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On the question of stepwise vs concerted cleavage of RNA models promoted by a synthetic dinuclear Zn(II) complex in methanol: implementation of a noncleavable phosphonate probe.

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Materials. Methanol (99.8% anhydrous), sodium methoxide (0.5M solution in methanol), phenylphosphonic dichloride (technical grade 90%), sodium hydride (60% dispersion in oil), 4-nitrophenol, 3-nitrophenol (99%), 4-chlorophenol (99%), phenol (99+%), 4-methoxyphenol (99%), 2,4-dimethylphenol (98%), triethylamine (99%), phenylphosphonic acid (98%), propylene oxide (ReagentPlus 99%) and $Zn(CF_3SO_3)_2$ were purchased from Aldrich and used without any further purification. Methylphosphonic dichloride was purchased from Fluka and used without further purification. 1,3-bis-N1-(1,5,9-triazacyclododecyl)propane was synthesized according to the published procedure.[1] The dinuclear (CH_3O^-): Zn_2([12]aneN3)$_2$ complex **4** was prepared as a 2.5 mM solution in methanol by sequential addition of aliquots of stock solutions of sodium methoxide, 1,3-bis-N1-(1,5,9-triazacyclododecyl)propane and $Zn(CF_3SO_3)_2$ such that the relative amounts were 1:1:2. It has been found that this order of addition is essential for the formation of the complex and even then complete formation of the complex was achieved only after 40 minutes (as monitored by the change in catalytic activity).[2]

Synthesis of 2-hydroxypropyl phenylphosphonate 6a. Phenylphosphonate **6a** was prepared by adapting a procedure reported for its phosphate analogue.[2] Phenyl phosphonic acid (820 mg, 5.2 mmol) was dissolved in 10mL H_2O. Sodium hydroxide (430 mg, 10.4 mmol) was dissolved in 10 mL H_2O. The phosphonic acid solution and the sodium hydroxide solution were mixed together followed by the addition of neat propylene oxide (8.7g, 10.5 mmol). After stirring the mixture at ambient temperature for 15 hours a ^{31}P NMR spectrum was obtained that indicated ~50% conversion. The reaction mixture was concentrated by removing the unreacted propylene oxide under reduced pressure. The residue was diluted to 500 mL with H_2O and acidified by the addition of perchloric acid (1.9 mL of 1.373 M solution, 2.6 mmol). The resulting solution was subjected to ion exchange column chromatography with DOWEX 1x8-200 (HCO_3- form), eluting over a linear gradient from 8 to 200 mM triethylammonium bicarbonate buffer solution. Fractions showing an absorbance at 263 nm were combined and concentrated under reduced pressure. The triethylammonium salt was first converted to the free acid and then the sodium salt by treatment with Amberlite IR-120H and subsequently Amberlite IR-120 (Na+) in a batch process. Removing the solvent of the resulting solution under reduced pressure gave **6a** (containing 4% of isomer **6b**) in an unoptimized yield of 4%.

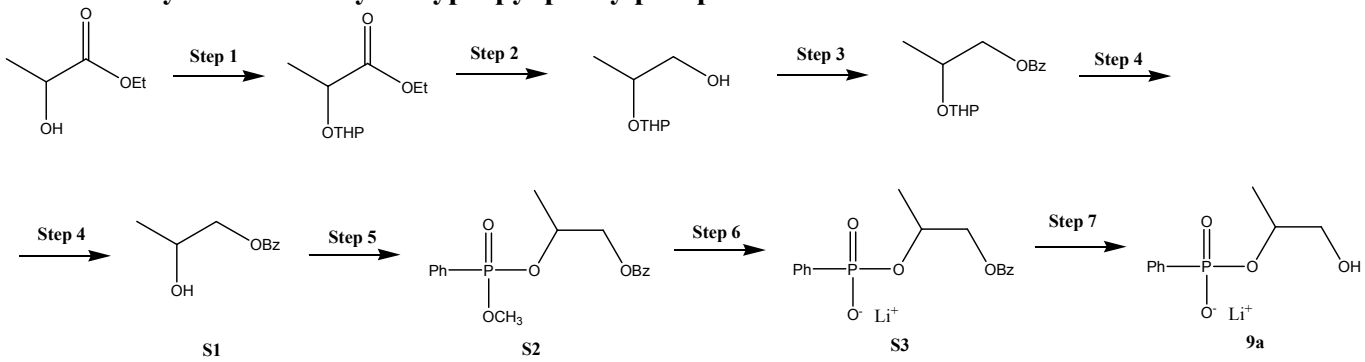
^{1}H NMR (600 MHz, CD_3OD, 25^{o}C) δ 7.80 (2H, m, Ar*H*), δ 7.40 (3H, m, Ar*H*), δ 3.83 (1H, m, C*H*), δ 3.60 (2H, m, CH_2), δ 1.09 (3H, d, CH_3). ^{31}P NMR (242.95 MHz, CD_3OD, 25^{o}C) δ 14.28. ^{13}C NMR (150.94 MHz, CD_3OD, 25^{o}C) δ 134.90 (d, J = 176.1 Hz), δ 131.15 (d, J = 9.06 Hz), δ 129.85 (d, J = 3.02 Hz), δ 127.47 (d, J = 13.58 Hz), δ 69.40 (d, J = 6.04 Hz), δ 66.69 (d, J = 7.55 Hz), δ 17.94. λ_{max}(MeOH)/nm 264 (ε/dm^{3}mol^{-1}cm^{-1} 427). HRMS (ESI-TOF): calcd 215.0478 amu, found 215.0479 amu.

Synthesis of phenyl phosphonate 6b. 1-hydroxy propyl phenylphosphonate **6b** was prepared in a seven-step synthesis (Scheme S1). The precursor **S1** was prepared according to the reported procedure and its identity was confirmed by ^{1}H NMR.[3] Synthetic intermediate **S2** was prepared in the following manner. To a slurry of sodium hydride (1.15g, 28.8 mmol, 60% dispersion in oil) in 50 ml dry THF was added **S1** (4g, 24 mmol) as a solution in 5 ml dry DMF. After stirring the mixture for 30 minutes at ambient temperature the mixture was transferred drop-wise into a solution of phenylphosphonic

dichloride (5.7g, 26.4 mmol) in 250 ml THF at 0 ^{o}C. The resulting solution was stirred for 15 hrs. Analysis by TLC (diethyl ether:hexanes (7:3), PMA stain) showed that **S1** (R_f = 0.29) was almost undetectable. To the reaction mixture was added 10 ml methanol and it was then left to stir for another 4 hours. The reaction mixture was then partitioned between diethyl ether and water. The organic layer was washed with brine and dried over anhydrous $MgSO_4$. Removal of solvent yielded the crude product **S2**. The desired compound **S2** (R_f = 0.33, ethyl acetate) was isolated by silica gel column chromatography eluting with ethyl acetate. Isolated **S2** was deemed sufficiently pure by ^{1}H NMR to be used directly in the subsequent demethylation step (step 6). Demethylation of **S2** was accomplished by combining **S2** (240mg, 0.75 mmol) and lithium chloride (30 mg, 0.71 mmol) in refluxing acetone for 2 days. Product **S3**, an insoluble white precipitate in acetone, was collected by filtration and washed with DCM (yield of **S3** from **S2** 25%). Debenzylation of **S3** by hydrogenation was carried out by combining **S3** (30mg, 0.096 mmol) and 10% Pd/C (6 mg) in ethanol using a balloon to supply hydrogen gas at atmospheric pressure for 20 hours. The reaction mixture was filtered through celite and the filtrate collected. Removal of solvent under reduced pressure furnished the final product **6b** in a 94% yield from synthetic intermediate **S3**.

^{1}H NMR (400 MHz, CD_3OD, 25 ^{o}C) δ 7.80 (2H, m, Ar*H*), δ 7.39 (3H, m, Ar*H*), δ 4.20 (1H, m, C*H*), δ 3.40-3.53 (2H, m, CH_2), δ 1.11 (3H, d, CH_3, J = 6.6 Hz). ^{31}P NMR (242.95 MHz, CD_3OD, 25^{o}C) δ 13.75. ^{13}C NMR (150.94 MHz, CD_3OD, 25^{o}C) δ 135.70 (d, J = 178.26 Hz), δ 131.116 (d, J = 8.91 Hz), δ 129.76 (d, J = 2.87 Hz), δ 127.38 (d, J = 13.74 Hz), δ 71.63 (d, J = 5.43 Hz), δ 66.50, δ 17.36. λ_{max}(MeOH)/nm 264 (ε/dm^{3}mol^{-1}cm^{-1} 421). HRMS (ESI-TOF): calcd 215.0478 amu, found 215.0558 amu.

Scheme S1: Synthesis of 1-hydroxypropyl phenylphosphonate 6b



Synthesis of phenylphosphonates 8a-f. The synthesis of **8d** is representative of the general procedure used for the preparation of all the *O*-aryl phenylphosphonates used in this study. Phenol (940 mg, 10 mmol) and triethylamine (1.3 g, 12.9 mmol) in 15 ml dry toluene were slowly added to a stirring solution of phenylphosphonic dichloride (2.3 g, 11.8 mmol) in 15 ml dry toluene maintained at 0 ^{o}C in an ice bath. Following the addition the ice bath was removed and the reaction left to stir at ambient temperature for a period of 30 minutes. Next 10 ml of 2 M NaOMe was slowly added to the stirring reaction and the contents left to stir at ambient temperature for a further 2 hours. The organic layer was washed with 0.3 M NaOH, dried with $MgSO_4$ and the volatiles removed under reduced pressure. The crude oil was purified by column chromatography eluting with hexanes/ethyl acetate (50:50). The neutral phosphonate was then taken up in 20 ml acetone containing LiCl (800 mg, 19 mmol) and refluxed for 4 hours. Acetone was removed under reduced pressure and the residual white solid taken up in distilled water and washed with diethyl ether. The aqueous layer was passed through an Amberlite IR120 ion exchange column and the acidic fractions collected and combined. Water was pumped off under reduced pressure with heating (50 ^{o}C) to reveal 306 mg of protonated phosphonate **8d**. Yield 13%. Protonated **8d** was treated with one equivalent of sodium methoxide in methanol and

stored as a 100 mM stock solution of the sodium salt to be used in all subsequent kinetic experiments. Analytical data for phenyl phosphonates **8a**[4] and **8d**[5] have been reported previously and that pertaining to substrates **8b,c,e,f** are presented here.

3-nitrophenyl phenylphosphonate 8b (acidic form): ^{1}H NMR (300 MHz, CD_3OD, 25 ^{o}C) δ 8.01-8.03 (2H, m, Ar*H*), δ 7.83-7.88 (2H, m, Ar*H*), δ 7.51-7.65 (5H, m, Ar*H*). ^{31}P NMR (121.49 MHz, CD_3OD, 25 ^{o}C) δ 15.61. ^{13}C NMR (150.94 MHz, CD_3OD, 25^{o}C) δ 153.66, δ 139.13, δ 134.28 (d, *J* = 181.13 Hz), δ 131.30 (d, *J* = 9.06 Hz), δ 130.35, δ 129.44, δ 127.56 (d, *J* = 15.09 Hz), δ 127.09, δ 117.30, δ115.56. λ_{max}(MeOH)/nm 264 (ε/dm^{3}mol^{-1}cm^{-1} 6724). HRMS (ESI-TOF): calcd 278.0223 amu, found 278.0223 amu.

4-chlorophenyl phenylphosphonate 8c (acidic form): ^{1}H NMR (300 MHz, $CDCl_3$, 25 ^{o}C) δ 7.71-7.86 (2H, m, Ar*H*), δ 7.50-7.64 (1H, m, Ar*H*), δ 7.37-7.50 (2H, m, Ar*H*), δ 6.95-7.21 (4H, m, Ar*H*). ^{31}P NMR (121.49 MHz, $CDCl_3$, 25 ^{o}C) δ 18.18. ^{13}C NMR (150.94 MHz, CD_3OD, 25^{o}C) δ 151.71, δ 131.30 (d, *J* = 9.06 Hz), δ 130.11, δ 128.49, δ 127.70, δ 127.43 (d, *J* = 13.58 Hz), δ 122.11 (d, *J* = 4.53 Hz), *ipso*-carbon of P-C_6H_5 not detected. λ_{max}(MeOH)/nm 271 (ε/dm^{3}mol^{-1}cm^{-1} 1082). HRMS (ESI-TOF): calcd 266.99833 amu, found 266.9983 amu.

4-methoxyphenyl phenylphosphonate 8e (acidic form): ^{1}H NMR (300 MHz, $CDCl_3$, 25 ^{o}C) δ 7.63-7.91 (2H, m, Ar*H*), δ 7.34-7.61 (3H, m, Ar*H*), δ 6.93-7.05 (2H, m, Ar*H*), δ 6.63-6.78 (2H, m, Ar*H*), δ 3.71 (3H, s, C*H*$_3$). ^{31}P NMR (121.49 MHz, $CDCl_3$, 25 ^{o}C) δ 18.68. ^{13}C NMR (150.94 MHz, CD_3OD, 25^{o}C) δ 155.55, δ 146.50, δ 135.06 (d, *J* = 179.62 Hz), δ 131.40, δ 129.89, δ 127.30 (d, *J* = 13.58 Hz), δ 121.42 (d, *J* = 4.53 Hz), δ 113.69, δ 54.60. λ_{max}(MeOH)/nm 281 (ε/dm^{3}mol^{-1}cm^{-1} 1812). HRMS (ESI-TOF): calcd 263.0478 amu, found 263.0478 amu.

2,4-dimethylphenyl phenylphosphonate 8f (acidic form): ^{1}H NMR (300 MHz, CD_3OD, 25 ^{o}C) δ 7.80-7.83 (2H, m, Ar*H*), δ 7.49-7.64 (3H, m, Ar*H*), δ 6.89-7.03 (3H, m, Ar*H*), δ 2.25 (3H, s, C*H*$_3$), δ 2.21 (3H, s, C*H*$_3$). ^{31}P NMR (121.49 MHz, CD_3OD, 25 ^{o}C) δ 15.02. ^{13}C NMR (150.94 MHz, CD_3OD, 25^{o}C) δ 148.99, δ 131.85, δ 131.26 (d, *J* = 9.06 Hz), δ 130.70, δ 129.83, δ 129.15 (d, *J* = 4.53 Hz), δ 127.35 (d, *J* = 13.58 Hz), δ 126.23, δ 120.06, δ 19.26, δ 15.45, *ipso*-carbon of P-C_6H_5 not detected. λ_{max}(MeOH)/nm 271 (ε/dm^{3}mol^{-1}cm^{-1} 750). HRMS (ESI-TOF): calcd 261.0686 amu, found 261.0684 amu.

Kinetics.

Substrates 6a and 6b: A 2.43 mmol/dm^3 mixture of phosphonate **6a** and **6b** (96:4) was subjected to reaction in the presence of 2.44 mmol/dm^3 catalyst **4** in anhydrous methanol at ambient temperature, $^{s}_{s}$pH 9.8 ± 0.1. Three individual reactions were each quenched after 5 minutes, 1 hour and 24 hours by the addition of 10 mmol/dm^3 HCl and 10 mmol/dm^3 LiCl. The volatiles were removed under reduced pressure and the crude reaction mixture reconstituted in d^4-methanol for ^{1}H NMR analysis. In order to further sharpen the signal intensities in the ^{1}H NMR spectrum it proved beneficial to add an additional aliquot of LiCl to the NMR samples bringing the total concentration of chloride ion to 142 mmol/dm^3. Shown in Figure S1(a-c) are the partial ^{1}H NMR spectrums (600 MHz) of the quenched reactions and in Figure S2 is a ^{31}P NMR spectrum corresponding to the reaction quenched after 24 hours which contains a single peak at δ 15.11 ppm identified to be *O*-methyl phenylphosphonate. An analogous set of ^{1}H NMR spectrums are shown in Figure S3(a-c) obtained for reaction of 2.43 mmol/dm^3 **6b** (isomerically pure) with 2.45 mmol/dm^3 **4** in anhydrous methanol at ambient temperature, $^{s}_{s}$pH 9.8 ± 0.1. As before the reactions were quenched at 5 minutes, 1 hour and 24 hours by the addition of 10 mmol/dm^3 HCl and LiCl. An estimate of the $^{s}_{s}$pKa for the 1,2-propanediol leaving group for **6b** (17.7) is available from previous work.[6] The $^{s}_{s}$pKa for the leaving group of **6a** was estimated by applying a correction factor of

-0.52 to the $^{s}_{s}$pKa of **6b** to account for the different methyl substitution pattern. This correction factor corresponds to the difference in $^{s}_{s}$pKa (in methanol) between 1-propanol and 2-propanol.

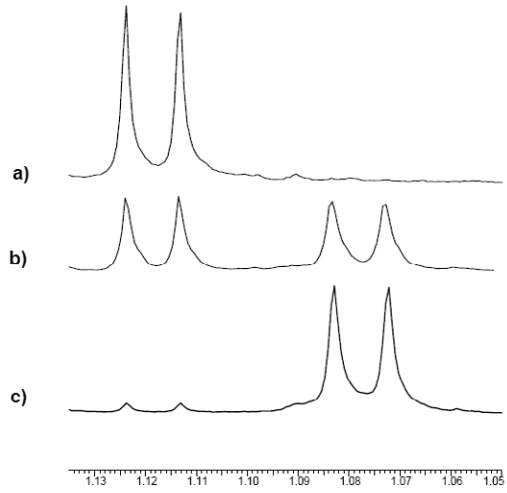


Figure S1: Partial ^{1}H NMR (600 MHz) spectrums obtained following the **4** catalyzed methanolysis of a mixture of **6a** and **6b** (96:4) showing the conversion of starting material into 1,2-propanediol after a) 24 hours; b) 60 minutes and c) 5 minutes. Identities of the peaks are as identified in the main text.

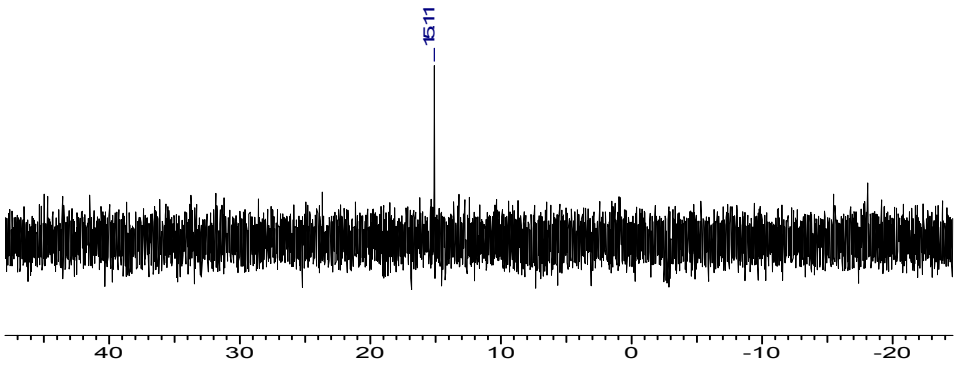


Figure S2: Partial ^{31}P NMR (242.95 MHz, CD_3OD, 25 ^{o}C) spectrum obtained following the **4** catalyzed methanolysis of a mixture of **6a** and **6b** (96:4) after 24 hours showing a single peak at δ 15.11 ppm identified as *O*-methyl phenylphosphonate.

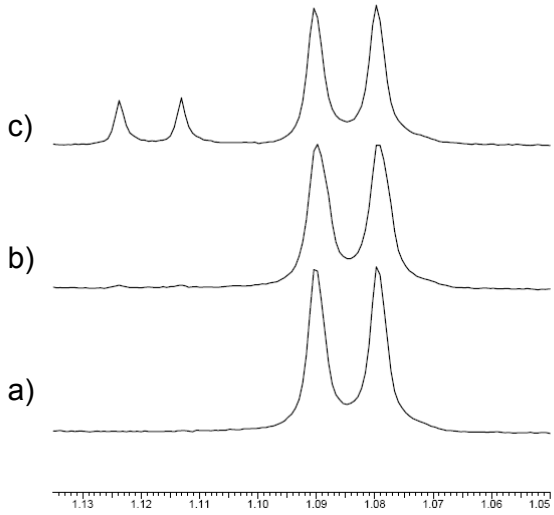


Figure S3: Partial ^{1}H NMR (600 MHz) spectrums obtained following the **4** catalyzed reaction of isomeric pure **6b** after a) 5 minutes b) 60 minutes and c) 24 hours. Identities of the peaks are as identified in the main text.

Substrates 8a-f: The rates of methanolysis of aryl phenylphosphonates **8a-f** (0.05 mmol/dm^3) catalyzed by the complex **4** were determined using an Applied Photophysics SX-17MV stopped-flow reaction analyzer at $^{s}_{s}$pH 9.8±0.1, 25.0 °C. Reactions were followed by monitoring the appearance of the product phenols at 320 (**8a**), 340 (**8b**), 284 (**8c**), 280 (**8d**), 292 (**8e**), 276 (**8f**) nm. Plots of k_{obs} versus $[\mathbf{4}]_{free}$ were fit to the universal binding equation S1 from which the unimolecular rate constant for decomposition of the Michealis complex, k_{cat}^{max}, and the binding constant K_b could be determined. Note that $[\mathbf{4}]_{free}$ used here refers to the total concentration of catalyst *free* from triflate inhibition as described previously.[2]

$$k_{obs} = k_{cat}^{max}(1 + K_B * [S] + [Cat] * K_B - X)/(2K_B)/[S] \qquad (S1)$$

where:

$$X = (1 + 2K_B * [S] + 2 * [Cat] * K_B + K_B^2 * [S]^2 - 2 * K_B^2 * [Cat][S] + [Cat]^2 * K_B^2)^{0.5}$$

Table 1S. Observed pseudo-first order rate constants for the methanolysis of **8a** (10^{-5} mol/dm^3) as a function of $[\mathbf{4}]_{free}$ determined at $^{s}_{s}$pH 9.8±0, 25.0 °C. Fit of the data to equation S1 gives k_{cat}^{max} = 5.29±0.1 s^{-1} and K_b = 2.80±0.17 dm^3/mmol.

$[Zn_2([12]aneN3)_2]$[a] (mmol/dm^3)	10^2 x k_{obs}[b] (s^{-1})
0.361	0.72
0.441	0.93
0.517	0.95
0.278	0.60
1.30	1.02

a. The catalyst concentration reported here is that determined to be free of triflate inhibition as discussed elsewhere.[1]
b. Observed rate constants represent the average of at least three runs where the average standard deviation is ±3%.

Table 2S. Observed pseudo-first order rate constants for the methanolysis of **8b** (10^{-5} mol/dm^3) as a function of $[\mathbf{4}]_{free}$ determined at $^{s}_{s}$pH 9.8±0, 25.0 °C. Fit of the data to equation S1 gives k_{cat}^{max} = 3.09±0.09 s^{-1} and K_b = 51.2±5.7 dm^3/mmol.

$[Zn_2([12]aneN3)_2]$[a] (mmol/dm^3)	10^2 x k_{obs} (s^{-1})
0.441	2.408 2.434 2.426 2.408 2.460
0.517	2.728 2.721 2.722 2.718 2.706
0.589	2.985 2.931 2.938 2.894 2.856 2.918
0.659	2.895 2.933 2.916 2.951 2.914

0.361	1.444 1.434 1.407 1.408
1.30	3.022 2.976 2.949 2.927 2.879

a. The catalyst concentration reported here is that determined to be free of triflate inhibition as discussed eleswhere.[1]

Table 3S. Observed pseudo-first order rate constants for the methanolysis of **8c** (10^{-5} mol/dm^3) as a function of [**4**]$_{free}$ determined at $^{s}_{s}$pH 9.8±0, 25.0 °C. Fit of the data to equation S1 gives k_{cat}^{max} = 0.48±0.01 s^{-1} and K_b = 10.6±1.4 dm^3/mmol.

$[Zn_2([12]aneN3)_2]^a$ (mmol/dm^3)	10^2 x k_{obs} (s^{-1})
0.361	0.2548 0.2477 0.2468 0.2451 0.2410
0.441	0.3371 0.3301 0.3360 0.3365 0.3314
0.517	0.3657 0.3657 0.3653 0.3713 0.3608
0.589	0.3753 0.3581 0.3701 0.3617 0.3623
0.278	0.1476 0.1548 0.1544 0.1544 0.1555 0.1530
0.788	0.4115 0.4061 0.4055 0.4003 0.4056

a. The catalyst concentration reported here is that determined to be free of triflate inhibition as discussed eleswhere.[1]

Table 4S. Observed pseudo-first order rate constants for the methanolysis of **8d** (10^{-5} mol/dm^3) as a function of $[\mathbf{4}]_{free}$ determined at $^{s}_{s}$pH 9.8±0, 25.0 °C. Fit of the data to equation S1 gives k_{cat}^{max} = (9.2±0.2) x10^{-2} s^{-1} and K_b = 46±12 dm^3/mmol.

$[Zn_2([12]aneN3)_2]$[a] (mmol/dm^3)	10^2 x k_{obs}[b] (s^{-1})
0. 306	0.0054
0.310	0.0057
0. 361	0.072
0.402	0.078
0.566	0.086
0.789	0.087

a. The catalyst concentration reported here is that determined to be free of triflate inhibition as discussed eleswhere.[1]
b. Observed rate constants represent the average of at least three runs where the average standard deviation is ±5%.

Table 5S. Observed pseudo-first order rate constants for the methanolysis of **8e** (10^{-5} mol/dm^3) as a function of $[\mathbf{4}]_{free}$ determined at $^{s}_{s}$pH 9.8±0, 25.0 °C. Fit of the data to equation S1 gives k_{cat}^{max} = (4.5±0.2) x10^{-2} s^{-1} and K_b = 22.9±7.7 dm^3/mmol.

$[Zn_2([12]aneN3)_2]$[a] (mmol/dm^3)	10^2 x k_{obs} (s^{-1})
0.278	0.02768 0.02763 0.02774
0.361	0.03370 0.03392 0.03328
0.441	0.03976 0.03930 0.03887
0.517	0.04041 0.03771 0.03910 0.03752
0.659	0.04116 0.04163 0.04043 0.04138 0.03990

a. The catalyst concentration reported here is that determined to be free of triflate inhibition as discussed eleswhere.[1]

Table 6S. Observed pseudo-first order rate constants for the methanolysis of **8f** (10^{-5} mol/dm^3) as a function of $[\mathbf{4}]_{free}$ determined at $^{s}_{s}$pH 9.8±0, 25.0 °C. Fit of the data to equation S1 gives k_{cat}^{max} = (1.1±0.1) x10^{-2} s^{-1} and K_b = 20±15 dm^3/mmol.

$[Zn_2([12]aneN3)_2]$[a] (mmol/dm^3)	10^2 x k_{obs} (s^{-1})
0.278	0.005919 0.006064 0.006040
0.361	0.007285 0.007084 0.007159 0.007309
0.441	0.008888 0.009357 0.009336 0.009734
0.517	0.009852 0.009293 0.009527 0.009370
1.30	0.009814 0.010900 0.009897

a. The catalyst concentration reported here is that determined to be free of triflate inhibition as discussed eleswhere.[1]

Figure S4: ^{1}H NMR spectrum (CD_3OD, 25 ^{o}C, 600 MHz) of 2-hydroxypropyl phenylphosphonate **6a**.

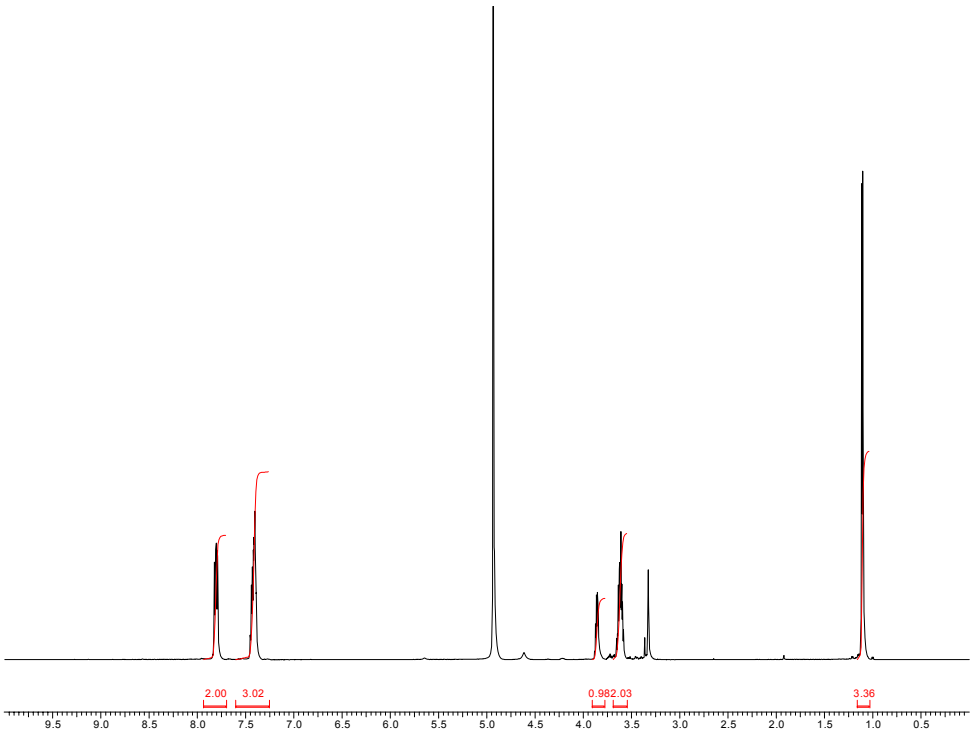


Figure S5: ^{1}H NMR spectrum (CD_3OD, 25 ^{o}C, 600 MHz) of 1-hydroxy propyl phenylphosphonate **6b**.

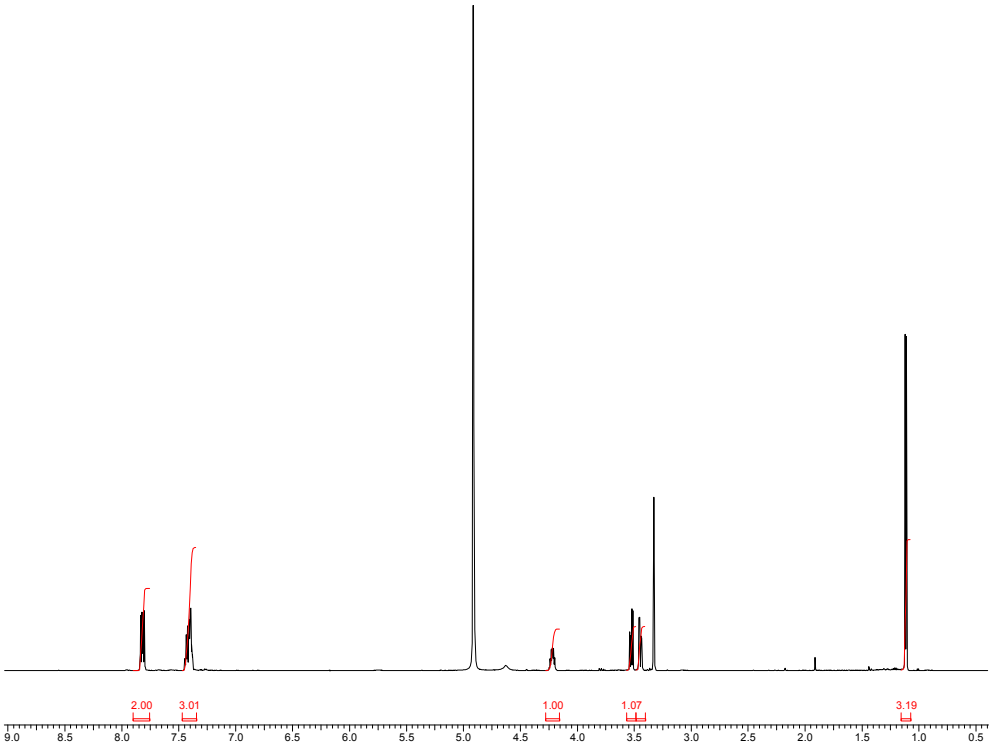


Figure S6: ^{1}H NMR spectrum (CD_3OD, 25 ^{o}C, 600 MHz) of 3-nitrophenyl phenylphosphonate **8b** (sodium salt).

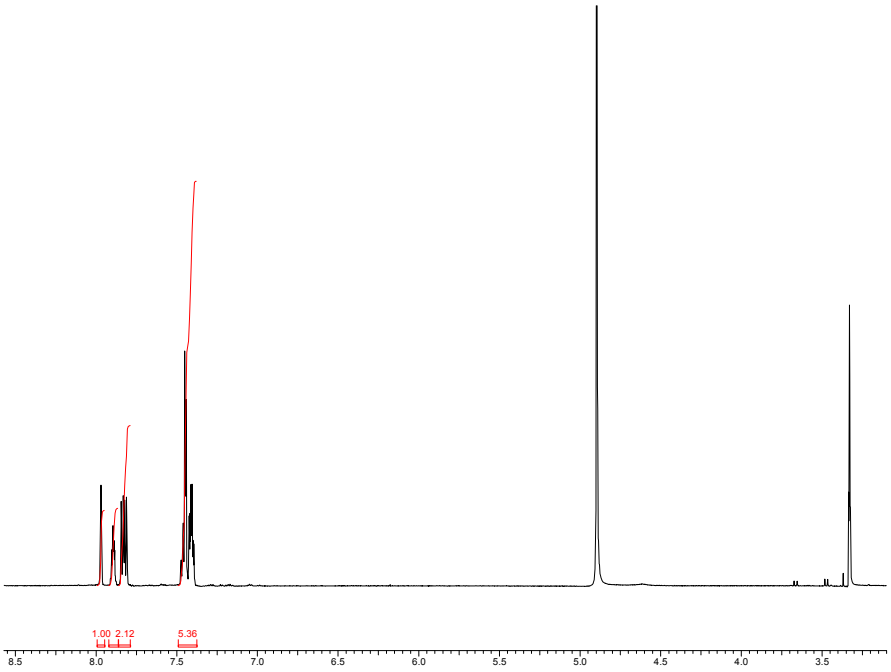


Figure S7: ^{1}H NMR spectrum (CD_3OD, 25 ^{o}C, 600 MHz) of 4-chlorophenyl phenylphosphonate **8c** **(**sodium salt**)**.

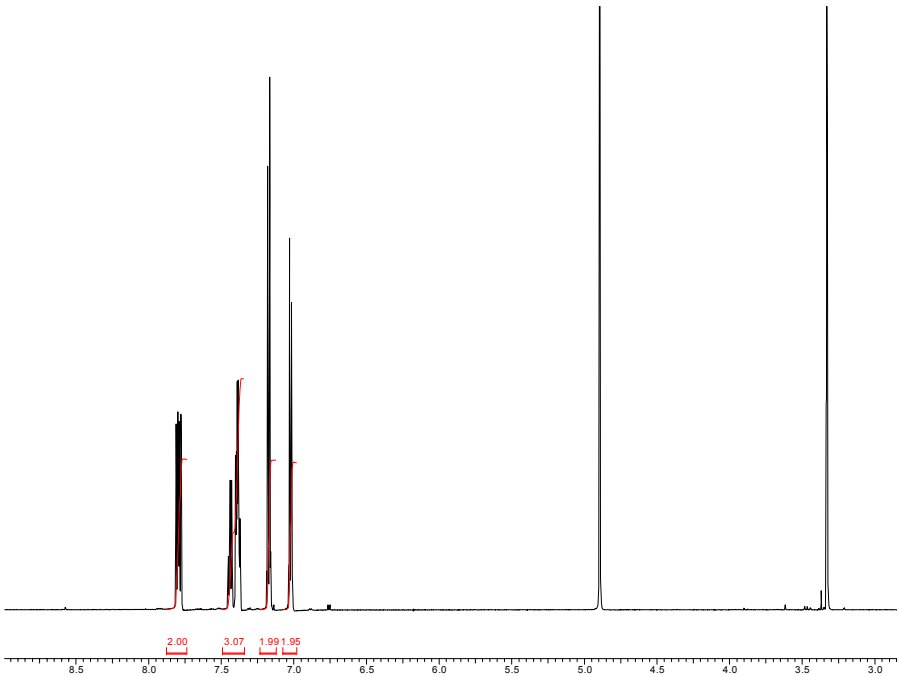


Figure S8: ^{1}H NMR spectrum (CD_3OD, 25 ^{o}C, 600 MHz) of 4-methoxyphenyl phenylphosphonate **8e** **(**sodium salt**)**.

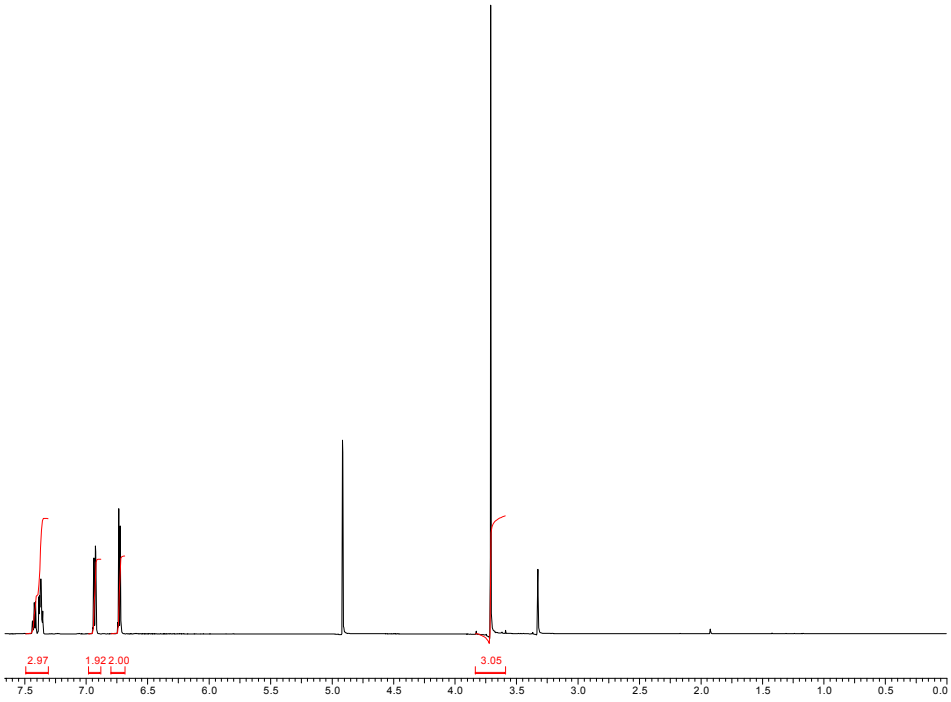
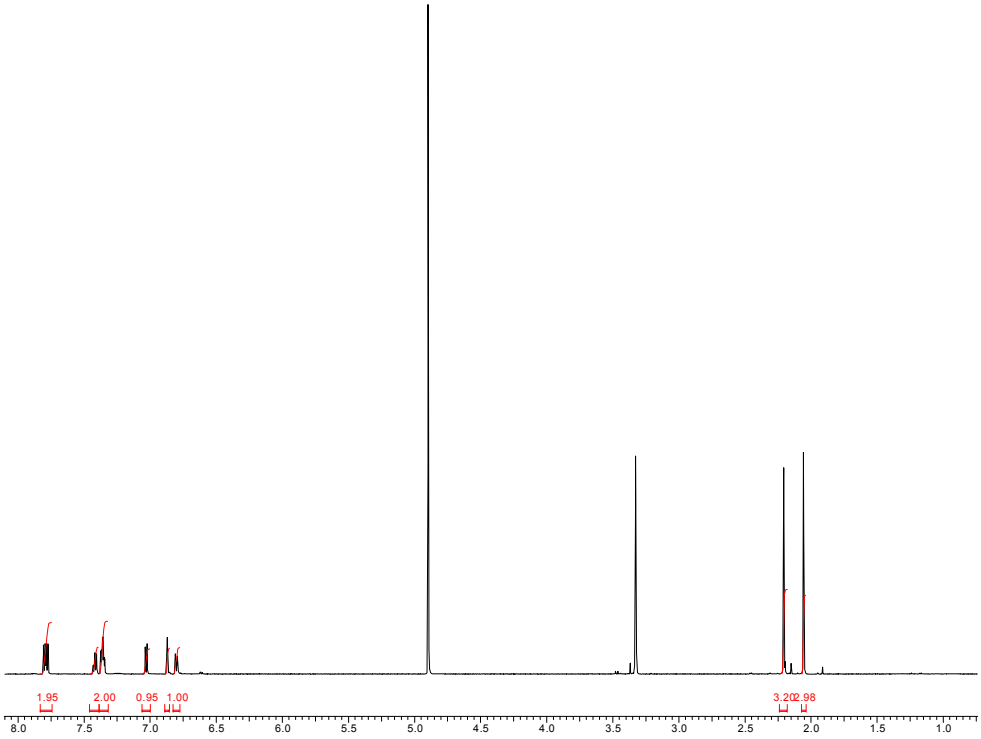


Figure S9: ^{1}H NMR spectrum (CD_3OD, 25 ^{o}C, 600 MHz) of 2,4-dimethylphenyl phenylphosphonate **8f** (sodium salt).



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