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Homogeneous Catalysed Hydrogenation of HMF

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Contents

1. General information

Unless stated otherwise, all reagents were handled in an MBraun glovebox using dry argon as inert atmosphere. Organic solvents were purchased dry from Aldrich. Commercially available chemicals were purchased from Aldrich, ABCR or TCI and were used as received unless stated otherwise. Analytical thin layer chromatography (TLC) was performed on pre-coated Macherey-Nagel POLYGRAM®SILG/UV254 polyester sheets. Visualization was achieved by dipping in a potassium permanganate stain [$KMnO_4$ (10 g), K_2CO_3 (65 g) followed by heating. Column chromatography was carried out on Aldrich silica gel (60 Å, 70-230 mesh, 63-200 µm). Concentration *in vacuo* was performed at 20-80 mbar and 40 °C, drying at ≈10^{-2} mbar and R.T. unless stated otherwise.[1]H and [13]C NMR spectra were recorded by the authors or the NMR service of the Institute of Organic Chemistry at Heidelberg University on either a Bruker Avance III 300, a Bruker Avance DRX 300, or a Bruker Fourier 300 spectrometer at ambient temperature. Chemical shifts δ are reported in ppm relative to either the residual solvent. Coupling constants J are reported in Hz. The multiplicities are reported as: s = singlet, bs = broad singlet, d = doublet, t = triplet, q = quartet, m= multiplet. All experiments were carried out in glass autoclaves produced by BASF with 60 mL nominal volume. The chemspeed screening reactions were conducted using a ChemSpeed Accelerator SLT 106 high-throughput robot system.

The ratios of products were determined either by proton or carbon NMR spectroscopy, as per established methods.[1] Since the tertiary carbons used to determine the *cis*:*trans* ratio are in significantly similar environments, one can assume that the difference in their relaxation times is negligible, as such the ratio was determined using standard C^{13}-proton decoupled measurements, rather than specialized quantitative experiments.

2. General procedures

GP 1: homogeneous hydrogenation of HMF, in a glass autoclave

In an Argon filled glovebox, the substrate (typically HMF, 100 mg, 1 eq.), the catalyst (4.5 mol %), the ligand (5 mol %) and hexa-methyl-benzene (approx. 8-10 mg) as internal standard were dissolved in the solvent (typically 10 mL toluene), in a microwave vial and sealed. The solution was sonicated for 15 mins or until full dissolution of the substrate. The solution was transferred to an N_2 purged glass autoclave, under a flow of N_2. The autoclave was tightly closed, purged with N_2 then H_2 (typically, 3 times each, 5 bars), and finally pressurized with H_2 to the desired pressure. An oil bath was used to bring the autoclave to the desired temperature (typically 120 °C), and was stirred for the specified duration (overnight). A sample was collected, the solvent was removed *in vacuuo*, the resulting oil was dissolved in d_6-DMSO and analysed by NMR. When the scale was increased for isolation, the purification was conducted by filtering the crude mixture through a thin pad of celite (followed by a wash with a further 15 mL toluene), and then column chromatography (EtOAc then pure MeOH).

GP 2: High pressure hydrogenation in steel autoclave

In an Argon filled glovebox, the substrate (HMF, 100 mg, 1 eq.) and the catalyst (4.5 mol %) were dissolved in the solvent (10 mL toluene), in a microwave vial fitted with a magnetic stirrer bar and sealed (two microwave vials were prepared in this manner to duplicate the results). The solution was sonicated until full dissolution of the substrate. The vials were placed in a high pressure Paar reactor autoclave, and sand was poured to immobilise the vials and to transfer heat. The autoclave was tightly closed and purged with Ar twice. The reactor was opened and the two microwave vial seals were perforated with wide bore needles to allow gas transfer, and the autoclave was sealed and purged with Ar then H_2 (3 times each, 10 bars), and finally pressurized with H_2 to the a pressure of 70 bar. A heating ring was used to bring the autoclave to the desired temperature (120 °C), and was stirred overnight. The autoclave was then vented and purged with Ar once. A sample was collected, the solvent was removed *in vacuuo*, the resulting oil was dissolved in d_6-DMSO and analysed by NMR.

GP 3: NHC-ligated hydrogenation

In a glove box, Ru(methylallyl)$_2$COD (4.5 mol %), imidazolium salt (9 mol %), anhydrous KO*t*Bu (13.5 mol %) and hexa-methyl-benzene (approx. 8-10 mg) as internal standard were added to a microwave vial equipped with a magnetic stir bar. The mixture was suspended in toluene (2 mL) and stirred at 50 °C overnight. Then the vessel was opened in a glovebox, and a further 8 mL of toluene and the HMF were added (100 mg, 1 eq.). The vial was stirred for a further hour (or until full dissolution of the HMF) and the solution was transferred to an N_2 purged glass autoclave, under a flow of N_2. The autoclave was tightly closed, purged with N_2 then H_2 (typically, 3 times each, 5 bars), and finally pressurized with H_2 to the desired pressure. An oil bath was used to bring the autoclave to the desired temperature (120 °C), and was stirred for the specified duration (overnight). A sample was collected, the solvent was removed *in vacuuo*, the resulting oil was dissolved in d_6-DMSO and analysed by NMR.

GP 4: Phosphite exchange experiments

In an Argon filled glovebox, a microwave vial fitted with a magnetic stirrer and loaded with a solution of the phosphinite or phosphite (0.5 mmol) and the alcohol dissolved (0.5 or 1.5 mmol) in 1mL of deuterated solvent in a ratio of either 1:1 or 1:3 as specified. The reaction was stirred overnight and loaded into an NMR tube closed with a Young's tap, and the NMR was measured.

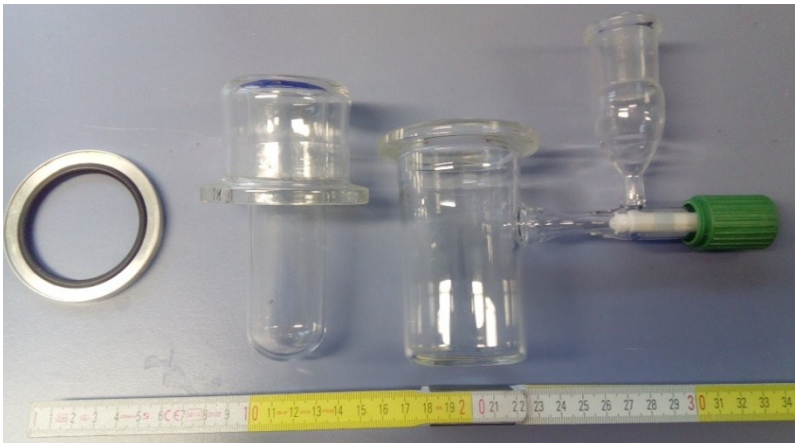
3. Sublimation procedure for the purification of HMF

The sublimation of HMF was carried out in one of two set ups. The first consisted of a cold finger (cooled by 3 °C water) and the second did not have a flow connection but instead the cold finger could be filed with a cold solution (see Picture 1).

1-Using the first system, the chamber was brought under vacuum (0.3 mbar) and heated to 50 °C for a period of an hour, while water at 3 °C was circulated through the cold finger. Then the temperature of the oil bath was increased to 130-135 °C. After most of the material had sublimed onto the finger, the vessel was re-pressurised with Argon and left to cool down. Of the 772 mg loaded into the sublimation chamber, approximately 450 mg were recovered as a white crystalline solid. The remaining material formed a dark brown "caramel" at the bottom of the sublimation chamber. (This experiment was first carried out on small scale leading to the isolation of ca. 30 mg out of 50 mg of starting HMF. The starting HMF was approx. 96% purity by HPLC).

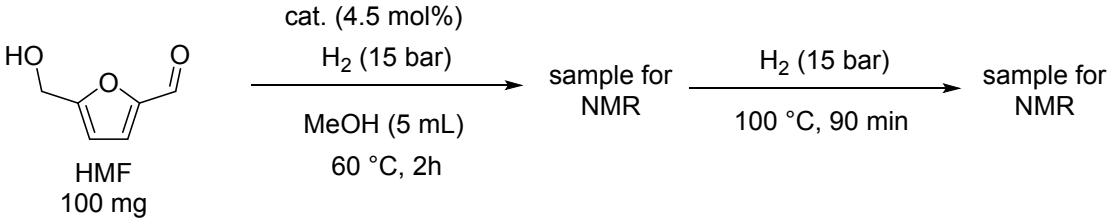
2-Using the Second system, the chamber was brought under vacuum (0.3 mbar) and the cooling finger was filled with a dry ice/acetone mixture. Then the temperature of the oil bath was increased to 50 °C for approximately 2 hours. The cooling solution had to be topped up with dry ice several times. The sublimation chamber was re-pressurised with argon and the cooling finger wiped clean. The sublimation chamber was reassembled and heated to 130-135 °C and After most of the material seemed to have sublimed onto the finger, the vessel was re-pressurised with Argon and left to cool down. The solid formed on the finger was off white, with crystalline appearance on the outer edges, but a solid (amorphous) mass had formed directly on the tip of the finger. Typical recovered yields ranged from 60-70%. When kept in an argon-filled glovebox, the HMF remained stable for approximately 6 weeks before degradation would lead to a drop in yield (as per GP1).

Without wiping the finger after the heating to 50 °C, the HMF deposited onto the cooling finger exhibited two different physical appearances: one white solid (grade 1) and one oily amorphous beige solid (grade 2). Some deliquescence of "grade 2"was observed as it reached room temperature, and the sample was dried *in vacuuo* (0.3 mbar, at R.T.) for 2 hrs. Of the 5.5 g loaded into the sublimation chamber, approximately 450 mg were recovered as a white solid (grade 1) from the tip of the finger, while the remaining beige material (grade 2) was found further up the finger. The remaining material formed a dark brown "caramel" at the bottom of the sublimation chamber, which only dissolved in acetone with difficulty. Both grade 1 and grade 2 gave identical results when subjected to the test reaction (4.5 mol% of BINAP-$RuOAc_2$, GP1).



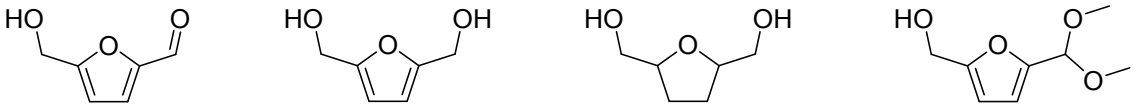
Picture 1: Sublimation system employed (measuring stick added for scale)

4. Preliminary Chemspeed screening



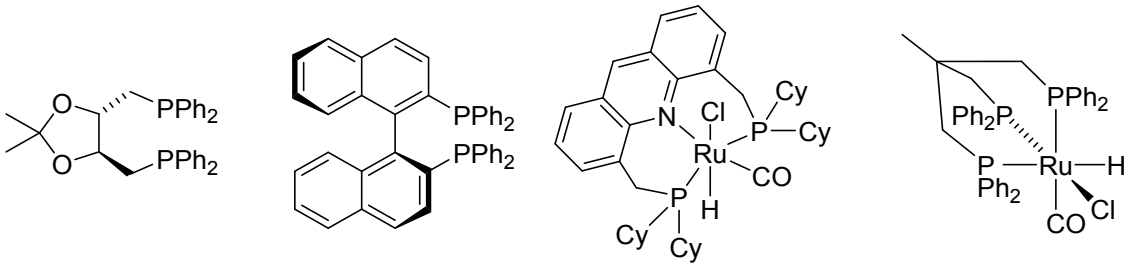
For the reactions, methanol based stock solutions of the metal pre-catalyst, the ligand and the substrate were prepared. All manipulations were conducted under a nitrogen atmosphere. In a steel block containing 16 autoclaves 1 mL of the metal solution was mixed with 1 mL of the ligand solution and 3 mL of the HMF solution, pressurized with 15 bars H_2, and stirred (vortex, 800 rpm) for 2 h at 60 °C. After cooling the reactors to 40 °C, samples were collected and concentrated in *vacuo*, all the while the autoclaves were repressurised to 15 bars of H_2, and heated for a further 1.5 h at 100 °C. The reactors were cooled to RT and another sample for NMR (1 mL) was collected from each well and concentrated in *vacuo.*

Observed products:



HMF **BHMF** **THF-DM** **HMF-Acetal**

Ligands and preformed catalysts:



(+)-DIOP **(S)-BINAP** **Ru-acridine** **Ru-Triphos**

Entry	Metal-Precursor	Ligand	Solvent	Conditions	Main Product	Side products
1.1	$RhCl(PPh_3)_3$	none	MeOH	15 bar H_2, 60 °C, 3 h	BHMF	-
1.2				→ 15 bar H_2, 100 °C, 1.5 h	BHMF	-
2.1	$RhCl(PPh_3)_3$	none	toluene	15 bar H_2, 60 °C, 2 h	HMF	BHMF
2.2				→ 15 bar H_2, 100 °C, 1.5 h	HMF	BHMF, HMF-Acetal
3.1	$RhCl(PPh_3)_3$	(+)-DIOP	MeOH	15 bar H_2, 60 °C, 3 h	HMF	BHMF
3.2				→ 15 bar H_2, 100 °C, 1.5 h	HMF	BHMF
4.1	$RhCl(PPh_3)_3$	(+)-DIOP	toluene	15 bar H_2, 60 °C, 2 h	HMF	BHMF
4.2				→ 15 bar H_2, 100 °C, 1.5 h	HMF	BHMF, HMF-Acetal
5.1	$RhCl(PPh_3)_3$	S-BINAP	MeOH	15 bar H_2, 60 °C, 2 h	BHMF	HMF

5.2				→ 15 bar H_2, 100 °C, 1.5 h	BHMF	-
6.1	$RhCl(PPh_3)_3$	S-BINAP	toluene	15 bar H_2, 60 °C, 2 h	HMF	BHMF
6.2				→ 15 bar H_2, 100 °C, 1.5 h	HMF	BHMF
7.1	$[RhCl(cod)]_2$	2 PPh_3	MeOH	15 bar H_2, 60 °C, 2 h	BHMF	HMF
7.2				→ 15 bar H_2, 100 °C, 1.5 h	BHMF	HMF-Acetal, HMF
8.1	$[RhCl(cod)]_2$	2 PPh_3	toluene	15 bar H_2, 60 °C, 2 h	HMF	BHMF
8.2				→ 15 bar H_2, 100 °C, 1.5 h	HMF	BHMF
9.1	$[RhCl(cod)]_2$	(+)-DIOP	MeOH	15 bar H_2, 60 °C, 2 h	HMF	(THF-DM)
9.2				→ 15 bar H_2, 100 °C, 1.5 h	several compounds	HMF, HMF-Acetal, THF-DM, unknown
10.1	$[RhCl(cod)]_2$	(+)-DIOP	toluene	15 bar H_2, 60 °C, 2 h	HMF	BHMF
10.2				→ 15 bar H_2, 100 °C, 1.5 h	HMF	BHMF
11.1	$[RhCl(cod)]_2$	S-BINAP	MeOH	15 bar H_2, 60 °C, 2 h	HMF-Acetal	BHMF, THF-DM
11.2				→ 15 bar H_2, 100 °C, 1.5 h	HMF-Acetal	unknown, HMF THF-DM
12.1	$[RhCl(cod)]_2$	S-BINAP	toluene	15 bar H_2, 60 °C, 2 h	HMF	BHMF
12.2				→ 15 bar H_2, 100 °C, 1.5 h	HMF	BHMF
13.1	$[Ir(cod)(PCy_3)py]PF_6$	none	MeOH	15 bar H_2, 60 °C, 2 h	HMF-Acetal	BHMF, (THF-Glycol)
13.2				→ 15 bar H_2, 100 °C, 1.5 h	HMF-Acetal	BHMF, (THF-Glycol)
14.1	$[Ir(cod)(PCy_3)py]PF_6$	none	toluene	15 bar H_2, 60 °C, 2 h	HMF	BHMF (traces)
14.2				→ 15 bar H_2, 100 °C, 1.5 h	HMF	unknown
15.1	$[Ir(cod)(PCy_3)py]PF_6$	(+)-DIOP	MeOH	15 bar H_2, 60 °C, 2 h	BHMF	HMF
15.2				→ 15 bar H_2, 100 °C, 1.5 h	BHMF	-
16.1	$[Ir(cod)(PCy_3)py]PF_6$	(+)-DIOP	toluene	15 bar H_2, 60 °C, 2 h	HMF	BHMF
16.2				→ 15 bar H_2, 100 °C, 1.5 h	BHMF	HMF, unknown
17.1	$[Ir(cod)(PCy_3)py]PF_6$	S-BINAP	MeOH	15 bar H_2, 60 °C, 2 h	HMF-Acetal	HMF, BHMF
17.2				→ 15 bar H_2, 100 °C, 1.5 h	HMF-Acetal	BHMF, HMF
18.1	$[Ir(cod)(PCy_3)py]PF_6$	S-BINAP	toluene	15 bar H_2, 60 °C, 2 h	HMF	BHMF (traces)
18.2				→ 15 bar H_2, 100 °C, 1.5 h	HMF	BHMF
19.1	$[Rh(cod)_2]OTf$	(+)-DIOP	MeOH	15 bar H_2, 60 °C, 2 h	several compounds	HMF-Acetal, HMF, BHMF, unknown
19.2				→ 15 bar H_2, 100 °C, 1.5 h	-	unknown
20.1	$[Rh(cod)_2]OTf$	(+)-DIOP	toluene	15 bar H_2, 60 °C, 3 h	HMF	another aldehyde
20.2				→ 15 bar H_2, 100 °C, 1.5 h	HMF	another aldehyde
21.1	$[Rh(cod)_2]OTf$	S-BINAP	MeOH	15 bar H_2, 60 °C, 2 h	HMF	HMF-Acetal, unknown
21.2				→ 15 bar H_2, 100 °C, 1.5 h	HMF	unknown, HMF-Acetal
22.1	$[Rh(cod)_2]OTf$	S-	toluene	15 bar H_2, 60	HMF	another aldehyde

		BINAP		°C, 3 h		
22.2				→ 15 bar H_2, 100 °C, 1.5 h	HMF	another aldehyde
23.1	Ru-Acridine	none	MeOH	15 bar H_2, 60 °C, 2 h	BHMF	Unknown (Methyl ester?)
23.2				→ 15 bar H_2, 100 °C, 1.5 h	BHMF	Unknown (Methyl ester?)
24.1	Ru-Acridine	none	toluene	15 bar H_2, 60 °C, 2 h	HMF	BHMF
24.2				→ 15 bar H_2, 100 °C, 1.5 h	BHMF	HMF, (THF-DM)
25.1	Ru-Triphos	none	MeOH	15 bar H_2, 60 °C, 2 h	BHMF	-
25.2				→ 15 bar H_2, 100 °C, 1.5 h	BHMF	THF-DM
26.1	Ru-Triphos	none	toluene	15 bar H_2, 60 °C, 2 h	HMF	BHMF
26.2				→ 15 bar H_2, 100 °C, 1.5 h	BHMF	-
27.1	$Ru(OAc)_2$(R-BINAP)	none	MeOH	15 bar H_2, 60 °C, 2 h	BHMF	HMF
27.2				→ 15 bar H_2, 100 °C, 1.5 h	BHMF	-
28.1	$Ru(OAc)_2$(R-BINAP)	none	toluene	15 bar H_2, 60 °C, 2 h	BHMF	THF-DM, HMF
28.2				→ 15 bar H_2, 100 °C, 1.5 h	THF-DM	BHMF

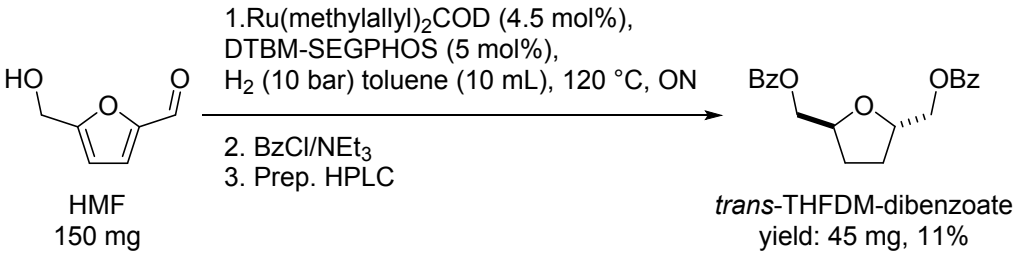
Table S1. Chemspeed screening of ligands and pre-catalysts. Compounds noted in brackets were present in only trace amounts.

5. Other reactions

(**THF-DM**) (tetrahydrofuran-2,5-diyl)dimethanol, mixture of *cis*:*trans* in a ratio of 4.7:1

Synthesized using the general procedure 1, with DTBM-SEGPHOS as ligand and Ru(methylallyl)$_2$COD as pre catalyst. After the reaction was complete, the crude mixture was filtered through a short pad of celite, which was subsequently washed with a further 10 mL of toluene. This filtrate was concentrated *in vacuo*, and dissolved in pure EtOAc and the title compound was purified by flash column chromatography on silica gel (EtOAc, then MeOH). The product was obtained as a pale beige oil (118mg, 78%). ^{1}H NMR (300 MHz, d_6-DMSO): δ= 4.57 (2H, bs), 3.76–3.94 (2H, m), 3.37 (4H, m), 1.74–1.90 (2H, m), 1.53–1.68 (2H, m). ^{13}C NMR (75 MHz, d_6-DMSO) δ 79.7 (d), 79.3 (d), 64.0 (t), 27.6 (t), 27.2 (t). The analytical data matched that of the previously reported mixture.[1]

(*trans*-**THF-DM-diBz**) *trans*-tetrahydrofuran-2,5-diyl)bis(methylene) dibenzoate,

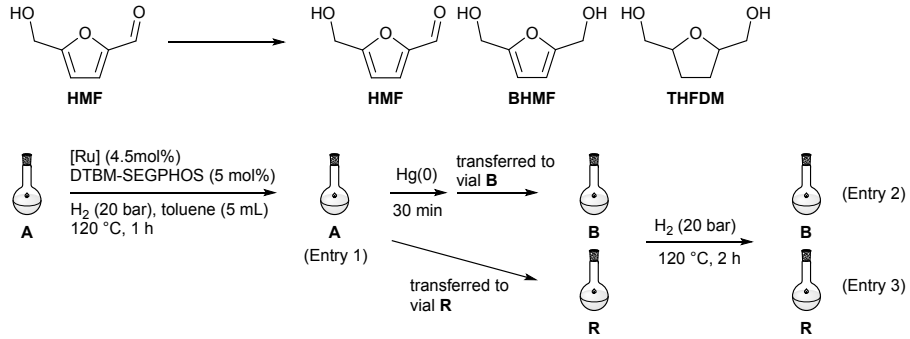


Synthesized using the general procedure 1, with DTBM-SEGPHOS as ligand and Ru(methylallyl)$_2$COD as pre catalyst. After cooling down to room temperature, the autoclave was opened and the crude mixture from the hydrogenation was poured into a round bottom flask and the autoclave was rinsed with a further 10 mL of toluene. The solution was cooled using an ice bath and while under stirring, trimethylamine (0.7 mL, 4 eq.) was added, followed by benzoylchloride (0.3 mL, 2.2 eq.). The reaction was allowed to gradually heat to room temperature and was stirred for 22 hrs. The resulting solution was concentrated *in vacuo*, purified by column chromatography (petrol ether: MTBE, 6:1, Rf ca 0.3), concentrated and purified by two sequential runs on a preparative HPLC (petrol ether: MTBE, 10:1, retention time *ca*. 36 mins, then 9:1 retention time *ca*. 27 minutes). The appropriate fractions were combined and concentrated *in vacuo*. *trans*-**THF-DM-diBz** was obtained as a colorless oil (45 mg, 11%). The analytical data matched that of the previously reported pure compound [2,3]. *trans*-**THF-DM-diBz** [2]**:** ^{1}H NMR (300 MHz, $CDCl_3$): δ= 8.03–8.08 (4H, m), 7.39–7.76 (6H, m), 4.39–4.50 (2H, m), 4.29–4.38(4H, m), 2.05–2.25 (2H, m), 1.75–1.94 (2H, m). ^{13}C NMR (50 MHz, $CDCl_3$): δ= 166.7, 133.2, 130.2, 129.8, 128.5, 77.3, 66.9, 28.4. *cis*-**THF-DM-diBz** [3]:a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ= 8.04–8.08 (2H, m), 7.53–7.59 (2H, m), 7.40–7.45 (4H, m), 4.40–4.48 (2H, m), 4.32–4.40 (4H, m), 2.07–2.18 (2H, m), 1.85–1.95 (2H, m). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.7, 133.2, 130.1, 129.8, 128.5, 77.7, 66.9, 28.0.

[1] G. Bottari, A. J. Kumalaputri, K. K. Krawczyk, B. L. Feringa, H. J. Heeres, K. Barta*, ChemSusChem***,** 2015, **8**, 1323–1327.
[2] W. S. Qayed, F. A. Luzzio, *Lett. Org. Chem.*, 2015, **12**, 622–630.
[3] V. Picciallim S. Zaccaria, G. Oliviero, S. D'Errico, V. D'Atri, N. Borbone, *Eur. J. Org. Chem.*, 2012, 4293–4305.

Mercury drop test

In an Argon filled glovebox, the substrate (HMF, 50 mg, 1 eq.), Ru(methylallyl)$_2$COD (4.5 mol %), DTBM-SEGPHOS (5 mol %) and hexamethylbenzene as an internal standard were dissolved in toluene (5 mL) in a vial **A** fitted with a magnetic stirrer bar and sealed. The solution was sonicated until full dissolution of the substrate. Vial **A** was placed in a high pressure Paar reactor autoclave. The reactor was opened and the vial seals were perforated with wide bore needles to allow gas transfer, and the autoclave was sealed and purged with N_2 then H_2 (3 times each, 10 bar), and finally pressurized with H_2 to a pressure of 20 bar. A heating ring was used to bring the autoclave to the desired temperature (120 °C), and was stirred for 1 h. The autoclave was cooled to room temperature then vented. Yield was determined by ^{1}H NMR in d_6-DMSO (Entry 1, Table S2). 2 mL of the reaction mixture was transferred to vial **R** as a reference. To vial **A**, two drops of Hg(0) (ca.15 μL × 2, ca. 2 eq. to Ru-catalyst) was added then stirred for 30 min. 2 mL of the supernatant in vial **A** was transferred to new vial **B**. Vials **B** and **R** were placed in the autoclave then the hydrogenation by the above method was carried out for 2 h. The autoclave was cooled to room temperature then vented. Yields were determined by ^{1}H NMR (Entries 2 and 3, Table S2).



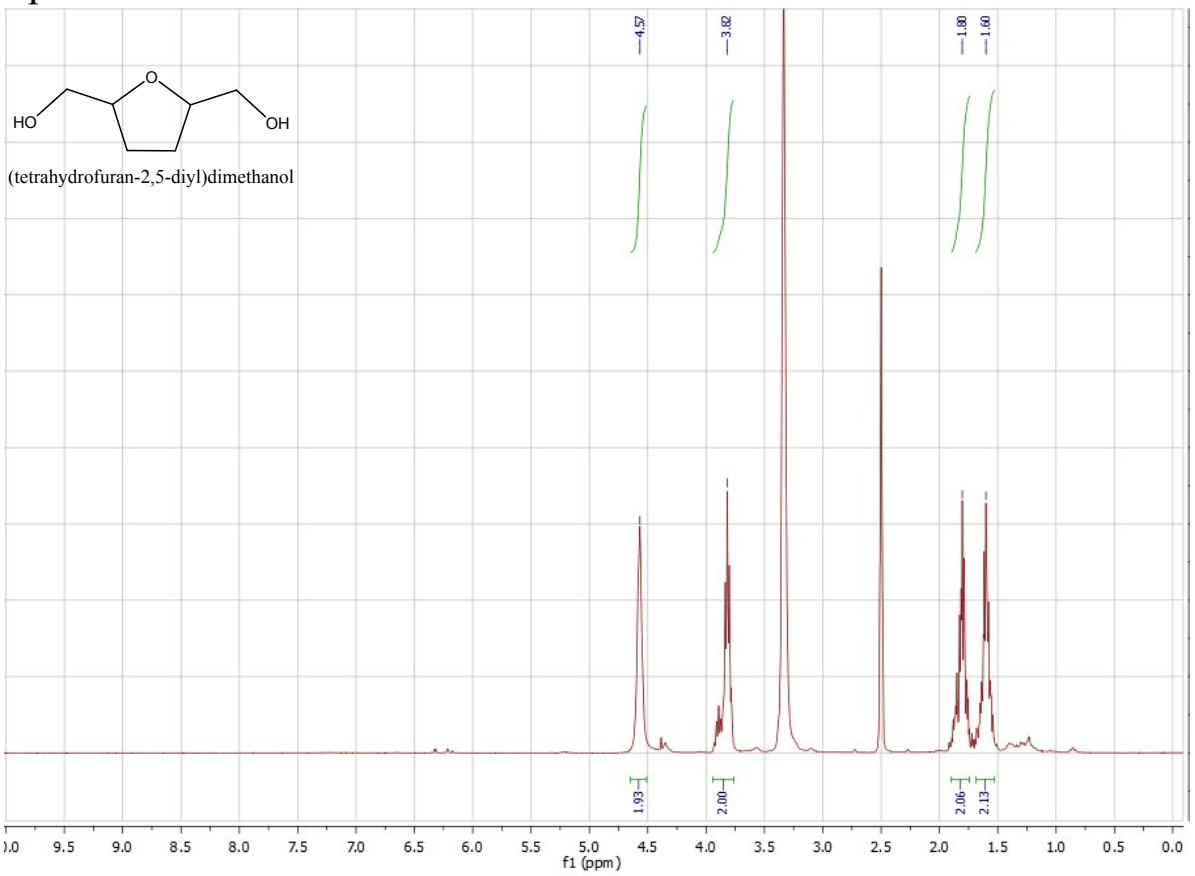
As can be seen, the hydrogenations in vial **B** proceeded similarly to vial **R**, even though the conversion of BHMF to THFDM is slightly lower (Entries 2 and 3). This would indicate that the hydrogenation is performed by a homogeneous Ru-catalyst rather than a heterogeneous one.

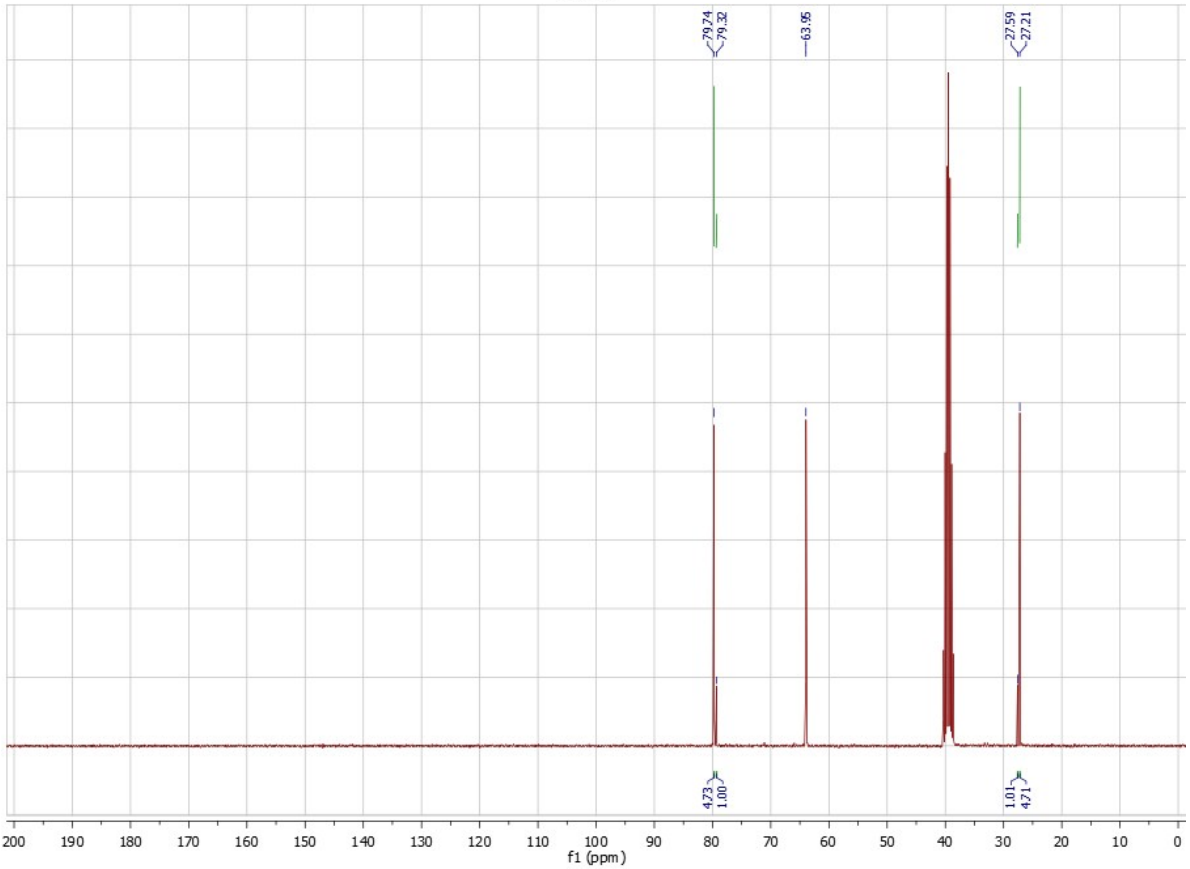
Entry	Vial	HMF[a]	BHMF[a]	THFDM[a]
1	**A**	0%	32%	44%
2	**B**	0%	8%	64%
3	**R**	0%	1%	67%

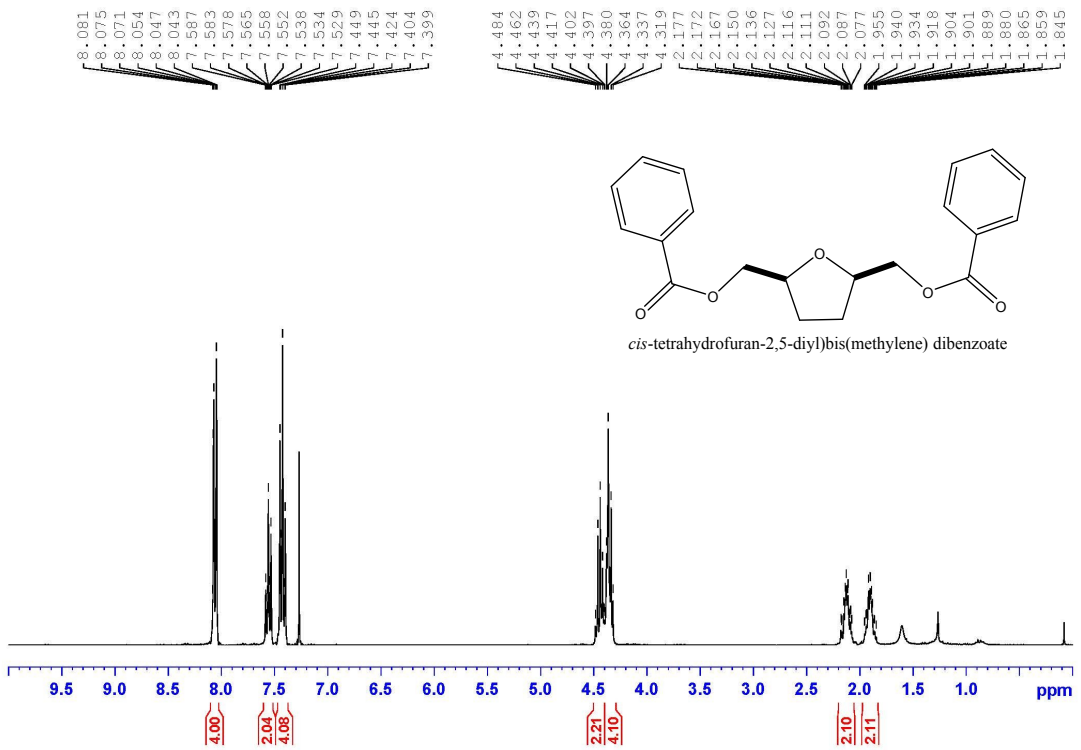
[a]: NMR yields were determined using hexamethylbenzene as an internal standard

Table S2. Mercury drop test.

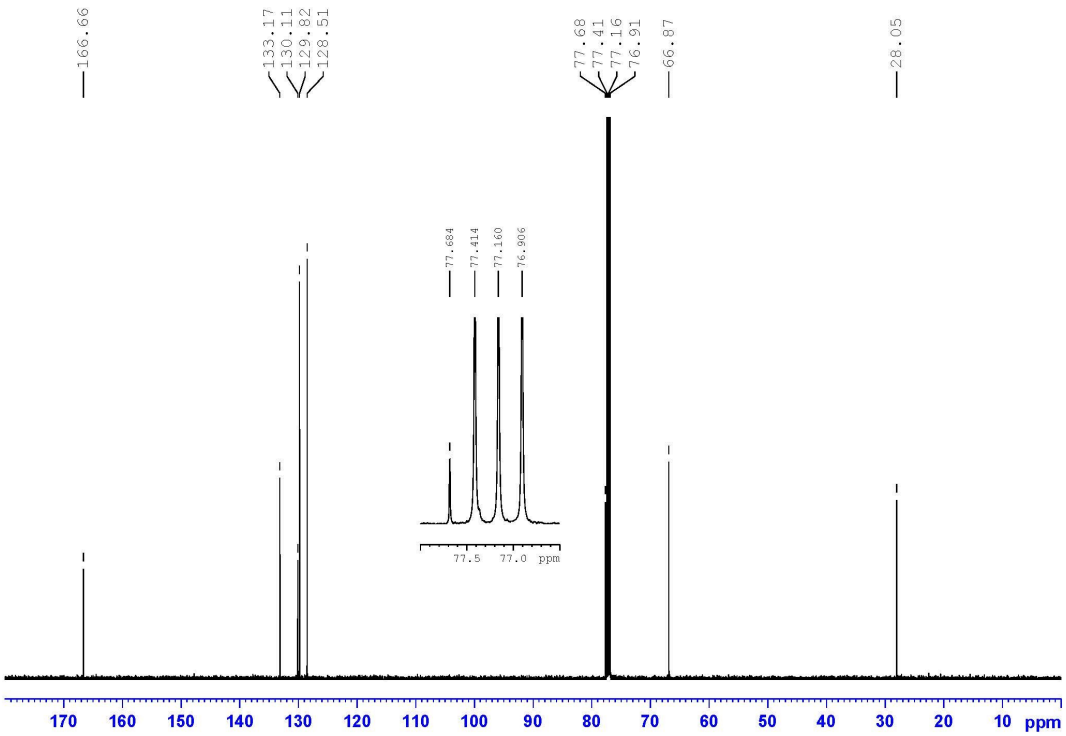
6. Spectra

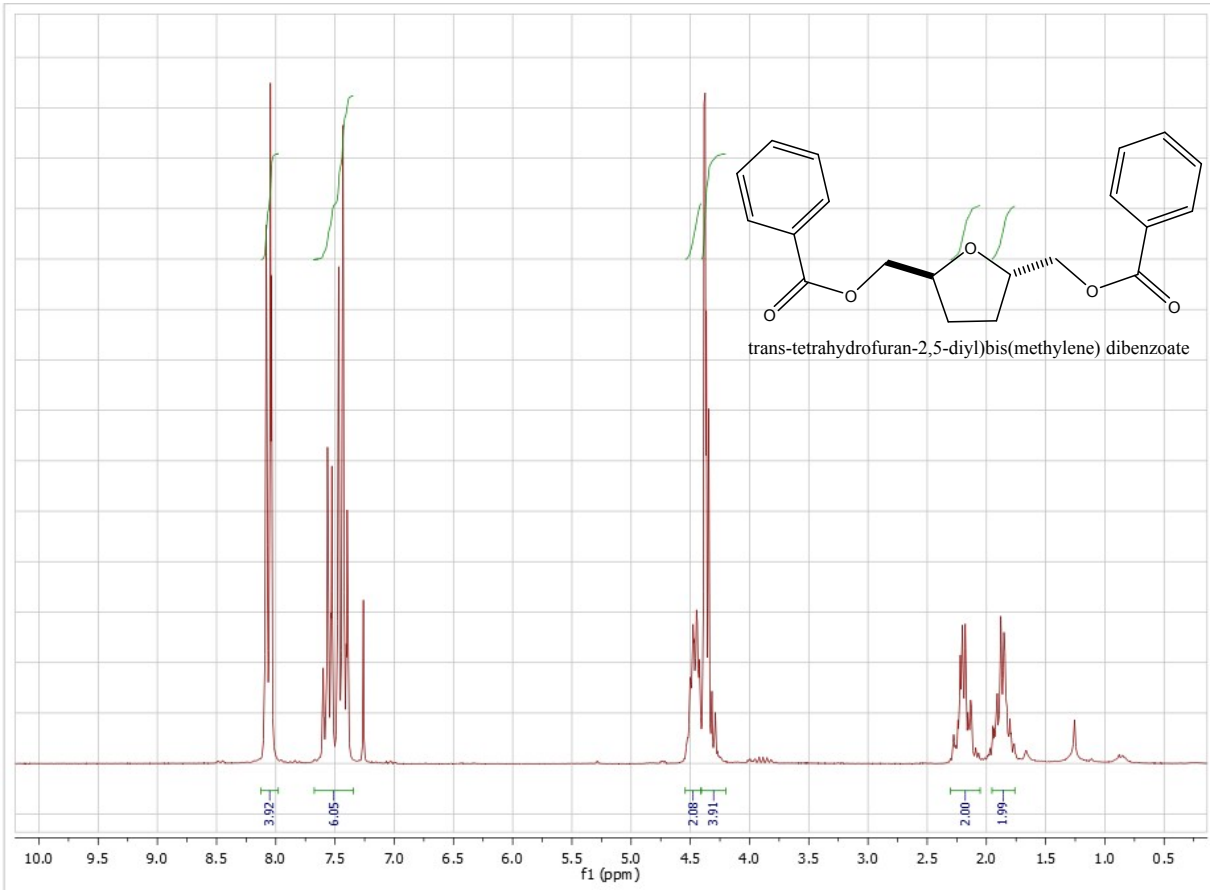

HO
O
OH
(tetrahydrofuran-2,5-diyl)dimethanol
4.57
3.82
1.80
1.60
1.93
2.00
2.06
2.13
f1 (ppm)

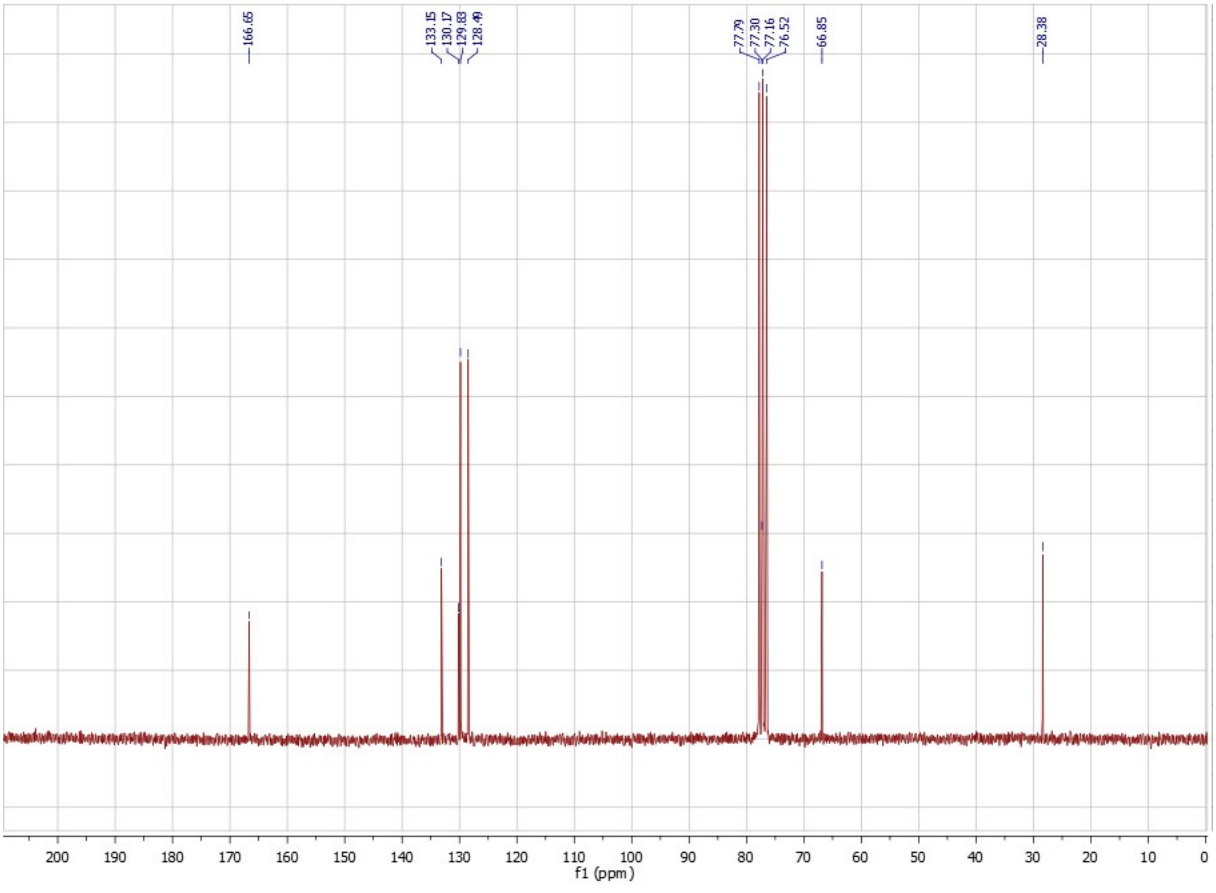

79.74
79.32
63.96
27.59
27.21
4.73
1.00
1.01
4.71
f1 (ppm)



cis-tetrahydrofuran-2,5-diyl)bis(methylene) dibenzoate




trans-tetrahydrofuran-2,5-diyl)bis(methylene) dibenzoate
3.92
6.05
2.08
3.91
2.00
1.99
f1 (ppm)


166.65
133.15
130.17
129.83
128.49
77.79
77.30
77.16
76.52
66.85
28.38
f1 (ppm)