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[Ru(triphos)(CH₃CN)₃](OTf)₂ as a homogeneous catalyst for the hydrogenation of biomass derived 2,5-hexanedione and 2,5-dimethyl-furan in aqueous acidic medium.

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Abstract

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The complex [Ru(triphos)(CH₃CN)₃](OTf)₂ is an effective catalyst for the hydrogenation of 2,5hexanedione and 2,5-dimethyl-furan in aqueous acidic medium at temperatures between 150 and 200 °C realizing up to 96 % combined yields of 2,5-hexanediol and 2,5-dimethyl-tetrahydrofuran with the product distribution being sensitive to the amount of acid co-catalyst (HOTf) present. For the furan, the reaction pathway is through an acid-catalyzed hydrolysis to the dione rather than direct hydrogenation of the ring. The hydrogenation of the dione shows a first order dependence on hydrogen pressure as determined by direct hydrogen uptake rate measurements at temperature and pressure (1.38 – 6.90 MPa at 150 °C) and is postulated to operate through a heterolytic activation of hydrogen gas by [Ru(H)_x(triphos)(Y)_y]ⁿ⁺ (Y = solvent, water, counter ion) species formed in situ by loss and hydrogenation of the nitrile ligands. In water the catalyst is deactivated by dimerization to [Ru₂(µ-OH)₃(triphos)₂](OTf).

Introduction

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The sugar-derivable furans furfural and 5-hydroxymethyl-furfural (5-HMF) are important platform molecules for the production of chemicals from biomass.¹⁻⁸ They are characterized by an extremely high intrinsic reactivity based on their high density of organic functionalities, which could be described as combining ether, cyclic bis-enol, aromatic, aldehyde and benzylic alcohol functions, all in the same molecule. This opens up multiple pathways for an uncontrolled decomposition and polymerization to molecularly poorly defined products generally referred to as humins,⁹⁻¹¹ which poses a substantial challenge to their conversion to value-added chemicals. In this context, the humins themselves, which are also formed directly from C6 sugars such as fructose (the precursor to 5-HMF as well as dihydropyrans as humin generating intermediates),¹² could however also be considered to simply be another recalcitrant feedstock of complex heterogeneous structure to be valorized.⁹ Using the hydrodeoxygenation (HDO) value chains leading from furfural to 1,4-pentanediol and 2-methyl-tetrahydrofuran and 5-HMF to 2,5hexanediol and 2,5-dimethyl-tetrahydrofuran, respectively, as examples, Scheme 1 illustrates this challenge and shows some of the conceivable reaction pathways leading to uncontrolled polymerization via direct benzylic-type alkylation, aldol condensation or Diels-Alder reactions, or any combination of the above. Similar challenges are present in alternative value chains, e.g., the highly desirable conversion of the same substrates to the corresponding α, ω -diols 1,5-pentanediol and 1.6-hexanediol that could find direct use in polyester and polyurethane (and with further derivation) polyamide formulations.¹³⁻¹⁸

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The key for any such processes to be viable is that the individual hydrodeoxygenation (HDO) steps, typically achieved by an iteration of acid-catalyzed loss (dehydration) or addition (hydrolysis) of water followed by metal catalyzed hydrogenation or hydrogenolysis, must in each case be kinetically competent over the various decomposition and polymerization pathways to humins from 5-HMF (or directly from fructose) or furfural or the resinification of furfuryl alcohol shown in Scheme 1. Furthermore, these non-productive pathways can not only lead to loss of substrate, but also have the potential to result in an irreversible deactivation of the catalyst system. This is true for both hetero- and homogeneously catalyzed HDO processes, with the former clearly dominating the research endeavours in this field.¹⁹⁻²³

As also indicated in Scheme 1, the propensity for humin formation is most pronounced for the extremely reactive 5-HMF, while the intermediates and products of subsequent HDO steps show – with the possible exception of the transient aldehyde or ketone hydrolysis products of the methyl-furans – a decreasing functionality density and reactivity, ultimate leading to diols and tetrahydrofurans. These products can be considered to be stable against polymerization in aqueous medium.



Scheme 1: Example reaction pathways and conceivable challenges to the conversion of biomass derived furans to hydrodeoxygenated value-added products.

Using almost exclusively processes in which both the acid dehydration/hydrolysis and metal hydrogenation/hydrogenolysis catalysts are heterogeneous, the production of both 2-methyl-furan and 2,5-dimethyl-furan has been realized following the sequences *hemi-cellulose* \rightarrow *xylose* \rightarrow *furfural* \rightarrow *furfuryl alcohol* \rightarrow 2*-methyl-furan* or *cellulose* \rightarrow *glucose* \rightarrow 5*-HMF* \rightarrow 2,5*-bis(hydroxymethyl)-furan* \rightarrow 2,5*-dimethyl-furan*, respectively.²⁴⁻⁴⁴ Here the work by Vlachos et al., that achieved very high yields and selectivities to furfuryl alcohol from furfural and 2,5-dimethyl-furan from 5-HMF by employing transfer hydrogenation over Ru/C under mild conditions, serves as a good example of how breaking the value-chain into separate optimized

steps with isolation of the intermediates can help to avoid humin formation.^{45, 46} Starting with the seminal work by Descotes et al.,⁴⁷ the direct "single-pot" heterogeneous hydrogenation and hydrogenolysis of either fructose/glucose or furfural/5-HMF to products beyond 2-methyl- and 2,5-dimethyl-furan, i.e., to tetrahydrofurans as well as diols and triols has also been extensively studied.^{17, 48-69} In contrast, the explicit production of 2,5-hexanedione, i.e., the hydrolysis product of the cyclic bis-enol 2,5-dimethyl-furan, from biomass has received less attention,⁷⁰⁻⁷⁵ even though its hydrogenation product 2,5-hexanediol is arguably the most valuable product of the example C6 value-chain shown in Scheme 1. 2,5-hexanediol could in principle serve as a polyester or polyurethane component and its derivative 2,5-Dimethyl-2,5-hexanediol (DMHD) is an intermediate in the preparation of pyrethroids and of 2,5-Dimethyl-2,5-bis(*tert*-butyl-peroxy)-hexane to produce polyethylene copolymers and polyethylene rubbers (by BASF).⁷⁶

As already stated, the vast majority of studies aimed at the HDO of sugars and sugar-derived furans have employed heterogeneous hydrogenation and hydrogenolysis catalyst systems, while attempts to use homogeneous catalyst systems based on transition metal complexes, that also tend to act only as hydrogenation, but not hydrogenolysis catalysts, are comparatively much fewer.⁷⁷⁻⁸⁷ Recent examples of the successful application of homogeneous catalysts to the hydrogenation of a biomass-derived furan substrates are the highly efficient solvent-free hydrogenation of furfural to furfuryl alcohol at up to 160 °C by a ruthenium complex formed in situ from Ru(acac)₃ and 1,4-bis(diphenylphosphino)butane,⁸⁸ and the metal-free hydrogenation of 2,5-dimethylfuran to 2,5-dimethyltetrahydrofuran in 64 % yield by the frustrated Lewis pair formed by a boron triaryl species and the THF solvent and product itself.⁸⁹

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The HDO of highly polar and reactive sugar-derived furans forces the use of a polar liquid reaction medium – most preferably water – rather than a reaction in the gas phase. Empirically, temperatures > 150 °C are also required to trigger any dehydration or hydrolysis steps required.⁸³ Under these conditions, both heterogeneous and homogeneous catalyst systems are subject to specific challenges of catalyst activity and stability. For heterogeneous catalysts, fouling or coking of the active surface can occur by substrate decomposition and polymerization (\rightarrow humin formation), which can in principle however be reversed by thermal and/or oxidative ("burn-off") re-activation. Other potential issues are the leaching of active metal and/or dissolution of the catalyst support by the reaction medium, which through the generation of water as the necessary reaction by-product of HDO reactions, will be aqueous in nature.^{23, 90}

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For homogeneous catalysts based on molecular dispersed transition metal complexes, the biggest challenge is product separation and recovery and reuse of the catalyst,^{83, 91}with successful recycling being to date limited to the ruthenium complex catalyzed hydrogenation of levulinic acid to γ -valerolactone.^{92, 93} Based on the required reaction conditions defined above, catalyst stability against loss of ligand and reduction of the hydrogenation metal to bulk material in oxidation state 0, i.e., effectively decomposition to a heterogeneous system, are then the key challenges that have to be resolved before recovery and reuse can be effected. It is therefore the opinion of the authors, that the design, characterization and synthesis of homogeneous catalysts with unprecedented thermal stability in aqueous (acidic) solution is the primary issue in the application of such systems to the hydrodeoxygenation of sugar-derived substrates.

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Further hypothesizing that homogeneous catalyst systems may in specific reaction sequences show advantages and result in different reactivity patterns and selectivities, we have developed a series of homogeneous hydrogenation catalysts based on variations of a pyridine chelate ligand theme coordinated to ruthenium(II). Exploiting the chelate effect,⁹⁴ these complex catalysts do indeed show unusually high, but still insufficient, stabilities at high-temperatures in aqueous acidic medium and are applicable to the HDO of terminal diols and glycerol as well as the conversion of 2,5-dimethyl-furan and 2,5-hexanedione to 2,5-dimethyl-tetrahydrofuran (as the *cis/trans* isomeric mixture), 2,5-hexandiol and hexane.^{82, 87, 95-100}

Specifically, the catalyst systems $[(4'-Ph-terpy)Ru(H_2O)_3](OTf)_2$ and [(4'-Ph-terpy)(quS)Ru(L)](OTf) (quS = 8-quinoline-thiol) can effect these transformations in moderate to good yields at T \geq 150 °C, but ultimately suffer from irreversible deactivation to the very stable coordinatively saturated [Ru(4'-Ph-terpy)_2](OTf)_2 and inactive Ru(0), severely limiting their recyclability.^{82, 87}

Previous work by the groups of Elsevier,^{101, 102} Bianchini,¹⁰³ Jun,¹⁰⁴ Kilner,¹⁰⁵ Dyson,¹⁰⁶ Miller, Cole-Hamilton, Klankermayer and Leitner¹⁰⁷⁻¹¹¹ as well as Beller,¹¹²⁻¹¹⁴ established the activity of the [Ru(triphos)] (triphos = 1,1,1-tris(diphenylphosphinomethyl)ethane) fragment as a versatile and very robust homogeneous hydrogenation catalyst for a broad range of substrates. Expanding our investigations to chelating tridentate phosphine ligands, we here explore the applicability, behaviour and limitations of this system for the conversions shown in Scheme 1 working "backwards" along value-chain starting with 2,5-hexandione.

Experimental

General. All reagents and solvents were purchased from commercial sources. 2,5-hexanedione, 2.5-dimethyl-furan and 1.4-dioxane were passed through a short plug of neutral Al_2O_3 (Brockmann Activity I) immediately before use to remove any impurities, peroxides or stabilizers present that could lead to false negatives in the catalytic reactions. All water used was HPLC grade. Trifluoromethanesulfonic (HOTf, triflic) acid was stored under argon atmosphere and measured into reaction mixtures using a micro-liter syringe. Catalyst syntheses were performed under argon using Schlenk-line techniques. atmosphere standard $[Ru_2(\mu-Cl)_3(triphos)_2]Cl$ and $[Ru(triphos)(CH_3CN)_3](OTf)_2$ (1) were obtained following the published procedure by Venanzi and co-workers in yields comparable to those previously reported.¹¹⁵ Pale vellow single crvstals of **1** suitable for X-ray analysis were obtained by slow diffusion of diethylether into a methanol solution of 1. In the same manner X-ray grade crystals of $[Ru_2(\mu-OH)_3(triphos)_2](OTf)$ (2) were obtained from an orange amorphous solid isolated from the catalytic reactions. All NMR spectra were obtained on 300 MHz, 400 MHz, or 600 MHz spectrometers and calibrated to the residual solvent signal. GC-MS analyses were performed on a Varian Saturn 2000 GC/MS using a 30 m Stabilwax-da (acid-deactivated polyethylene glycol) column running in CI (CH₃CN) mode. Reaction products were identified by comparison to the retention times and MS fragmentation patterns of authentic samples and database matches. GC analyses were performed on a Varian 3800 with FID detectors using the same column as the GC-MS. Quantification was carried out using internal standard calibration against 100 mmol L⁻¹ dimethyl sulfone (DMS) in a three level calibration against authentic samples of 2,5-hexanedione, 2,5-hexanediol, 2,5-dimethyl-furan and *cis/trans*-2,5-dimethyl-tetrahydrofuran (grouping and reporting the *cis/trans*-isomers of the latter 8

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as one product). Other products formed were quantified using the response factors of these compounds based on the concept of the effective carbon number.¹¹⁶ All hydrogenation experiments employed industrial grade H_2 gas (99.995 %). All preparative hydrogenation experiments were carried out in an Autoclave Engineers (AE) Mini-reactor with a 50 mL 316 stainless steel (316SS) reactor vessel and impeller. At a total reaction solution volume of 25 mL the reactor has a gasphase headspace of 50 mL (unused reactor body space and enclosed and pressurized magnet-drive stirring assembly) ensuring an adequate and not stoichiometrically limiting supply of hydrogen. Unless otherwise specified (cf. control experiments) reactor vessel and impeller were thoroughly cleaned and polished after every run by lathe at 600 rpm with 3M abrasive pads and sand-blasting, respectively. Regular control reactions without addition of catalyst showed only marginal conversion (< 5 %) of substrate to hydrogenated products (see main text) caused by the background activity of the reactor walls.¹¹⁷ Hydrogenation experiments aimed at determining the reaction order in hydrogen gas were carried out in the University of Guelph's dedicated High-Pressure Hydrogenation Facility using a 300 mL Autoclave Engineers Hastelloy[™] (C-276) reactor connected to a large high-pressure hydrogen reservoir via a mass flow controller and fitted with an automatic pressure and PID temperature control system. The system allows the direct measurement of hydrogen consumption at a constant (within $\pm 7 \text{ kPa} \equiv \pm 1 \text{ psi}$) pressure and thus provides a direct differential rate measurement at a given temperature (ambient to 723 K), pressure $(0.69 - 10.3 \text{ MPa} \equiv 100 - 1500 \text{ psi})$ and stirring rate. In these reactions a total reaction volume of 50 mL was employed providing for a pressurized headspace gas volume of > 250 mL (see further discussion on mass flow limitations in main text). A single batch of catalyst 1 (X-ray grade

crystals) was used for the kinetic study. Control reactions in the absence of catalyst showed no background activity of the Hastelloy[™] reactor material.

Representative procedure for a preparative catalytic hydrogenation reaction.

In a 25 mL volumetric flask were combined catalyst **1** (0.0286 g, 0.025mmol) and ~ 10 mL of water (for 2,5-hexanedione substrate) or a 5:1 mixture of 1,4-dioxane/water (for the 2,5-dimethyl furan substrate) to form a pale yellow suspension (water) or solution (1,4-dioxane/water). Methylsulfone (0.235 g, 2.5 mmol, GC internal standard), 2,5-hexanedione (2.853 g, 25 mmol) or 2,5-dimethyl-furan (2.4105 g, 25 mmol) and (where applicable) 1-5 equivalents HOTf with respect to ruthenium content were added and the volume made up to 25 mL with water or the 5:1 mixture of 1,4-dioxane/water. The solution was then thoroughly mixed by vigorous manual shaking of the flask for 60 seconds, placed in an Autoclave Engineers MiniReactor and purged three times with hydrogen. The reactor was twice pressurized to 5.5 MPa (800 psi) with H₂(g) and vented and then re-pressurized to this working pressure, sealed and heated to the set temperature (150-225 °C), which in all cases was reached in \leq 20min. The reaction was stirred (500 rpm) at temperature for 16 h and then cooled to ambient. The reaction products were analyzed and quantified by GC/GC-FID.

Procedure for the determination of the reaction order of hydrogen gas in the hydrogenation of 2,5-hexanedione to 2,5-hexanediol.

In a 50 mL volumetric flask 2,5-hexanedione (5.706 g, 50 mmol) was dissolved in a 5:1 mixture of 1,4-dioxane/water. The solution was then thoroughly mixed by vigorous manual shaking of the flask for 60 seconds and placed into the 300 mL reactor vessel and an open glass (5 mm NMR) 10

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tube reaching several centimeters above the liquid level and containing catalyst 1 (0.0572 g, 0.050

mmol) placed into the reactor. (See ESI for images of this set-up). This isolates the catalyst from

the solution during pressurizing and heating. The reactor was twice pressurized to 5.5 MPa (800 psi) with H₂(g) and vented and then re-pressurized to the desired working pressure heated to 423 K (150 °C) using a PID controller to prevent temperature overshoot. Once this temperature had been reached (~ 60 min.) the mechanical stirrer was started (500 rpm), which breaks the glass tube inside the reactor releasing the catalyst into solution. This marks time = 0 for the hydrogen uptake rate measurements. Hydrogen uptake at constant temperature 423 K (150 °C) and pressure (200, 400, 600, 800 and 1000 psi = 1.38, 2.76, 4.14, 5.12 MPa) was followed by data-logging from the mass flow controller at 1 s time intervals until it ceased, i.e., over 1-3.5 hours depending on hydrogen pressure.

Results

Catalyst synthesis and characterization. The complex $[Ru(triphos)(CH_3CN)_3](OTf)_2$ (1) was selected as the catalyst, as it is easily prepared via $[Ru_2(\mu-Cl)_3(triphos)_2]Cl$ (2) following the protocol by Venanzi et al.¹¹⁵ We anticipated that it a) should be soluble in polar aqueous media, b) should generate a catalytically active ruthenium hydride species of the type $[Ru(H)_x(triphos)(Y)_v]^{n+}$ (Y = solvent, water, counter ion) by loss of the labile CH₃CN ligands followed by heterolytic activation of $H_2(g)$ to Ru-H and HY, ^{106, 111} and c) would allow more precise control of the amount of coordinated ruthenium present rather than rely on *in situ* coordination of the triphos ligand to $Ru(acac)_3$ or similar.

A control reaction in which **1** was dissolved in CH₃CN and heated to 423 K under 5.5 MPa H₂(g) resulted in the quantitative conversion of the solvent to ethylamine, limited only by the amount of H₂(g) supplied. This established that at $T \ge 423$ K any ethylamine generated by this process does – even when present in large amounts – not coordinatively inhibit the catalyst. This is as expected based on the studies by Bianchini and Beller that employed the [Ru(triphos)] system as a catalyst for the hydrogenation of nitriles.^{103, 112}

In order to obtain samples of high purity of **1** for catalysis and kinetic studies, it was recrystallized by diffusion of Et_2O into a methanolic solution yielding pale yellow crystals of sufficient quality for X-ray analysis. Figure 1 shows the structure of **1**.

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Figure 1: ORTEP of the cation of $[(triphos)Ru(CH_3CN)_3](OTf)_2$ (1) at the 50 % probability level oriented to show the 3-fold symmetry of the complex. (Triflate counter ion and hydrogens omitted for clarity).

Hydrogenation of 2,5-hexanedione by 1 in water.

Table 1 summarizes the results of a temperature dependence study of the activity of 1 for the hydrogenation of 2,5-hexanedione in water. While **1** is only marginally soluble in water at ambient temperature and the concentration employed, quantitative conversion of the substrate to 2,5hexanediol is realized under 5.5 MPa H₂(g) at 150 and 175 °C (entries 1 and 2) giving a turn over number (TON) of 2000 (due 2 equivalents of $H_2(g)$ consumed per mol of substrate) and turn over frequency of 125 h⁻¹ as the lower limits for these reaction conditions and time (16 h). No catalyst activity was observed at 125 °C or lower, while at higher temperatures (200 and 225 °C, entries 3 and 4) relatively small, but increasing amounts of substrate decomposition (determined by the mass balance deficiency against the GC internal standard – last column in Table 1) are observed along with 11 % of dehydration ring-closure to *cis/trans*-2,5-dimethyl-tetrahydrofuran at the highest temperature (225 °C) attempted. Carrying out a reaction with a 10-fold increase in substrate concentration under otherwise identical conditions (Table 1, entry 5) also gives full conversion yielding a viscous solution of ~ 2:1 2,5-dimethyl-tetrahydrofuran and 2,5-hexanediol and establishes a catalyst turn over number (TON) of 20,000 and TOF of 1250 h⁻¹ as the lower limits in this case.

The reactions generate orange solutions along with a small amount of an orange coating of an amorphous solid on the reactor body that readily dissolves in MeOH. Running a reaction without cleaning this coating from the reactor body gives only marginal conversion, i.e., this material is inactive as a catalyst (entry 6), instead giving large amount of substrate decomposition (39 %) and leaving unreacted substrate (49 %). Carrying out a control reaction after cleaning the reactor and

without addition of **1** gives a very similar result with the marginal conversion of substrate to diol attributed to the background activity of the 316SS reactor body material.¹¹⁷ In contrast, twice replenishing the filtered reaction solution obtained from a reaction at 150 °C (entry 1) with the same amount of substrate (entries 8 and 9), again results in full conversion to 2,5-hexanediol. This establishes that under these conditions the observed catalytic hydrogenation activity does in fact reside in the homogeneous solution and not in the reactor body or heterogeneous catalyst decomposition products such as the orange solid.

Entry	T		~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	OH OH OH		Mass Balance Deficiency ^c
	[°C]	[%] ^b	[%] ^b	[%] ^b	[%] ^b	[%] ^b
1	150	0	0	100	0	0
2	175	0	0	100	0	0
3	200	0	0	95	2	3
4	225	0	11	76	2	11
5 ^d	150	0	66	34	0	0
6 ^e	200	49	0	5	7	39
7 ^f	200	45	0	7	9	39
8 ^g	150	0	0	100	0	0
9 ^h	150	0	0	100	0	0

Table 1: Hydrogenation of 2,5-hexanedione by [Ru(triphos)(CH₃CN)₃](OTf)₂ (1) in water.^a

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^aReaction conditions: 2,5-Hexanedione [1000 mmol/L] in water, 5.5 MPa (800 psi) $H_{2 (g)}$, dimethylsulfone (ISTD) [100 mmol/L], catalyst load [1 mmol/L = 0.1% w.r.t. substrate], reaction time = 16 h. ^bBy quant. GC-FID against internal standard; ±1%; ^cMass Balance Deficiency due to decomposition of the substrate and/or products to insoluble and non-volatile polymers and solids (humins) not quantifiable by GC. ^dReaction carried out at 10,000 mmol/L substrate concentration, i.e., 0.01 % catalyst load. ^eControl reaction without catalyst and in presence of an orange precipitate partially coating the reactor. ^fControl reaction without catalyst after cleaning reactor. ^gFirst re-use of solution of reaction 1 with same amount of substrate re-added. ^hSecond re-use of solution of reaction 7 with same amount of substrate re-added.

Recrystallization of the orange solid from MeOH/Et₂O enabled single-crystal X-ray analysis that identified it as $[Ru_2(\mu-OH)_3(triphos)_2](OTf)$ (2) and established a deactivation pathway of catalyst 1 in aqueous solution under these conditions by dimerization via three bridging hydroxyl ligands.¹¹⁸ Figure 2 shows the structure of **2**. The binuclear complex has each Ru(II) center in distorted octahedral coordination by three O-atoms from bridging hydroxyl anions and three Patoms of the chelating ligand. The Ru-O and Ru-P distances are within 2.13-2.16 and 2.25-2.28 Å, respectively. The O-Ru-O, P-Ru-P and O-Ru-P angles range from 73.1-74.6, 85.8-88.2 and 93.4-105.3°, respectively. The Ru-Ru distance is 3.09 Å. The cation has approximate symmetry of a three-fold rotation axis. As a whole, the cation is similar to other previously reported binuclear $[Ru_2(PMe_3)_6(OH)_3](BF_4)^{119}$, Ru(II) complexes with three hydroxyl bridges, e.g., [Ru₂(PMe₃)₂(OH)₃](BPh₄),¹²⁰ and [Ru₂(PMe₃)₂(OH)₃](phenolate)•(phenol) and others.¹²¹

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Figure 2: ORTEPs of $[Ru_2(\mu-OH)_3(triphos)_2](OTf)$ (**2**) at the 50 % probability level in *side* and *axial* view showing the position of the three bridging hydroxyl functions. (Oxygens in red. Triflate counter ion, carbon-bound hydrogens and solvent molecules omitted for clarity).

Hydrogenation of 2,5-dimethyl-furan in 5:1 1,4-dioxane/water

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Taking one step back in the value chain of Scheme 1, towards 5-HMF as one of the ultimately desirable starting materials, the hydrogenation of 2,5-dimethyl-furan by **1** in water was attempted. Scheme 2 summarizes the overall reaction cascade with the observed side- and follow-up reactions already described in our previous study using $[(4'-Ph-terpy)Ru(H_2O)_3](OTf)_2$ as the catalyst.⁸²



Scheme 2: Reaction cascade and observed intermediates and reaction products for the hydrodeoxygenation of 2,5-hexanedione and 2,5-dimethyl-furan in aqueous acidic medium.⁸²

However, compared to our earlier results with [(4'-Ph-terpy)Ru(H₂O)₃](OTf)₂ as the catalyst in which the same reaction gave up to 65 % conversion,⁸² the bi-phasic emulsions formed did not give any hydrogenated products, but resulted in complete rapid decomposition and polymerization of the substrate to brown sticky resins in the reactor, i.e., quantitative formation of humins, precluding the use of pure water as the reaction medium in this case. We attribute this to the much lower solubility of **1** in pure water compared to [(4'-Ph-terpy)Ru(H₂O)₃](OTf)₂, which as an aqua complex is freely soluble. In contrast, in the biphasic emulsion **1** more readily dissolves in the furan substrate phase where interaction of the catalyst with the undiluted furan then results in the observed decomposition to humins, which can be caused either by the generation of free HOTf by the catalyst or conceivably the metal centre directly acting as a Lewis acid catalyst. Together both **1** and 2,5-dimethyl-furan do however freely dissolve in a variety organic solvents. However, no

catalytic activity against 2,5-dimethyl-furan was observed in toluene or other non-polar solvents, even when biphasic aqueous mixtures of these solvents in the presence of phase-transfer catalysts were employed (e.g., sodium dodecyl benzoic acid or NaBPh4), i.e., while 2,5-dimethyl-furan is insoluble in water, its hydrolysis to 2,5-hexandione as the actual hydrogenation substrate is a prerequisite for its conversion by the homogeneous catalyst system. This reaction pathway is also supported by the observation of 2,5-hexanediol in reactions starting from 2,5-dimethyl-furan and by control reactions from our previous study,⁸² in which no hydrolysis of 2,5-dimethyltetrahydrofuran to 2,5-hexanediol was observed even under much more extreme reaction conditions (225 °C with added acid in water). This – by necessity – means that any 2,5-hexanediol formed from 2,5-dimethyl-furan can only originate from 2,5-hexandione generated by hydrolysis of 2,5-dimethyl-furan and not from the hydrolysis of 2,5-dimethyl-tetrahydrofuran generated by the direct hydrogenation of 2,5-dimethyl-furan. Following our previous reports,^{82, 87, 122} 1,4dioxane was therefore again selected as the reaction medium on the basis of its anticipated inertness and similarity to the possible ultimate reaction product *cis/trans-2,5-dimethyl*tetrahydrofuran and its full miscibility with water. The reaction medium was therefore modified to the azeotropic 5:1 mixture of 1,4-dioxane/water, in which both the substrate and catalyst $\mathbf{1}$ are fully soluble at ambient temperature. Control reactions, in which a 1 mol/L solution of 2,5dimethyl-furan in this solvent mixture was heated to 125 or 150 °C in the presence of 0.1 mol % $(= 1 \text{ mmol/L}) [H_3O^+][OTf]$,¹²³ but absence of **1** does in fact lead to hydrolysis of the furan to 2,5hexanedione, but is dominated by substrate decomposition to humins. Figure 3 shows the evolution of the composition of this mixture over 7 hours at 150 °C. The azeotropic reaction medium also in principle allows for a simple separation of products, solvent and catalyst by distillation. At a lower

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1,4-dioxane/water ratio the furan is not fully soluble and phase separation is observed. The amount of water in this mixture thus represents its optimized maximum concentration and enables the hydrolysis of the furan to 2,5-hexanedione while also serving to supress condensation reactions to humins by aldol condensation (cf. pathway b, Scheme 1).



2,5-dimethylfuran 2,5-hexanedione Decomposition (Humins)
Figure 3: Control experiment for the hydrolysis of 2,5-dimethyl-furan to 2,5-hexanedione in 5:1

1,4-dioxane/water at 150 $^{\circ}\text{C}$ in the presence of 0.1 mol % HOTf.

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As the results of a temperature dependence study summarized in entries 1-5 of Table 2 show, in the presence of **1** much less humin formation and instead conversion to 2,5-hexanediol and 2,5-dimethyltetrathydrofuran occurs in moderate to good yields reaching an optimum at 200 °C with 65 % yield of hydrogenated products.

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In the absence of added acid co-catalyst, reusing the solution from this reaction by replenishing with the same amount of substrate gives substantially lower conversions due to catalyst deactivation by formation of **2**, which in the dioxane/water mixture remains dissolved forming deep orange solutions.

With the addition of increasing amounts of HOTf (1 to 5 equivalents with respect to 1) as a hydrolysis co-catalyst, almost complete conversion (up to 96 %, entry 9) to hydrogenated products is achievable at 150 °C, with a TON/TOF of only 120/7.5 h⁻¹ to 2,5-hexanediol, but 1800/112.5 to 2,5-dimethyl-tetrahydrofuran, i.e., in the more acidic solution, ring closure to *cis/trans*-2,5-dimethyl-tetrahydrofuran becomes the increasingly dominant product by acid-catalyzed ring-closure of the diol (Scheme 2), which is consistently generated as a ~ 1:1.25 *trans:cis* isomeric mixture from all reactions.¹²⁴ In the presence of 5 equivalents of acid, clear orange solutions are still obtained and reusing the solution (Entry 10, Table 2) still realizes 80 % of hydrogenated products. Repeating the reaction of entry 9 at higher hydrogen pressure for shorter times (entry 11, 13.8 MPa for 3 h) enhances the yield of the more desirable 2,5-hexanediol, but also gives a higher amount of humin formation, which is however an artifact of the required reactor set-up at these higher pressures (see Discussion section).

Entry	Т	HOTf	~	ОН	- Com	O OH	o	Mass Balance Deficiency ^c
	[°C]	[eqv. to Ru]	[%] ^b					
1	150	0	83	2	2	0	0	13
2	175	0	31	35	21	0	0	13
3	200	0	16	45	20	0	0	19
4 ^d	200	0	55	20	5	0	0	20
5	225	0	21	36	19	1	0	23
6	150	1	73	2	0	0	6	19
7	150	3	4	54	25	0	0	17
8	150	4	0	22	64	0	0	14
9	150	5	0	6	90	0	0	4
10 ^e	150	5	7	39	41	0	0	13
11 ^f	150	5	0	40	48	0	0	12

Table 2: Hydrogenation of 2,5-dimethyl-furan by [Ru(triphos)(CH₃CN)₃](OTf)₂ (1) in 5 : 1 1,4-dioxane/water.^a

^aReaction conditions: 2,5-dimethyl-furan [1000 mmol/L] in 5:1 1,4-dioxane : water, 5.5 MPa (800 psi) $H_{2(g)}$, dimethylsulfone (ISTD) [100 mmol/L], catalyst load [1 mmol/L = 0.1% w.r.t. substrate], reaction time = 16 h. ^bBy quant. GC-FID against internal standard; ±1%; ^cMass Balance Deficiency due to decomposition of the substrate and/or products to insoluble and non-volatile polymers and solids (humins) not quantifiable by GC. ^dRe-use of solution of reaction 3 with same amount of substrate re-added. ^eRe-use of solution of reaction 9 with same amount of substrate re-added. ^fReaction time 3 h at 13.8 MPa (2000 psi) H₂(g).

Kinetic studies

In order to gain some insight into the mechanism and limiting factors of the reactions catalyzed by 1 in aqueous media, the reaction order of hydrogen gas in the hydrogenation of 2,5-hexanedione at 150 °C (473 K) was determined by directly measuring the rate of hydrogen uptake at five constant pressures ranging from 1.32 MPa (200 psi) to 6.90 MPa (1000 psi). To ensure that the data obtained is not skewed by solubility limitations of the catalyst, the reactions were conducted in 5:1 1,4-dioxane/water, in which 1 is completely soluble at ambient temperature at the concentrations employed (identical to those used in the preparative reactions described above, cf. Tables 1 and 2). To further ensure that the measured rates of hydrogen uptake do not simply reflect 21

the diffusion limit of hydrogen gas into the reaction solution, we explicitly calculated the actual amount of hydrogen present in 50 mL of water at temperature and pressure using the data and models provided by Baranenko and Kirov.^{125,126} The calculation establishes that even at the lowest constant pressure employed (1.38 MPa = 200 psi) the molar ratio of $[H_2]/[Ru]$ is never less than 10. This calculation actually provides only a lower limit of hydrogen solubility and availability in our reaction solutions, as the solubility of hydrogen is comparatively lower in water than in less polar organic solvents or mixtures of these with water. The more limited data and models provided by Brunner suggest that hydrogen solubility is in fact substantially higher in the 1,4-dioxane/water mixture than in pure water.¹²⁷ Taking further into account that the literature data refer to static gas dissolution equilibria, while the reactions were stirred at 500 rpm, which should substantially enhance gas diffusion into the reaction solution, we have high confidence that the hydrogen uptake rates reported in Table 3, which represent a direct differential reaction rate measurement, do not reflect any mass transport limitations in the reactor, but are in fact the true hydrogen consumption rates by the catalytic system under the chosen reaction conditions. In addition, this approach has the advantage that rate data is obtained without disturbing the reaction equilibria of the reaction by drawing samples for quantitative analysis, e.g., by GC, and determining reaction order by plotting concentration changes over time.

Entry	p(H ₂) ^b (295 K) [psi]	p(H ₂) ^b (295 K) [MPa]	p(H ₂) ^c (422 K) [psi]	p(H ₂) ^c (422 K) [MPa]	Rate of H ₂ uptake [scc/s] ^d	Rate of H ₂ uptake [µmol/s]	p(H ₂) normalized [dimensionless] ^f	log [p(H ₂)] normalized [dimensionless] ^f	Rate of H2 uptake normalized [dimensionless] ^f	log [Rate of H ₂ uptake] normalized [dimensionless] ^f
1	200	1.38	303	2.089	0.0897	7.868	1.000	0.0000	1.000	0.0000
2	400	2.76	531	3.661	0.1633	14.32	1.752	0.2437	1.821	0.2602
3	600	4.14	796	5.488	0.2873	25.20	2.627	0.4195	3.203	0.5055
4	800	5.52	1061	7.315	0.3264	28.63	3.502	0.5443	3.639	0.5610
5	1000	6.90	1300	8.963	0.4435	38.90	4.290	0.6325	4.944	0.6941

Table 3: Measured rates of hydrogen uptake in the hydrogenation of 2,5-hexanedione by $[Ru(triphos)(CH_3CN)_3](OTf)_2$ (1) in 5:1 1,4-dioxane/water at 150 °C (423 K) as a function of hydrogen pressure.

^aReaction conditions: 50 mL solution of 2,5-hexanedione [1000 mmol/L] in 5:1 1,4-dioxane : water, catalyst load [1 mmol/L = 0.1% w.r.t. substrate]. ^bH₂(g) reactor fill pressure at ambient condition (293 K). ^cPressure in reactor reached at 423 K – held constant at this temperature to \pm 1 psi. ^dssc/s = standard cubic centimeter of hydrogen uptake per second as measured by calibrated mass flow controller at NIST NTP (T = 293.15 K, p = 101.325 kPa). ^eAssuming ideal gas behaviour for H₂(g). ^fBy division by data from 1st entry.

The rates of hydrogen uptake at a given pressure listed in Table 3 were constant over the range of 10-90 % of substrate conversion (total amount 50 mmol) and the total uptake of hydrogen gas after completion of the reaction (after 0.75-3.5 h depending on pressure) closely matched the expected amounts (100 mmol for complete and selective conversion to 2,5-hexanediol). As the data in Table 3 shows the measured rates of hydrogen uptake scale with the applied pressure. Determination of the reaction order of hydrogen follows Equation (1).¹²⁸

$$rate = \frac{mmols \, of H_2}{time} = k' \times [H_2]^a \tag{1}$$
$$k' = [catalyst]^b \times [substrate]^c \times \dots$$

As the actual (and constant) hydrogen concentrations in the solutions are not exactly known, pressures and rates were normalized to dimensionless numbers by division of the data for Entry 1 in Table 3. Direct or log/log plots of these normalized rate vs the normalized pressures both give slopes close to unity with acceptable correlation coefficients (Figure 4) indicating a 1^{st} order in H₂(g).



Figure 4: Direct and log/log plots of the normalized rates vs normalized pressures.

Discussion

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Previous mechanistic studies – both by NMR and in silico^{106, 111, 129} – suggest that the [Ru(triphos)] fragment can heterolytically activate $H_2(g)$ into an active Ru-H species and a proton, i.e., activation of $H_2(g)$ by **1** can generate at least one equivalent of acid. Starting from **1** such a Ru-H species must be generated by dissociation of (at least) one of the CH₃CN ligands from **1**. The proton is then taken up either by ethylamine generated by hydrogenation of the nitrile ligands in **1** or – in the presence of excess acid (cf. entries 6-10, Table 2) – water as the strongest available base in the aqueous medium. A [Ru(triphos)(H)_n(L)_m]⁽²⁻ⁿ⁾⁺ (n, m = 1 or 2, L = labile ligand: H₂O, solvent, substrate, product) species and either H₃CCH₂NH₃⁺or hydronium together could then act as a ionic hydrogenation catalyst ¹³⁰

From the reaction of entry 9, Table 1, the lower TON and turn over frequency (TOF) limits for **1** in this reaction are 20,000 and 1,250 h⁻¹, but possibly are substantially higher, which was however not further explored in this study. The reaction order for $H_2(g)$ (cf. Table 3 and Figure 4) suggests that in the hydrogenation of 2,5-hexanedione by **1** in aqueous medium, the activation of hydrogen 24

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by a [Ru(triphos)] fragment is the rate-determining step. As the only species in the system capable of activating hydrogen gas is such a [Ru(triphos)] fragment, this then suggests that the reaction is also (at least) 1st order in ruthenium catalyst and operates through a Ru-H species of unknown structure.¹³¹

Comparison of the results of the hydrogenation reactions of 2,5-hexanedione vs 2,5-dimethyl-furan for reactions under identical conditions (entries 1-3 in Tables 1 and 2) shows that this kinetic model clearly does not apply to the furan substrate. Instead (and with reference to Figure 3), the hydrolytic ring opening to the dione as the actual hydrogenation substrate must be the rate determining step, which then in turn is dependent on the relative concentration of acid catalyst and water, i.e., HDO reactions targeting furans should – substrate solubility permitting – best be conducted in pure water. However, as already stated above, in the 1,4-dioxane/water azeotrope, the relative concentration of water is at its maximum for a homogeneous solution of 2,5-dimethyl-furan, i.e., for this substrate this parameter cannot be further optimized in this solvent system. The limited solubility of **1** in pure water then represents a further limitation of this system. The amount of acid added in the hydrolysis control reaction illustrated in Figure 3 represents the maximum concentration of H_3O^+ that could be generated by 1, assuming formation of a single hydride ligand through the heterolytic activation of hydrogen gas. The fact that in the absence of added acid at temperatures from 150-225 °C (Table 2, entries 1-5) **1** gives much less humin formation than free acid at a ruthenium equivalent concentration (0.1 mol % of substrate = 1 equivalent/Ru) suggests that either not all of **1** participates in the activation of hydrogen gas, necessarily resulting in a lower overall acid concentration, or – more likely – that a continuous hydrogenation of 2,5-hexanedione prevents humin formation via the aldol condensation pathway of the dione substrate (cf. Scheme 25

1), or both. Two significant trends emerge from the acid concentration series reactions represented by entries 1 and 6-9 in Table 2: in the presence of metal catalyst higher acid concentrations (unexpectedly) give lower amounts of humin and (expectedly) higher amounts of ring closure THF product. These trends are visualized in Figure 5.



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Figure 5: Product distribution in the hydrogenation of 2,5-dimethyl-furan by **1** at 423 K at 5.5 MPa $H_2(g)$ in 5:1 1,4-dioxane/water as a function of the equivalents of HOTf acid co-catalyst added. (2,5-DMF = 2,5-dimethylfuran; 2,5-HDO = 2,5-hexanedione; 2,5-DMTHF = 2,5-dimethyltetrahydrofuran; MBD = Mass Balance Deficiency due to humin formation).

Higher acid concentration thus accelerates hydrolysis, limiting humin formation directly from the furan. Suppression of humin formation by acid catalyzed aldol condensations of the hydrolysis product 2,5-hexanedione (by pathway b) in Scheme 1) is then mainly contingent on the kinetic

competency of the metal-catalyzed hydrogenation reactions to the diol. A limit on the maximum viable substrate concentration (not explored here) would however be reached if the condensation reactions a) or b), both of which must be 2^{nd} order in either dione or furan, would become faster than hydrogenation.

Beyond its role in the hydrolysis ring-opening of the furan to the actual dione hydrogenation substrate, the HOTf acid co-catalyst also appears to prevent deactivation of the catalyst by formation of **2**. It could do so by protonating one or several of the μ -OH bridges in the dinuclear species (**2**) that does not possess a free coordination site for H₂(g) activation, generating species with labile aquo ligands. In any of these the labile aquo ligand can be displaced by an η^2 -H₂ ligand,¹³² ultimately leading to formation of an active hydride species. It is then further conceivable that any of the resulting and still mono- or bis-hydroxy bridged dimeric species could also be active as hydrogenation catalysts, which – at least in the absence of acid – would lead formally to fractional reaction orders larger than unity for **1**, which is undesirable. Therefore an optimized amount of acid co-catalyst could not only impact the furan hydrolysis to the dione hydrogenation substrate, but also helps to maximize the efficient use of ruthenium present in the system.

According to our kinetic study even lower degrees of humin formation should in principle be achievable by applying both higher acid co-catalyst concentrations and higher $H_2(g)$ pressures, as this should enhance the kinetic competency of both the hydrolysis and the hydrogenation steps. However, as the reaction of entry 11 of Table 2 shows, which resulted in a higher degree of humin formation than the same reaction at lower pressure, this approach is in the batch reactors employed met with some technical limitations. In order to operate at the higher pressure of 13.9 MPa (2,000 **Green Chemistry Accepted Manuscript**

psi, cold), this reaction had to be conducted in the much larger 300 mL Hastelloy reactor with higher mass and heat capacity, which – in order to avoid temperature overshoots that destroy the catalyst – requires a heat up time to the catalyst activation temperature of 423 K that is about 3 times longer (20 vs 60 min.) than for the 50 mL mini-reactor employed in all other reactions listed in Tables 1-3. During this heat-up time hydrolysis of the furan substrate and decomposition either directly or via acid-catalyzed aldol condensation of the dione already occurs before the catalyst activates to transform the substrate to the stable diol or THF product. (In contrast, this is not a problem in the kinetic studies on 2,5-hexanedione, which were conducted in the absence of acid co-catalyst). As this reaction also ceased to consume hydrogen after 3 hours, it was stopped at this time resulting in a higher yield of the diol vs the THF product indicating that acid-catalyzed ring-closure to the ether is comparatively slow in the 1,4-dioxane/water azeotrope. Both observations illustrate that awareness of chemical engineering parameters reaching beyond any intrinsic chemical limitations is important when considering transformations of biomass-derived substrates with high self-reactivity, in particular when running in batch reactors as in the present case.

Conclusions

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The factors that limit a successful HDO of the biomass derived substrates targeted here are specific to each actual substrate in the value chain, as the different steps in the reaction cascades have very different rate-limiting features. For the actual hydrogenation substrate 2,5-hexanedione they are dependent on hydrogen pressure and by necessary extension metal catalyst concentration, while for the furan substrate, which cannot be directly hydrogenated by the homogeneous catalyst, the relative concentrations of water and acid co-catalyst that govern the hydrolysis step are decisive.

This constitutes a unique challenge, as in homogeneously catalyzed batch reactions the entire reaction cascade takes place simultaneously, with the role of the catalyst in the system presented here solely being the hydrogenation of 2,5-hexandione, while the product selectivities (diol vs THF) are dependent on the multiple (de-)hydration ring-opening/closing equilibria in the reaction cascade shown in Scheme 2. For both substrates, conducting the reactions in pure water would therefore be advantageous, as this would maximize the rate of furan hydrolysis to the actual dione hydrogenation substrate, suppress the aldol condensation pathway of the latter and maximize the yield of the – arguably – most valuable 2,5-hexanediol by inhibiting ring-closure to 2,5dimethyltetrahydrofuran. The inactivity of the catalyst against furans thus presents an opportunity that differentiates this homogeneous system from heterogeneous systems that directly yield the tetrahydrofuran rather than diol products from biomass derived furans. The ultimately desirable extension of the experiments described here to targets further "back" in the value chain will then also require the ability to conduct reactions in pure water at optimized minimal acid co-catalyst concentrations in order to supress humin formation anticipated to be much more severe with these higher reactivity substrates. In light of the now known deactivation pathway of $\mathbf{1}$ and the insolubility of 2 in water, realizing an increased catalyst solubility and activity in water – again at optimized minimal acid co-catalyst concentrations – by modification of its structure in addition to a further enhanced thermal catalyst stability will thus be a key issue to improve on the current system to make it directly applicable to the conversion of the more reactive and more water-soluble substrates furfural or furfuryl alcohol and 5-HMF or 2,5-(bis-hydoxymethyl)-furan to diols rather than tetrahydrofurans.

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Conflict of Interest

There are no conflicts of interest to declare.

Acknowledgements

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Electronic Supporting Information (ESI)

Compound Data Sheets and spectra for complexes 1 and 2. GC methods and representative traces and retention times. Images of high-pressure hydrogenation reactor set-up. Live spreadsheets for the calculation of $H_2(g)$ solubility in xlsx and ods formats. CIF files for 1 and 2 have been deposited with the Cambridge Crystallographic Data Centre as #1535963 (1) and #1527925 (2).

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