Supporting Information

Cyanohydrin Hydration with [Ru(η^6-*p*-cymene)Cl_2PR_3] Complexes

Spring Melody M. Knapp,[†] *Tobias J. Sherbow,*[†] *J. Jerrick Juliette,*[§] *David R. Tyler**[†]

[†]Department of Chemistry, University of Oregon, Eugene, OR 97403, and [§] Dow Advanced Materials-Performance Monomers, The Dow Chemical Company, Deer Park, TX 77536

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1. Experimental:

Materials and Methods. Unless stated otherwise, all manipulations were carried out in either a N_2-filled Vacuum Atmospheres Co. glove box or on a Schlenk line using N_2. HPLC grade THF, dichloromethane, hexanes, acetonitrile, and diethyl ether (Burdick and Jackson) were dried and deoxygenated by passing them through commercial columns of CuO, followed by alumina under argon atmosphere. Chloroform was distilled under N_2 from CaH_2 and degassed via three freeze-pump-thaw cycles. Petroleum ether (35-60 °C) (Mackron Chemicals) was degassed via three freeze-pump-thaw cycles. HPLC grade water or D_2O were degassed by sparging with N_2. $[RuCl_2(\eta^6\text{-}p\text{-cymene})]_2$ was purchased from Strem. Acetone cyanohydrin, lactonitrile, and glycolonitrile (55 wt% in H_2O), were purchased from Sigma Aldrich. Tris(dimethylamino)phosphine was purchased from TCI America. Cyanohydrins were distilled prior to use. All other commercially available reagents were used as received. $[Ru(\eta^6\text{-}p\text{-cymene})Cl_2(P(NMe_2)_3)]$,[1] $[Ru(\eta^6\text{-}p\text{-cymene})Cl_2(P(OMe)_3)]$,[2] and $[Ru(\eta^6\text{-}p\text{-cymene})Cl_2(PEt_3)]$,[3] were synthesized following literature procedure.

Instrumentation and Procedures. Nuclear magnetic resonance spectra were recorded on a Varian Unity/Inova 300 MHz (^{1}H, 299.94 MHz; ^{31}P, 121.41 MHz, ^{13}C, MHz) spectrometer, a 500 MHz (^{1}H, 500.10 MHz; ^{31}P, 202.45 MHz; ^{13}C, 125.77 MHz) spectrometer, or a 600 MHz (^{1}H, 500.10 MHz; ^{31}P, 202.45 MHz; ^{13}C, 125.77 MHz) spectrometer. The ^{1}H chemical shifts were referenced to the solvent peak or TMS (0.00ppm), the ^{13}C chemical shifts were referenced to the solvent peak, or to methanol (49.5 ppm) if D_2O was the NMR solvent, and the ^{31}P chemical shifts were referenced to H_3PO_4 (0.00 ppm). IR spectra were recorded on a Nicolet magna 550 FT-IR or a Nicolet 6700 FT-IR with OMNIC software. Samples were prepared as KBr pellets or as THF solutions in CaF liquid cells. All hydration reaction samples were

prepared in a glove box under an atmosphere of N_2 in Wilmad 9 in. precision NMR tubes or in 1-dram screwcap vials fitted with septum caps. Reactions carried out in the Wilmad 9 in. NMR tubes were flame-sealed. Reaction tubes and vials were heated in an oil bath. Cyanohydrin hydration reactions were performed using a variety of reaction conditions. Representative procedures that gave the best results are given below.

General Procedure for the Hydration of Acetonitrile. [Ru(η^6-arene)$Cl_2(PR_3)$] (0.02 mmol) was added to 3 mL degassed D_2O in a 1 dram screwcap vial fitted with a septum cap. To this was added 0.45 mmol acetonitrile to form a 150 mM nitrile solution. This solution was heated to 100 °C with stirring. Aliquots (0.1 mL) were removed periodically using a gas-tight syringe, and were combined in an NMR tube with 0.6 mL D_2O and 0.1 mL of a 3.8 mM NMe_4PF_6 in D_2O internal standard solution. The progress of the reaction was monitored via ^{1}H NMR spectroscopy by observing the disappearance of the acetonitrile resonance at 2.01 (s, CH_3CN), and the appearance of acetamide at 1.93 ppm (s, CH_3C(O)ND_2).

HCl Control Reaction. [Ru(η^6-*p*-cymene)$Cl_2(P(NMe_2)_3)$] (0.11 g, 0.23 mmol) was dissolved in 7 mL degassed D_2O. In a 1 dram screwcap vial fitted with a septum cap, 0.55 mL of the Ru(η^6-*p*-cymene)$Cl_2(P(NMe_2)_3)$] stock solution was combined with acetonitrile (21 μL, 0.4 mmol). Concentrated HCl (0 – 40 μL) and D_2O (2.10 – 2.06 mL) were added to achieve a final volume of 2.67 mL, with the ratio of HCl and D_2O varied to obtain the following pH solutions: 8.5, 6.0, 5.3, 4.5, 4.0, and 3.5. Each solution was heated to 100 °C with stirring. Aliquots (0.1 mL) were removed periodically using a gas-tight syringe, and were combined in an NMR tube with 0.6 mL D_2O and 0.1 mL of a 3.8 mM NMe_4PF_6 in D_2O internal standard solution. The progress of the reaction was monitored via ^{1}H NMR spectroscopy by observing the

disappearance of the acetonitrile resonance at 2.01 (s, CH_3CN), and the appearance of acetamide at 1.93 ppm (s, CH_3C(O)ND_2).

NaCl Control Reaction. [Ru(η^6-*p*-cymene)Cl_2(P(NMe_2)$_3$)] (0.05 g, 0.11 mmol) was dissolved in 13 mL degassed D_2O and NaCl (3.0 g, 51.4 mmol) was dissolved in 10 mL degassed D_2O.

0 equivalents NaCl: In a 1 dram screwcap vial fitted with a septum cap, 2 mL of the Ru(η^6-*p*-cymene)Cl_2(P(NMe_2)$_3$)] stock solution was combined with 0.4 mL D_2O and 20 μL acetonitrile to form a 0.16 mM nitrile solution.

10 equivalents NaCl: In a 1 dram screwcap vial fitted with a septum cap, 2 mL of the Ru(η^6-*p*-cymene)Cl_2(P(NMe_2)$_3$)] stock solution was combined with 0.36 mL D_2O, 35 μL of the NaCl stock solution, and 20 μL acetonitrile.

100 equivalents NaCl: In a 1 dram screwcap vial fitted with a septum cap, 2 mL of the Ru(η^6-*p*-cymene)Cl_2(P(NMe_2)$_3$)] stock solution was combined with 0.05 mL D_2O, 0.35 mL of the NaCl stock solution, and 20 μL acetonitrile.

Each solution was heated to 100 °C with stirring. Aliquots (0.1 mL) were removed periodically using a gas-tight syringe, and were combined in an NMR tube with 0.6 mL D_2O and 0.1 mL of a 3.8 mM NMe_4PF_6 in D_2O internal standard solution. The progress of the reaction was monitored via ^{1}H NMR spectroscopy by observing the disappearance of the acetonitrile resonance at 2.01 (s, CH_3CN), and the appearance of acetamide at 1.93 ppm (s, CH_3C(O)ND_2).

General Procedure for the Hydration of Cyanohydrins.

Glycolonitrile. In a 9 in. NMR tube, [Ru(η^6-arene)Cl_2(PR_3)] (4.8 μmol) was combined with 0.65 mL D_2O and glycolonitrile (9.5 μL of a 55% solution in H_2O, 0.095 mmol) and the solution was allowed to react at 25 °C. The progress of the reaction was monitored via ^{1}H NMR

spectroscopy by observing the disappearance of the glycolonitrile resonance at 4.45 (s, 2H, HOCH_2CN), and the appearance of glycolamide at 4.09 ppm (s, 2H, HOCH_2C(O)ND_2).

Lactonitrile. In a 9 in. NMR tube, [Ru(η^6-arene)Cl_2(P(NMe_2)$_3$)] (4.8 μmol) was combined with 0.65 mL D_2O and 3.2 μL of concentrated HCl to obtain a pH 3.5 solution. Lactonitrile (6.75 μL, 0.095 mmol) was added to the solution, which was allowed to react at 25 °C. The progress of the reaction was monitored via ^{1}H NMR spectroscopy by observing the disappearance of the lactonitrile resonances at 4.74 ppm (q, J = 6.9 Hz, (CH_3)(HO)CHCN) and 1.56 ppm (d, J = 6.9 Hz, (CH_3)(HO)CHCN), and the appearance of lactamide at 4.27 ppm (q, J = 6.9 Hz, (CH_3)(HO)CHC(O)ND_2) and 1.39 ppm (d, J = 6.9 Hz, (CH_3)(HO)C CHC(O)ND_2).

Acetone Cyanohydrin. In a 1 dram screwcap vial fitted with a septum cap, [Ru(η^6-arene)Cl_2(P(NMe_2)$_3$)] (20 μmol) was combined with 0.55 mL H_2O, 2.1 mL acetone, and 2.7 μL of concentrated HCl to obtain a pH 3.5 solution. Freshly distilled acetone cyanohydrin (37 μL, 0.40 mmol) was added to the solution, which was allowed to react at 25 °C, and 0.1 mL aliquots were removed periodically and combined with 0.1 mL of 17.4 mM NMe_4PF_6 in d_6-acetone and 0.5 mL d_6-acetone. The progress of the reaction was monitored via ^{1}H NMR spectroscopy by observing the disappearance of the methyl peak of acetone cyanohydrin resonance at 1.57 ppm (s, 6H, HO(CH_3)$_2$CCN) and the appearance of the α-hydroxyisobutyramide resonance at 1.34 ppm (s, HO(CH_3)$_2$CC(O)NH_2).

2. Techniques for determining H-bond acceptor strength.

The strength of a hydrogen bond, and therefore, the strength of a hydrogen-bond acceptor, can be determined using a few different measuring systems. The Kamlett-Taft parameter for the hydrogen-bond accepting ability of a solvent is the β-value, which is measured on a scale of 0.0

to ≥ 1.0, where non-hydrogen-bond accepting solvents (such as hexanes) have a β-value = 0.0, and very strong hydrogen-bond accepting groups (such as amines) have β-values ≥ 0.6. Ethers typically have β-values ≅ 0.48.[4] In the solid state, there is a shortening of the proton-acceptor bond of an X---H---A type bond (where X is the hydrogen-bond donor, and A is the acceptor).[5] A strong hydrogen bond is 1.2 – 1.5 Å, a moderate hydrogen bond is 1.5 – 2.2 Å, and a weak hydrogen bond is >2.2 Å.[6]

A number of different techniques have been used to either measure the β-value of a compound, or measure the X---H---A bond lengths. These include IR, UV-Vis, and NMR spectroscopy, and X-ray crystallography. Some of these techniques were applied to complexes **1** – **3** to determine a relative trend in their hydrogen-bond acceptor strength.

The β-value of a compound can be measured via UV-Vis by determining the $\Delta\lambda_{max}$ of N-methyl-4-nitroaniline, which is a hydrogen-bond donating probe.[7] This shift is compared to the $\Delta\lambda_{max}$ of N,N-diethyl-4-nitroaniline, which accounts for differences in solvent polarity. Using this method, the β-values of **1** – **3** are 0.31, 0.29, and 0.06, respectively.

Alternatively, the β-value can be measured with ^{19}F NMR spectroscopy by measuring the Δ^{19}F NMR signal of the 4-fluorophenol hydrogen-bond donating probe, with reference to an internal standard.[8] With this method, the β-values of **1** – **3** are 0.14, 0.05, and 0.11, respectively. While these values are significantly lower than expected, this technique is inherently prone to error (some solvents, when measured, had much lower Δ^{19}F NMR shifts than expected based on their known β-value). Additionally, both the UV-Vis and the ^{19}F NMR techniques are known to display variation in the β-value measured, depending on the steric bulk of the hydrogen-bond acceptor.

Advanced 2-D NMR spectroscopy techniques have been used to detect hydrogen-bonding interactions between amino acid residues in proteins. Several papers have investigated the hydrogen bond scalar couplings, which can be used to observe all partners in the hydrogen bond (donor, proton, and acceptor) using a COSY correlation experiment.[9] Additionally, the size of the coupling constant between the donor and acceptor is directly related to the hydrogen-bond distances and angles, which provides information about the strength of the hydrogen bond.[10] An excellent protocol for this technique has been published.[11]

Finally, assuming that one can obtain a co-crystal of a hydrogen-bond donor-acceptor pair, X-ray crystallography can be used to measure the bond length of the hydrogen-acceptor bond, and therefore, directly measure the relative strength of the hydrogen-bond accepting group. As stated above, shorter H---A bond lengths correlate with stronger hydrogen-bonds.

3. Liquid Cell FT-IR data

Solution phase IR spectra were recorded on a Nicolet 6700 FT-IR with OMNIC software with a peak resolution of 2 cm^{-1}. Samples were prepared as THF solutions in CaF liquid cells with a 1:1 ratio of complex:phenol. The observed phenol OH stretch for each solution is shown in the table below.

Solution	**Phenol ν(OH) (cm^{-1})**
phenol	3293
phenol + [Ru(η^6-*p*-cymene)$Cl_2P(NMe_2)_3$] (**1**)	3281
phenol + [Ru(η^6-*p*-cymene)$Cl_2P(OMe)_3$] (**2**)	3284
phenol + [Ru(η^6-*p*-cymene)Cl_2PEt_3] (**3**)	3283
phenol + acetamide	3222

phenol + decane	3293

The IR data shows that **1** is a stronger hydrogen-bond acceptor than **2** or **3**, which matches the trend observed in the rate of acetonitrile hydration. The difference in ν(OH) between the three complexes is much smaller in solution. This difference may be due to the low concentrations of the complexes and phenol in solution (approximately 7 mM), or because THF itself can act as a hydrogen-bond acceptor. This solution phase experiment was attempted in dichloromethane, which is not a hydrogen-bond accepting solvent. However, there were too many interfering peaks in the ν(O-H) region to make any conclusive statements about the position of the phenol ν(OH).

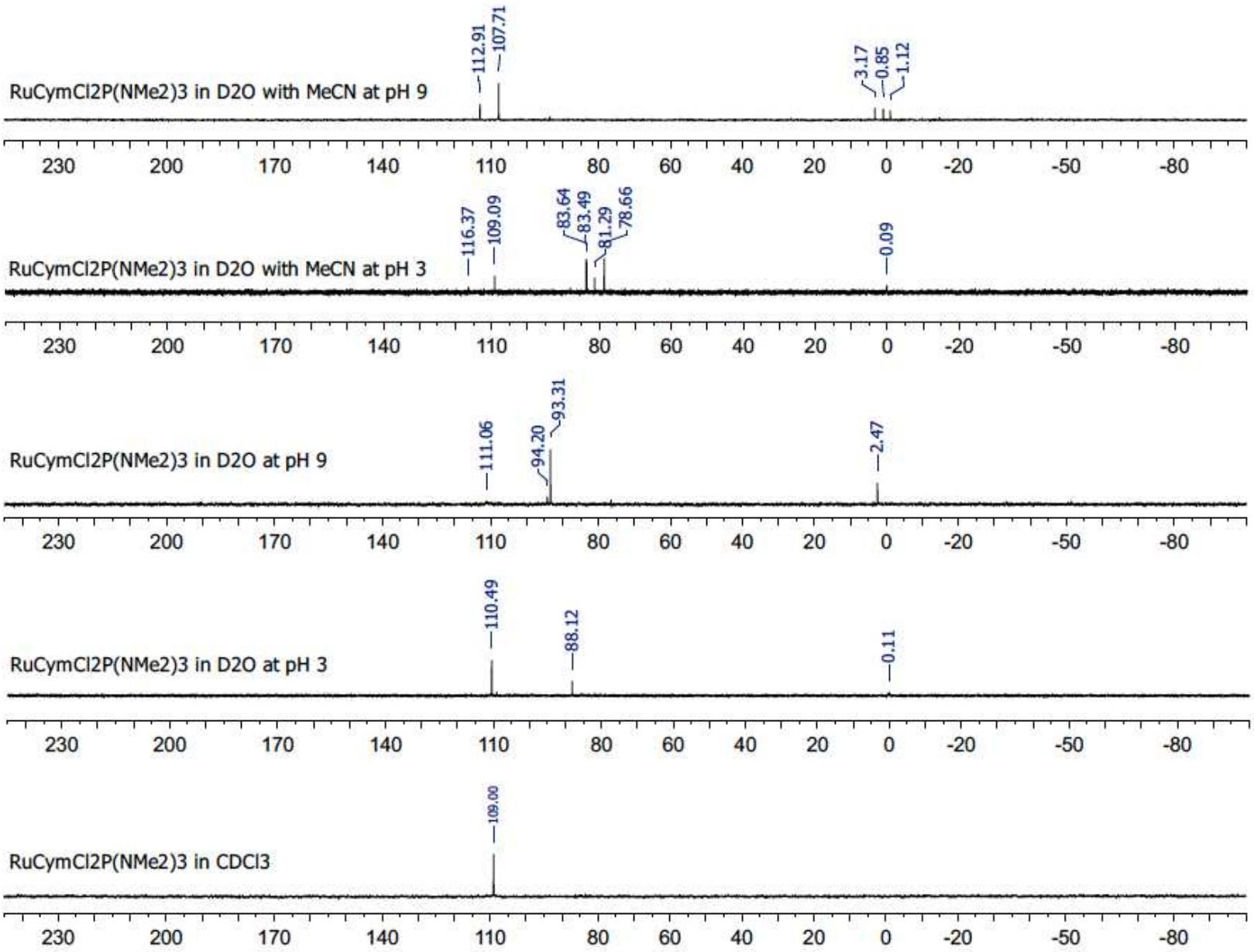
4. Aqueous speciation of [Ru(η^6-*p*-cymene)Cl_2P(NMe_2)$_3$]

Previous studies conducted by Cadierno and co-workers stated that the complex [Ru(η^6-*p*-cymene)Cl_2(P(NMe_2)$_3$)] degrades in aqueous conditions, as evidenced by the formation of several peaks in the ^{31}P NMR spectra. Over the course of hydration of acetonitrile, glycolonitrile, lactonitrile, and acetone cyanohydrin, the ^{31}P NMR spectra of the complex were collected to determine the effect of catalyst degradation on the catalyst activity. Those spectra can be found below. The units for all spectra are ppm, and all spectra were acquired at 44 hours.

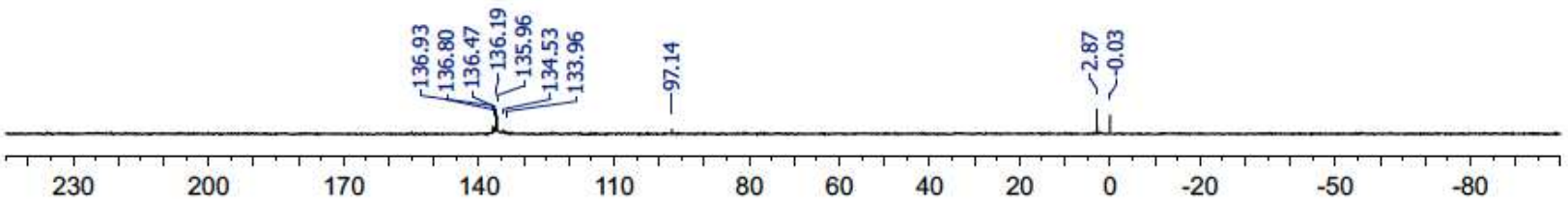
In $CDCl_3$, the ^{31}P NMR signal for [Ru(η^6-*p*-cymene)Cl_2(P(NMe_2)$_3$)] appears at 109 ppm. When dissolved in D_2O, several new peaks appear between 100 – 80 ppm. Additionally, a peak around 0 ppm was observed. The peaks between 80 – 100 ppm may correspond to [Ru(η^6-*p*-cymene)Cl_2(P(NMe_2)$_{3-y}$(OH)$_y$)], and the peak around 0 ppm is likely H_3PO_4, which would form

by hydrolysis of $P(NMe_2)_3$. Interestingly, the hydrolysis reaction occurs faster at high pH, indicating that the catalyst is active for longer at low pH because it is not degrading as quickly.

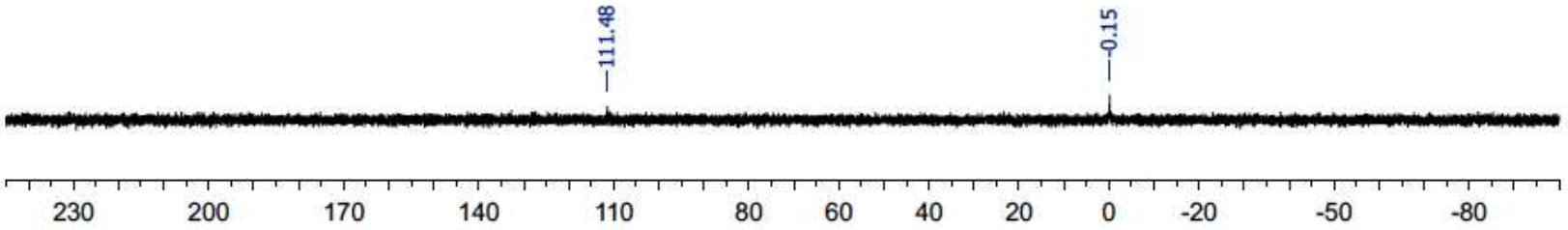
For the acetonitrile hydration reaction, several peaks were observed downfield between 110-116 ppm, which may be attributed to various catalyst species, including [Ru(η^6-*p*-cymene)$Cl_{2-x}(CH_3CN)_x(P(NMe_2)_3)$], and [Ru($\eta^6$-*p*-cymene)$Cl_{2-x}(CH_3CN)_x(P(NMe_2)_{3-y}(OH)_y)$]. Additionally, there are several peaks between -3 - 3 ppm, which likely correspond to free phosphine ligand, $(P(NMe_2)_{3-y}(OH)_y)$. In the presence of cyanohydrins, several new peaks appear between 116 – 137 ppm, which are likely due to cyanide coordination to the catalyst, [Ru(η^6-*p*-cymene)$Cl_{2-x-y}(RCN)_x(CN)_y(P(NMe_2)_{3-z}(OH)_z)$]. However, even in the presence of these species, the catalyst is still active.


RuCymCl2P(NMe2)3 in D2O with MeCN at pH 9
112.91
107.71
3.17
0.85
1.12
RuCymCl2P(NMe2)3 in D2O with MeCN at pH 3
116.37
109.09
83.64
83.49
81.29
78.66
0.09
RuCymCl2P(NMe2)3 in D2O at pH 9
111.06
94.20
93.31
2.47
RuCymCl2P(NMe2)3 in D2O at pH 3
110.49
88.12
0.11
RuCymCl2P(NMe2)3 in CDCl3
109.00
230
200
170
140
110
80
60
40
20
0
-20
-50
-80

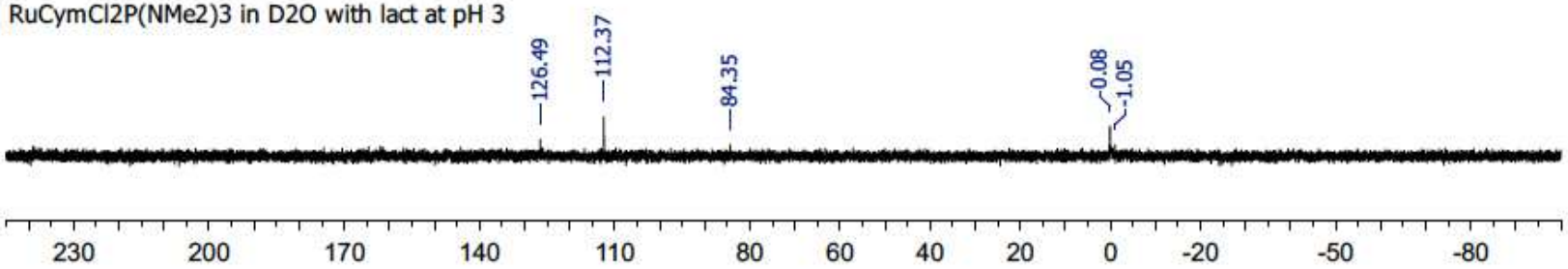
RuCymCl2P(NMe2)3 in D2O with ACH at pH 9



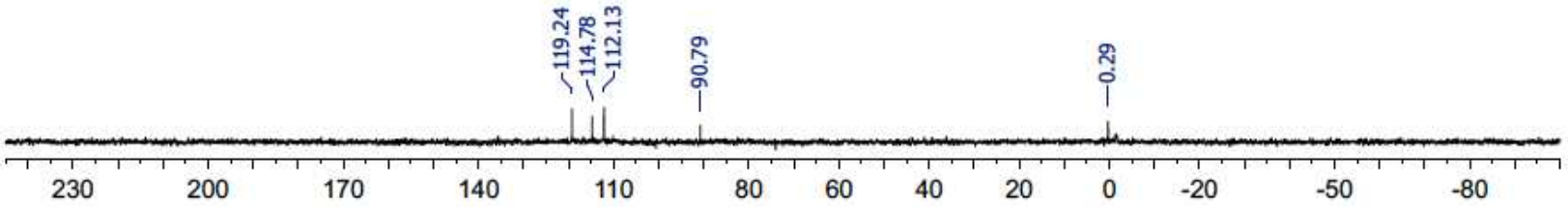
RuCymCl2P(NMe2)3 in D2O with ACH at pH 3



RuCymCl2P(NMe2)3 in D2O with lact at pH 3



RuCymCl2P(NMe2)3 in D2O with gly at pH 9



5. References.

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