Catalytic base-free transfer hydrogenation of biomass derived furanic aldehydes with bioalcohols and PNP pincer complexes

Padilla, Rosa; Ni, Zhenwei; Mihrin, Dmytro; Larsen, René Wugt; Nielsen, Martin

Published in:
ChemCatChem

Link to article, DOI:
10.1002/cctc.202200819

Publication date:
2023

Document Version
Peer reviewed version

WILEY-VCH

RESEARCH ARTICLE

Catalytic base-free transfer hydrogenation of biomass derived furanic aldehydes with bioalcohols and PNP pincer complexes

Rosa Padilla*,[a] Zhenwei Ni,[a] Dmytro Mihrin,[a] René Wugt Larsen,[a] Martin Nielsen*[a]

[a] Dr. R. Padilla, Z. Ni, Dr. D. Mihrin, Dr. R. W. Larsen, Dr. M. Nielsen
Department of chemistry
Technical University of Denmark
Kemitorvet 207, Building 206
E-mail: marnie@kemi.dtu.dk, rmar@kemi.dtu.dk

Supporting information for this article is given via a link at the end of the document.

Abstract: The base-free transfer hydrogenation of biomass derived furanic aldehydes with ruthenium and iridium pincer complexes was studied using bio-alcohols as the hydrogen source. The furanic substrates, such as 5-hydroxymethyl furfural (HMF) and thiophene-2-carboxaldehyde (TC), were reduced under mild conditions (35-80 °C) affording the desired alcohols with excellent conversions and yields. It was also possible to extend this methodology for the transfer hydrogenation of 5-formylfurfural (DFF) at 130 °C. Deuterium labelling of C-H functions in the furanic alcohols was also investigated in the presence of ethanol-d_6. Finally, proposed catalytic resting species derived from the interactions between one of the catalysts and furanic reagents/product as well as the solvent during the transfer hydrogenation (TH) reaction were analysed.

Introduction

Reduction reactions are among the simplest transformations in organic chemistry.[1] The reduction of aryl aldehydes produces alcohols, which are important intermediates in the synthesis of bulk chemicals and pharmaceutical compounds.[1-3] Significant efforts have been made to exert catalytic systems to efficiently and selectively hydrogenate C=O bonds of the substrates using hydrogen (H_2) as the reductant. In this regard, cutting-edge homogeneous systems using Noyori bifunctional metal-ligand catalysis for the catalytic hydrogenation of carbonyl compounds have been reported.[4] After that, significant advances have been made in this field using mainly Ru, Rh, Ir, Mn, and Fe for hydrogenation of carbonyl functionalities providing saturated aldehydes or unsaturated alcohols of industrial importance.[5-7]
The catalytic reduction of biomass is one of the major research areas for the formation of platform chemicals from renewable resources.[8] In particular, bioderived furanic chemicals are important feedstock obtained by the selective dehydration of hexose and pentose sugars.[9] Furthermore, furan derivatives such as 5-hydroxymethyl furfural (HMF), furfural (FAL), 5-methylfurfural (MF), thiophene-2-carboxaldehyde (TC), 5-formylfurfural (DFF), and 5-formyl-2-furoic acid (FFCA) are used as valuable C5/C6 resources for the synthesis of value-added chemicals and biofuel components.[10]
Different metal-based catalysts have been reported to promote the selective hydrogenation of furanic compounds.[11,12] However, the need for high-pressure equipment and concerns about safety issues limit the applicability of this method. Compared with common hydrogenation, easily accessible hydrogen sources are used in transfer hydrogenation (TH) instead of H_2,[3,13] such as isopropanol (*i*PrOH) and formic acid. In contrast, the simplest alcohols such as methanol (MeOH) and ethanol (EtOH) have been less employed.[14]

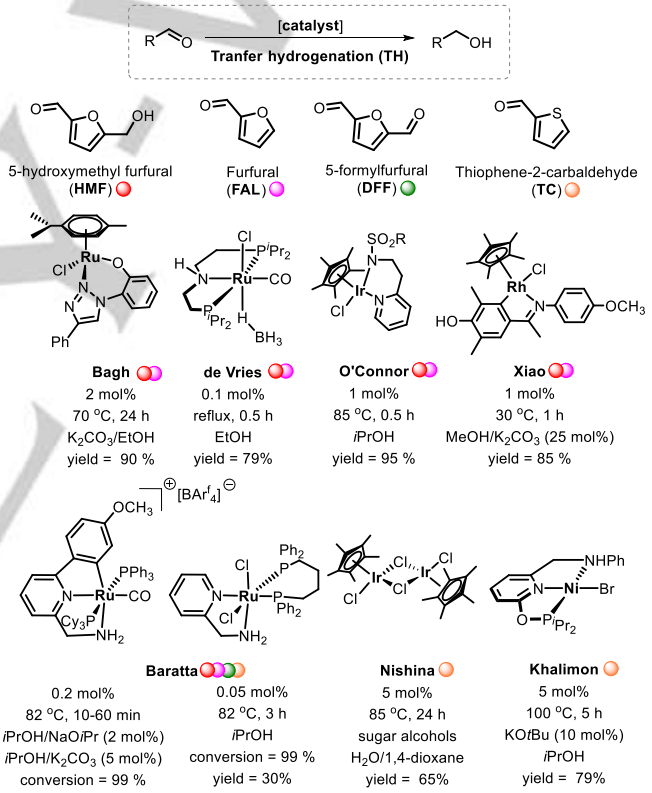


Figure 1. Reported catalysts for the transfer hydrogenation (TH) of furanic aldehydes.

Indeed, selective TH of carbonylic functionalities present in bioderived furanic substrates offers practical advantages for the production of green platform chemicals as sustainable alternatives to fuels and bulk chemicals.[15] However, there are few reports of homogeneous catalysts capable of performing the TH of furanic aldehydes without base or formation of side products (Figure 1). For instance, O'Connor described the TH of FAL and HMF under base-free conditions employing *i*PrOH as hydrogen source with a Cp*Ir(pyridinesulfonamide)Cl complex (1 mol%) at 85 °C for 30 min.[16] Both furanic aldehydes were reduced towards their corresponding alcohols in 99% and 95%

yield, respectively. Lately, Xiao described the TH of HMF using catalytic amounts of a rhodacycle (1 mol%) in MeOH and Cs_2CO_3 as base affording 82% yield at 90 °C for 1 h.[17] Similarly, de Vries reported the TH of FAL using Ru-MACHO-BH (0.1 mol%) complex in the presence of *i*PrOH as hydrogen source. The furfuryl alcohol (FA) was isolated in 79% yield after 2-30 min under reflux.[18] Bagh and coworkers recently reported the TH of FAL using phosphine-free air-stable ruthenium(II)-triazole complex (2 mol%) in presence of EtOH and K_2CO_3 as the base at 70 °C.[19] The sequential TH/hydrogenolysis of FAL has been also described by Vlachos using Lewis acid-Ru/C catalyst or Fe_2O_3-supported Cu, Ni, and Pd-catalyst, with *i*PrOH as hydrogen donor at high temperatures.[20] In other attempts, Nishina reported the reduction of thiophene 2-carbaldehyde (TC) through TH using a homogeneous catalyst $[IrCp^*Cl_2]_2$ (5 mol%) in presence of sugar alcohols or carbohydrates as the hydrogen source at 85 °C, and 24 h. The product 2-thiophenemethanol (TM) was isolated in 65% yield. In order to dissolve glucose, a mixture of water/1,4-dioxane was required for this reaction.[21] Baratta also reported the chemoselective reduction of HMF, FAL, DFF and TC to the corresponding furanic alcohols using a Ru-ampy complex (0.05-0.2 mol%) in *i*PrOH as hydrogen donor at 82 °C for 3 h. An auxiliary base was added to promote the TH process (NaO*i*Pr or K_2CO_3).[22] Likewise, Khalimon used the aminophosphinite pincer complex ($POCN^H$)NiBr (5 mol%) for the TH of the heteroaromatic aldehyde (TC) with *i*PrOH and KO*t*Bu (10 mol%) as a base at 100 °C for 5 h. The resulting product was isolated in 79% yield.[23] Homogeneous base-free TH applied to furanic aldehydes is still underdeveloped and requires synthetic efforts to improve the efficiency and versatility of this catalytic process.

Herein, we report the use of well-defined pincer Ru and Ir based catalysts for the transfer hydrogenation of bioderived furanic aldehydes in the absence of base. Notably, different alcohols (EtOH, *i*PrOH, and MeOH) are employed as hydrogen sources under additive free and mild conditions and HMF, FAL, DFF and TC are all viable substrates.

Results and Discussion

The Ru-PNP and Ir-PNP family of complexes are excellent catalysts for the dehydrogenation of alcohols, hydrogen production and the hydrogenation of a large number of carbonylic functionalities,[24] including base-free transfer hydrogenation reactions.[3,18,25] Indeed, we have continuously contributed to these developments ourselves.[26] Herein, we show the use of these catalysts in the transfer hydrogenation of bio-based furanic aldehydes in EtOH as hydrogen source and solvent owing to its accessibility from renewable biomass.

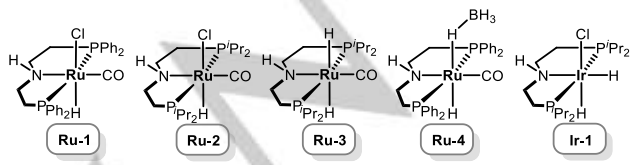


Figure 2. Selected pincer complexes for the catalyst screening.

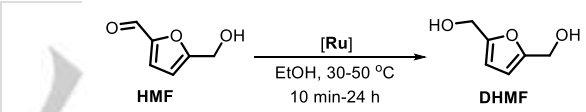
We initially explored the TH of the model substrate HMF (0.5 mmol) with 1.0 mol% of the Ru-MACHO complex **Ru-1** and its congeners **Ru-2** and **Ir-1** at 25 °C for 18 h (SI, Table S1). However, these chloride derivatives were not active under these reaction conditions.

On the other hand, the dihydride and borohydride analogues (**Ru-3** and **Ru-4**, respectively) enabled moderate conversions (20%) of HMF towards the desired product. Particularly **Ru-4** showed a poor solubility at this temperature, likely to slowing down the catalytic initiation and the reaction rate (see SI).

To circumvent these issues, we refluxed an EtOH solution containing **Ru-4** until a completely homogeneous solution was obtained according to eye inspection. Next, the addition of the substrate was carried out at 30 °C. Employing 1.0 mol% of **Ru-4** under this these settings afforded 28% conversion after 10 minutes (Table 1, Entry 1). Furthermore, it was possible to convert HMF to DHMF with 99% conversion at as low temperatures as 35 °C for 6 h (Entry 3).

Increasing the reaction temperature to 50 °C without preheating led to complete conversion within 1 h (Entry 4). To our delight, lowering the catalyst loading of **Ru-3** or **Ru-4** to 0.6 mol% afforded the complete conversion of HMF to DHMF at 50 °C in 2 h (Entries 6 and 9). Ethyl acetate was detected by ^{1}H NMR and GC-MS as the byproduct, likely resulting from the dehydrogenation of a hemiacetal obtained from the formed acetaldehyde and another molecule of ethanol (see SI). The data in table 1 shows some key features of the TH reactions with HMF as model substrate.

Table 1. Catalyst screening for the transfer hydrogenation of HMF to DHMF.



Entry[a]	Catalyst (mol%)	Temperature [°C]	Time	Conversion [%][b]
1[c]	**Ru-4** (1.0)	30	10 min	28
2[c]	**Ru-4** (1.0)	35	4 h	85
3[c]	**Ru-4** (1.0)	35	6 h	≥99
4	**Ru-4** (1.0)	50	1 h	≥99
5	**Ru-4** (0.6)	50	1 h	50
6[d]	**Ru-4** (0.6)	50	2 h	≥99
7	**Ru-4** (0.1)	50	6 h	23
8	**Ru-4** (0.1)	50	24 h	48
9	**Ru-3** (0.6)	50	2 h	≥99

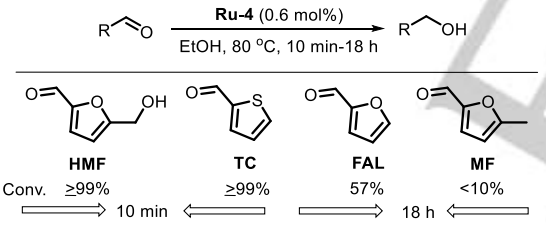
[a] Reaction conditions: 0.5 mmol HMF, 0.1-1.0 mol% [catalyst], 5 mL alcohol at 30-50 °C . [b] Determined by ^{1}H NMR analysis. [c] Prior to addition of HMF, **Ru-4** is dissolved in refluxing EtOH followed by cooling to given reaction temperature. [d] Isolated yield = 81%.

The applicability of these catalytic systems was also evaluated with other furanic substrates such as FAL and MF. Noteworthy, the base-free catalytic TH of these compounds is scarcely

reported in the literature. Moderate conversions were detected with FAL (57%) and MF (<10%) in presence of **Ru-4** (0.6 mol%) at 50 °C for 2 h (SI, Table S2). Within the scope of furanic aldehydes, the reaction was found to tolerate other heteroaromatic functionalities such as sulfur present in TC. Thus, the selective TH of TC to TM was achieved with 99% conversion using **Ru-4** (0.6 mol%) at 50 °C after 2 h (SI, Table S11). It is worth mentioning that, TM is a heterocyclic building block used in pharmaceutical and organic synthesis.[27]

Attempts to increase the conversion of the selected furanic aldehydes by increasing the temperature to 80 °C were successful. As such, TH of the model substrate HMF was evaluated with the complexes **Ru-3** and **Ru-4** (0.6 mol%) in presence of EtOH. Interestingly, both catalysts showed comparable behavior affording 99% conversion in only 10 min (Scheme 1). Additionally, iridium complex **Ir-1** (0.6 mol%) was tested during the optimization reactions. This complex showed lower catalytic activity for the aldehyde reduction reaction affording 71% conversion at 80 °C in 18 h (SI, Table S3).

Interestingly, the selective transformation of TC to TM was also achieved in 99% conversion with **Ru-4** (0.6 mol%) over 10 min in EtOH at 80 °C leading to almost quantitative yield (≥95%, Scheme 1). However, FAL was reduced to the corresponding alcohol in only moderate conversion (up to 57%) under similar reaction conditions. Notably, lower conversion was observed for the reaction with MF (<10%). We observed similar differences in reactivities among the furanics for the hydrogenation with H_2 to the corresponding alcohols.[11d] Besides the variations in reactivities of the different furanics, the lower conversions with FAL and MF might also be attributed to catalyst deactivation or detrimental change in solubility of substrates.



Scheme 1. Catalytic TH of furanic aldehydes at 80 °C.

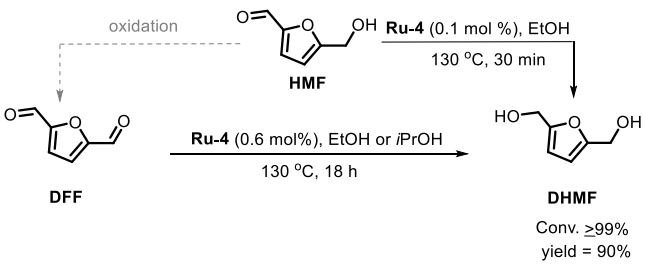
Next, *i*PrOH and MeOH were tested as hydrogen sources for the transformation of HMF at 80 °C. In fact, the secondary alcohol *i*PrOH has been used as the solvent and hydrogen source in the majority of the catalytic transfer hydrogenation reactions.[28] The complex **Ru-3** (0.6 mol%) showed a moderate HMF conversion of 48% after the first 10 min, which increased to merely 67% after 18 h in *i*PrOH (SI, Table S4). Interestingly, using **Ru-4** (0.6 mol%) at 80 °C led to lower conversion (<10%) over the first 10 min and 33% after 30 min, but only required 3 h to achieve complete conversion (≥99%) (SI, Table S4). This might compare to the results described by de Vries as mentioned earlier.[18]

As expected, acetone was detected as the dehydrogenation product. It can be argued that EtOH is a more promising hydrogen donor than *i*PrOH or MeOH in terms of sustainability for the conversion of biomass.[29] In fact, only a few reports describe the use of EtOH or MeOH as the hydrogen source in catalytic TH.[17-19,26d] Based on our results, we decided to evaluate the use of MeOH as a source of hydrogen for the TH of the model substrate HMF. Thus, the detected conversion using the complexes **Ru-3** or **Ru-4** (0.6 mol%) corresponds to 90% at 80 °C for 18 h (SI, Table S5). In addition to the formation of DHMF, we observed methyl formate as the dehydrogenation product of MeOH.

We also tested the tolerance of the catalytic systems **Ru-3** and **Ru-4** in presence of water by running a benchmark experiment with HMF in a mixture of EtOH/H_2O (9:1). As expected, the presence of water diminished the catalytic activity of **Ru-3** resulting in low conversion (<10%) at 80 °C even after extended reaction time (18 h, SI, Table S6). In addition, it is known that this bishydrido compound is more sensitive than other pincer precatalysts in the presence of water.[20] On the contrary, **Ru-4** provided 26% conversion after 18 h at 80 °C. All the studied reactions in mixtures of *i*PrOH/H_2O or MeOH/H_2O showed very low conversion (<10%) (SI, Table S6).

After further optimization of the reaction with HMF in presence of different alcohols, we evaluated the stability of the catalysts at higher temperatures. Upon increasing the reaction temperature to 130 °C, full conversion of HMF was achieved with merely 0.1 mol% of **Ru-3, Ru-4**, or **Ir-1** within 30 min in presence of EtOH or *i*PrOH (Table 2). On the other hand, the conversion rate of HMF was significantly lower when using MeOH. In fact, a higher catalyst loading of **Ru-3** (0.3 mol%) was necessary to afford 85% conversion towards DHMF at 130 °C and 30 min (SI, Table S2). Notably, the catalyst **Ru-4** (0.3 mol%) showed better catalytic performance under similar reaction conditions, showing 99% conversion in 30 min. The **Ir-1** (0.3 mol%) complex afforded 85% conversion at 130 °C in MeOH. The more sluggish reactivity in MeOH compared to EtOH and *i*PrOH might be reflected from the thermodynamically less favorable generation of H_2 or metal hydrides via MeOH dehydrogenation.[30] In fact, the addition of base (K_2CO_3) has been used by Xiao and coworkers to promote the TH of FAL and TC in MeOH with relatively high catalyst loading of cyclometalated rhodium complex (1 mol%) at 30 °C.[31]

With these outcomes in hand, we explored the substrate scope employing other important furanic aldehydes such as FAL using EtOH or *i*PrOH as hydrogen sources. The transformation of FAL to FA at 130 °C with **Ru-3** (0.1 mol%) in presence of EtOH displayed moderate conversion (30%). Interestingly, **Ru-4** (0.1 mol%) afforded a higher conversion of 99% under the same reaction conditions in presence of EtOH or *i*PrOH. Interestingly, no catalytic activity was detected with **Ir-1** complex. We previously demonstrated the catalytic hydrogenation of MF to 5-methyl furfuryl alcohol (MFA) with systems based on Ru or Ir PNP chloride complexes.[11d] However, for TH reactions only **Ru-4** (0.6 mol%) was active showing complete conversion (99%) of MF in EtOH at 130 °C for 18 h (SI, Table S9). Noteworthy, when lowering the catalyst loading of **Ru-4** (0.3 mol%), the conversion decreased (<10%) in either *i*PrOH or EtOH.

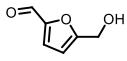
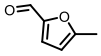
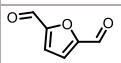


Scheme 2. Direct transformation of DFF to DHMF using **Ru-4** in EtOH or *i*PrOH.

We then studied the TH of other biomass derived feedstock containing two aldehydes groups such as 5-formylfurfural (DFF). The conversion of DFF to value-added DHMF in a one-pot reaction is an interesting synthetic approach. When the reaction was performed with **Ru-3** or **Ru-4** (0.6 mol%) in presence of alcohol (EtOH or *i*PrOH) at 130 °C both aldehyde groups were reduced towards the formation of DHMF with high conversion (99%) after 18 h (Table 2). To the best of our knowledge, there are no examples of direct TH of this substrate in the absence of additives. For instance, Huang and coworkers reported the selective hydrogenation of DFF using a PN_3-pincer manganese complex (2 mol%) in presence of K*t*BuO (10 mol%) and 35 bar H_2 in MeOH. However, they extended the reaction time to 48 h to afford the selective formation of DHMF and avoid the generation of HMF as a side product.[7j] Similarly, Baratta observed incomplete reduction of DFF to DHMF using a Ru-ampy complex (0.2 mol%) and the addition of an excess base (K_2CO_3) was necessary to afford the transformation of the substrate in *i*PrOH.[22a]

In addition, the complete catalytic reduction of TC to TM was achieved in the presence of 0.1 mol% of **Ru-4** catalyst at 130 °C in EtOH or *i*PrOH for 30 min with 99% conversion and nearly quantitative yield.

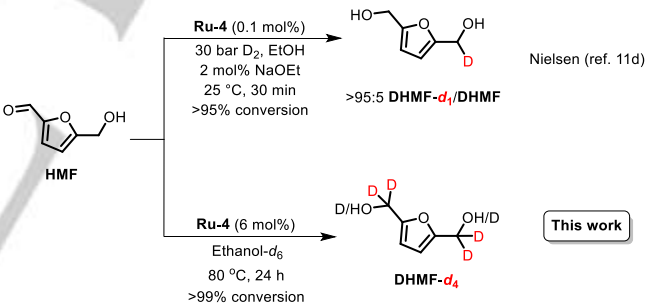
Table 2. Catalytic transfer hydrogenation of furanic aldehydes at 130 °C.

Entry [a]	Furanic aldehyde	Catalyst (mol%)[b]	Alcohol[c]	Time [h]	Conv. [%] [c]
1	 HMF	**Ru-3** (0.1)	EtOH or *i*PrOH	0.5	≥99
2		**Ru-3** (0.3)	MeOH	0.5	85
3		**Ru-4** (0.1)	EtOH or *i*PrOH	0.5	≥99
4		**Ru-4** (0.3)	MeOH	0.5	≥99
5		**Ir-1** (0.1)	EtOH or *i*PrOH	0.5	≥99
6		**Ir-1** (0.3)	MeOH	0.5	85
7	 FAL	**Ru-3** (0.1)	EtOH	0.5	30
8		**Ru-4** (0.1)	EtOH or *i*PrOH	0.5	≥99
9		**Ir-1** (0.1)	EtOH or iPrOH	0.5	-
10	 MF	**Ru-4** (0.6)	EtOH or *i*PrOH	18	≥99
11		**Ru-4** (0.3)	EtOH or *i*PrOH	18	<10
12	 DFF	**Ru-3** (0.6)	EtOH	18	≥99
13		**Ru-4** (0.6)	EtOH or *i*PrOH	18	≥99
14	 TC	**Ru-3** (0.1)	EtOH	18	≥99
15		**Ru-4** (0.1)	EtOH or *i*PrOH	18	≥99

[a] Reaction conditions: 0.5 mmol HMF, 0.1-0.6 mol% catalyst and 5 mL alcohol at 130 °C. [c] Determined by ^{1}H NMR analysis.

Furthermore, we evaluated the robustness of the catalytic system by scaling up the reaction and lowering the catalyst loadings. Thus, we evaluated whether ppm-range loadings of **Ru-4** would facilitate the conversion of 4.7 mmol (452 mg) of FAL at 130 °C with 20 mL of EtOH. Indeed, using 0.05 mol% of **Ru-4** led to ≥95% conversion after 30 min and an isolated yield of 85% (SI, Table S8). Moreover, this methodology allowed a TON = 1941 and TOF= 65 min^{-1}. Again, this result might compare to the reported findings by de Vries.[18]

The degree of deuterium-labelling in the transformation of HMF into DHMF was evaluated at 80 °C employing the complex **Ru-4** and ethanol-d_6 as solvent and hydrogen source (Scheme 3, lower reaction). The deuterium incorporation was observed in 99% in the methylene position, leading to the shown DHMF-d_4 with even the HMF aldehyde- and hydroxymethylene hydrogens exchanged in the final product. Interestingly, this finding suggests that a highly dynamic process takes place during the course of HMF conversion to DHMF, with a significant amount of back-formation to HMF occuring. We have previously observed a selective monodeuteration of HMF when using hydrogenation conditions with D_2 (Scheme 3, upper reaction).[11d] Thus, it is possible to selectively incorporate either one or four deuterium atoms on the methylene positions of HMF. Importantly, the regioselective deuterium-labelled alcohol derivatives have a wide range of applications, such as unraveling chemical or biosynthetic reaction mechanisms.[32] Conventionally, the incorporation of deuterium into alcohols at the C–H position can be achieved by multistep organic synthesis in presence of hazardous deuterated reducing reagents such as $NaBD_4$ or $LiAlD_4$.[33] Therefore, our regioselective and straightforward TH method based on direct catalytic H/D exchange using **Ru-4** and ethanol-d_6 as deuterium source is of high interest.

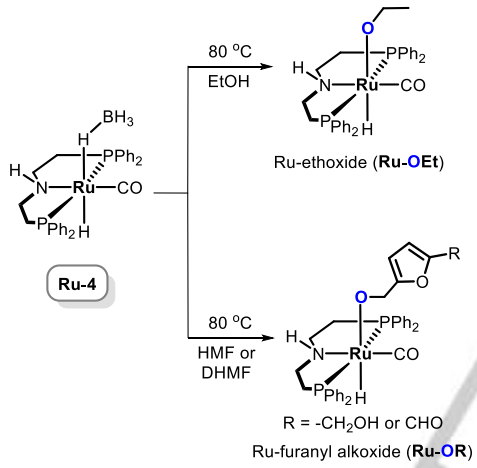


Scheme 3. Deuterium labelling experiments of HMF with **Ru-4** and ethanol-d_6.

As illustrated in Scheme 4, the NMR studies of this reaction suggested that upon thermal activation of the precatalyst **Ru-4** in the TH process, the main resting species is likely to be a Ru-ethoxide (**Ru-OEt**) or Ru-furanyl alkoxide (**Ru-OR**).[11d] To corroborate this observation, the crude reaction in EtOH was studied with ^{1}H and ^{31}P NMR before and after evaporation of ethanol of a reaction with **Ru-4** (6 mol%) (SI, Figures S23 and S24). An intensification of a triplet resonance at approximately -16.80 ppm upon EtOH removal indicates that this peak might be assigned to the hydride ligand in **Ru-OR**. To further support our findings, a number of NMR experiments with EtOH, FA, FAL, or HMF and the precatalyst **Ru-4** in toluene-d_8 have been investigated. The treatment of **Ru-4** with EtOH in toluene-d_8 at 80 °C revealed the formation of the ethoxide complex (**Ru-OEt**) exhibiting a hydride signal at -16.85 ppm (SI, Figures S21 and S22). The formation of this species from **Ru-4** has previously been described in the literature.[18,34] Upon reaction of complex **Ru-4** with FAL or HMF under similar reaction conditions, the analogous furanyl alkoxide species were detected at almost identical chemical shift. In addition, the resonance for the known

Ru-amido intermediate was observed at -17.20 ppm. Interestingly, the reaction with FA showed broad multiple signals in the same hydride region (-16.80 to -17.10 ppm), which might be due to the addition of the OH group from the furanic alcohol across the N-H and Ru-hydride bond (SI, Figure S22).

Finally, we also studied an ethanol-d_6 solution of the complex **Ru-4** and HMF which was heated up to 80 °C for 24 h in tol-d_8. The NMR spectra revealed the formation of **Ru-OR** species detected in the hydride region (SI, Figures S17-S20). For instance, the triplet resonance at -16.80 ppm can be assigned to the hydride ligand in **Ru-OR.** The intensity of the signal of these species in ethanol-d_6 increases as the temperature is elevated during the transfer hydrogenation reaction under the given reaction conditions. The $^{31}P\{^1H\}$ NMR shift of the P-atoms in the resting species displayed a signal at 56.50 ppm. Interestingly, the intensities of the hydride peaks are still fairly strong despite the fact that a deuterium donor is used instead of the typical hydrogen donors.



Scheme 4. Resting species **Ru-OEt** and **Ru-OR** identified in this study.

Additional spectroscopic studies were carried out for the resting species using *in situ* IR spectroscopy under conditions that are identical to those above described. Thus, monitoring the Ru-alkoxide species derived from EtOH revealed an intense band at 1910 cm^{-1} that is characteristic of the terminal CO ligand present in **Ru-OEt**. The **Ru-OR** species derived from HMF or FA showed a band around 1914 cm^{-1}. These assignments were confirmed by comparison to authentic samples of **Ru-4** and **Ru-OEt**.[35] Furthermore, the IR analysis features the qualitative evolution of the generated species. The observed absorbance profile of the crude reactions containing **Ru-OEt** and **Ru-OR** indicated that these intermediates are predominant in the reaction mixture. The complex **Ru-4** is gradually consumed as evidenced by the disappearance of the four medium-strong BH_4 bands assigned at 2367, 2330, 2286 and ~1850 cm-1 (SI, Figures S27-S28).

Conclusion

In conclusion, we demonstrate an efficient, selective, and rapid catalytic method for reducing furanic aldehydes employing transfer hydrogenation with EtOH, *i*PrOH, or MeOH as hydrogen sources. Our results underline the remarkable activity of Ru-MACHO-BH complex (**Ru-4**) for the reduction of furanic aldehydes with a maximum TON of 1941 and almost quantitative yields under mild reaction conditions. This benign reduction process operates in absence of additive, with low catalyst loadings, and on practical substrate scales. Importantly, it is a highly selective TH methodology that enables the synthesis of furanic alcohols at nearly room temperature using bioalcohols as the hydrogen source. Finally, we also performed deuterium labelling studies as well as NMR and IR investigations of the fate of the catalyst under additive-free reaction conditions.

Experimental Section

Most chemicals were purchased from commercial suppliers and used without further purification unless otherwise stated. Hydroxymethylfurfural (HMF, 99%), 5-methylfurfural (MF, 99%), furfural (FAL, 99%), **Ru-1**, **Ru-2**, **Ru-4**, and **Ir-1** are commercially available and used without further purification. **Ru-3** was prepared using the methodology described in the literature.[36] All reactions dealing with air or moisture-sensitive compounds were performed using standard Schlenk techniques or in an argon-filled glovebox. The ^1H, ^2H, ^{31}P, and ^{13}C NMR spectra were recorded on a Bruker Avance III 400 MHz or 800 MHz spectrometer and were referenced on the solvent peak ($CDCl_3$ or tol-d_8). All the starting materials and products are literature-known compounds, and the experimental data fit those reported. The resting species were identified only by NMR.

General procedure for the catalytic transfer hydrogenation of furanic aldehydes. In a typical experiment, a Schlenck pressure tube containing a magnetic stirrer was charged with the catalyst (0.1-1.0 mol%) in the glovebox. The pressure vessel was sealed with a Teflon screw cap and the furanic substrate (0.5 mmol) was added under argon flow using the Schlenk line. Degassed and dry EtOH, *i*PrOH, or MeOH (5 mL) was added through the septum rubber cap. The reaction container was sealed and the reaction mixture was stirred at 30-80 °C for the specified time after which it was quickly cooled to room temperature. A sample was taken from the container, diluted in $CDCl_3$, and analysed by NMR spectroscopy.

The screening experiments at 130 °C, were carried out in a stainless-steel high-pressure reactor that was sealed and flushed with argon (three times). The pressure reactor was stirred for 0.5-18 h (850 rpm) at the desired temperature. After this time, the reactor was cooled to room temperature before the hydrogen was released. The crude reaction mixture was then analyzed using ^1H NMR spectroscopy in $CDCl_3$. When the transfer hydrogenation of FAL was carried out on a large scale (4.7 mmol), the raw material, complex **Ru-4** (0.05-0.1 mol%) and solvent (EtOH or *i*PrOH, 20.0 mL) were charged into a 50 mL high-pressure reactor. The autoclave was tightened and flushed with argon three times. The reaction mixture was stirred (900 rpm) at 130 °C for the desired time. After the reaction, the autoclave pressure was released carefully. The reaction mixture was analyzed by using NMR as described above. In order to isolate the product (FAL), we performed a filtration of the crude reaction using a silica gel pad and *i*PrOH to wash it; after that, the solvent was evaporated under vacuum to form a brown oil in good yield (85%).

Deuterium labeling experiments. Conventional experiment procedure was carried out using HMF as substrate on 0.079 mmol

scale, and complex **Ru-4** (6 mol%) in 1 mL of ethanol-d_6. All the chemicals were charged into a Schlenck pressure tube under argon flow. The reaction mixture was stirred (900 rpm) at 80 °C for 24 h. After the reaction time, the tube was cooled down and the pressure was released carefully. The reaction mixture (0.4 mL) was analyzed by ^{1}H, ^{2}H, ^{31}P and ^{13}C NMR using a J. Young NMR tube. The D-incorporation label was calculated by partial integration of ^{13}C NMR signals of -CH_2OH/-CHDOH at 56.82 ppm.

Resting species experiments. The precatalyst **Ru-4** (6 mol%) and substrates (HMF, FAL or FA) on 0.079 mmol scale, were weighed into a Schlenck pressure tube under argon flow. Then 2 mL of solvent (ethanol-d_6, EtOH, tol-d_8 or C_6D_6, respectively) were added to the glass vessel through the septum rubber cap. The container was sealed with a Teflon screw cap and the reaction mixture was stirred (900 rpm) at 80 °C for 3 h. After the reaction time, the tube was cooled down and the pressure was released carefully. The solvent was evaporated and remnant solid from the crude reaction mixture (0.4 mL) was analyzed by ^{1}H, ^{2}H, ^{31}P NMR and IR.

IR measurements. The attenuated-total-reflectance (ATR) Fourier Transform infrared (FTIR) spectra have been collected by a Bruker VERTEX80v FTIR vacuum spectrometer employing a single-reflection germanium ATR accessory (IRIS) from PIKE Technologies, Inc. The FTIR apparatus was configured with a KBr/Ge beam splitter, a liquid nitrogen cooled HgCDTe detector and a globar thermal radiation source. The collected ATR spectra of 1 cm^{-1} resolution have been corrected for residual water vapor absorption and the resulting absorption spectra consisting of 1600 co-added scans have been corrected for minor baseline drifts. Subsequently, extended ATR corrections have been applied to account for the wavelength-dependent penetration depth of the infrared probe beam into the samples. The bond stretching assignments of the resting species **Ru-OEt** and **Ru-OR** were confirmed by comparison to authentic samples of **Ru-4** and **Ru-OEt**.

Acknowledgements

This work was supported by a research grant (19049) from VILLUM FONDEN and a research grant (NNF20OC0064560) from the Novo Nordisk Foundation, which RP, ZN, and MN are all grateful for. ZN thanks China Scholarship Council (201906230349) for generous funding.

Keywords: transfer hydrogenation • furanics • green • bioalcohols

[1] E. A. Verochkina, N. V. Vchislo, I. B. Rozentsveig, *Molecules* **2021**, *26*, 4297.

[2] M. C. Bryan, P. J. Dunn, D. Entwistle, F. Gallou, S. G. Koenig, J. D. Hayler, M. R. Hickey, S. Hughes, M. E. Kopach, G. Moine, P. Richardson, F. Roschangar, A. Steven, F. J. Weiberth, *Green Chem*. **2018**, *20*, 5082-5103.

[3] R. Padilla, S. Koranchalil, M. Nielsen, *Catalysts* **2021**, *11*, 1371.

[4] a) R. Noyori, *Angew. Chem. Int. Ed*. **2002**, 41, 2008.b) H. J. Federsel, *Nat. Rev. Drug Discov.* **2005**, *4*, 685–697.

[5] For Ru: a) T. Ohkuma, H. Ooka, S. Hashiguchi, T. Ikariya, R. Noyori, *J. Am. Chem. Soc.* **1995**, *117*, 2675–2676. b) H. Doucet, T. Ohkuma, K. Murata, T. Yokozawa, M. Kozawa, E. Katayama, A. F. England, T. Ikariya, R. Noyori, *Angew. Chem. Int. Ed*. **1998**, *37*, 1703–1707. c) T. vom Stein, M. Meuresch, D. Limper, M. Schmitz, M. Hölscher, J. Coetzee, D. J. Cole Hamilton, J. Klankermayer, W. Leitner, *J. Am. Chem. Soc*. **2014**, *136*, 13217- 13225. d) C. P. Casey, N. A. Strotman, S. E. Beetner, J. B. Johnson, D. C. Priebe, I. A. Guzei, *Organometallics* **2006**, *25*, 1236–1244.

[6] For Ir and Rh: T. P. Brewster, A. J. M. Miller, D. M. Heinekey, K. I. Goldberg, *J. Am. Chem. Soc*. **2013**, *135*, 16022–16025.

[7] For Fe and Mn: a) I. Bauer, H.-J. Knölker, *Chem. Rev*. **2015**, *115*, 3170–3387. b) A. Lator, S. Gaillard, A. Poater, J.-L. Renaud, *Chem. Eur. J.* **2018**, *24*, 5770–5774. c) F. Kallmeier, R. Kempe, *Angew. Chem. Int. Ed*. **2018**, 57, 46–60. d) R. P. Yu, J. M. Darmon, J. M. Hoyt, G. W. Margulieux, Z. R. Turner, P. J. Chirik, *ACS Catal.* **2012**, *2*, 1760–1764. e) R. Langer, G. Leitus, Y. Ben-David, D. Milstein, *Angew. Chem. Int. Ed.* **2011**, *50*, 2120–2124. f) T. Zell, Y. Ben-David, D. Milstein, *Angew. Chem. Int. Ed.* **2014**, *53*, 4685–4689. g) R. Huber, A. Passera, A. Mezzetti, *Organometallics* **2018**, *37*, 396–405. h) G. Bauer, K. A. Kirchner, *Angew. Chem. Int. Ed*. **2011**, *50*, 5798–5800. i) S. Chakraborty, H. Dai, P. Bhattacharya, N. T. Fairweather, M. S. Gibson, J. A. Krause, H. Guan, *J. Am. Chem. Soc*. **2014**, *136*, 7869–7872. j) S. S. Gholap, A. A. Dakhil, P. Chakraborty, H. Li, I. Dutta, P. K. Das, K.-W. Huang, *Chem. Commun*. **2021**, *57*, 11815–11818.

[8] a) P. J. Deuss, K. Barta, J. G. de Vries, *Catal. Sci. Technol*. **2014**, 4, 1174–1196. b) F. Zeng, K. L. Hohn, in Catalysis (Eds.: J. Spivey, Y.-F. Han, D. Shekhawat), *Royal Society Of Chemistry, Cambridge*, **2019**, pp. 1–36.

[9] X. Tong, Y. Ma, Y. Li, *Appl. Catal. A: Gen.* **2010**, *385*, 1–13.

[10] Y. Nakagawa, M. Tamura, K. Tomishige, *ACS Catal*. **2013**, *3*, 2655–2668.

[11] a) E. Jansen, L. S. Jongbloed, D. S. Tromp, M. Lutz, B. de Bruin, C. J. Elsevier, *ChemSusChem* **2013**, *6*, 1737–1744. b) A. Cadu, K. Sekine, J. Mormul, D. M. Ohlmann, T. Schaub, A. S. K. Hashmi, *Green Chem*. **2018**, *20*, 3386–3393. c) T. Pasini, G. Solinas, V. Zanotti, S. Albonetti, F. Cavani, A. Vaccari, A. Mazzanti, S. Ranieri, R. Mazzoni, *Dalton Trans*. **2014**, *43*, 10224–10234. d) R. Padilla, S. Koranchalil, M. Nielsen, *Green Chem*. **2020**, *22*, 6767–6772. e) F. Huang, W. Li, Q. Lu, X. Zhu, *Chem. Eng. Technol*. **2010**, *33*, 2082–2088. f) Z. Strassberger, M. Mooijman, E. Ruijter, A. H. Alberts, C. de Graaff, R. V. A. Orru, G. Rothenberg, *Appl. Organometal. Chem*. **2009,** *24*, 142-146.

[12] a) R. M. Bullock, *Science* **2013**, 342, 1054–1055. b) G. Wienhöfer, F. A. Westerhaus, K. Junge, R. Ludwig, M. Beller*, Chem. Eur. J.* **2013**, *19*, 7701–7707. c) N. Gorgas, B. Stöger, L. F. Veiros, K. Kirchner, *ACS Catal*. **2016**, *6*, 2664–2672. d) S. Weber, J. Brünig, V. Zeindlhofer, C. Schröder, B. Stöger, A. Limbeck, K. Kirchner, K. Bica, *ChemCatChem* **2018**, *10*, 4386–4394. e) Z. Csendes, J. Brünig, N. Yigit, G. Rupprechter, K. Bica-Schröder, H. Hoffmann, K. Kirchner, *Eur. J. Inorg. Chem.* **2019**, *2019*, 3503‐3510. f) A. Mukherjee, D. Milstein, *ACS Catal*. **2018**, *8*, 11435–11469. g) W. Yang, I. Yu. Chernyshov, R. K. A. van Schendel, M. Weber, C. Müller, G. A. Filonenko, E. A. Pidko, *Nat. Commun.* **2021**, *12*, 12. h) M. Glatz, B. Stöger, D. Himmelbauer, L. F. Veiros, K. Kirchner, *ACS Catal*. **2018**, *8*, 4009–4016. i) S. Elangovan, C. Topf, S. Fischer, H. Jiao, A. Spannenberg, W. Baumann, R. Ludwig, K. Junge, M. Beller, *J. Am. Chem. Soc.* **2016**, *138*, 8809–8814.

[13] a) G. Zassinovich, G. Mestroni, S. Gladiali, *Chem. Rev*. **1992**, *92*, 1051–1069. b) Y.-H. Li, X.-H. Ding, Y. Zhang, W.-R. He, W. Huang, *Inorg. Chem. Commun.* **2012**, *15*, 194–197.

[14] T. A. Natsir, T. Hara, N. Ichikuni, S. Shimazu, *Bull. Chem. Soc. Jpn.* **2018**, *91*, 1561–1569.

[15] Q. Hou, X. Qi, M. Zhen, H. Qian, Y. Nie, C. Bai, S. Zhang, X. Bai, M. Ju, *Green Chem*. **2021**, *23*, 119–231.

[16] T. M. Townsend, C. Kirby, A. Ruff, A. R. O'Connor, *J. Organomet. Chem.* **2017**, *843*, 7–13.

[17] A. H. Aboo, E. L. Bennett, M. Deeprose, C. M. Robertson, J. A. Iggo, J. Xiao, *Chem. Commun*. **2018**, *54*, 11805–11808.

[18] R. A. Farrar-Tobar, Z. Wei, H. Jiao, S. Hinze, J. G. de Vries, *Chem. Eur. J*. **2018**, *24*, 2725–2734.

[19] R. Ghosh, N. Ch. Jana, S. Panda, B. Bagh, *ACS Sustain. Chem. Eng.* **2021**, *9*, 4903–4914.

[20] a) P. Panagiotopoulou, D. G. Vlachos, *Appl. Catal. A: Gen.* **2014**, *480*, 17–24. b) M. J. Gilkey, P. Panagiotopoulou, A. V. Mironenko, G. R. Jenness, D. G. Vlachos, B. Xu, *ACS Catal.* **2015**, *5*, 3988–3994.

[21] Y. Nishina, *Inorganics* **2019**, 7, 114.

[22] a) R. Figliolia, P. Cavigli, C. Comuzzi, A. Del Zotto, D. Lovison, P. Strazzolini, S. Susmel, D. Zuccaccia, M. Ballico, W. Baratta, *Dalton Trans*. **2020**, *49*, 453–465. b) S. Baldino, S. Facchetti, A. Zanotti-Gerosa, H. G. Nedden, W. Baratta, *ChemCatChem* **2016**, *8*, 2279–2288.

[23] M. Segizbayev, Ö. Öztopçu, D. Hayrapetyan, D. Shakhman, K. A. Lyssenko, A. Y. Khalimon, *Dalton Trans*. **2020**, *49*, 11950–11957.

[24] a) C. Gunanathan, D. Milstein, *Acc. Chem. Res.* **2011**, *44*, 588-602. b) W. H. Bernskoetter, N. Hazari, *Acc. Chem. Res.* **2017**, *50*, 1049-1058. c) K. Sordakis, C. Tang, L. K. Vogt, H. Junge, P. J. Dyson, M. Beller, G. Laurenczy, *Chem. Rev.* **2018**, *118*, 372-433. d) L. Piccirilli, D. L. J. Pinheiro, M. Nielsen, *Catalysts* **2020**, *10*, 773. e) N. Trincado, J. Bösken, H. Grützmacher, *Coord. Chem. Rev.* **2021**, *443*, 213967.

[25] a) D. L. J. Pinheiro, M. Nielsen, *Catalysts* **2021**, *11*, 558. b) A. Messori, A. Fasolini, R. Mazzoni, *ChemSusChem* **2022**, e202200228, DOI: 10.1002/cssc.202200228.

[26] See for example: a) M. Nielsen, A. Kammer, D. Cozzula, H. Junge, S. Gladiali, M. Beller, *Angew. Chem. Int. Ed.* **2011**, *50*, 9593-9597. b) Y. Li, P. Sponholz, M. Nielsen, H. Junge, M. Beller, *ChemSusChem* **2015**, *8*, 804-808. c) R. Padilla, M. S. B. Jørgensen, M. W. Paixao, M. Nielsen, *Green Chem.* **2019**, *21*, 5195-5200. d) D. L. J. Pinheiro, M. Nielsen, *J. Org. Chem.* **2022**, *87*, 5419-5423.

[27] M. Faisal, Q. ul Aein, A. Saeed, A. Mumtaz, F. A. Larik, *Heliyon* **2020**, *6*, e05731.

[28] Z. E. Clarke, P. T. Maragh, T. P. Dasgupta, D. G. Gusev, A. J. Lough, K. Abdur-Rashid, *Organometallics* **2006**, *25*, 4113–4117.

[29] K. Tekin, N. Hao, S. Karagoz, A. J. Ragauskas, *ChemSusChem* **2018**, *11*, 3559–3575.

[30] A. Song, S. Liu, M. Wang, Y. Lu, R. Wang, L.-B. Xing, *J. Catal.* **2022**, *407*, 90–96.

[31] Z. Chen, G. Chen, A. H. Aboo, J. Iggo, J. Xiao, *Asian J. Org. Chem*. **2020**, *9*, 1174–1178.

[32] a) S. Kopf, F. Bourriquen, W. Li, H. Neumann, K. Junge, M. Beller, Chem. Rev. **2022**, *122*, 6634–6718. b) L. Zhang, D. H. Nguyen, G. Raffa, S. Desset, S. Paul, F. Dumeignil, R. M. Gauvin, *Catal. Commun.* **2016**, *84*, 67–70.

[33] D. Klomp, T. Maschmeyer, U. Hanefeld, J. A. Peters, *Chem. Eur. J*. **2004**, *10*, 2088–2093.

[34] a) A. Kaithal, M. Schmitz, M. Hölscher, W. Leitner, *ChemCatChem* **2020**, *12*, 781–787. b) D. H. Nguyen, G. Raffa, Y. Morin, S. Desset, F. Capet, V. Nardello-Rataj, F. Dumeignil, R. M. Gauvin, *Green Chem.* **2017**, *19*, 5665–5673.

[35] For the synthesis of Ru-OEt species: A. Kaithal, M. Schmitz, M. Hölscher, W. Leitner, *ChemCatChem* **2019**, *11*, 5287–5291.

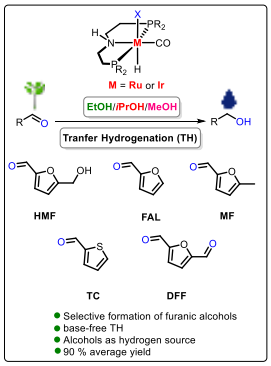
[36] L. Zhang, G. Raffa, D. H. Nguyen, Y. Swesi, L. Corbel-Demailly, F. Capet, X. Trivelli, S. Desset, S. Paul, J.-F. Paul, P. Fongarland, F. Dumeignil, R. M. Gauvin, *J. Catal.* **2016**, *340*, 331–343.

10.1002/cctc.202200819

WILEY-VCH

RESEARCH ARTICLE

Entry for the Table of Contents



Synthetic upgrading of furfurals is highly relevant in biorefinery and homogeneous catalysis. The Ru-PNP and Ir-PNP complexes efficiently catalyze the base-free transfer hydrogenation of furanic aldehydes under mild reaction conditions using alcohols as both hydrogen source and solvent. This benign reduction process operates in absence of additives, with low catalyst loadings, and on practical substrate scales.

Institute and/or researcher Twitter usernames: DTU-Kemi/ @MariaMppaz and @MartinN42661278