Supporting Online Information

A Study on the Transesterification of Methyl Aryl Phosphorothioates in Methanol Promoted by Cd(II), Mn(II) and a Synthetic Pd(II) Complex.

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Contents:

1. Materials.

Sodium methoxide (0.5 M solution in methanol, titrated against N/50 Fisher Certified standard aqueous HCl solution and found to be 0.49 M), NBu$_4$OMe (1.0 M solution in methanol, titrated against N/50 Fisher Certified standard aqueous HCl solution), Ag(CF$_3$SO$_3$), dimethyl chlorothiophosphate (98%), 2-chloro-4-nitrophenol (97%), 4-nitrophenol (98%), 4-chlorophenol (99+%), phenol (99%), sodium hydride (60% dispersion in mineral oil) and La(CF$_3$SO$_3$)$_3$ (99.999% metals basis) were purchased from Aldrich and used without further purification. Anhydrous methanol and tetrahydrofuran were acquired from EMD chemicals. Methyl aryl phosphorothioates **2a-d** were prepared from the corresponding dimethyl aryl phosphorothioates by LiCl promoted mono-demethylation in acetone.[1] The ^{1}H NMR, ^{31}P NMR, and mass spectra obtained were all consistent with the structures. Purity of **2a-d** is estimated to be >95% as determined by complete methanolysis and comparison of the extinction coefficients of the product solutions to that of the authentic phenols. Sodium *O,O*-dimethyl phosphorothioate **(2e)** was prepared by hydrolysis of dimethyl chlorothiophosphate in THF/H$_2$O. Catalyst **3** can be obtained by treating a methanol solution containing di-μ-chlorobis(*N,N*-dimethylbenzylamine-2-C,N)dipalladium(II)[2] with two equivalents of Ag(OTf) followed by sonication at room temperature for 10 minutes and subsequent centrifugation to remove AgCl. Typically, stock solutions of **3** were prepared at < 10 mM and used immediately. An alternative method to prepare **3** *in situ* consisted of addition to the reaction solution of di-μ-chlorobis(*N,N*-dimethylbenzylamine-2C,N)dipalladium(II) (10-20 mM in CH$_2$Cl$_2$) in the presence of 2 mM La(OTf)$_3$. Control experiments indicated that the rate of reaction for cleavage of **2b** was experimentally indistinguishable using the two methods to prepare **3**. The pincer palladacycle, **4** was prepared according to a published procedure.[3]

2. Methods

2.1 $_s^s$pH measurement. The $CH_3OH_2^+$ concentrations were determined potentiometrically using a combination glass electrode (Radiometer model XC100-111-120-161) calibrated with certified standard aqueous buffers (pH = 4.00 and 10.00) as described previously.[4] The $_s^s$pH values in methanol were obtained by subtracting a correction constant of -2.24[4] from the electrode readings: the autoprotolysis constant for methanol was taken to be $10^{-16.77}$ M^2. The $_s^s$pK$_a$ values of the substituted phenols in methanol used in this study can be found in a previous report.[5]

2.2. ^{31}P NMR spectrum of 3:2e.

A deuterium lock was obtained on CD_3OD in an NMR tube containing **2e**, and the magnetic field was shimmed and the probe tuned to ^{31}P. The blank sample was ejected and replaced with one containing **2e** (1.5 mM) and **3** (3.0 mM) in neutral CH_3OH. The ^{31}P NMR spectrum was obtained on the unlocked sample at 298 K on a spectrometer operating at 202 MHz. Chemical shifts are referenced to 70% phosphoric acid.

2.3. Kinetics.

2.3.1. Metal ion promoted methanolysis of 2b. The kinetic data for the metal ion promoted methanolysis of **2b** was obtained using standard UV-vis spectrophotometry at 25 ^{o}C. The metal ions $La(OTf)_3$, $Cd(ClO_4)_2$, $Mn(OTf)_2$ or **3** were first added to the UV-cells followed by the addition of one half equivalent of NaOMe. Reactions were initiated by the addition of **2b** (9 x 10^{-5} M) and the reaction progress monitored for at least five half lives at 336 nm (Cd(II)), 338 nm (La(III)), 390 nm (Mn(II)) and 320 nm (**3**). Observed rate constants were determined by fits of the plots of absorbance vs time data to a standard first order exponential equation. Plots of k_{obs} versus [metal ion] are shown in the Supporting Information along with a description of the treatment of the rate data to obtain the second order rate constants listed in Table 1.

2.3.2 $_s^s$pH rate profile for the 3-catalyzed methanolysis of 2b. Plots of k_{obs} versus [**3**] for the

methanolysis of **2b** (2 x 10^{-5} M) were fit to equation 2 over the $_s^s$pH range 5.6-14.95, T = 25 °C. A

standard UV-vis spectrophotomer was used to monitor all reactions except those run at $_s^s$pH 11.35,

14.07 and 14.95 which required the use of a stopped-flow reaction analyzer. For this series of

experiments, constant $_s^s$pH was maintained using the following buffer systems: 2.6 mM Yb(OTf)$_3$/2.6

mM NaOMe ($_s^s$pH 5.60), La(OTf)$_3$ and various ratios of NaOMe ($_s^s$pH 7.06-11.35) and excess NaOMe

($_s^s$pH 14.07-14.95). Reactions were monitored at 320 nm ($_s^s$pH 5.60), 338 nm ($_s^s$pH 7.06-11.35) and 400

nm ($_s^s$pH > 14). The $_s^s$pH rate profile (Figure 5) was constructed using catalytic rate constants (k_{cat}^{corr})

corrected for buffer catalysis as described in the Results section.

2.3.3 Linear free energy relationship for the 3-catalyzed methanolysis of phosphorothioates 2.

Plots of k_{obs} versus [**3**] were determined for **2a-d** (5 x 10^{-5} M) at $_s^s$pH 8.7 ([La^{3+}] = [$^-$OMe] = 2 mM) and

the catalytic rate constants computed from the fits of the rate data to eq. 2 (*vide infra)* were corrected for

buffer catalysis to determine k_{cat}^{corr} as described in the Results section. Reaction progress was monitored

at 400 nm (**2a**), 338 (**2b**), 284 nm (**2c**), 277 nm (**2d**). Plots of k_{obs} vs [**3**] were determined for

methanolysis of **2b-d** (5 x 10^{-5} M) at $_s^s$pH 14.1 in the presence of 2 mM NaOMe, T = 25 °C and fits of

the rate data to eq. 2 provided the kinetic parameters listed in Table 3.

2.3.4 Activation parameters for the 3-catalyzed methanolysis of 2b. The activation parameters for

the **3** (1.2 x 10^{-4} M) catalyzed methanolysis of substrate **2b** (5 x 10^{-5} M) were determined at $_s^s$pH 8.8 in

the presence of [La^{3+}] = [NaOMe] = 1.68, 3.36 and 5.04 mM over a temperature range spanning 10-43

^{o}C. The $k_2{}^{La}$ and k_{cat}^{corr} data were obtained as the gradients and y-intercepts respectively in the plots of

k_{obs} versus $[La^{3+}]_{total}$. Fitting the data to the Eyring equation provided the activation parameters.

2.4. UV-vis titration of 3 with 2e. The UV-vis spectrum of a neutral unbuffered methanol solution

containing **3** (5.8×10^{-5} M) was obtained from 400 to 250 nm at 25°C. Aliquots of **2e** (1.8×10^{-5} M)

were sequentially added and the UV-vis spectrum obtained. The absorbance at $\lambda = 325$ nm was recorded

as a function of [**2e**] as shown in Figure 2.

<u>**General method for the preparation of 2a-d.**</u>

The following method is general for the preparation of **2a-d**. Into a round bottomed flask equipped

with a magnetic stirring bar was added (1.34g, 10 mmol) 2-chloro-4-nitrophenol to 30 ml anhydrous

tetrahydrofuran. The reaction vessel was cooled in an ice bath prior to the addition of (440 mg, 11

mmol) sodium hydride as a 60% dispersion in mineral oil. The reaction vessel was left to warm to room

temperature and then (720 mg, 4.5 mmol) dimethyl chlorothiophosphate was added dropwise. The

reaction was left to stir at ambient temperature for 24 hours prior to the removal of the volatiles under

reduced pressure. The crude material was taken up in diethyl ether, washed with saturated aqueous

K_2CO_3 (x3), brine (x1), dried with $MgSO_4$ and the volatiles removed under reduced pressure. The crude

material was then taken up in 20 ml acetone and to this was added (420 mg, 10 mmol) LiCl and (26 mg,

0.1 mmol) 18-crown-6. The reaction was left to stir at ambient temperature for 48 hours and then

acetone was removed under reduced pressure. The white solid residue was taken up in water, washed

with CH_2Cl_2 (x 2). The aqueous layer was acidified to pH ~1 and washed with CH_2Cl_2 (x2). Next the

aqueous layer was acidified to 6 M HCl and extracted with CH_2Cl_2 until the organic fraction no longer

showed a UV observable spot by TLC analysis. The collected organic fractions were combined and

solvent removed under reduced pressure to reveal compound **2a** in its protonated form in a yield of 28%.

The title compounds **2a-d** were generally treated with 0.95 equivalents of methoxide and stored as stock

solutions in methanol placed in the fridge. The analytical data for new compounds **2a,c,d** is presented

below. The analytical data determined for **2b** in the current study is consistent with its structure as reported.[6]

Analytical data:

Methyl 2-chloro-4-nitrophenylphosphorothioate **2a** (H$^+$-form): ^{1}H NMR (500 MHz, D$_2$O) δ 8.29-8.41 (1H, m, Ar*H*), δ 8.04-8.17 (1H, m, Ar*H*), δ 7.44-7.58 (1H, m, Ar*H*), δ3.73 (3H, d, P-OC*H$_3$* *J* = 13.2 Hz). ^{13}C NMR (125.8 MHz, D$_2$O) δ153.55, δ 143.74, δ 126.79, δ 126.27, δ 123.97, δ 122.04 and δ 54.34. ^{31}P NMR (202.5 MHz, D$_2$O) δ 55.24. λ$_{max}$(MeOH)/nm 289 (ε/M^{-1}cm^{-1} 6238 ±303). HRMS (ESI-TOF) calculated for C$_7$H$_6$O$_5$PSNCl [M-H]$^-$ 281.9386 *m/e*; found 281.9392.

Methyl 4-chlorophenylphosphorothioate **2c** (Na$^+$-form): ^{1}H NMR (500 MHz, CD$_3$OD) δ 7.16-7.27 (4H, m, Ar*H*), δ3.67 (3H, d, P-OC*H$_3$* *J* = 13.21 Hz). ^{13}C NMR (125.8 MHz, CD$_3$OD) δ 127.44, δ 126.96, δ 121.11 and δ 51.49 (*ipso* P-OAr carbon not observed). ^{31}P NMR (202.5 MHz, CD$_3$OD) δ 55.02. λ$_{max}$(MeOH)/nm 272 (ε/M^{-1}cm^{-1} 261). HRMS (ESI-TOF) calculated for C$_7$H$_7$O$_3$PSCl [M-Na]$^-$ 236.9539 *m/e*; found 236.9542.

Methyl phenylphosphorothioate **2d** (Na$^+$-form): ^{1}H NMR (600 MHz, CD$_3$OD) δ 7.18-7.28 (4H, m, Ar*H*), δ 7.01-7.06 (1H, m, Ar*H*), δ3.67 (3H, d, P-OC*H$_3$* *J* = 12.84 Hz). ^{31}P NMR (243 MHz, CD$_3$OD) δ 54.66. λ$_{max}$(MeOH)/nm 264 (ε/M^{-1}cm^{-1} 223). HRMS (ESI-TOF) calculated for C$_7$H$_7$O$_3$PSCl [M-Na]$^-$ 202.9922 *m/e*; found 202.9931.

Preparation of dimethyl phosphorothioate (2e). (3.2 g, 20 mmol) Dimethyl chlorothiophosphate was added dropwise to a round bottomed flask containing 20 ml THF, 10 ml H$_2$O and (1.7 g, 42 mmol) NaOH. The reaction was left to stir for 2 hours and then the volatile organic material removed under reduced pressure. The alkaline aqueous solution was washed with CH$_2$Cl$_2$ (x2) and then acidified to 6 M HCl. The acidic aqueous solution was then extracted with CH$_2$Cl$_2$ (x4) to collect dimethyl phosphorothioate in its protonated form. The organic layer was concentrated under reduced pressure, taken up in 10 ml water and passed through an ion exchange column (Na$^+$ form). Sodium dimethyl

phosphorothioate was obtained in a 50% yield. ^{1}H and ^{31}P NMR data were consistent with the proposed

structure.[7]

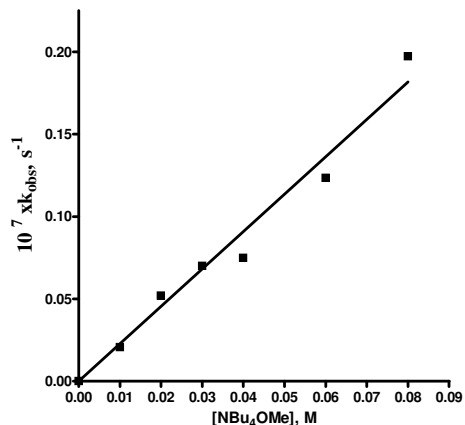## 3. Plots of k_{obs} versus [metal] or [NBu$_4$OMe] for the methanolysis of 2b.

Figure S1: Plot of k_{obs} versus [NBu$_4$OMe] for the methanolysis of **2b** (9 x10^{-5} M) at 25 ^{o}C determined by UV-vis spectrophotometry for product formation at 399 nm. A standard linear regression provides the second order rate constant k_2 = (2.3 ±0.2) x10^{-7} M^{-1}s^{-1} (r^2 0.9736, 6 data).
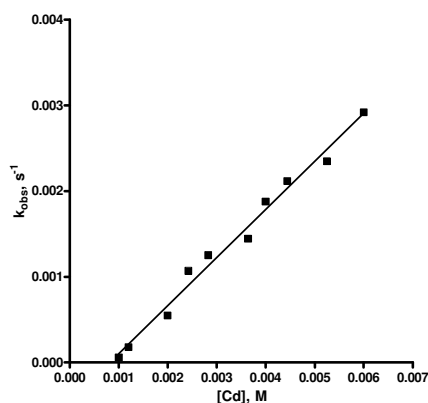

Figure S2: Plot of k_{obs} versus [Cd(ClO$_4$)$_2$] for the methanolysis of **2b** (9 x10^{-5} M) at 25 ^{o}C, ^s_spH 10.0 determined by UV-vis spectrophotometry for product formation at 336 nm. A standard linear regression provides the second order rate constant k_2 = 0.56 ±0.02 M^{-1}s^{-1} and an observable x-intercept of 8.1 ±0.2 M (r^2 0.9859, 10 data).[8]

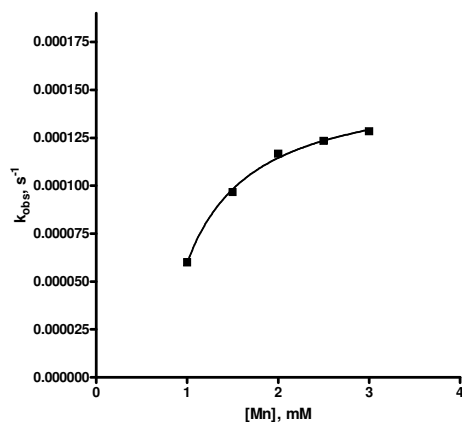Figure S3: Plot of k_{obs} versus [Mn(OTf)$_2$] for the methanolysis of **2b** (9 x10^{-5} M) at 25 °C, ^S_SpH 9.6 determined by UV-vis spectrophotometry for product formation at 390 nm. A fit of the data to the universal binding equation 2 of the main text provides k_{cat} = (1.54 ±0.06) x10^{-4} s^{-1}, K_b = 2.3 ±0.5 mM^{-1} and an observable x-intercept of 0.70 ±0.04 mM.[8] The second order rate constant is calculated as k_2 = k_{cat} x K_b = 0.35 M^{-1}s^{-1}.
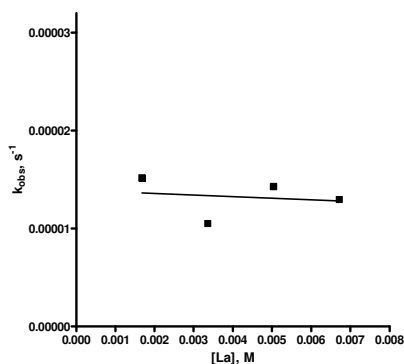
Figure S4: Plot of k_{obs} versus [La(OTf)$_3$] for the methanolysis of **2b** (9 x10^{-5} M) at 25 °C, ^S_SpH 8.4 determined by UV-vis spectrophotometry for product formation at 338 nm. An average observed rate constant of (1.3 ±0.2) x10^{-5} s^{-1} is determined.

Note 1: The second order rate constant for methanolysis of **2b** (9 x10^{-5} M) at 25 °C, ^S_SpH 11.2 catalyzed by **3** (5 x10^{-4} M) as reported in Table 1 of the main text was calculated by first determining an observed rate constant of 0.13 s^{-1} under conditions of saturating metal ion by following product formation at 400 nm. The second order rate constant was then obtained by k_2 = k_{cat} x K_b = 0.13 s^{-1} x (4.2 x10^5) M^{-1} = (5.5 ±1.7) x10^4 M^{-1}s^{-1}. The binding constant used in this calculation came from UV-vis spectrophotometric titration of **3** with dimethylphosphorothioate.

4. Tables of observed rate constants for the methanolysis of 2b catalyzed by 3 (5.60 ≤ ^S_SpH ≤ 14.95, T = 25 °C).

Table S1: Observed rate constants determined for the **3** catalyzed methanolysis of **2b** determined at ^S_SpH 5.60, 25 °C. The reported observed rate constants are the average of duplicate runs.

[**3**], mM	k_{obs}, minutes^{-1}
0.58 x10^{-1}	0.36
0.86 x10^{-1}	0.50
0.12	0.55
0.17	0.67
0.23	0.65
0.29	0.67

Table S2: Observed rate constants determined for the **3** catalyzed methanolysis of **2b** determined at $_s^s$pH 7.06, 25 ^{o}C. The reported observed rate constants are the average of duplicate runs.

10 x [**3**], mM	k_{obs}, minutes^{-1}
0.16	0.15
0.32	0.33
0.48	0.44
0.64	0.46
0.96	0.51
1.1	0.55

Table S3: Observed rate constants determined for the **3** catalyzed methanolysis of **2b** determined at $_s^s$pH 7.65, 25 ^{o}C. The reported observed rate constants are the average of duplicate runs. The catalytic rate constant, k_{cat}, was corrected for buffer effects using the equation $k_{cat} = (2.87 \pm 0.12 \text{ M}^{-1}\text{s}^{-1})[\text{La}^{3+}] + (1.41 \pm 0.05) \text{ x}10^{-2} \text{ s}^{-1}$; where k_{cat}^{corr} at [La] = 0 M is determined to be $(1.41 \pm 0.05) \text{ x}10^{-2} \text{ s}^{-1}$.

10 x [**3**], mM	k_{obs}, minutes^{-1}
0.08	0.30
0.16	0.44
0.32	0.77
0.40	0.93
0.56	1.07
0.80	1.18
2.4	1.20

Table S4: Observed rate constants determined for the **3** catalyzed methanolysis of **2b** determined at $_s^s$pH 8.80, 25 °C. The reported observed rate constants are the average of duplicate runs. The catalytic rate constant, k_{cat}, was corrected for buffer effects using the equation $k_{cat} = (7.55 \pm 0.64 \ M^{-1}s^{-1})[La^{3+}] + (2.61 \pm 0.20) \times 10^{-2} \ s^{-1}$; where k_{cat}^{corr} at [La] = 0 M is determined to be $(2.61 \pm 0.20) \times 10^{-2} \ s^{-1}$.

10 x [**3**], mM	k_{obs}, minutes^{-1}
3.8×10^{-1}	0.29
9.6×10^{-1}	1.24
0.15	1.62
0.23	2.04
0.28	2.12
0.29	2.31
0.31	2.38
0.46	2.45
0.77	2.54

Table S5: Observed rate constants determined for the **3** catalyzed methanolysis of **2b** determined at $_s^s$pH 10.38, 25 °C. The reported observed rate constants are the average of duplicate runs. The catalytic rate constant, k_{cat}, was corrected for buffer effects using the equation $k_{cat} = (1.18 \pm 0.22 \ M^{-1}s^{-1})[La^{3+}] + (4.56 \pm 0.09) \times 10^{-2} \ s^{-1}$; where k_{cat}^{corr} at [La] = 0 M is determined to be $(4.56 \pm 0.09) \times 10^{-2} \ s^{-1}$.

10 x [**3**], mM	k_{obs}, minutes^{-1}
0.16	0.74
0.24	1.11
0.32	1.77
0.60	2.41
0.80	2.56
1.2	2.47

Table S6: Observed rate constants determined for the **3** catalyzed methanolysis of **2b** determined at $_s^s$pH 11.35, 25 °C. This set of reactions was run on an Applied Photophysics SX-17MV stopped-flow reaction analyzer and observed rate constants represent the average of at least 3 determinations. The catalytic rate constant, k_{cat}, was corrected for buffer effects using the equation $k_{cat} = (14.84 \pm 1.70 \ M^{-1}s^{-1})[La^{3+}] + (3.28 \pm 0.26) \times 10^{-1} \ s^{-1}$; where k_{cat}^{corr} at [La] = 0 M is determined to be $(3.28 \pm 0.26) \times 10^{-1} \ s^{-1}$.

10 x [3], mM	k_{obs}, s^{-1}
0.29	0.085
0.58	0.74
0.86	1.11
1.44	1.77

Table S7: Observed rate constants determined for the **3** catalyzed methanolysis of **2b** determined at ^s_spH 14.07, 25 °C. This set of reactions was run on an Applied Photophysics SX-17MV stopped-flow reaction analyzer and observed rate constants represent the average of at least 3 determinations.

10 x [3], mM	k_{obs}, s^{-1}
0.22	0.58
0.43	2.63
0.86	4.33
1.30	4.66
1.72	4.80

Table S8: Observed rate constants determined for the **3** catalyzed methanolysis of **2b** determined at ^s_spH 14.95, 25 °C. This set of reactions was run on an Applied Photophysics SX-17MV stopped-flow reaction analyzer and observed rate constants represent the average of at least 3 determinations.

10 x [3], mM	k_{obs}, s^{-1}
0.22	0.23
0.43	0.58
0.86	2.04
1.30	3.30
1.72	4.22
2.59	5.27
3.0	4.99

Tables of observed rate constants for the methanolysis of 2acd catalyzed by 3 at $_s^s$pH 7.60 and 14.1, T = 25 ºC).

Table S9: Observed rate constants determined for the **3** catalyzed methanolysis of **2a** determined at $_s^s$pH 7.60, 25 ºC. The reported observed rate constants are the average of duplicate runs. Buffer catalysis was not observed for reaction of **2a** and so the k_{cat} determined directly from equation 2 of the main text was used in the construction of the Brønsted plot.

10 x [**3**], mM	k_{obs}, minutes^{-1}
0.19	0.35
0.38	0.76
0.56	0.96
0.75	1.09
1.13	1.26

Table S10: Observed rate constants determined for the **3** catalyzed methanolysis of **2c** determined at $_s^s$pH 7.60, 25 ºC. The reported observed rate constants are the average of duplicate runs. The catalytic rate constant, k_{cat}, was corrected for buffer effects using the equation $k_{cat} = (4.33 \pm 0.65 \text{ M}^{-1}\text{s}^{-1})[\text{La}^{3+}] + (1.9 \pm 0.1) \times 10^{-1} \text{ s}^{-2}$; where k_{cat}^{corr} at [La] = 0 M is determined to be $(1.9 \pm 0.1) \times 1 0^{-1} \text{ s}^{-2}$.

10 x [**3**], mM	k_{obs}, minutes^{-1}
0.14	0.40
0.29	0.72
0.58	1.06
0.86	1.32
1.15	1.28
1.44	1.46

Table S11: Observed rate constants determined for the **3** catalyzed methanolysis of **2d** determined at $_s^s$pH 7.60, 25 ºC. The reported observed rate constants are the average of duplicate runs. The catalytic rate constant, k_{cat}, was corrected for buffer effects using the equation $k_{cat} = (4.39 \pm 0.63 \text{ M}^{-1}\text{s}^{-1})[\text{La}^{3+}] + (1.55 \pm 0.27) \times 10^{-1} \text{ s}^{-2}$; where k_{cat}^{corr} at [La] = 0 M is determined to be $(1.55 \pm 0.27) \times 10^{-1} \text{ s}^{-2}$.

10 x [**3**], mM	k_{obs}, minutes^{-1}

0.29	0.82
0.43	1.22
0.58	1.27
0.86	1.49
1.15	1.50
1.44	1.48

Table S12: Observed rate constants determined for the **3** catalyzed methanolysis of **2c** determined at $_s^s$pH 14.1, 25 °C. The reported observed rate constants are the average of duplicate runs.

10^4 x [**3**], M	k_{obs}, minutes^{-1}
0.21	1.74
0.42	2.44
0.64	2.53
0.85	2.61
1.06	2.62
1.27	2.62

Table S13: Observed rate constants determined for the **3** catalyzed methanolysis of **2d** determined at $_s^s$pH 14.1, 25 °C. The reported observed rate constants are the average of duplicate runs.

10^4 x [**3**], M	k_{obs}, minutes^{-1}
0.21	0.65 x10^{-1}
0.42	0.15
0.64	0.25
0.85	0.30
1.06	0.36
1.30	0.38

**5. Determination of the activation parameters for the methanolysis of 2b catalyzed by 3 at 25 °C.**

The activation parameters for the **3** (1.2 x 10^{-4} M) catalyzed methanolysis of substrate **2b** (5 x 10^{-5} M) were determined at $_s^s$pH 8.8 in the presence of [La^{3+}] = [NaOMe] = 1.68, 3.36 and 5.04 mM over a temperature range spanning 10- 43 °C. The k_2^{La} and k_{cat}^{corr} data were obtained as the gradients and y-

intercepts respectively in the plots of k_{obs} versus $[La^{3+}]_{total}$. Fitting the rate data to the Eyring equation provided the activation parameters. The observed rate constants listed below are averages of duplicate runs.

Temperature, Kelvin	$[La^{3+}]$ = [NaOMe], mM	k_{obs}, minutes^{-1}
283	1.68	0.56
283	3.36	1.06
283	5.04	1.51
289	1.68	0.85
289	3.36	1.41
289	5.04	1.88
298	1.68	1.66
298	3.36	2.48
298	5.04	2.98
307	1.68	2.58
307	3.36	4.01
307	5.04	4.78
316	1.68	4.38
316	3.36	5.91
316	5.04	7.35

6. Ionization of 6 and alternative mechanisms for the pH independent pathway.

Scheme 1S
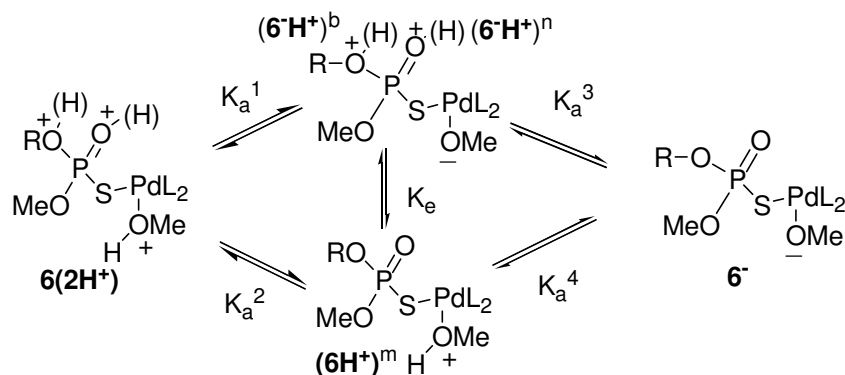
Speciation of **6** at different values $_s^s pH$ can be described by the ionization diagram presented in Scheme

1S, where K_a^n refer to various microscopic $_s^s pK_a$ values. Only one of the $_s^s K_a^n$ values can be

determined experimentally, but for others an educated estimate can be given.

$_s^s K_a^4$ refers to the dissociation constant of a Pd-coordinated methanol molecule in the

palladacycle/substrate complex $(6H^+)^m$, experimentally determined to be $10^{-12.7}$ M (see Figure 5 in the

main manuscript). $^s_s K_a{}^2$ can be estimated based on the pK_a determined for dissociation of the protonated phosphoryl oxygen of trimethyl phosphate or dimethyl phosphate in water[9] (-3.6 and -2.6). While phosphate ester **2** carries a negative charge, its coordination to the positively charged Pd(I) palladacycle and formation of a strong S-Pd interaction should result in a neutral, or close to neutral, charge for **2** in the bound form **6**. We therefore assume that the $^s_s pK_a{}^2$ of the phosphoryl-H$^+$ in the **6(2H$^+$)** is ~-3, midway between that of protonated trimethyl phosphate and dimethyl phosphate, assuming that the differential effect of the solvent (water vs. methanol) should be quite limited due to the ionization process where the solvation of the species on each side of the equation is similar (HOS + $^+$H-Sub $\leftrightarrow$ H$_2{}^+$OS + Sub), as is known to be the case for ionization of protonated amines, where the pK_a values in water and ethanol are quite similar[10].

$^s_s K_a{}^1$ refers to the ionization of the Pd-coordinated methanol of complex (**6(2H$^+$)**). While it is difficult to predict exactly the value of this constant it should lie between those for the for free palladacycle (-10$^{-10.8}$)[2] and that of complex **6H$^+$**(10$^{-12.7}$) as found in this study, and probably closer to the former value considering the overall neutral charge of phosphate moiety in **6(2H$^+$)**. We therefore assume that the value of $^s_s K_a{}^1$ is ~10$^{-11.8}$. In order to determine the value of $^s_s K_a{}^3$, we consider the thermodynamic cycle $K_a{}^1 K_a{}^3 = K_a{}^2 K_a{}^4$ which allows us to calculate $K_a{}^3 = K_a{}^2 K_a{}^4 / K_a{}^1 = 10^2$ M ($^s_s pK_a{}^3 = -2$). Due to the wide spread between $^s_s pK_a{}^2$ and $^s_s pK_a{}^4$ (-3 and 12.7 correspondingly), the main form of **6** over the broad $^s_s pH$ range between ~-2 and ~11 is **6H$^+$** (depicted in the lower center of Scheme 1S) which exists in an isoprotonic equilibrium with the very minor form **6$^-$H$^+$** (depicted in the upper corner of Scheme 6). The equilibrium constant between those two forms K_e can be determined as $K_e = {}^s_s K_a{}^2 / {}^s_s K_a{}^1 = [(\mathbf{6H^+})^m]/[(\mathbf{6^-H^+})^n] = 10^{14.8}$.

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