Supporting Information:

Mechanistic Insights into Hydroacylation with Non-chelating Aldehydes

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1 General Considerations

All reactions were run in oven-dried or flame-dried glassware under an atmosphere of N₂. Solvents used in hydroacylations were purchased as anhydrous grade, degassed by three freeze-pump-thaw cycles, and stored over 3 Å MS within an N_2 filled glove box. Solvents used for substrate synthesis were purified using an Innovative Technologies Pure Solv system. All of the vinylphenols used in this study were described in our previous report (Murphy, S.K.; Bruch, A.; Dong, V.M. Angew. Chem. Int. Ed. 2014, 53, 2455.). The molarity of organolithium reagents was determined by titration with isopropanol/1,10-phenanthroline. Liquid aldehydes were distilled under reduced pressure and degassed by three freeze-pumpthaw cycles prior to use. Solid aldehydes were purified either by washing with saturated aqueous sodium bicarbonate solution or by column chromatography. Reactions were monitored either via gas chromatography-mass spectrometry (GC-MS) using an Agilent Technologies 7890A GC system equipped with an Agilent Technologies 5975C inert XL EI/CI MSD, or by analytical thin-layer chromatography on EMD Silica Gel 60 F₂₅₄ plates. Visualization of the developed plates was performed under UV light (254 nm) or KMnO₄ stain. Column chromatography was performed with Silicycle Silia-P Flash Silica Gel using glass columns. Automated column chromatography was performed using either a Biotage SP1 or Teledyne Isco CombiFlash Rf 200 purification system. ¹H, ¹³C, ¹⁹F, and ³¹P NMR spectra were recorded on a Bruker DRX-400 (400 MHz ¹H, 100 MHz ¹³C, 376.5 MHz ¹⁹F, 161.9 ³¹P), GN-500 (500 MHz ¹H, 125.7 MHz ¹³C) or CRYO-500 (500 MHz ¹H, 125.7 MHz ¹³C) spectrometer. ¹H NMR spectra were internally referenced to the residual solvent signal or TMS. ¹³C NMR spectra were internally referenced to the residual solvent signal. Data for ¹H NMR are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), coupling constant (Hz), integration. Data for ¹³C NMR are reported in terms of chemical shift (δ ppm). Infrared spectra were obtained on a Thermo Scientific Nicolet iS5 FT-IR spectrometer equipped with an iD5 ATR accessory. High resolution mass spectra (HRMS) was performed by the University of California, Irvine Mass Spectrometry Center. X-ray crystallography was performed by the University of California, X-ray Crystallography Facility.

2 Preparation of substrates

d₁-2-naphthaldehyde

To a round bottom flask equipped with a stir bar was added sequentially N-(methoxy)methylammonium chloride (0.512 g, 5.25 mmol, 1 equiv), DMAP (0.064 g, 0.525 mmol, 0.1 equiv), dichloromethane (20 mL), triethylamine (1.536 mL, 11.02 mmol, 2.1 equiv), and 2-naphthoyl chloride (1.000 g, 5.25 mmol, 1 equiv). The solution was stirred for 10 minutes and then concentrated under reduced pressure. Ethyl acetate was added and the solution was washed twice with saturated NH₄Cl(aq) and then NaHCO₃(aq) solution. The organic layer was dried with MgSO₄ and then filtered and concentrated under reduced pressure to give the weinreb amide as a clear light yellow oil (0.920 g, 81 % yield) which was used without further purification. The weinreb amide was added to a second round bottom flask equipped with a stir bar and septum, along with THF (25 mL). The flask was lowered into an ice bath, and then LiAID₄ (0.197 g, 4.70 mmol, 1.1 equiv) was added slowly. After 10 minutes, the reaction was worked up using the Feiser and Feiser method and purified by column chromatography to give the product as a white solid (0.636 g, 95%). ¹H NMR (500 MHz, CDCl₃) δ 8.35 (s, 1H), 8.02 (d, *J* = 8.1 Hz, 1H), 8.00 – 7.87 (m, 3H), 7.66 (t, *J* = 7.4 Hz, 1H), 7.60 (t, *J* = 7.1 Hz, 1H).

*d*₁-hydrocinnamaldehyde

O TH D Ca

The title compound was synthesized according to a literature procedure (Jean, M.; Renault, J.; Uriac, P.; Capet, M.; van de Weghe, P. *Org. Lett.* **2007**, *9*, 3623). ¹**H NMR** (400 MHz, CDCl₃) δ 7.39 – 7.10 (m, 5H), 2.96 (t, *J* = 7.6 Hz, 2H), 2.78 (t, *J* = 7.6 Hz, 2H).

3 Rh-catalyzed Hydroacylation to Synthesize Branched Ketones

The hydroxyketone products of this study can exist in equilibrium with two diastereomeric hemiketal forms in widely varying ratios and this is noted where appropriate in the characterization data. This phenomenon can give rise to very complicated NMR spectra because purified compounds can exist in three different isomeric forms. For more examples of this phenomenon, see (Murphy, S.K.; Bruch, A.; Dong, V.M. *Angew. Chem. Int. Ed.* **2014**, *53*, 2455.).

4-(2-hydroxy-5-nitrophenyl)-1-phenylpentan-3-one-5-d



To a 1 dram vial was added 4 mol % $[Rh(COD)OMe]_2$ and 8 mol % dcpm. The vinyl phenol (0.2 mmol, 1 equiv), aldehyde (1.5 equiv), and THF (200 µL) were added to the vial which was then sealed with a Teflon-lined screw cap. The reaction was heated to 60 °C for 24 hours and then cooled to room temperature. The branched to linear ratio was determined by integration of the methine proton

(quartet) of the branched product versus the methylene protons of the linear product (triplets) in the crude ¹H NMR spectrum. The product was isolated by preparatory TLC as a colorless oil (54.0 mg, 90%). This compound has very concentration dependent ¹H NMR spectrum and sharp peaks can only be obtained under very dilute conditions. The additional peaks in the

¹H NMR correspond to hemiketal isomers of the product. Only the peaks corresponding to the open-chain form are tabulated here. ¹H NMR (400 MHz, CDCl₃) δ 8.08 (d, *J* = 8.9 Hz, 1H), 7.97 (s, 1H), 7.30 – 7.23 (m, 2H), 7.22 – 7.09 (m, 3H), 6.92 (d, *J* = 8.9 Hz, 1H), 3.92 (br s, 1H), 3.10 – 2.69 (m, 4H), 1.46 (d, *J* = 7.3 Hz, 2H). ²H NMR (77 MHz, CDCl₃) δ 1.47. ¹³C NMR (126 MHz, CDCl₃) δ 213.96, 160.51, 141.14, 140.21, 128.50, 128.18, 126.59, 126.24, 125.38, 124.98, 117.03, 48.51, 43.06, 29.52, 15.20. LRMS (ESI): calcd for [C₁₇H₁₅DNO₄]⁻ 299.11 (100%), 300.12 (18.4%), 301.12 (1.6%), found 298.0 (2.0%), 299.3 (100%), 300.31 (17.0%), 301.35 (2.0%).

4-(2-hydroxy-5-nitrophenyl)-1-phenylpentan-3-one-5-d



To a 1 dram vial was added 4 mol % $[Rh(COD)OMe]_2$ and 8 mol % dcpm. The vinyl phenol (0.2 mmol, 1 equiv), aldehyde (1.5 equiv), and 1,4-dioxane (200 µL) were added to the vial which was then sealed with a Teflon-lined screw cap. The reaction was heated to 100 °C for 24 hours and then cooled to room temperature. The branched to linear ratio was determined by integration of the

methine proton of the branched product versus the methylene protons of the linear product in the crude ¹H NMR spectrum. The product was isolated by preparatory TLC as a white solid (50.3 mg,78%). The compound was isolated with a 92:8 branched:linear ratio. ¹H NMR (500 MHz, CDCl₃) *Linear isomer*: δ 9.36 (s, 1H), 8.71 (s, 1H), 8.25 (d, *J* = 1.8 Hz, 1H), 8.18 – 7.87 (m, 4H), 7.67 (t, *J* = 7.4 Hz, 1H), 7.61 (t, *J* = 7.4 Hz, 1H), 7.03 (d, *J* = 8.9 Hz, 1H), 5.28 (t, *J* = 6.9 Hz, 1H), 1.72 (d, *J* = 6.9 Hz, 1H). *Branched isomer*: δ 3.69 (d, *J* = 6.0 Hz, 1H), 3.17 (t, *J* = 6.0 Hz, 1H). ²H NMR (77 MHz, CDCl₃) δ 1.70. ¹³C NMR (126 MHz, CDCl₃) δ 204.55, 161.05, 141.25, 136.17, 132.46, 132.43, 131.36, 129.97, 129.43, 129.07, 127.88, 127.25, 126.23, 125.18, 124.14, 117.91, 44.23, 17.21 (t, *J* = 20.2 Hz).

4 Preparation of Organometallic Complexes

CL

[Rh(dcpm)]₂Cl



To a 1 dram vial was added [Rh(COD)Cl]₂ (20 mg, 0.041 mmol, 1 equiv) and dcpm (66 mg, 0.162 mmol, 4 equiv). Chloroform (0.5 mL) was added and a homogenous solution was obtained.

 c_{y_2} c_{y_2} Precipitate began to form after approximately 30 seconds. Hexanes was added and the product was collected by decantation. The powder was triturated with hexanes and decanted twice. The product was obtained as an orange powder (33.6 mg, 86 % yield). ¹H NMR (400 MHz, CDCl₃) δ 3.08 – 3.00 (m, 4H), 2.28 – 1.05 (m, 88H). ³¹P NMR (162 MHz, CDCl₃) δ -16.9 (d, *J* = 110.8 Hz). LRMS (ESI) calcd for [C₅₀H₉₂P₄Rh]+ 919.5, found 919.5.

[Rh(4-nitro-2-vinyl-phenolate)₂][(18-crown-6)K]



To a 1 dram vial was added [Rh(COD)OMe]₂ (10 mg, 0.0207 mmol, 1 equiv), 4-nitro-2-vinylphenol (13.6 mg, 0.0826 mmol, 4 equiv), ^tBuOK (4.6 mg, 0.0414 mmol, 2 equiv), and 18-crown-6 (10.9 mg, 0.0414 mmol, 2 equiv). THF (0.650 mL) was added and the solution was shaken for 5 minutes. Hexanes was added to afford a yellow

solid which was decanted, triturated with hexanes, decanted again, and finally dried under vacuum. The product was

obtained as a yellow solid (21 mg, 67% yield). X-ray quality crystals were obtained after two rounds of crystallization from saturated THF/Hexanes solutions. ¹H NMR (600 MHz, d_8 -THF) δ 7.78 (dd, J = 9.0, 2.8 Hz, 2H), 7.67 (d, J = 2.8 Hz, 2H), 6.19 (d, J = 9.0 Hz, 2H), 3.65 (dd, J = 12.1, 8.0 Hz, 2H), 3.61 (s, 24H), 3.50 (dd, J = 12.1, 2.6 Hz, 2H), 2.08 (d, J = 8.0 Hz, 2H), 3.61 (s, 24H), 3.50 (dd, J = 12.1, 2.6 Hz, 2H), 2.08 (d, J = 8.0 Hz, 2H), 3.61 (s, 24H), 3.50 (dd, J = 12.1, 2.6 Hz, 2H), 2.08 (d, J = 8.0 Hz, 2H), 3.61 (s, 24H), 3.50 (dd, J = 12.1, 2.6 Hz, 2H), 2.08 (d, J = 8.0 Hz, 2H), 3.61 (s, 24H), 3.50 (dd, J = 12.1, 2.6 Hz, 2H), 2.08 (d, J = 8.0 Hz, 2H), 3.61 (s, 24H), 3.50 (dd, J = 12.1, 2.6 Hz, 2H), 3.61 (s, 24H), 3.50 (dd, J = 12.1, 2.6 Hz, 2H), 3.61 (s, 24H), 3.51 (s, 24H), 3.50 (dd, J = 12.1, 2.6 Hz, 2H), 3.61 (s, 24H), 3.51 (s, 24H), 3.50 (dd, J = 12.1, 2.6 Hz, 2H), 3.61 (s, 24H), 3.51 (s, 24H), 3.50 (s, 24H), 3.51 (s, 25H), 3.51 (s, 25H)2H). ¹³C NMR (126 MHz, d_8 -THF) δ 180.10, 136.31, 135.73, 126.11, 123.06, 116.42, 75.34 (d, J = 12.0 Hz), 71.27, 58.06 (d, J = 15.4 Hz). LRMS (ESI) calcd for $[C_{16}H_{12}N_2O_6Rh]^- 431.0$, found 431.0.

[Rh(dcpm)]₂[Rh(4-nitro-2-vinyl-phenolate)₂]



To a 1 dram vial was added [Rh(COD)OMe]₂ (10 mg, 0.0207 mmol, 1 equiv), dcpm (16.9 mg, 0.0413 mmol, 2 equiv), and 4-nitro-2vinylphenol (6.8 mg, 0.0413 mmol, 2 equiv). THF (0.400 mL) was

added and the solution was heated to 60 °C until the reaction became homogeneous. The solution was cooled to room temperature and filtered into a separate vial. Hexanes (2 mL) was added to the solution and then the vial was sealed and placed in a -30 °C freezer for 24 hours. The precipitate was decanted, triturated with hexanes, decanted again, and finally dried under reduced pressure. The product was obtained as an orange powder (35.0 mg, 75 % yield) contaminated with approximately 10% of $[Rh(dcpm)_2]^+(4-nitro-2-vinylphenolate)^-$. Spectroscopic data were very similar to $[Rh(dcpm)_2]^2Cl$ and $[Rh(4-nitro-2-vinyl-phenolate)_2][(18-crown-6)K]$. ¹H NMR (600 MHz, d_8 -THF) δ 7.77 (dd, J = 9.1, 2.8 Hz, 2H), 7.66 (d, J = 9.1, 2.8 Hz 2.8 Hz, 2H), 6.13 (d, J = 9.1 Hz, 2H), 3.64 - 3.56 (m, 2H), 3.49 (dd, J = 12.1, 2.2 Hz, 1H), 3.26 - 3.20 (m, 4H), 2.19 (d, J = 12.1, 2.2 Hz, 1H), 3.26 - 3.20 (m, 4H), 2.19 (d, J = 12.1, 2.2 Hz, 1H), 3.26 - 3.20 (m, 4H), 2.19 (d, J = 12.1, 2.2 Hz, 1H), 3.26 - 3.20 (m, 4H), 2.19 (d, J = 12.1, 2.2 Hz, 1H), 3.26 - 3.20 (m, 4H), 2.19 (d, J = 12.1, 2.2 Hz, 1H), 3.26 - 3.20 (m, 4H), 3.26 (m, 11.8 Hz, 8H), 2.05 (d, J = 7.9 Hz, 2H), 1.97 – 1.20 (m, 80H). ¹³C NMR (126 MHz, d_8 -THF) δ 181.30, 136.69, 136.47, 126.91, 123.72, 116.88, 75.92 (d, J = 11.9 Hz), 58.52 (d, J = 15.2 Hz), 38.41 (d, J = 5.1 Hz), 31.46, 30.10, 29.23 - 28.97 (m), 28.76 – 28.63 (m), 27.76 (s). ³¹**P** NMR (162 MHz, d_8 -THF) δ -17.2 (d, J = 110.7 Hz). LRMS (ESI) calcd for $[C_{50}H_{92}P_4Rh]^+$ 919.5, found 919.5; calcd for [C₁₆H₁₂N₂O₆Rh]⁻ 431.0, found 431.0.

[Rh(dcpm)(COD)]BF₄



A solution of dcpm (20 mg, 0.0493 mmol, 1 equiv) in DCM (1.5 mL) was added dropwise to a BF₄⁻ solution of [Rh(COD)₂]BF₄ (20 mg, 0.0493 mmol, 1 equiv) in DCM (1.5 mL) in a 20 mL vial. The resulting solution was filtered and the solvent was removed under reduced pressure. The solid was triturated with hexanes and decanted. The solid was dissolved in chloroform and THF and then precipitated with hexanes. The product was isolated as an orange powder (25 mg, 69 % yield). ¹H NMR (400 MHz, CDCl₃) δ 5.37 (s, 4H), 3.28 (t, J =

9.9 Hz, 2H), 2.33 (s, 8H), 2.18 – 1.13 (m, 44H). ³¹P NMR (162 MHz, CDCl₃) δ -27.1 (d, J = 125.0 Hz). LRMS (ESI) calcd for $[C_{33}H_{58}P_2Rh]^+$ 619.3, found 619.2.

[Rh(dcpm)(4-nitro-2-vinylphenolate)]



To a 1 dram vial was added [Rh(dcpm)(COD)]BF₄ (6.4 mg, 0.0089 mmol, 1 equiv.), 4-nitro-2vinylphenol (1.5 mg, 0.0089 mmol, 1 equiv.) and ^tBuOK (1.0 mg, 0.0089 mmol). d₈-THF (0.65 mL) was added and a white precipitate formed (KBF₄). The solution was transferred to an NMR

tube and sealed with a septum and parafilm. The product was formed in ca. 98% NMR yield. Repeating this experiment on larger scale lead to NMR yields that varied from 90-99%. Attempts to crystallize this compound were unsuccessful. The coupling of the carbons of the olefin and both Rh and P in the ¹³C NMR are characteristic of the title compound. ¹H NMR (400 MHz, d_8 -THF) δ 7.69 (d, J = 9.2 Hz, 1H), 7.61 (s, 1H), 6.08 (d, J = 9.2 Hz, 1H), 5.49 – 5.40 (m, 1H), 4.63 (d, J = 14.8 Hz, 1H), 4.51 – 4.42 (m, 1H), 3.02 – 2.72 (m, J = 27.5 Hz, 2H), 2.44 – 0.71 (m, 44H). ¹³C NMR δ 135.44, 132.83, 130.08, 127.17, 124.62, 118.03, 94.94 – 94.64 (m), 78.49 – 78.10 (m), 32.60, 31.7 – 31.3 (m), 29.72, 28.92 (d, J = 12.0 Hz), 27.84. ³¹P NMR (162 MHz, CDCl₃) δ 0.41 (dd, J = 125.4, 92.3 Hz), -27.15 (dd, J = 147.9, 92.3 Hz).

[Rh(dcpm)(4-nitro-2-vinylphenolate)(hydrocinnamaldehyde)]



To the NMR sample from the synthesis of [Rh(dcpm)(4-nitro-2-vinylphenolate)] (above) was added 5 µL of hydrocinnamaldehyde. The title compound could be observed in small quantities (ca. 10 %) transiently before being converted to the hydroacylation product below. Larger quantities could be formed if excess 4-nitro-2vinylphenol and aldehyde were added to establish a steady state concentration of the title compound. However, due to the high concentration of

reagents required to form this complex, we could only characterize it by ³¹P NMR. We assign the structure as the title compound by comparison of the chemical shift and coupling constants to [Rh(dcpm)(4-nitro-2-vinylphenolate)]. Both the title compound and [Rh(dcpm)(4-nitro-2-vinylphenolate)] display a ³¹P peak at about 1 ppm with a coupling constant to Rh of ca. 125 Hz. We assign this peak as the phosphine trans to the phenoxide. A new peak at -9.9 ppm is present in the title compound which we assign as the phosphine trans to the aldehyde. ³¹P NMR (162 MHz, CDCl₃) δ 1.7 (dd, *J* = 126, 69 Hz), -9.9 (dd, *J* = 117, 69 Hz).

[Rh(dcpm)(COD)][4-nitro-2-(3-oxo-5-phenlypentan-2-yl)phenolate]



The title compound was synthesized according to the same procedure for [Rh(dcpm)(4-nitro-2-vinylphenolate)(hydrocinnamaldehyde)] except that a large excess of hydrocinnamaldehyde (100 µL) was added which resulted in immediate hydroacylation at room temperature (ca. 80% yield). ³¹P analysis

showed a doublet at -27.1 ppm indicative of the [Rh(dcpm)(COD)]⁺ fragment based on analogy to [Rh(dcpm)(COD)]BF₄. Analysis of the reaction mixture by ESI MS confirmed formation of [Rh(dcpm)(COD)]⁺ and the anion of the hydroacylation product. As well, a dimer of the hydroacylation product and its phenolate was observed by ESI MS when both excess aldehyde and olefin were added. ³¹P NMR (162 MHz, CDCl₃) δ -26.95 (d, *J* = 125.7 Hz). LRMS (ESI) calcd for [C₃₃H₅₈P₂Rh]+ 619.3, found 619.2. Calcd for [C₁₇H₁₆NO₄]- 298.1, found 298.3. Calcd for [C₃₄H₃₃N₂O₈]- 597.2, found 597.4.

8 NMR Spectra











S9















[(18-crown-6)K]⁺





















(from a reaction with excess aldehyde and olefin at steady state concentration, peaks in red brackets correspond to the title compound)







8. Crystallographic Data



Tuble 1. Crystal data and structure reminent for vindify.				
Identification code	vmd13			
Empirical formula	$\mathrm{C}_{28}\mathrm{H}_{36}\mathrm{K}\mathrm{N}_{2}\mathrm{O}_{12}\mathrm{Rh}\bullet\mathrm{C}_{4}\mathrm{H}_{8}\mathrm{O}$			
Formula weight	806.70			
Temperature	88(2) K			
Wavelength	0.71073 Å			
Crystal system	Monoclinic			
Space group	Cc			
Unit cell dimensions	a = 13.6052(6) Å	a= 90°.		
	b = 19.6523(9) Å	b= 105.5588(5)°.		
	c = 14.3113(7) Å	g = 90°.		
Volume	3686.2(3) Å ³			
Z	4			
Density (calculated)	1.454 Mg/m ³			
Absorption coefficient	0.640 mm ⁻¹			
F(000)	1672			
Crystal color	yellow			
Crystal size	0.315 x 0.175 x 0.144 mm ³			
Theta range for data collection	1.868 to 27.103°			
Index ranges	$-17 \le h \le 17, -25 \le k \le 25, -18 \le l \le 18$			
Reflections collected	20977			

Table 1. Crystal data and structure refinement for vmd13.

Independent reflections	8111 [R(int) = 0.0170]	
Completeness to theta = 25.242°	99.9 %	
Absorption correction	Numerical	
Max. and min. transmission	0.9581 and 0.8741	
Refinement method	Full-matrix least-squares on F ²	
Data / restraints / parameters	8111 / 2 / 423	
Goodness-of-fit on F ²	1.067	
Final R indices [I>2sigma(I) = 7920 data]	R1 = 0.0258, wR2 = 0.0650	
R indices (all data, 0.78Å)	R1 = 0.0267, wR2 = 0.0658	
Absolute structure parameter	0.51(3)	
Largest diff. peak and hole	0.550 and -0.336 e.Å ⁻³	