Electronic Supplementary Material (ESI) for Faraday Discussions. This journal is © The Royal Society of Chemistry 2019

# Insight into Catalyst Speciation and Hydrogen Co-Evolution during Enantioselective Formic Acid-driven Transfer Hydrogenation with Bifunctional Ruthenium Complexes from Multi-technique *operando* Reaction Monitoring

Daniel B. G. Berry,<sup>a</sup> Anna Codina,<sup>b</sup> Ian Clegg,<sup>b</sup> Catherine L. Lyall, <sup>a,c</sup> John P. Lowe, <sup>a,c</sup>

Ulrich Hintermair\*a,c,d

# **Supplementary Information**

d. Centre for Sustainable Chemical Technologies, University of Bath, Claverton Down, BA2 7AY Bath, UK.

\* <u>u.hintermair@bath.ac.uk</u>

*a.* Department of Chemistry, University of Bath, Claverton Down, BA2 7AY Bath, UK.

b. Bruker UK Ltd, Banner Lane, CV4 9GH Coventry, UK.

<sup>&</sup>lt;sup>c.</sup> Dynamic Reaction Monitoring Facility, University of Bath, Claverton Down, BA2 7AY Bath, UK.

## Table of Contents

General
Synthesis
Unsaturated complex 2
Hydride complex <b>4</b> 4
Formate complex <b>3</b> 5
Analysis
FlowNMR Spectroscopy6
Chiral HPLC7
UV-Vis Spectroscopy8
Headspace Mass Spectrometry9
Catalysis11
General procedure for batch reactions11
General procedure for flow runs11
Additional Data12
<sup>1</sup> H FlowNMR spectra12
<sup>13</sup> C FlowNMR spectrum15
Further NMR experiments16
References

### General

All reagents and solvents were sourced from major commercial suppliers, and reactions were carried out in flame-dried glassware under an atmosphere of dry argon inside a glovebox or using Schlenk techniques.

Stock solutions (200 mL) were prepared using THF freshly distilled from potassium and 1,3,5-trimethoxybenzene (TMB, 3.36g, 20 mmol) dried in *vacuo*, and stored under argon for no longer than a week. Acetophenone was distilled, stored under argon and kept in the dark at room temperature.

Reagent grade triethylamine was dried over calcium hydride at 75 °C for 2 hours before being distilled at 105 °C under argon. Reagent grade formic acid was distilled under argon at 135 °C using a fractional distillation column, the first fraction of which was discarded.

Distilled formic acid (92.5 mL, 2.45 mol) was charged to a distillation apparatus with a dropping funnel attached. The formic acid was cooled to 0 °C and distilled triethylamine (136.5 mL, 0.98 mol) was charged to the dropping funnel and added to the formic acid dropwise over 1 hour. The mixture was then distilled at 145 °C and 5 mbar, and the ratio of components in the azeotropic distillate was confirmed by <sup>1</sup>H NMR to be 5:2.

# Synthesis

Unsaturated complex 2



Potassium tert-butoxide (2.2 mg, 0.020 mmol) was added to a solution of [(mesitylene)RuCl(*R*,*R*)-(TsDPEN)]) in dry THF (1 mL of 2mM) to give a deep purple solution. The mixture was stirred for 5 minutes at room temperature. Passing through a 0.2  $\mu$ m PTFE syringe filter yielded a 2 mM solution of **2**<sup>1,2</sup> which was immediately analysed by UV-vis spectroscopy under argon to give a molar absorptivity of  $\epsilon$  = 1380 M<sup>-1</sup>cm<sup>-1</sup> at  $\lambda_{max}$  = 565 nm.





#### Hydride complex 4



Isopropanol (5  $\mu$ L, 0.065 mmol) was added to a solution (1 mL of 16 mM) of complex **2** in d<sub>8</sub>-THF yielding a yellow-brown solution leading to immediate formation of [(mesitylene)RuH(*R*,*R*)-(TsDPEN)] (**4**)<sup>2,3</sup> as confirmed by its characteristic <sup>1</sup>H NMR resonances:

<sup>1</sup>H NMR (500 MHz, 25°C, THF)  $\delta$  = -5.59 (s, 1H, Ru-*H*), 2.03 (s, 3H, CH<sub>3</sub> in Ts), 2.22 (s, 9H, CH<sub>3</sub> in mesitylene), 4.03 (m, 1H, NH*H*), 4.37 (m, 1H, N*H*H), 4.83 (s, 3H, C*H* in mesitylene).



Figure S2: Partial <sup>1</sup>H NMR spectrum for hydride complex **4** at 16 mM in THF (64 scans, 1.64 s acquisition time, 1 s delay time) with the characteristic Ru-H resonance highlighted in blue.

#### Formate complex 3



[(mesitylene)RuH(R,R)-(TsDPEN)] (4) in d<sub>8</sub>-THF (1 mL of 16 mM) was charged to a pressure resistant NMR tube under argon and pressurised with 5 bar of CO<sub>2</sub>. Upon mixing the yellow-brown solution turned bright yellow indicative of the formation of formate complex **3**.<sup>3</sup>

<sup>1</sup>H NMR (500 MHz, 25°C, THF)  $\delta$  = 2.21 (s, 3H, CH<sub>3</sub> in Ts), 2.28 (s, 9H, CH<sub>3</sub> in mesitylene), 5.25 (s, 3H, CH in mesitylene), 8.10 (s, 1H, OCHO), 9.06 (m, 1H, NHH).



Figure S3: Partial <sup>1</sup>H NMR spectrum of formate complex **3** at 16 mM in  $d_8$ -THF (4 scans, 1.64 s acquisition time, 1 s delay time) with characteristic N-H and C-H resonances highlighted in blue.

### Analysis

#### **FlowNMR Spectroscopy**



Figure S4: Schematic of the operando recirculating flow setup.

Reactions were carried out in round-bottomed glass flasks with a magnetic stir bar under argon. A peristaltic pump (Vapourtec SF-10) was used to drive the reaction mixture around the flow path to a Bruker InsightMR flow tube inserted into a Bruker 500 MHz Avancell+ Ultrashield with a Prodigy BBO Cryoprobe. Polyetheretherketone (PEEK) tubing was used for the flow path (O.D. 1/16", I.D. = 0.75 mm) and the flow tube (O.D. = 1/32", I.D. = 0.125 mm). This tubing was connected to the reaction flask via a standard rubber seal with connections sealed using silicone grease. The system was heat regulated by two heat exchangers, one which connected to the flow path and the flow tube and a second which was connected to the reactor jacket (DrySyn Snowstorm ONE).

NMR spectra were acquired (number of scans: 8, acquisition time: 1.64 s, delay: 1 s, receiver gain: 4, lock: off) at 0 and 4 mL/min served to calculate integral correction factors accounting for flow effects using the following equations.<sup>4</sup>

Equation 1:	I_Corrected = CF ×I
Equation 2:	CF = I_static/I_flow

Concentrations of species were then calculated by referencing peak integrals to the TMB internal standard.

Selectively excited <sup>1</sup>H spectra were acquired at a much higher receiver gains than ordinary proton spectra (number of scans: 8, acquisition time: 2 s, delay: 1 s, receiver gain: 203, lock: off, constant 21: -6, constant 55: 3,  $O_1P$ : -5) and therefore require a correction factor to allow quantitative

comparison between peaks on the two different spectra. This was done by calculating a Reduced Integral Value (RIV) for the selectively excited hydride peak and then multiplying this by the concentration of the internal standard as per the following equations:<sup>2,4</sup>

$$RIV = \frac{I_{hydride} \times RG_{normal} \times RGCF}{RG_{hydride}}$$

Equation 3:

 $[Hydride] = RIV \times \frac{[TMB]}{I_{TMB} / Number of protons associated with TMB peak}$ 

Equation 4:

Where  $I_{hydride}$  = Integral of the hydride peak,  $RG_{normal}$  = receiver gain for selective excitation of internal standard,  $RG_{hydride}$  = receiver gain for selective excitation experiment of hydride, RGCF = Receiver gain correction factor calculated by plotting the integral of an internal standard of a range of receiver gains,  $I_{TMB}$  = integral of internal standard (TMB).

#### **Chiral HPLC**

Inserted into the flow path was a valve drive connected to the HPLC. The valve, sample loops and intermediate tubing between the flowpath and the HPLC was connected via HPLC standard stainless-steel tubing (I.D. 180  $\mu$ m) and fittings. A 50  $\mu$ L aliquot of reaction mixture was taken by the sample valve every 30 minutes. The sample was flowed to a secondary valve drive using an external pump (IPA at 0.25 mL/min). The secondary valve drive then resampled 5  $\mu$ L of the original aliquot for analysis. This configuration was found to offer the highest quality chromatograms as a result of 'refocussing' the sample (eliminating peak tailing from back mixing), while also allowing for full customisability of solvent composition and sample dilution.

HPLC data was acquired using an Agilent 1260 Infinity II LC equipped with a Chiracell OD-H column (Daicell chiral, 250 mm length, 4.6 mm diameter, 5  $\mu$ m particle size) which was preceded by a guard column (Chiracell OD-H 10 mm length, 4 mm diameter, 5  $\mu$ m particle size) to prevent contamination. The eluent used was 9:1 hexane/IPA at 1 mL/min, and eluents were analysed using a UV detector at 254 nm.

Typical retention times (verified by injecting pure samples of each component) and peak separations were as shown in the example chromatogram below.



Figure S5: Example HPLC chromatogram of transfer hydrogenation reaction mixture taken in automation (t = 8.3 hours)

Enantiomeric excess was calculated using the following equation:

$$\% ee = \frac{[R] - [S]}{[R] + [S]} \times 100$$

#### **UV-Vis Spectroscopy**

UV-visible spectroscopic data was collected using an Ocean Optics fibre-optic setup consisting of a deuterium-halogen light source (DH-2000-BAL) connected to a 0.5 cm lensed PEEK SMA-Z flow cell and a QEPro spectrometer (10  $\mu$ m slit) via SMA-terminated 400  $\mu$ m solarisation-resistant light guides. OceanView 1.6.5 software was used for continuous spectral acquisition from 200 – 1000 nm resolution with an integration time of 10 ms and averaging 100 scans.

The light source was allowed to warm up for a minimum of 30 minutes prior to data acquisition. Modules within the OceanView software were used to acquire light and dark references and convert transmission to absorbance using the following equation:

Equation 5

Absorbance = 
$$log_{10} - 1(\frac{sample - dark reference}{light reference - dark reference})$$

Once the references were taken data was set to save every minute and acquisition was started.



Figure S6: 3D plot of UV spectra acquired during catalytic transfer hydrogenation of acetophenone (2 mM **1**, 400 mM acetophenone, 2.1 mL formic acid/triethylamine 5:2 azeotrope, 7.43 mL 0.1 M TMB in THF at 40 °C)



Figure S7: Sample UV spectrum taken at t = 15 hours during the catalytic transfer hydrogenation of acetophenone (2 mM 1, 400 mM acetophenone, 2.1 mL formic acid/triethylamine 5:2 azeotrope, 7.43 mL 0.1 M TMB in THF at 40  $^{\circ}$ C)

#### Headspace Mass Spectrometry

Headspace mass spectrometry data was collected using a Hiden HPR-20 R&D quadrupole mass spectrometer with a detection mass range of 1-300 amu coupled to QIC (Quartz Inert Capillary) fast sampling inlet. Relative sensitivities of H<sub>2</sub> and CO<sub>2</sub> in Ar were calibrated using a multiple calibration method in the Hiden quantitative gas analysis (QGA) software. The calibration mixtures used were 5% H<sub>2</sub>, 5% CO<sub>2</sub>, and 5% H<sub>2</sub> + 5% CO<sub>2</sub> in argon, respectively. The relative sensitivities of these gases were measured to be 2.27 (H<sub>2</sub>), 1.08 (CO<sub>2</sub>) and 1.00 (Ar). Gases present within the reaction mixture were identified by the scout spectra observed in S8 and S9 below.



Figure S8: Headspace mass spectrometry scout spectrum taken at t = 4 hrs during the asymmetric transfer hydrogenation of acetophenone (Mass range 0-50, 2 mM **1**, 400 mM acetophenone, 1.05 mL formic acid/triethylamine 5:2 azeotrope, 3.71 mL 0.1 M TMB in THF at 40 °C).



Figure S9: Headspace mass spectrometry data point taken at t = 4 hrs during the asymmetric transfer hydrogenation of acetophenone. (2 mM 1, 400 mM acetophenone, 1.05 mL formic acid/triethylamine 5:2 azeotrope, 3.71 mL 0.1 M TMB in THF at 40 °C). Masses observed were confirmed to be unique to the gas analysed compound using Hiden QGA software ( $H_2 - 2$ , CO – 12, Ar – 40, CO<sub>2</sub> – 44,)

The QIC heating at 145°C and MS were allowed to stabilise for at least 30 minutes prior to acquisition. A blank test was carried out sampling air before switching to a method designed in the QGA software (Start range: 5, settle speed: normal, dwell speed: normal, electron energy: 70, emission current: 1). The PEEK sampler tubing was inserted through the rubber seal of the reaction flask, sealed with silicone grease and data acquisition was started. Argon was dosed to the reaction

mixture at 30  $L_n$ /hr and the QIC sampling inlet sampled at 16 cm<sup>3</sup>/min, data was acquired every 1.5 seconds for the masses of H<sub>2</sub> (2), CO<sub>2</sub> (44) and Ar (40).

## Catalysis

#### General procedure for batch reactions

RuCl[(*R*,*R*)-TsDPEN(mesitylene)] (12.4 mg, 0.020 mmol) was charged to a Schlenk flask and dissolved in 7.43 mL of a stock solution of THF containing 1, 3, 5-trimethoxybenzene as an internal reference (0.1 M) and heated to 40 °C. Subsequently a 5:2 mixture of formic acid/triethylamine (2.10 mL) and acetophenone (0.467 mL, 4.0 mmol) were added to start the reaction. 0.3 mL of the reaction mixture were periodically withdrawn from the mixture to analyse reaction progress via <sup>1</sup>H NMR using the 1phenylethanol CH quartet at 4.80 ppm and the acetophenone CH<sub>3</sub> singlet at 2.55 ppm versus the 6.08 ppm signal of the TMB standard (see Figure S10).

#### General procedure for flow runs

The flowtube and flowpath (outlined in black and red respectively in Figure S4) was purged with argon for a minimum of 30 minutes to ensure a dry and inert atmosphere. The systems heat control was turned on at this stage to allow for equilibration. The heat exchanger controlling the flow path and flow tube was set to 50 °C (to account for heat loss over the length of the system), the reaction vessel was heated to 40 °C and the NMR probe was set to 30 °C (improved shimming at this temperature).

The system was subsequently primed with a stock solution of THF containing 1,3,5trimethoxybenzene as an internal reference (0.1 M) for 15 minutes at 4 mL/min. The PEEK tubing of the flowpath (in and out) was then pushed through the rubber seal of a Schlenk flask containing THF/TMB stock solution (5.43 mL) and 5:2 mixture of formic acid/triethylamine (2.10 mL). The solution was flowed through the apparatus for 10 minutes (4 mL/min) at 40 °C under an argon atmosphere to ensure homogeneity.

After inserting the flow tube into the spectrometer the flow was stopped. Frequency lock was disabled and automated shimming and tuning routines were applied. Flow was then resumed, and data acquisition (number of scans: 8, acquisition time: 1.64 s, delay: 1 s, receiver gain: 4, lock: off) started using and automated kinetic routine on InsightMR reaction monitoring software.

RuCl[(R,R)-TsDPEN(mesitylene)] **1** (12.4 mg, 0.020 mmol) dissolved in 2 mL of THF/TMB stock solution was added to the reaction vessel via syringe and the mixture was stirred for 15 minutes. At this point acetophenone (0.467 mL, 4.0 mmol) was added to start the reaction.

## Additional Data

### <sup>1</sup>H FlowNMR spectra



Figure S10: <sup>1</sup>H FlowNMR spectrum of reaction mixture



Figure S11: Generalised catalyst structure of all key in-cycle intermediates where XX = HCl (1), HH (4), OCOH (3) or nothing (2).



Figure S12: <sup>1</sup>H FlowNMR spectrum of reaction mixture prior to substrate addition with shift regions of catalyst signatures (see Figure S11) highlighted.



Figure S13: <sup>1</sup>H FlowNMR spectrum of reaction mixture at t = 4 hrs with shift regions of catalyst signatures (see Figure S11) highlighted.

## <sup>13</sup>C FlowNMR spectrum



Figure S14: <sup>13</sup>C FlowNMR spectrum of reaction mixture.



Figure S15: Selective 1D EXSY NMR data with excitation of the formic acid CH peak (8.43 ppm, red arrow)
displaying an exchange signal (-5.57 ppm, red circle) to hydride intermediate 4. Negative peaks observed are NOESY interactions for formic acid and 1-phenyl ethanol. (20 mM (1), 0.8 M acetophenone, 4 M formic acid/triethylamine mixture (5:2), 0.1 M 1,3,5 trimethoxybenzene, 0.5 mL dry THF-d8, 25°C). 1D NOESY using selective refocussing with a shaped pulse (128 scans, 1.64 s acquisition time, 2 s delay time, 0.5 s mixing time).



Figure S16: <sup>1</sup>H NMR (64 scans, 1.64 s acquisition time, 1 s delay time) data of the hydride complex **4** (20 mg, 0.032 mmol) in 0.5 mL THF-D8 before (blue) and after (red) the addition of one equivalent of formic acid (1.2  $\mu$ L, 0.032 mmol).



Figure S17: <sup>1</sup>H NMR (64 scans, 1.64 s acquisition time, 1 s delay time) data of the hydride complex **4** (20 mg, 0.032 mmol) in 0.5 mL THF-D8 before (blue) and after (red) the addition of one equivalent of formic acid (1.2 μL, 0.032 mmol) showing characteristic NH (8.67 ppm) and CH (7.97 ppm) peaks of the formate complex **3**<sup>3</sup> (green circles) as well as CH resonance for formic acid (8.17 ppm).

### References

- 1. Haack, K.-J.; Hashiguchi, S.; Fujii, A.; Ikariya, T.; Noyori, R.: The Catalyst Precursor, Catalyst and Intermediate in the Ru(II)-Promoted Asymmetric Hydrogen Transfer between Alcohols and Ketones. *Angew. Chem. Int. Ed.* **1997**, *36*, 285-288.
- Hall, A. M. R.; Dong, P.; Codina, A.; Lowe, J. P.; Hintermair, U.: Kinetics of Asymmetric Transfer Hydrogenation, Catalyst Deactivation, and Inhibition with Noyori Complexes as Revealed by Real-Time High-Resolution FlowNMR Spectroscopy. ACS Catal. 2019, 9, 2079-2090.
- 3. Koike, T.; Ikariya, T.: Mechanistic Aspects of Formation of Chiral Ruthenium Hydride Complexes from 16-Electron Ruthenium Amide Complexes and Formic Acid: Facile Reversible Decarboxylation and Carboxylation. *Adv. Synth. Catal.* **2004**, *346*, 37-41.
- 4. Hall, A. M. R.; Chouler, J. C.; Codina, A.; Gierth, P. T.; Lowe, J. P.; Hintermair, U.: Practical Aspects of Real-time Reaction Monitoring using Multi-nuclear High Resolution FlowNMR Spectroscopy. *Catal. Sci. Tech.* **2016**, *6*, 8406-8417.