# Co(II)-Catalyzed Isomerization of Enals using Hydrogen Atom Transfer

Qiqige Qiqige,[1] Edward Richmond,[2]* Rocco Paciello,[2] Mathias Schelwies,[2] Rylan J. Lundgren[1]*

1. Department of Chemistry, University of Alberta, Edmonton, Alberta T6G 2G2, Canada
2. BASF SE, Synthesis & Homogeneous Catalysis, Carl-Bosch-Strasse 38, 67056 Ludwigshafen am Rhein, Germany

*Corresponding authors; email: edward.richmond@basf.com; rylan.lundgren@ualberta.ca

## Contents

## I. General Considerations

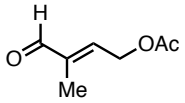
Unless noted, all reactions were set up in a $N_2$-filled glovebox. All glassware was oven-dried prior to use. Parr high pressure reactors (Series 4750 vessels with split ring closure) were used for high pressure reactions. Unless noted, yields and conversions were determined by quantitative $^1H$ NMR with NMP as the internal standard. Flash chromatography was performed as described by Still and co-workers[1] (SiliaFlash P60, 40-63μm, 60Å silica gel, Silicycle) or by automated flash chromatography (Isolera, HP-SIL silica cartridges, Biotage). Analytical thin-layer chromatography was performed using glass plates pre-coated with silica (SiliaPlate G TLC - Glass-Backed, 250μm, Silicycle). TLC plates were visualized by UV light and/or staining with aqueous basic potassium permanganate. HRMS analyses of the products were performed on an Agilent Technologies 6220 oaTOF instrument (ESI, APPI, APCI) in positive or negative ionization mode or a Kratos MS50G Double Focussing Sector (EB/EI) instrument in positive mode. NMR spectra ($^1H$, $^{13}C$, $^{19}F$) were obtained on an Agilent VNMRS 700 MHz, Varian VNMRS 600 MHz, Varian VNMRS 500 MHz, or Varian 400 MHz spectrometer. The chemical shifts are given as parts per million (ppm) and were referenced to the residual solvent signal ($CDCl_3$: $\delta H$ = 7.26 ppm, $\delta C$ = 77.06 ppm). $Co(dmgBF_2)_2 \bullet 2H_2O$ and $Co(dmgH)_2 \bullet 2H_2O$ was synthesized using a literature procedure.[2] Ligands were purchased from Sigma-Aldrich, Strem Chemicals, Combi-blocks, Alfa Aesar, or Acros. Substrates were obtained from commercial vendors and used as supplied. Substrates (**4, 5, 8, 9**),[3] **6**,[4] **7**,[5] **10**,[6] **11**,[7] **12**,[8] **13**,[9] **14**,[10] **15**,[11] **16**,[12] (**17**, **18**),[13] **20**[14] and **21**[15] were synthesized by literature procedures.

## II. Procedure for Isomerization

**General Procedure 1 (Co-catalyzed isomerization):** In a glovebox filled with $N_2$, $Co(dmgBF_2)_2 \bullet 2H_2O$ (0.0125 mmol, 5.3 mg) was added in a 2-dram vial followed by substrate **1** (0.5 mmol, 71.0 mg) and N-methyl-2-pyrrolidone (5–10 mg). Toluene (5.0 mL) and a stir-bar was added into the mixture, the vial was sealed with a PTFE-line cap pierced with an 18-gauge needle, then the vial was placed into a high-pressure reactor. The high-pressure reactor was sealed and taken out of the glovebox. The $N_2$ atmosphere of the reactor was replaced by $H_2$ by charging to 50–150 psi, then carefully releasing the pressure, this process was repeated two more times. The reaction mixture was stirred under corresponding $H_2$ pressure (75–100 psi) at 50 ºC for two hours. Upon completion of the reaction, the reactor was cooled to room temperature, and $H_2$ was released. The reaction vial was taken out from the reactor and the crude yield was determined using $^1H$ NMR by removing a small aliquot (~10 μL) of the reaction mixture and diluting with $CDCl_3$. Reported terminal NMR yields were obtained in a similar manner. The product was then purified by silica gel chromatography by loading the reaction mixture directly on to the column.

**General Procedure 2 (Rh-catalyzed isomerization):** In a glovebox filled with $N_2$, a stock solution was made by mixing $RhCl_3 \bullet 3H_2O$ (0.015 mmol, 3.9 mg) with 4-4′-dimethyl-2-2′-bipyridine (0.015 mmol, 2.7 mg) in a 1:1 molar ratio in dioxane (3.6 mL) at room temperature for 30 minutes. The catalyst solution (2.4 mL, 0.01 mmol) was transferred into a 2-dram vial charged with substrate **1** (0.2 mmol, 28.4 mg) and NMP (5–10 mg) in EtOH (1.4 mL). A stir-bar was added into the mixture, the vial was sealed with a PTFE-line cap and taken out of the glovebox. Then, 0.2 mL pH 7 buffer (dihydrogen potassium phosphate-sodium phosphate dibasic, 0.05 M in $H_2O$) was added using a syringe, and the reaction mixture was stirred at 80 ºC overnight. The reaction was monitored periodically until the consumption of the starting material stopped, and the crude yield was determined using $^1H$ NMR by removing a small aliquot (~10 μL) of the reaction mixture and diluting with $CDCl_3$.

## III. Specific Experimental Details and Product Characterization Data



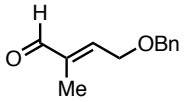

**2** Prepared according to General Procedure 1 from the corresponding enal **1** (71.0 mg, 0.50 mmol), 50 ºC, 2 h. $^1$H NMR conversion: 90%, crude yield: 90%. Isolated in 96% yield as a mixture of product and substrate (87% yield of **2** with 91:9 **2**/**1**) and as a colourless oil after purification by silica column chromatography (25% pentane in diethyl ether).

**$^1$H NMR** ($CDCl_3$, 500 MHz, product) δ 9.45 (s, 1H), 6.49 (tq, *J* = 6.0, 1.4 Hz, 1H), 4.89 (dq, *J* = 6.0, 1.1 Hz, 2H), 2.12 (s, 3H), 1.79 (d, *J* = 1.1 Hz, 3H);

**$^1$H NMR** ($CDCl_3$, 500 MHz, residual substrate) δ 9.54 (s, 1H), 6.34 (s, 1H), 6.10 (s, 1H), 4.18 (t, *J* = 6.6 Hz, 2H), 2.59 (td, *J* = 6.6, 1.1 Hz, 2H), 2.02 (s, 3H);

**$^{13}$C NMR** ($CDCl_3$, 125 MHz) δ 194.1, 170.6, 145.7, 140.6, 60.9, 20.8, 9.5;

**HRMS (ESI):** calcd. for $C_7H_{10}O_3Na$ $[M+Na]^+$ 165.0522. Found 165.0521.

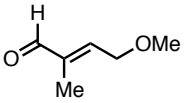



**4-H** Prepared according to General Procedure 1 from the corresponding enal **4** (95.0 mg, 0.50 mmol), 50 ºC, 2 h. $^1$H NMR conversion: 94%, crude yield: 94%. Isolated in 90% yield as a colourless oil after purification by silica column chromatography (25% pentane in diethyl ether).

**$^1$H NMR** ($CDCl_3$, 500 MHz) δ 9.45 (s, 1H), 7.39–7.31 (M, 5H), 6.61 (tq, *J* = 5.6, 1.3 Hz, 1H), 4.59 (S, 2H), 4.36 (dq, *J* = 5.6, 1.1 Hz, 2H), 1.73 (s, 3H);

**$^{13}$C NMR** ($CDCl_3$, 125 MHz) δ 194.5, 149.5, 139.5, 137.5, 128.6, 128.1, 127.9, 73.2, 66.8, 9.6;

**HRMS (ESI):** calcd. for $C_{12}H_{14}O_2Na$ $[M+Na]^+$ 213.0886. Found 213.0885.

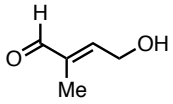



**5-H** Prepared according to General Procedure 1 from the corresponding enal **5** (57.0 mg, 0.50 mmol), 50 ºC, 2 h. $^1$H NMR conversion: 94%, crude yield: 81%. Isolated in 84% yield as a colourless oil after purification by silica column chromatography (25% pentane in diethyl ether).

**$^1$H NMR** ($CDCl_3$, 500 MHz) δ 9.44 (s, 1H), 6.54 (tq, *J* = 5.6, 1.2 Hz, 1H), 4.27 (dq, *J* = 5.6, 1.2 Hz, 2H), 3.41 (s, 3H), 1.75 (q, *J* = 1.2 Hz, 3H);

**$^{13}$C NMR** ($CDCl_3$, 125 MHz) δ 194.4, 149.4, 139.5, 69.3, 58.8, 9.5;

**HRMS (ESI):** calcd. for $C_6H_{10}O_2Na$ $[M+Na]^+$ 137.0573. Found 137.0573.

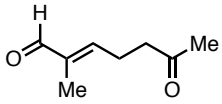



**6-H** Prepared according to General Procedure 1 from the corresponding enal **6** (100.1 mg, 1.00 mmol), 50 ºC, 2 h. $^1$H NMR conversion: 98%, crude yield: 90%. Isolated in 90% yield as a colourless oil after purification by silica column chromatography (30% pentane in diethyl ether).

**$^1$H NMR** ($CDCl_3$, 500 MHz) δ 9.44 (s, 1H), 6.60 (tq, *J* = 5.7, 1.3 Hz, 1H), 4.57–4.53 (m, 2H), 2.00 (brs, 1H), 1.77 (s, 3H);

**$^{13}$C NMR** ($CDCl_3$, 125 MHz) δ 194.7, 151.6, 138.8, 59.8, 9.5;

**HRMS (ESI):** calcd. for $C_5H_8O_2Na$ $[M+Na]^+$ 123.0417. Found 123.0418.



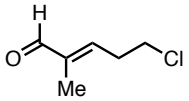

**7-H** Prepared according to General Procedure 1 from the corresponding enal **7** (35.0 mg, 0.25 mmol), 50 ºC, 2 h. $^1$H NMR conversion: >99%, crude yield: >98%, 92:8 *E*/*Z* ratio. Isolated in 88% yield as a mixture of geometric isomers (92:8 *E*/*Z*) and as a colourless oil after purification by silica column chromatography (25% pentane in diethyl ether).

**$^1$H NMR** ($CDCl_3$, 500 MHz, major, *E*-product) δ 9.37 (s, 1H), 6.42 (tq, *J* = 7.0, 1.4 Hz, 1H), 2.67–2.64 (m, 2H), 2.62–2.57 (m, 2H), 2.18 (s, 3H), 1.76 (d, *J* = 1.4 Hz, 3H);

**$^1$H NMR** ($CDCl_3$, 500 MHz, minor, *Z*-product) δ 9.47 (s, 1H), 6.74 (tq, *J* = 6.9, 1.4 Hz, 1H), 3.51 (d, *J* = 7.0Hz, 2H), 2.67–2.64 (m, 2H), 2.25 (s, 3H), 1.75 (s, 3H);

**$^{13}$C NMR** ($CDCl_3$, 125 MHz, major, *E*-prod) δ 206.8, 195.1, 152.4, 140.1, 41.8, 29.9, 23.0, 9.2;

**HRMS (ESI):** calcd. for $C_8H_{12}O_2Na$ $[M+Na]^+$ 163.0730. Found 163.0729.

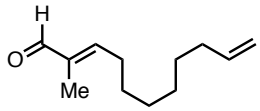


**8-H** Prepared according to General Procedure 1 from the corresponding enal **8** (66.5 mg, 0.50 mmol), 50 ºC, 2 h. $^1$H NMR conversion: >99%, crude yield: 91%. Isolated in 81% yield as a colourless oil after purification by silica column chromatography (20% pentane in diethyl ether).

**$^1$H NMR** ($CDCl_3$, 500 MHz) δ 9.45 (s, 1H), 6.51 (tq, *J* = 7.3, 1.4 Hz, 1H), 3.67 (t, *J* = 6.7 Hz, 2H), 2.83 (dt, *J* = 7.3, 6.7 Hz, 2H), 1.78 (s, 3H);

**$^{13}$C NMR** ($CDCl_3$, 125 MHz) δ 194.8, 184.7, 141.4, 42.6, 31.9, 9.5;

**HRMS (ESI):** calcd. for $C_6H_9ONa$ $[M+Na]^+$ 155.0234. Found 155.0232.

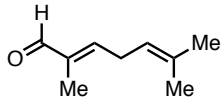



**9-H** Prepared according to General Procedure 1 from the corresponding enal **9** (90.0 mg, 0.50 mmol), 50 ºC, 2 h. $^1$H NMR conversion: >99%, crude yield: 90%. Isolated in 89% yield as a colourless oil after purification by silica column chromatography (5% pentane in diethyl ether).

**$^1$H NMR** ($CDCl_3$, 500 MHz) δ 9.40 (s, 1H), 6.49 (tq, *J* = 7.5, 1.3 Hz, 1H), 5.85–5.76 (m, 1H), 5.02–4.92 (m, 2H), 2.35 (td, *J* = 7.3, 7.3 Hz, 2H), 2.05 (td, *J* = 7.5, 6.7 Hz, 2H), 1.74 (s, 3H), 1.54–1.48 (m, 2H), 1.42–1.32 (m, 6H);

**$^{13}$C NMR** ($CDCl_3$, 125 MHz) δ 195.4, 155.0, 139.4, 139.0, 114.4, 33.7, 29.2, 29.0, 28.9, 28.8, 28.4, 9.2;

**HRMS (ESI):** calcd. for $C_{12}H_{20}ONa$ $[M+Na]^+$ 203.1406. Found 203.1402.

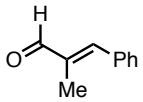



**10-H** Prepared according to General Procedure 1 from the corresponding enal **10** (69.0 mg, 0.50 mmol), 50 ºC, 2 h. $^1$H NMR conversion: >99%, crude yield: 90%. Isolated in 90% yield as a colourless oil after purification by silica column chromatography (5% pentane in diethyl ether).

**$^1$H NMR** ($CDCl_3$, 500 MHz) δ 9.39 (s, 1H), 6.43 (tq, *J* = 6.7, 1.3 Hz, 1H), 5.16 (t, *J* = 7.2 Hz, 1H), 3.03 (dd, *J* = 7.2, 6.7 Hz, 2H), 1.77 (s, 3H), 1.73 (s, 3H), 1.67 (s, 3H);

**$^{13}$C NMR** ($CDCl_3$, 125 MHz) δ 195.4， 153.2， 138.9， 134.6， 119.3， 28.2， 25.7， 17.9， 9.2;

**HRMS (ESI):** calcd. for $C_9H_{14}ONa$ $[M+Na]^+$ 161.0937. Found 161.0937.

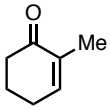



**11-H** Prepared according to General Procedure 1 from the corresponding enal **11** (73.0 mg, 0.50 mmol), 50 ºC, 2 h. $^1$H NMR conversion: >99%, crude yield: 98%. Isolated in 93% yield as a colourless oil after purification by silica column chromatography (5% pentane in diethyl ether).

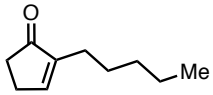
**$^1$H NMR** ($CDCl_3$, 500 MHz) δ 9.60 (s, 1H), 7.55–7.53 (m, 2H), 7.47–7.44 (m, 2H), 7.42–7.40 (m, 1H), 7.27 (d, *J* = 1.1 Hz, 1H), 2.09 (d, *J* = 1.1 Hz, 3H);

**$^{13}$C NMR** ($CDCl_3$, 125 MHz) δ 195.6, 149.8, 138.4, 135.2, 130.1, 129.6, 128.7, 11.0;

**HRMS (ESI):** calcd. for $C_{10}H_{10}ONa$ $[M+Na]^+$ 169.0624. Found 169.0625.




**12-H** Prepared according to General Procedure 1 from the corresponding enone **12** (11.0 mg, 0.10 mmol), 50 ºC, 2 h. $^1$H NMR conversion: >99%, crude yield: >98%. Spectroscopic data for the product agreed with the literature.[16]

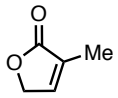



**13-H** Prepared according to General Procedure 1 from the corresponding enone **13** (76.0 mg, 0.50 mmol), 50 ºC, 2 h. $^1$H NMR conversion: >99%, crude yield: 85%. Isolated in 82% yield as a colourless oil after purification by silica column chromatography (5% pentane in diethyl ether).

**$^1$H NMR** ($CDCl_3$, 500 MHz) δ 7.30–7.28 (m, 1H), 2.57–2.54 (m, 2H), 2.40–2.38 (m, 2H), 2.18–2.13 (m, 2H), 1.50–1.44 (m, 2H), 1.34–1.26 (m, 4H), 0.89–0.87 (m, 3H);

**$^{13}$C NMR** ($CDCl_3$, 125 MHz) δ 210.1, 157.3, 146.6, 34.7, 31.6, 27.5, 26.5, 24.8, 22.5, 14.0;

**HRMS (ESI):** calcd. for $C_{10}H_{16}ONa$ $[M+Na]^+$ 175.1093. Found 175.1090.

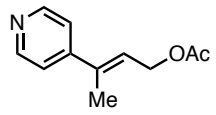


**14-H** Prepared according to General Procedure 1 from the corresponding lactone **14** (49.0 mg, 0.50 mmol), 50 ºC, 2 h. $^1$H NMR conversion: >99%, crude yield: 98%. Isolated in 94% yield as a colourless oil after purification by silica column chromatography (25% pentane in diethyl ether).

**$^1$H NMR** ($CDCl_3$, 500 MHz) δ 7.14–7.12 (m, 1H), 4.76–4.74 (m, 2H), 1.94–1.92 (m, 3H);

**$^{13}$C NMR** ($CDCl_3$, 125 MHz) δ 174.8, 144.9, 130.0, 70.0, 10.7;

**HRMS (ESI):** calcd. for $C_5H_6O_2Na$ $[M+Na]^+$ 121.0260. Found 121.0260.

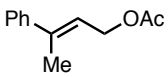



**15-H** Prepared according to General Procedure 1 from the corresponding substrate **16** (19.1 mg, 0.10 mmol), 50 ºC, 2 h. $^1$H NMR conversion: 94%, crude yield: 49%. Reduced yield is likely due to substrate hydrogenation. Isolated in 50% yield as a mixture of product and substrate (90:10 *E*/**16**) colourless oil after purification by silica column chromatography (25% pentane in diethyl ether).

**$^1$H NMR** ($CDCl_3$, 500 MHz, major, *E*-product) δ 8.56–8.55 (m, 2H), 7.29–7.28 (m, 2H), 6.07 (tq, *J* = 6.8, 1.3 Hz, 1H), 4.80 (dd, *J* = 6.8, 0.7 Hz, 2H), 2.10 (s, 6H);

**$^{13}$C NMR** ($CDCl_3$, 125 MHz, major, *E*-product) δ 171.0, 150.0, 149.6, 137.4, 124.8, 120.4, 61.4, 21.0, 15.5;

**HRMS (ESI):** calcd. for $C_{11}H_{14}O_2N$ $[M+H]^+$ 192.1019. Found 192.1019.



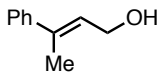

**16-H** Prepared according to General Procedure 1 from the corresponding substrate **17** (34.2 mg, 0.18 mmol), 50 ºC, 2 h. $^1$H NMR conversion: 86%, crude yield: 86%, 76:24 *E*/*Z* ratio. Isolated in 90% yield as a mixture of geometric isomers (77:18:5 *E*/*Z*/**17**) as a colourless oil after purification by silica column chromatography (10% pentane in diethyl ether).

**$^1$H NMR** ($CDCl_3$, 500 MHz, major, *E*-product) δ 7.42–7.40 (m, 2H), 7.35–7.32 (m, 2H), 7.29–7.26 (m, 1H), 5.90 (tq, *J* = 7.0, 1.4 Hz, 1H), 4.79 (d, *J* = 7.0 Hz, 2H), 2.12 (s, 3H), 2.09 (s, 3H);

**$^1$H NMR** ($CDCl_3$, 500 MHz, minor, *Z*-product) δ 7.35–7.26 (m, 3H), 7.19–7.17 (m, 2H), 5.66 (tq, *J* = 7.2, 1.5 Hz, 1H), 4.50 (dd, *J* = 7.2, 0.9 Hz, 2H), 2.11 (d, *J* = 0.9 Hz, 3H), 2.05 (s, 3H);

**$^{13}$C NMR** ($CDCl_3$, 125 MHz, major, *E*-product) δ 171.1, 142.6, 140.2, 128.3, 127.6, 125.9, 121.4, 61.7, 21.1, 16.2;

**HRMS (ESI):** calcd. for $C_{12}H_{14}O_2Na$ $[M+Na]^+$ 213.0886. Found 213.0883.

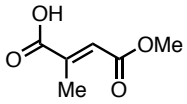



**17-H** Prepared according to General Procedure 1 from the corresponding substrate **18** (74.0 mg, 0.5 mmol), 50 ºC, 2 h. $^1$H NMR conversion: 83%, crude yield: 69%, 77:23 *E*/*Z* ratio. Isolated in 55% yield as a mixture of product and substrate (95:5 *E*/**18**) as a colourless oil after purification by silica column chromatography (30% pentane in diethyl ether).

**$^1$H NMR** ($CDCl_3$, 500 MHz) δ 7.42–7.41 (m, 2H), 7.35–7.32 (m, 2H), 7.28–7.26 (m, 1H), 5.98 (tq, *J* = 6.7, 1.3 Hz, 1H), 4.37 (d, *J* = 6.7 Hz, 2H), 2.09 (s, 3H);

**$^{13}$C NMR** ($CDCl_3$, 125 MHz) δ 142.9, 138.0, 128.3, 127.3, 126.5, 125.8, 60.0, 16.1;

**HRMS (ESI):** calcd. for $C_{10}H_{12}ONa$ $[M+Na]^+$ 171.0780. Found 171.0779.




**18-H** Prepared according to General Procedure 1 from itaconic acid monomethyl ester **19** (14.4 mg, 0.10 mmol), 80 ºC, 5 h. $^1$H NMR conversion: 79%, crude yield: 75%. Isolated in 68% yield as a white solid after purification by silica column chromatography (10% hexane in EtOAc).

**$^1$H NMR** ($CDCl_3$, 500 MHz) δ 6.89 (q, *J* = 1.6 Hz, 1H), 3.15 (s, 3H), 2.30 (d, *J* = 1.6 Hz, 3H);

**$^{13}$C NMR** ($CDCl_3$, 125 MHz) δ 171.4, 166.1, 142.7, 128.3, 51.9, 14.0;

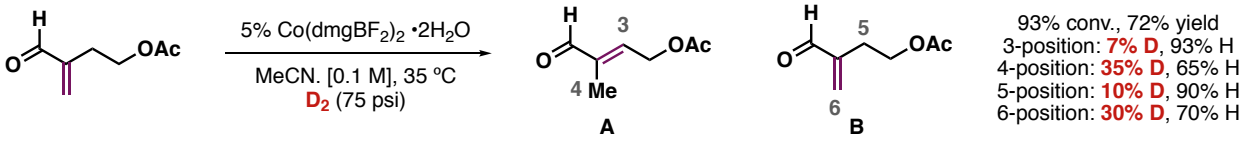
**HRMS (ESI):** calcd. for $C_6H_7O_4$ $[M-H]^-$ 143.0350. Found 143.0351.

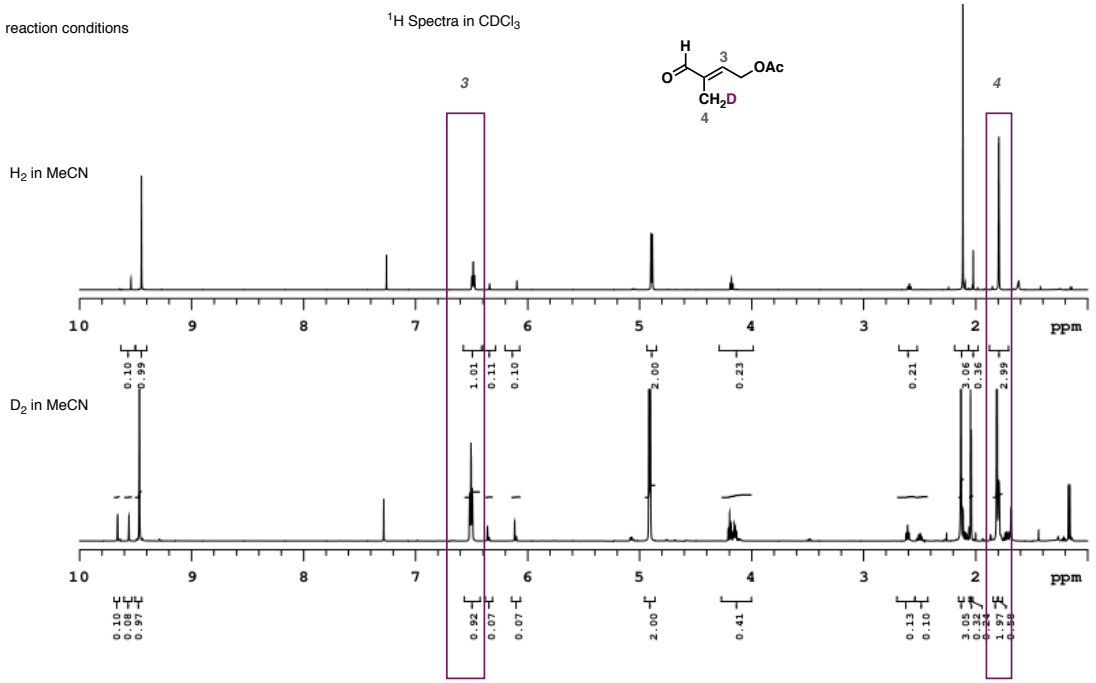
## IV. H/D Labeling Experiments

### 1. General Procedure for D-labeling experiments

In a glovebox filled with $N_2$, $Co(dmgBF_2)_2 \bullet 2H_2O$ (0.0025 mmol, 2.1 mg) was added in a 2 mL vial followed by substrate **1** (0.1 mmol, 14.2 mg) and N-methyl-2-pyrrolidone (5–10 mg). Acetonitrile (1.0 mL) and a stir-bar was added into the mixture, the vial was sealed with a PTFE-line cap pierced with an 18-gauge needle, then the vial was placed into a high-pressure reactor. The high-pressure reactor was sealed and taken out of the glovebox. The $N_2$ atmosphere of the reactor was replaced by $D_2$ by charging to 50–150 psi, then carefully releasing the pressure, this process was repeated two more times. The reaction mixture was stirred under corresponding $D_2$ pressure (75–100 psi). Upon completion of the reaction, the reactor was cooled to room temperature, and $D_2$ was released. The reaction vial was taken out from the reactor and the crude yield was determined using $^1H$ NMR by removing a small aliquot (~10 μL) of the reaction mixture and diluting with $CDCl_3$.

## 2. D-Labeling results with Substrate 1



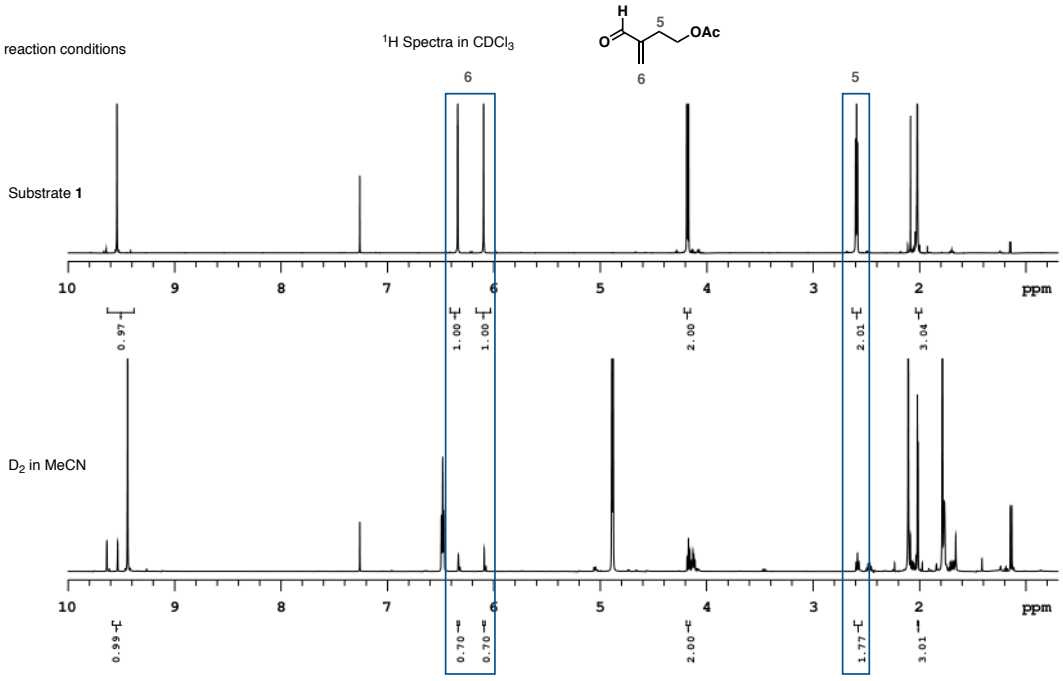
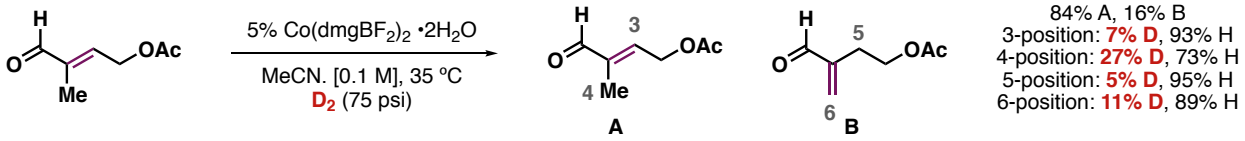



**Fig S1**. Overview of D-labeling results with substrate **1**. Estimated error in values is ~5% due to small amounts of over-hydrogenation and error in integration

### 3. D-Labeling results with 2



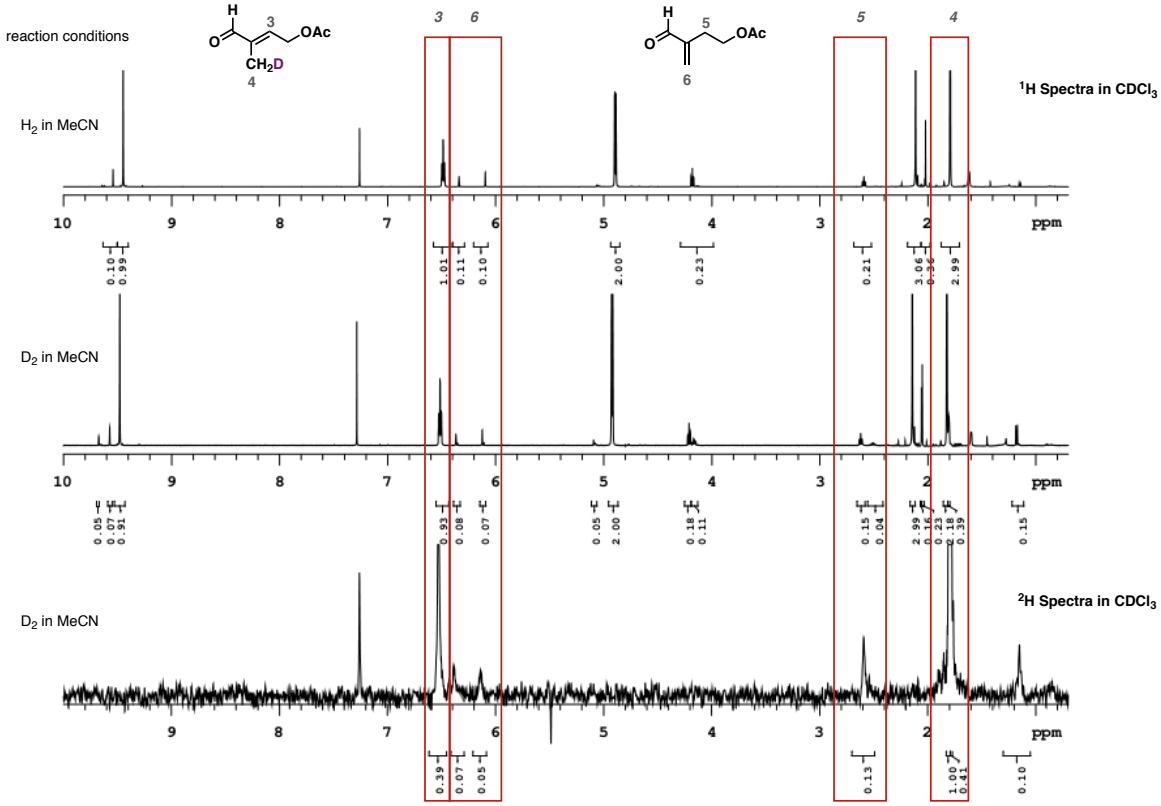




**Fig S2**. Overview of D-labeling results with substrate **2**. Estimated error in values is ~5% due to small amounts of over-hydrogenation and error in integration.

## V. Reaction Kinetics

### 1. [Co]-condition

In a glovebox filled with $N_2$, $Co(dmgBF_2)_2 \bullet 2H_2O$ (0.0025 mmol, 2.1 mg) was added in a GC vial followed by substrate **1** (0.1 mmol, 14.2 mg) and N-methyl-2-pyrrolidone (5–10 mg). $d_3$-Acetonitrile (1.0 mL) and a stir-bar was added into the mixture, the vial was sealed and stirred at room temperature until everything dissolved (~10 min). The reaction mixture (0.7 mL) was transferred to a J. Young NMR tube, and the tube was sealed and taken out of the glovebox. The $N_2$ atmosphere of the tube was replaced by $H_2$ by purging with a $H_2$ balloon for ~5 min. Then, the mixture was sealed under $H_2$ and warmed to 35 ºC while analyzing by NMR.

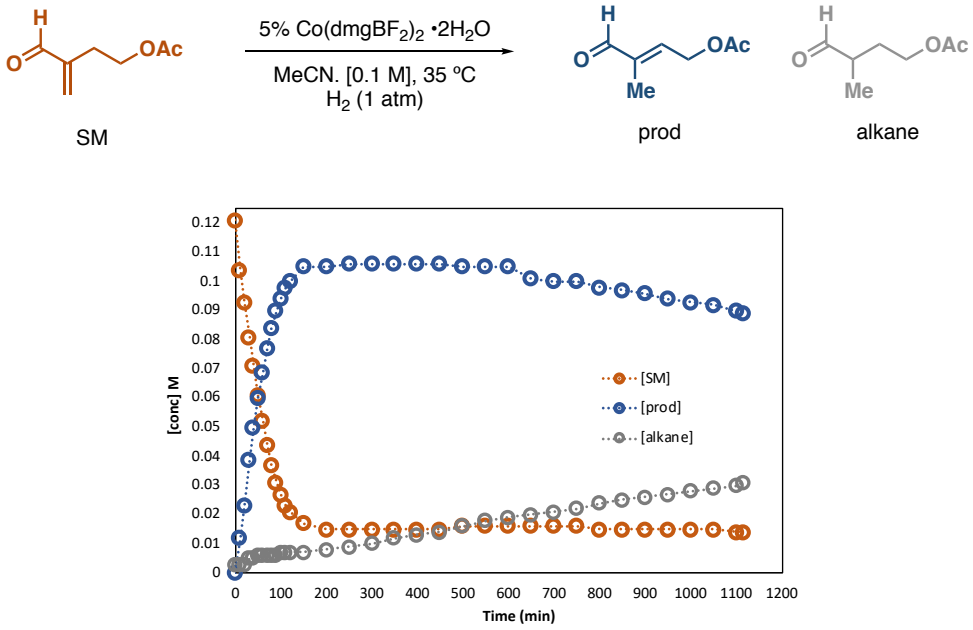
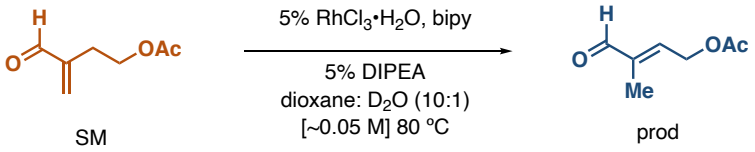
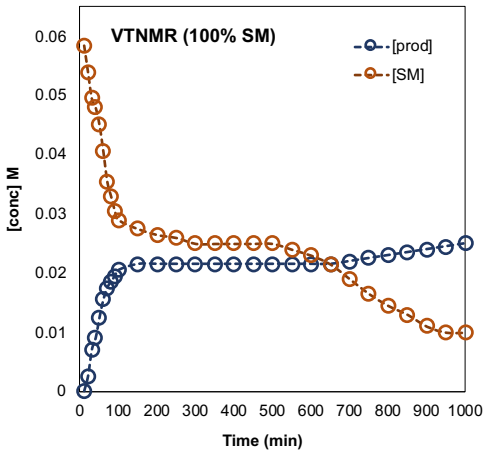


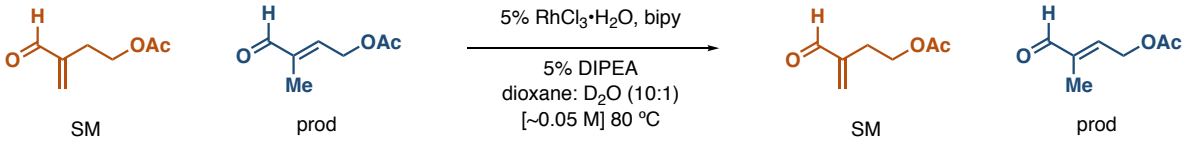

**Fig S3**. VTNMR experiments under [Co]-catalyzed condition. VTNMR setup: reaction at rt ~20 mins to exchange $H_2$ gas, then, start at 35 ºC on NMR.

**2. [Rh]-condition**

In a glovebox filled with $N_2$, a stock solution was made by mixing $RhCl_3 \bullet 3H_2O$ (0.015 mmol, 3.9 mg) with 4-4′-dimethyl-2-2′-bipyridine (0.015 mmol, 2.7 mg) in a 1:1 molar ratio in dioxane (5.4 mL) at room temperature for 30 minutes. The catalyst solution (3.60 mL, 0.01 mmol) was transferred into a 2-dram vial charged with substrate **1** (0.2 mmol, 28.4 mg), N,N-Diisopropylethylamine (0.01 mmol, 1.80 μL) and N-methyl-2-pyrrolidone (5–10 mg) in $D_2O$ (0.36 mL). A stir-bar was added into the mixture, the vial was sealed and stirred at room temperature until everything dissolved (~20 min). The reaction mixture (0.70 mL) was transferred to a J. Young NMR tube, and the tube was sealed and taken out of the glovebox. The NMR tube was placed into the NMR instrument and warmed to 80 ºC over 20 minutes.



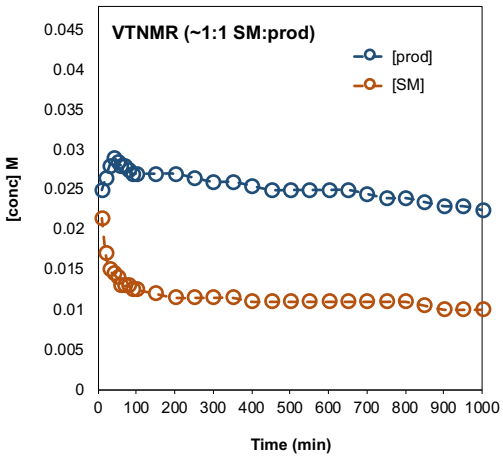




**Fig S4**. VTNMR experiments under [Rh]-catalyzed condition. VTNMR setup: reaction at rt ~20 mins warmed to 80 ºC over 20 mins.

## VI. Stability of the Product Under Standard Conditions

### 1. [Co] Catalyzed Conditions

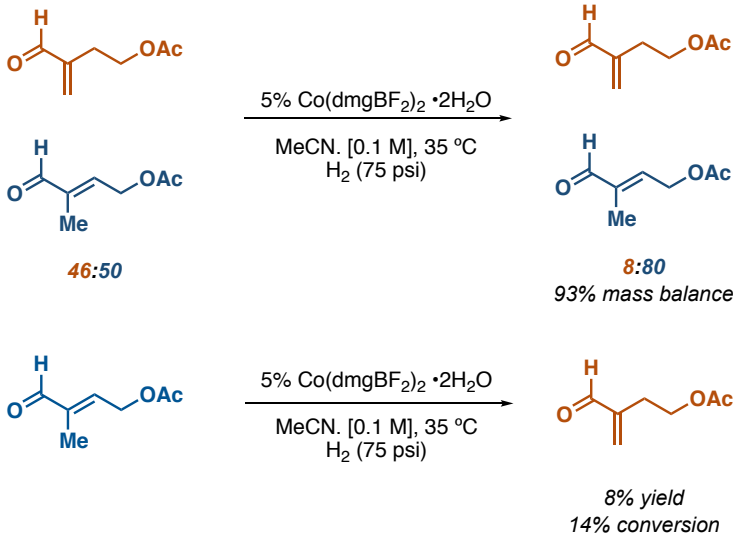



**Fig S5**. Reactivity of Product Under [Co]-Catalyzed Isomerization Conditions

### 2. [Rh] Catalyzed Conditions

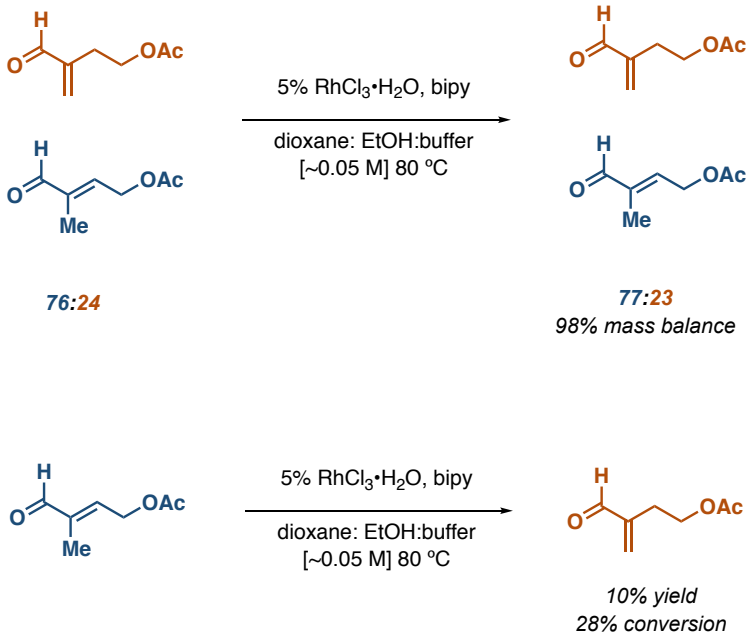
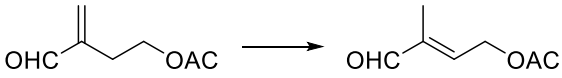


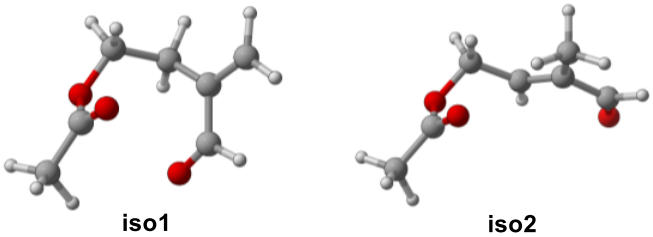

**Fig S6**. Reactivity of Product Under [Rh]-Catalyzed Isomerization Conditions

## VII. Computation Data




| | C5-Acetate | td. ratio |
|---|---|---|
| 0.0 kJ mol$^{-1}$ | −1.9 kJ mol$^{-1}$ (Bulk) | 33:67 (70:30 to 10:90) |
| | −2.4 kJ mol$^{-1}$ (THF) | 30:70 (66:34 to 9:91) |
| | −1.0 kJ mol$^{-1}$ (Acetonitrile) | 41:59 (76:24 to 13:87) |

with assumed accuracy of 1 kcal mol$^{-1}$



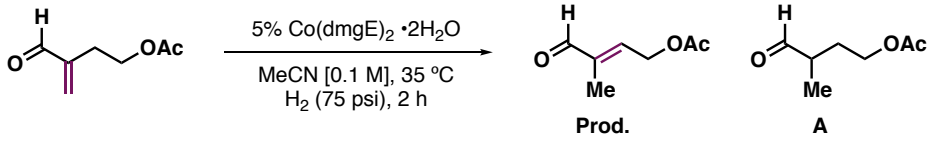
**iso1** **iso2**

$\Delta G^{298}$ in kJ mol$^{-1}$; | PBE0-D3(BJ)/def2-QZVPP//BP86/def2-SV(P); COSMO-RS(Solvent): CREST Conformer Screening

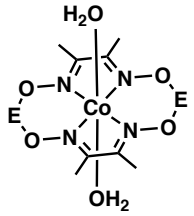
td. = thermodynamic

## VIII. Additional Optimization Data

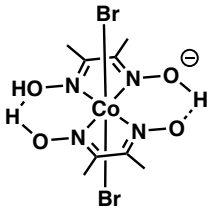
### 1. [Co] Catalyzed Conditions



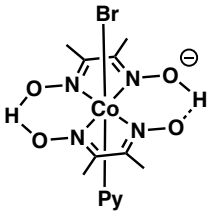

**impact of catalyst**



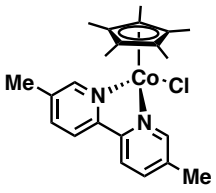
**E = $BF_2$;** 93% conv., 80% yield
**E = H;** 90% conv., 83% yield[e,f]



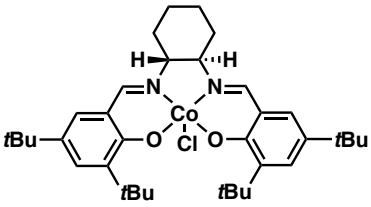
**Co(dmgH)(dmgH$_2$)Br$_2$**
0% conv., 0% yield



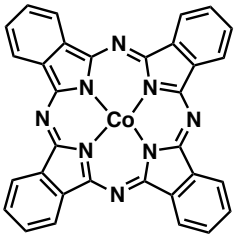
**Co(dmgH)$_2$(Py)Br**
0% conv., 0% yield



**CoCp*(bipy)Cl**
0% conv., 0% yield



**(*R,R*)-Co(salen$^{tBu,tBu}$)Cl**
0% conv., 0% yield



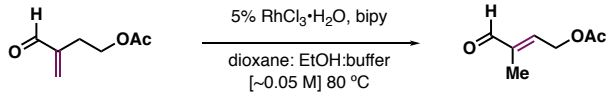
**Cobalt(II) phthalocyanine Co(Pc)**
0% conv., 0% yield

**Impact of Reaction Parameters**

| | conv. | prod | A |
|---|---|---|---|
| as above | 93 | 80 | 5 |
| 80 °C instead of 35 °C[a] | 98 | 65 | 23 |
| toluene instead of MeCN | 94 | 84 | 12 |
| 1 atm $H_2$ instead of 75 psi[b,d] | 90 | 66 | 23 |
| 19 h instead of 2 h | >99 | 0 | 98 |
| 2.5% [Co] instead of 5%[b,d] | 84 | 76 | 8 |
| 1% [Co] instead of 5%[b,c] | 84 | 70 | 4 |
| 0.5% instead of 5%[c,d,e] | 91 | 77 | 14 |
| no addition of $H_2$ | 4 | 4 | 1 |
| $H_2O$ instead of MeCN | 5 | 4 | 2 |

[a] 1 h instead of 2 h. [b] Reaction at 50 °C. [c] 24 h instead of 2 h. [d] toluene instead of MeCN [e] reaction at 80 °C. [f]THF instead of MeCN, 5h.

## 2. [Rh] Catalyzed Conditions




**Impact of Metal Catalyst**

| | conv. (%) | prod (%) | A (%) |
|---|---|---|---|
| $RhCl_3 \cdot 3H_2O$ | 75 | 55 | 0 |
| $IrCl_3 \cdot H_2O$ | 0 | 2 | 4 |
| $RuCl_3 \cdot H_2O$ | 0 | 0 | 0 |
| $Pd(OAc)_2$ | 0 | 0 | 0 |
| $Rh(acac)_3$ | 0 | 0 | 0 |
| $[RhCp^*Cl_2]_2$ | >99 | 0 | 26 |
| $[Rh(C_2H_4)_2Cl]_2$[a] | 19 | 7 | 0 |
| $[Rh(COD)Cl]_2$[a] | 10 | 0 | 0 |
| $[Rh(COE)_2Cl]_2$[a] | 12 | 4 | 0 |

**Control Experiment**

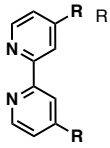
| | | | |
|---|---|---|---|
| as above | 75 | 55 | 0 |
| no alcohol | 29 | 25 | 0 |
| no alcohol, no buffer | 0 | 0 | 0 |
| no dioxane | 27 | 9 | 0 |
| double buffer addition | 55 | 36 | 0 |
| no $RhCl_3$ | 0 | 0 | 0 |
| no ligand | 44 | 16 | 0 |

**Impact of Reaction Conditions**

| | conv. (%) | prod (%) | A (%) |
|---|---|---|---|
| DIPEA with $H_2O$ instead of buffer | 45 | 40 | 0 |
| $KH_2PO_4$ instead of buffer | 52 | 0 | 0 |
| $Cs_2CO_3$ instead of buffer | 70 | 2 | 4 |
| DME:EtOH (2:1) | 58 | 47 | 0 |
| IPA instead of EtOH | 54 | 44 | 0 |
| MeOH instead of EtOH | 49 | 33 | 0 |
| 5:1 solvent:buffer | 70 | 2 | 13 |
| addition of 6% super hydride soln. | 16 | 0 | 8 |
| 2,6-lutidine with $H_2O$ instead of buffer | 19 | 9 | 0 |
| 1 equiv. bipy loading | 0 | 0 | 0 |
| addition of 5% $BH_3$•THF | 50 | 0 | 0 |
| addition of 10% $HCO_2H$:$NEt_3$ (5:2) | 52 | 3 | 38 |
| addition of 5% NaCl | 58 | 41 | 0 |
| addition of 5% NaBr | 70 | 50 | 0 |
| addition of 5% HCl | 52 | 37 | 0 |
| addition of 5% $AgPF_4$ | 0 | 0 | 0 |
| addition of 5% $AgClO_4$ | 10 | 7 | 0 |

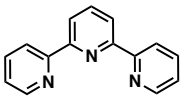
**Impact of Ligands**

| | conv (%) | yield (%) |
|---|---|---|
| $NEt_3$ | 40 | 30 |
| DABCO | 24 | 15 |
| Pyridine | 13 | 0 |
| Pyrrplidine | 20 | 3 |
| TMEDA | 0 | 0 |
| $PPh_3$ | 15 | 3 |
| $P(OPh)_3$ | 19 | 6 |
| TPPTS | 42 | 18 |
| xantphos | 29 | 11 |

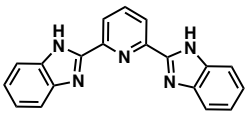



R = H; 61% conv., 52% yield
= Me; 78% conv., 62% yield
= *t*Bu; 74% conv., 60% yield
= OMe; 72% conv., 51% yield

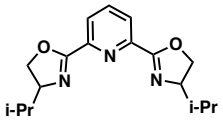

R = H, R' = H; 87% conv., 47% yield
R = Cl, R' = H; 51% conv., 37% yield
R = $NO_2$, R' = H; 0% conv., 0% yield
R = Me, R' = Me; 72% conv., 57% yield




0% conv., 0% yield



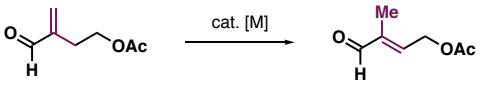

24% conv., 15% yield




0% conv., 0% yield

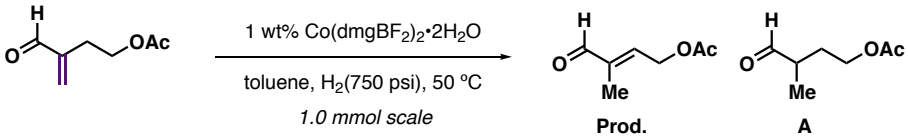
[a] no addition of bipy

## 3. Other Selected Conditions




| | | |
|---|---|---|
| 5% $RhCl_3 \cdot H_2O$, bipy, dioxane:EtOH:ph 7 buffer, 80 ºC 75% conv., 55% yield | 5% $RhCl_3 \cdot H_2O$, bipy dioxane:EtOH, 80 ºC 26% conv., 0% yield | $[Rh(COD)Cl]_2$ $CO/H_2$ 600 psi, 100 ºC 40% conv., 0% yield |
| 1% $RhH(CO)PPh_3$ **toluene, 100 ºC** 0% conv., 0% yield | 1% $RhH(CO)(xantphos)(PPh_3)$ **toluene, 100 ºC** 0% conv., 0% yield | 1% $Rh(CO)_2$acac,xantphos $H_2$-activation MeOH, rt 25% conv., 0% yield |
| 2.5% $[Rh(C_2H_4)_2Cl]_2$ DME:EtOH:ph 7 buffer, 80 ºC 19% conv., 7% yield | 2.5% $[Rh(COE)_2Cl]_2$ DME:EtOH:ph 7 buffer, 80 ºC 12% conv., 4% yield | 2.5% $[RhCp^*Cl]_2$ DME:EtOH:ph 7 buffer, 80 ºC 93% conv., 0% yield |
| 1% Pd/C $H_2$-activation **toluene, 75 ºC** 57% conv., 10% yield | 1% Pd/C $Me_4$-thiourea $H_2$-activation **toluene, 75 ºC** 0% conv., 0% yield | 10% $Ru_3(CO)_{12}$ $NEt_3$, dioxane, 80 ºC >99% conv., 0% yield |
| 5% $RuHCl(CO)(PPh_3)_3$ toluene, 110 ºC 14% conv., 0% yield | 5% $Ni(PPh_3)_4$ toluene, 30 ºC 0% conv., 0% yield | 5% $Co(dmgBF_2)_2 \cdot H_2O$ $H_2$ 75 psi toluene, 50 ºC 94% conv., 84% yield |

## 4. Higher Pressure/$SnCl_2$ Comparison Screens




(1) with 0.1 wt% $SnCl_2$, 12 h
QQ-09-167-A

| Time | conv. | Prod | A |
|---|---|---|---|
| 12 h | 95 | 85 | 15 |

(2) no $SnCl_2$, 12 h
QQ-09-167-B

| Time | conv. | Prod | A |
|---|---|---|---|
| 12 h | 99 | 65 | 28 |

***Patent results: 94.02% conv., 90.54% prod., 5.14% side prod.***

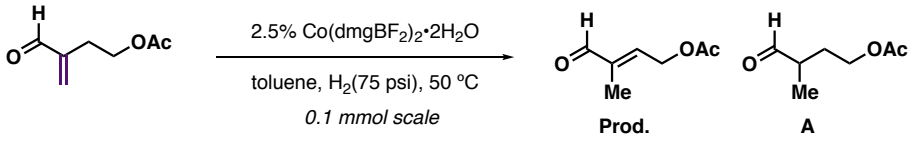
(1) with 0.5 wt% cat and 0.05 wt% $SnCl_2$, 6 h
QQ-09-173-A

| Time | conv. | Prod | A |
|---|---|---|---|
| 6 h | 79 | 71 | 7 |

(2) with 0.5 wt% cat and no $SnCl_2$, 6 h
QQ-09-173-B

| Time | conv. | Prod | A |
|---|---|---|---|
| 6 h | 78 | 71 | 6 |

- 1 wt% cat = 0.34 mol% cat




| (1) with 0.25% $SnCl_2$ QQ-09-169-A | | | |
|---|---|---|---|
| Time | conv. | Prod | A |
| 2 h | 91 | 76 | 15 |

| (2) no $SnCl_2$ QQ-09-169-B | | | |
|---|---|---|---|
| Time | conv. | Prod | A |
| 2 h | 94 | 86 | 18 |

## IX. References


1. W.C. Still, M. Kahn, A. Mitra, *J. Org. Chem*. 1978, ***43***, 2923-2925.

2. G. Li, A. Han, M. E. Pulling, D. P. Estes, J. R. Norton, *J. Am. Chem. Soc*. 2012, ***134***, 14662-14665.

3. J. Peed, I. R. Davies, L. R. Peacock, J. E. Taylor, G. Kociok-Köhn, S. D. Bull, *J. Org. Chem.* 2012, ***77***, 543-555.

4. (a) A. E. Hurtley, Z. Lu, T. P. Yoon, *Angew. Chem. Int. Ed*., 2014, ***53***, 8991-8994. (b) R. Batt, E. Bourcet, Y. Kassab, F. Fache, *Synlett* 2007, 1869-1872. (c) R. C. Hughes, C. A. Dvorak, A. I. Meyers, *J. Org. Chem*. 2001, ***66***, 5545-5551.

5. (a) F. Douelle, A. S. Capes, M. F. Greaney, *Org. Lett*., 2007, ***9***, 1931-1934. (b) M. A. Larsen, E. T. Hennessy, E. T.; M. C. Deem, Y. H. Lam, J. Saurí, A. C. Sather, *J. Am. Chem. Soc.* 2020, ***142***, 726-732.

6. A. M. Al Hazmi, N. S. Sheikh, C. J. R. Bataille, C. A. A. M. Al-Hadedi, S. V. Watkin, T. J. Luker, N. P. Camp, R. C. D. Brown, R. *Org. Lett*. 2014, ***16***, 5104-5107.

7. A. Erkkilä, P. M. Pihko, *Eur. J. Org. Chem*. 2007, 4205-4216.

8. A. Bugarin, K. D. Jones, B. T. Connell, *Chem. Commun.* 2010, ***46***, 1715-1717.

9. J. Li, Y. Zhu, Y. Lu, Y. Wang, Y. Liu, D. Liu, W. Zhang, W., *Organometallics* 2019, ***38***, 3970-3978.

10. L. Song, H. Yao, L. Zhu, R. Tong, *Org. Lett.* 2013, ***15***, 6-9.

11. Y. Yao , J. Liu, J. Xi, B. Miu, G. Liu, G., S. Wang, L. Meng, Z. Yao, *Chem. Eur. J.* 2011, ***17***, 10462-10469.

12. (a) S. Chatterjee, S. Mallick, F. Buzzetti, G. Fiorillo, T. M. Syeda, P. Lombardi, K. D. Saha, K. G. S. Kumar, *RSC Adv*. 2015, ***5***, 90632-90644. (b) G. N. Shivers, S. L. Tun, S. L. McLean, F. C. Pigge, *Synlett* 2022, ***33***, 1902-1906.

13. C. Shu, R. S. Mega, B. J. Andreassen, A. Noble, V. K. Aggarwal, *Angew. Chem. Int. Ed*., 2018, ***57***, 15430-15434.

14. Yao , Y.-S., Liu, J.-L., Xi, J., Miu, B., Liu, G.-S., Wang, S., Meng, L. and Yao, Z.-J., *Chem. Eur. J.* **2011**, *17*, 10462-10469.
15. Deska, J.; Kazmaier, U., *Chem. Eur., J.* **2007**, *13*, 6204-6211.
16. Gradillas, A., Belmonte, E., da Silva, R.F. and Pérez-Castells, J., *Eur. J. Org. Chem*., **2014**: 1935-1941.