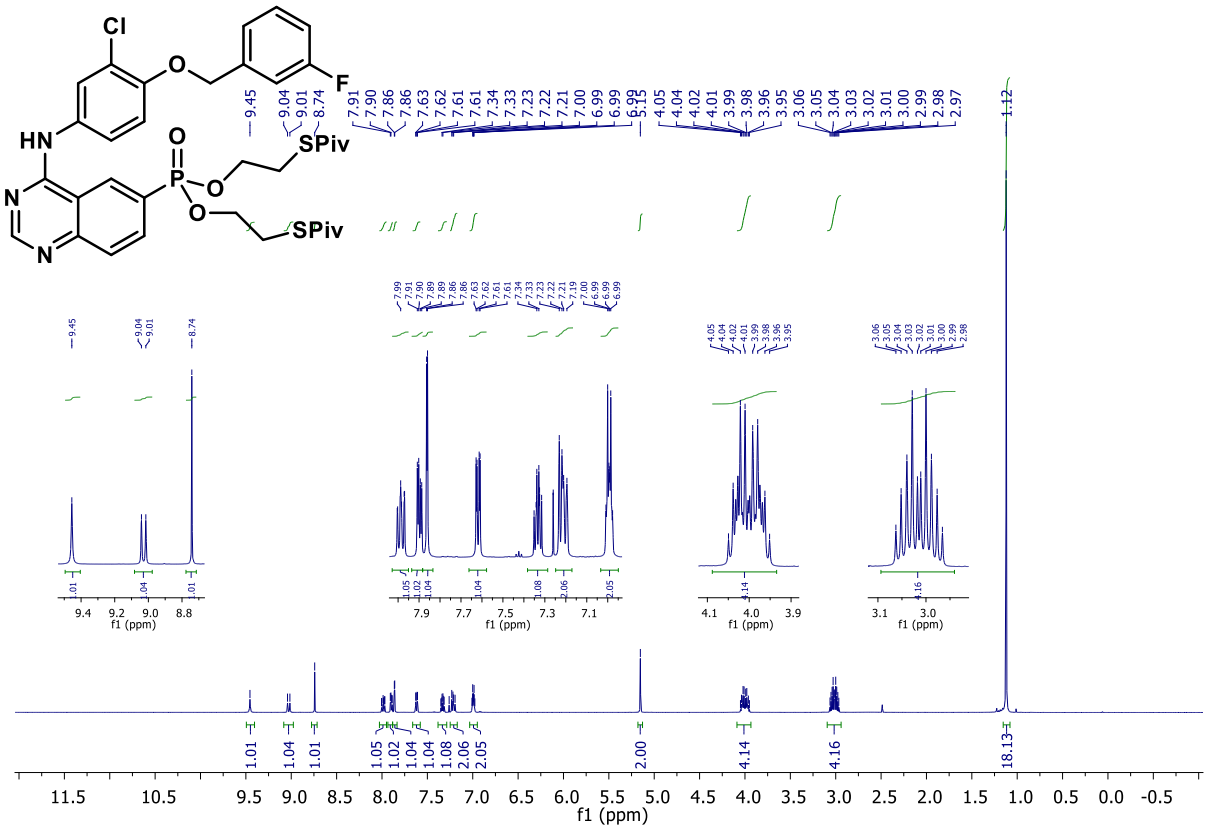


$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3/CD_3OD$ ~10:1) spectrum of **79·TFA** in more detail.

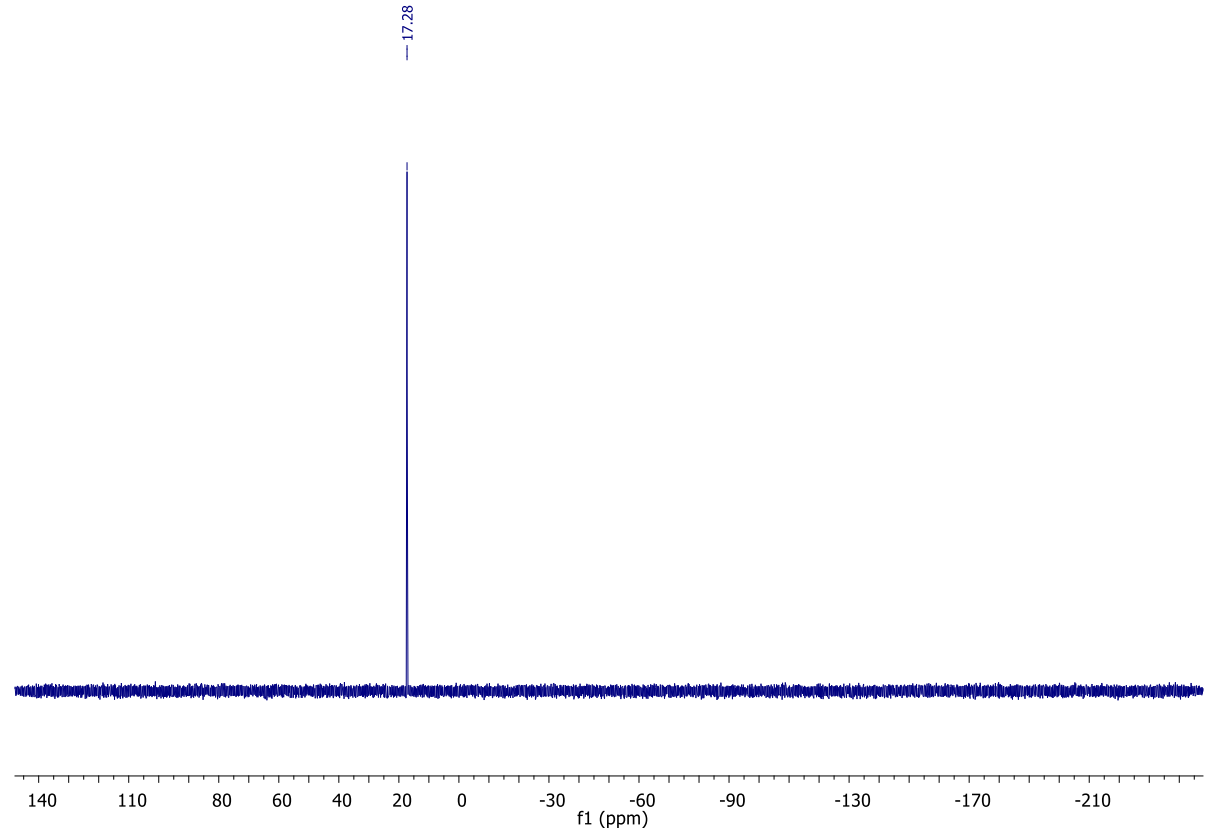


HRMS (ESI-TOF) spectrum of compound **79·TFA** ([M–TFA+H]$^+$ signal was detected and is shown).

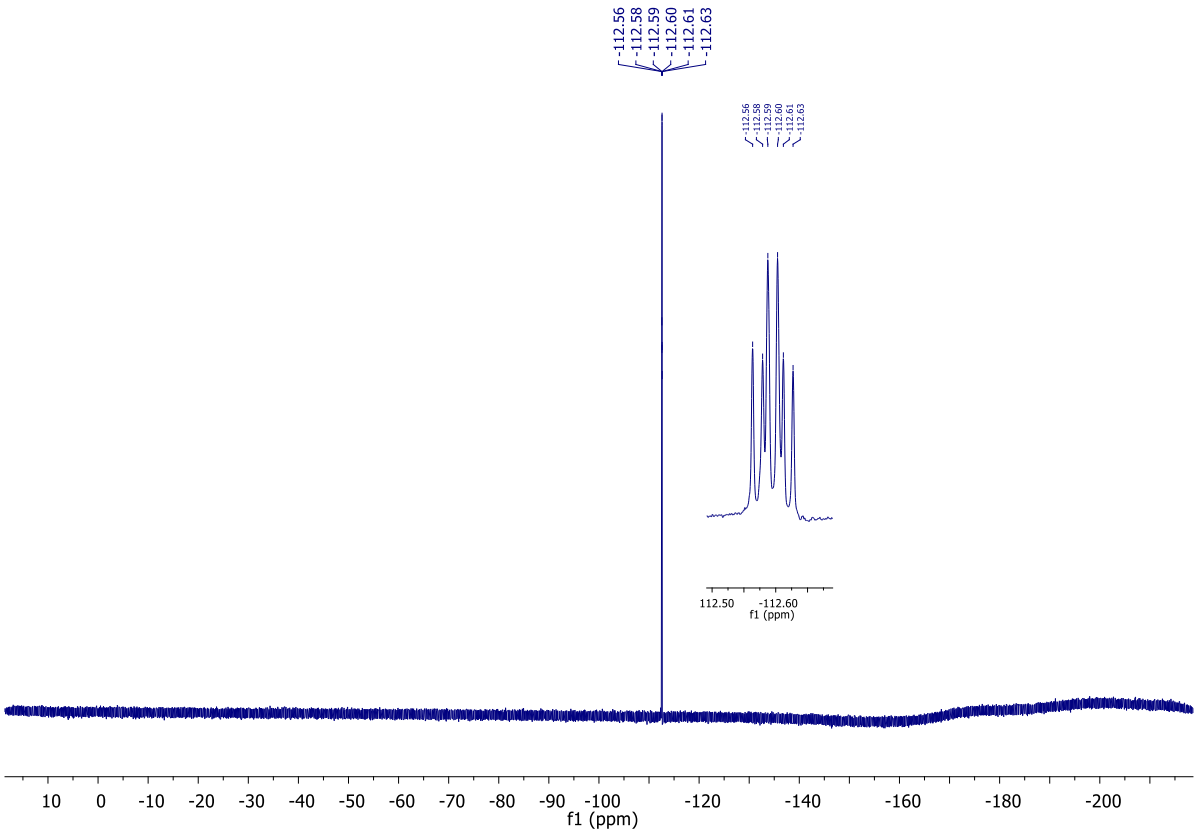
Compound 80



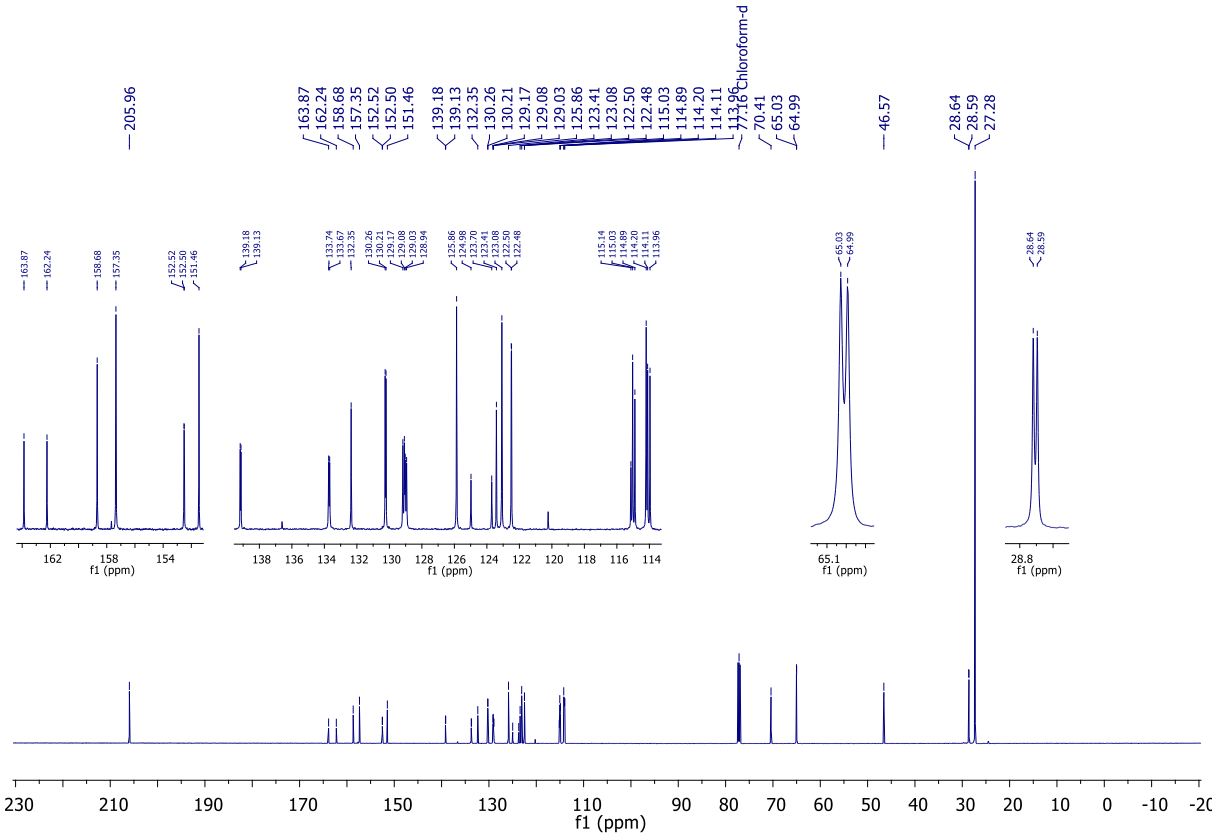
^{1}H NMR (600 MHz, $CDCl_3$) spectrum of **80**.



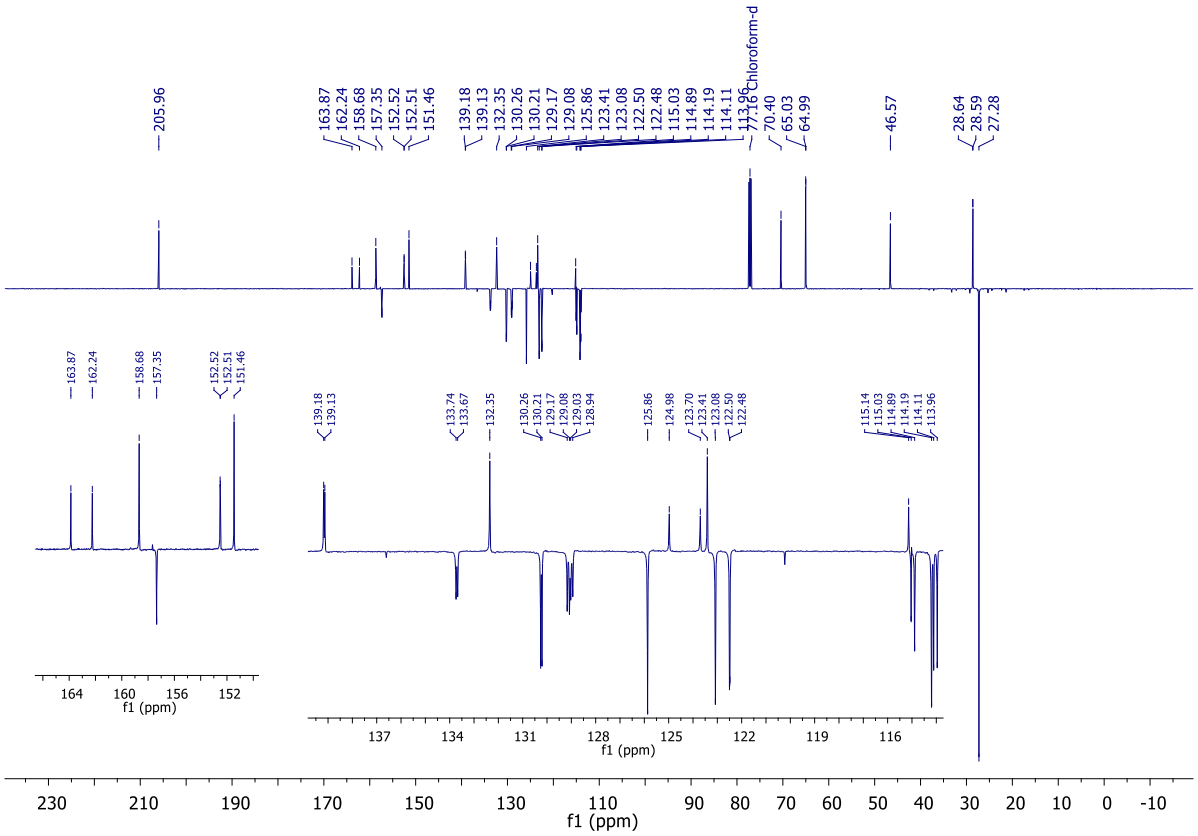
$^{31}P\{^{1}H\}$ NMR (162 MHz, $CDCl_3$) spectrum of **80**.



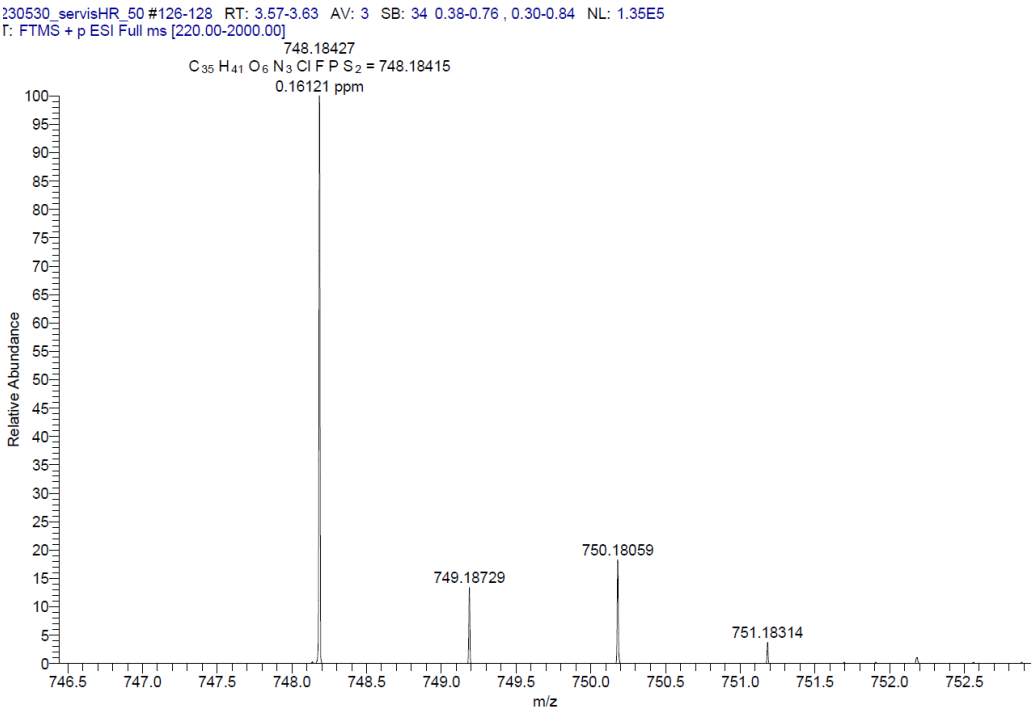
^{19}F NMR (376 MHz, $CDCl_3$) spectrum of **80**.



^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) spectrum of **80**.

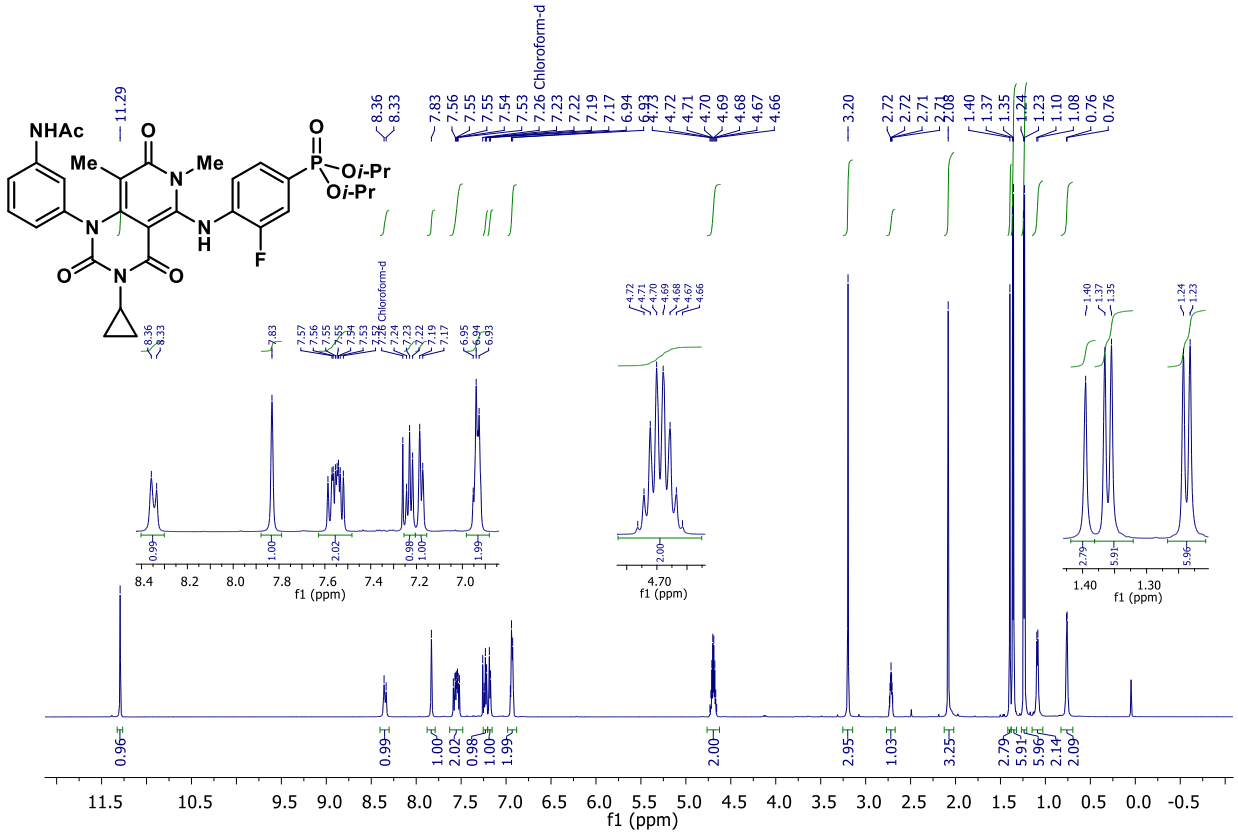


$^{13}C\{^{1}H\}$ APT NMR (151 MHz, $CDCl_3$) spectrum of **80**.

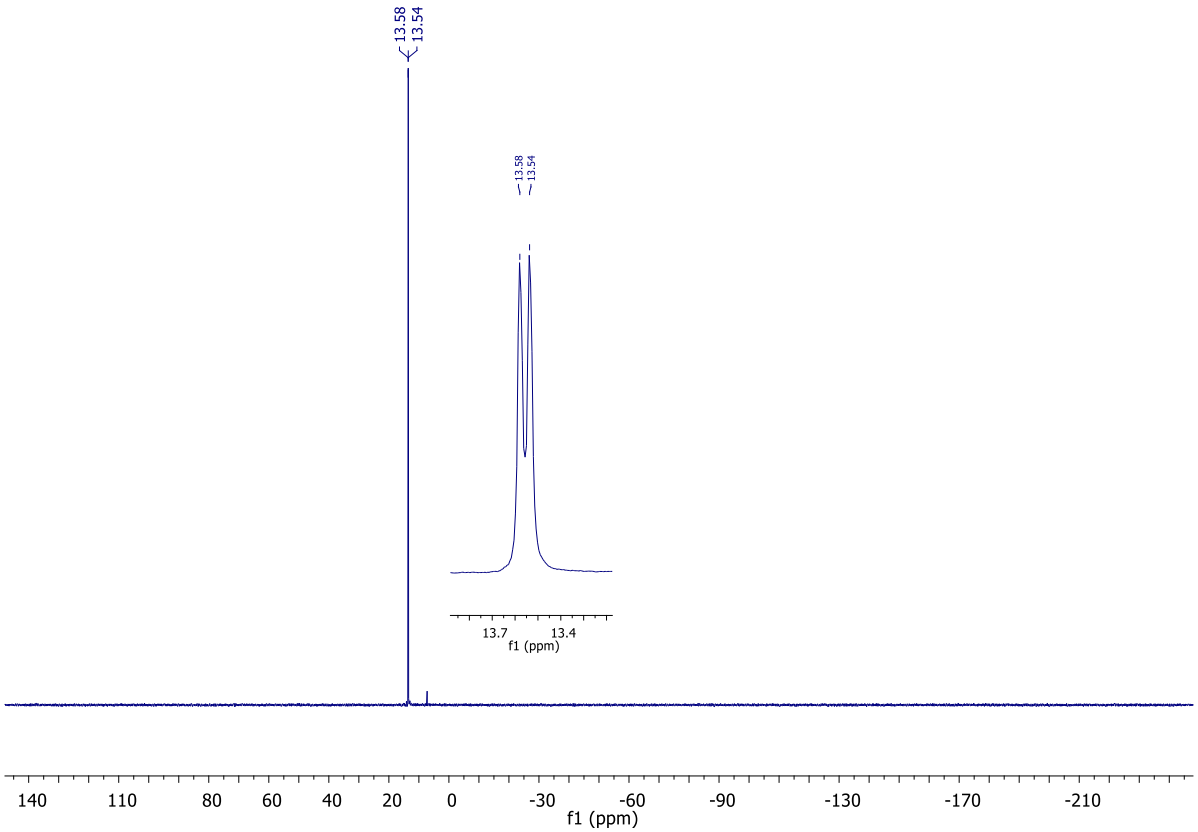


HRMS (ESI-TOF) spectrum of compound **80**.

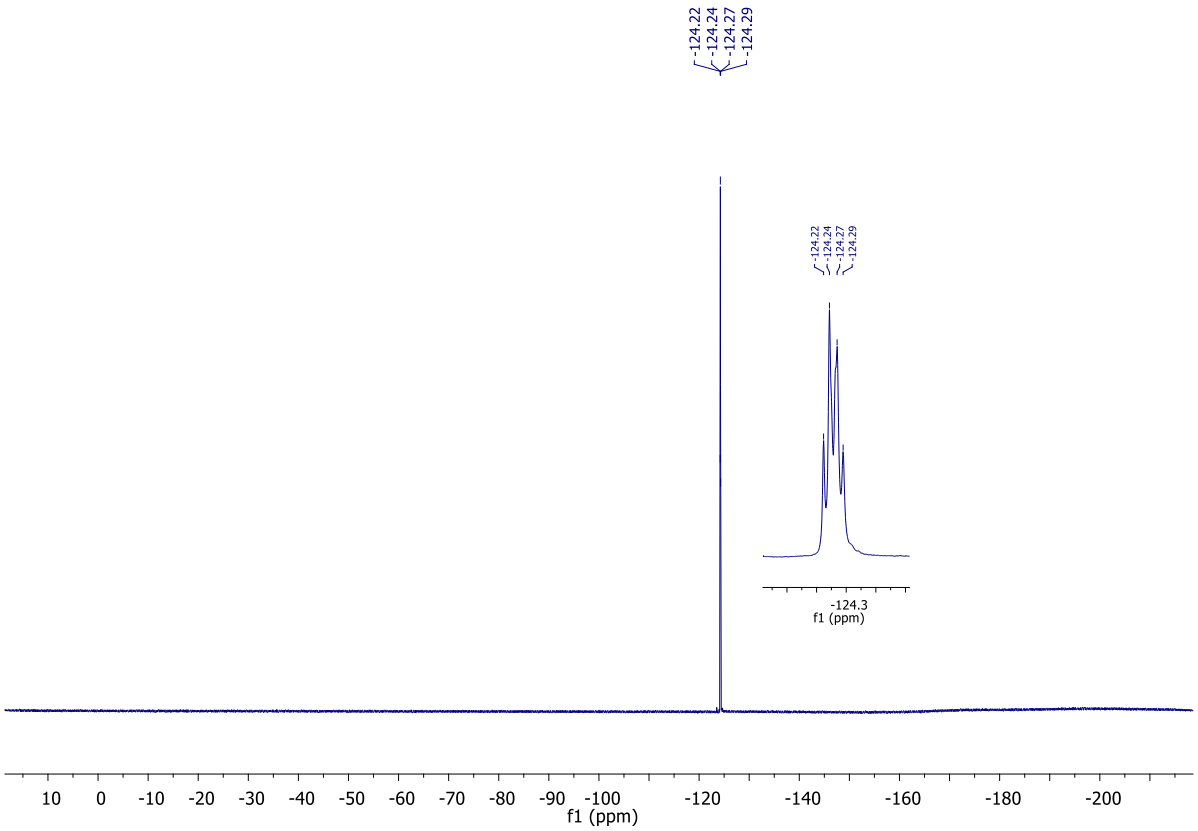
Compound 81



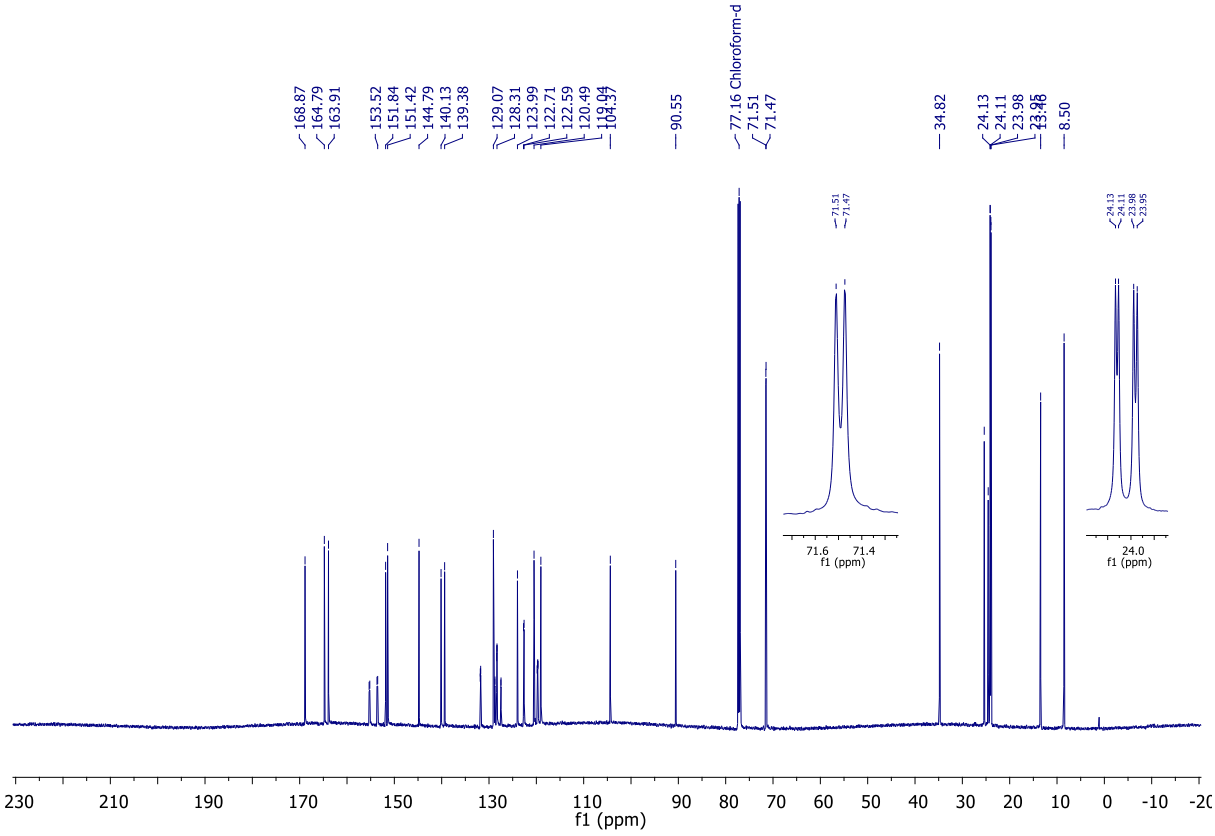
^{1}H NMR (600 MHz, $CDCl_3$) spectrum of **81**.



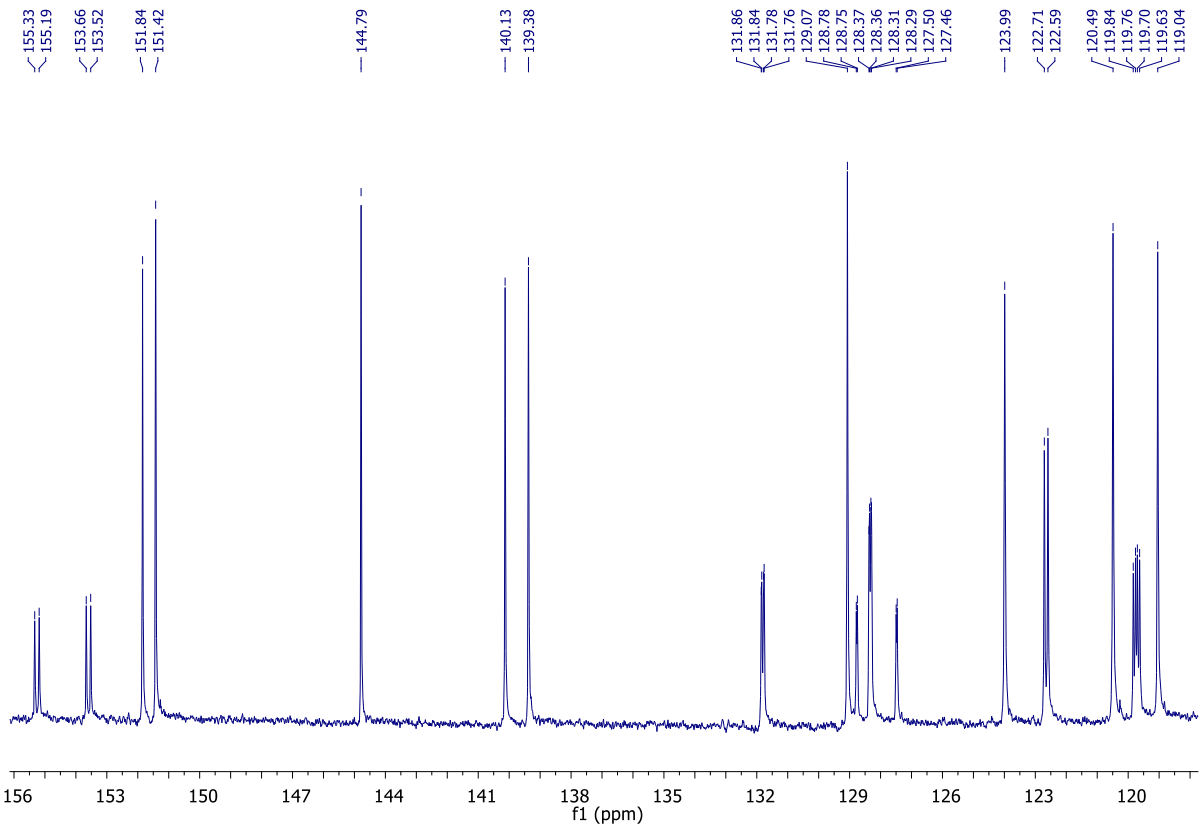
^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$) spectrum of **81**.



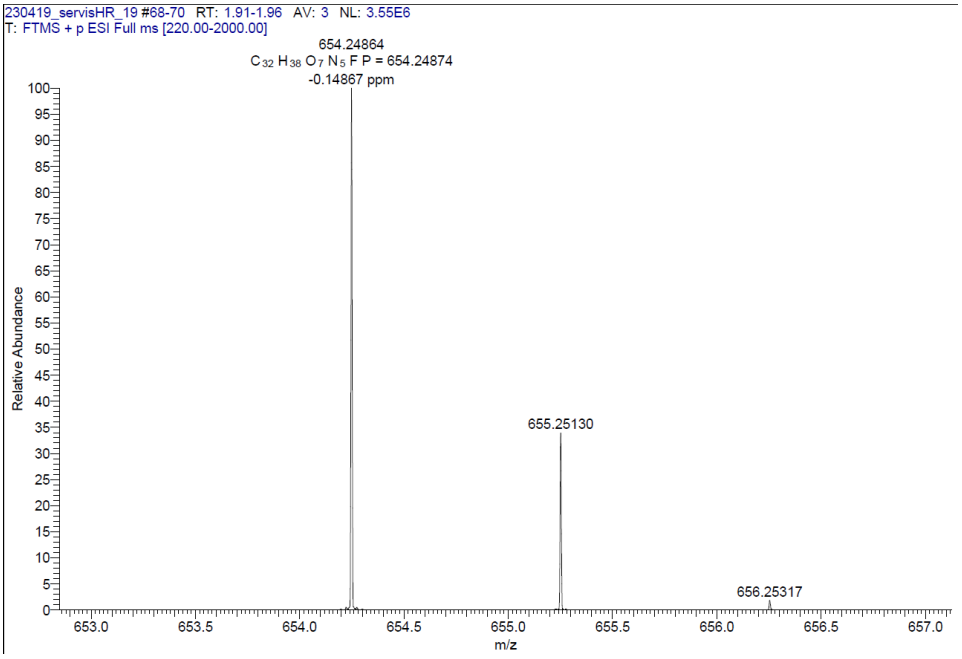
^{19}F NMR (376 MHz, $CDCl_3$) spectrum of **81**.



^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) spectrum of **81**.

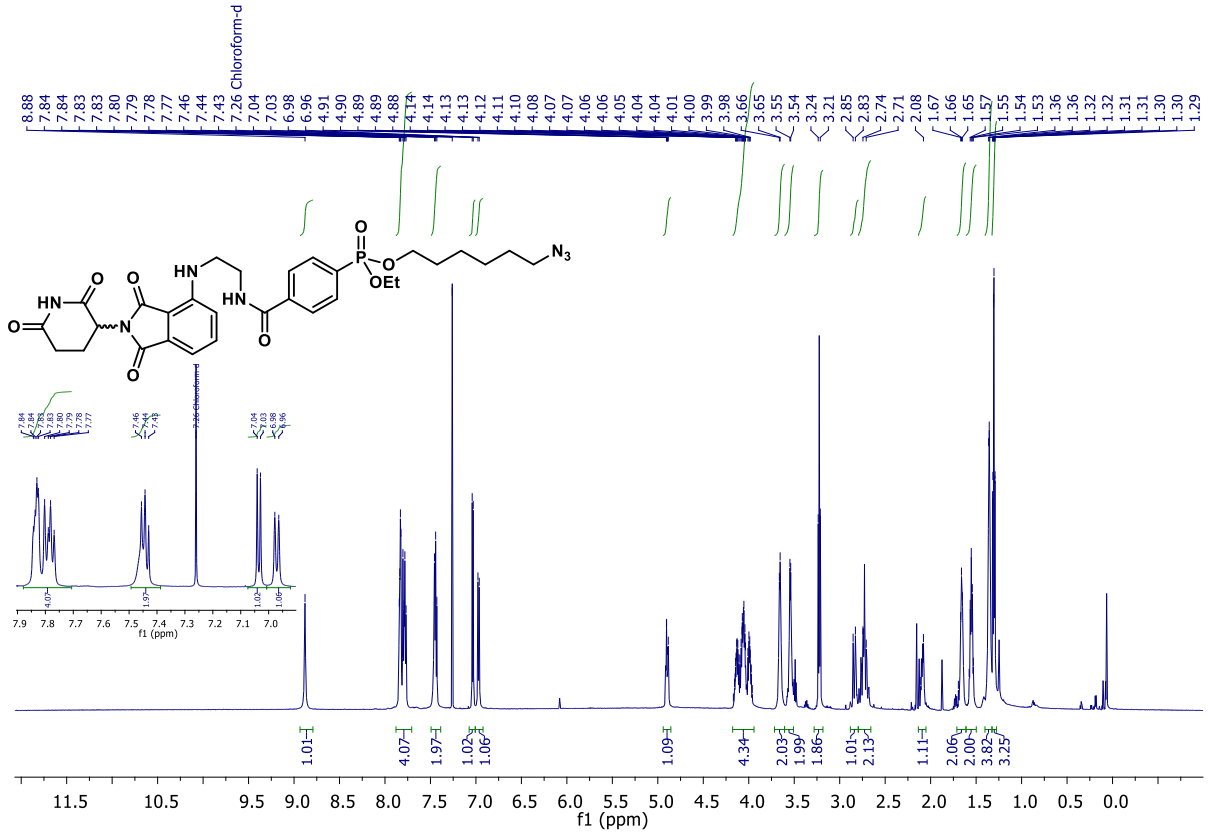


$^{13}C\{^{1}H\}$ NMR (151 MHz, $CDCl_3$) spectrum of **81** in more detail.

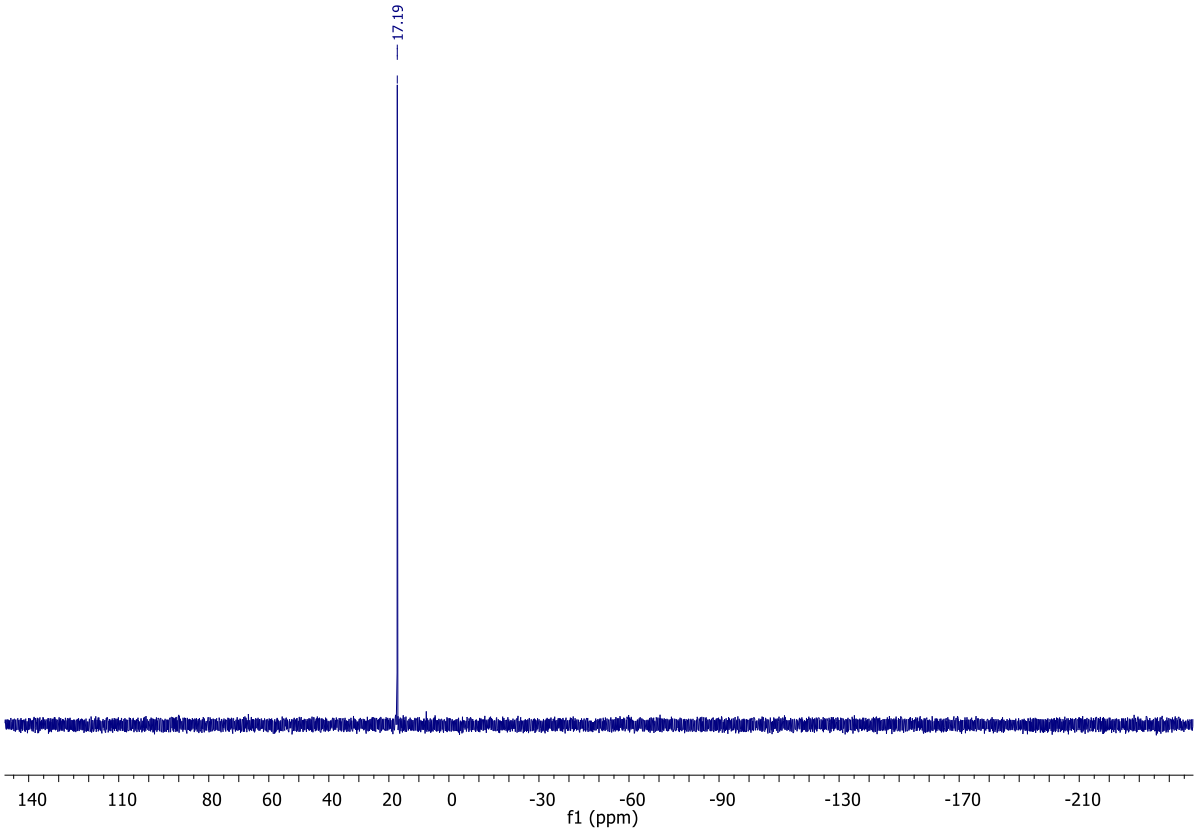


HRMS (ESI-TOF) spectrum of compound **81**.

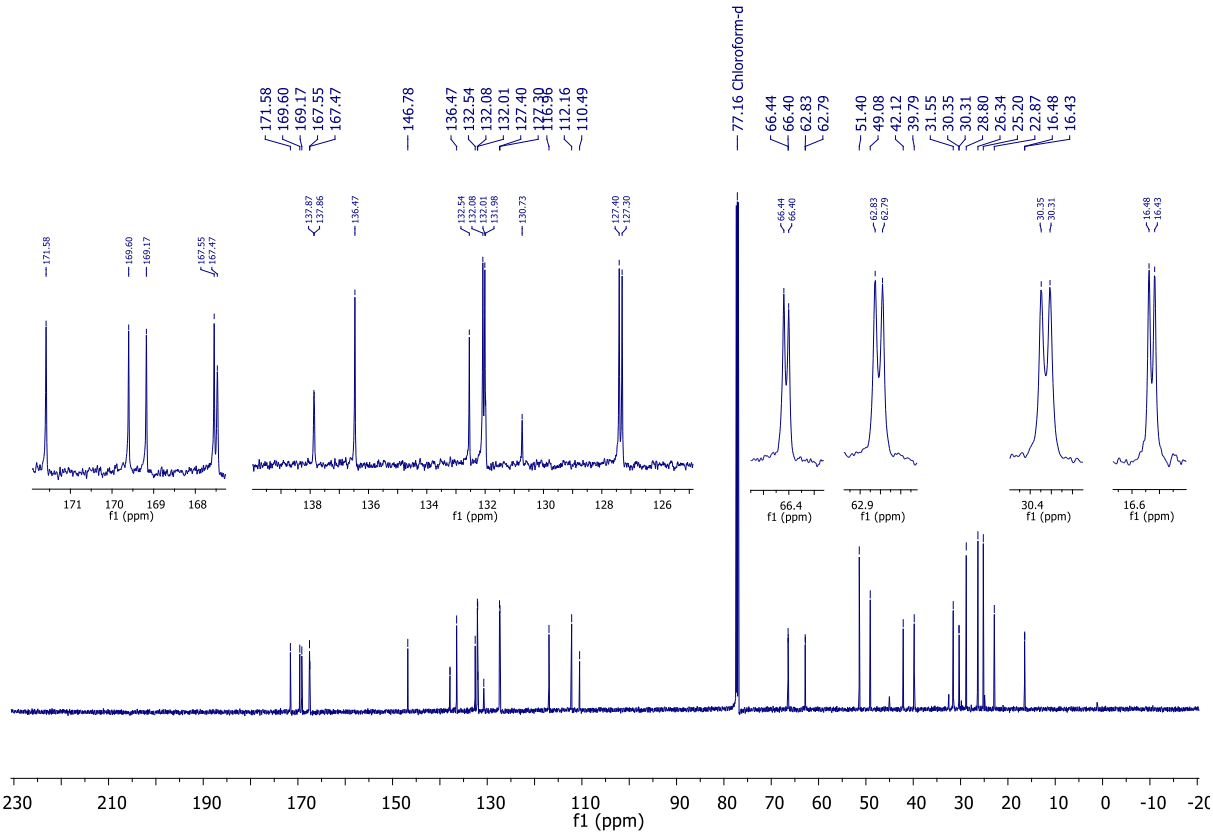
Compound 82



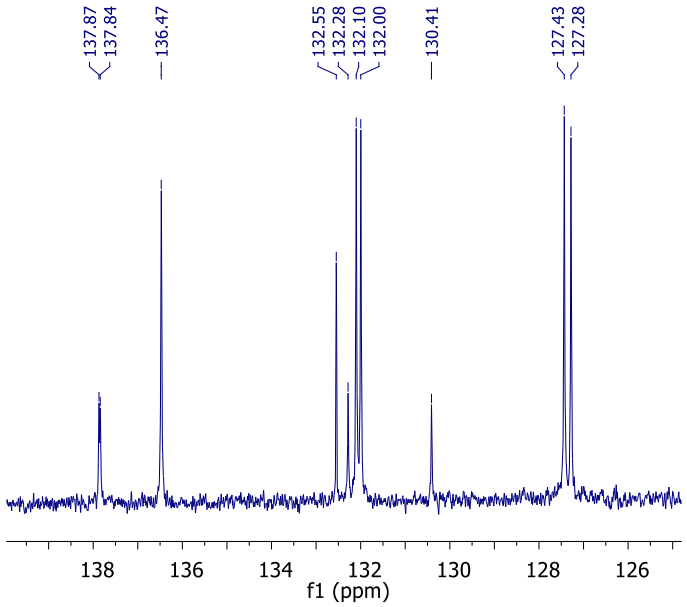
^{1}H NMR (600 MHz, $CDCl_3$) spectrum of **82**.



^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$) spectrum of **82**.

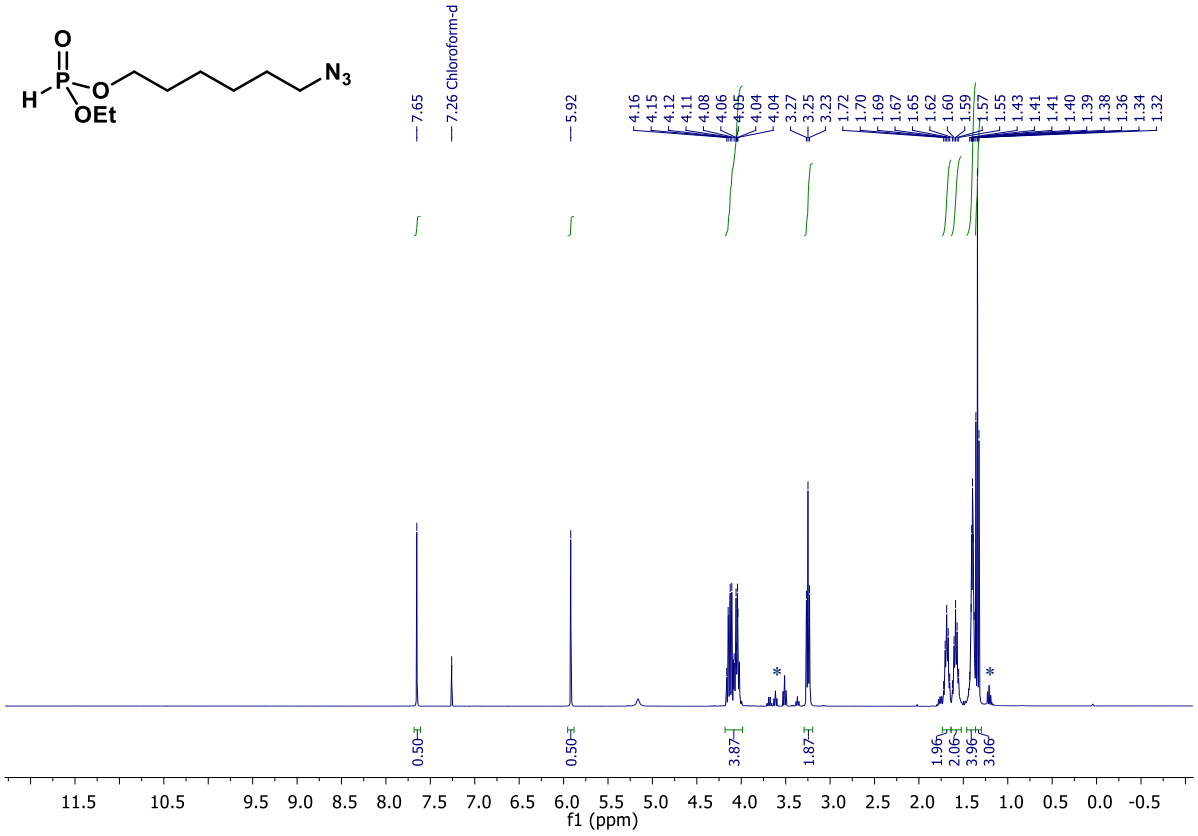


$^{13}C\{^{1}H\}$ NMR (151 MHz, $CDCl_3$) spectrum of **82**.

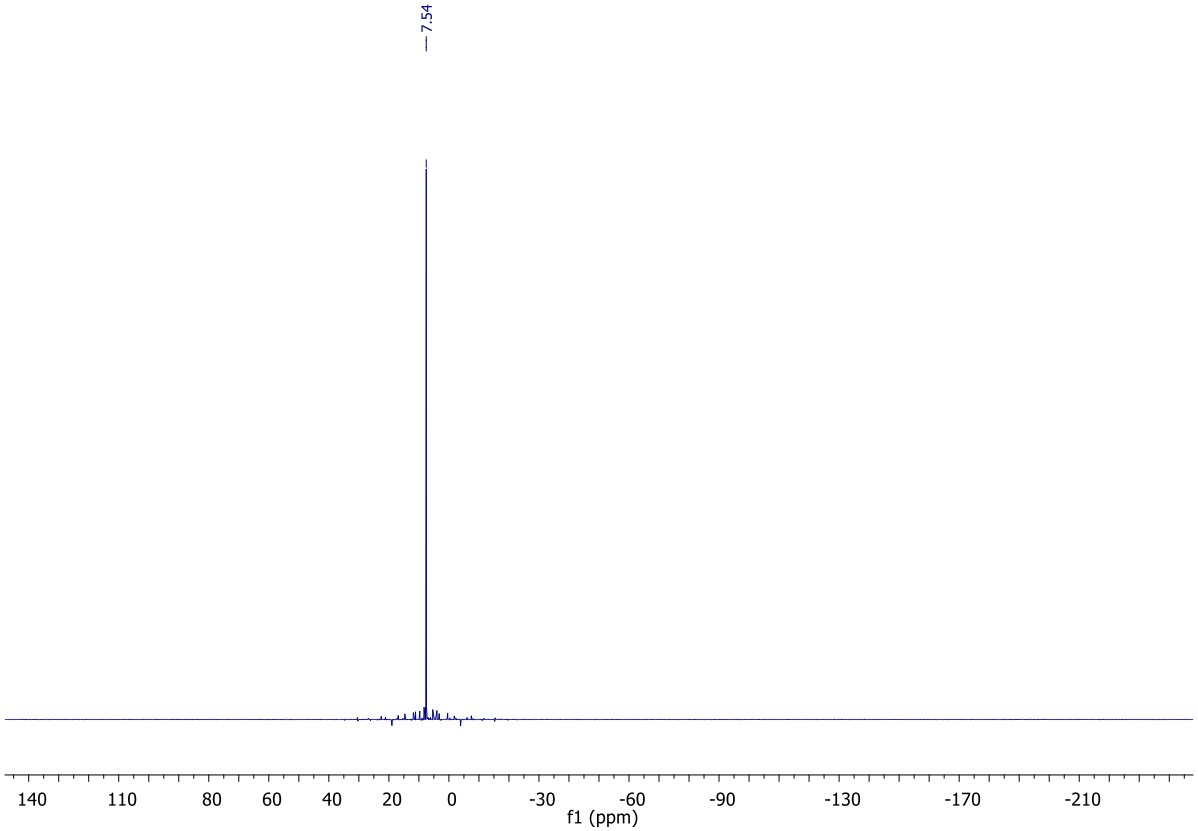


Part of the **$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$)** spectrum of **82** which was used to assign the C(sp^2)–P signal based on its *J* value ($^{13}C\{^{1}H\}$ 151 MHz: δ 131.4 (d, *J* = 189.1 Hz) ppm; $^{13}C\{^{1}H\}$ 100 MHz: δ 131.3 (d, *J* = 187.2 Hz) ppm).

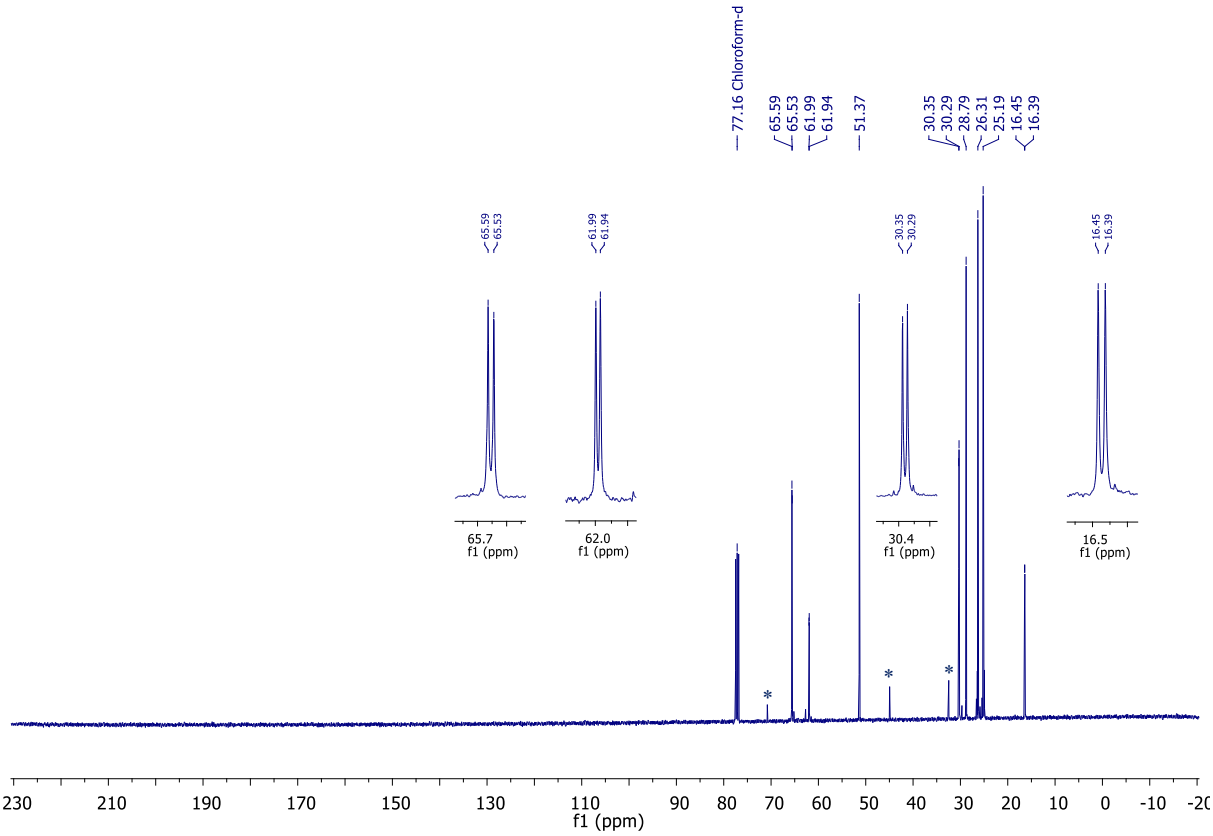
Compound 83



^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **83**. Asterisks denote impurities inseparable due to instability of **83** on silica gel.

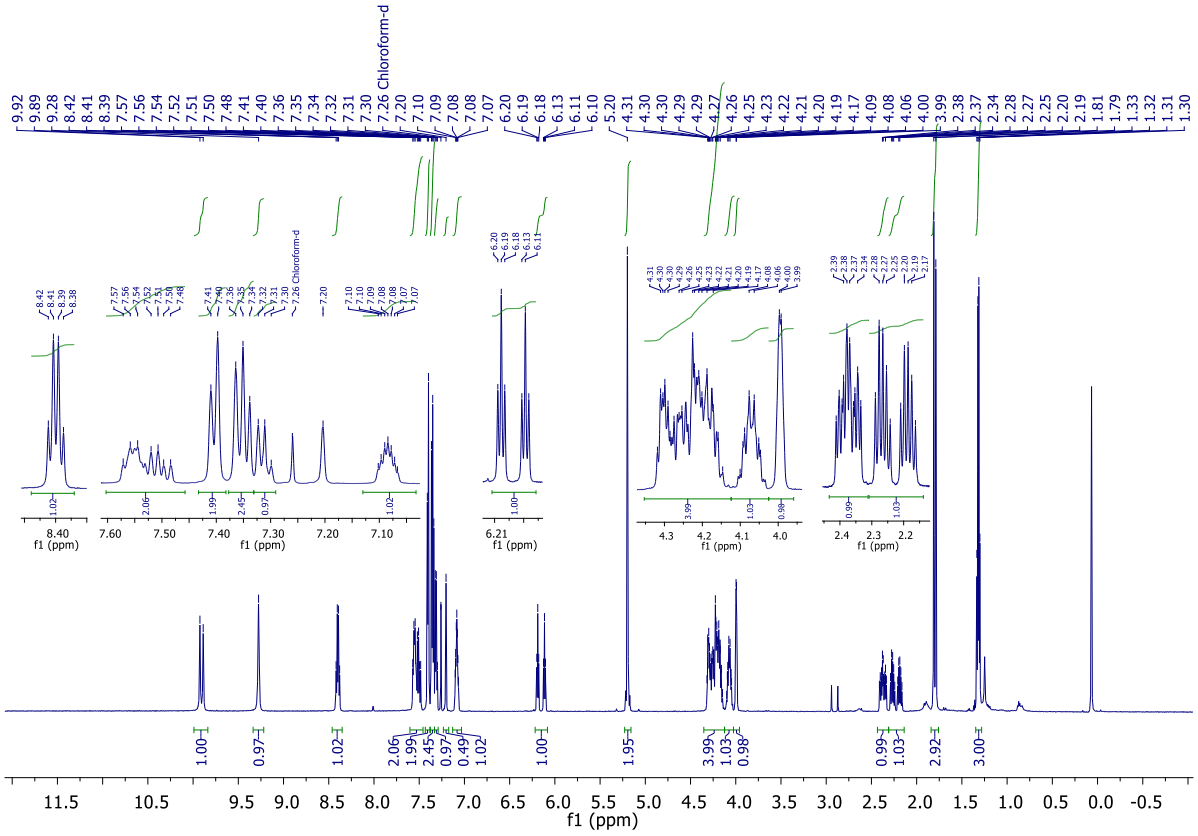


^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$) spectrum of **83**.

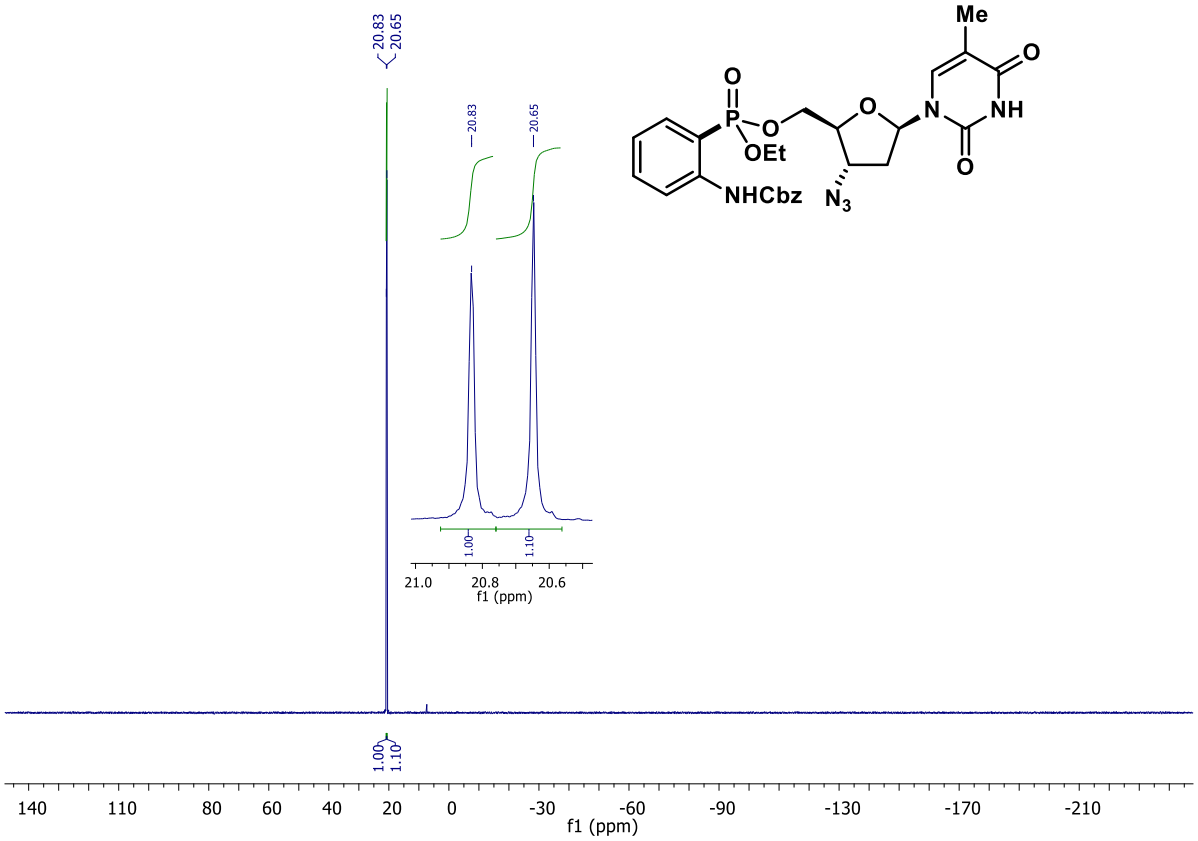


$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) spectrum of **83**. Asterisks denote impurities inseparable due to instability of **83** on silica gel.

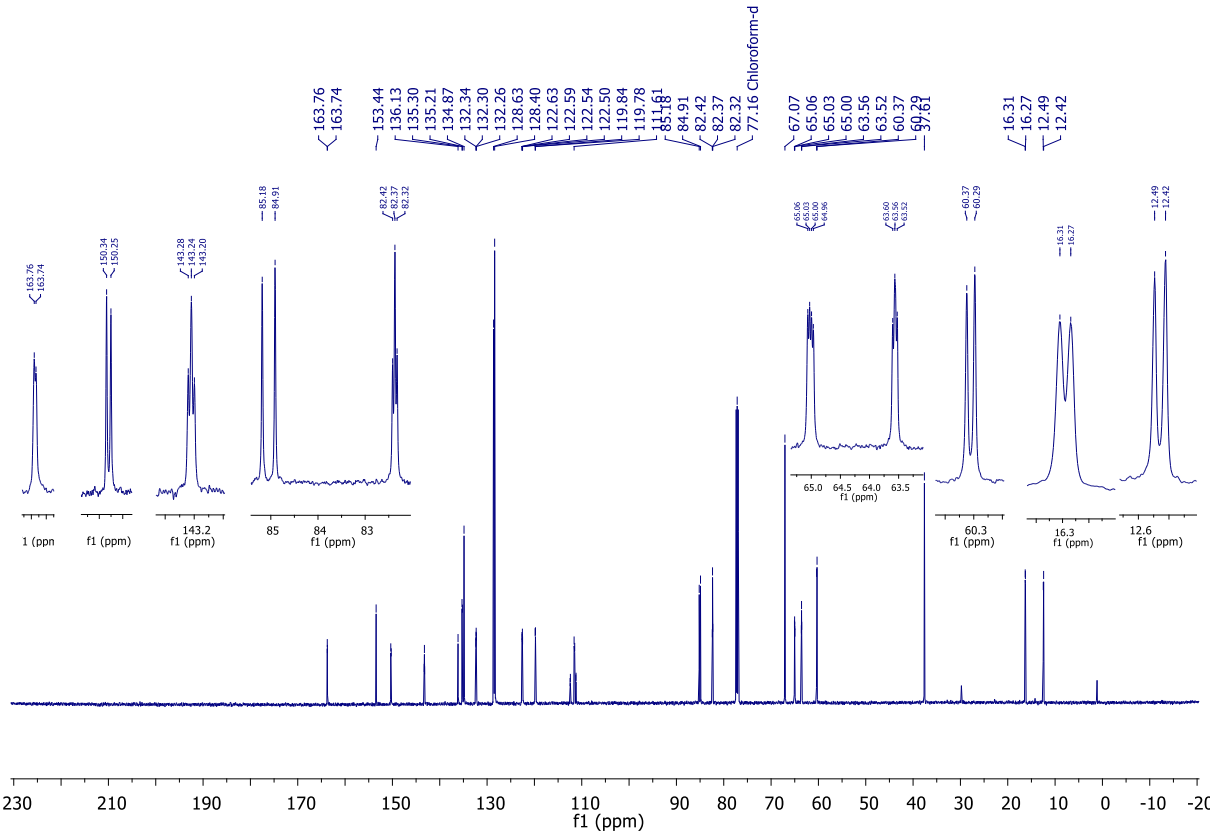
Compound 84



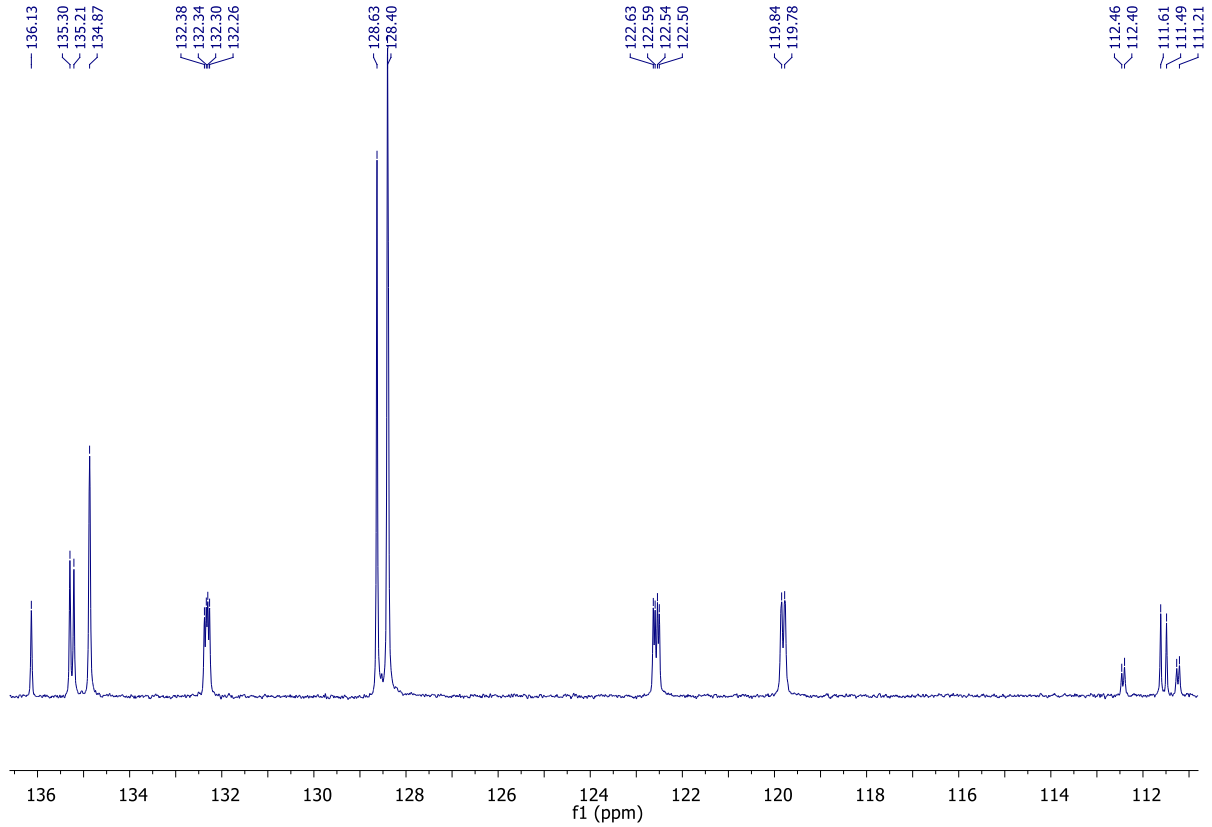
^{1}H NMR (600 MHz, $CDCl_3$) spectrum of **84**.



^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$) spectrum of **84**.

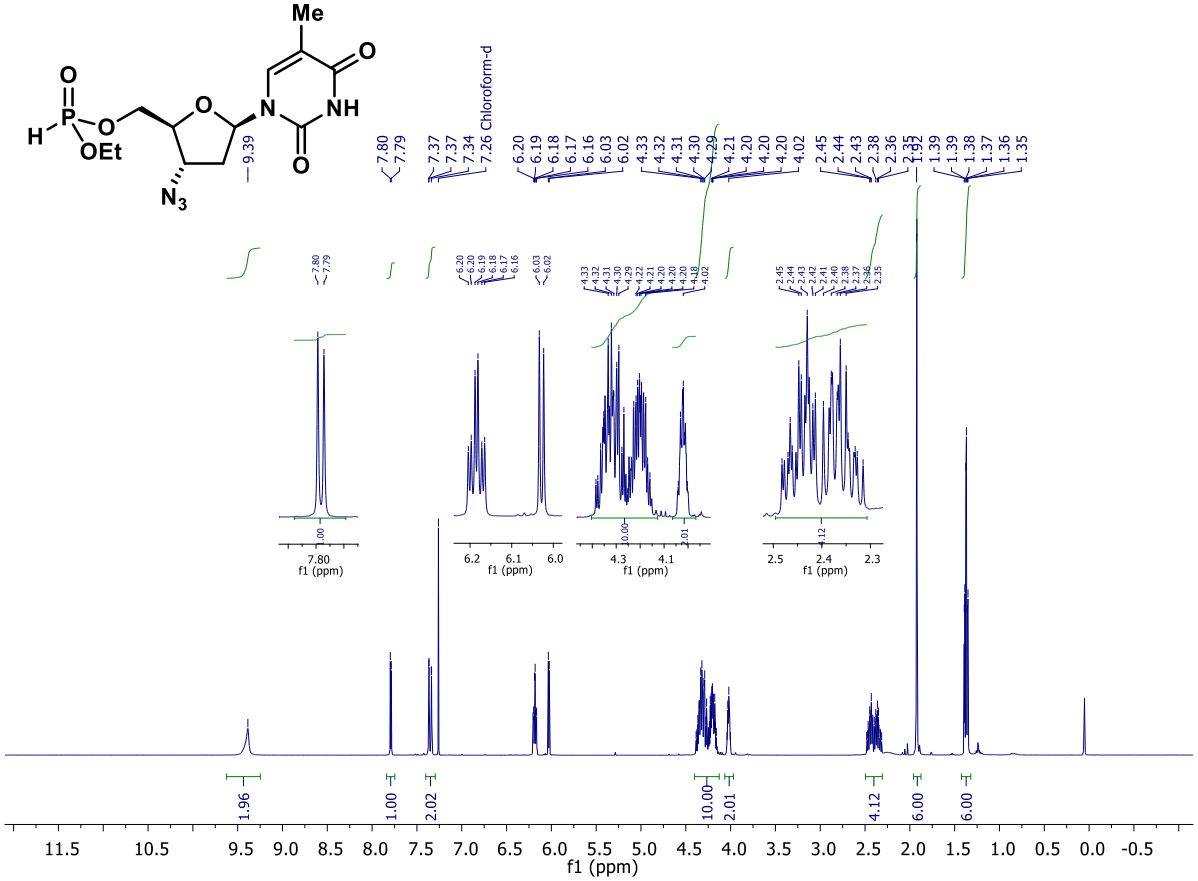


$^{13}C\{^{1}H\}$ NMR (151 MHz, $CDCl_3$) spectrum of **84**.

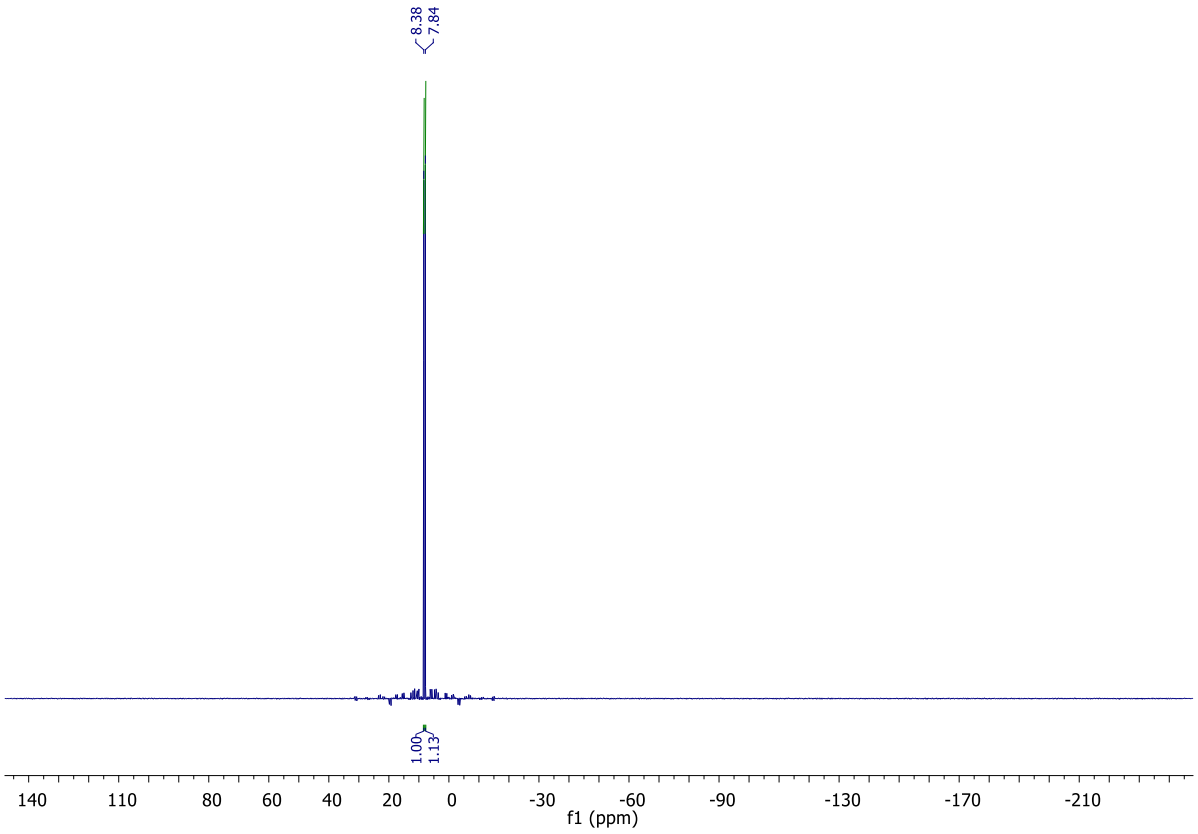


$^{13}C\{^{1}H\}$ NMR (151 MHz, $CDCl_3$) spectrum of **84** in more detail.

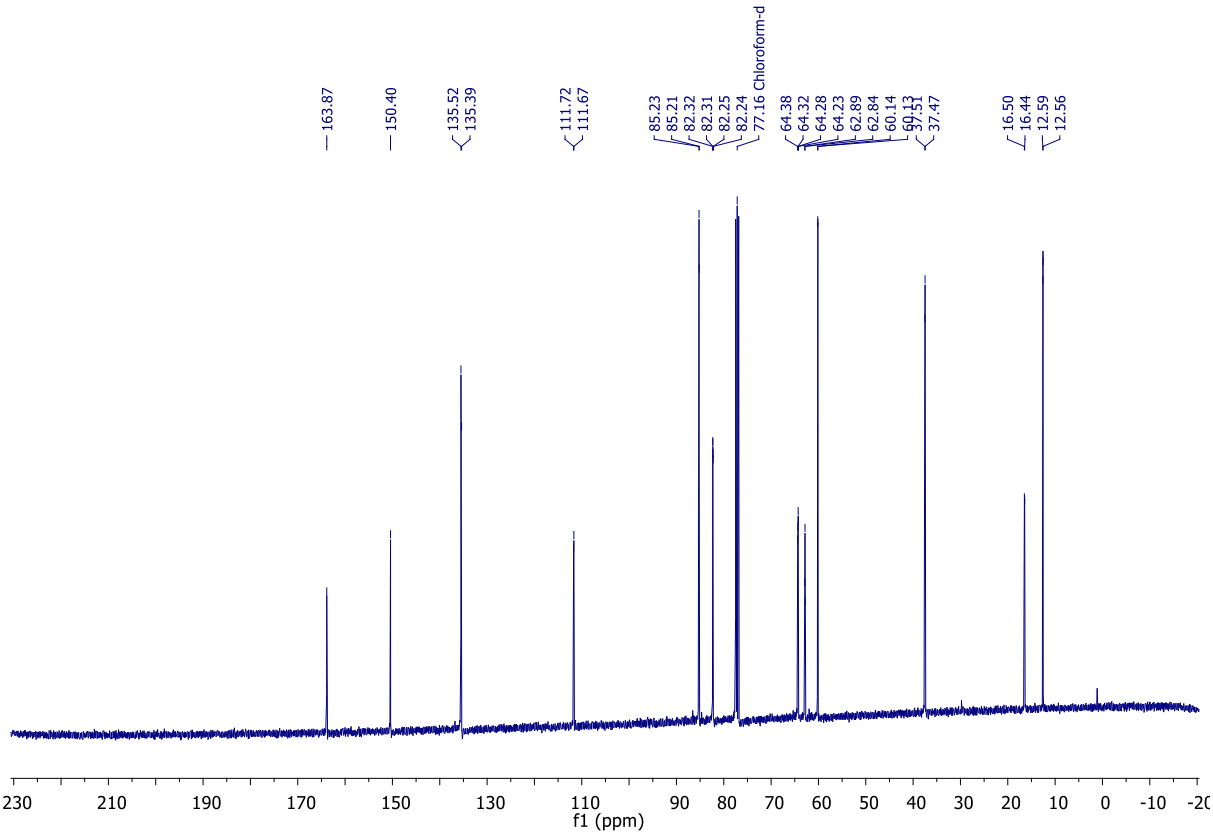
Compound 85



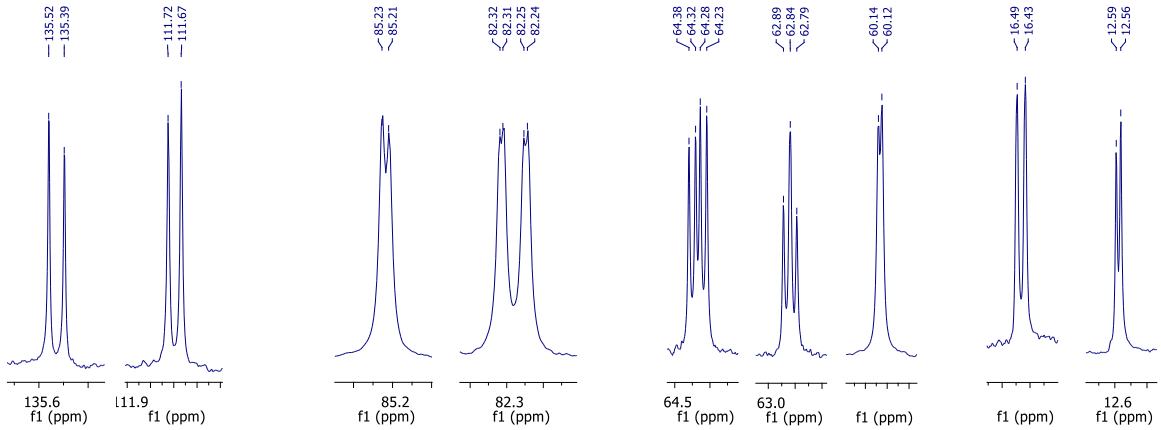
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **85**.



^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$) spectrum of **85**.

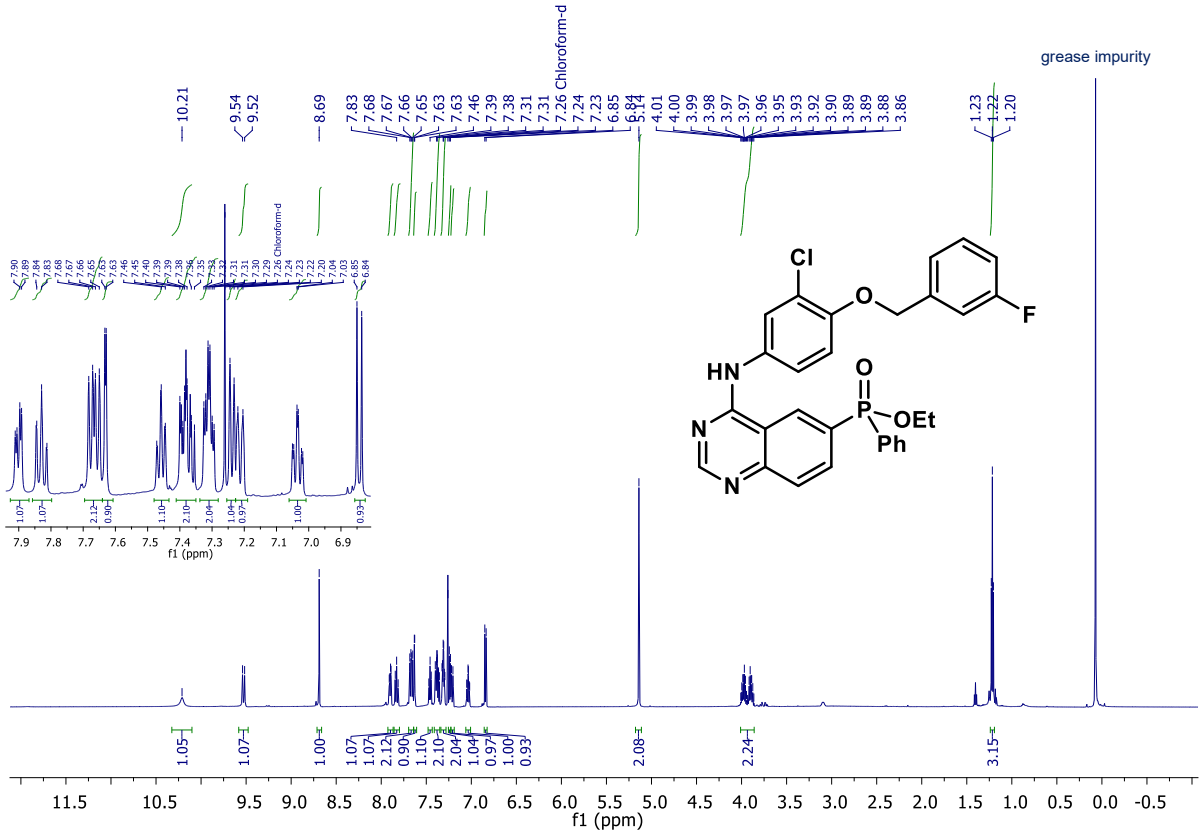


$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) spectrum of **85**.

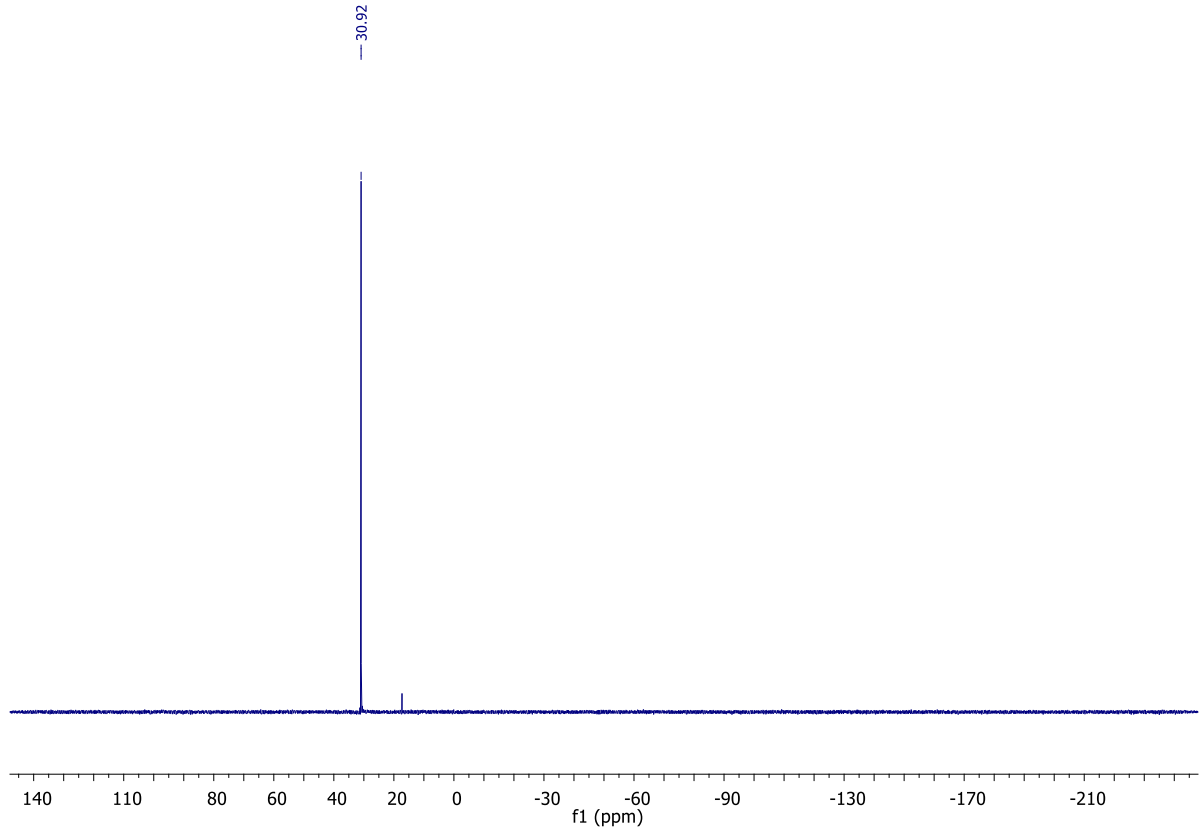


Details of ^{13}C NMR signals of **85**.

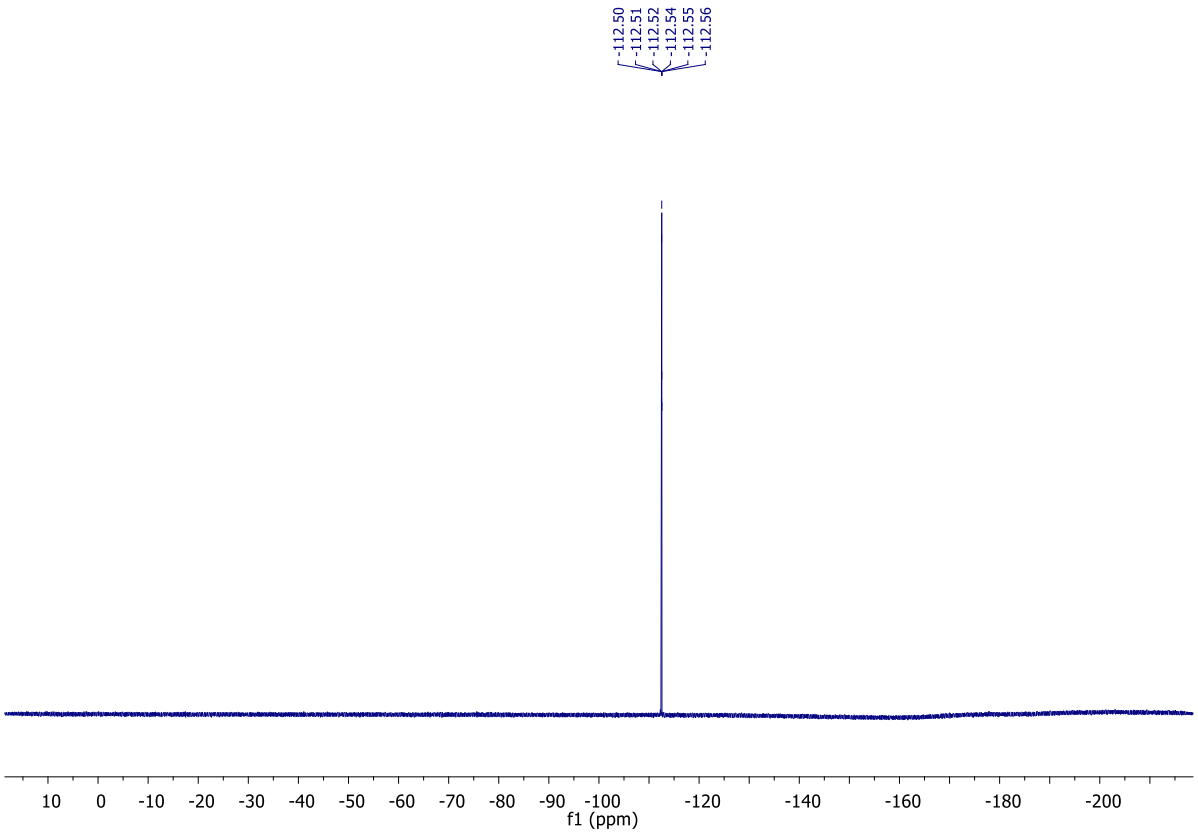
Compound 88



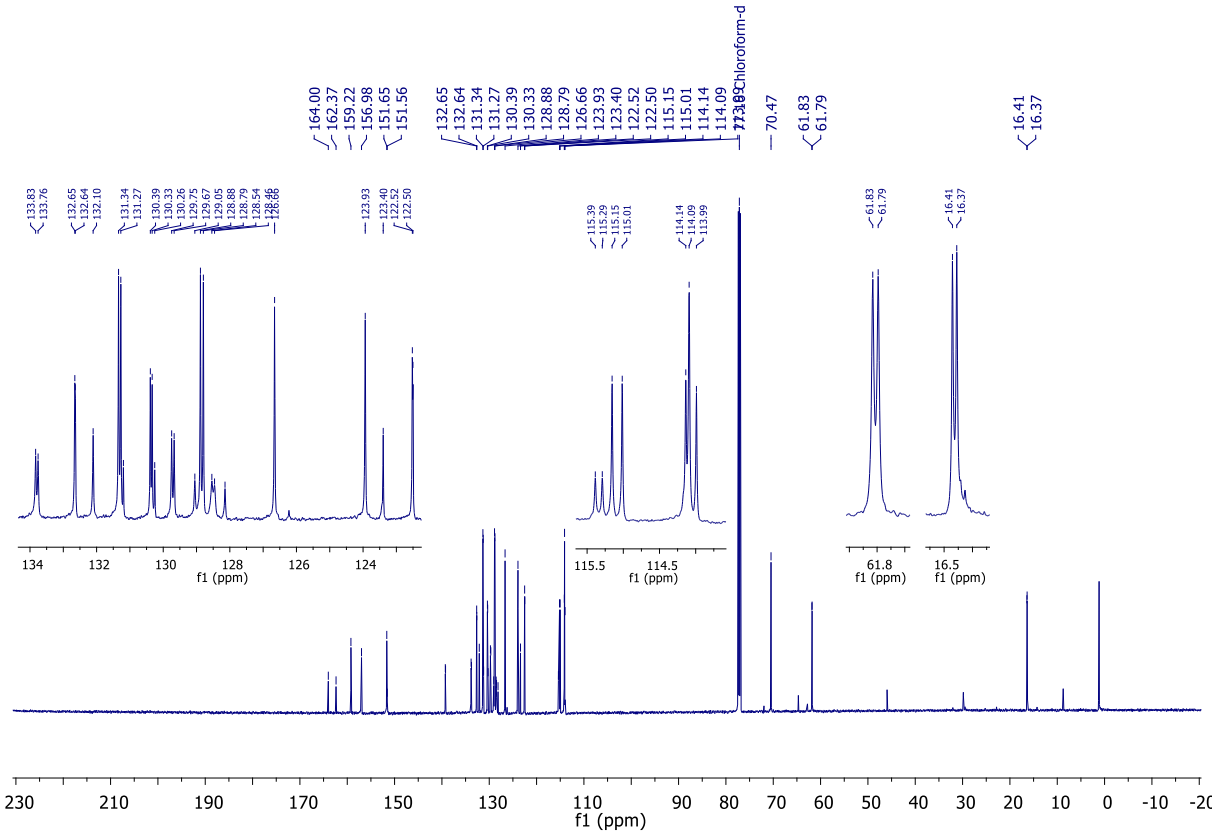
^{1}H NMR (600 MHz, $CDCl_3$) spectrum of **88**.



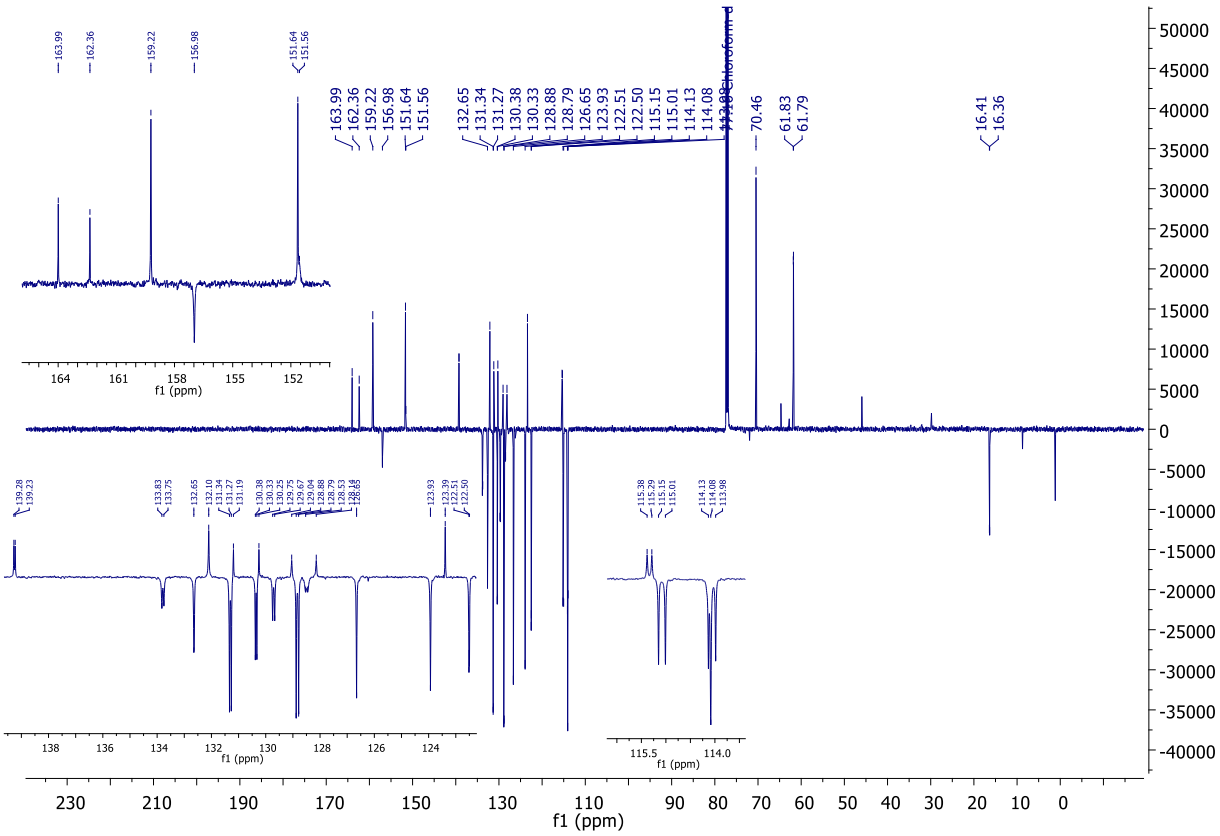
^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$) spectrum of **88**.



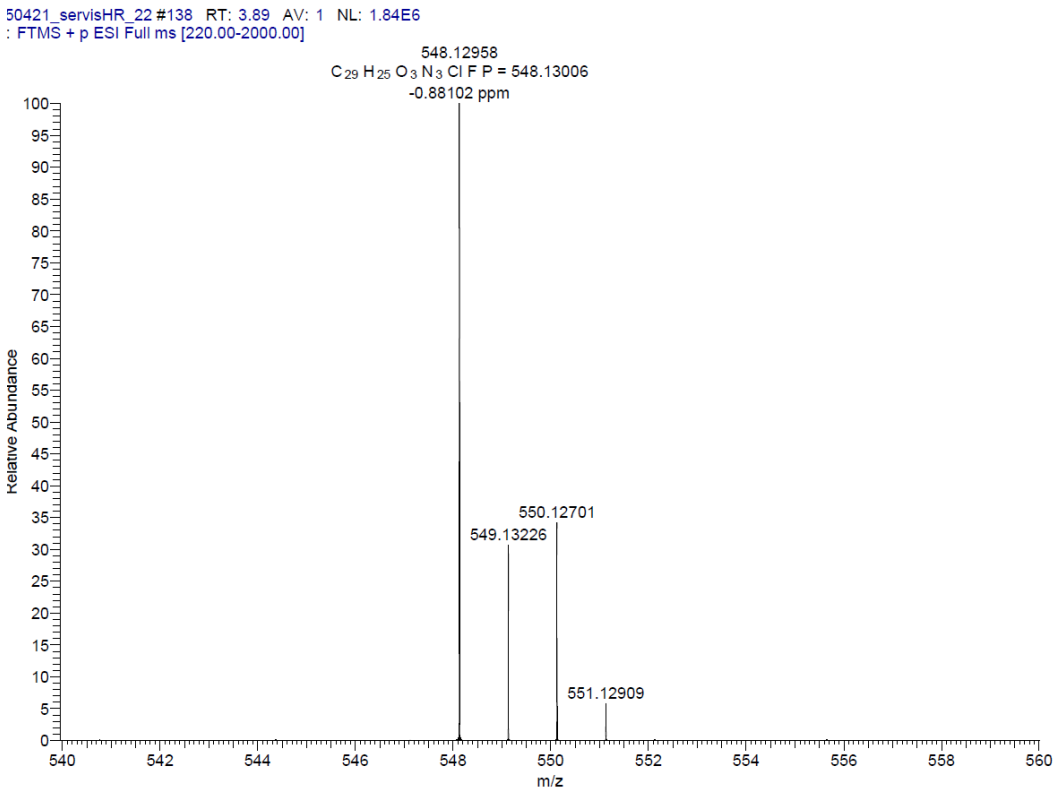
^{19}F NMR (376 MHz, $CDCl_3$) spectrum of **88**.



^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) spectrum of **88**.

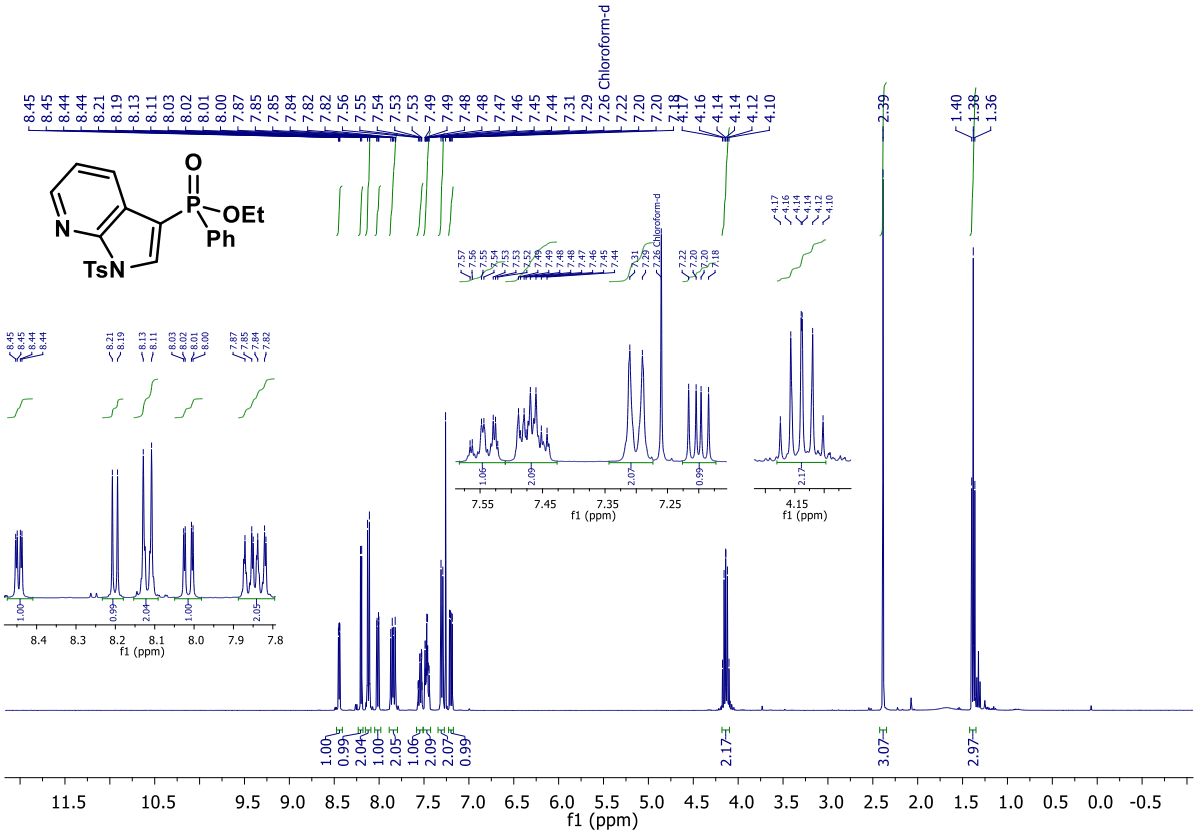


$^{13}C\{^{1}H\}$ APT NMR (151 MHz, $CDCl_3$) spectrum of **88**.

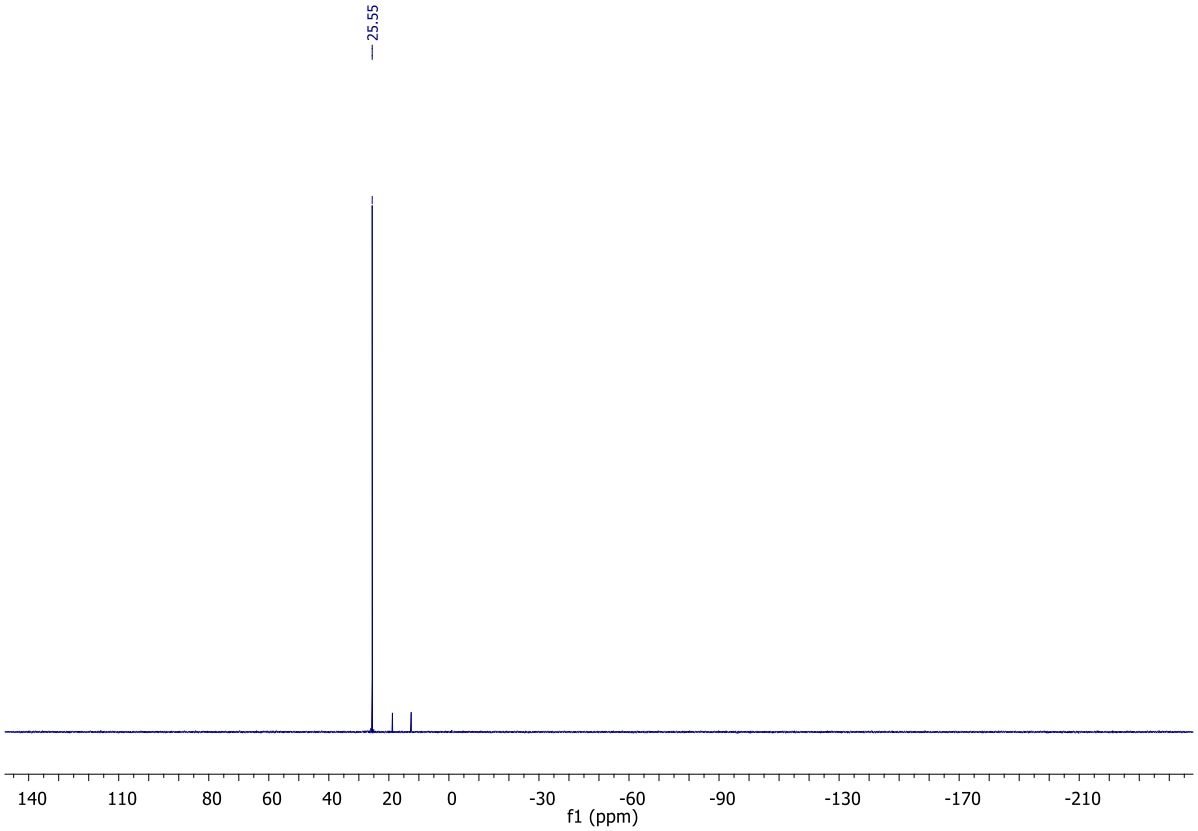


HRMS (ESI-TOF) spectrum of compound **88**.

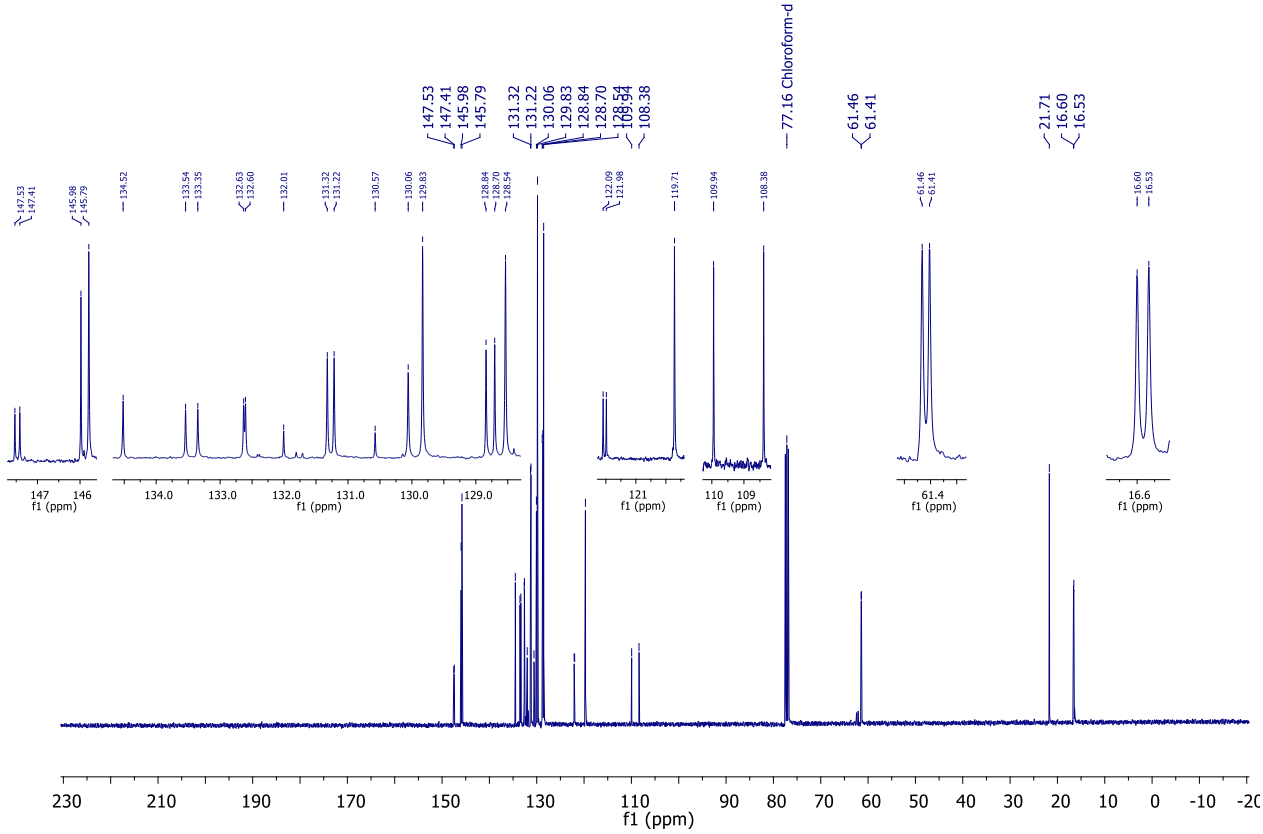
Compound 89



^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **89**.

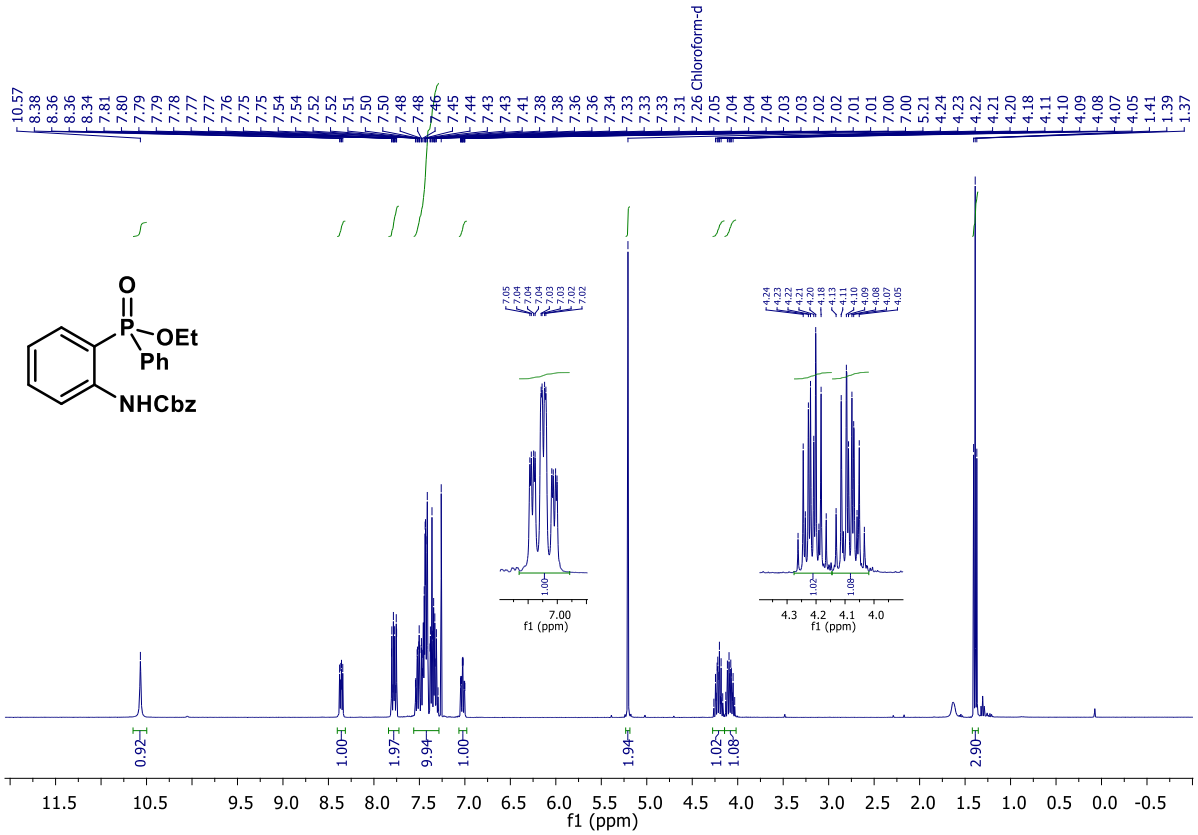


^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$) spectrum of **89**.

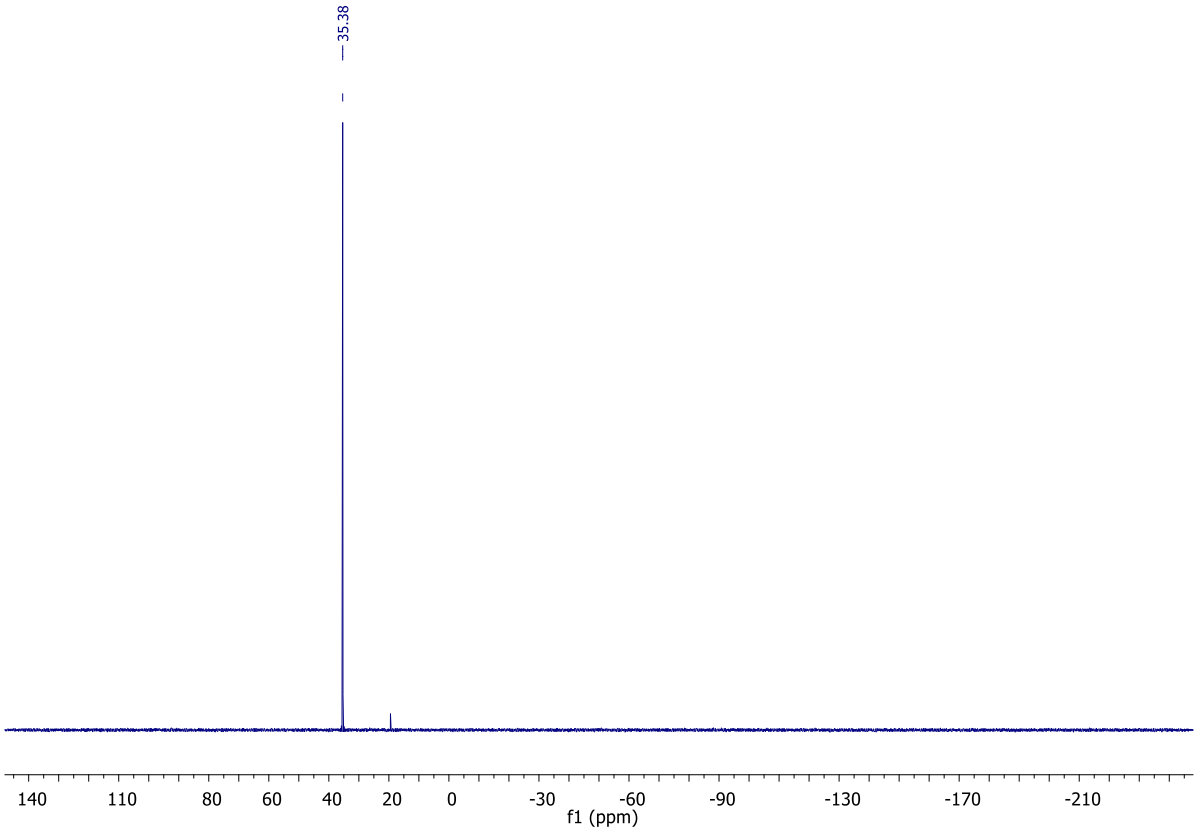


$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) spectrum of **89**.

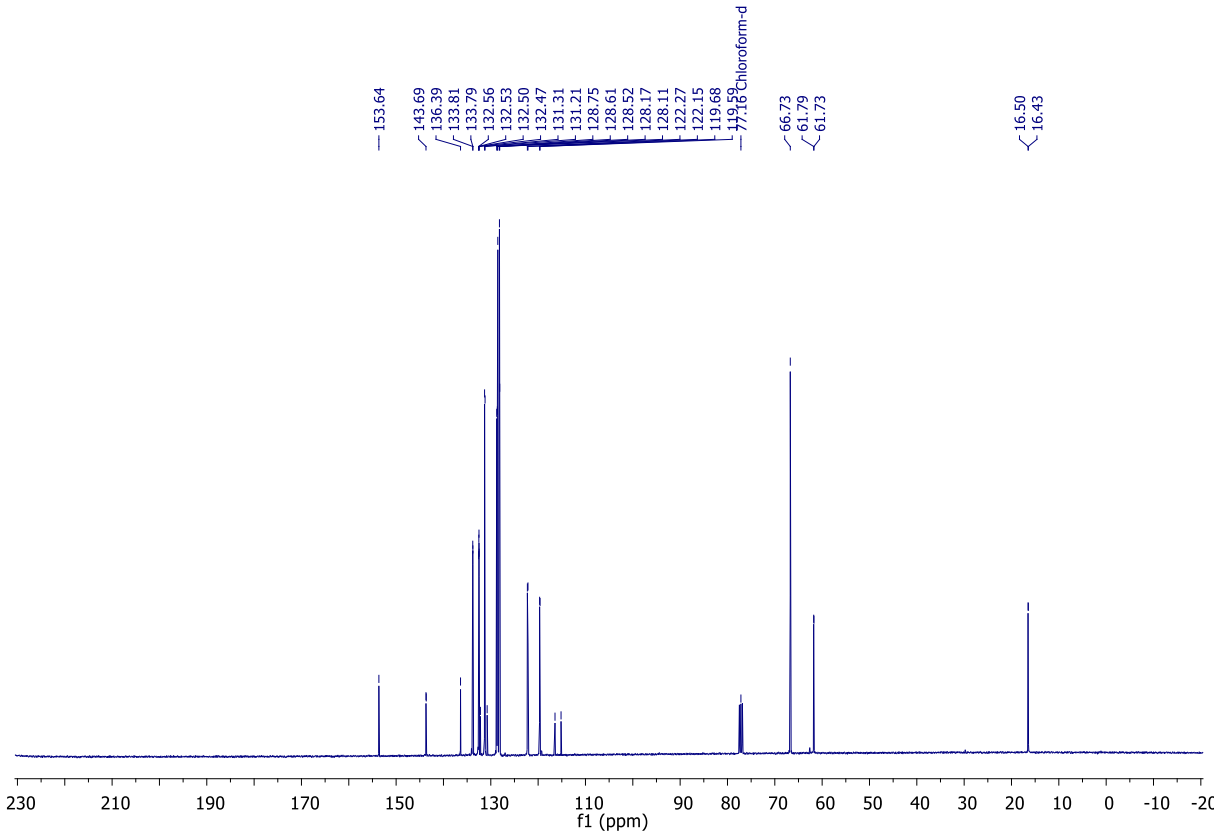
Compound 90



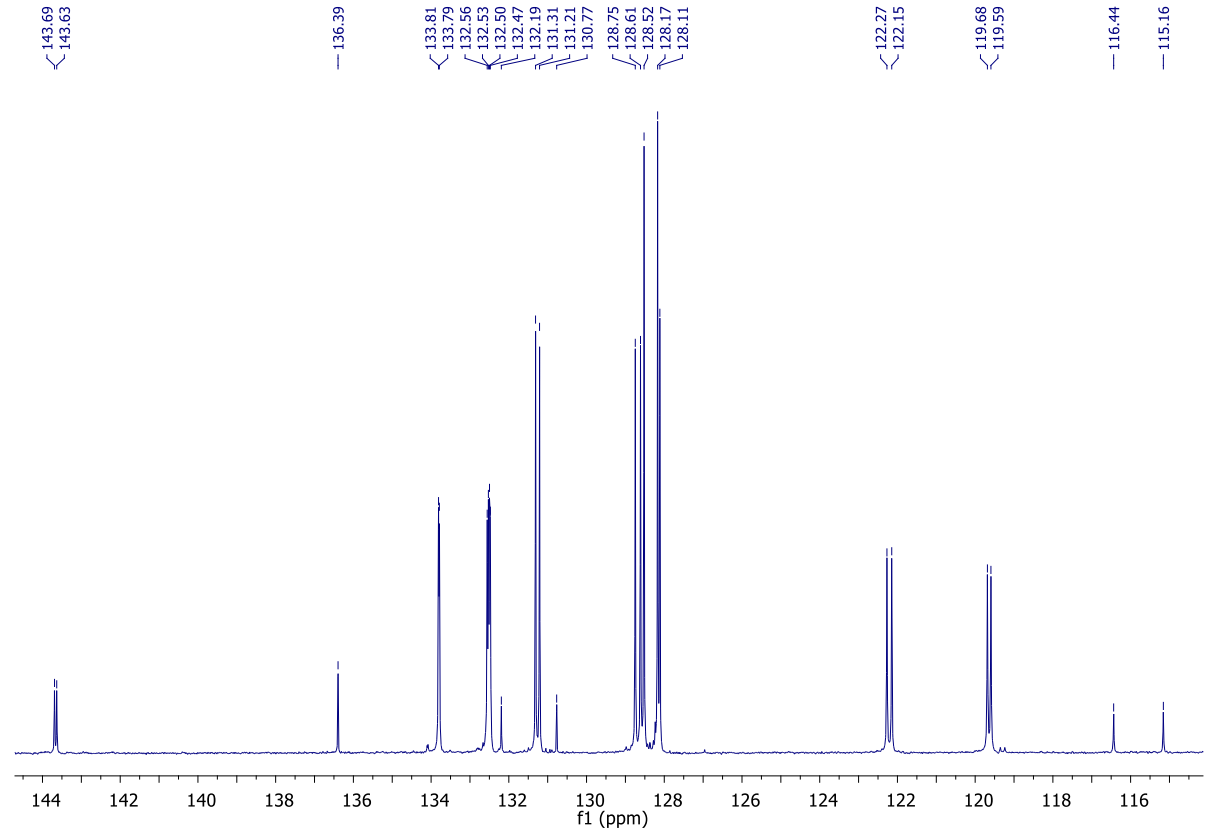
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **90**.



^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$) spectrum of **90**.

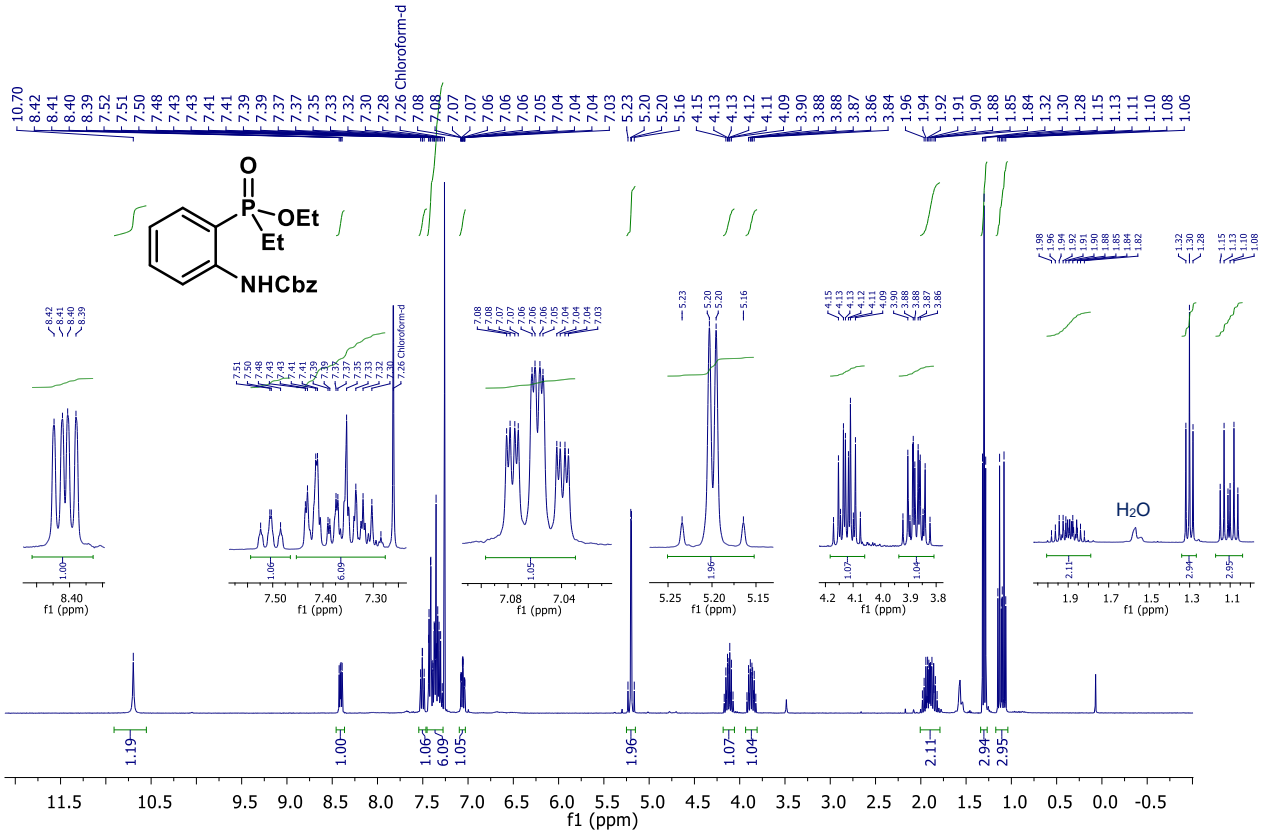


$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) spectrum of **90**.

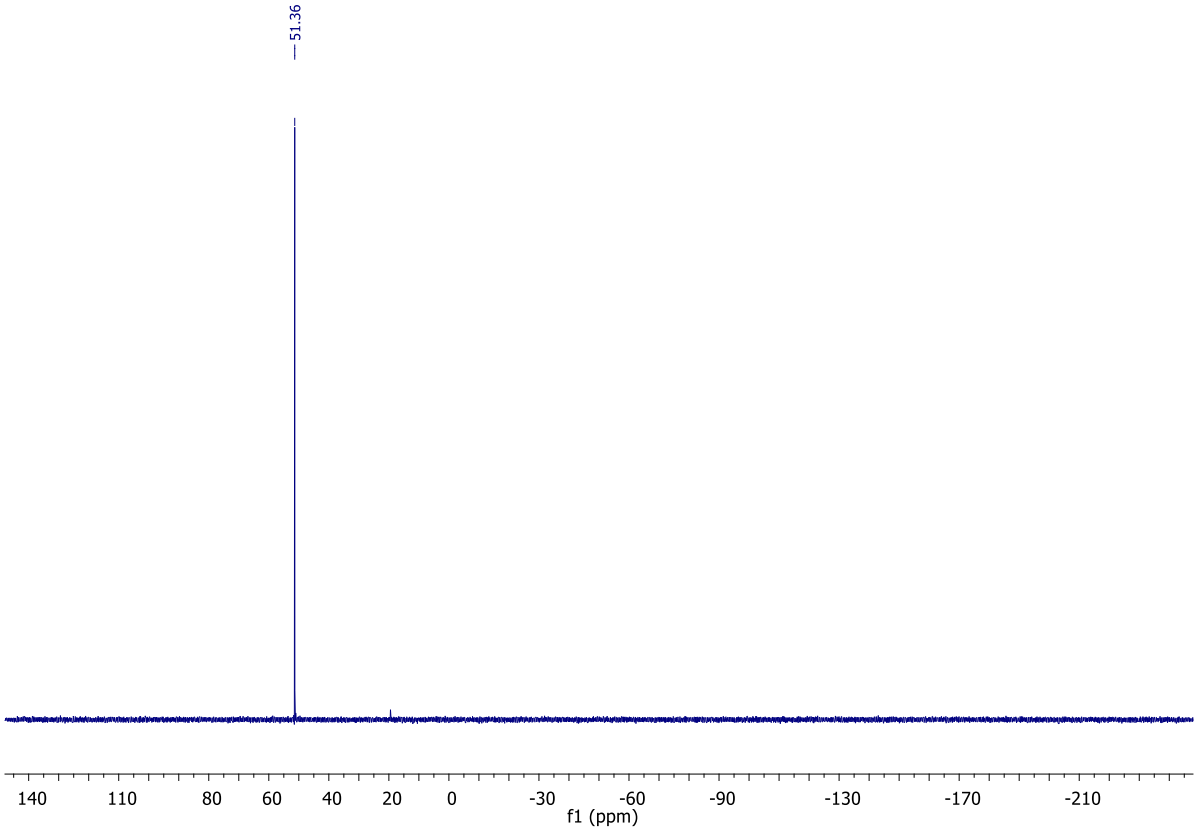


$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) spectrum of **90** in more detail.

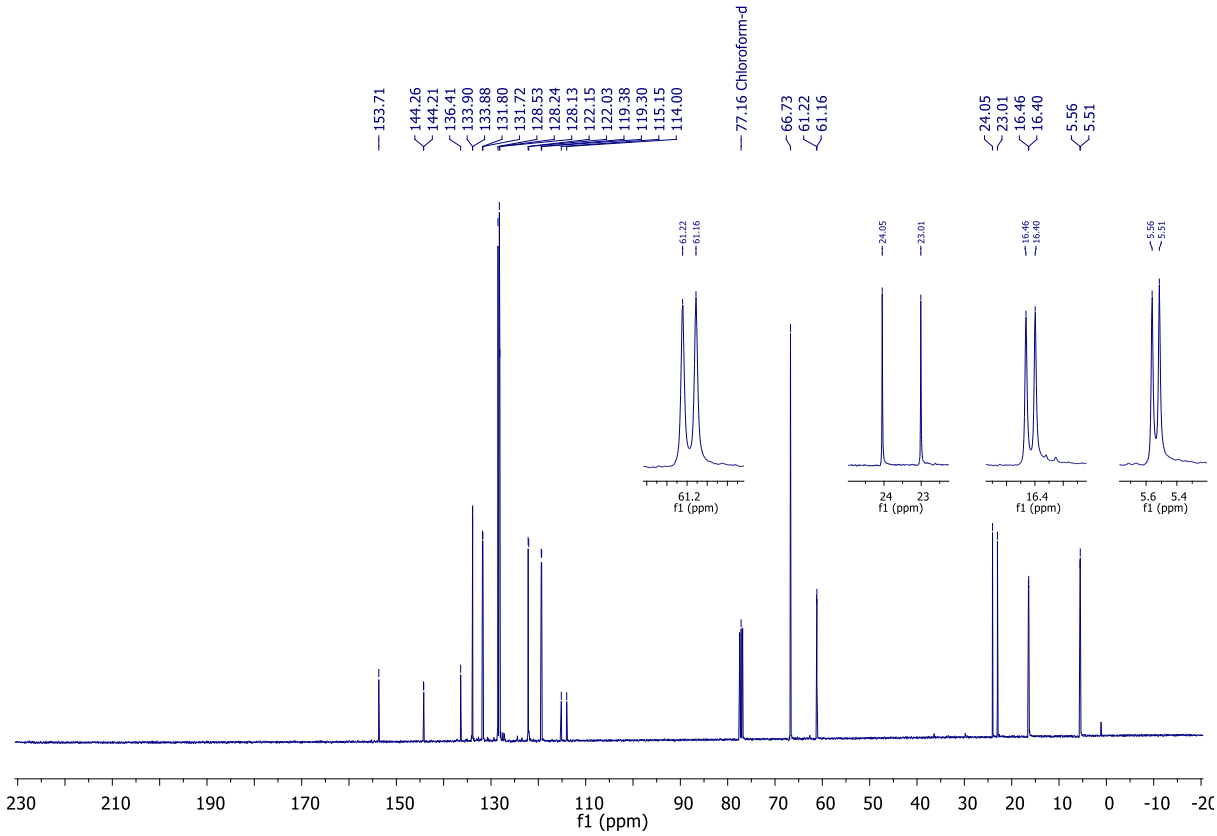
Compound 91



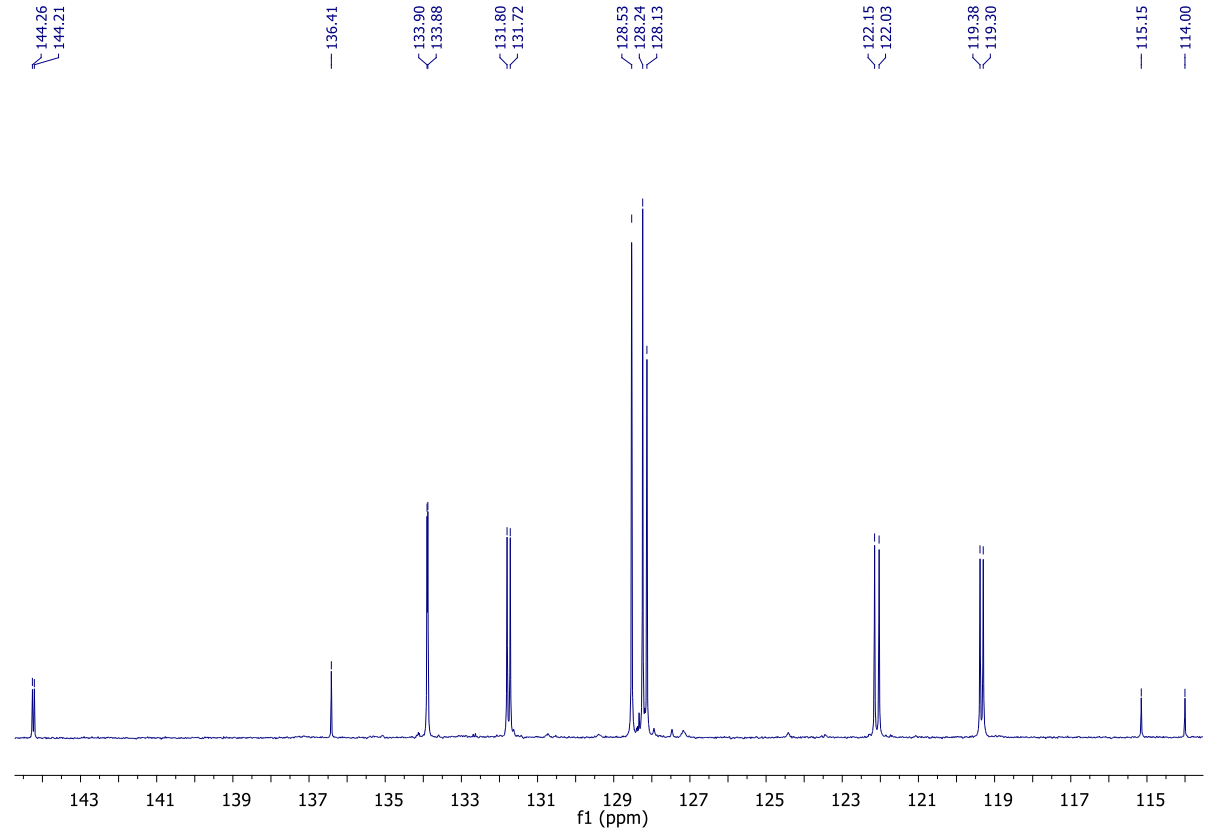
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **91**.



^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$) spectrum of **91**.

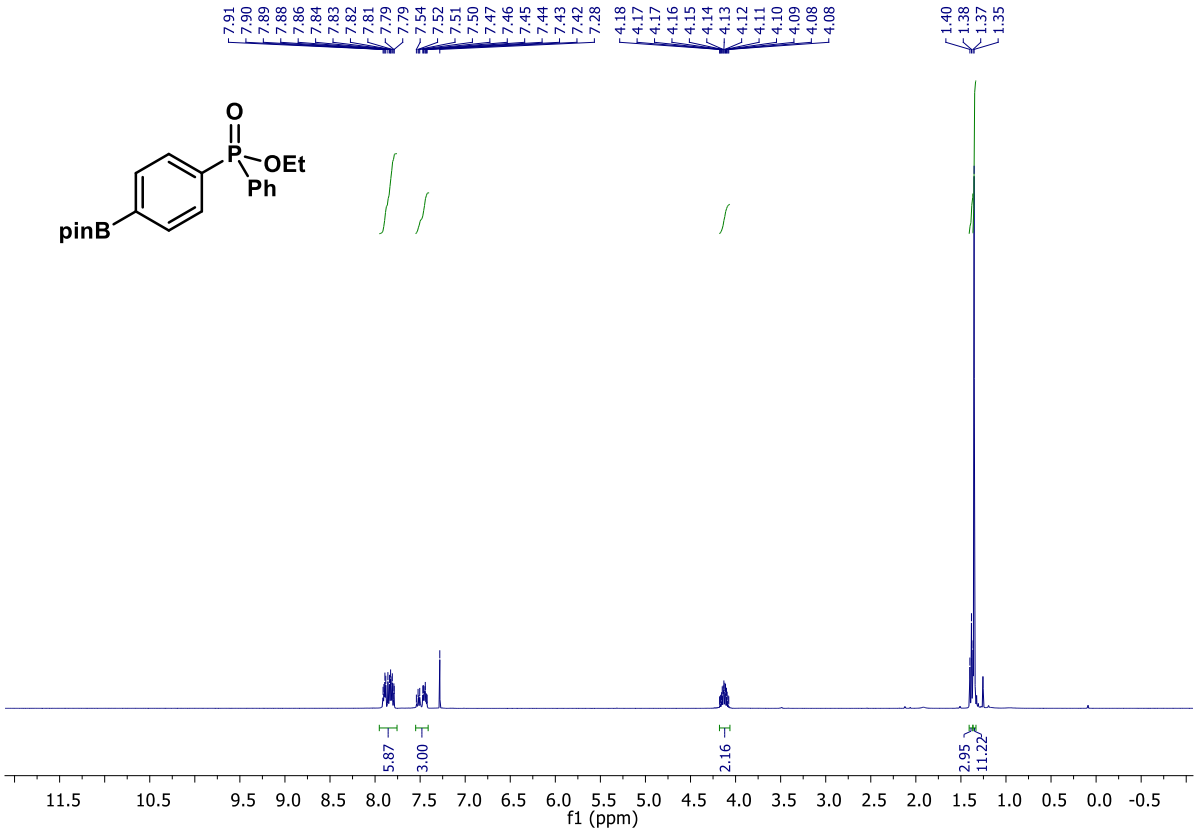


$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) spectrum of **91**.

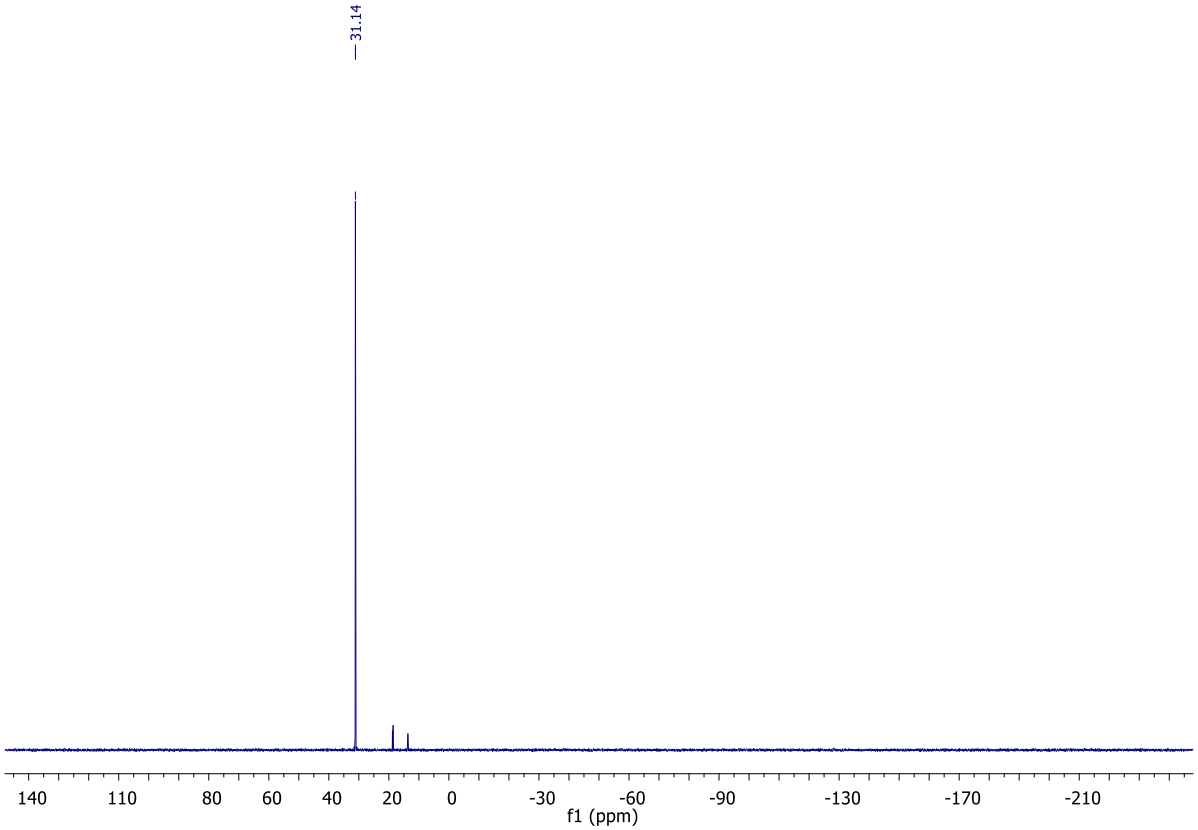


$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) spectrum of **91 i**n more detail.

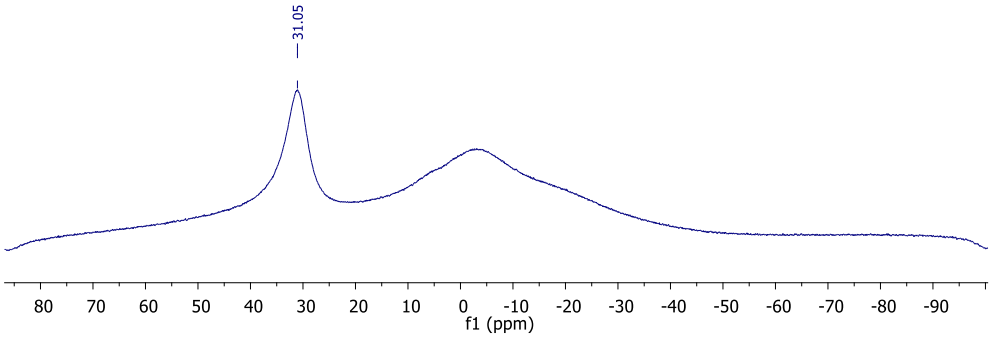
Compound 92



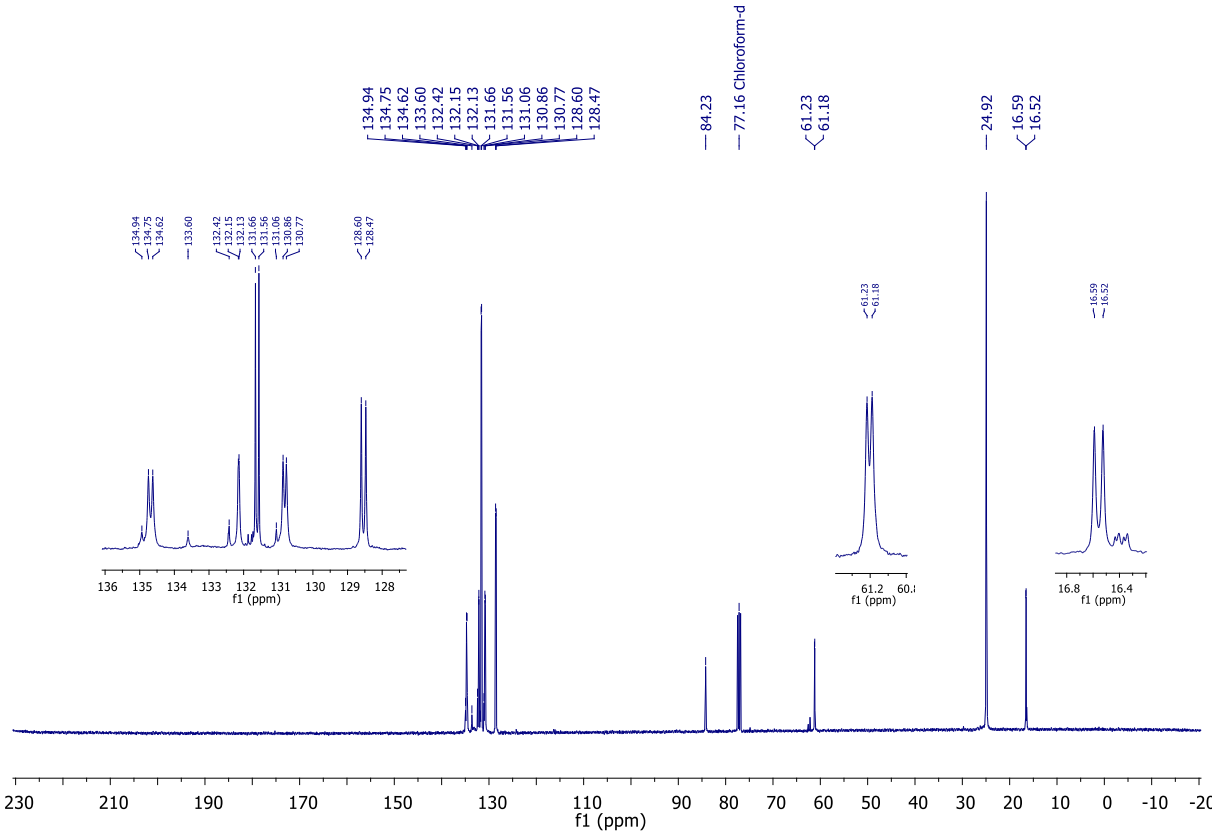
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **92**.



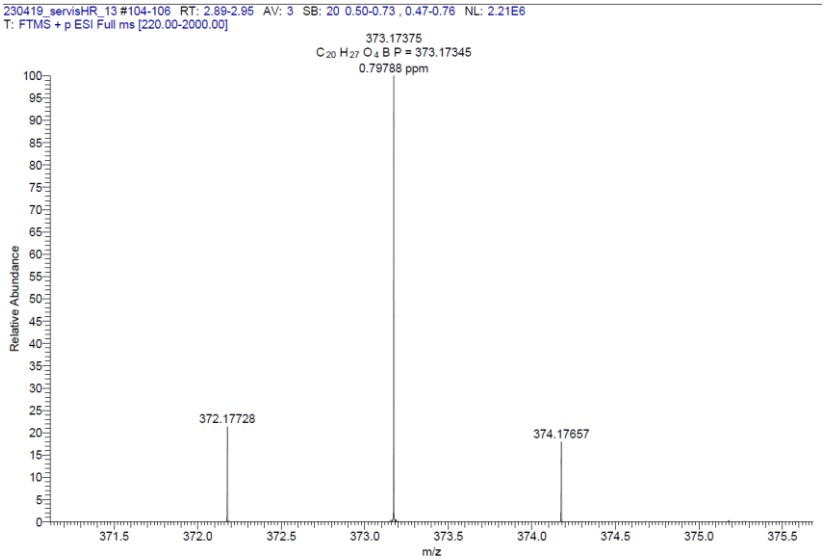
^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$) spectrum of **92**.



^{11}B NMR (128 MHz, $CDCl_3$) spectrum of **92**.

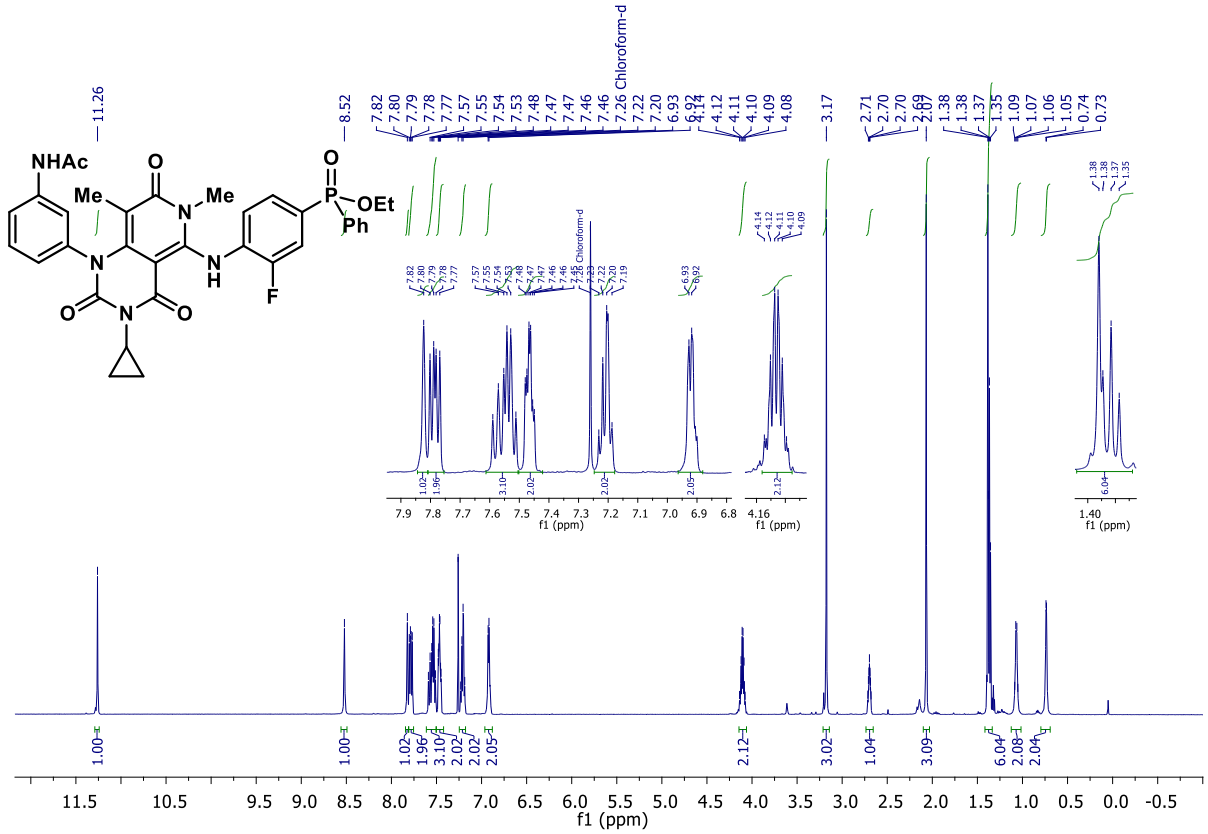


^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) spectrum of **92**.

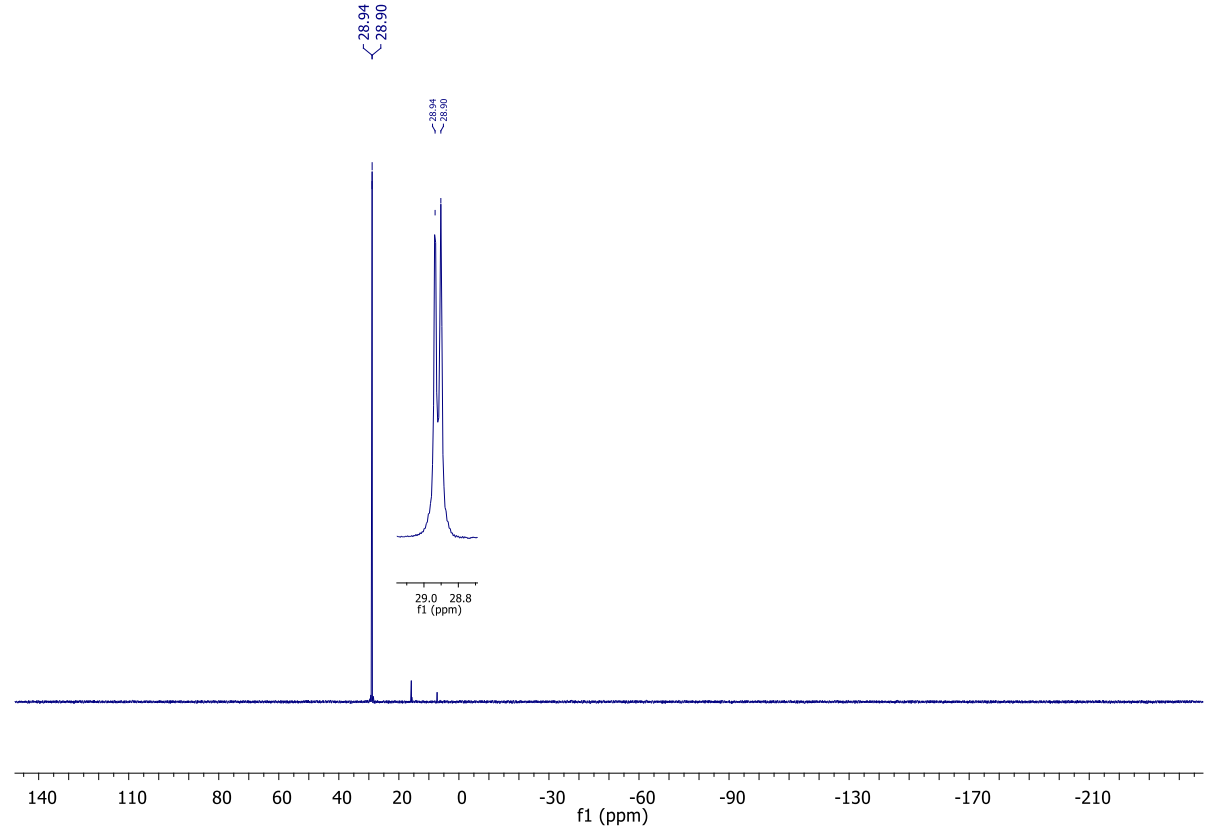


HRMS (ESI-TOF) spectrum of compound **92**.

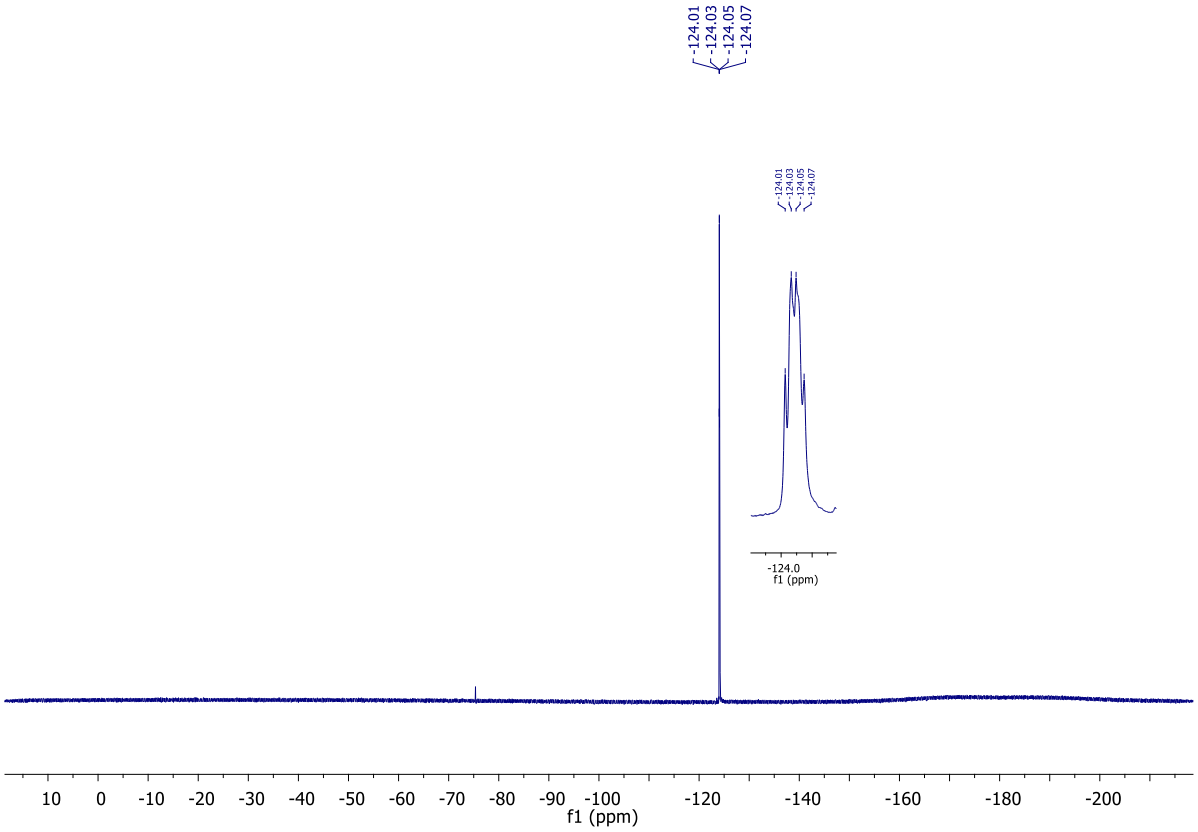
Compound 93



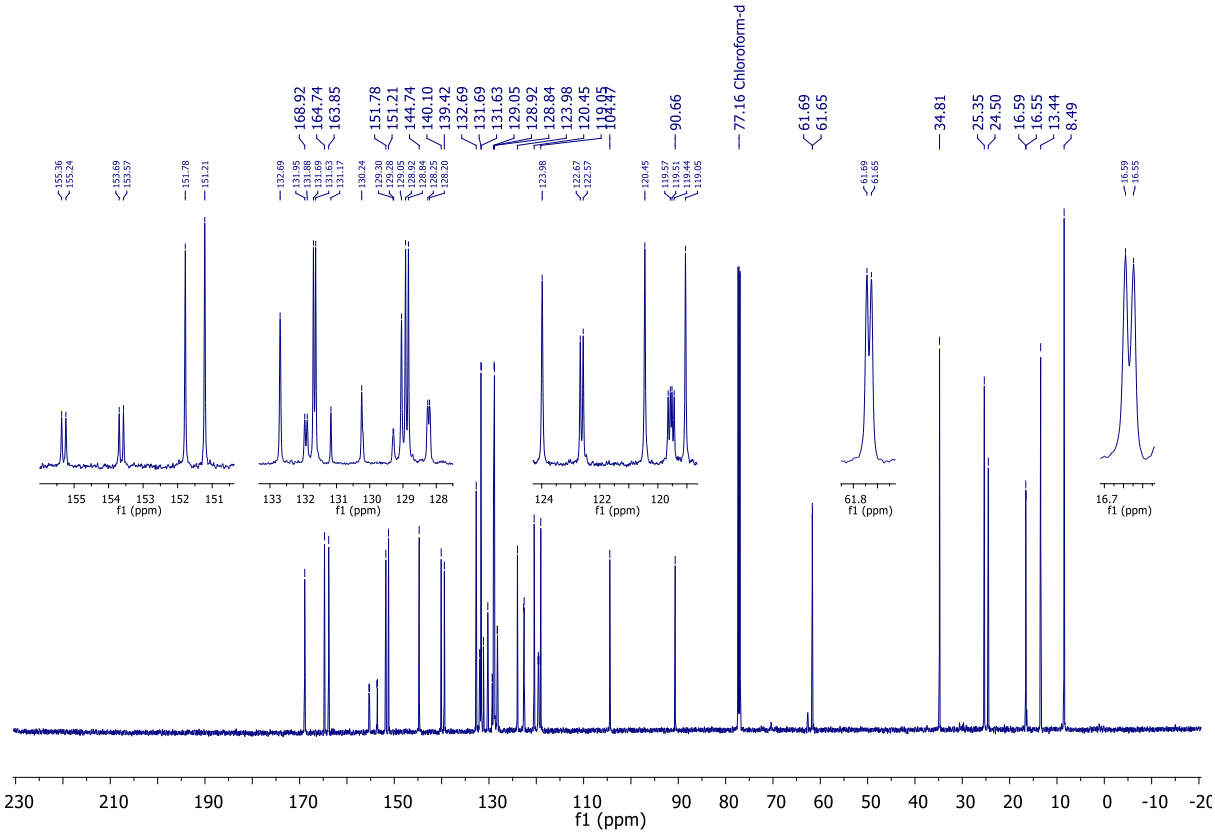
^{1}H NMR (600 MHz, $CDCl_3$) spectrum of **93**.



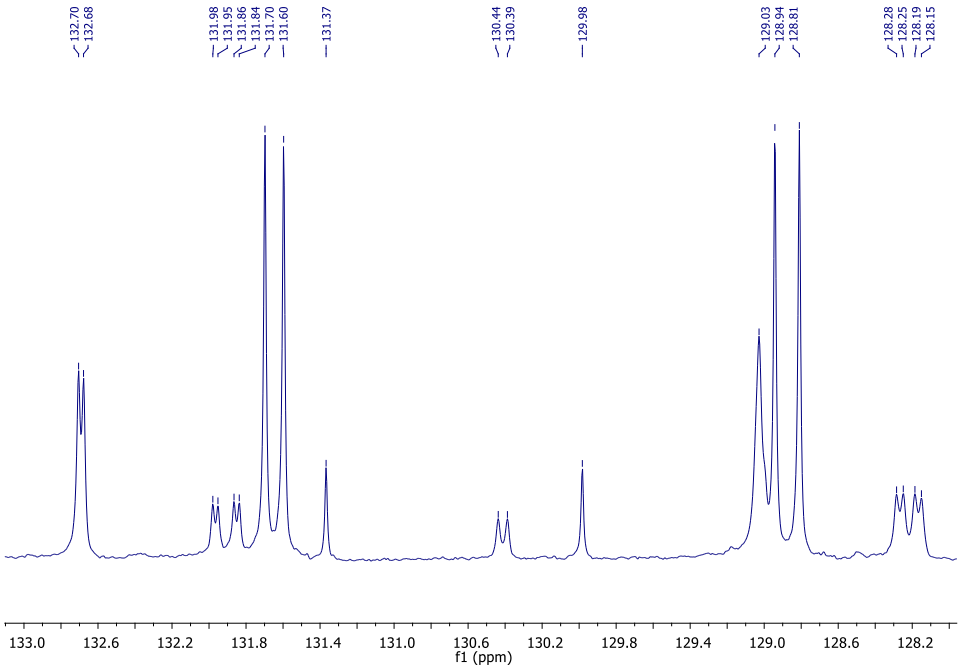
^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$) spectrum of **93**.



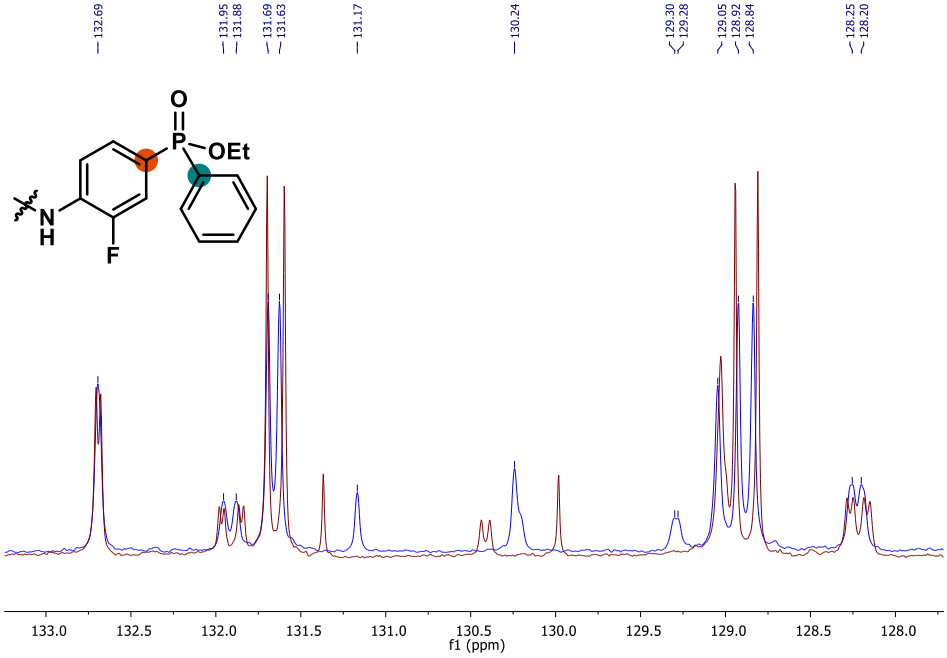
^{19}F NMR (376 MHz, $CDCl_3$) spectrum of **93**.



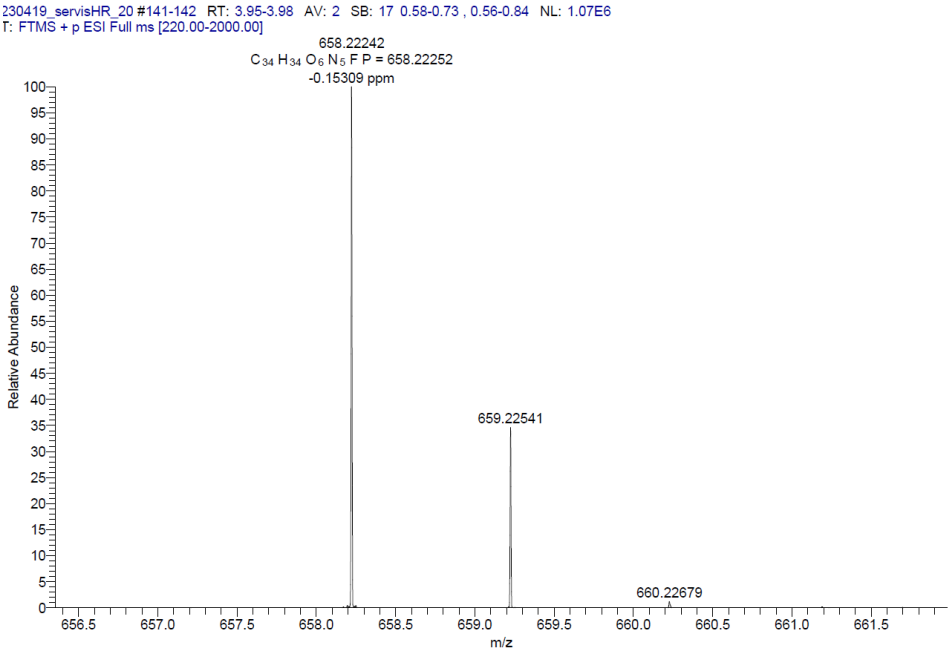
^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) spectrum of **93**.



Detail of the **$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$)** spectrum of **93**.

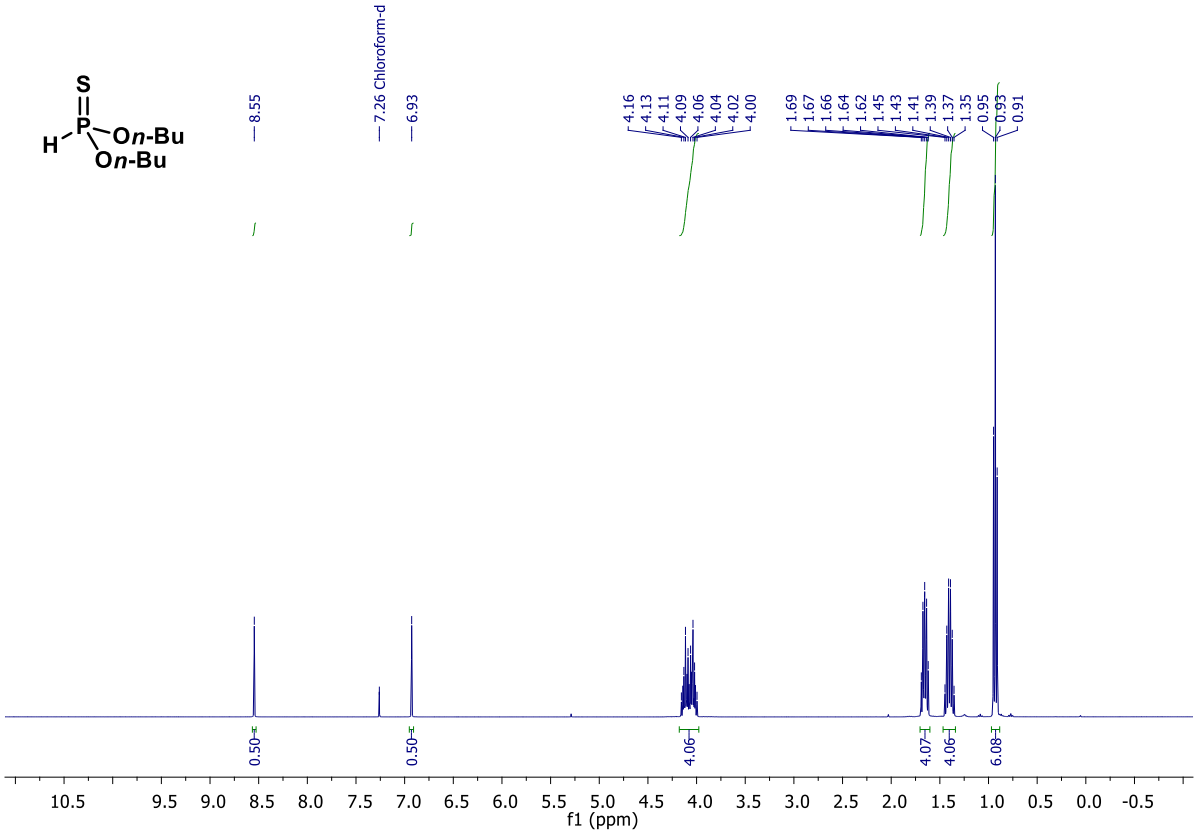


Comparison of $^{13}C\{^{1}H\}$ NMR spectra of **93** (151 MHz in blue trace, 100 MHz in red trace) which were used to assign the two C(sp^2)–P signals based on their *J* values. $^{13}C\{^{1}H\}$ 151 MHz: δ 130.7 (d, *J* = 139.7 Hz, carbon in green), 129.8 (dd, *J* = 142.4, 2.9 Hz, carbon in orange) ppm; $^{13}C\{^{1}H\}$ 100 MHz: δ 130.7 (d, *J* = 138.4 Hz, carbon in green), 129.7 (dd, *J* = 140.9, 4.9 Hz, carbon in orange) ppm.

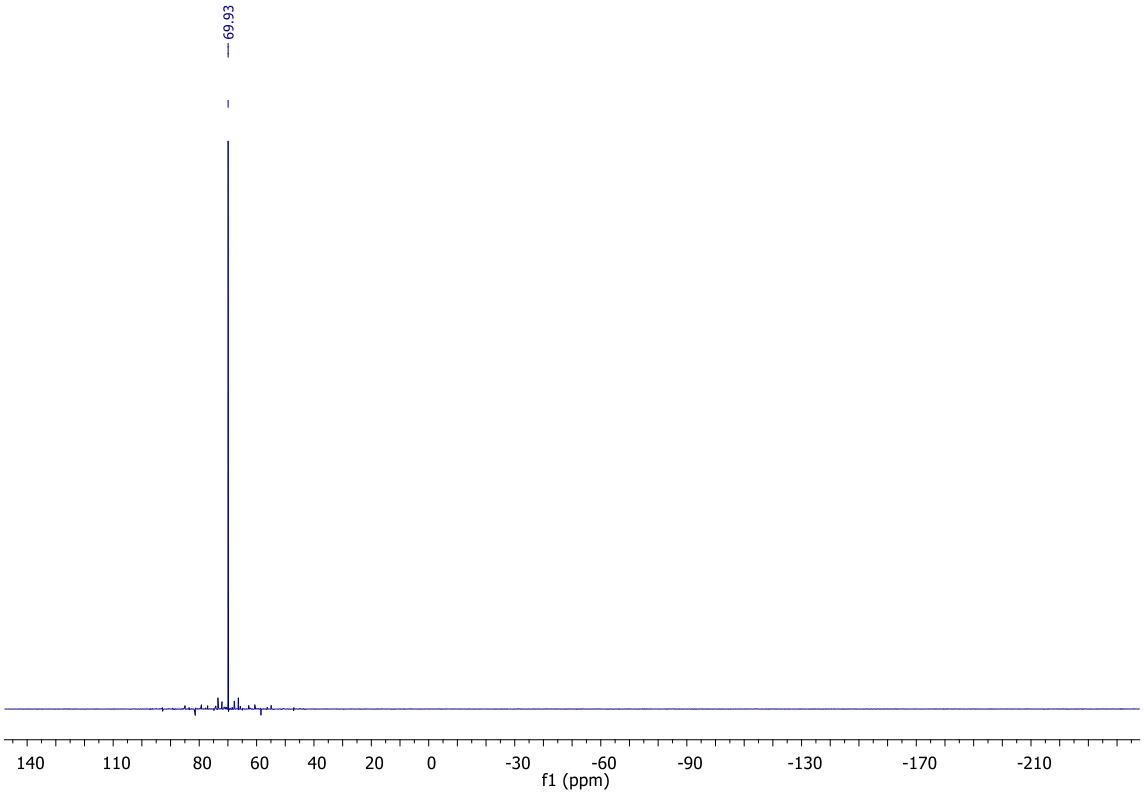


HRMS (ESI-TOF) spectrum of compound **93**.

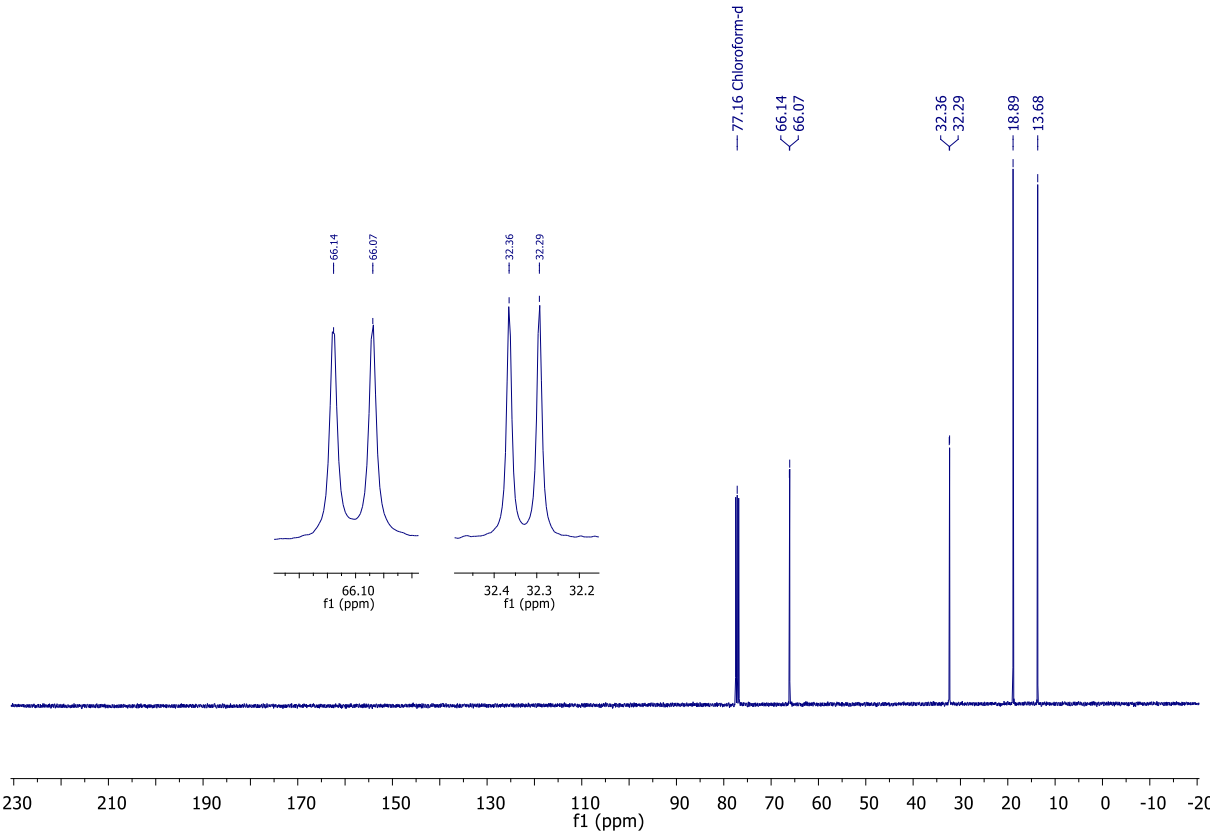
Compound 94



^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **94**.

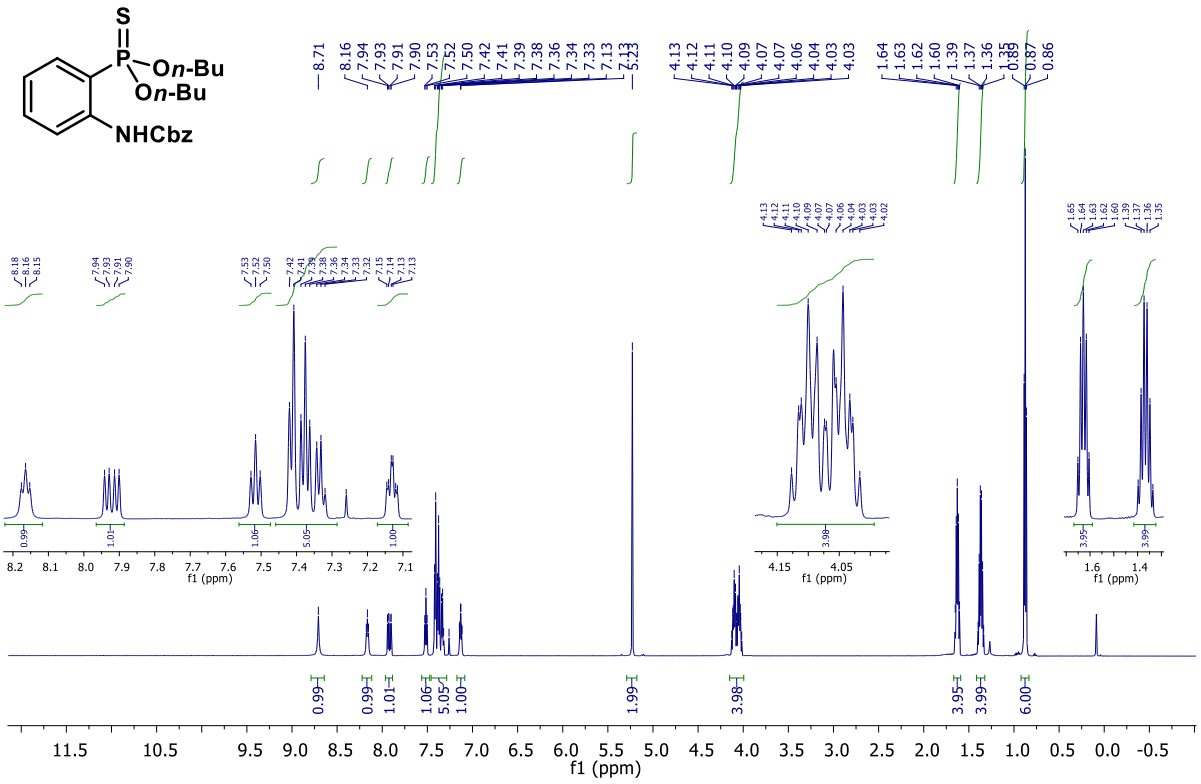


^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$) spectrum of **94**.

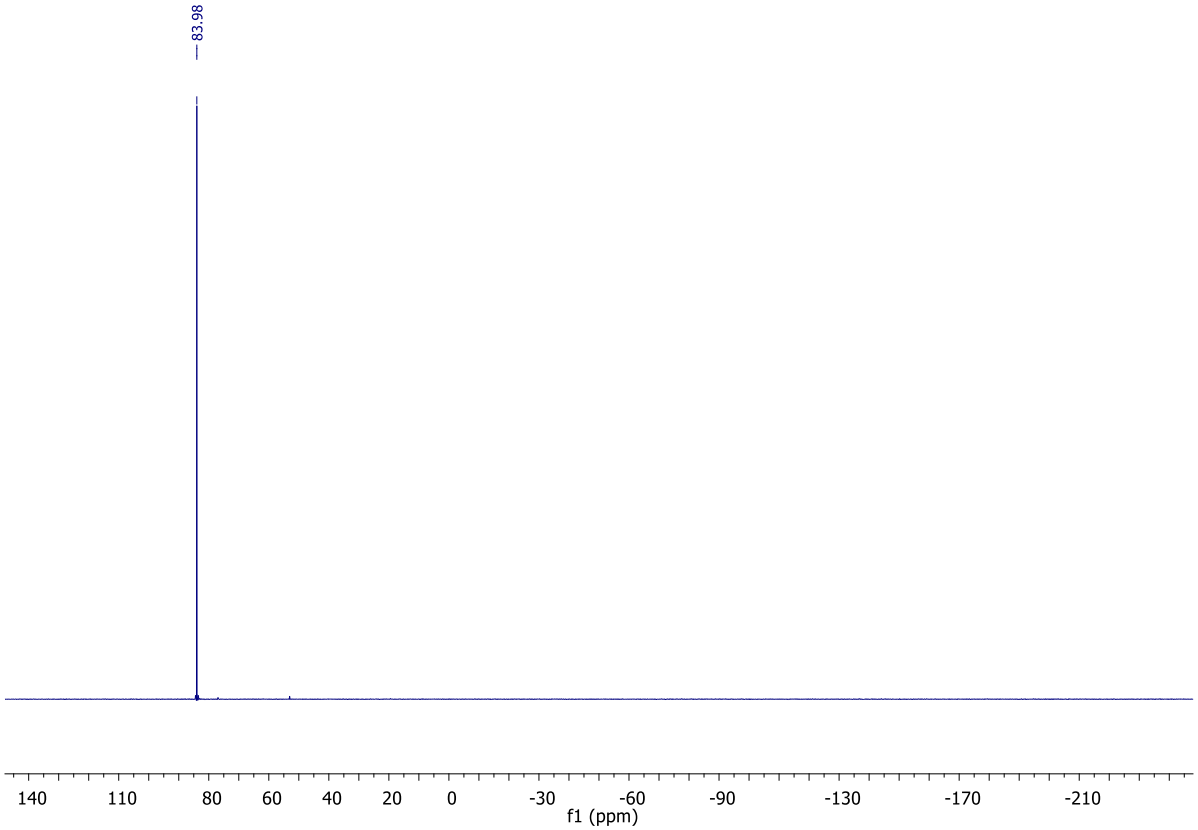


$^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$) spectrum of **94**.

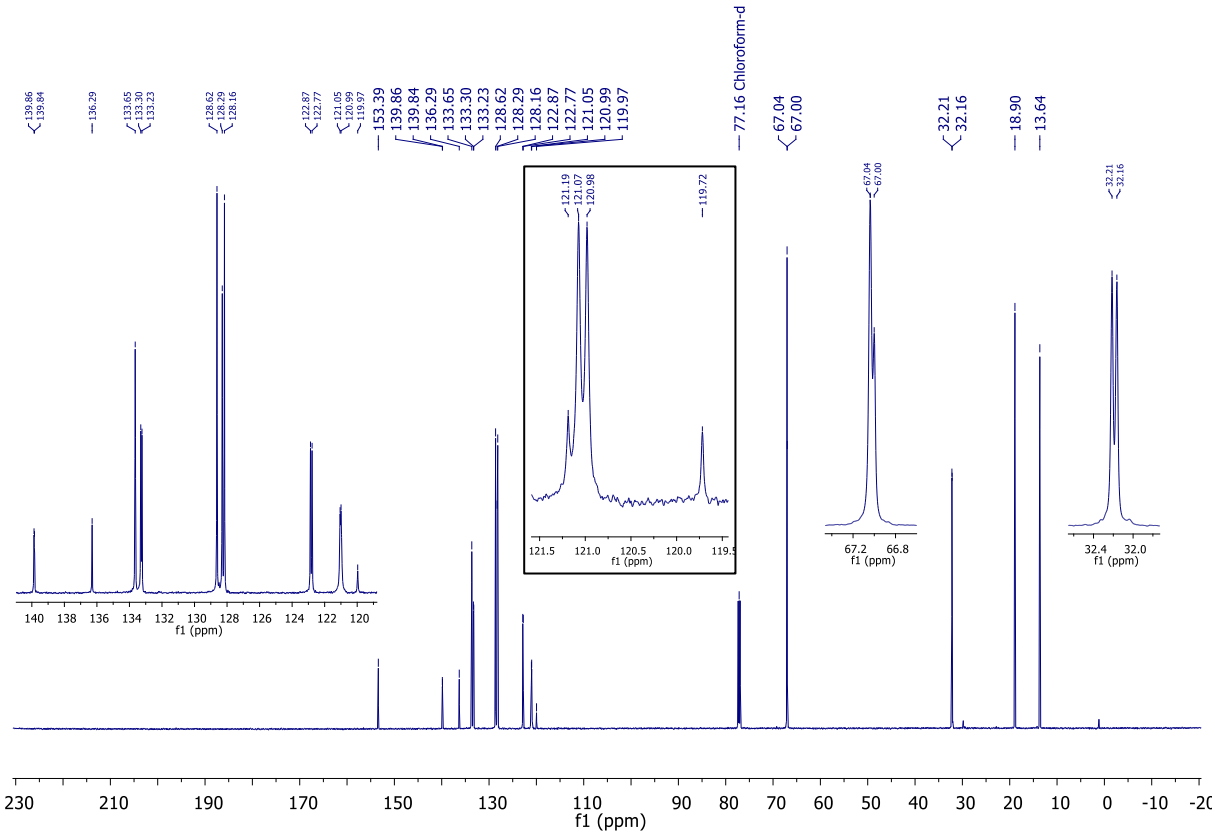
Compound 95



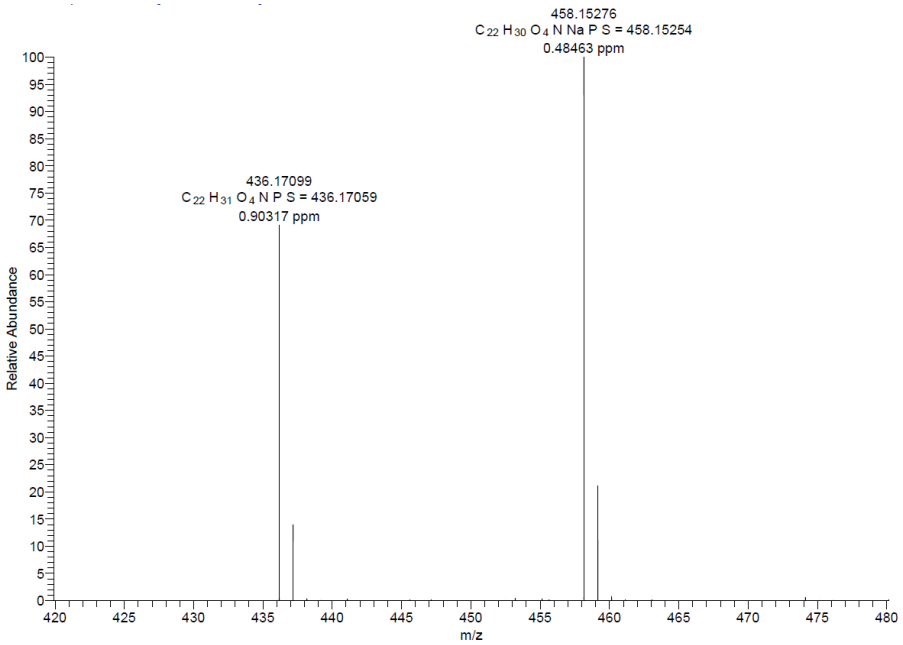
^{1}H NMR (600 MHz, $CDCl_3$) spectrum of **95**.



^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$) spectrum of **95**.

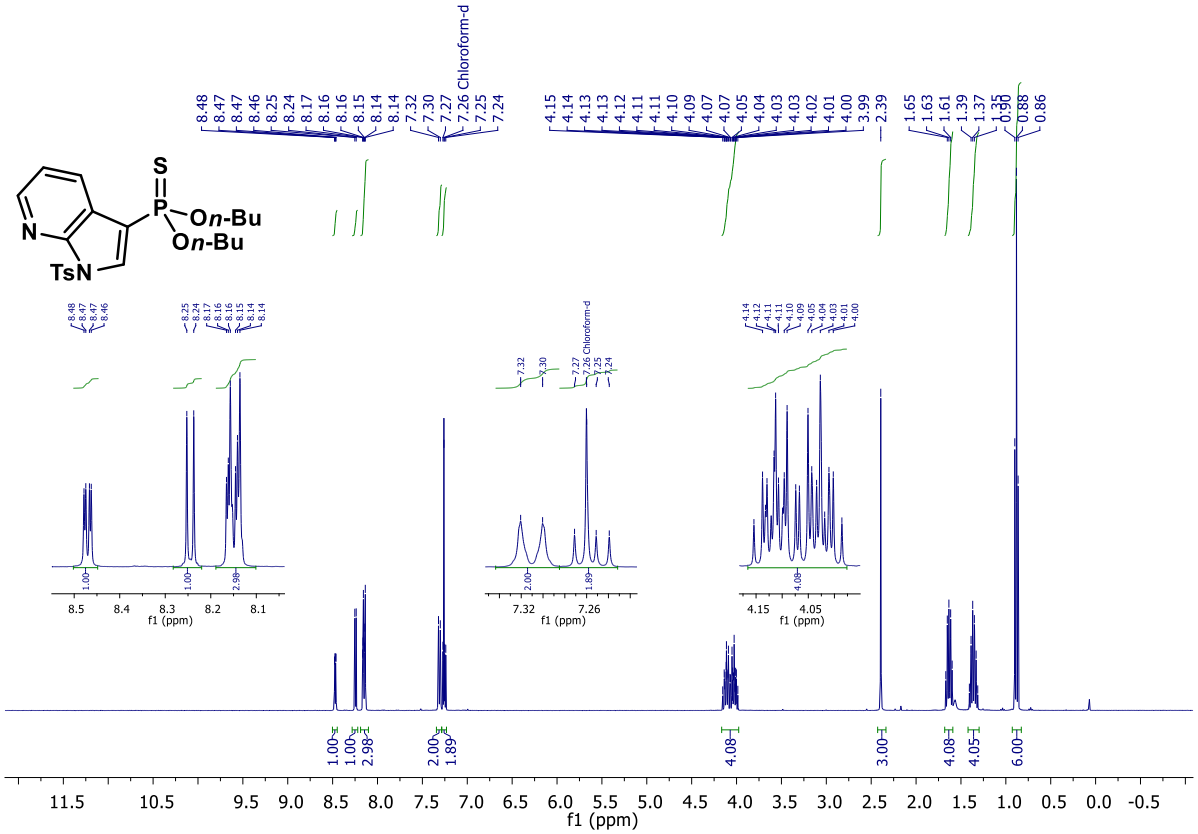


$^{13}C\{^{1}H\}$ NMR (151 MHz, $CDCl_3$) spectrum of **95**. $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$, shown in the black box) was used to assign the C–P signal (δ 120.5 ppm, d, J = 146.9 Hz) which is partially overlapped in the 125 MHz $^{13}C\{^{1}H\}$ spectrum.

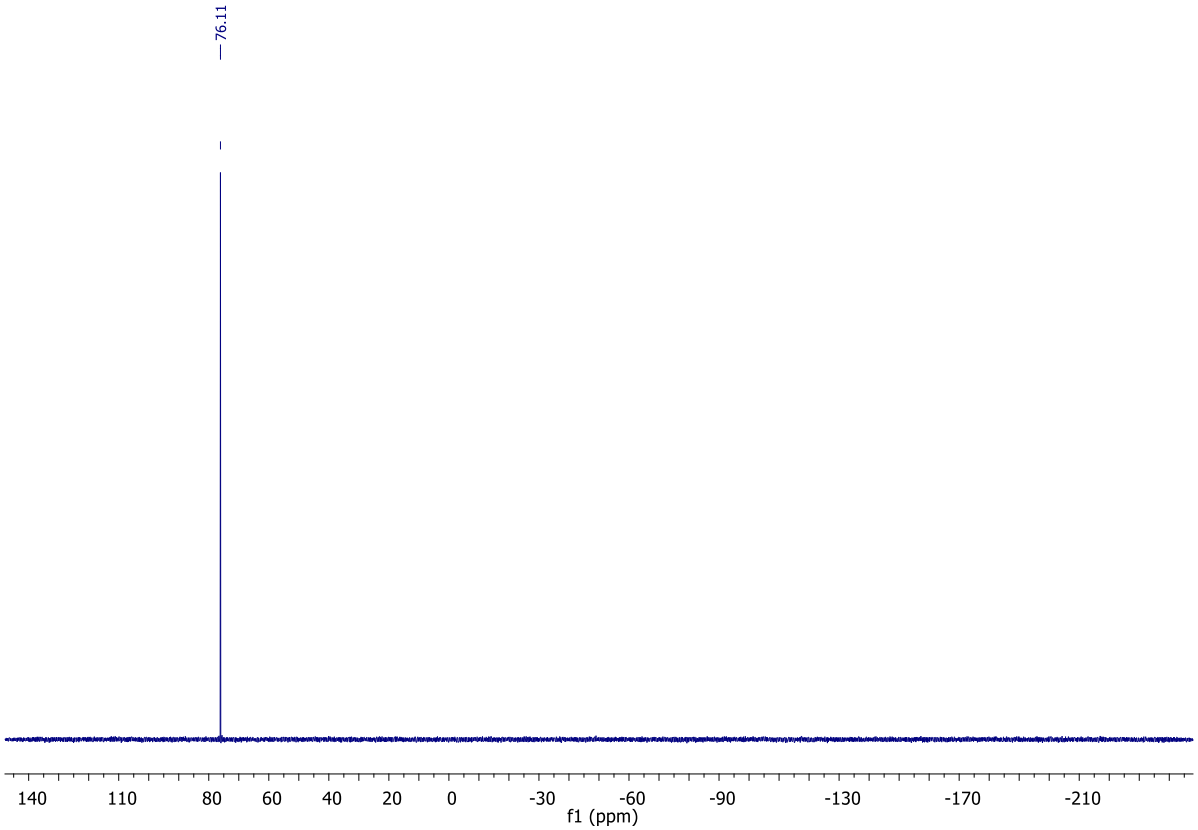


HRMS (ESI-TOF) spectrum of compound **95**.

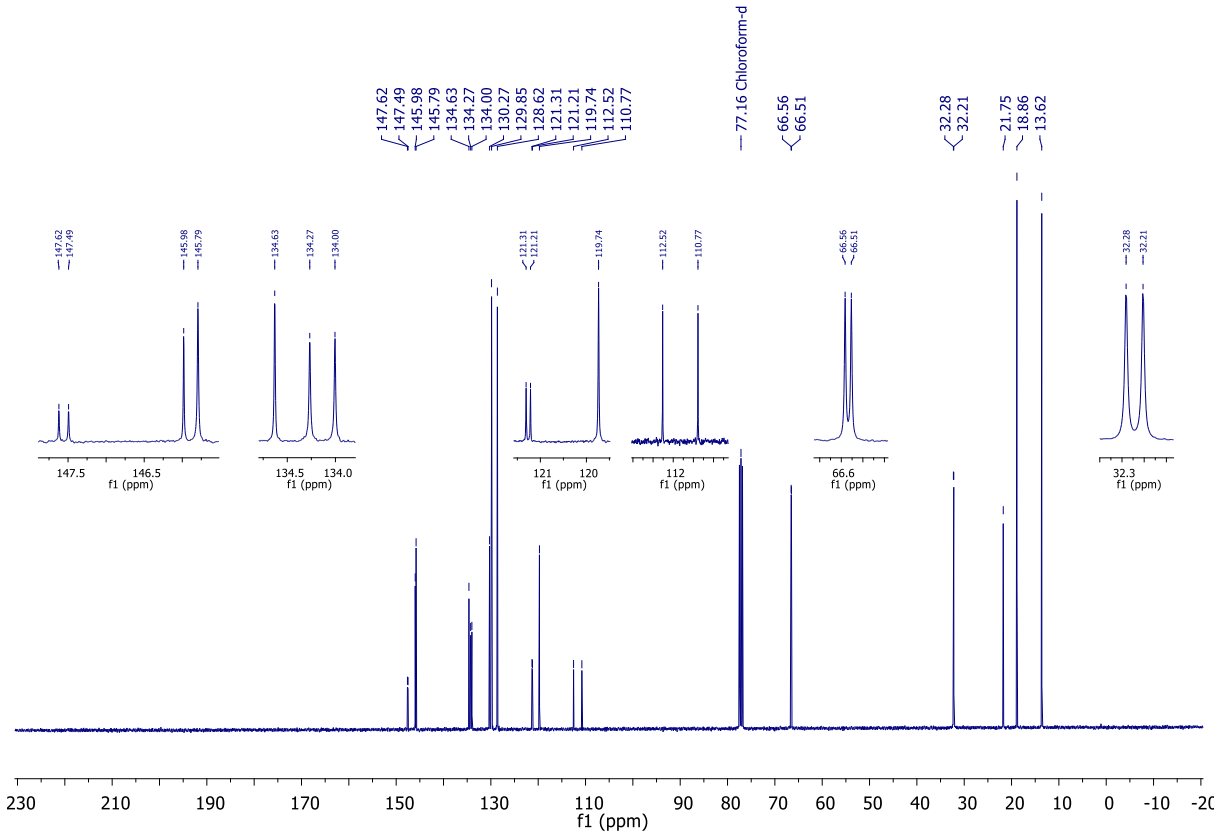
Compound 96



^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **96**.

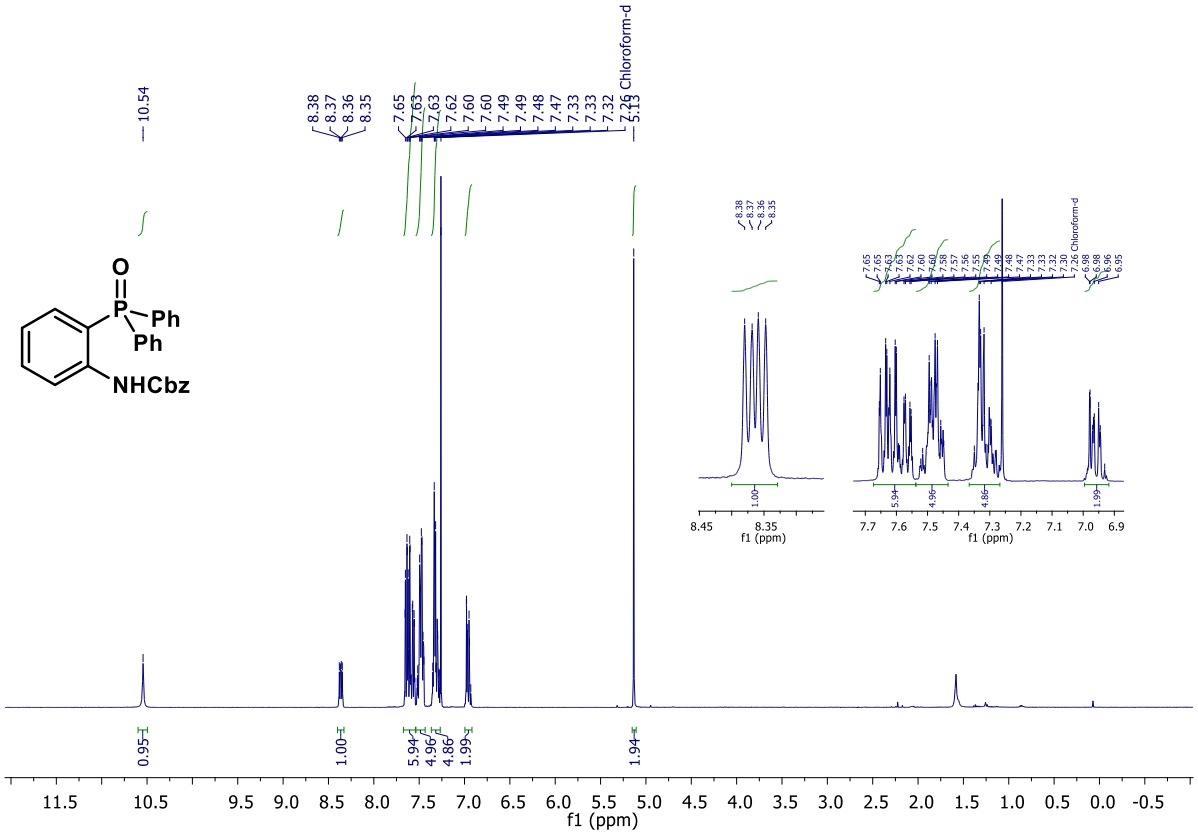


^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$) spectrum of **96**.

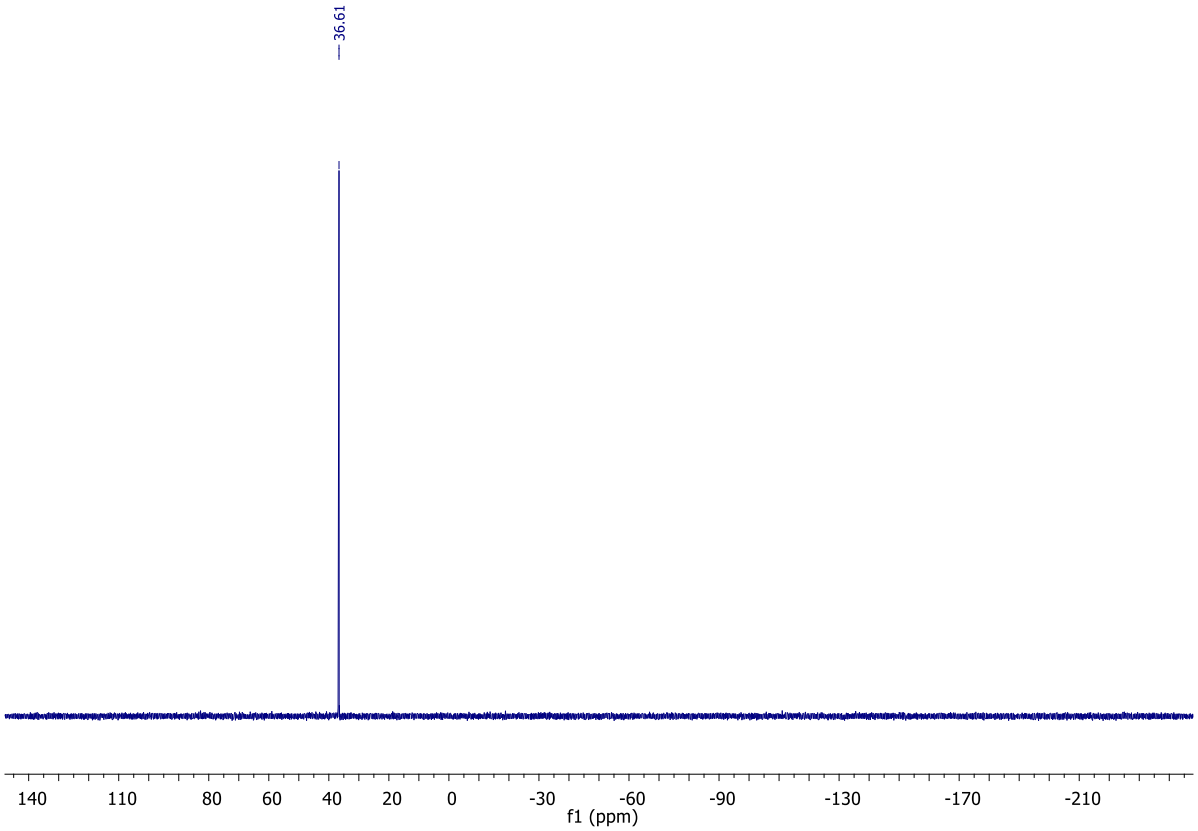


$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) spectrum of **96**.

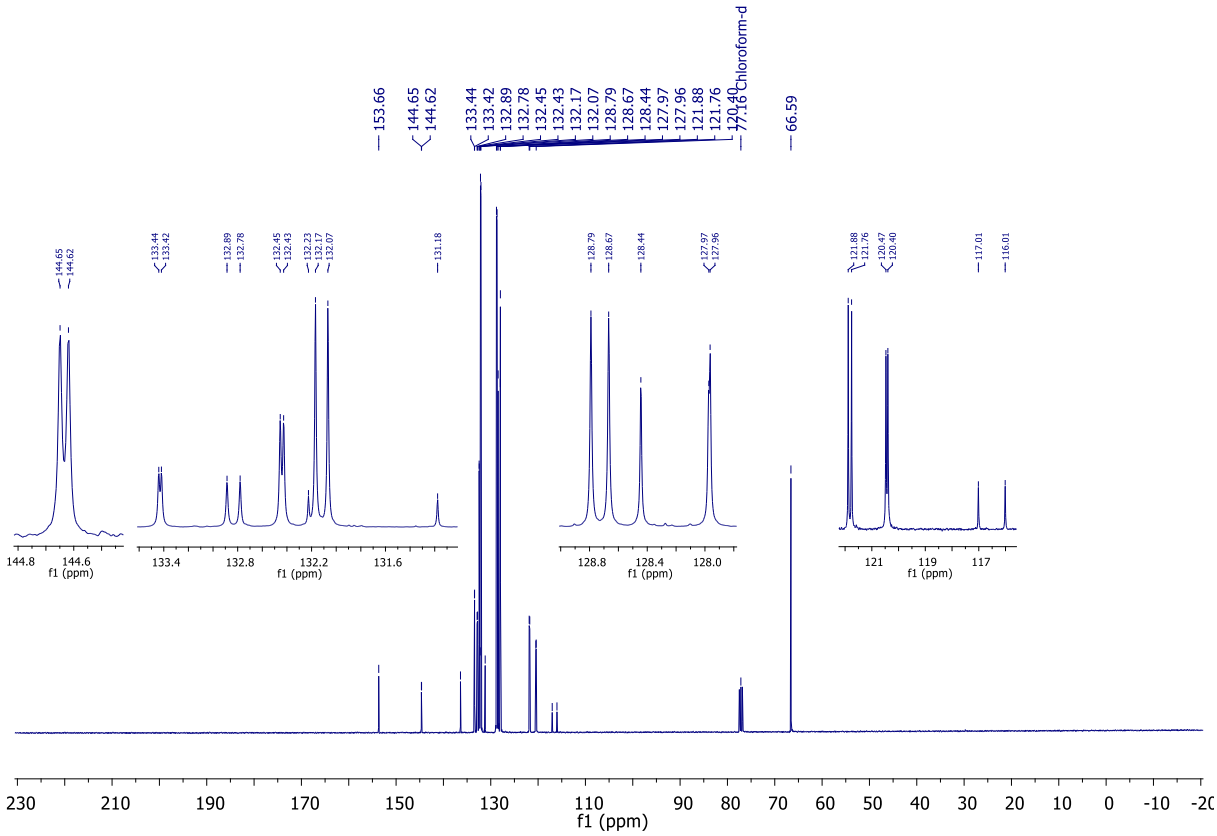
Compound 99



^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **99**.

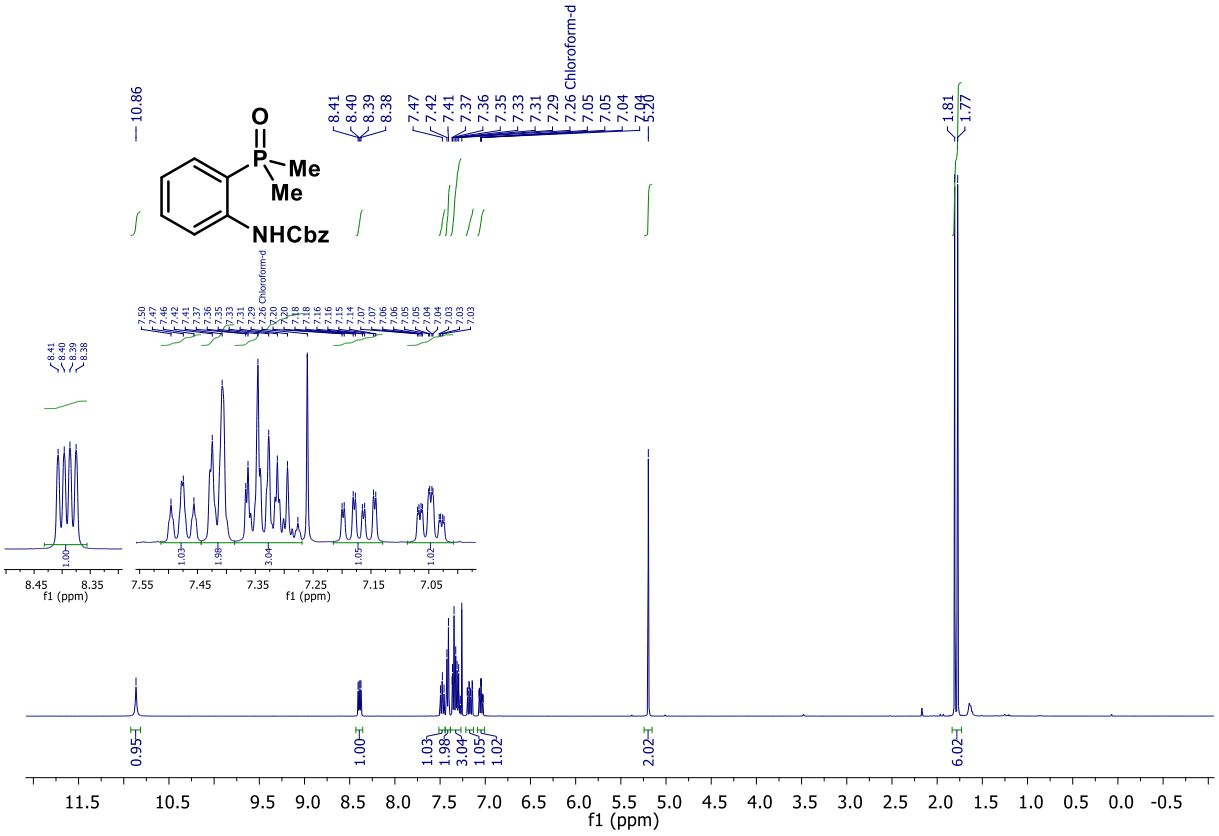


^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$) spectrum of **99**.

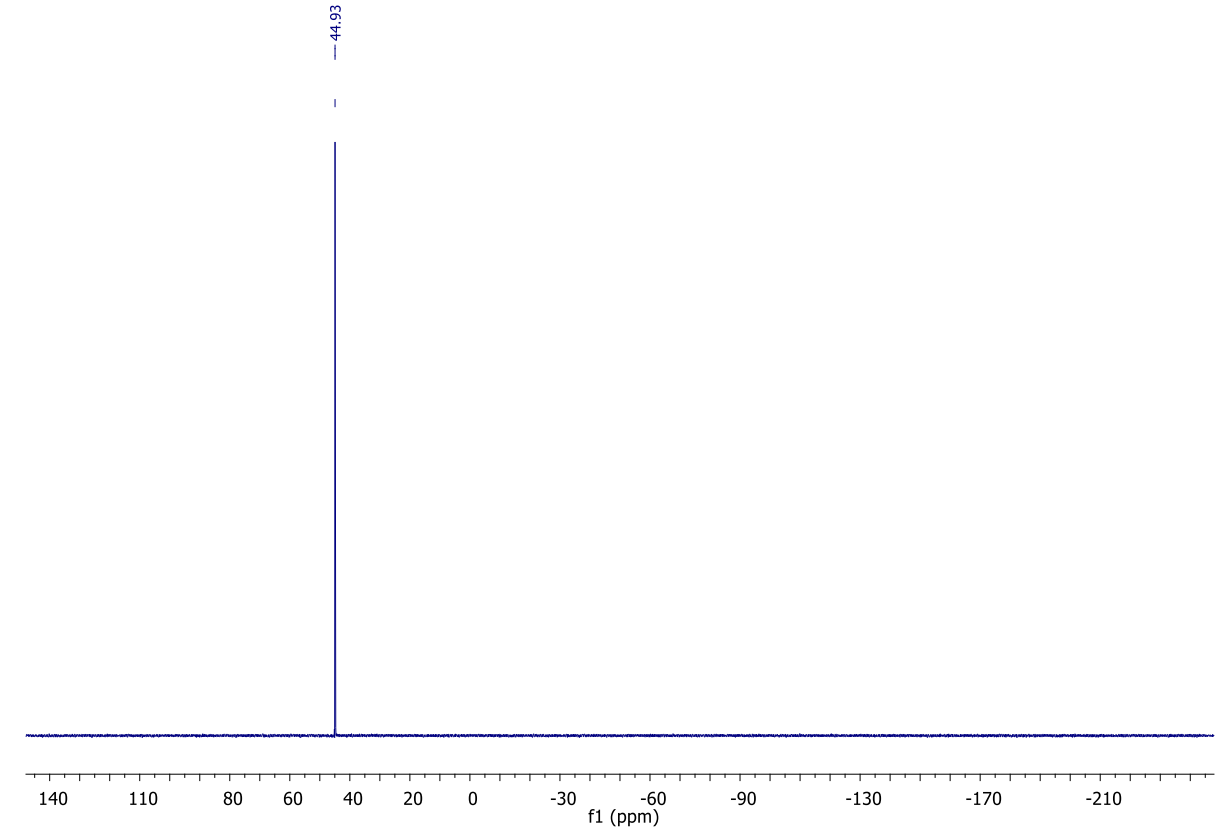


$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) spectrum of **99**.

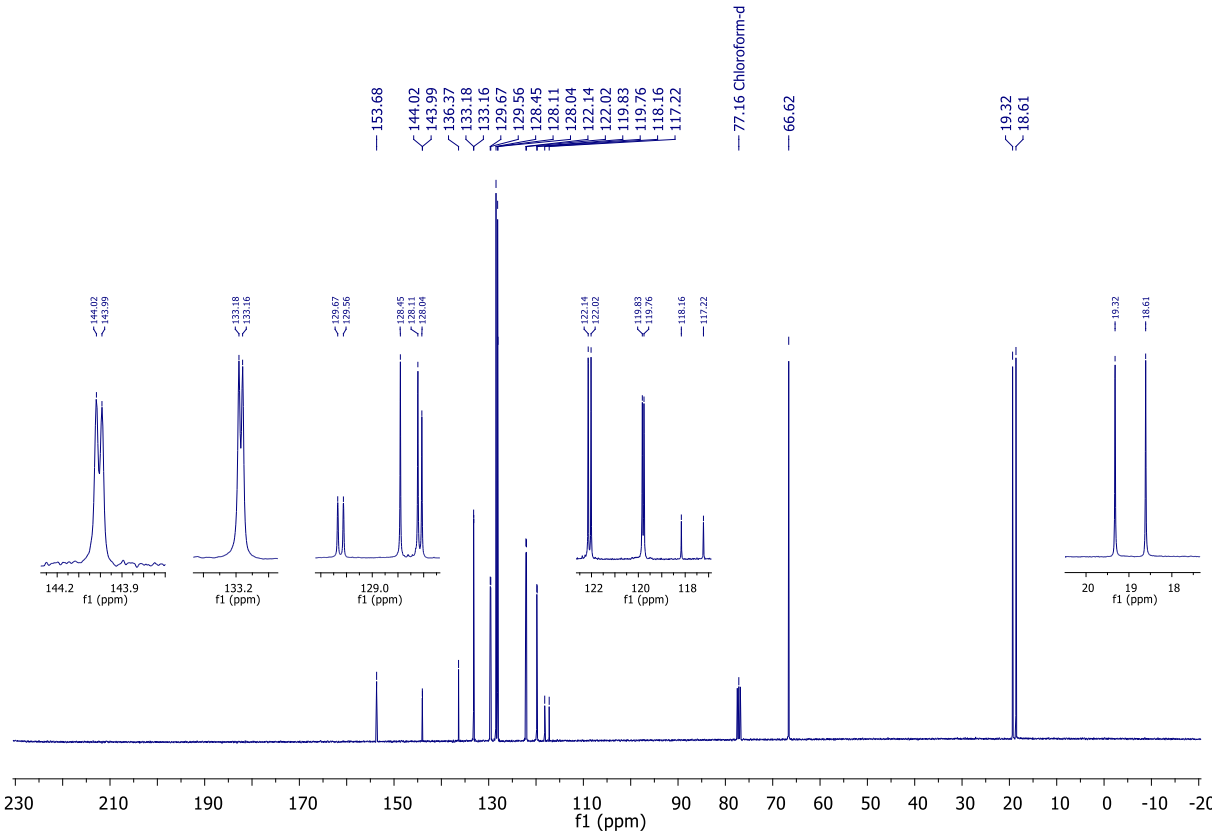
Compound 100



^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **100**.

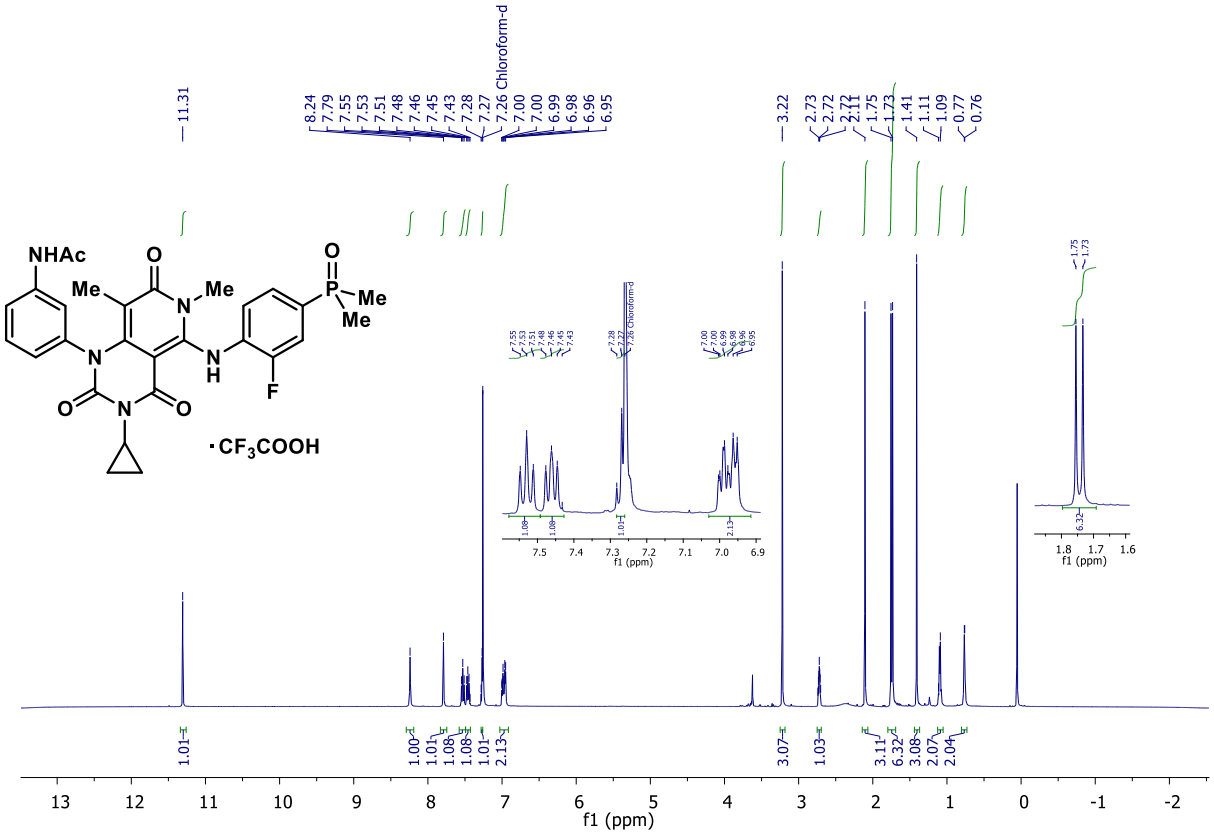


^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$) spectrum of **100**.

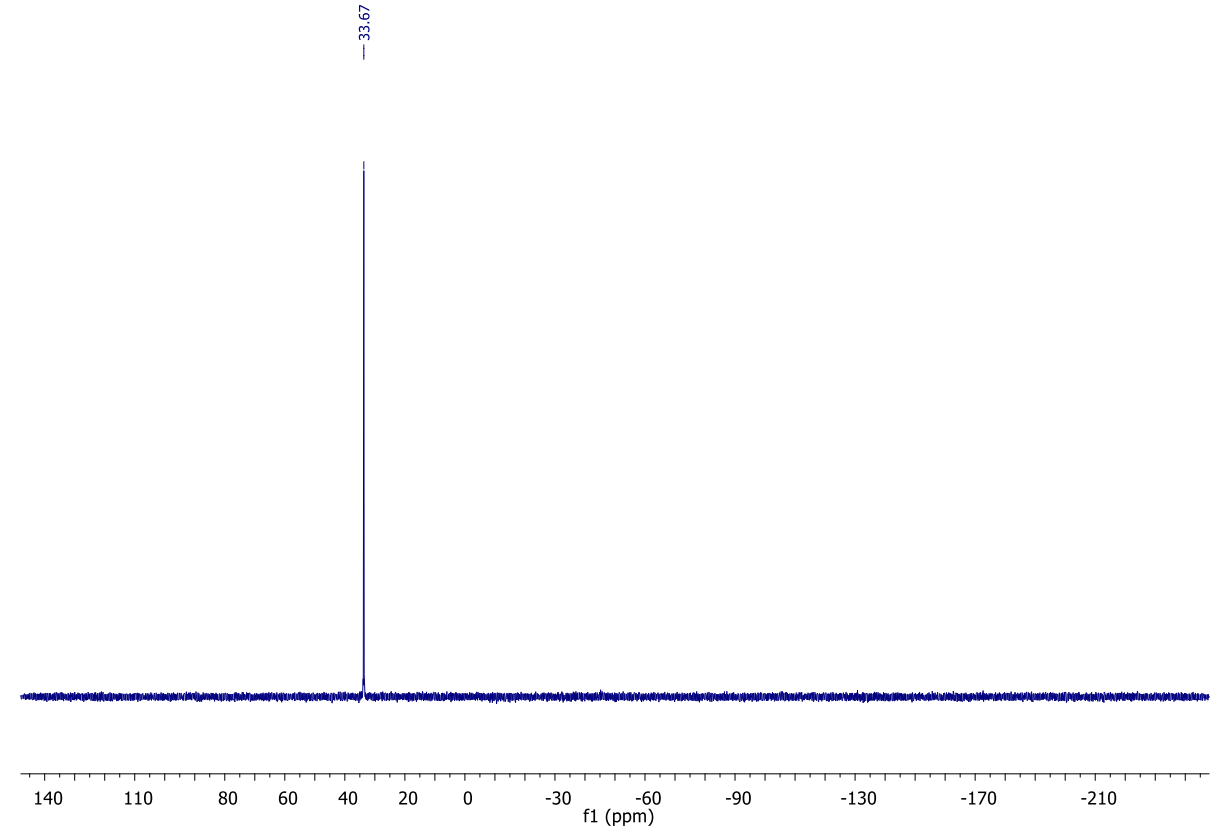


$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) spectrum of **100**.

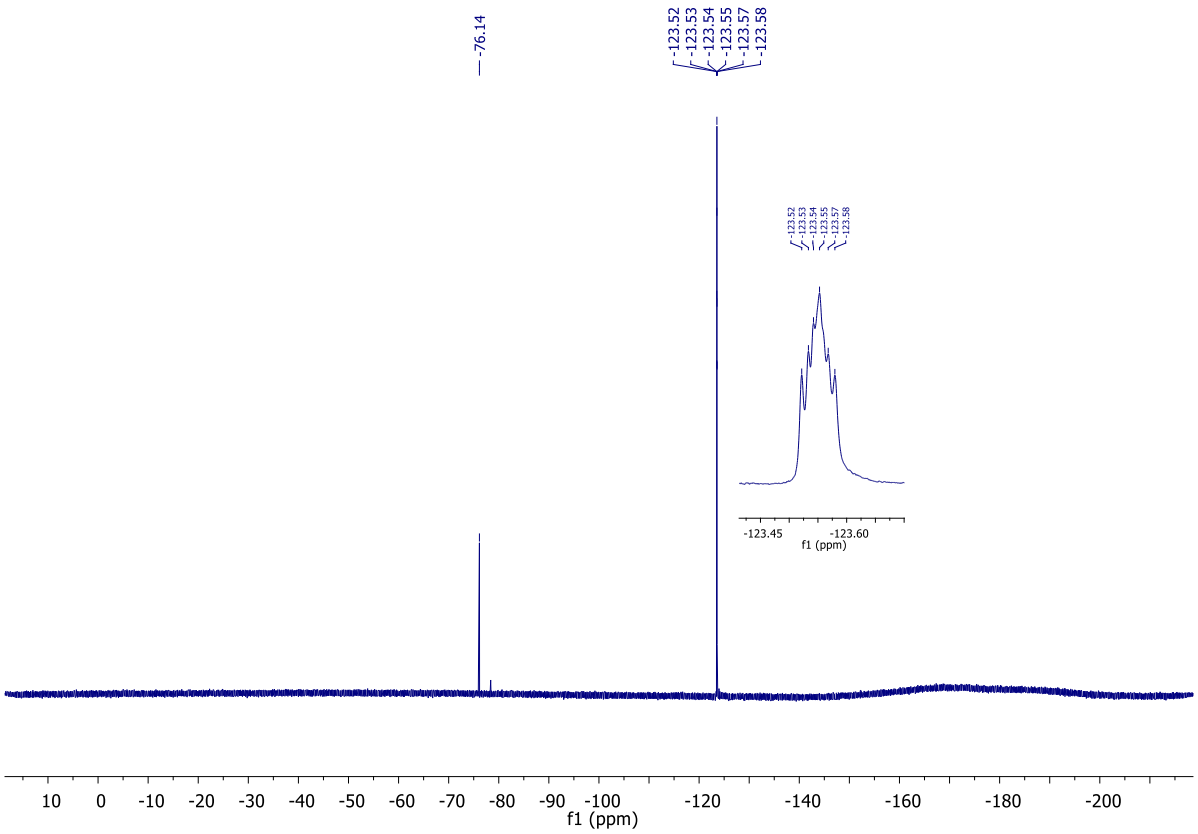
Compound 102·TFA



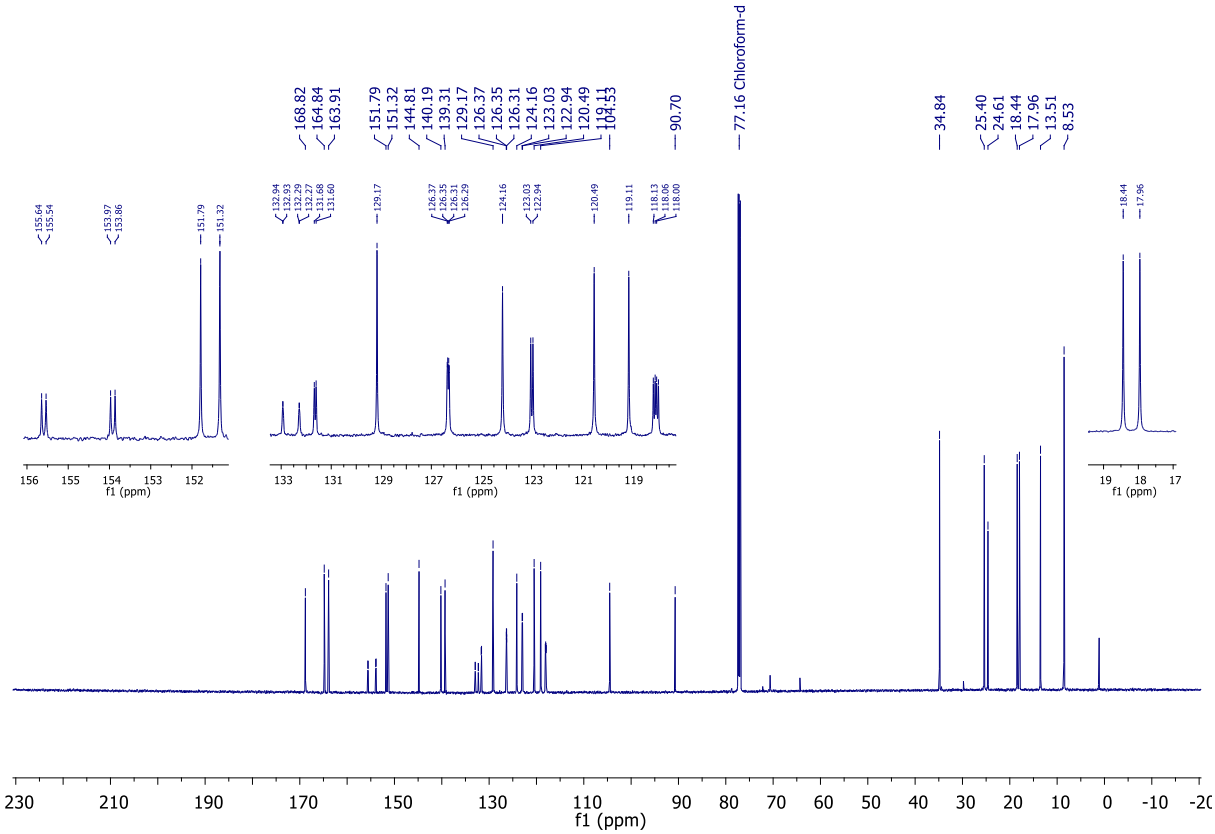
^{1}H NMR (600 MHz, $CDCl_3$) spectrum of **102·TFA**.



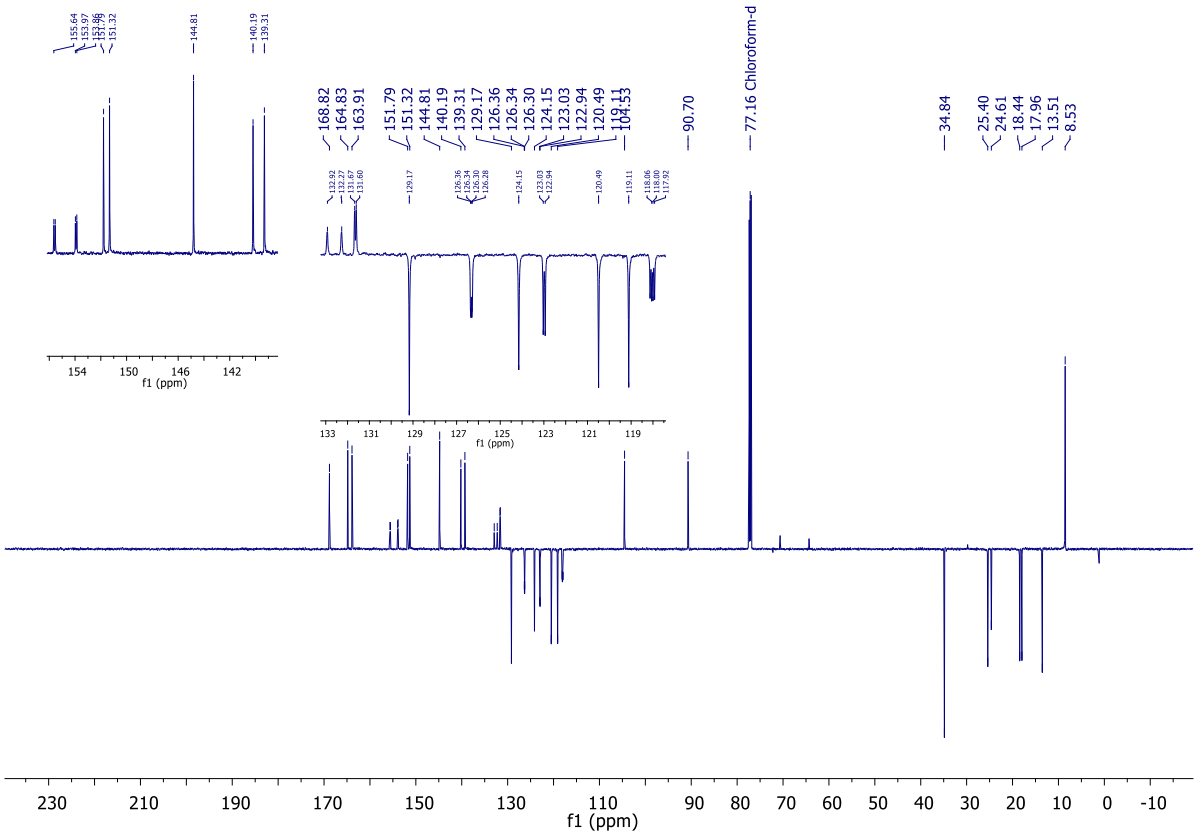
^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$) spectrum of **102·TFA**.



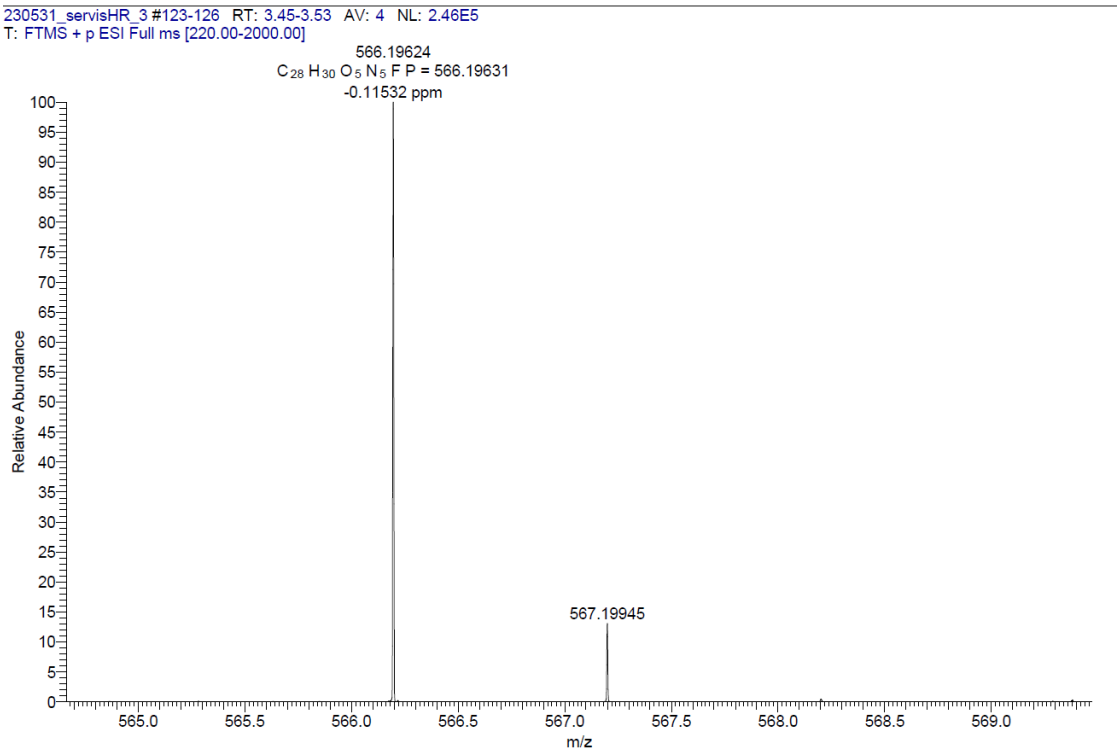
^{19}F NMR (376 MHz, $CDCl_3$) spectrum of **102·TFA**.



^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) spectrum of **102·TFA**.

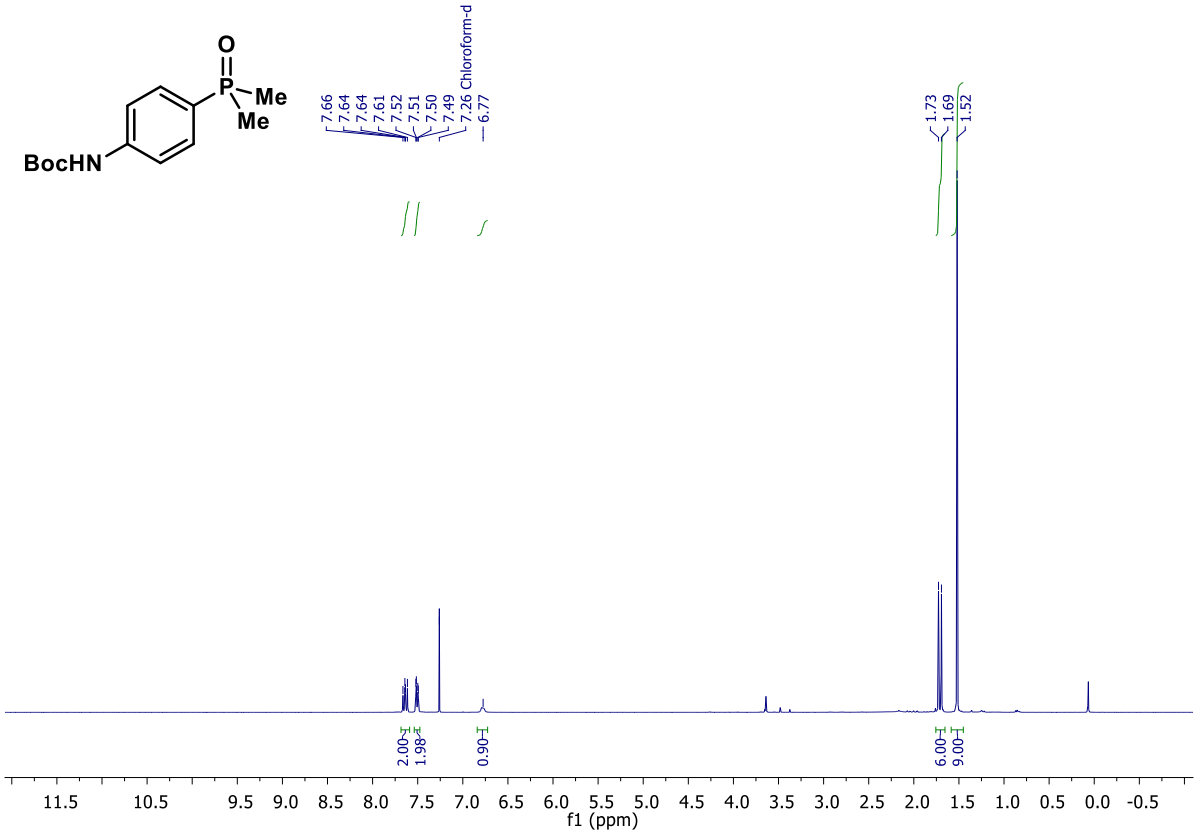


$^{13}C\{^{1}H\}$ APT NMR (151 MHz, $CDCl_3$) spectrum of **102·TFA**.

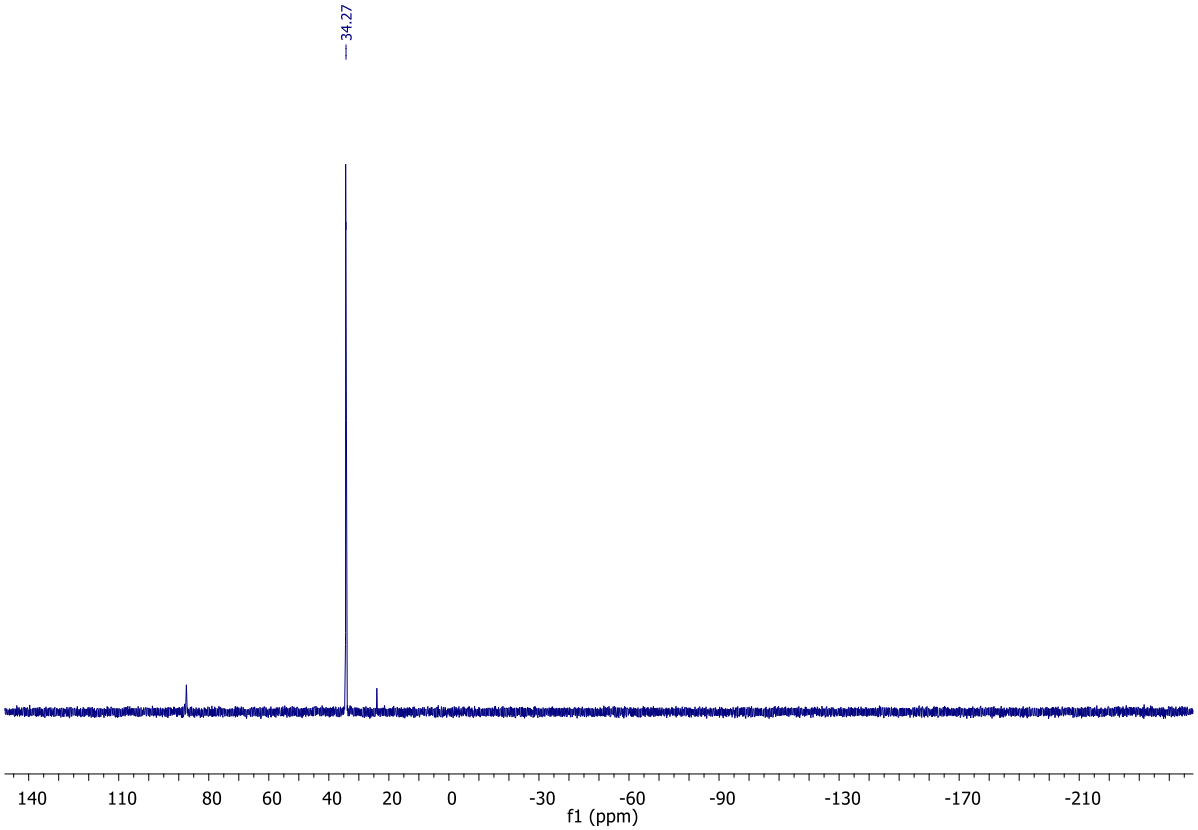


HRMS (ESI-TOF) spectrum of compound **102·TFA**.

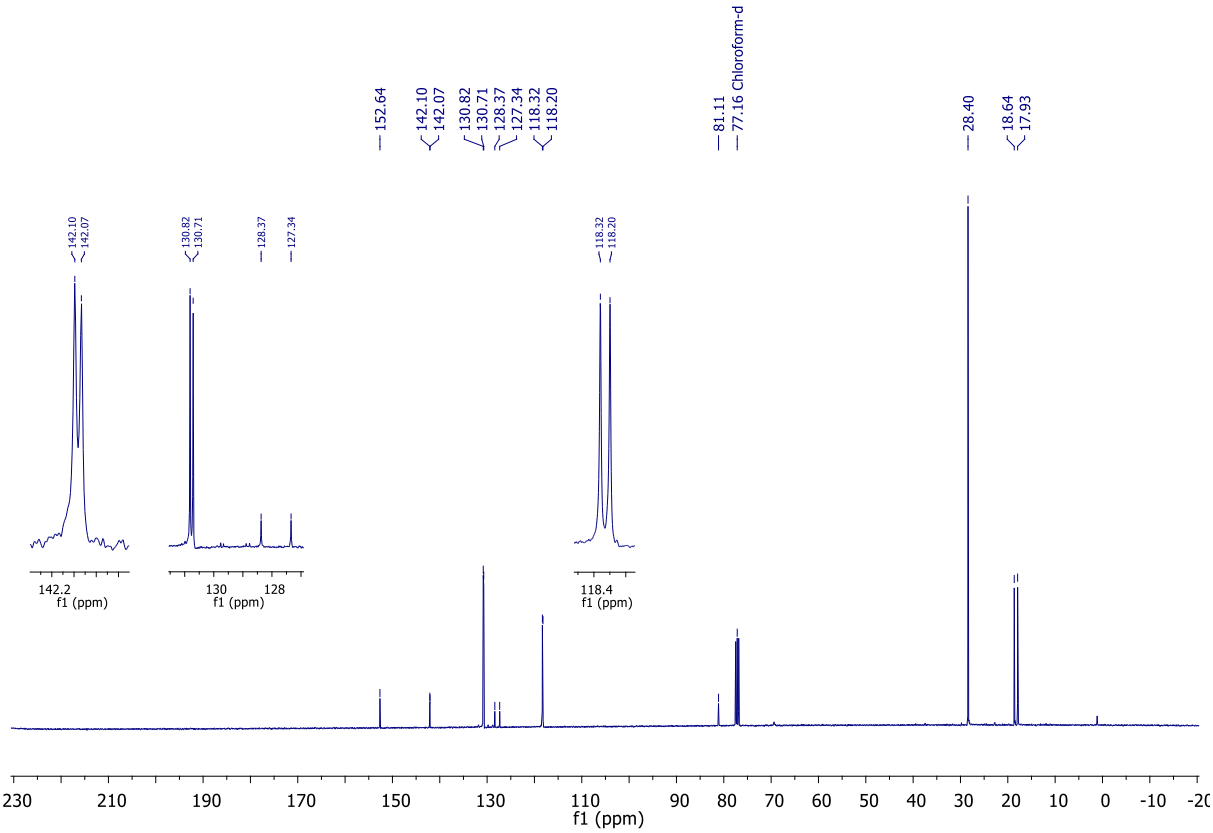
Compound 104



^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **104**.

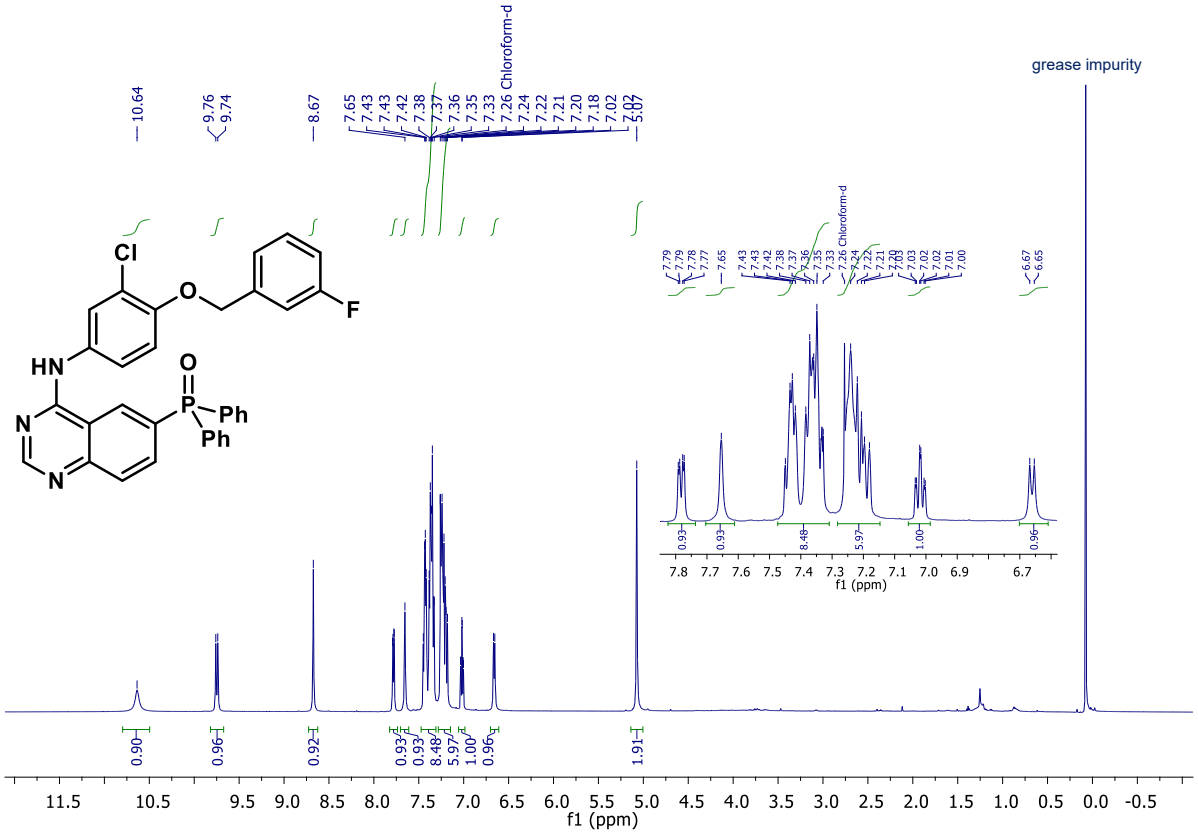


^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$) spectrum of **104**.

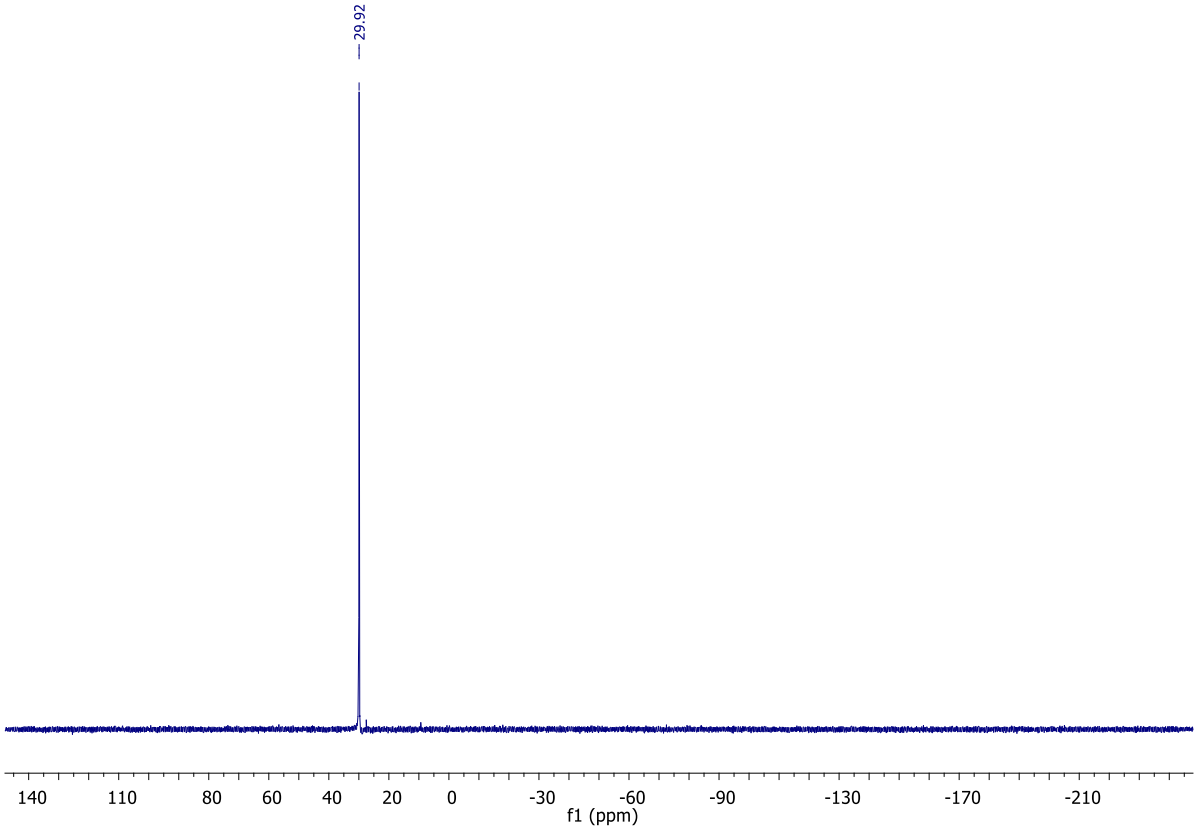


$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) spectrum of **104**.

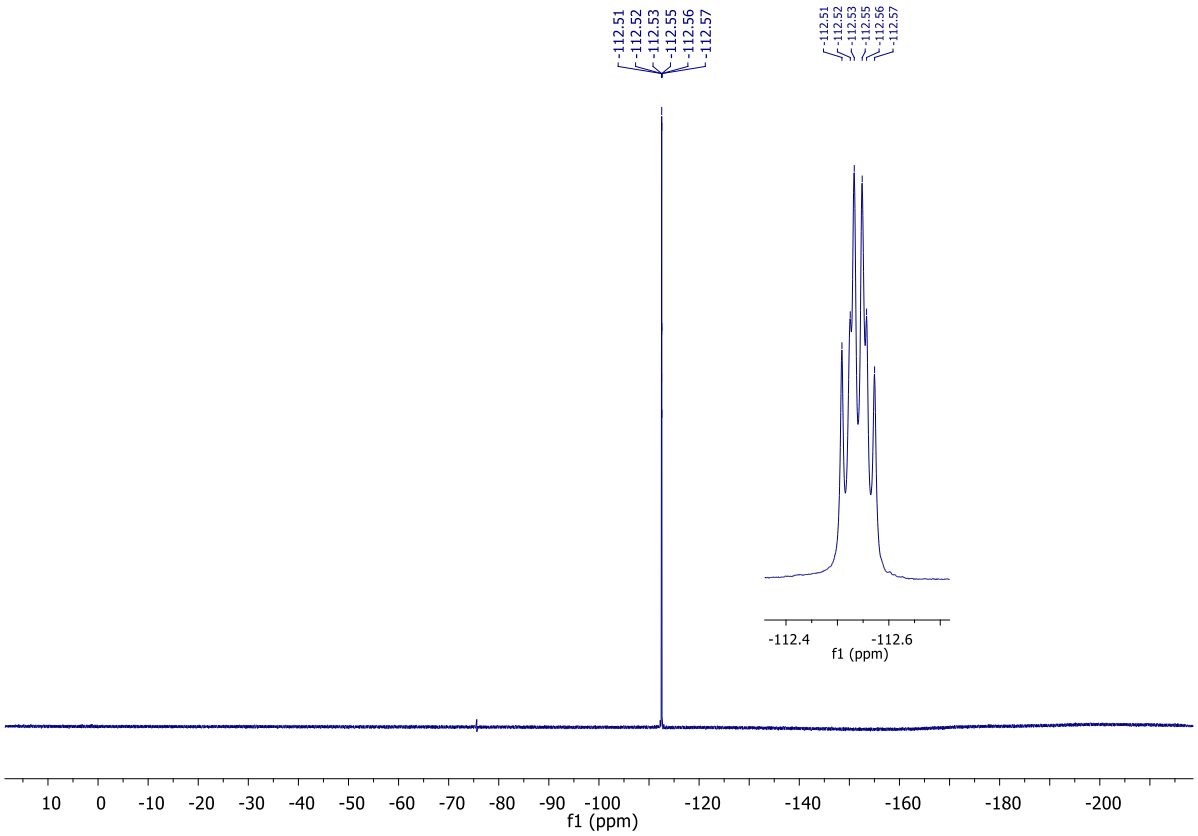
Compound 106



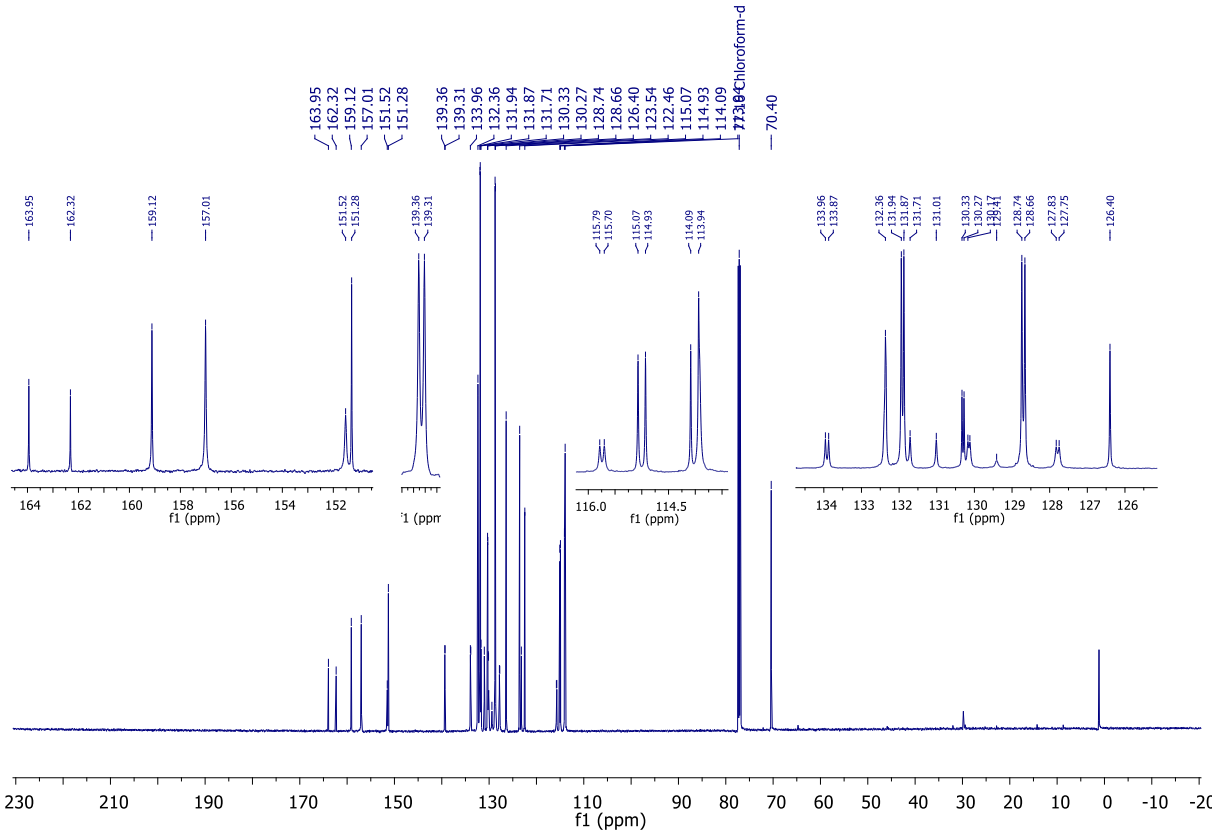
^{1}H NMR (600 MHz, $CDCl_3$) spectrum of **106**.



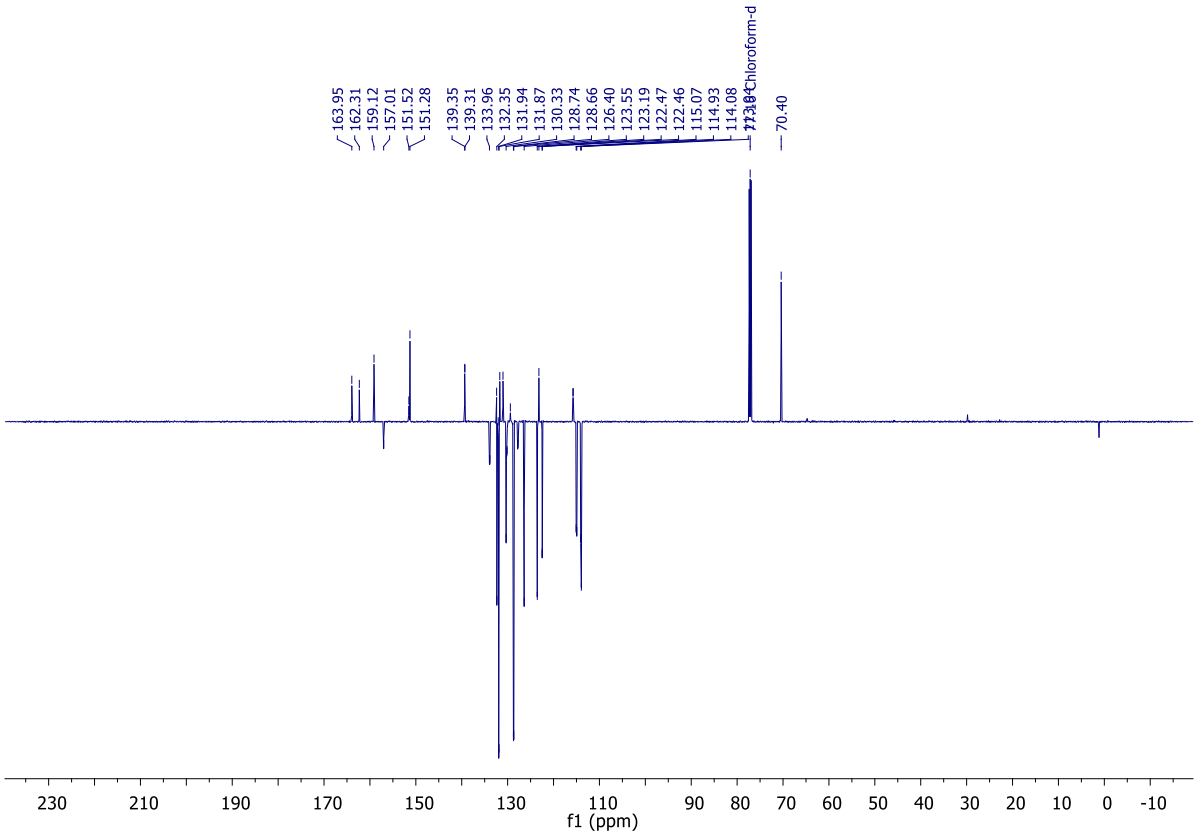
^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$) spectrum of **106**.



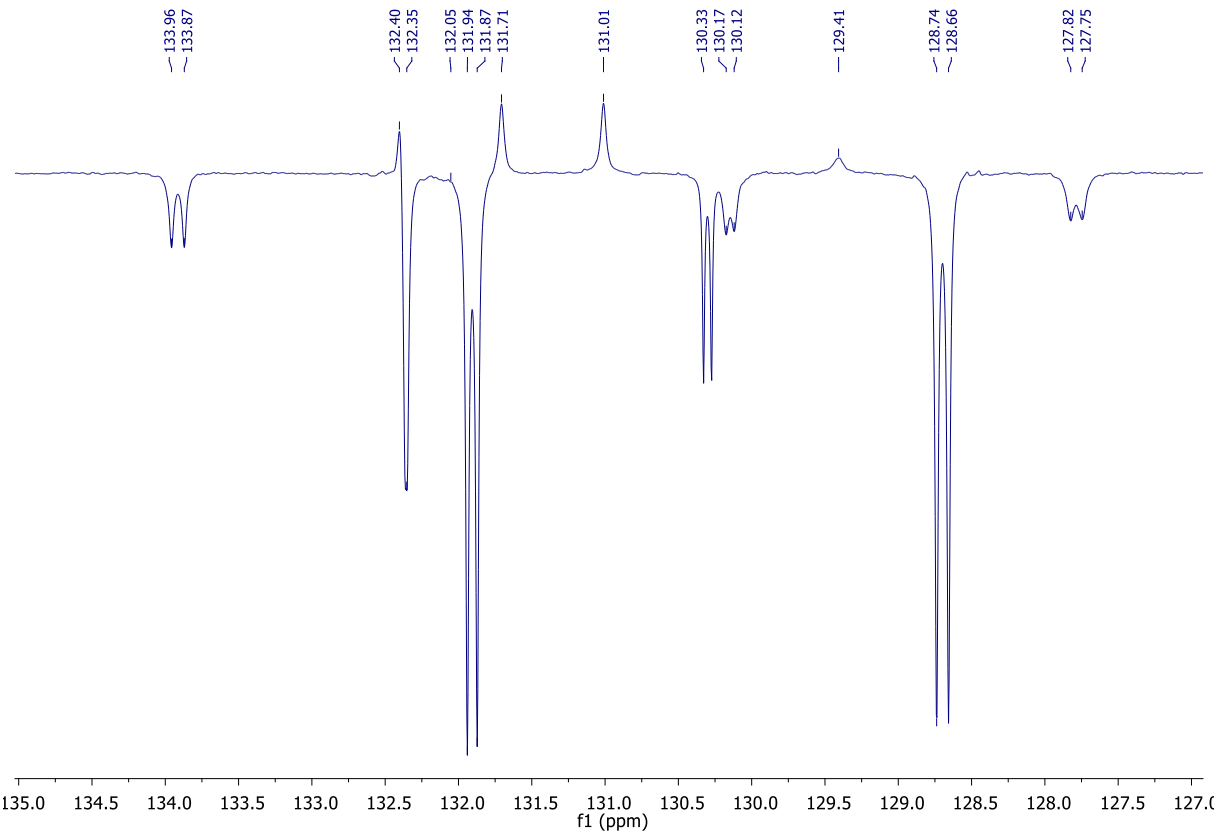
^{19}F NMR (376 MHz, $CDCl_3$) spectrum of **106**.



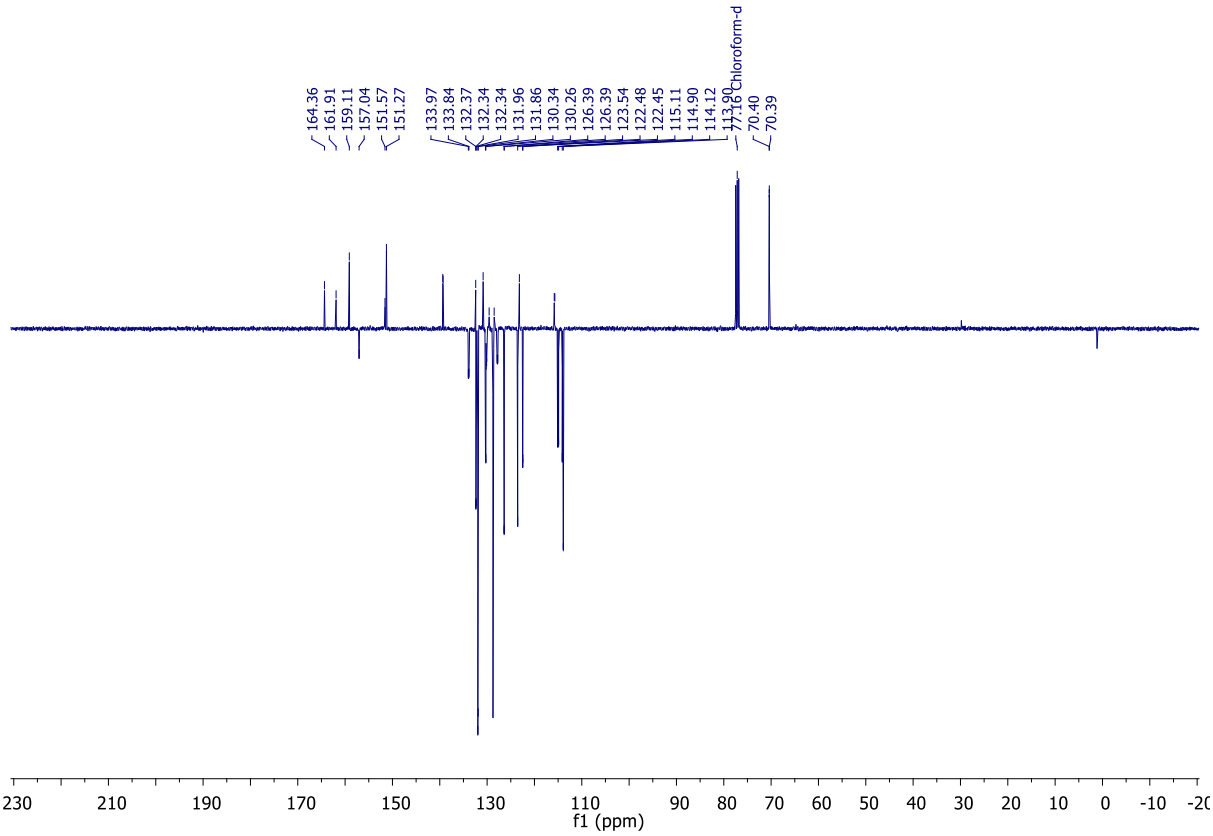
^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) spectrum of **106**.



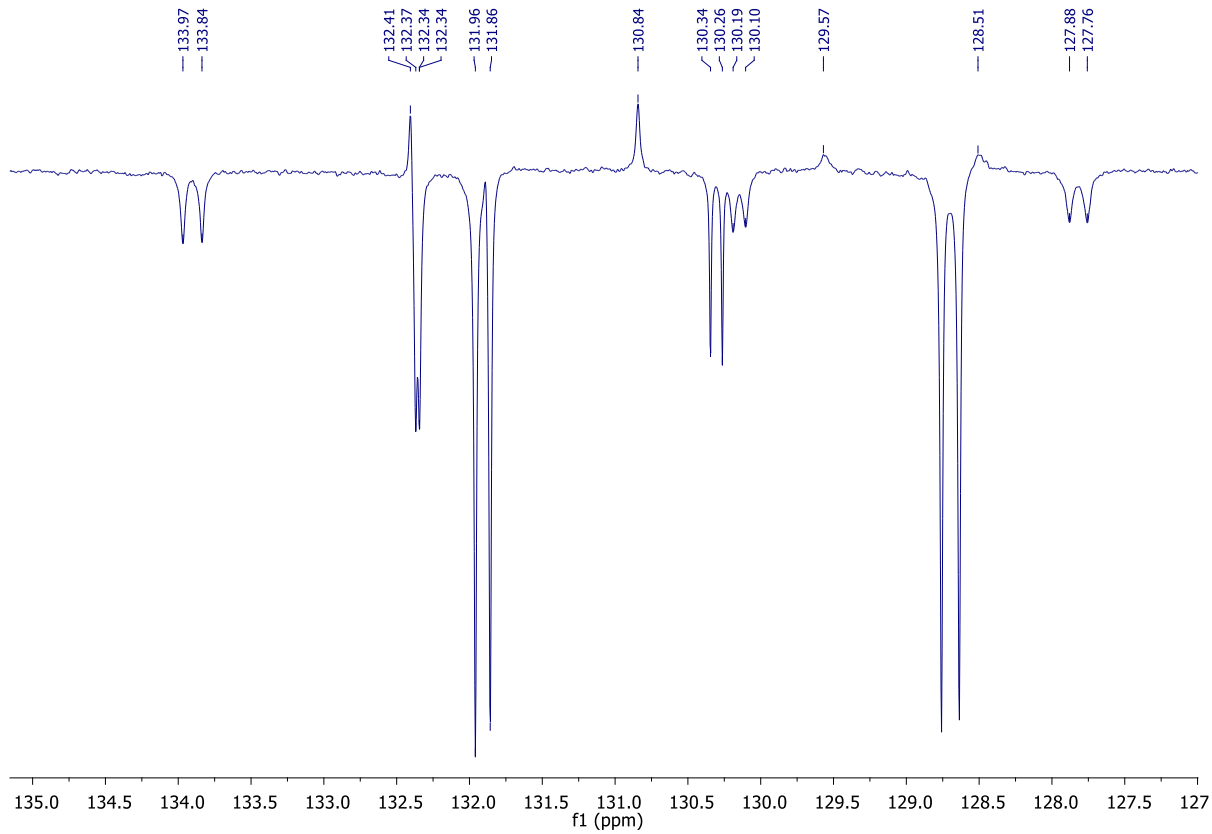
$^{13}C\{^{1}H\}$ APT NMR (151 MHz, $CDCl_3$) spectrum of **106**.



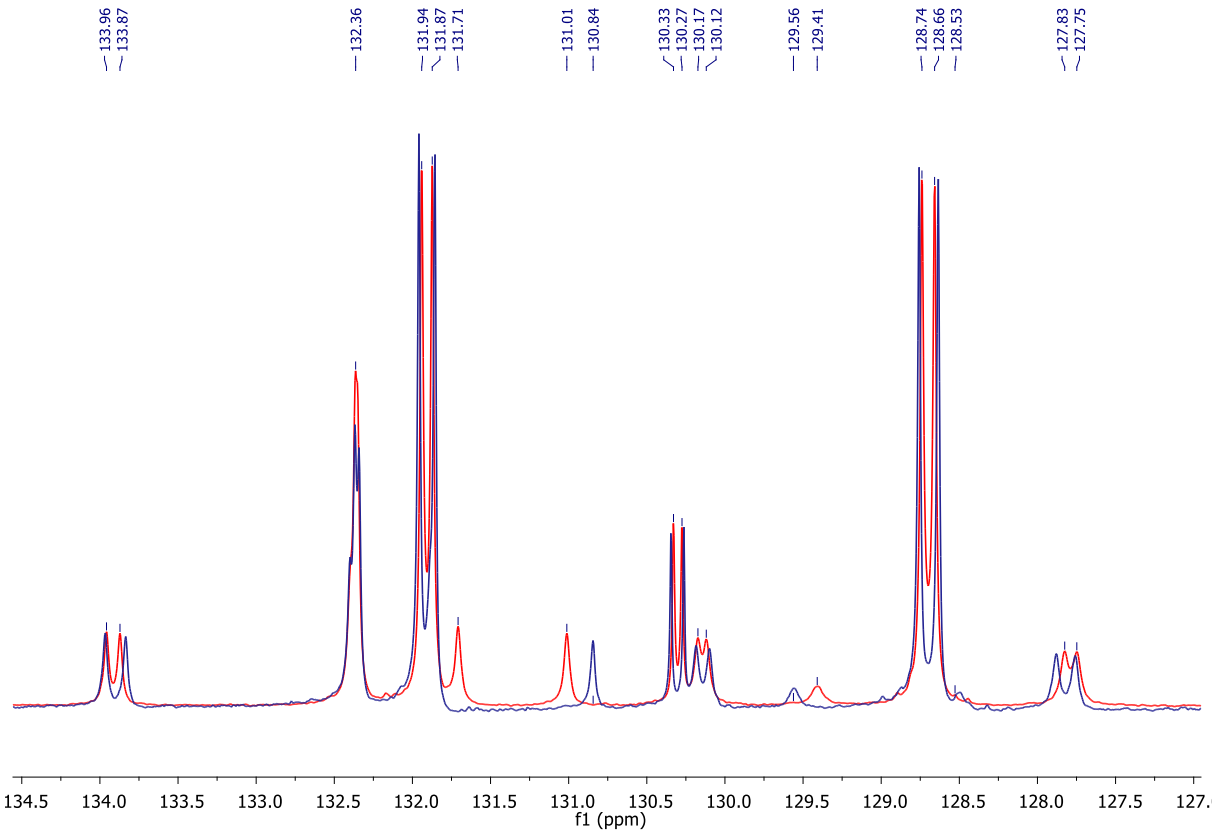
Detail of the **$^{13}C\{^{1}H\}$ APT NMR (151 MHz, $CDCl_3$)** spectrum of **106**.



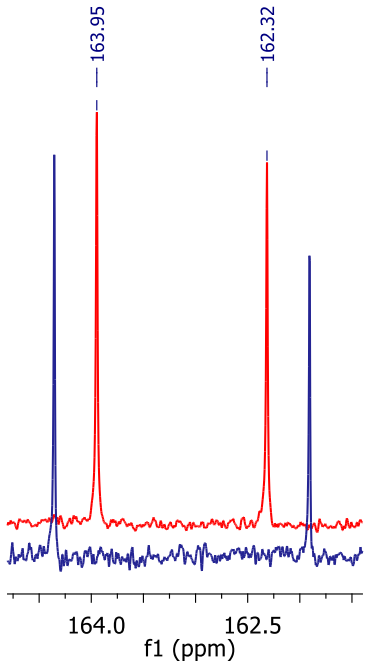
$^{13}C\{^{1}H\}$ APT NMR (100 MHz, $CDCl_3$) spectrum of **106**.



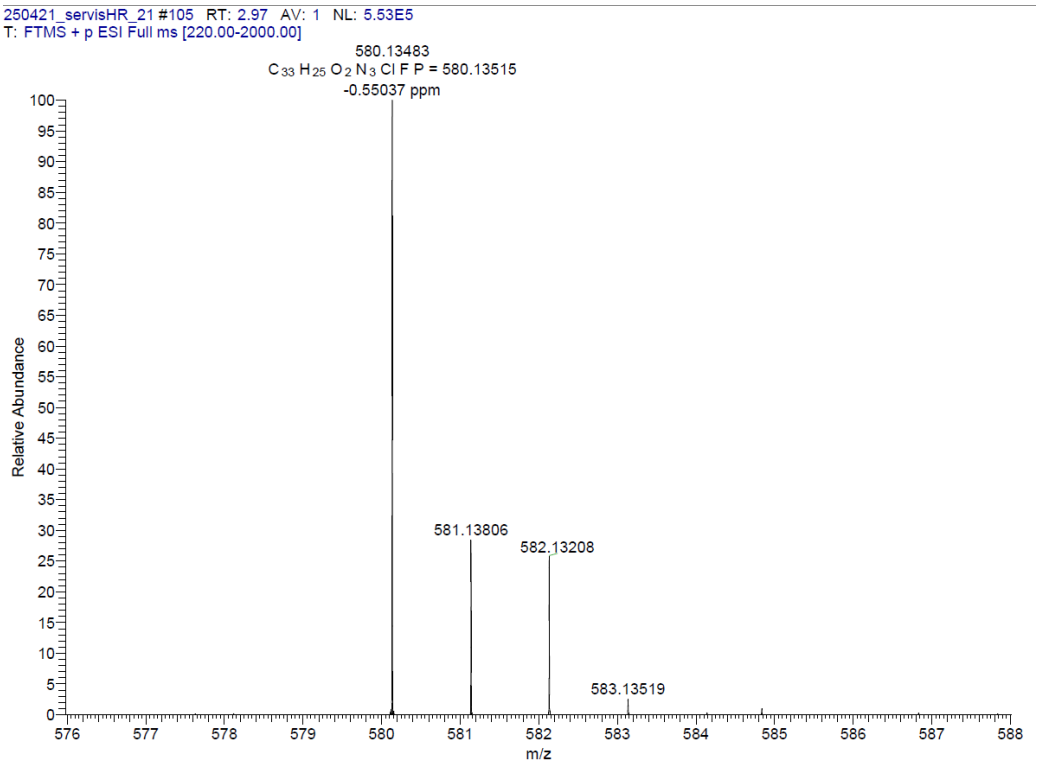
Detail of the **$^{13}C\{^{1}H\}$ APT NMR (100 MHz, $CDCl_3$)** spectrum of **106**.



Comparison of $^{13}C\{^{1}H\}$ NMR spectra of **106** (151 MHz in red trace, 100 MHz in blue trace) which were used to assign the two C–P signals based on their *J* values. $^{13}C\{^{1}H\}$ 151 MHz: δ 131.4 (d, *J* = 105.1 Hz), not determined ppm; $^{13}C\{^{1}H\}$ 100 MHz: δ not determined, 129.0 (d, *J* = 160.7 Hz) ppm.

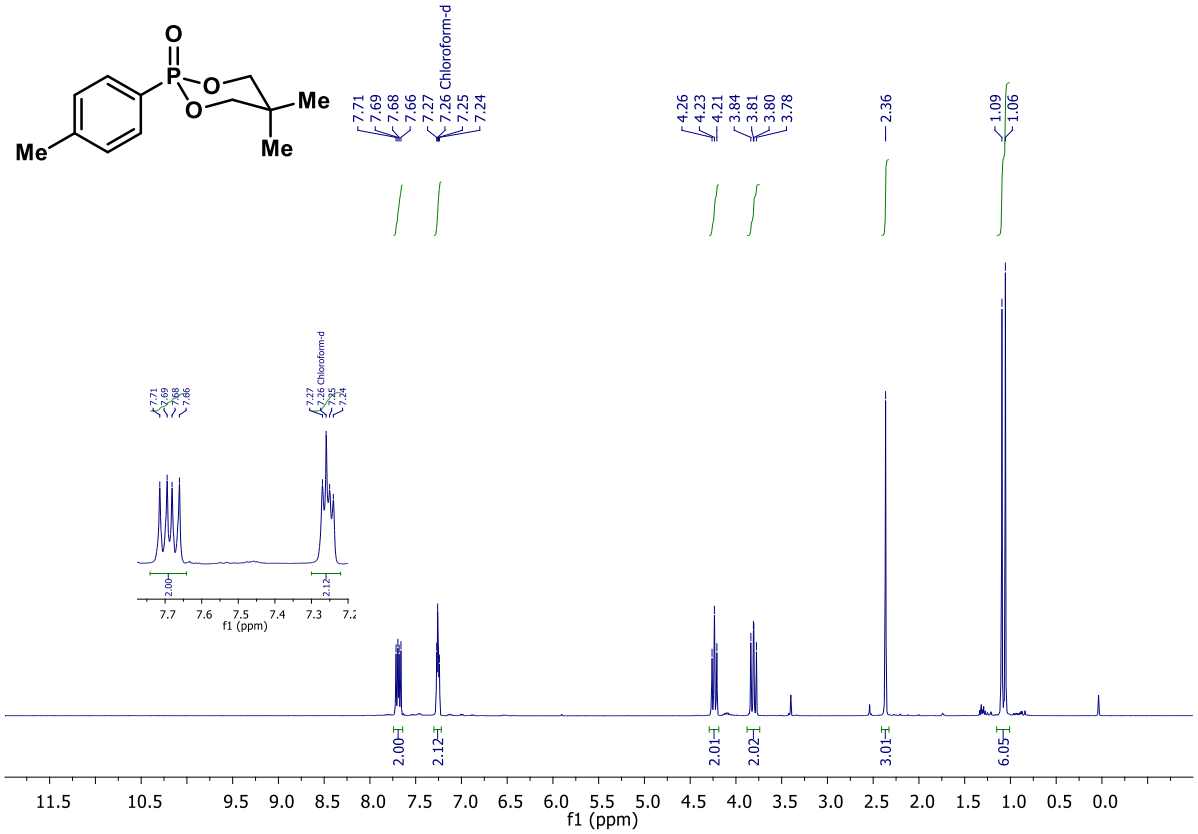


Comparison of $^{13}C\{^{1}H\}$ NMR spectra of **106** (151 MHz in red trace, 100 MHz in blue trace) which were used to assign the C–F signal based on its *J* values.

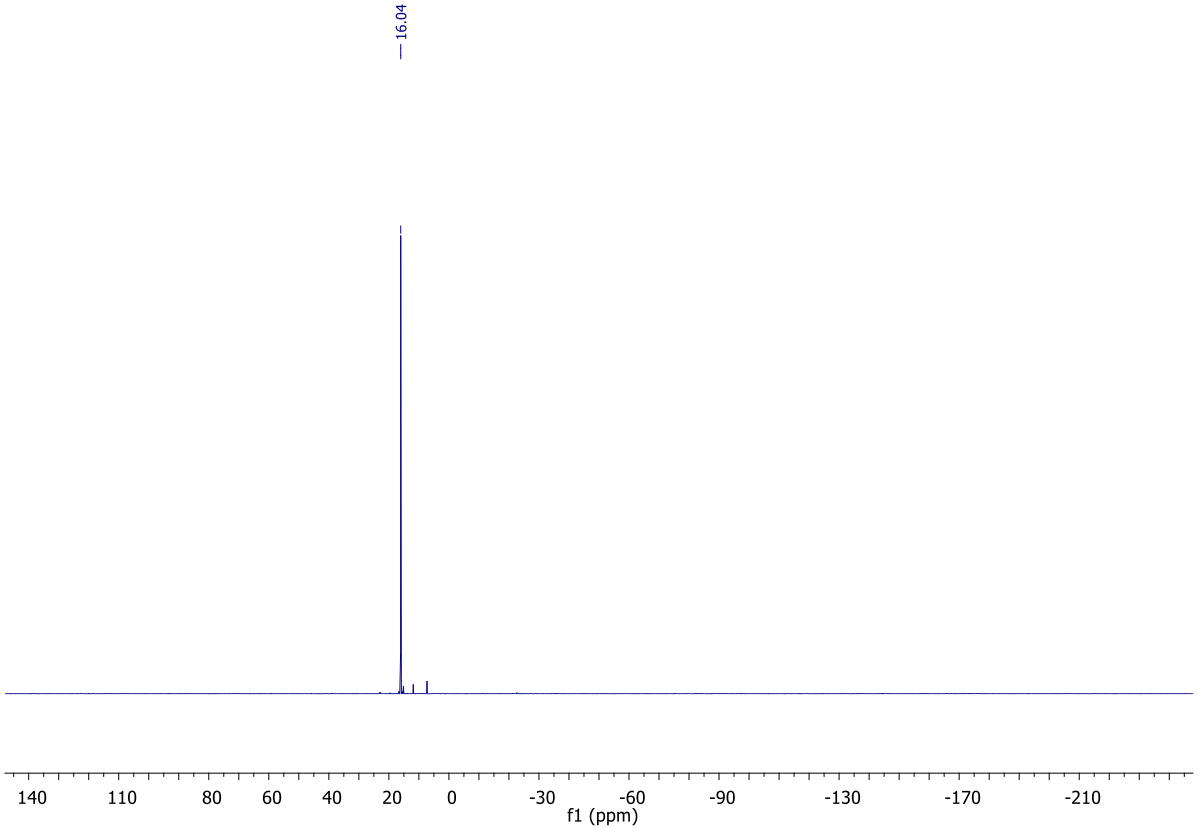


HRMS (ESI-TOF) spectrum of compound **106**.

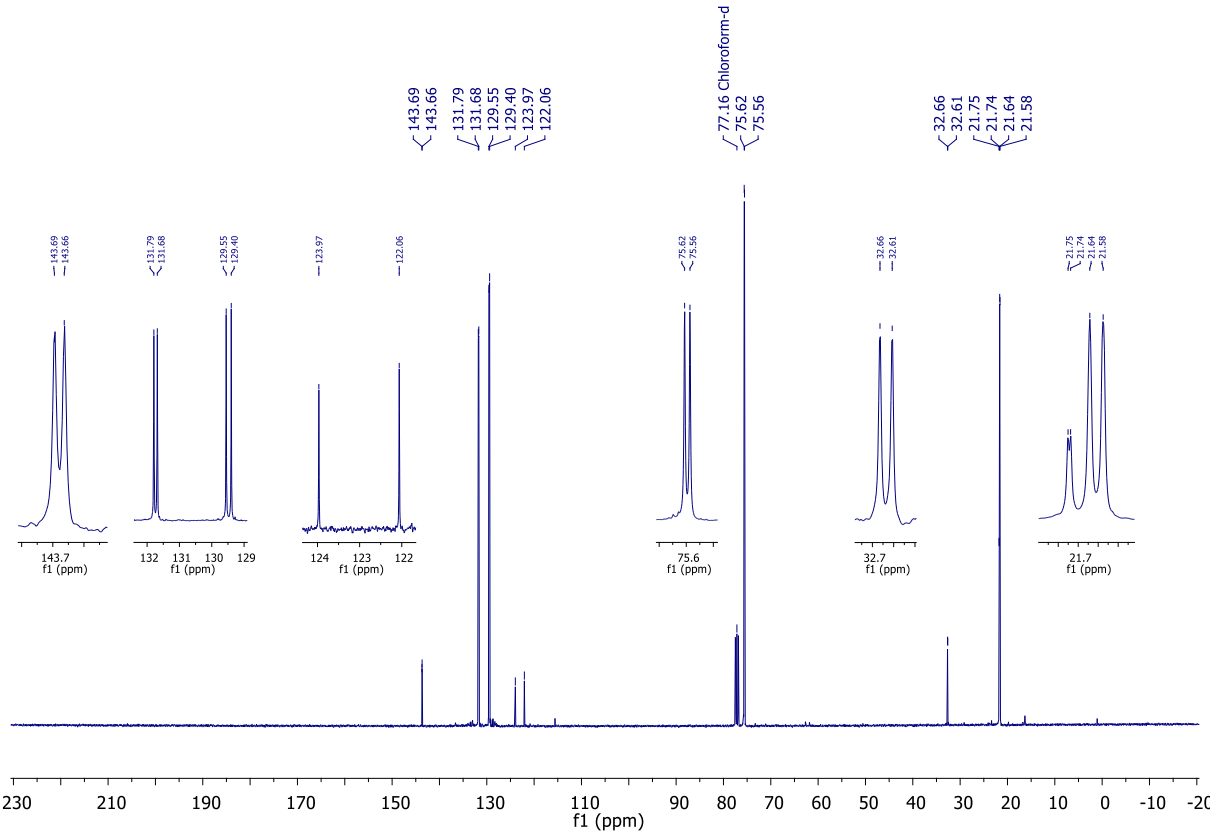
Compound 111



^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **111**.

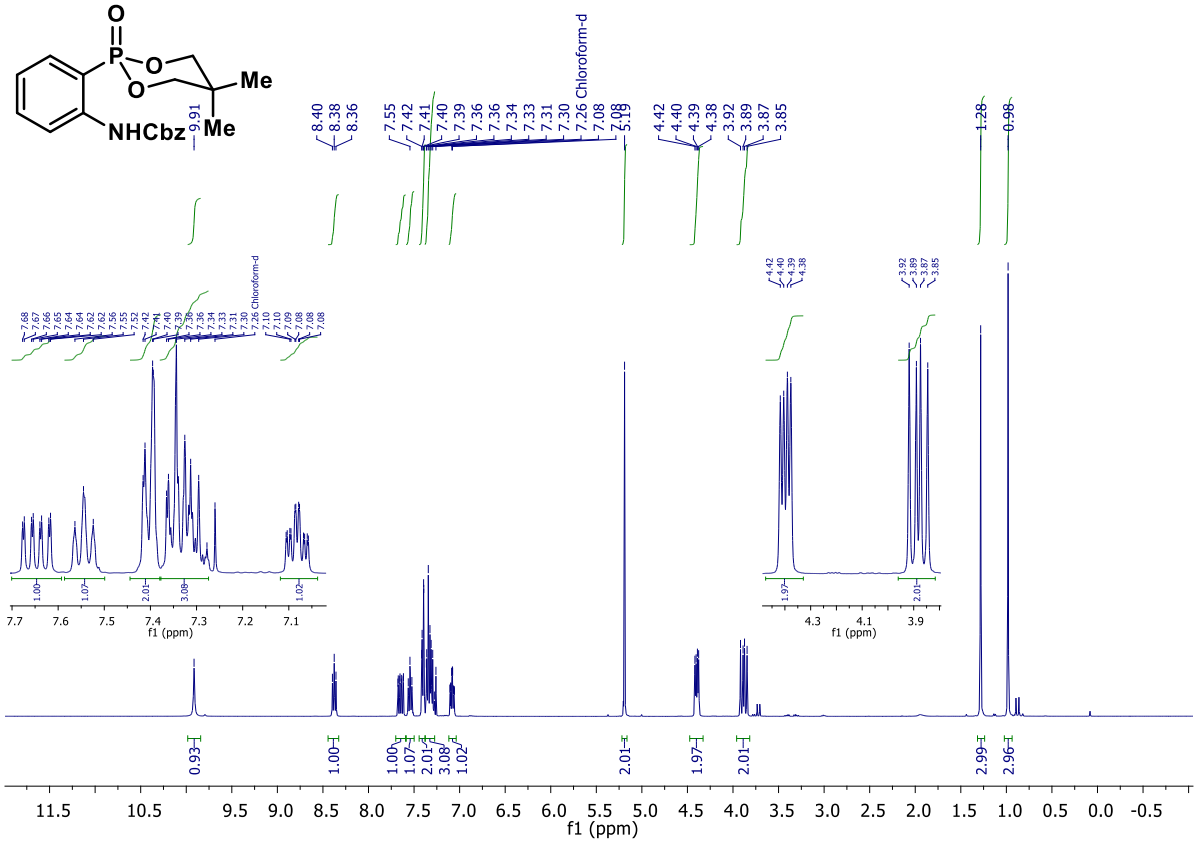


^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$) spectrum of **111**.

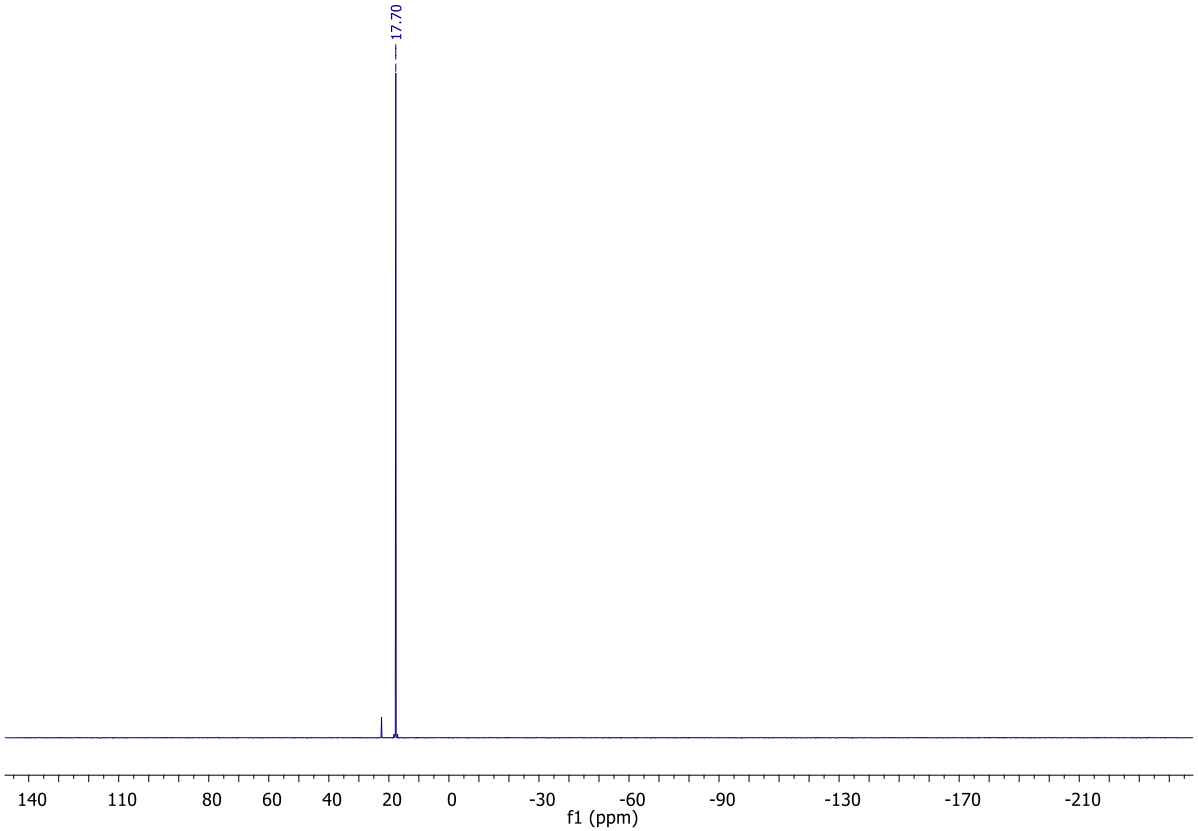


$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) spectrum of **111**.

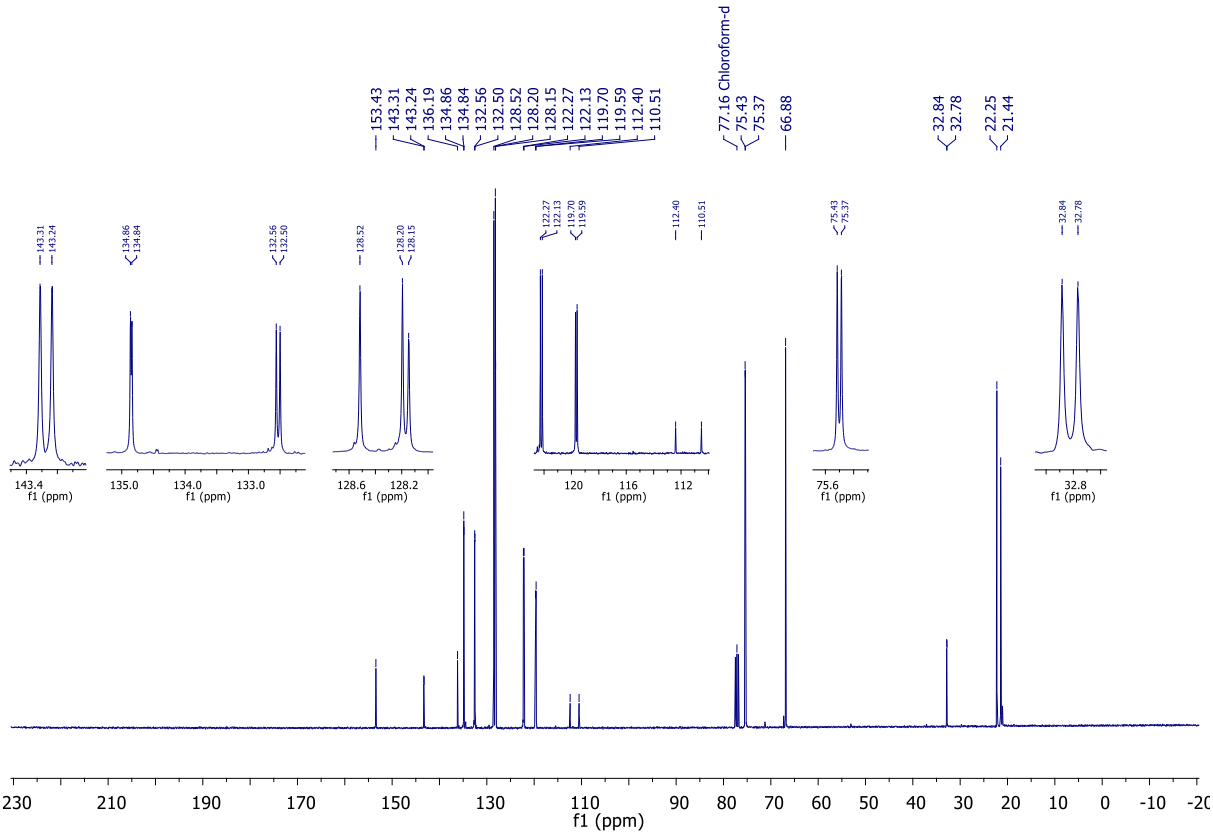
Compound 112



^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **112**.

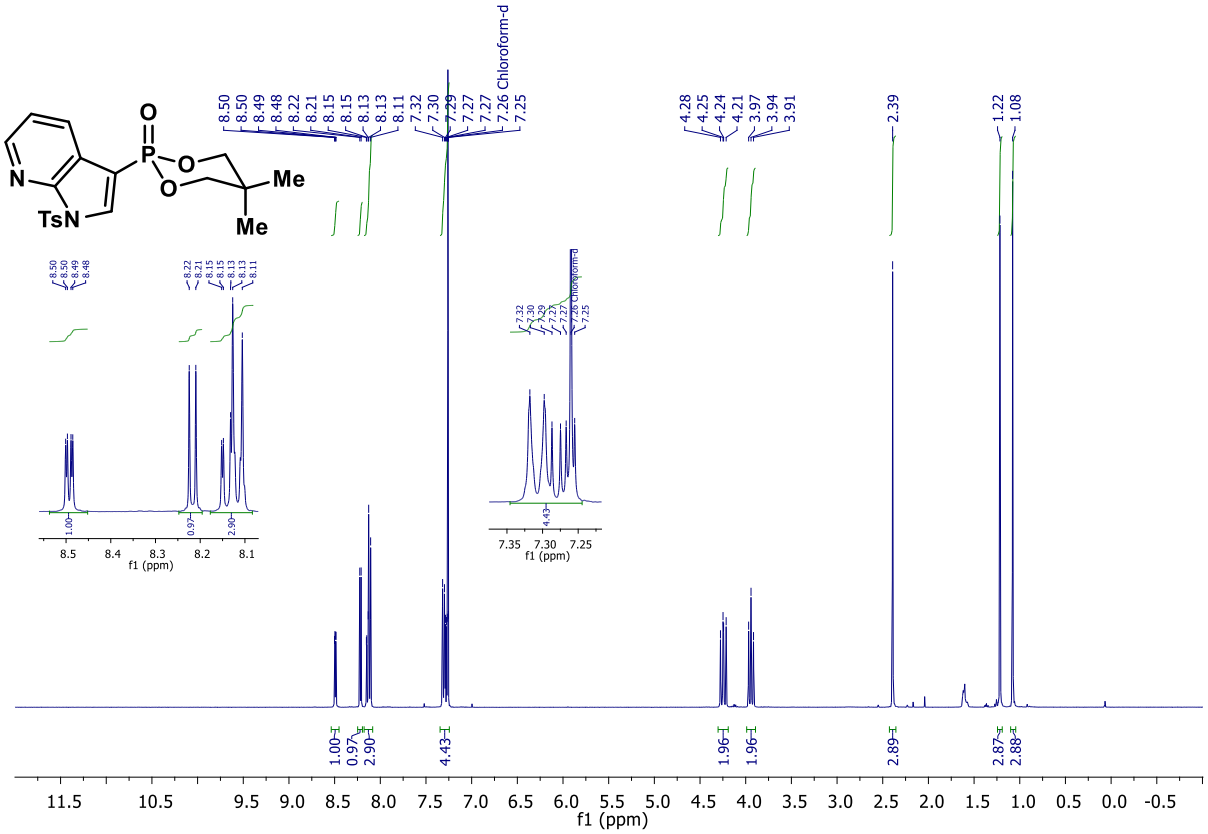


^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$) spectrum of **112**.

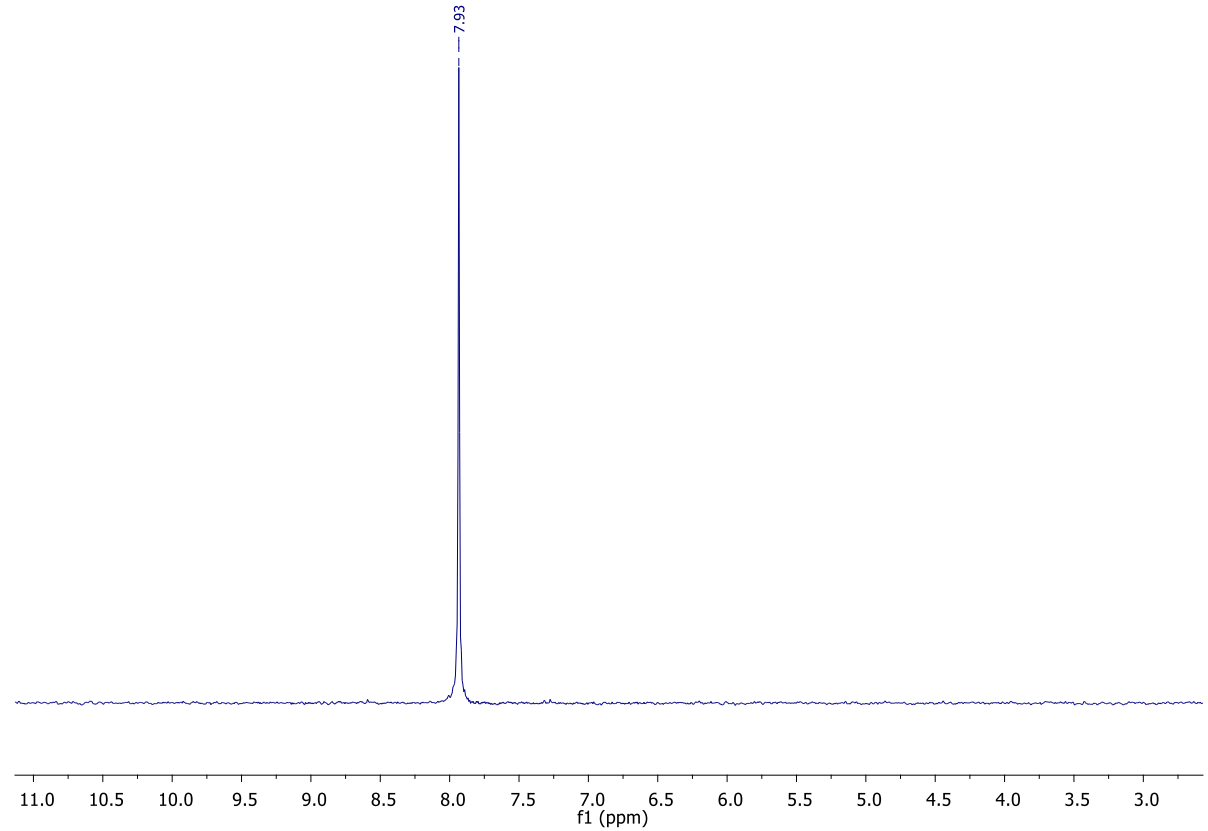


$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) spectrum of **112**.

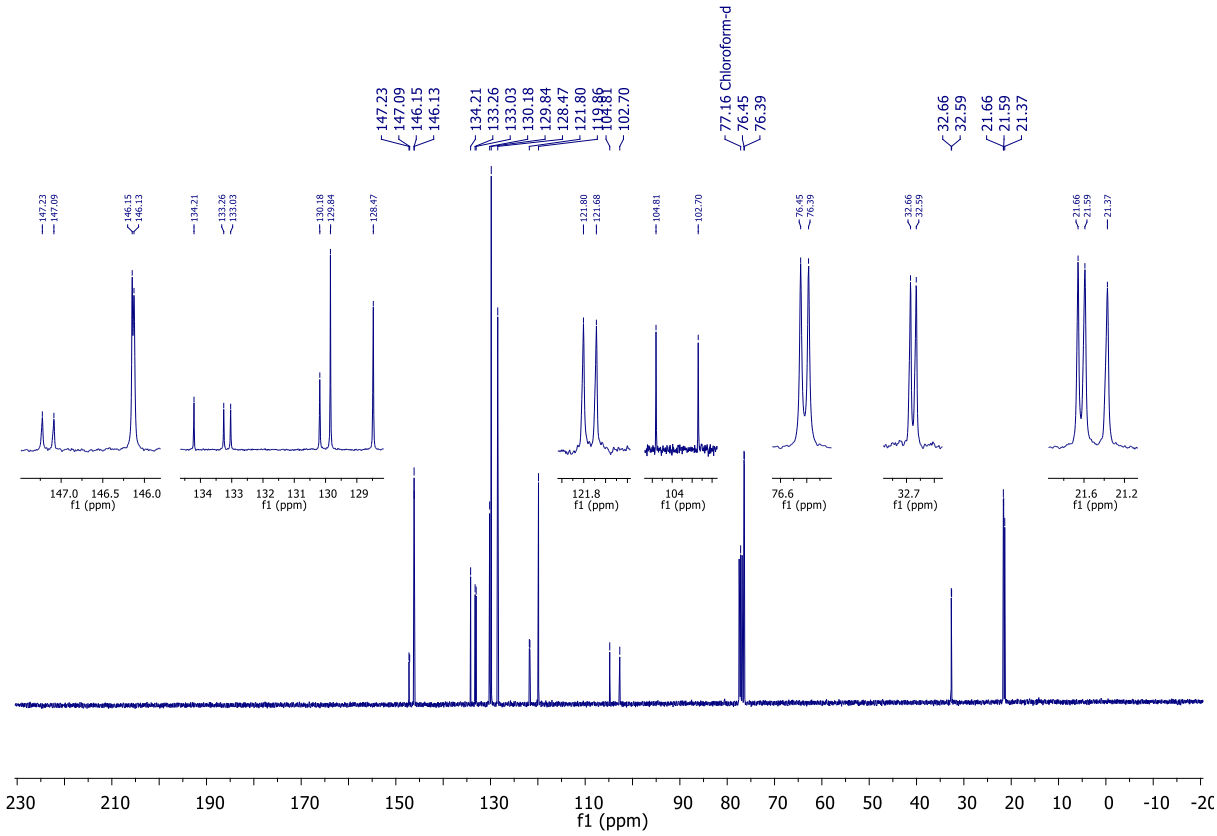
Compound 113



^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **113**.

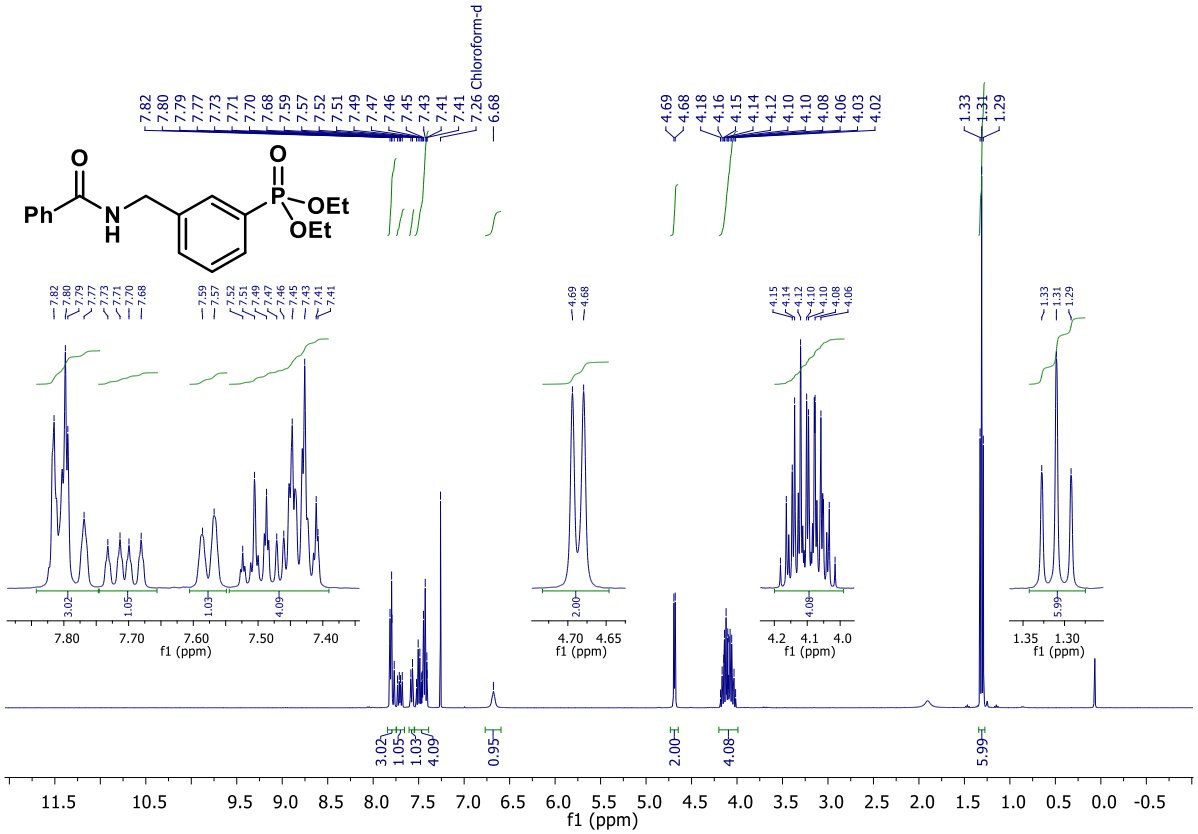


^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$) spectrum of **113**.

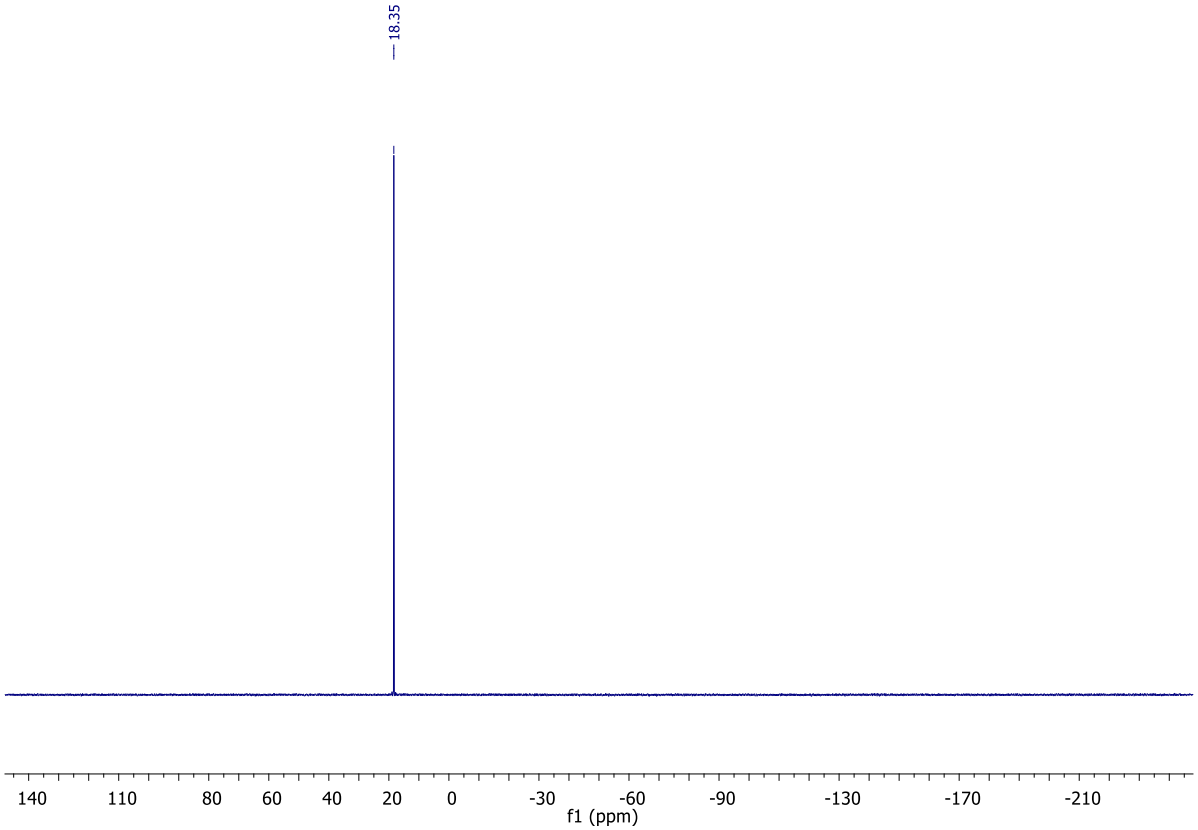


$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) spectrum of **113**.

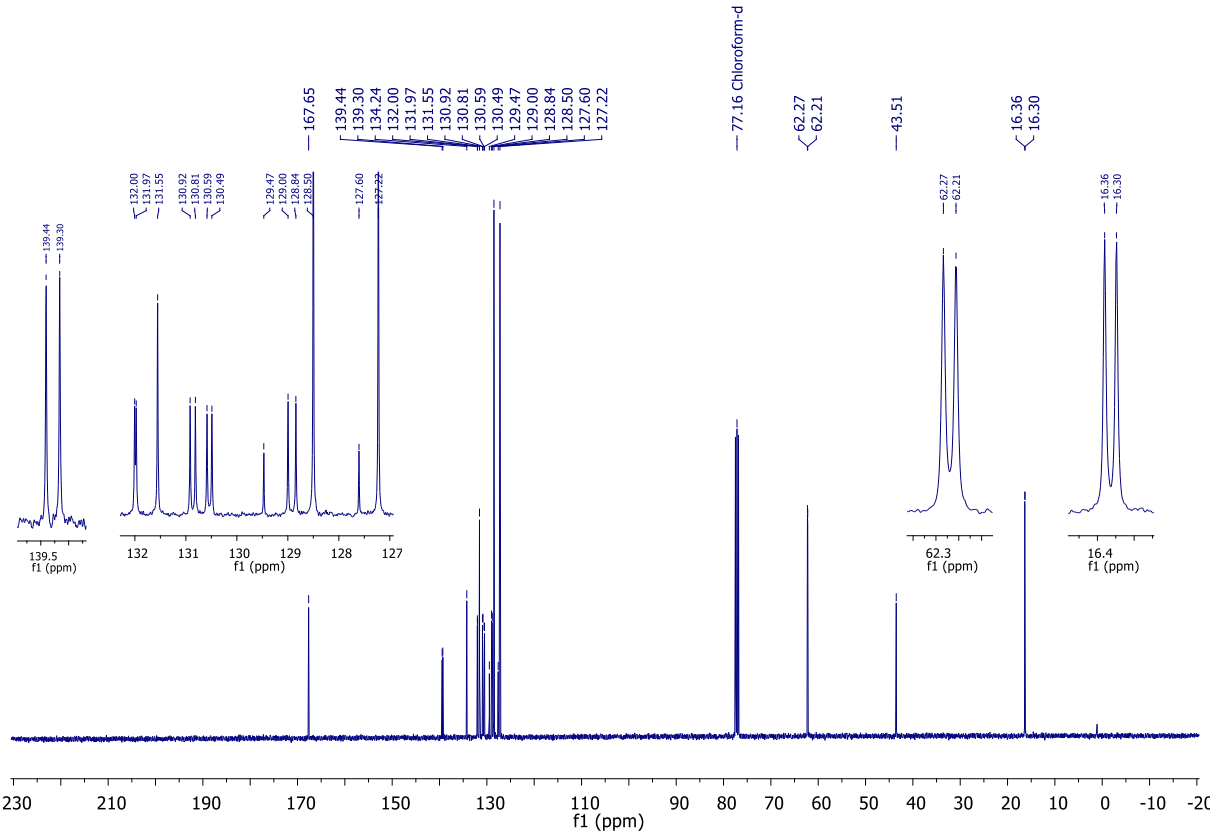
Compound 118



^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **118**.

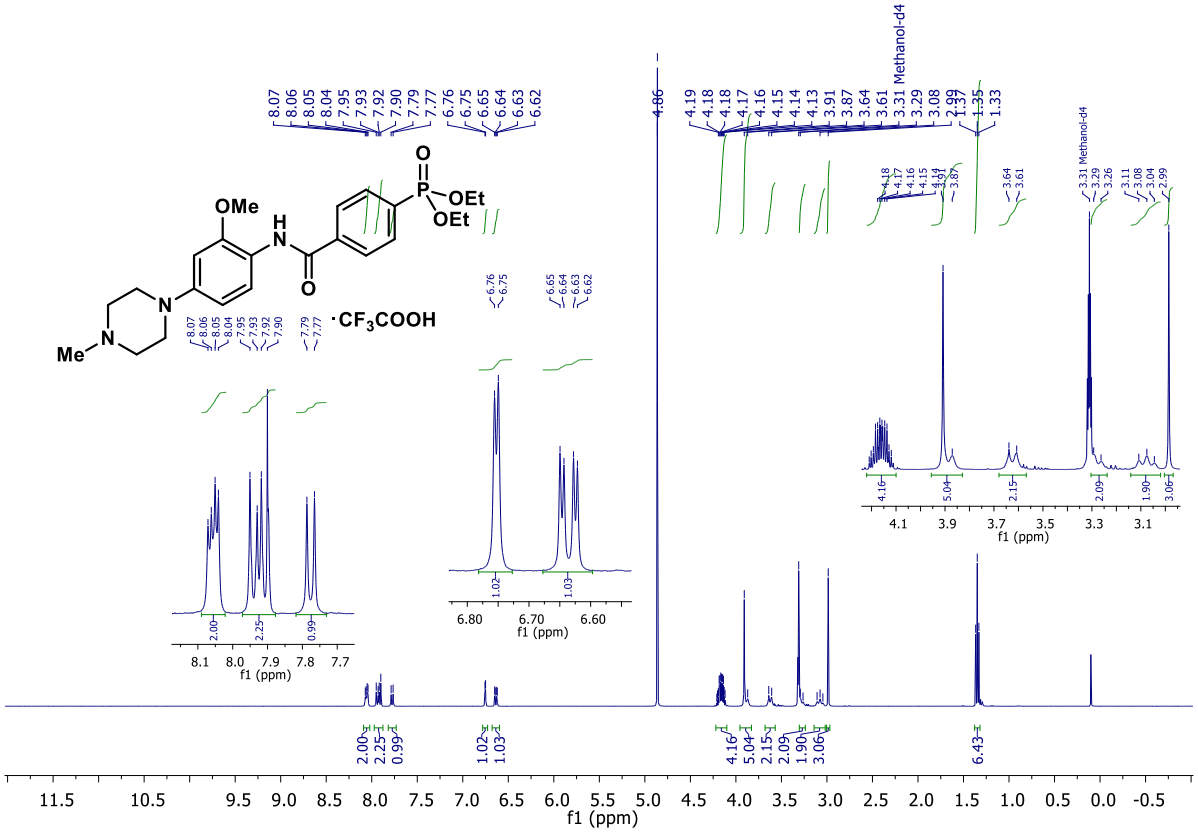


^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$) spectrum of **118**.

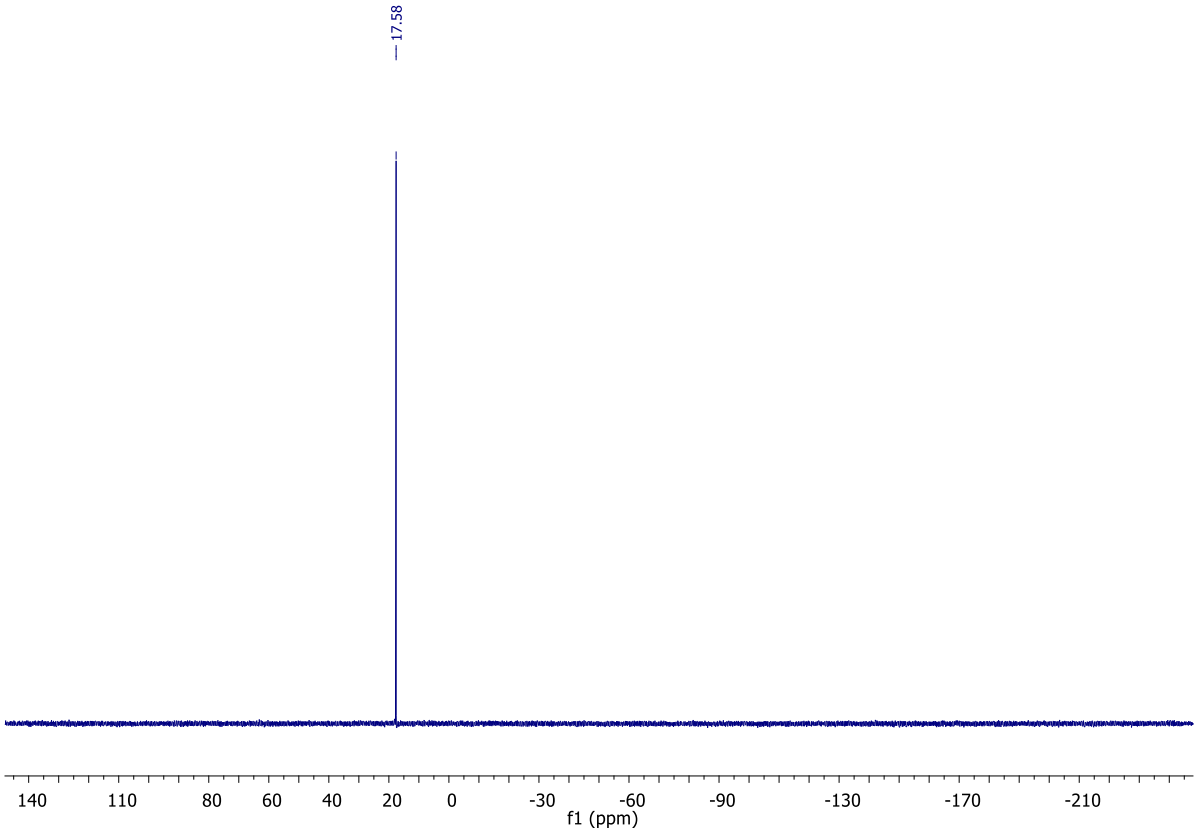


$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) spectrum of **118**.

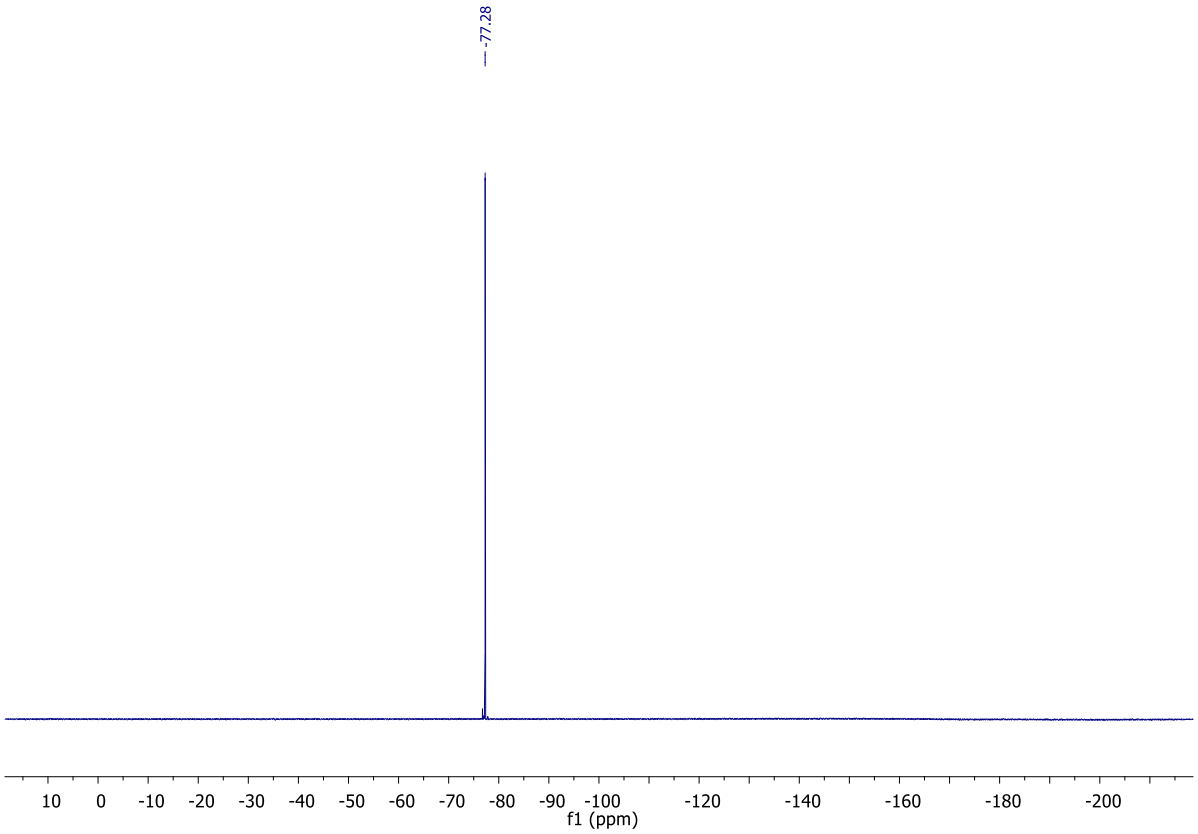
Compound 125



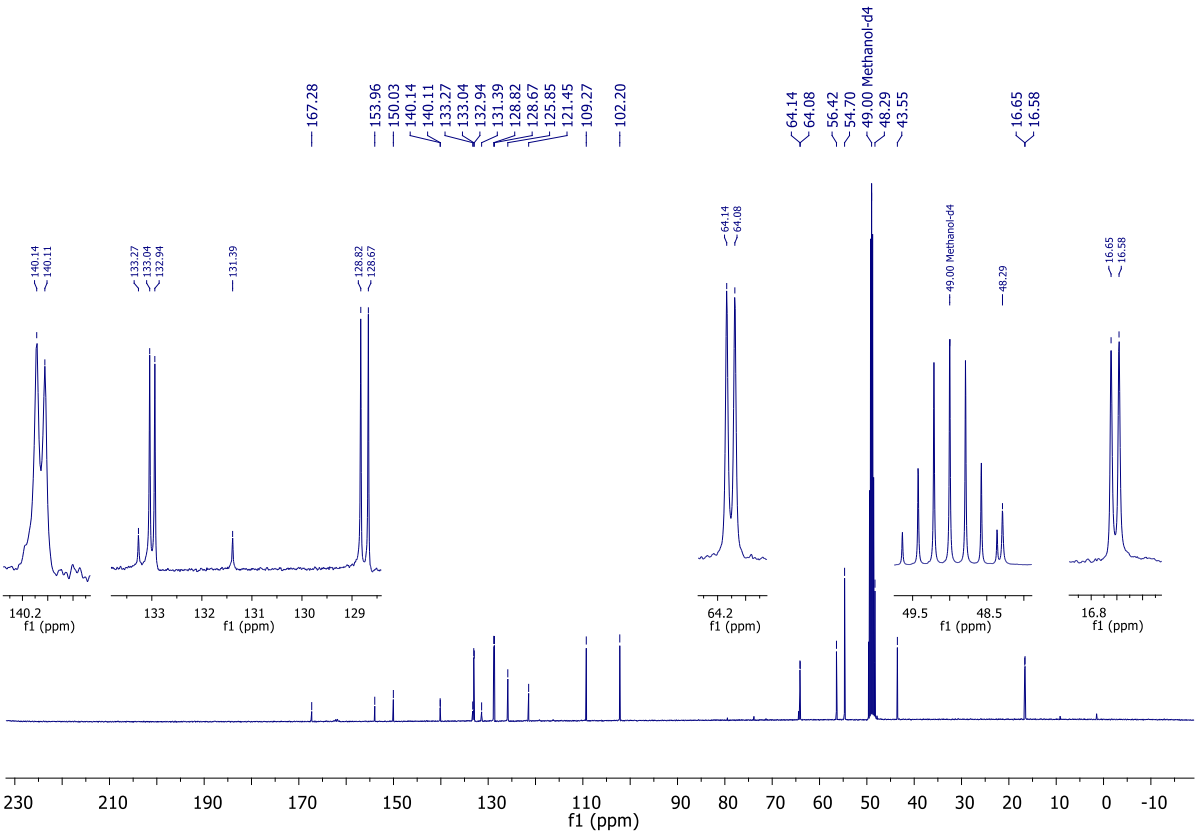
^{1}H NMR (400 MHz, CD_3OD) spectrum of **125·TFA**.



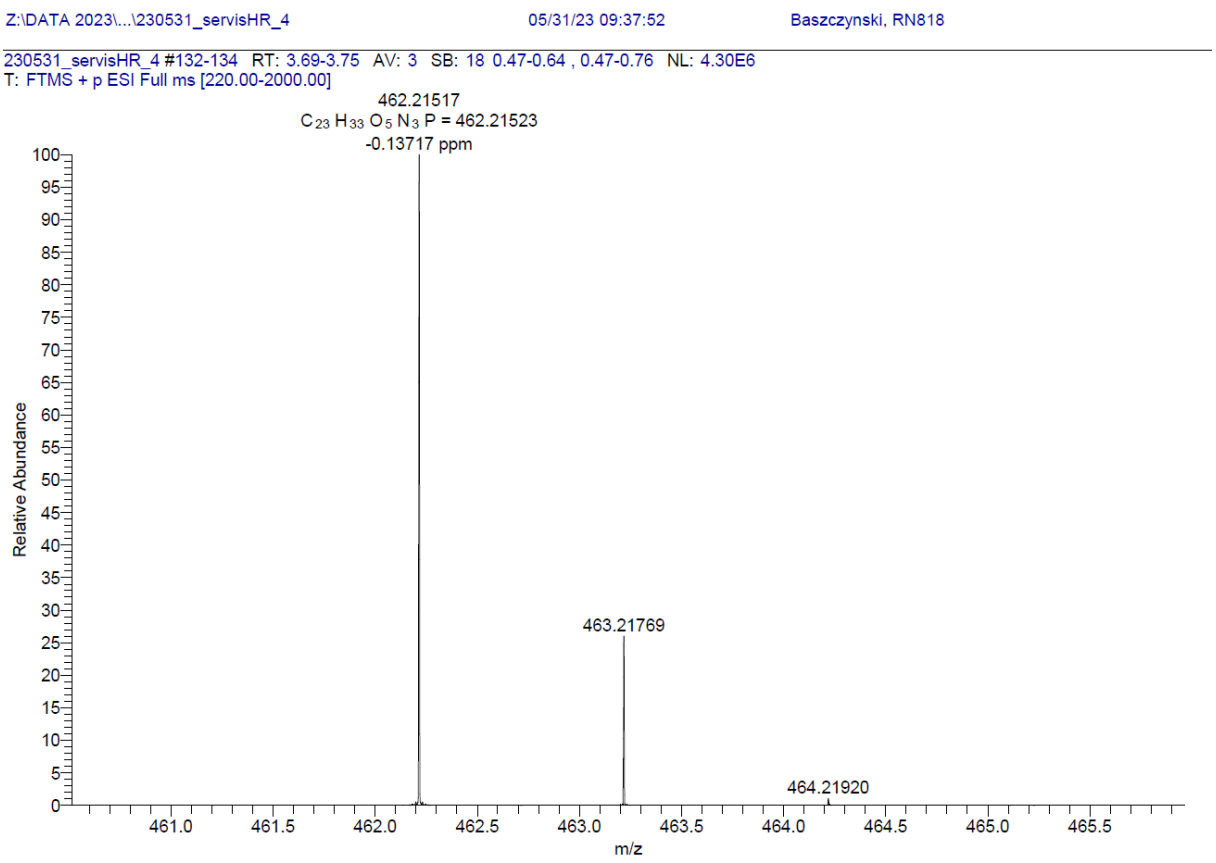
^{31}P{^{1}H} NMR (162 MHz, CD_3OD) spectrum of **125**.



^{19}F NMR (376 MHz, CD_3OD) spectrum of **125**.



^{13}C{^{1}H} NMR (100 MHz, CD_3OD) spectrum of **125**.



HRMS (ESI-TOF) spectrum of compound **125**.

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