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Electronic Supplementary Information

Poly(N-Acyliminophosphoranes): Main Chain Functionalized Poly(ylides) with pH-Dependent Degradation

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1. Experimental

1.1 Materials

Reagents were obtained from Sigma Aldrich/Merck (Zwijndrecht, The Netherlands), Fluorochem BV (Amsterdam, The Netherlands) and TCI Europe (Zwijndrecht, Belgium) and were used without purification unless otherwise stated. $FeCl_2$ and $Fe(OAc)_2$ were obtained from Fluorochem. Solvents were obtained from VWR, Fisher, Acros Organic and Sigma Aldrich/Merck. Solvents were dried by passing over activated alumina columns in a MBraun MB SPS800 under a nitrogen atmosphere and stored under argon. Reactions were carried under air unless stated otherwise. Typically, such air-sensitive reactions were carried out under atmosphere of nitrogen using Schlenk technique.

Reactions and fractions from flash column chromatography were monitored by thin layer chromatography using glass TLC plates (Merck, TLC Silica gel 60 F_{254}) and if necessary visualized by staining with $KMnO_4$ solution. Column chromatography was performed on VWR SiO_2 Type (40-63 mesh).

1.2 Instrumentation and Characterisation

Nuclear Magnetic resonance (NMR) characterization was carried out on a Bruker AVANCE HD nanobay console with a 9.4 T Ascend magnet (400 MHz) and a Bruker AVANCE III console with a 11.7 T UltraShield Plus magnet (500 MHz) equipped with a Bruker Prodigy cryoprobe, in chloroform ($CDCl_3$) or D_3COD-d_4. NMR spectra were recorded at 298 K unless otherwise specified. Chemical shifts are given in parts per million (ppm) with respect to tetramethylsilane (TMS, δ 0.00 ppm) as internal standard for ^1H NMR. ^{31}P-NMR spectra were recorded without internal standard. Coupling constants are reported as J values in Hz. Peak assignment is based on 2D COSY, $^1H–^{13}C$ HSQC, and $^1H–^{13}C$ HMBC spectra. The splitting patterns are indicated as follows: s, singlet; br. s, broad singlet; d, doublet; t, triplet; m, multiplet. Gel permeation chromatography (GPC) equipped with PL gel 5 µm mixed D column calibrated for polystyrene (580− 377400 g/mol) was carried out on a Shimadzu instrument with THF as eluent using differential refractive index.

2. Supporting Figures

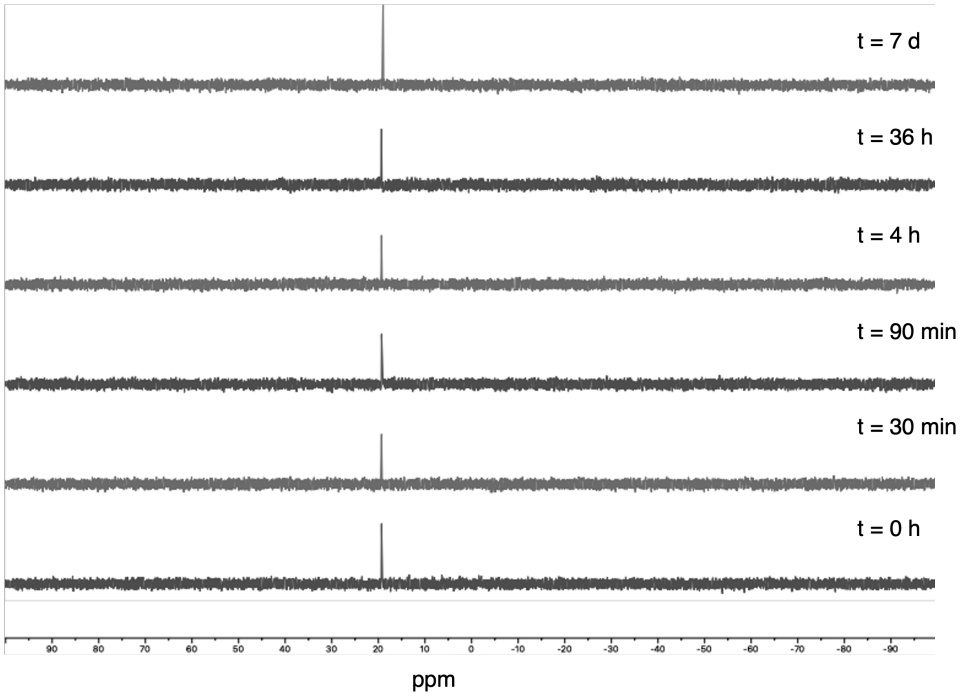

Figure S1. Stability of aryl-bearing phosphorous ylide **2** in buffer (pH 7.4) with DMSO-d_6 (2/1, v:v).

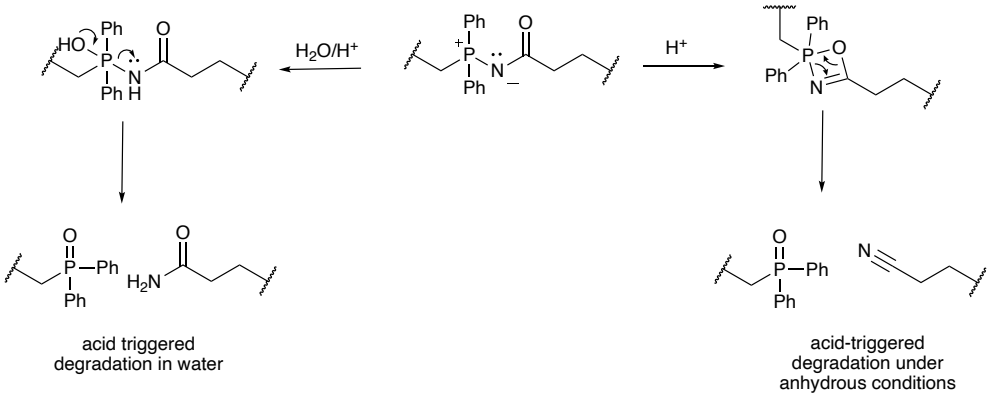

Figure S2. Postulated mechanisms for the acid-triggered degradation under aqueous and anhydrous conditions.

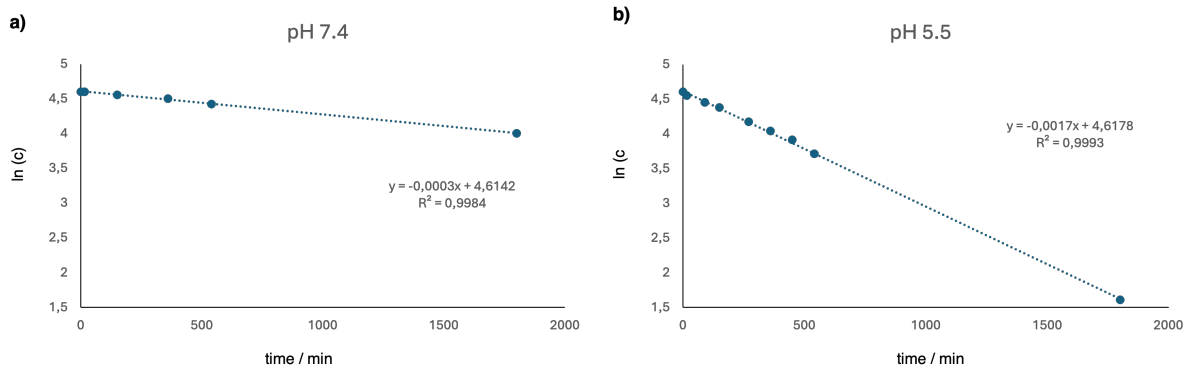

Figure S3. Differences in stability when comaparing polymers incubated **a)** pH 7.4 (PBS buffer, 50 mM) and **b)** pH 5.5 (NaOAc buffer, 50 mM) and. Conversion was determined by ^{31}P-NMR. Conversion was calculated by normalizing the integrals of polymer (P) and monomer (M) to their total sum (P + M = 1) and applying the equation: conversion = ($P_{initial}$ – P_t) / $P_{initial}$, where $P_{initial}$ is the normalized integral at time zero and P_t at the corresponding time point.

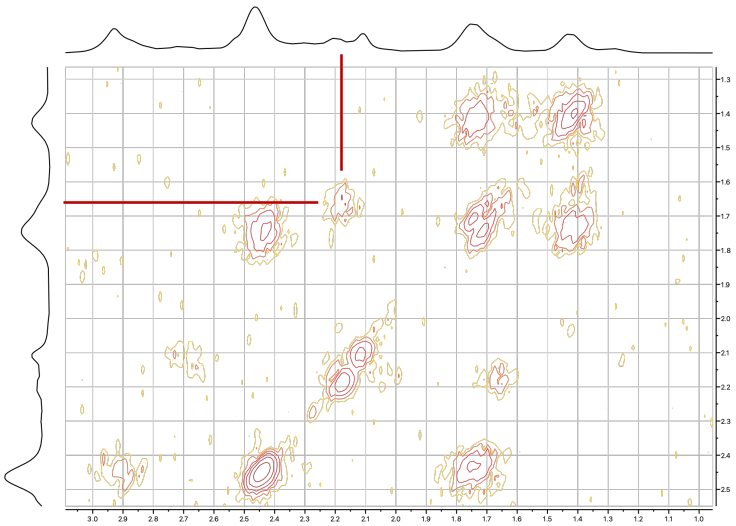

Figure S4. 2D ^{1}H-^{1}H COSY of poly(iminophosphorane) with indicated couplings of terminal protons adjacent to -COOH or -$CONH_2$ with beta-methylene group. A polymer sample with lower conversion was selected for the measurement to enhance the signal of the terminal residues relative to the backbone.

Molar fractions of possible end groups were determined with the help of ^{31}P-NMR and ^{1}H-NMR for quantification of phosphine oxides and primary amide/carboxylic acid, respectively (Figure S4). Degree of polymerisation and molecular weight was determined using Carothers equation expressed towards $DP = \frac{2}{f_a + f_b}$ with f_a and f_b being the mole fractions of the terminal groups.[1]

Table S1. Solubility of poly(imino phosphoranes) in varying solvents (green = good, orange = medium, red = bad).

	Water	Methanol	DMSO	Chloroform
Polymer				

Computational Details

To characterize and compare the structure, H-bond network, and dipole moment of the iminophosphorane and sulfur ylide molecules in an aqueous environment, we prepared a simulation box of 15.6 Å x 15 Å x 15 Å containing one solute molecule (either the iminophosphorane or the sulfur ylide) and 121 water molecules. This simulation box was used to run Born-Oppenheimer Molecular Dynamics (DFT-MD) simulations. All the DFT-MD simulations have been run with the Cp2k code.[2] Periodic boundary conditions have been applied in all three dimensions. We used the BLYP functional augmented with the D2 dispersion corrections.[3,4] A hybrid Gaussian and plane waves (GPW) basis set, consisting of a 350 Ry energy cutoff plane-wave basis set, coupled with the DZVP-MOLOPT-SR-GTH basis set, was selected.[5] Pseudopotentials of the GTH type (Goedecker-Teter-Hutter) were also adopted.[6]

At each time step, the electronic wave function has been converged. The forces acting on the classical nuclei have been computed. The classical Newton equations of motion for the nuclei were integrated through the velocity Verlet algorithm with a time step of 0.5 fs.

The simulations were run in the NVT ensemble, i.e., constant temperature and volume ensemble. For all the simulations, the system's average temperature was set to 300 K using a CSVR thermostat[7] with a time damping constant of 300 fs. The total simulation time was 55 ps, divided in 5 ps of equilibration and by 50 ps of production.

Table S1 reports the average value obtained for the C=O bond distance, the (O=)C to X distance (where X=S,P), and the number of hydrogen bonds of the C=O group. We adopted the following definition of the (C=O) to HOH hydrogen bond: C=O···O ≤ 3.2 Å and the (C=O) to H-OH angle in the range of [140−220]°. The value of 3.2 Å has been selected by looking at the first minimum of the radial pair distribution function. Interestingly, the C=O of the iminophosphorane forms on average a lower number of H-bonds compared to the sulfur ylide C=O (0.95 compared to 1.45). Finally, we extracted 11 snapshots from each of the MD simulations, and for each snapshot, we computed the set of maximally localized Wannier functions[8] and corresponding Wannier centers. Using these letters, we estimated the dipole moment of the iminophosphorane and Sulfur ylide molecules in water. Interestingly, the dipoles of the two molecules are quite similar despite the different H-Bond networks.

In addition to the water calculation, the iminophosphorane's gas phase dipole moment has been estimated using a similar approach, employing a 25 ps BLYP DFT-MD trajectory (5ps of equilibration + 20 ps of production). This simulation was conducted with the iminophosphorane molecule placed in a box measuring 20.0 Å x 20.0 Å x 20.0 Å, following the same computational setup used for the other simulations. As previously seen in the case of the Sulfur Ylide XX (whose value we report in Table S1 for comparison), the iminophosphorane molecule was shown to be quite polarizable with an environmentally sensitive dipole. The dipole passes to be 8.58±0.89 Debye in water to only 5.06±0.11 Debye in the gas phase.

Table S2. Obtained structural information from MD simulations.

Parameter	Iminophosphorane (water)	Sulfur Ylide (water)	Iminophosphorane (gas)	Sulfur Ylide (gas)
Dipole (debye)	8.58±0.89	8.70±1.02	5.06±0.11	5.5±0.5
Number (C=)O H-bonds	0.95	1.45	n.a.	n.a.
C=O(pm)	127.8±2.3	128.4±2.6	125.3±0.7	125.±1.1
(O=)C-X(pm)	262.3±5.9	270.9±6.3	n.a.	n.a.

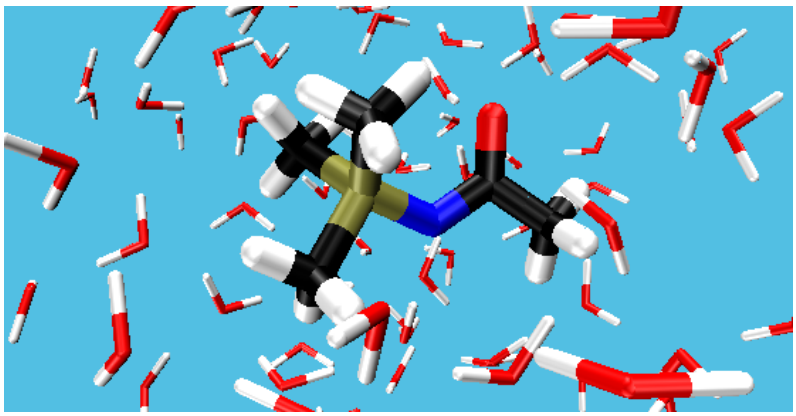

Figure S5. Screenshot of simulated N-acyliminophosphorane in water.

3. Synthesis

N-(pivaloyloxy)-vinyl benzamide S1

Vinyl benzoic acid (1.0 equiv, 500 mg, 3.3 mmol) was dissolved in THF (0.5 M) at room temperature. After addition of CDI (1.2 equiv, 655 mg, 4.0 mmol), the solution was left to stir for 2 hours. Hydroxylamine hydrochloride (1.5 equiv, 350 mg, 5.0 mmol) was added as a solid and the reaction was left to stir overnight at room temperature. Pivalic acid anhydride (2.0 equiv, 1.36 mL, 6.6 mmol) was added to the suspension and stirred for additional six hours. The solution was diluted with CH_2Cl_2 and washed with 10 w% citric acid solution (2x), water (2x) and brine. After drying over magnesium sulphate and concentration in vacuum, the crude passed over a silica plug (EtOAc: heptane, v/v, 1/2). **S1** was obtained in moderate yields (450 mg, 55 %). Please note that the product was isolated as a mixture (1:2) with *N*-(pivaloyloxy)-pivalic acid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.75 (1H, bs, NH), 7.76 (2H, d, *J* 8.44 Hz, Ar-H), 7.43 (2H, d, *J* 8.35 Hz, Ar-H), 6.71 (1H, dd, *J* 10.91 Hz, 17.6 Hz, CH), 5.81 (1H, dd, *J* 0.66 Hz, 17.61 Hz, CH), 5.35 (1H, dd, *J* 0.80 Hz, 11.62 Hz, CH), 1.33 (9H, s, $C(CH_3)_3$.^{13}C NMR (101 MHz, $CDCl_3$) δ 177.0, 166.45, 141.8, 135.9, 123.0, 127.9, 126.5, 116.6, 38.5, 27.12.

MS (ESI): calculated for $[C_{14}H_{17}NO_3H]^+$: m/z 248.29 , found : m/z 248.20.

N-(pivaloyloxy)-β-alanine S2

N-Boc β-alanine (1.0 equiv, 1.00 g, 5.3 mmol) was dissolved in THF (0.5 M) at room temperature. After addition of CDI (1.2 equiv, 1.02 g, 6.3 mmol), the solution was left to stir for 2 hours. Hydroxylamine hydrochloride (1.5 equiv, 0.55 g, 7.9 mmol) was added as a solid and the reaction was left to stir overnight at room temperature. Pivalic acid anhydride (2.0 equiv, 2.15 mL, 10.5 mmol) was added to the suspension and stirred for additional six hours. The solution was diluted in CH_2Cl_2 and washed with 10 w% citric acid solution (2x), water (2x) and brine. After drying over magnesium sulphate and concentration in vacuum, the crude was purified on silica chromatography (EtOAc: heptane, v/v, 1/1). Product **S2** was obtained in good yields (1.31 g, 85 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.03 (1H, br s, N-H), 5.35 (1H, br s, N-H), 3.42 (2H, t, *J* 6.4 Hz, CH_2), 2.46 (2H, t, *J* 6.4 Hz, CH_2), 1.40 (9H, s, $C(CH_3)_3$), 1.28 (9H, s, $C(CH_3)_3$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.4, 169.7, 156.4, 79.6, 38.3, 36.4, 33.2, 28.4, 27.1.

HRMS (ESI): calculated for $[C_{13}H_{24}N_2O_5H]^+$: m/z 289.1758, found : m/z 289.1747.

***N*-(tributyl-phosphaneylidene)-vinyl benzoic acid 1**

N-Acyloxyamide **S1** (1 equiv, 150 mg, 0.61 mmol) was dissolved in acetonitrile (0.4 M) at room temperature. Tributylphoshine (1.1 equiv, 0.165 mL, 0.66 mmol) and subsequently $FeCl_2$ (20 mol%) were added and the solution stirred for 6 h. After high conversion was indicated on TLC, the solution was diluted with CH_2Cl_2 and washed with sat. $NaHCO_3$, water and brine. After drying over $MgSO_4$, and concentration in vacuum, the crude was purified on silica chromatography (EtOAc: heptane, v/v, 2/3). The product was obtained as white solid in moderate yields (105 mg, 55 %).

^{1}H NMR (400 MHz, CD_3OD) δ 7.87 (2H, d, *J* 8.35 Hz, Ar-H), 7.45 (2H, d, *J* 8.51 Hz, Ar-H), 6.79 (1H, dd, *J* 4.8 Hz, 17.5 Hz, CH), 5.86 (1H, dd, *J* 0.66 Hz, 17.61 Hz, CH), 5.31 (1H, dd, *J* 0.80 Hz, 11.62 Hz, CH), 2.17 – 2.11 (6H, m, P-CH_2-), 1.64 – 1.44 (12H, m, 2xCH_2), 0.96 (9H, t, *J* 7.15 Hz, -CH_3).^{13}C NMR (101 MHz, CD_3OD) δ 178.0 (identified in HMBC), 156.2, 140.1, 136.3, 128.9, 128.8 114.0, 23.8, 23.6, 23.3, 22.7, 12.5. ^{31}P NMR (161.9 MHz, CD_3OD): δ 42.3.

MS (ESI): calculated for $[C_{21}H_{34}NOPH]^+$: m/z 318.48 , found : m/z 318.25.

***N*-(triphenyl-phosphaneylidene)-β-alanine 2**

N-Acyloxyamide **S2** (1 equiv, 250 mg, 0.86 mmol) was dissolved in acetonitrile (0.4 M) at room temperature. Triphenylphosphine (1.1 equiv, 260 mg, 0.95 mmol) and subsequently $FeCl_2$ were added and the solution stirred for 6 h. After high conversion was indicated on TLC, the solution was diluted with CH_2Cl_2 and washed with sat. $NaHCO_3$, water and brine. After drying over $MgSO_4$, and concentration in vacuum, the crude was purified on silica chromatography (EtOAc: heptane, v/v, 2/3). The product was obtained as white solid in poor yields (95 mg, 25 %).

The poor yield resulted from Boc-removal upon exposure to HCl released during the reaction.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 – 7.69 (6H, m, Ar-H), 7.55 – 7.47 (9H, m, Ar-H), 5.69 (1H, br s, N-H), 3.46 – 3.42 (2H, m, CH_2), 2.64 (2H, t, *J* 6.35 Hz, CH_2), 1.42 (9H, s, $C(CH_3)_3$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 183.6, 156.2, 133.2, 132.4, 128.9, 127.8, 78.6, 40.1, 37.9, 28.6.

HRMS (ESI): calculated for $[C_{26}H_{29}N_2O_3PH]^+$: m/z 449.1989 , found : m/z 449.1996.

Difunctional *N*-(pivaloyloxy) pimelic amide

Pimelic acid (1.0 equiv, 1.00 g, 6.2 mmol) was dissolved in THF (0.25 M) at room temperature. After addition of CDI (3.0 equiv, 3.04 g, 18.8 mmol), the solution was left to stir for 2 hours. Hydroxylamine hydrochloride (4.0 equiv, 1.7 g, 24.8 mmol) was added as a solid and the reaction was left to stir overnight at room temperature. Pivalic acid anhydride (5.0 equiv, 7.73 mL, 30.1 mmol) was added to the suspension and stirred for additional six hours. The solution was diluted in CH_2Cl_2 and washed with 10 w% citric acid solution (2x), water (2x) and brine. After drying over magnesium sulphate and concentration in vacuum, the crude was purified on silica chromatography (EtOAc: heptane, v/v, 2/3). The product was obtained in good yields as waxy white solid (1.77 g, 80 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.21 (2H, br s, NH), 2.26 (4H, t, *J* 6.5 Hz, 2xCH_2), 1.69 (4H, m, 2xCH_2), 1.46 – 1.40 (4H, m, 2xCH_2), 1.30 (18H, s, 2xC(CH_3)$_3$). ^{13}C NMR (101 MHz, $CDCl_3$): δ 177.2, 171.9, 38.8, 32.9, 28.6, 27.5, 24.7.

HRMS (ESI): calculated for $[C_{17}H_{30}N_2O_6H]^+$: m/z 359.2177, found : m/z 359.2184.

General protocol for polymerisation of poly(imino phosphoranes)

N-(Pivaloyloxy) pimelic amide **M1** was dissolved in anhydrous solvent (1.0 M) and added to a suspension of difunctional phosphine **M2** in anhydrous solvent (1.0 M). The solution was purged with Argon for 5 min and the catalyst was added as a solid. The solution was stirred under exclusion of air and the suspension typically fully dissolved after 10 min. After 24 hours, the solution was given into a buffered EDTA solution (pH 7.4, 50 mM) and extracted with DCM, washed with saturated $NaHCO_3$, water and brine. After drying over sodium sulfate, solvent was removed under reduced pressure and the product was obtained as a pale-yellow solid. For entry 5, 6 and 8, the polymer was obtained in good yields (> 75%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89 – 7.12 (20H, Ar-H), 3.02 – 2.62 (4H, 2xCH_2), 2.54 – 2.28 (4H, 2xCH_2), 1.88 – 1.61 (4H, 2xCH_2), 1.53 – 1.21 (2H, CH_2). ^{31}P NMR (161.9 MHz, $CDCl_3$): δ 33.2 – 32.4 (P(V)=O), 23.4 – 22.1 (P(V)=N-R), - 12.6 (P(III)).

Please note that in case of entry 6, ferrocen (20 mol%) as an additive to prevent oxidation was added together with the catalysts to the raection mixture.

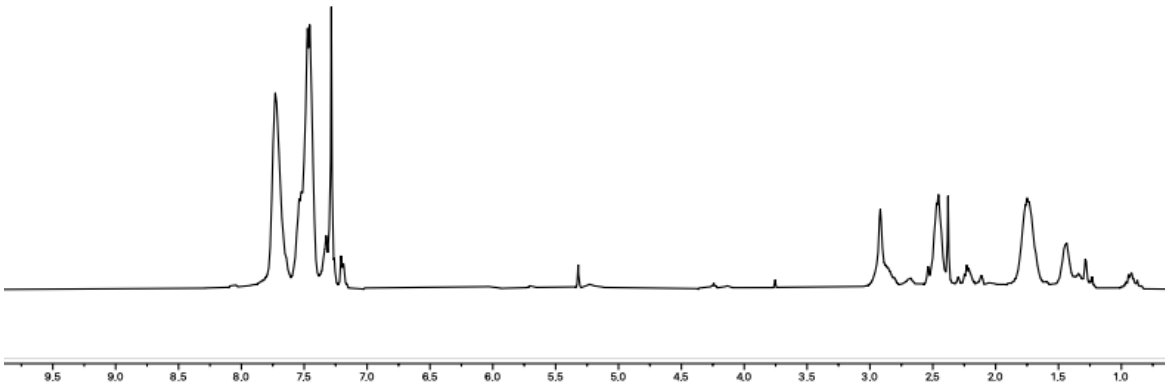

Figure S6. Characteristic ^{1}H-NMR of P(ImPhos).

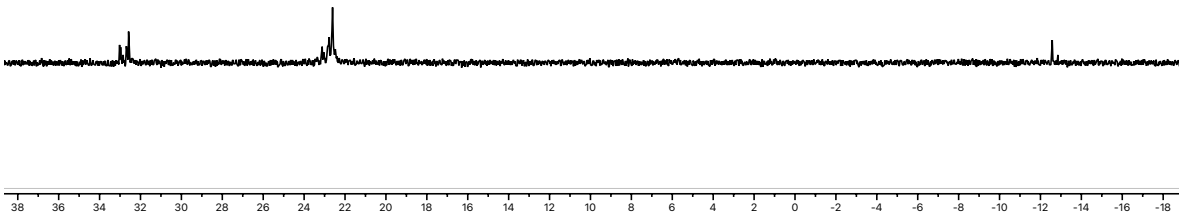

Figure S7. Characteristic ^{31}P-NMR of P(ImPhos).

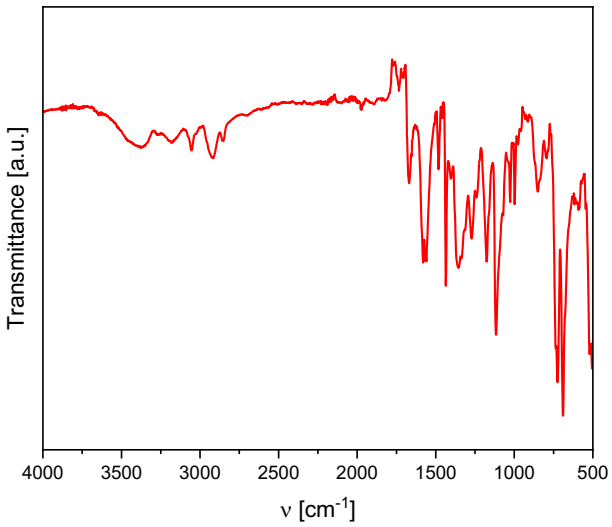

Figure S8. Representative IR spectra of P(ImPhos) with P=N vibration visible around 1350 cm^{-1}.

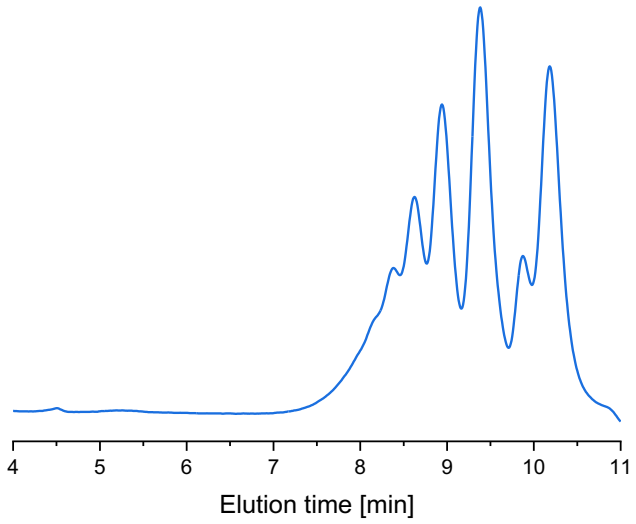

Figure S9. GPC elugram of P(ImPhos) from entry with most species being oligomers or cyclised products.

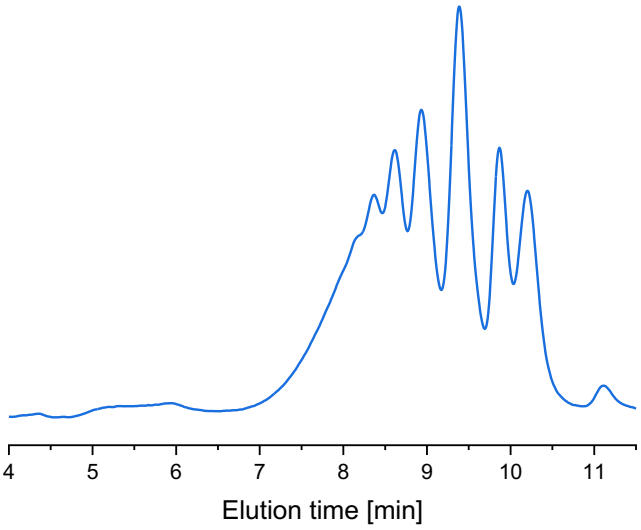

Figure S10. GPC elugram of P(ImPhos) from entry 5.

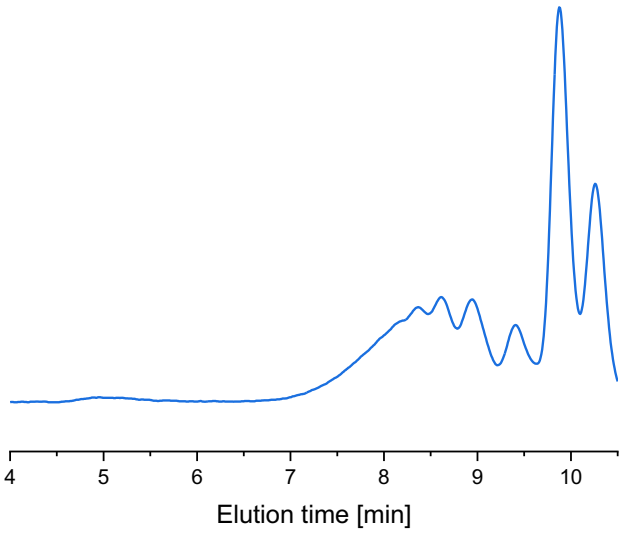

Figure S11. The GPC elugram of P(ImPhos) from entry 8 shows only minor amounts of oligomers. The signal around 9.5 min is attributed to a cyclized product, a characteristic feature of step-growth polymerizations.

4. NMR Spectra

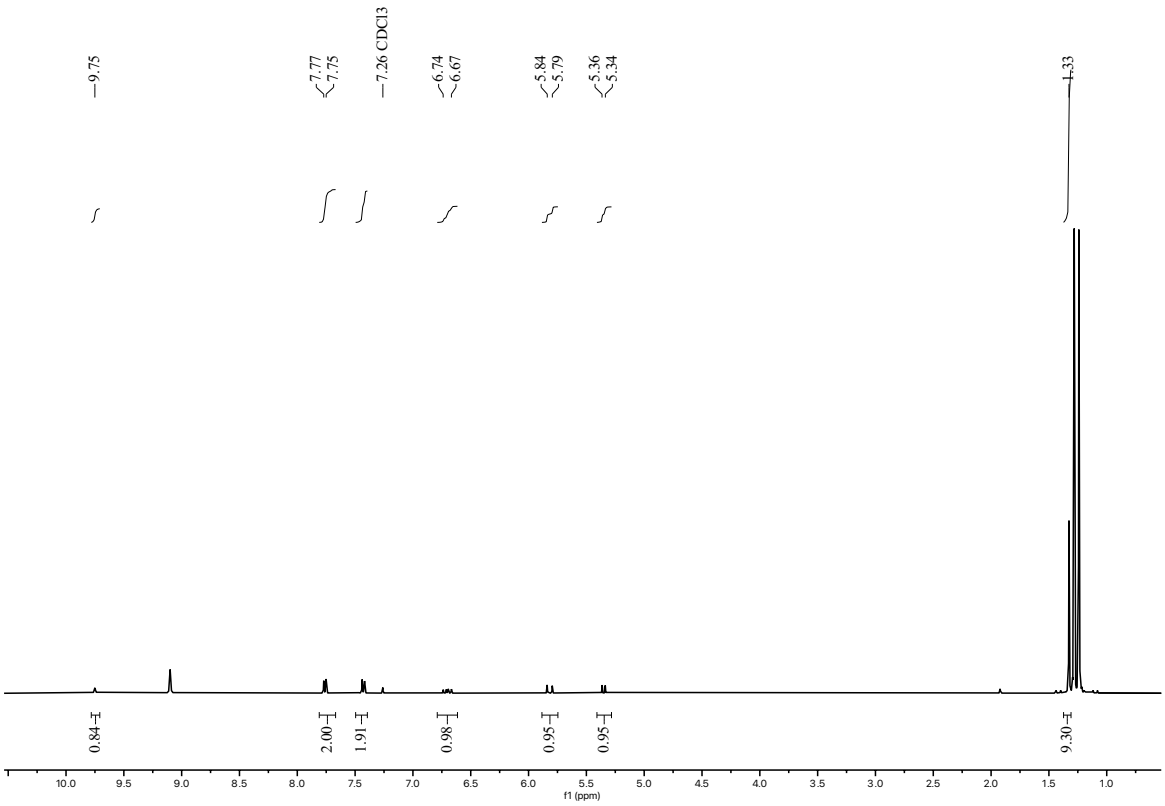

Figure S12. ^{1}H-NMR of ylide S**1.**

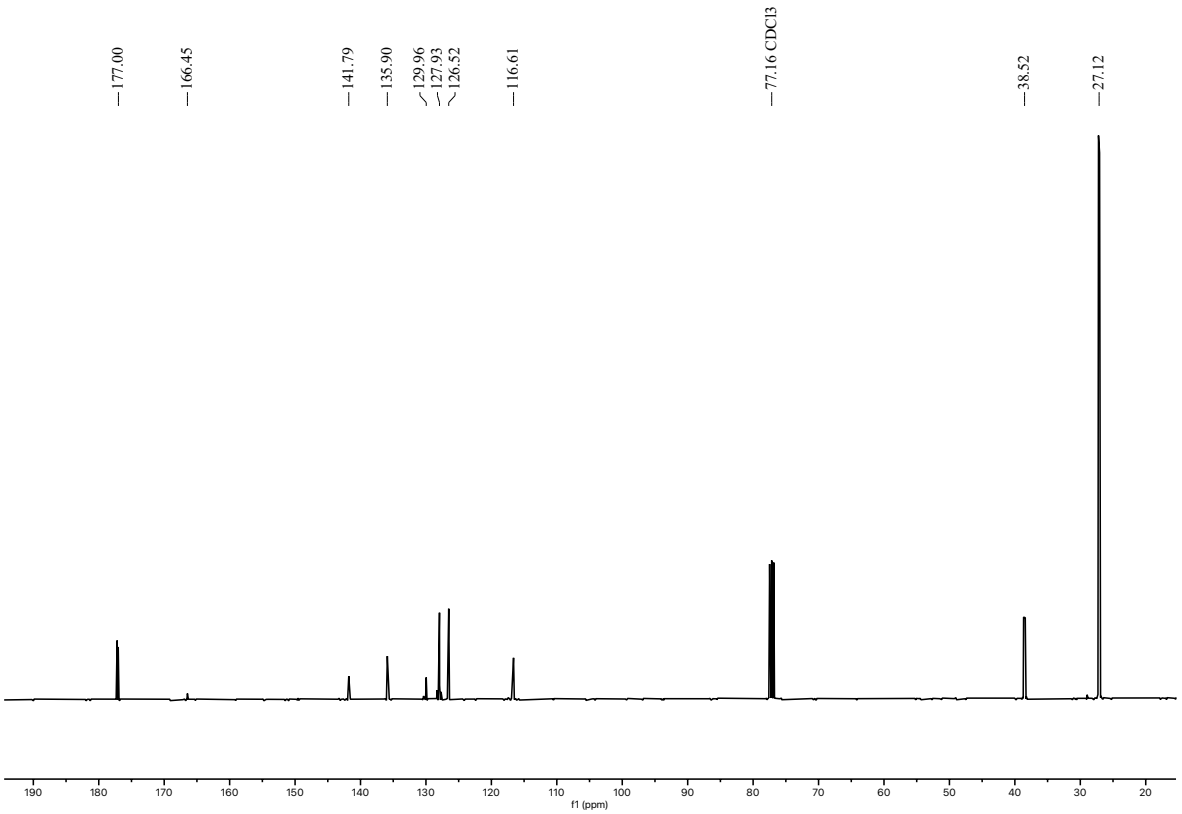

Figure S13. ^{13}C-NMR of ylide S**1.**

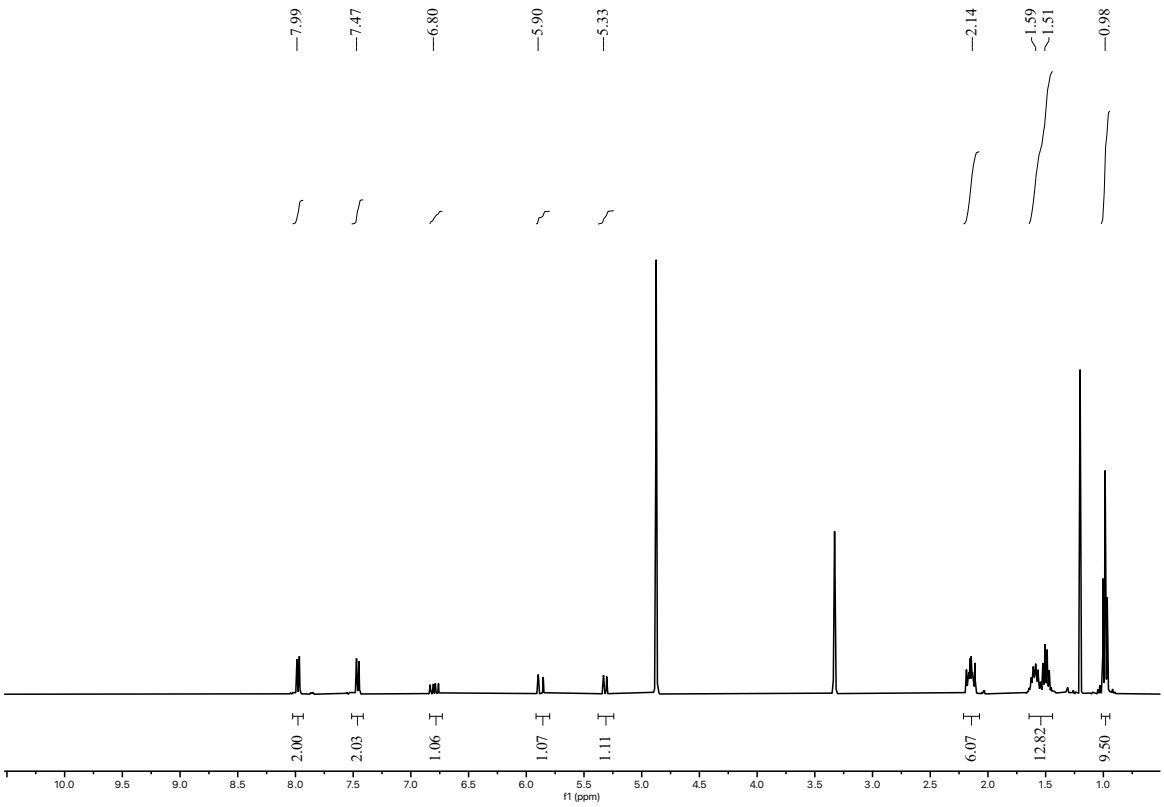

Figure S14. ^{1}H-NMR of ylide **1.**

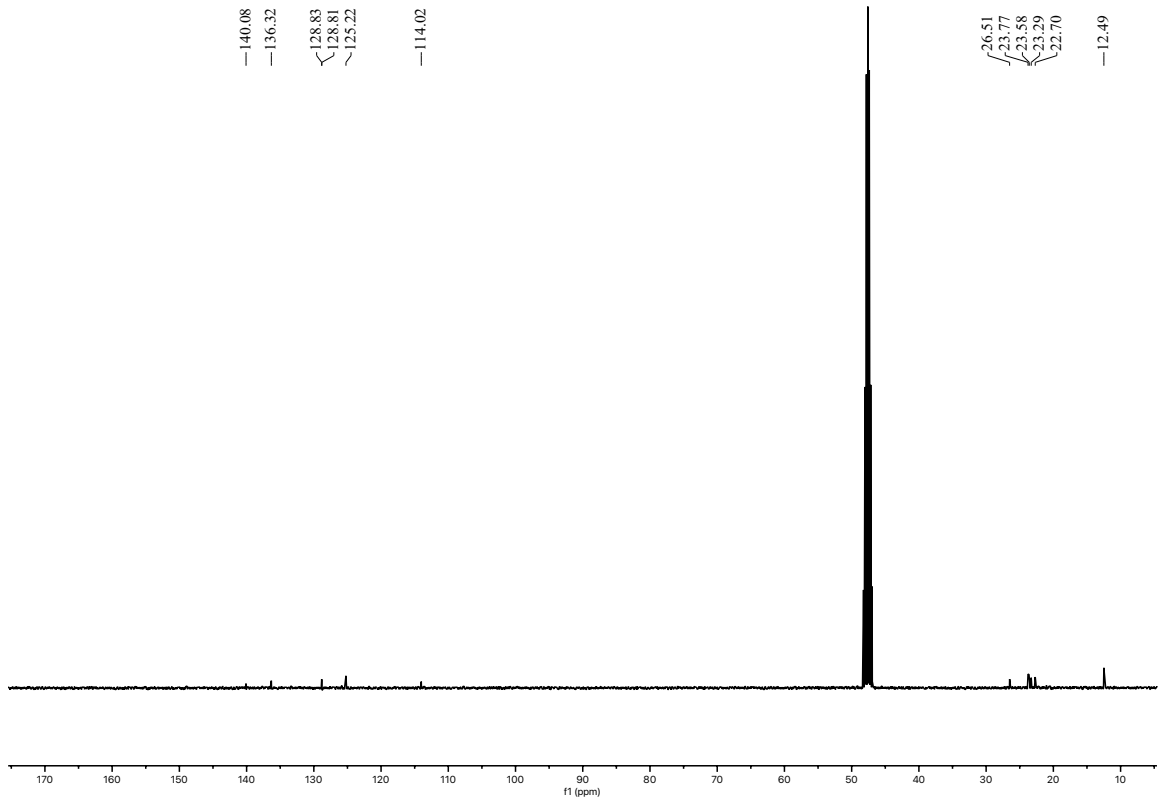

Figure S15. ^{13}C-NMR of ylide **1.** Not all quaternary carbons are visible.

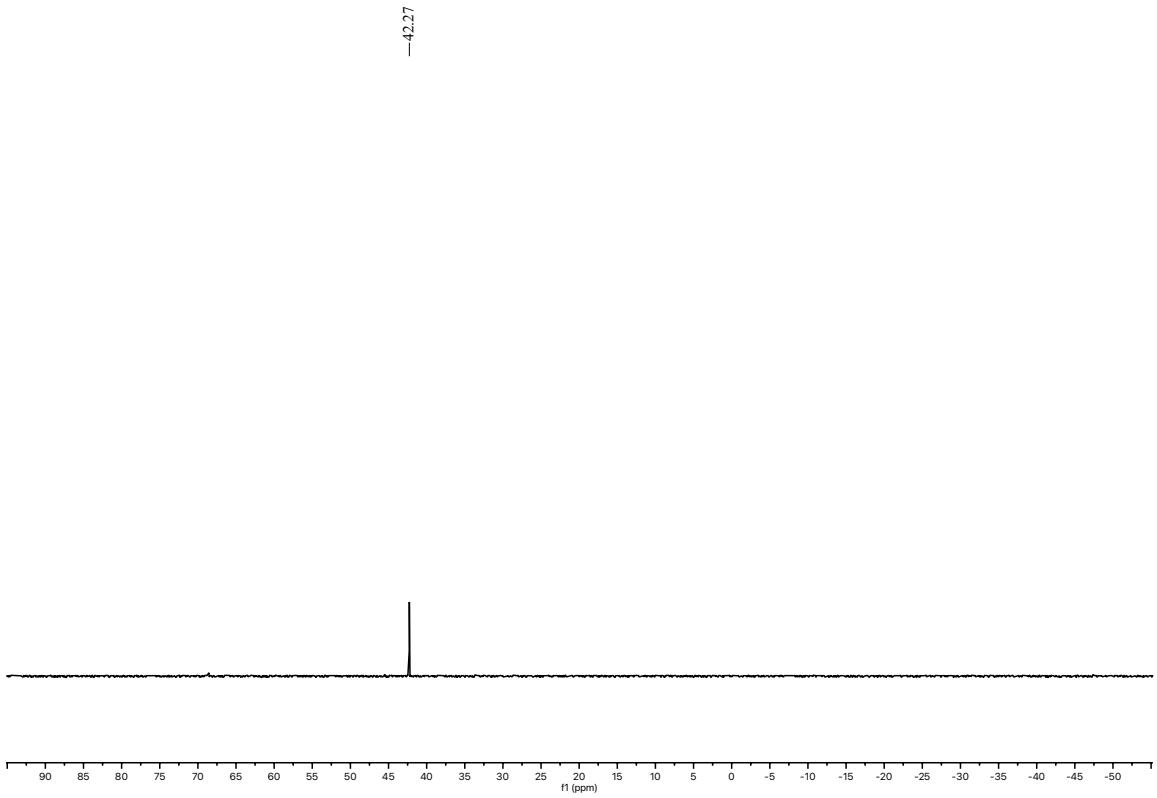

Figure S16. ^{31}P-NMR of ylide **1**.

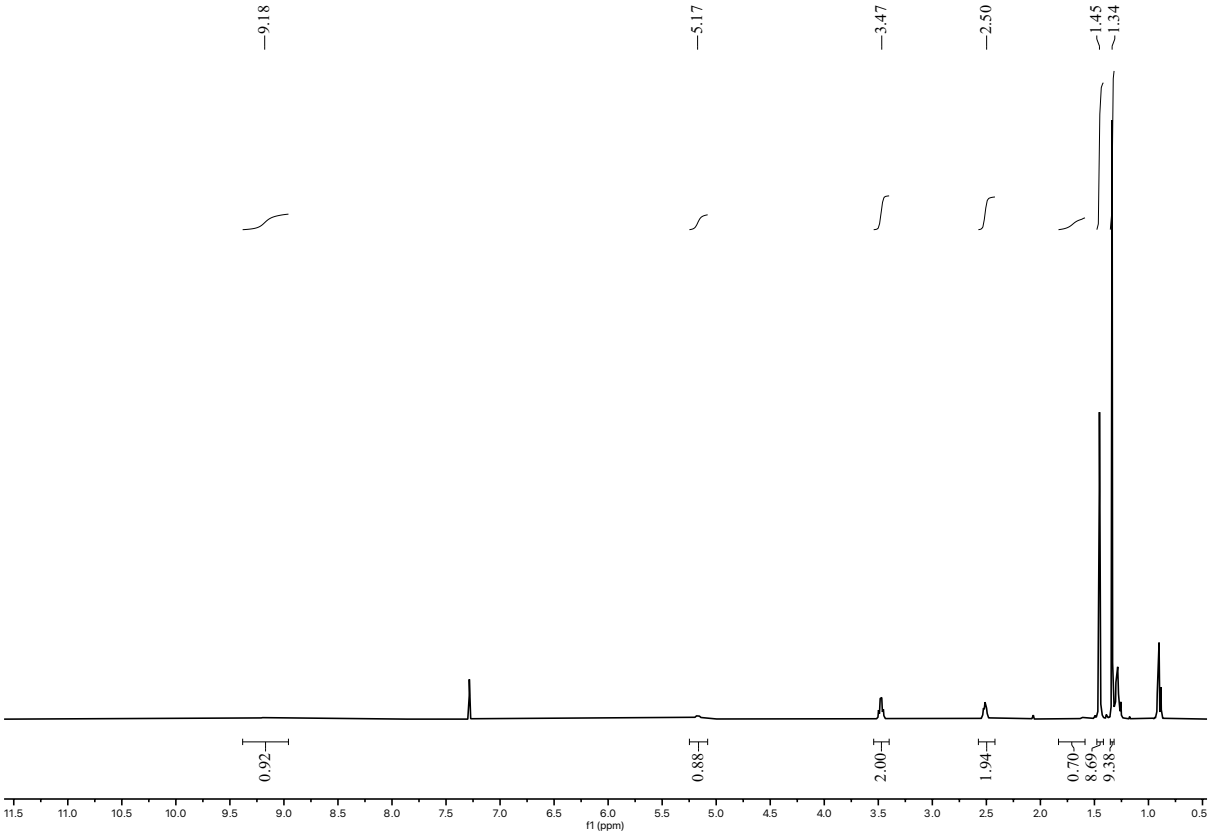

Figure S17. ^{1}H-NMR of **S2.**

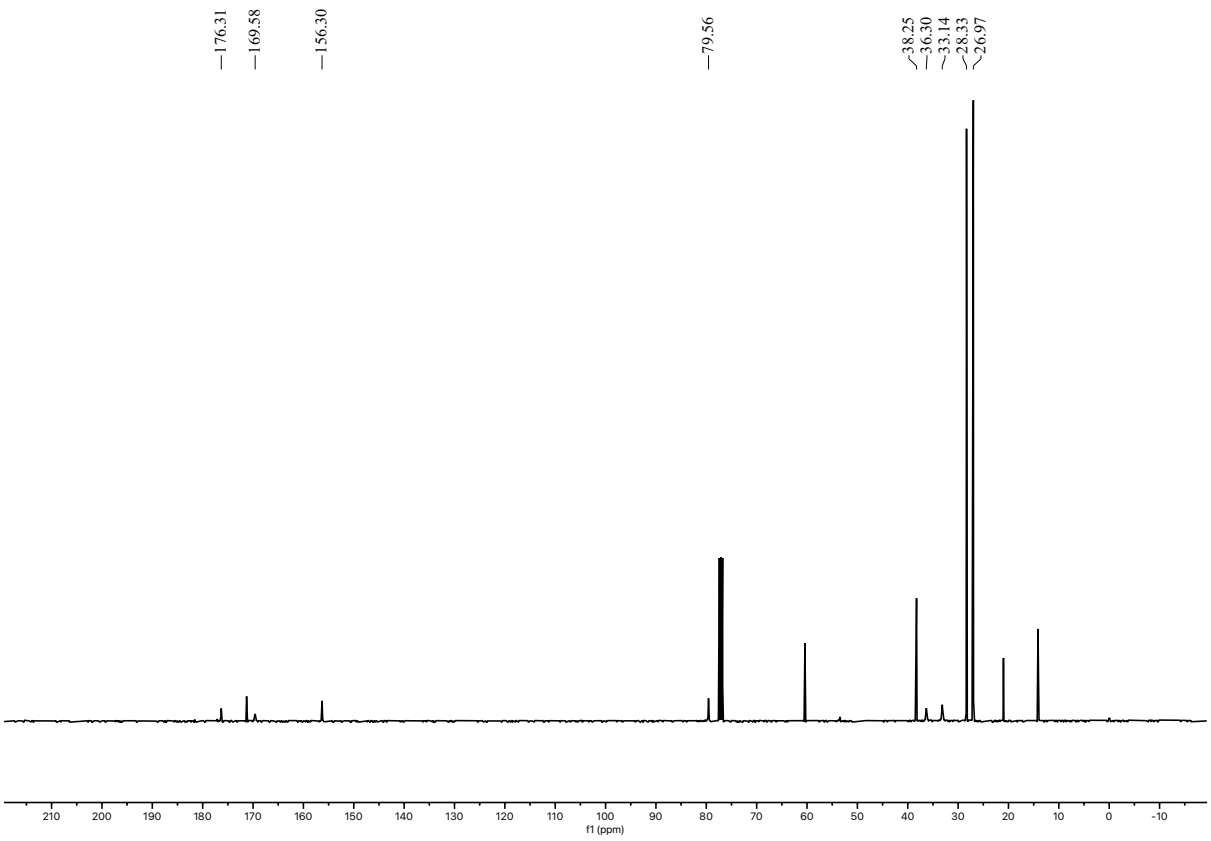

Figure S18. ^{13}C-NMR of **S2.**

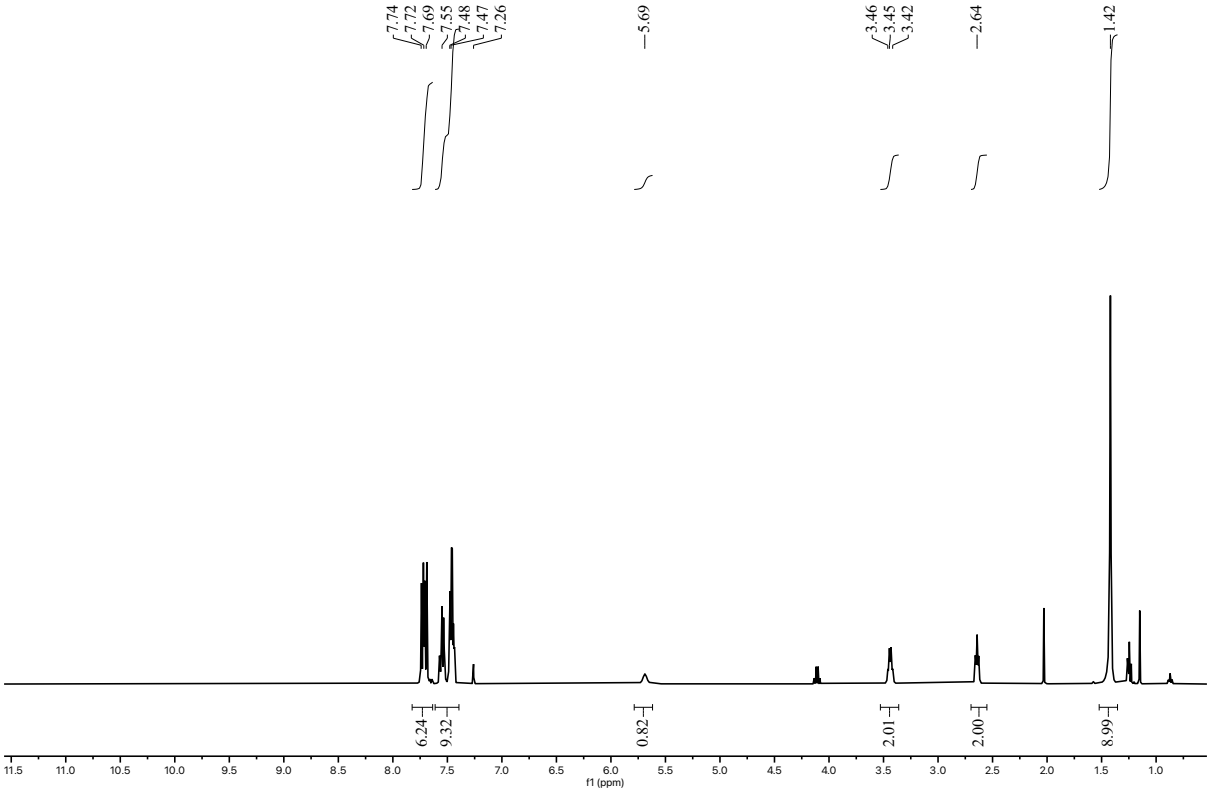

Figure S19. ^{1}H-NMR of ylide **2.**

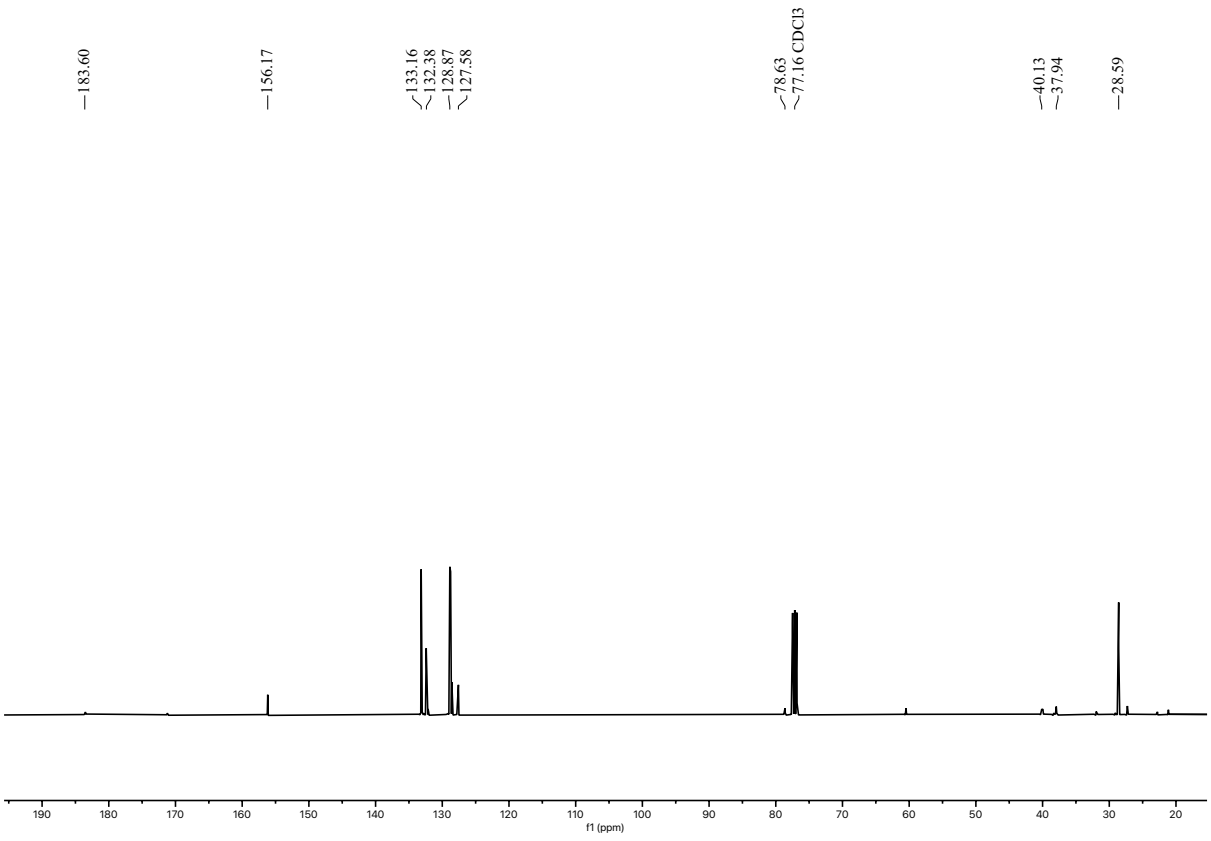

Figure S20. ^{13}C-NMR of ylide **2.**

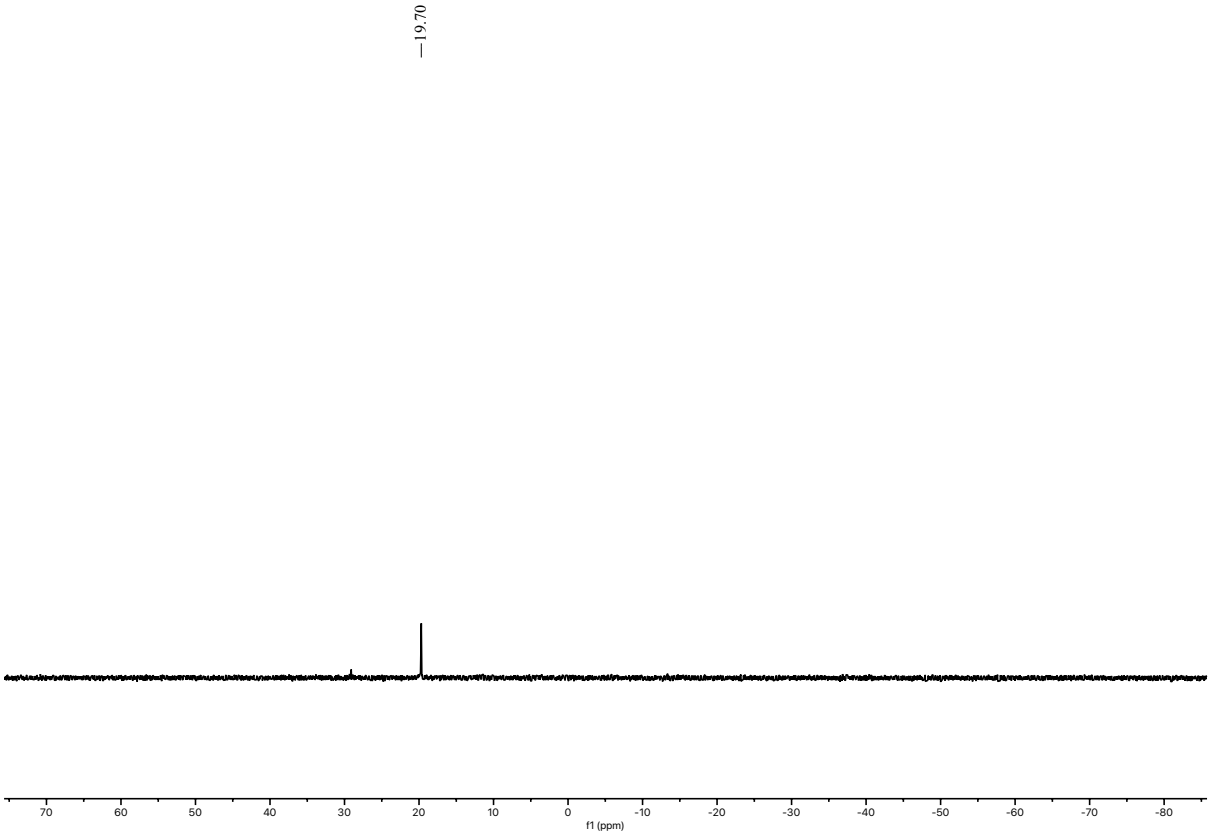

Figure S21. ^{31}P-NMR of ylide **2.**

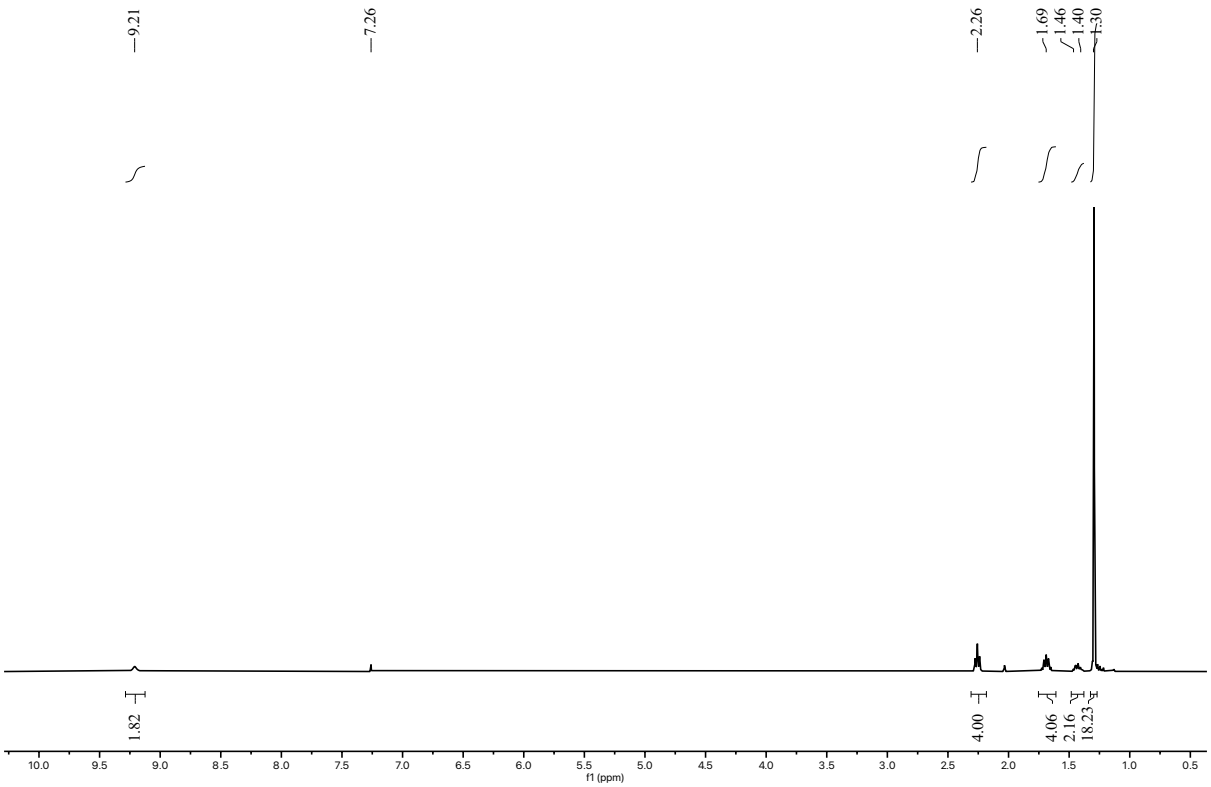

Figure S22. ^{1}H-NMR of **M1.**

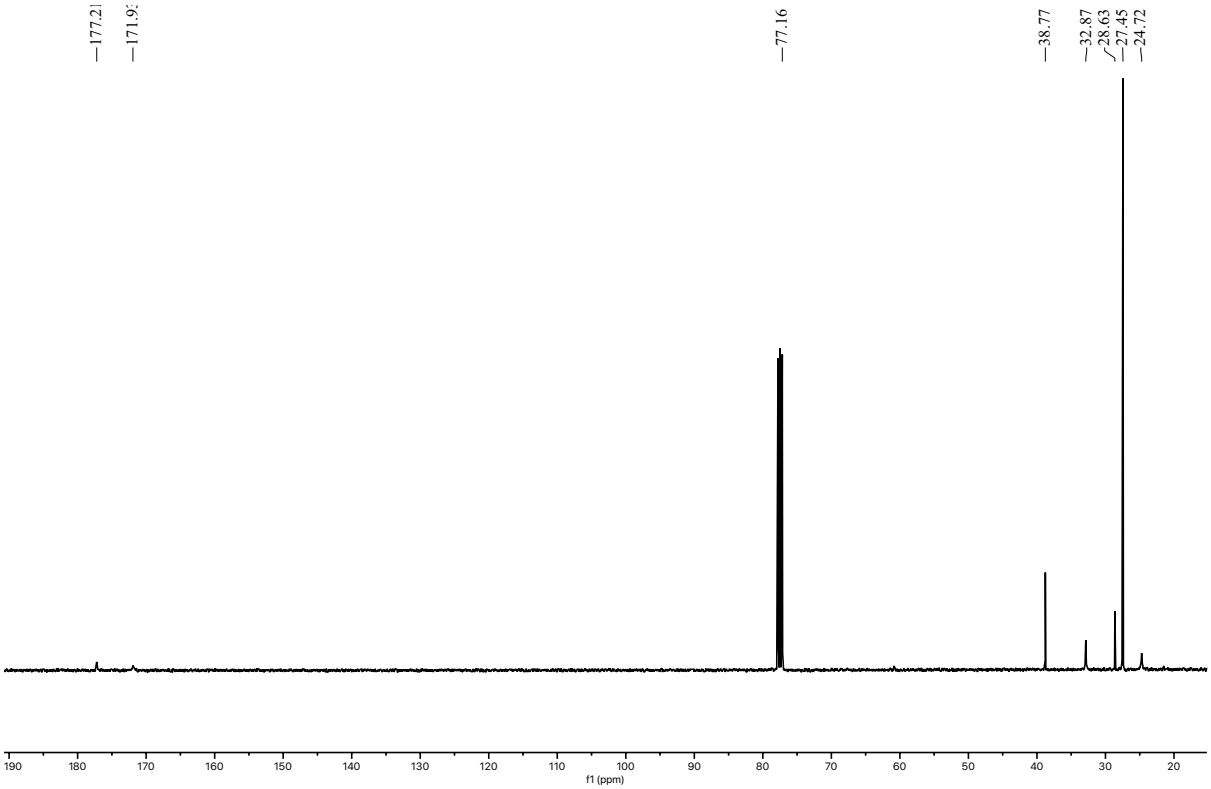

Figure S23. ^{31}C-NMR of **M1.**

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