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The Shvo's catalyzed selective hydrogenation of HMF to BHMF showed substrate and product effects on the reaction rate ascribable to the presence of the -CH$_2$OH moiety. DFT calculation suggested the formation of several intermediates influencing the catalytic cycle. The catalyst can be recycled without loss of activity.
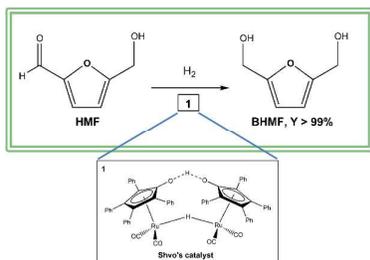
Substrate and product role in the Shvo's catalyzed selective hydrogenation of the platform bio-based chemical 5-hydroxymethylfurfural

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Abstract

The bio-based substrate and target product 2,5-bishydroxymethylfuran (BHMF) demonstrated to influence the reaction kinetics in the homogeneous reduction of 5-hydroxymethylfurfural (HMF) catalyzed by the Ru-based Shvo's catalyst. A combined experimental and computational study supports an important role of the $-CH_2OH$ moiety which may be involved in the catalytic cycle toward the formation of different intermediates from HMF and BHMF. The reaction is selective and leads to quantitative formation of BHMF working under mild conditions. Furthermore, an optimized recycling procedure which avoid the use of water, allows recover and reuse of the catalyst without loss of activity. The mechanistic insights from this work may be extended to provide a general description of the chemistry of the Shvo's catalyst feeding further bio-based molecules.

Introduction

Biorefinery concept is an important approach to address the increasing demand of energy and chemical building blocks for a diverse range of applications, that gradually may replace current dependence on fossil fuel resources.[1] Among other primary renewable building blocks, 5-hydroxymethylfurfural (HMF) is considered an important intermediate due to its rich chemistry and potential availability from carbohydrates, such as fructose, glucose, sucrose, cellulose and inulin.[2] The structural moieties present in HMF, allow synthetic transformations to other target molecules

by means of selective reactions such as oxidation of the formyl group,[3] reduction of the formyl group and/or the furan ring,[4] deoxygenation of the hydroxyl groups to 2,5-dimethylfuran,[5] etherification and carbonylation,[6] and hydrogenolysis transformations.[7] In particular, selective reduction of 5-hydroxymethylfurfural (HMF) provides access to the diol 2,5-bishydroxymethylfuran (BHMF), an important building block for the production of polymers and polyurethane foams.[8,3c] These molecules may be also[7a] converted into a range of polyol derivatives, with application as monomers in polymer industry. HMF reduction may be conducted under stoichiometric conditions in the presence of $NaBH_4$[9] or by using aqueous solutions of HCHO and $NaOH$[10] whereas typical catalysts reported for this reaction are copper chromite,[11] Ni Raney,[12] Pt-, Pd- or Ru-supported catalysts.[5a, 13] Main drawbacks in these reactions are the toxicity of some of the catalysts employed and the high temperature (140-200 °C) and pressure (70-75 bar) required.[1e]

Even though metal-ligand bifunctional catalysts for the hydrogenation of polar double bonds provide a "green" alternative to stoichiometric reducing agents,[14] homogeneous catalysis, that in principle might improve selectivity and require mild reaction conditions, has been scarcely investigated in this field (hydrogenation of HMF has been accomplished by hydrogen-transfer catalysts using HCOOH as H-donor).[15] On the light of these considerations we decided to employ a ruthenium based homogeneous hydrogenation catalyst, known as the Shvo's catalyst $[Ph_4(\eta^5\text{-}C_4CO)_2H(CO)_4Ru_2](\mu\text{-}H)$ (**1**) (Figure 1),[16] which recently demonstrated to be effective in the upgrading of bio-oil from white poplar by means of hydrogenation of polar double bonds,[17] in the selective reduction of HMF to BHMF.
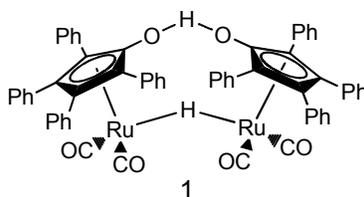
Figure 1 Chemical structure of the Shvo's catalyst **1**.

The dinuclear complex **1** has been successfully applied in a broad scope of hydrogen-transfer processes such as hydrogenation of carbonyls and imines, oxidation of alcohols and amines, and dynamic kinetic resolution of secondary alcohols and primary amines in combination with lipases.[18] The reduction reaction takes place by transferring a hydride (bonded to the metal centre) and a proton (bonded to a ligand) from the active catalytic species to a double bond. The reaction mechanism for the hydrogen-transfer process has been a matter of controversy, nevertheless several experiments[19] and theoretical studies,[20] support an outer sphere concerted carbonyl hydrogenation. Isolation of ruthenium-alcohol complexes, as intermediates, is far to be trivial and, to the best of our

knowledge, an equivalent species has been observed by Casey et al. at -60°C in an ^{1}H-NMR experiment.[19f]

Herein we report about a work aimed to the investigation of the Shvo's catalyst **1** in the hydrogenation of the bio-based HMF to BHMF both in homogeneous (toluene) and biphasic (water/toluene) reaction mixtures under mild conditions. The reaction is selective and a successful recycling method, tuned up avoiding the use of water, is also presented and discussed. Furthermore reactivity studies on the target reaction showed a surprising substrate and product effect on the reaction rate. A combined experimental and computational study supports an important role of the – CH_2OH moiety which may be involved in the catalytic cycle toward the formation of different intermediates involving Ru species and HMF/BHMF.

Results and Discussion

Effect of the reaction conditions on catalyst performances

The hydrogenation of 5-hydroxymethylfurfural (HMF) to 2,5-dihydroxymethylfurfural (BHMF) (Scheme 1) was carried out employing homogeneous Shvo's catalyst (**1**). Screening experiments were initially developed in order to evaluate the activity and selectivity of this catalyst toward the target reaction, and to study the effect of hydrogen pressure, temperature and reaction time on catalytic performances; all reactions have been performed in toluene solution and conversions obtained by HPLC analyses. The reaction is totally selective toward the formation of BHMF, thus BHMF yields actually correspond to HMF conversions.
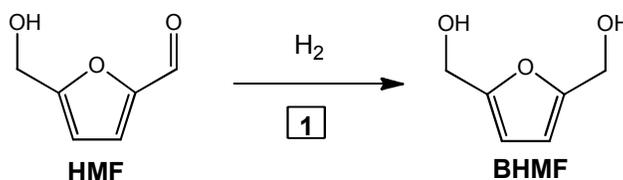
Scheme 1 Hydrogenation of HMF to BHMF catalyzed by Shvo's catalyst **1**.

Table 1 shows the behavior of catalyst **1** at different reaction temperatures and H_2 pressures. Under the conditions reported it is totally inactive at 30 °C (entry 1) while, increasing the reaction temperature up to 60 °C, it leads to a slight formation of BHMF (25% yield, entry 2). A significant improvement of the catalytic activity is observed performing the reaction at 90 °C. After 1h at this temperature a BHMF yield of 99% is obtained without formation of any by-products, being the reaction completely selective toward hydrogenation of the aldehyde (entry 3). BHMF yield improves significantly when increasing the H_2 pressure (see Table 1) from 3 (yield = 68%, entry 4) up to 10 bar (yield 99%, entry 3); at higher pressures, in fact, H_2 dissolution in the liquid phase increases, favouring regeneration of the active complex.

Table 1 Effect of temperature and H_2 pressure on BHMF yield. Reaction conditions: HMF/**1** = 1000, t = 1h, [HMF] = 0.05 M, catalyst **1** = 1.71 mg, 1.58 µmol, toluene: 30 mL.

Entry	H_2 Pressure (bar)	Temperature (°C)	BHMF yield (mol%)
1	10	30	0
2	10	60	25
3	10	90	99
4	3	90	68
5	7	90	75

Conditions employed in Table 1 entry 3, leading to complete conversion within 1h, have been chosen in order to follow the BHMF yield in function of time. The reaction displays some interesting and unusual kinetic features. Figure 2 shows a comparison of the hydrogenation rates of HMF (solid line) and benzaldehyde (dashed line), both reactions being performed with the Shvo's catalyst **1** under the same conditions. Hydrogenation of the benzaldehyde shows a conversion rate profile corresponding to that reported by Casey and co-workers in the reduction of benzaldehyde catalysed by Shvo complex at 60 °C and 35 bar of H_2,[19e] whereas HMF hydrogenation exhibits a very steep increase of conversion rate within the first 20 min of reaction (corresponding to about 70%), followed by a pronounced downward curvature (corresponding to the 70 - 90% conversion range). An unexpected rate increase is then observed within the last 10 minutes of reaction (between 90% and complete conversion). These observations seem to indicate an inhibition effect due to the reagent HMF and the product BHMF. A more detailed investigation on this peculiar reaction rate profile is described below (see *in situ* NMR experiments).
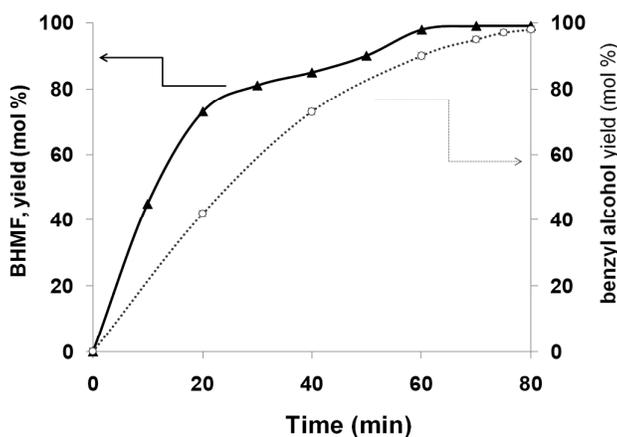
Figure 2 HMF hydrogenation to BHMF (▲) or benzaldehyde hydrogenation to benzyl alcohol (○) at different reaction times. Reaction conditions: $P(H_2)$ = 10 bar, T = 90 °C, substrate/**1** = 1000, [substrate] = 0.05 M (HMF or benzaldehyde), catalyst **1**: 1.71 mg, 1.58 µmol, toluene: 30 mL.

Hydrogenation of HMF in the presence of co-reactants

HMF hydrogenation has been performed in the presence of co-reactants such as the furan ring containing BHMF, furfuryl alcohol or 2,5-bismethoxymethylfuran respectively containing two, one or zero $-CH_2OH$ moiety in order to establish if the reduction rate is affected by the presence of the two hydroxyl groups of BHMF. The reactions have been performed under the conditions employed, while starting from the pure HMF, to reach a BHMF yield (corresponding to HMF conversion) around 70% (entry 1, Table 2) and resulted in all cases to be selective toward the transformation of HMF to BHMF. Reaction mixtures analysis showed unreacted furfuryl alcohol or 2,5-bismethoxymethylfuran confirming that they are inert under the conditions employed. Turn over frequencies calculated in the presence of furfuryl alcohol and 2,5-bismethoxymethylfuran (entry 3 and 4) are comparable with the one obtained starting from the pure HMF (entry 1). On the other hand, if BHMF is added from the beginning of the reaction a significant reduction of the reaction rate is registered (entry 2).

Table 2 Catalytic hydrogenation of HMF in the presence of co-reactants. Reaction conditions: $P(H_2) = 10$ bar, T = 90 °C, HMF/**1** = 1000, [HMF] = 0.05M, catalyst **1**: 1.71 mg, 1.58 µmol, t = 20 min, HMF/co-reactant = 1,5.

Entry	Co-reactant	HMF conversion (mol %)	TOF (min^{-1})
1	none	73	37
2	BHMF[a]	50	25
3	Furfuryl alcohol	71	36
4	2,5-bismethoxymethylfuran	72	36

[a] The same reaction performed in the presence of 1,3-benzenedimethanol as co-reactant did not affect the catalytic activity because it is completely insoluble under the conditions employed (toluene, 90 °C).

Neither furfuryl alcohol nor 2,5-bismethoxymethylfuran affect the reaction rate, supporting the hypothesis of an active role played by the two hydroxyl groups of BHMF. The non-furan derived 1,3-benzenedimethanol (containing two $-CH_2OH$ moiety as the BHMF) have been also tested, but the complete insolubility under the reaction conditions avoid the co-reactant to participate to the catalytic cycle, leaving unaltered the turn over frequency. Anyway all the co-reactants tested contained the furan ring, so the difference between non-inhibiting co-reactants and BHMF regards the presence of two $-CH_2OH$ moieties.

Effect of biphasic water/toluene conditions on catalyst performances

Easy separation and reuse of expensive catalysts or products by means of aqueous/organic biphasic reactions that employ single phase soluble catalysts or products is an attractive goal. Thus, we extended our studies to hydrogenation of HMF in water/toluene mixture with the aim of partitioning the formed BHMF in water, and keeping the Shvo's catalyst **1** in the organic phase. Furthermore this *in situ* separation, should, in principle, avoid the above underlined competitive influence of the product on the reaction rate.

Biphasic water/toluene reactions were carried out using tailed off quantity of water. Catalyst **1** resulted to be selective even in the presence of water. BHMF yields under different conditions are collected in Table 3. High water/toluene ratio resulted in lower conversion to BHMF (water/toluene = 10, yield = 11% after 30 min, entry 1) compared to reactions performed in toluene (yield = 80%, entry 5). Reduction of the water content improves the catalytic activity: a toluene/water ratio of 29/1 (yield = 68% after 30 min, entry 3) allows in fact to reach quantitative yield within 120 min (entry 4).

Table 3 HMF hydrogenation to BHMF in biphasic systems, with different toluene/water ratio. Reaction conditions: catalyst **1**: 1.71 mg, 1.58 µmol, HMF/**1** = 1000, P(H$_2$) = 10 bar, T = 90 °C.

Entry	Toluene/H$_2$O (v/v)	Time (min)	BHMF yield (mol%)
1	1/10	30	11
2	9/1	30	34
3	29/1	30	68
4	29/1	120	99
5	Toluene	30	80

In order to understand the BHMF influence on the catalytic behaviour, a comparison between the activity as a function of time for the Shvo's catalyst **1** in toluene (solid line) and in the optimized biphasic system (toluene/water ratio 29/1, dashed line) is reported in Figure 3. In the case of biphasic reaction the lower conversion rate is ascribable to the high affinity of HMF and BHMF for water solution which makes the substrate less available to enter the catalytic cycle. Since, as the best of our knowledge partition ratios (organic solvents/water) for BHMF are not available in the literature, a biphasic NMR experiment in D$_2$O and toluene-d$_8$ has been performed in order to evaluate the distribution of substrate and product in the two solvents. The spectra (available in the supporting information) show that the large majority of HMF and BHMF reside in the D$_2$O phase. Actually in the present case a very low concentration of HMF and BHMF are available during all the reaction reducing the reactant and product inhibition. Indeed, the *in situ* BHMF removal

operated by water in biphasic mixture lead to a rate profile (Figure 3-dashed line) similar to the one obtained performing benzaldehyde reduction (Figure 2-dashed line).
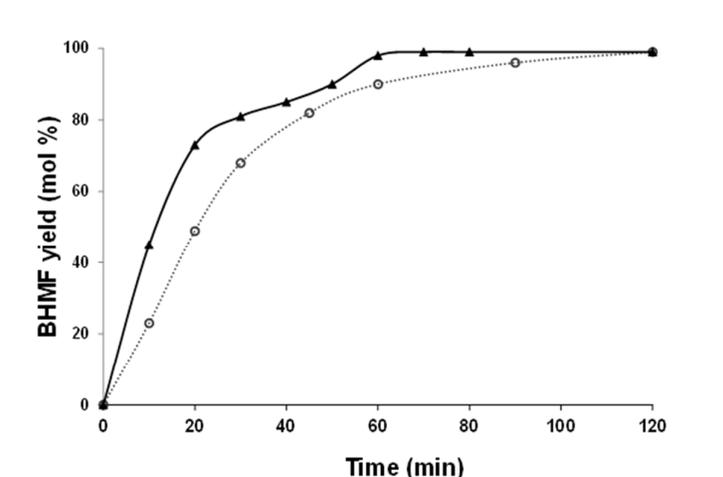
Figure 3 BHMF yield as a function of the reaction time in: toluene (▲) or biphasic mixture (toluene/H_2O = 29) (○). Reaction conditions: catalyst **1**: 1.71 mg, 1.58 µmol, HMF/**1** = 1000, P(H_2) = 10 bar, T = 90 °C.

Catalyst stability and recyclability

In order to test recyclability of catalyst **1** we have investigated its recovery and reuse employing two different recycling methods.

Product extraction by water. At first, since the catalyst is insoluble in water, HMF and BHMF were recovered at the end of every cycle (performed under conditions reported in Table 1 entry 3) by water extraction. The toluene solution, containing the used Shvo's catalyst **1**, was recycled. The white bars in Figure 4 correspond to the selective conversion of HMF to BHMF in the five reaction cycles and show that yields progressively decreases from 99% (first cycle) to about 30% (fifth cycle). XRF analysis of the extracted water-phase indicated the absence of water-soluble Ru species; on the other hand the analysis of an insoluble residue found at the end of the recycling experiments showed the presence of Ru traces, indicating that a partial catalyst decomposition occurs using this approach. The isolated residue was completely insoluble in the most common organic solvents and from its IR spectrum (KBr) no absorbance ascribable to the Shvo **1** complex were detectable confirming that it arises from catalyst decomposition.

Product removal by filtration. Most effective recycle method was obtained avoiding the use of water. Surprisingly by cooling the autoclave as soon as the complete conversion was reached (1h), BHMF quantitatively precipitated from the toluene reaction mixture. Recover of the catalyst-containing solution could be then performed by simple filtration at the end of every cycle. No loss of activity was observed utilizing this procedure during five runs (black bars in Figure 4), emphasizing that the Shvo's catalyst **1** can be easily recovered and reused. Indeed avoiding the

water extraction no catalyst decomposition was observed, as confirmed both by absence of insoluble Ru-species in the recycled toluene-catalyst **1** solution and by its IR analysis, that showed the typical absorbance of Shvo **1** species in the carbonyl region ($\upsilon(CO) = 2039, 2008, 1979$ cm^{-1}).
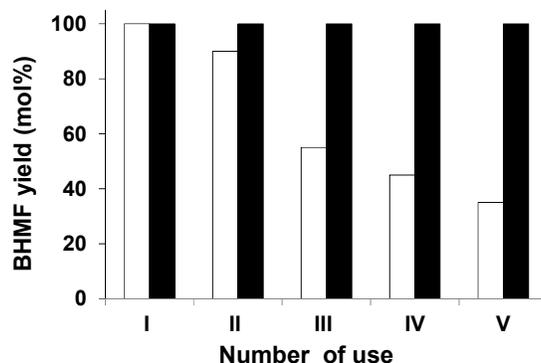
Figure 4 BHMF yields obtained reusing the catalyst **1** employing different recycling procedures: □ water extraction; ■ BHMF precipitation by quick cooling. Reaction conditions: catalyst **1**: 1.71 mg, 1.58 µmol, HMF/**1** = 1000, $P(H_2)$ = 10 bar; T = 90 °C, t = 1h, toluene = 30 mL.

The latter recycling method is reproducible and represents a convenient way of synthesis of BHMF in lab scale. The practical use of this preparation has been also verified on a larger scale. Experiments performed on 4,90 mmol of HMF lead to quantitative conversion to BHMF. The potential of the catalyst recycling has been confirmed up to nine cycles.

In situ NMR experiments

Minute-by-minute monitoring of the Shvo's catalyzed hydrogenation of HMF.

The hydrogenation of HMF (1.98 mg, 0.0157 mmol) with catalyst **1** (0.0676 mg, 0.0628 µmol, HMF/**1** = 250) under 3 bar of hydrogen at 90 °C in 0.7 mL of toluene-d$_8$ was monitored by *in situ* NMR spectroscopy by warming at 90 °C the sample in the pre-heated NMR probe. The conversion of HMF, which corresponds to the yield of BHMF, was evaluated by integration of the ^{1}H-NMR signals of HMF and BHMF and spectra acquired every 60 seconds. During the whole reaction carried out with HMF/**1** ratio of 250, no signals ascribable to intermediates and to the free Shvo catalyst were observed, due to the tiny concentration. The complete conversion was reached within 530 min. The kinetic curve depicted in Figure 5 (see supporting information for further details) confirmed that the conversion of HMF (i.e. the yield of BHMF) follows a complex rate law, as for the behavior observed performing the reaction in autoclave (Figure 3). The experiment was proved to be reproducible. A plot of ln([HMF]/[HMF]$_0$) vs time for the first 50 minutes of reaction (up to 23% conversion) showed to fit a trend (Figure 6) demonstrating a pseudo-first order rate for HMF

conversion in the first part of the reaction. On increasing the amount of BHMF a decrease in the reaction rate was confirmed, as well as the step increase after 90% yield (in figure 5- around 430 min- as in Figure 3- around 50 min) which allows to reach quantitative yield in 530 min (60 min in the autoclave conditions).
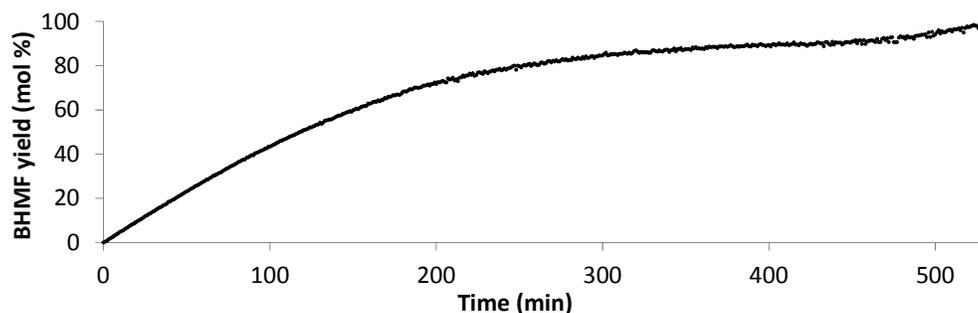
Figure 5 *In situ* NMR experiment (BHMF yield vs time). Reaction conditions: catalyst **1** (0.0676 mg, 0.0628 µmol), HMF (250 eq., 1.98 mg, 0.0157 mmol), toluene-d_8 (0.7 mL), 90 °C, p(H_2) (3 bar). Spectra acquired every 60 seconds.
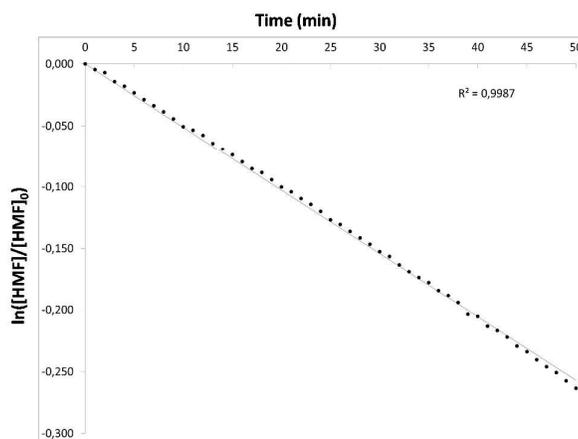
Figure 6 Plot of $\ln([HMF]/[HMF]_0)$ vs time for hydrogenation of HMF ($[HMF]_0 = 0.022$ M) with catalyst **1** (0.088 mM)

The same procedure has been extended to 60 minutes long minute-by-minute NMR monitored experiments performed by varying HMF/**1** ratio, keeping constant catalyst **1** (0.0676 mg, 0.0628 µmol) and all the other conditions (selected data are available in the supporting information). Turn over frequencies calculated at 10 minutes (low conversion 1.5-12.8%) plotted versus HMF/**1** ratio (Figure 7), demonstrate an effect of the substrate on the catalyst behaviour which could be both ascribed to the formation of a complex between HMF and the active catalyst **A** in Scheme 2 by

means of the aldehyde moiety or to the formation of a complex between HMF and the 16 electron specie **B** in Scheme 2, also involved in the catalytic cycle, by means of the CH_2OH function.
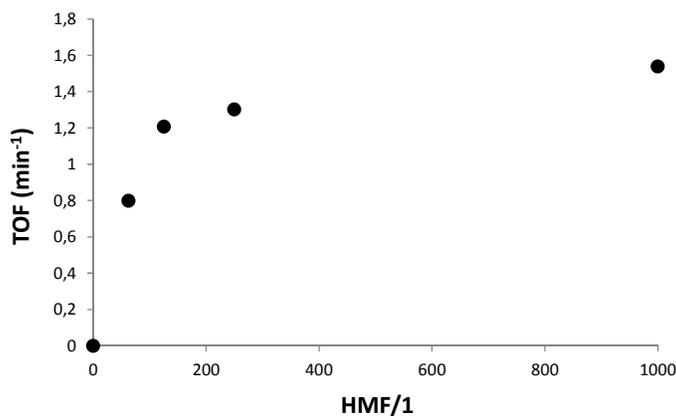
Figure 7 *In situ* NMR experiment (TOF vs HMF/**1**). Reaction conditions: catalyst **1** (0.0676 mg, 0.0628 μmol), toluene-d_8 (0.7 mL), 90°C, $p(H_2)$ (3 bar), reaction time (10 min).

In order to gain a better understanding of the reaction, the kinetic profile has been also NMR-monitored up to the end of the reaction in the case of HMF/**1** = 125 (corresponding to $[HMF]_0$ = 0.011 M). When performing the reaction with half-concentration, less pronounced inhibition effect of the reagent was confirmed (see supporting information), in agreement with the fact that a substrate to catalyst ratio of 125, fall within the linear part of the TOF vs HMF/**1** ratio graphic (Figure 7).

From the above described results, a role for HMF and BHMF in the kinetic behavior of the reaction has to be taken into account. Obviously, BHMF inhibition (product inhibition) is expected to slow the reaction rate at high conversions and, on the contrary, HMF inhibition should inhibit the rate at low conversions. The overall result is more complex to predict and depends on the dominating effect: if HMF inhibition prevails, then initial inhibition should be gradually alleviated, and at high conversions BHMF inhibition would take over, giving rise to a sigmoidal conversion curve; if BHMF inhibition is stronger than HMF inhibition, then the conversion should not go to completion and rates would strongly decrease with time. The kinetic profile observed both in the autoclave (see Figure 3) and in the *in situ* NMR experiments (see Figure 5) is more complex (i.e. the pronounced rate decrease between 70% and 90%, followed by an acceleration between 90% and 100% conversion) and not fully consistent with a gradual replacement of the HMF inhibition effect with the BHMF inhibition. This suggests more complex inhibiting effect, or an even more intriguing combination of inhibiting and substrate acceleration effects that we are unable to explain at the present stage.

In addition, a number of *in situ* NMR experiments with HMF or BHMF and the catalyst **1** in toluene-d$_8$ under nitrogen or hydrogen atmosphere have been also investigated, and details are reported in the supplementary material. Experiments have been performed with a substrate/**1** ratio = 4, that is much lower compared to the experiments described in previous paragraphs. The aim was to detect possible intermediates or evidence potential interactions between catalytic species that might affect hydrogenation (or dehydrogenation) and explain the observed inhibition effect. Experiments included hydrogenation (H$_2$ 3 bar, at 90°C) of HMF in the presence of **1** and reactions of HMF and BHMF, respectively, with catalyst **1** under N$_2$ atmosphere. Both hydrogenation and dehydrogenation were observed by monitoring HMF and BHMF selective interconversion. Moreover, reaction between BHMF and catalyst **1** under H$_2$ atmosphere confirmed that H$_2$ atmosphere suppresses dehydrogenation.[19]

Results were consistent with what reported for the reactivity of Shvo complex **1** with other substrates,[19] confirming that **1**, upon activation at 90°C, works as a reducing agent in the form of the 18 electron species, or as an oxidative agent in the form of the 16 electron species (**A** and **B**, respectively in Scheme 2). Neither intermediates, nor species that should be associated to interactions between ruthenium complexes and products/reagents, were detected. Finally, any attempt to isolate possible stable intermediates from the almost stoichiometric solutions used in these NMR experiments, gave crystals of Shvo complex **1**. Since the structure of **1** was not yet available we report its crystal data in the Cambridge database (see supporting information).

Proposed reaction intermediates and DFT calculations

Although no intermediates were experimentally detectable, in view of the peculiar behaviour of the reaction rate profile, we speculated that the presence of the second hydroxyl group in the product BHMF and the presence of the OH in HMF itself might be the principal responsible for the reaction rate inhibition experimentally observed. This consideration implies that this moiety has to take a part during the catalytic cycle, and also the presence of the oxygen on furan should be considered. These functional groups were not present in the corresponding hydrogenation reaction of benzaldehyde to benzyl alcohol (the latter follows the catalytic cycle proposed by Casey *et al.*).[19e]

DFT calculations[21] were performed to check if a transition state corresponding to that reported by Casey could be influenced by the presence of the second hydroxyl group. At the same time, the geometries and energies of some feasible intermediates were calculated, in order to check if they really corresponded to energy minima and if they could influence the reaction rate. Proposed intermediates involving BHMF and Ru species are shown in Scheme 2. Calculations have been performed on the complete catalyst using B3LYP[22] and the LANL2DZ basis set[23] on all atoms. The

solvent (toluene) was included in the calculations using the PCM method.[24] Given the known X-ray data and calculations[25, 20] available for these compounds, the helical disposition of the four phenyl groups was employed in all the starting geometries.
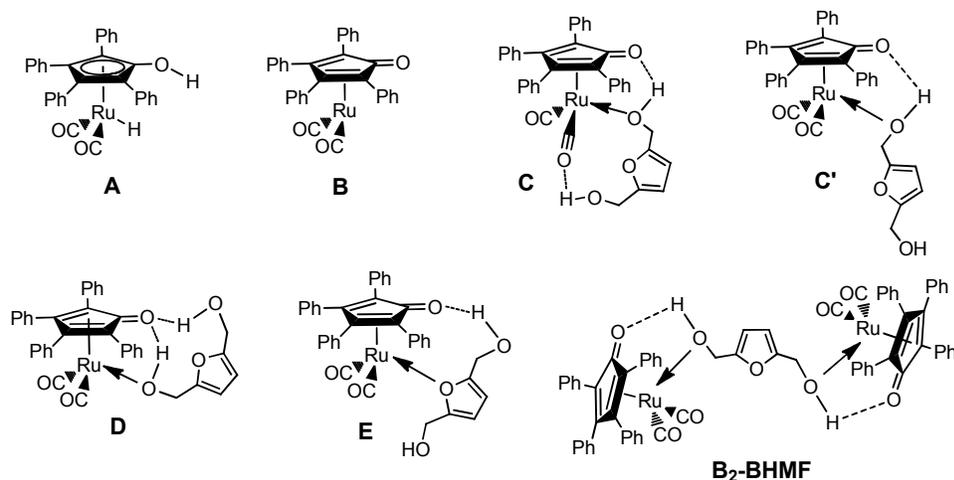
Scheme 2. Possible intermediates in Shvo's catalyzed hydrogenation of HMF

As widely proposed,[20] calculated transition state for the reduction of HMF corresponds to the simultaneous transfer of two hydrogens from the active catalyst **A** to HMF in an outer-sphere mechanism (see Figure 8, center).[26] Because of the presence of the free OH of HMF, at a variance with the literature data, the actual transition state exhibits an additional interaction of the CH_2OH of HMF with one carbonyl of the ruthenium by an hydrogen bond with the oxygen of CO. The calculated free energy barrier for the hydrogenation (9.2 kcal/mol) is in agreement with other reported values.[20]

From this transition state, an IRC calculation [in the IRC the solvent was not included to reduce the computational cost] was performed to find the intermediates on the forward and backward pathway (see Supporting information for the graphics). In the case of the backward directions, the optimization localized a situation where HMF is coordinated to the active catalyst by two hydrogen bonds (Figure 8, left), whereas the forward pathway optimization found an intermediate where the BHMF is still coordinated to the catalyst by two hydrogen bonds (Figure 8, right). Both structures are minima of energy, as confirmed by frequency calculations. The latter intermediate subsequently evolves to the 16-electron species **B** and BHMF. The presence of the CH_2OH moiety of HMF seems therefore to play a relevant role in the pre-TS coordination. To confirm the importance of the hydroxyl group of HMF, the analogue transition state was calculated for furfural and a completely different disposition of the furanic ring was found, whereas the O-H and Ru-H distances are

identical in both structures (See Supporting information). The latter TS is very similar to that proposed by Casey.[19b]
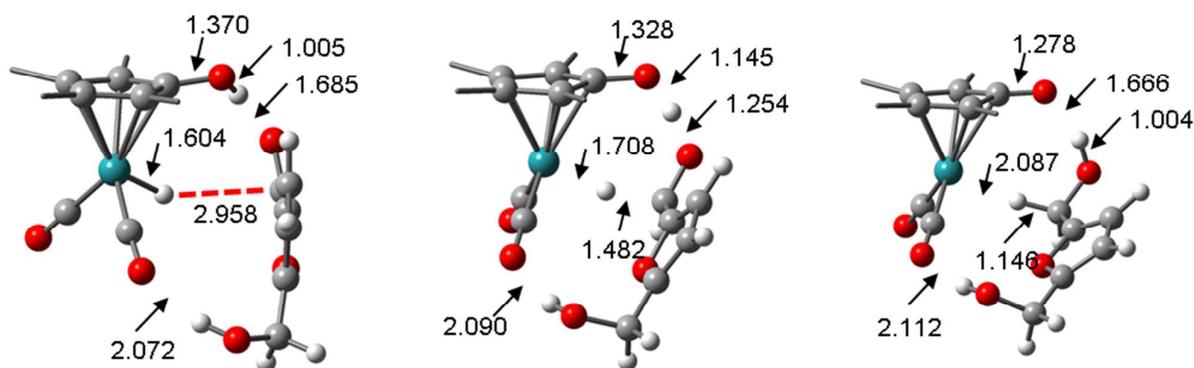
Figure 8 Center: transition state for the reduction of HMF and the two intermediates found by IRC calculations. On the left is reported the catalyst **A** coordinated with HMF. On the right is reported the intermediate between **B** and BHMF. The phenyl groups of the catalyst were removed for clarity. Distances in Å.

When BHMF is formed and leaves the catalytic cycle, it is still able to compete with H_2 in the coordination to the dehydrogenated catalyst **B**. Several intermediates, sketched as **C**, **C'**, **D**, **E** and **B$_2$-BHMF** in Scheme 2, might be proposed. The optimized geometries of **C**, **C'**, **D**, and **E** did correspond to energy minima (no imaginary frequencies were observed in the frequency analysis), and the optimized Ru-C bond length were very similar to that observed in the solid state for similar compounds.[19i, 20d] Whilst the relative energy of **E** is much higher, the calculated energies for **C**, **C'** and **D** are similar, and the lowest energy structure depends on the calculation parameters. Intermediate **C** was calculated to be the most stable if the internal energy is considered (by 2.2 kcal/mol vs **C'** and 0.5 kcal/mol vs **D**). If the solvent is included (toluene, PCM method[24]) **C** was more stable than **C'** and **D** by 2.0 kcal/mol and 1.2 kcal/mol respectively. If Gibbs free energy is considered (with solvent), **C** and **C'** are isoenergetic and more stable than **D** by 2.9 kcal/mol (mainly because of the entropic factor).

Given the presence of two hydroxyl groups in BHMF, an alternative framework speculates the interaction of a second molecule of the 16-electron species **B** with the free hydroxyl moiety of complex **C'** to yield a bis-ruthenium complex (**B$_2$-BHMF**). The optimization of the 2:1 complex at the B3LYP/LANL2DZ level of theory confirmed that it did correspond to an energy minimum with global C_2 symmetry (Figure 9).
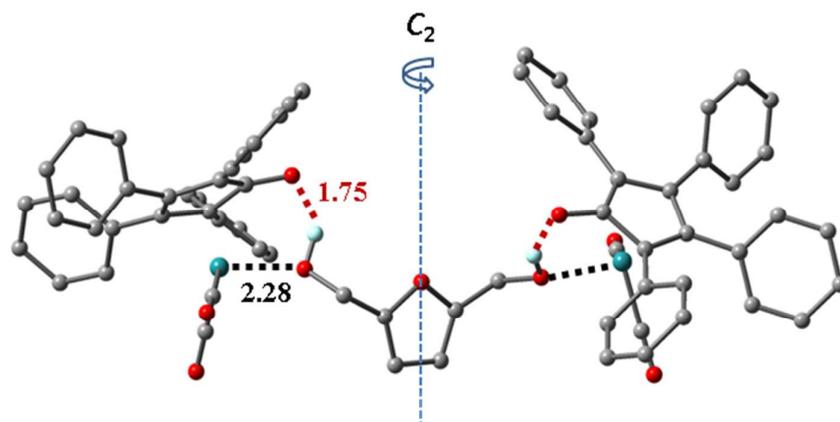
Figure 9 DFT optimized structure for the **B₂-BHMF** complex (PCM-B3LYP/LANL2DZ level). All the hydrogen atoms, except for the two hydroxyls (cyan), were removed for clarity. Distances in Å.

A reliable calculation of the stabilization energy of **B₂-BHMF** with respect to the **C'** complex is not straightforward because of the known effect of basis set superimposition error (BSSE).[27] When the stabilization energy between the **B₂-BHMF** and the 1:1 complex **C'** was calculated by the sum of the energies of the 1:1 complex **C'** and one molecule of free **B**,[20d] the dimeric structure was favored by 22.1 kcal/mol as internal energy without thermochemical corrections, by 5.0 kcal/mol if Gibbs free energies were considered (Solvent included with PCM method). When BSSE was taken into account by the counterpoise method (without solvent),[28] the stabilization was still 17.4 kcal/mol (3.4 kcal/mol with Gibbs free energies).

Thus, regardless the calculation method, the **B₂-BHMF** complex appears to be largely stabilized with respect to **C**, **C'** and **D** complexes. Although it is statistically disfavored due to the high dilution and to the entropic factor, the large stabilization energy could be sufficient to drive the formation of the dimer that subtract the active intermediate from the catalytic cycle, thus reducing the reaction rates when increasing the BHMF concentration.

As a last consideration, also HMF itself could be involved in the formation of a complex similar to **C'** where the free hydroxyl can coordinate with **B** (**F** in Scheme 3). The formation of this intermediate might deliver inhibition of the reaction in the early stages, where the concentration of HMF is very high. Scheme 3 summarizes the energy profile for hydrogenation of HMF.
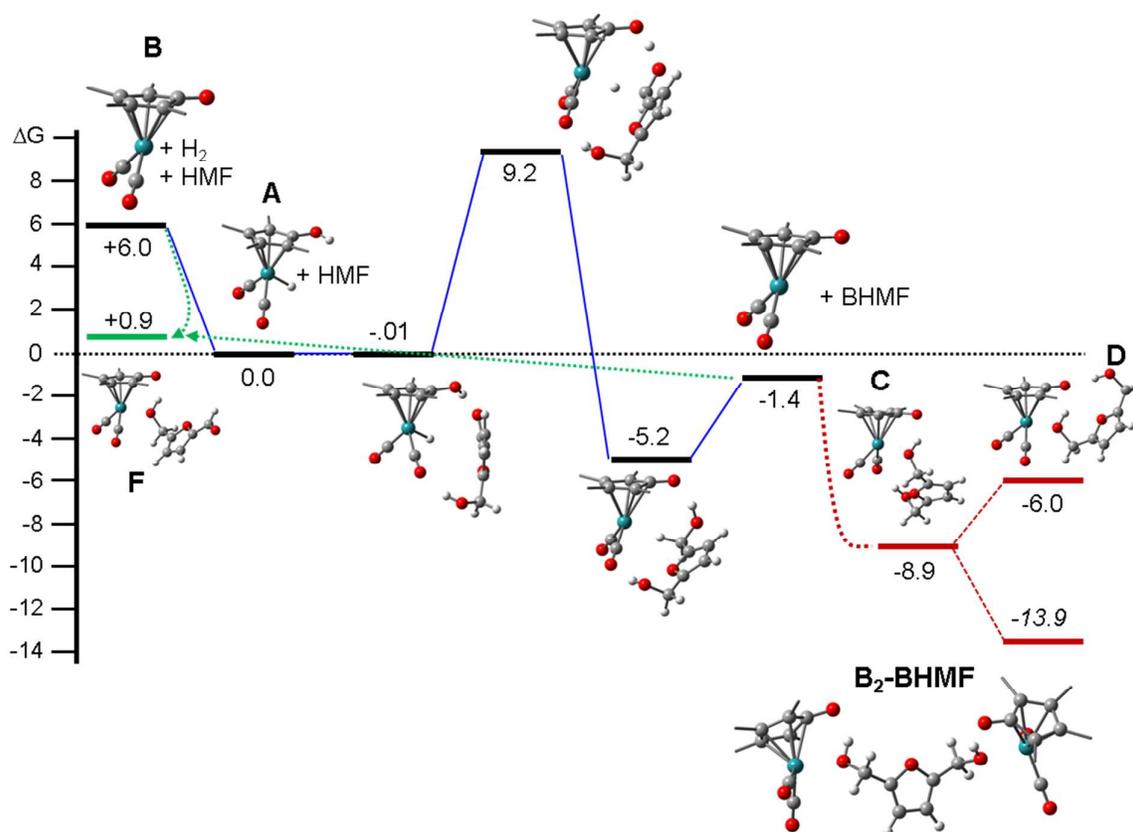
Scheme 3 Energy profile for hydrogenation of HMF. Energy values (B3LYP/LANL2DZ level) are free Gibbs energies in kcal/mol, and including the solvent with PCM method. The same profile with thermal corrected enthalpies is reported in the Supporting information. Dotted red and green lines indicate the formation of intermediates that could inhibit the main reaction cycle.

At a first sight, it could seem odd that the **A**-HMF complex is calculated to have the same energy of the separate species,[20a] because the two hydrogen bonds should substantially stabilize the complex. However, the entropic factor disfavor the complex. When the thermal corrected enthalpy is considered to produce the analogue scheme, this complex is stabilized by 12.6 kcal/mol (see Supporting Information).

Conclusion

The Shvo's catalyst **1** has been successfully employed in the selective homogeneous hydrogenation of HMF to BHMF. The reaction occurs under mild conditions and it is fully selective toward the formation of the desired product. The catalyst may be successfully recycled avoiding the use of water and removing the produced BHMF from the reaction mixture by precipitation and filtration. Reactivity studies and *in situ* NMR monitored experiments on the target hydrogenation reaction showed an unusual and intriguing kinetic profile, being of the pseudo-first order in the first part of

the reaction, and assuming a complex rate in the last part, which is likely to be associated to the sum of different inhibition effects.

In particular, lowering of the reaction rate at conversions higher than 70% suggests an inhibition effect due to the BHMF product. This has been evidenced by further experiments in which the BHMF resulted to reduce the turn over frequency of catalyzed HMF reduction. Interestingly, only BHMF exhibits this effect and not related species such as furfuryl alcohol, or 2,5-dimethoxymethylfuran, indicating that inhibition is likely to be related to the presence of two CH_2OH functions. In addition, also HMF was found to exert some inhibition effect (demonstrated by increasing HMF initial concentration in NMR monitored experiments). DFT calculations suggest the availability of several intermediates that might play a role in the observed inhibition. Also the key transition state of reduction seems to be affected by an additional interaction of the hydroxyl group of HMF that interacts with one carbonyl group of the catalyst.

The overall results show that Shvo's catalyst provides a valuable tool in the hydrogenation of biomass derived building blocks. At the same time, the work pointed out some unforeseen effects associated to the interaction of alcohols and polyols, commonly present in biomass products, with Ru active catalytic species, which need to be considered and studied in more detail for the development of effective hydrogenation up-grading technologies.

Experimental Section

Materials

Solvents: water has been freshly distilled; methanol (MeOH), toluene, $CDCl_3$, toluene-d_8 (Sigma Aldrich) and reagents: tetraphenylcyclopentadienone, furfuryl alcohol (Sigma Aldrich), triruthenium-dodecacarbonyl ($Ru_3(CO)_{12}$) (Strem), 5-hydroxymethylfurfural (HMF), 2,5-bishydroxymethylfuran (BHMF) (SAFC) have been employed as purchased. 2,5-bismethoxymethylfuran has been prepared as described in the literature.[29]

Analytical methods

HPLC analyses where performed on an Agilent Technologies 1260 Infinity instrument, equipped with a C-18 core shell column 50x4.6mm employing a solution of 80% of 0.01 M H_3PO_4 and 20% acetonitrile as mobile phase. Identification of compounds was achieved by calibration using reference commercial samples. The NMR spectra were recorded using Varian Inova 300 (^{1}H, 300.1; ^{13}C, 75.5 MHz), Varian Mercury 400 (^{1}H, 399.9; ^{13}C, 100.6 MHz), Varian Inova 600 (^{1}H, 599.7, ^{13}C, 150.8 MHz) spectrometers. Infrared spectra were recorded at 298 K on a Perkin-Elmer

Spectrum 2000 FT-IR spectrophotometer. XRF analysis were carried out using a Panalytical Axios Advanced equipped with a Rh-target X-ray tube (4kW power) at 298 K. Powder analysis were recorded in vacuum (10^{-5} bar) while liquid tests were carried out using Helium at atmospheric pressure.

Catalyst preparation

The catalyst $[Ph_4(\eta^5\text{-}C_4CO)_2H(CO)_4Ru_2](\mu\text{-}H)$ (**1**) has been prepared following a procedure reported in the literature[19g] by refluxing 3 equivalents of tetraphenylcyclopentadienone with 1 equivalent of $Ru_3(CO)_{12}$ in MeOH for 40h. The catalyst has been purified by precipitation and identified by comparison with literature data (IR, ^{1}H-NMR, ^{13}C-NMR).

Hydrogenation of HMF

HMF hydrogenation were carried out using an autoclave (Parr Instrument series 4560) reactor (300 mL) equipped with a mechanical stirrer (0–1200 rpm) and provision for measurement of temperature and pressure. In a typical experiment the reactor was charged with HMF (0.200 g, 1.58 mmol), catalyst **1** (1.71 mg, 1.58 μmol; HMF/**1** molar ratio = 1000) and 30 mL of toluene ([HMF] = 0.05 M, in case of homogeneous reactions) or toluene/water (in variable ratio in case of biphasic reactions). The autoclave was purged 2 times with N_2 (40 bar) and then pressurized at 10 bar (H_2). The temperature was increased to 90 °C and the reaction mixture was stirred at ca. 1000 rpm for the time requested. At the end of reaction, the reactor was cooled to room temperature and the final product BHMF (or the mixture HMF/BHMF) was separated from catalyst **1** by precipitation (or by water extraction). All samples were carefully weighed and analysed using HPLC. Particular care was devoted to determination of the C balance, which was found to always fall between 95 and 105% (calculated as the comparison between converted HMF and product yields).

General procedure for *in situ* NMR experiments

In a J. Young valve equipped NMR tube, catalyst **1** (*e.g.* 0,0676 mg, 0,0628 μmol) and the substrate HMF (*e.g.* 250 eq., 1,98 mg, 0,0157 mmol) were added and dissolved in 0.7 mL of toluene-d_8 under nitrogen atmosphere. The samples solutions have been frozen in liquid nitrogen, the nitrogen inside the tube removed under vacuum and restored with 3 bar of H_2. The *in situ* experiments have been performed in a Varian Inova 600 (^{1}H, 599.7, ^{13}C, 150.8 MHz) spectrometers at 90°C. A spectrum was acquired and recorded every 60 seconds.

<u>Calculations</u>

All the calculations were performed using Gaussian 09 rev A.02. All the geometries were fully optimized at the B3LYP/LANL2DZ level including the solvent with the PCM method. Vibrational analysis were done on all the optimized geometries to confirm if they corresponded to energy minima (no imaginary frequencies) or to transition states (one imaginary frequency). In the case of transition state for hydrogenation, an IRC calculation[30] was performed using standard parameters.

Acknowledgements

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