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A Comparative Study of Structurally Related Homogeneous Ruthenium and Iron Catalysts for the Hydrogenation of Levulinic Acid to γ-Valerolactone

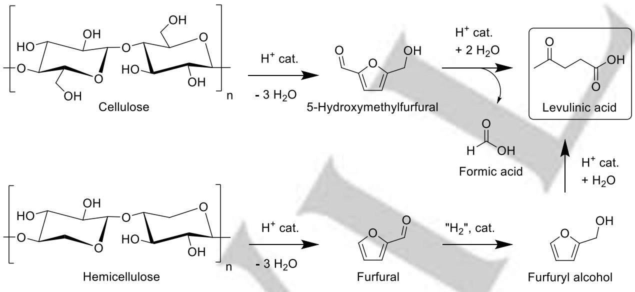
Christian A. M. R. van Slagmaat,[a] Stefaan M. A. De Wildeman *[a]

Abstract: The conversion of levulinic acid to γ-valerolactone was investigated by employing the homogeneous Shvo catalyst (**Ru-1)** and iron Knölker-type catalysts, in order to evaluate the possibility to replace ruthenium with cheap, earth-abundant iron for this catalytic reaction. While the ruthenium-catalyzed reactions readily proceed, the activating agent required for the iron complex was found to interfere with the levulinic acid. This problem could be circumvented by pre-activating the original Knölker complex (**Fe-1)** into the corresponding dicarbonyl mono-acetonitrile iron species (**Fe-3**). The pre-activated iron catalyst deactivated after a few turn-overs in transfer hydrogenation reactions with isopropanol, however, highly improved γ-valerolactone yields were achieved under H_2 pressure to a notable maximum of 570 turn-overs for **Fe-3**. Nevertheless, comparative screening experiments with various solvents and kinetic studies showed that **Ru-1** is still superior over **Fe-3** in terms of catalytic activity.

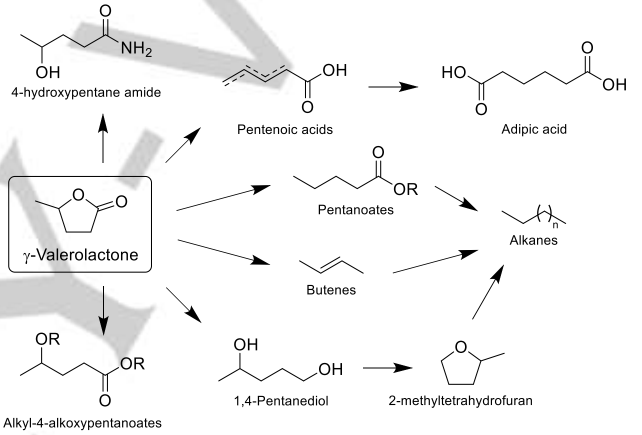
Introduction

Lignocellulosic biomass is emerging as the prime targeted resource for the sustainable production of high-value platform molecules and alternative fuels, for it is the most abundant and renewable carbon-rich material, which is readily accessible on earth.[1] Various biomass-derived feedstocks such as cellulosic carbohydrates (e.g. fructose, sucrose) as well as the hemi-cellulosic contenders (e.g. arabinose, xylose) and their polymeric variants can be utilized for the acid-mediated transformation to 5-hydroxymethylfurfural (HMF)[2] and to furfural,[3] respectively. Subsequent reductive and/or hydrolytic transformations of these compounds then lead to the communal platform molecule levulinic acid (LA) through both chemical pathways, albeit formic acid is a stoichiometric byproduct from HMF (Scheme 1).[4]

LA forms a precursor for a variety specialized compounds, of which several have a commercial application.[5] Notably, products such as maleic anhydride,[5c] succinic acid,[5d] and diphenolic acid[5e] can be used as monomers in the polymer industry. Here, we highlight γ-valerolactone (GVL) as the most versatile derivate from LA.



Scheme 1. Syntheses of levulinic acid from biomass-derived feedstocks.



Scheme 2. Chemical transformations of GVL to high-value compounds.

GVL is proposed as a sustainable liquid, since it features many advantageous characteristics in terms of physical- and chemical properties, and has a low toxicity.[6] It has a high boiling point and low melting point of 204°C and -31°C, respectively, which offer a wide range of operating temperatures suitable for facile liquid transportation and for the use as a green solvent. Its high flash point of 96°C, low vapor pressure of 3.5 kPa at 80°C, and high stability in air and water at neutral pH[7] make GVL a considerably safe chemical for large-scale utility and storage. GVL is non-toxic and naturally found in fruits, has a pleasant herbal odor,[8] and its high solubility in water promotes facile biodegradation. Hence, commercial applications in nutrition, cosmetics and other domestic consumables have already been found for this material.[6c,9] Moreover, enantio-pure GVL can be applied as a chiral building block for pharmaceutical products.[10]

Racemic GVL can also be used as a platform molecule for the synthesis of various fine chemicals and intermediates such as pentanoates,[11] pentenoic acids and butenes,[12] alkanes,[9a] 4-hydroxypentanoates,[13] and 4-hydroxypentane-amide.[14] A multistep transformation via pentenoic acids can yield adipic acid as well.[15] In addition, under certain hydrogenative conditions GVL can be converted to 1,4-pentanediol[16] and/or 2-methyltetrahydrofuran[9a,17], which have gained significant attention for their potential use as bio-based monomer and green solvent, respectively (Scheme 2).

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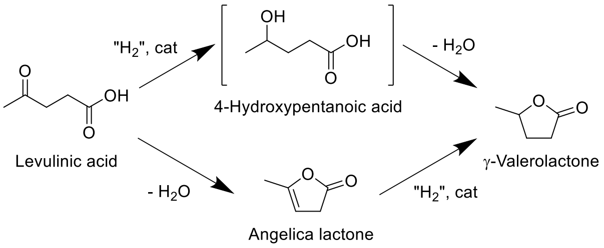
GVL is typically synthesized by the catalytic hydrogenation and dehydration of LA. At high temperatures the gas phase reaction will proceed via the dehydrative cyclization to Angelica lactone,[18] followed by metal-catalyzed reduction of the C=C bond to GVL.[9b,19] On the other hand, the liquid phase carbonyl reduction of LA affords 4-hydroxypentanoic acid, which readily cyclizes to GVL (Scheme 3). The latter route has been subjected to numerous examples of heterogeneous catalysis over the last couple of decades.[20] Notably, supported Ru catalysts were employed,[21] however, examples of Ni,[16,22] Cu,[19b] Zr,[23] Pd,[9b,24] Re,[24,25] Ir,[24] Pt,[9b,24] and Au[26] are also known.



Scheme 3. Possible reductive transformation routes from LA to GVL.

In more recent years an increasing interest for the homogeneously catalyzed LA hydrogenation has emerged.20 Despite the higher difficulty for separation and recycling, homogeneous catalysts can in general operate under milder conditions, and can be structurally tuned to improve their activity and selectivity in catalysis. The majority of the reports on homogeneous catalysis towards GVL involve Ru-phosphine catalysts,[9a,17a-b,27] while several other studies focused on different precious metals such as Ir[27h,28] and Pd.[29] Herein, exceptionally high activities were achieved by Li *et al.* with iridium PNP-pincer complexes (TON = 71000),[28a] by Dutta-Chowdhury *et al.* using Ru(acac)$_3$ and triphos ligands (TON = 73142),[27e] and by Tukacs *et al.* using Ru(acac)$_3$ and diphos ligands (TON = 12740).[27f] Furthermore, several examples of LA hydrogenation towards enantio-selective GVL by using chiral Ru and Ir catalysts have been demonstrated as well, leading to proficient yields and enantio-selectivities.[30]

Although precious-metal catalysts usually render superior catalytic performance, the corresponding precious-metal resources are limited, more costly, and also possess a significant toxicity. Therefore, to make the transition to abundant, cheap, and less toxic base-metals would be a logical step towards sustainable chemistry as well. Within the context of LA hydrogenation to GVL a few reports on the use of iron-based catalysts have appeared.[31] Metzker *et al.* demonstrated a catalytic system based on homogeneous iron nanoparticles formed from $Fe_3(CO)_{12}$ with imidazole or pyridine and using formic acid (FA) as hydrogen donor. In their work certain reaction conditions such as 180°C and 15 hours were essential in order to obtain significant LA conversion, which corresponded with a TON of 24.[31a] Shortly after, Gowda *et al.* reported a similar catalytic concept employing various metal carbonyls, including heterogeneous iron nanoparticles, in the presence of triethylamine or potassium hydroxide. Interestingly, for this transfer hydrogenation of LA under microwave irradiation at 180°C greatly enhanced the reaction rate, leading to a TON of 300 within 20 minutes.[31b] In addition, iron catalysts with a more well-defined structure were mimicked by Fu *et al.*[31c] from the corresponding Ru-triphos examples. Testing of these iron complexes in transfer hydrogenation of ethyl levulinate (EL) rendered a maximum TON of 20.

To our interest, another example of development from a precious-metal catalyst to its iron contender for the transformation of LA to GVL was described for homogeneous catalysts with a cyclopentadienone ligand (Figure 1). Fábos *et al.* reported on the highly selective hydrogenation of LA with Shvo's catalyst (**Ru-1**) and FA as hydrogen source.[32] A robust system with industrially attractive features such as solvent-free conditions, TON's over 1000 leading to complete LA conversion, and multiple recycling steps without loss of activity was achieved. Shortly after, Dai *et al.* applied the structurally related iron analogue, Casey's catalyst (**Fe-2**), in the isopropanol-mediated transformation of EL into GVL.[33] A beneficial effect caused by the addition of certain bases was demonstrated, leading to a maximal TON of 610 under optimized conditions, which resembles the most active catalytic system based on iron for the hydrogenative transformation of EL to GVL.

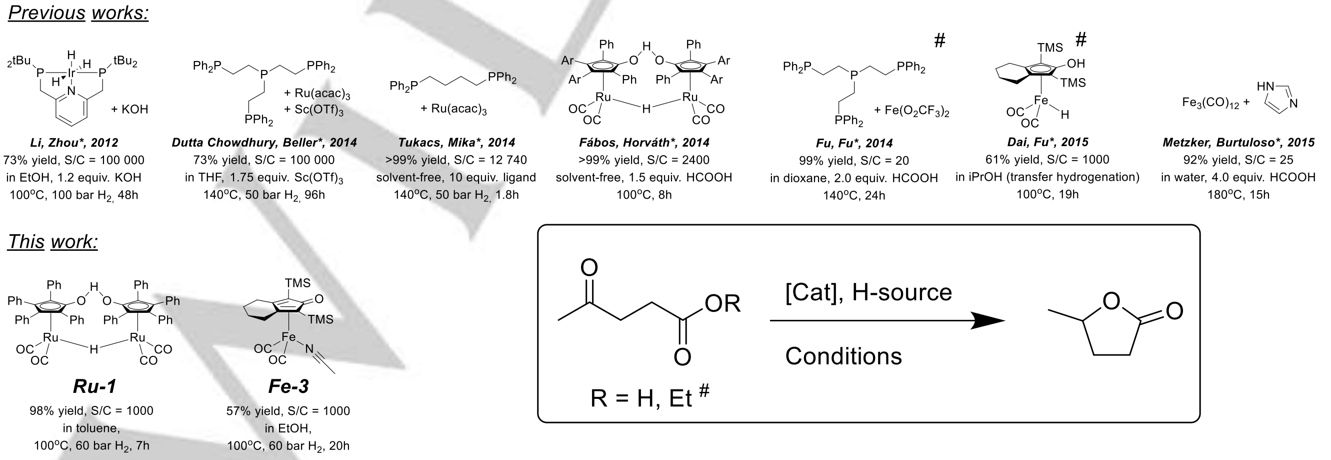


Figure 1. Relevant history on homogeneously catalyzed LA to GVL.

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Inspired by these literature reports, we were interested whether Casey's catalyst is also active for the hydrogenation of non-esterified LA, and to what extent it can compete with Shvo's catalyst. According to a computational study **Fe-2** could be even more active than **Ru-1** for the FA-assisted transfer hydrogenation of LA[34], however, experimental data indicated that **Fe-2** yields more favorable results by using other hydrogen donors such as isopropyl alcohol (IPA) and H_2 for the hydrogenation of EL.[33] The use of these hydrogen donors bears considerable advantages over FA, since they do not produce CO_2 waste during the process, and their use in hydrogenation of non-esterified LA is not reported yet for **Ru-1** and **Fe-2**. In the case that such advances can indeed be realized for efficient and selective LA hydrogenation by these catalysts, this can very well compensate for the use of elaborate and more costly ligand systems in these homogeneous catalysts.

Hence, in this work we describe useful alternative methods for the reductive transformation of LA to GVL. Transfer hydrogenation using IPA as hydrogen source was established with Casey's catalyst, and evaluated against the performance of Shvo's catalyst under equal conditions. Subsequently, steps were undertaken to improve the catalytic performance of both catalysts by altering the reaction conditions.

Results and Discussion

We started our research with the examination of **Ru-1** for the hydrogenation of LA in combination with FA, IPA, or H_2 as hydrogen donor (Table 1).

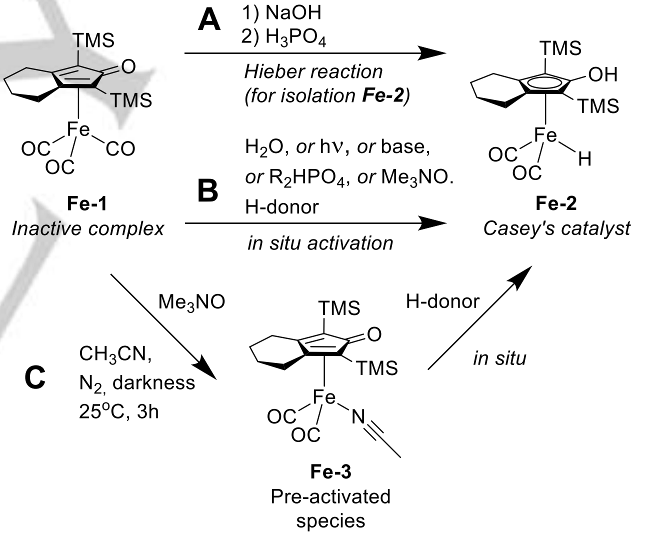
Table 1. Exploratory hydrogenation experiments of LA to GVL with Shvo and Knölker-type catalysts.

Entry	Catalyst	C/S (%)	H-donor (eq. to sub)	Solvent	T (°C)	t (h)	Yield (%) [g]
1[a]	**Ru-1**	1.0	FA (2.0)	toluene	100	20	95
2	**Ru-1**	1.0	IPA (25)	IPA	80	16	99
3[a]	**Ru-1**	1.0	H_2 (50 bar)	toluene	100	16	99
4[b], [c]	**Ru-1**	0.4	IPA (2.5)	toluene	100	24	95
5[c], [d]	**Ru-1**	0.1	H_2 (25 bar)	toluene	100	5	43
6[e], [f]	**Fe-1**	4.0	IPA (25)	toluene	80	20	0
7[a], [f]	**Fe-1**	1.0	H_2 (50 bar)	IPA	100	16	0
8	**Fe-3**	4.0	IPA (25)	IPA	80	20	14
9[b], [e]	**Fe-3**	4.0	IPA (25)	toluene	80	20	38
10[b], [e]	**Fe-3**	1.0	IPA (25)	toluene	100	20	5

[a] 1.0 M LA in solvent. [b] 4:5 IPA / toluene ratio. [c] 2.25 M LA in total mixture. [d] Higher TON and average TOF observed than for entry 4. [e] 0.172 M LA in total mixture. [f] 2 equivalents of Me_3NO added for catalyst activation. [g] GVL yields determined by GC-fid, and calibrated against hexadecane external standard.

Toluene was occasionally used as solvent in order to promote the solvation of **Ru-1**. Initial experiments with a catalyst loading of 1% rendered near-complete conversions to GVL. Herein, potential side products such as 1,4-pentanediol or 2-methyltetrahydrofuran were not observed in GC analysis. However, trace amounts of isopropyl 4-hydroxypentanoate were detected occasionally in transfer hydrogenation with IPA. Under more stringent conditions for catalysis high GVL yields were still observed.

Encouraged by the potential of **Ru-1**, we were interested to test the iron Knölker complex (**Fe-1**) for this transformation as well. Dai *et al.* had reported earlier on the transfer hydrogenation of EL by using Casey's catalyst (**Fe-2**)[33], which is the catalytically active species. They prepared and isolated the highly air-sensitive **Fe-2** by means of an available method: the *Hieber reaction* from **Fe-1** (Scheme 4, route A).[35] Alternatively, **Fe-2** can be generated *in situ* by using water[36], UV-light[37], a base[38], diyl hydrogen phosphate[39] , or Me_3NO[40] as decarbonylative agent for **Fe-1** in the presence of a hydrogen donor (Scheme 4, route B). We preferred to apply the *in situ* method with the conventional use of Me_3NO, because **Fe-1** is tolerant towards air exposure and column chromatography, which allows facile handling and a significantly longer storage time.[40b,41]



Scheme 4. Possible chemical pathways towards Casey's catalyst.

Nevertheless, no activity for the transfer hydrogenation of LA was attained with a relatively high catalyst loading of 4% of **Fe-1** and 2 equivalents of Me_3NO. Even the addition of 50 bar H_2 pressure did not lead to improvement. These negative results prompted us to perform a control experiment involving the stoichiometric addition of Me_3NO to LA, which was observed to turn from colorless to brown. ^{1}H-NMR analysis of this mixture revealed changes in the chemical shifts of the LA signals; notably, the signal for the acidic LA proton shifted from 9.8 ppm to 12.9 ppm. In addition, FT-IR analysis showed the disappearance of the vibration band in the range of 2800 – 3500 cm^{-1} that corresponds with the carboxylic acid functionality of LA.

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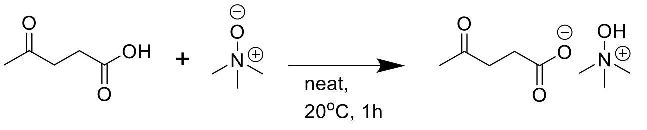
Based on these observations, we suspect an acid-base interaction of the two compounds to take place to form hydroxylammonium levulinate ionic liquid (Scheme 5). Hence, regarding the catalytic experiments it is very likely that Me_3NO interacts faster with the abundantly present LA before it can activate **Fe-1**, which makes the use of Me_3NO incompatible for this hydrogenation reaction.



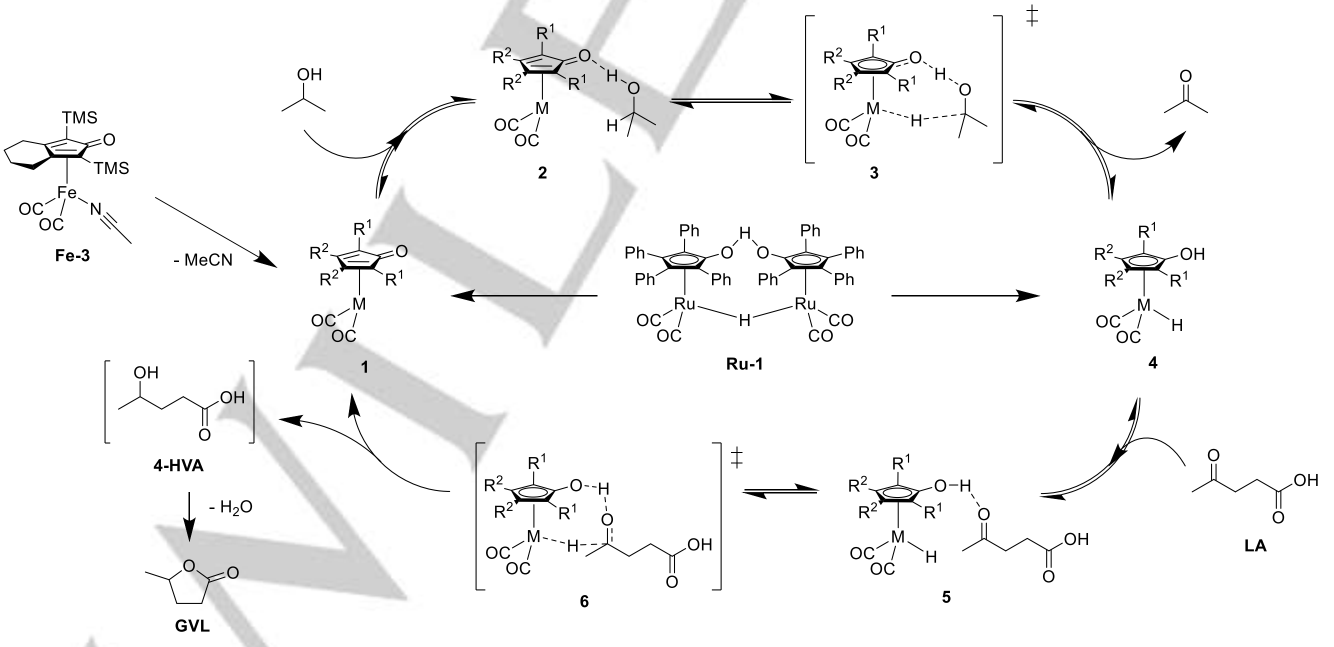
Scheme 5. Proposed ionic liquid formation from LA and Me_3NO.

Fortunately, inspiration for an alternative approach was derived from literature concerning a useful transformation of **Fe-1** into the corresponding dicarbonyl mono-acetonitrile analogue (**Fe-3**). While the first synthesis of **Fe-3** was achieved by Knölker *et al.*[42] via photochemical ligand exchange, Moulin *et al.* devised a more facile treatment of **Fe-1** with Me_3NO in acetonitrile at room temperature for 3 hours (Scheme 4, route C).[39] Compounds like **Fe-3** have been used successfully in (transfer) hydrogenation[41,43] and Oppenauer oxidation[43a] without the aid of an activating agent (e.g. base, Me_3NO).

Moreover, several η_4-cyclopentadienone iron dicarbonyl mono-acetonitrile complexes are also known as versatile platform molecules for the synthesis of the related N-heterocyclic carbene-ligated iron complexes[44], and for the synthesis of specialized iron catalysts with a Si-H or Ge-H tether on the cyclopentadienone ligand.[45]

Since the acetonitrile ligand of **Fe-3** is rather labile in solution, it is readily replaced by alcohols or H_2.[41] Therefore, **Fe-3** can be considered as a 'pre-activated' catalyst, that directly enters the catalytic cycle. In the IPA-mediated transfer hydrogenation of LA **Fe-3** and **Ru-1** follow the same catalytic mechanism (Scheme 6).[32b,35] While the dimeric **Ru-1** structure is split upon solvation and heating into two unequal counterparts – and active and inactive species – **Fe-3** undergoes acetonitrile dissociation to form the inactive species only. The structure of this species is generalized as η^4-cyclopentadienone M(0) dicarbonyl (**1**). Subsequent 'outer-sphere' coordination of IPA onto the non-innocent ligand provides intermediate **2**, which can then engage a concerted hydrogen transfer via transition state **3**. Upon dissociation of acetone the active catalytic species **4** is formed, featuring a generalized η^5-hydroxycyclopentadienyl M(II) dicarbonyl hydride structure. From here, LA can coordinate with its carbonyl group onto the protonated ligand to form intermediate **5**, which then undergoes another concerted hydrogen transfer via transition state **6**. The newly formed 4-hydroxyvaleric acid will dissociate from the catalyst and readily cyclizes into GVL under the release of water, while the inactive species **1** is regenerated.

On the basis of this catalytic mechanism it can be rationalized, that the use of **Fe-3** ultimately leads to the *in situ* formation of **Fe-2**, and should therefore not lead to a different catalytic performance in principle, disregarding the more stable nature of **Fe-3** over **Fe-2**. In this work the avoidance of requiring an activating agent was shown to be essential for acquiring catalytic activity of Knölker-type catalysts towards the LA hydrogenation. Our initial attempts with **Fe-3** rendered a GVL yield of 38% at highest in transfer hydrogenation (Table 1, entry 9).



Scheme 6. The proposed catalytic mechanism for the IPA-mediated transfer hydrogenation of LA to GVL, generalized for both **Ru-1** and **Fe-3**.

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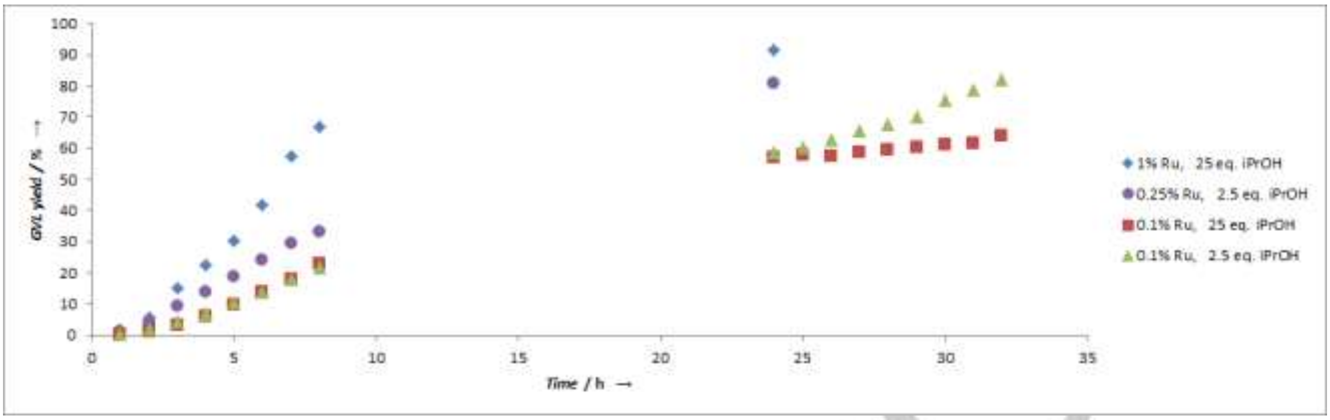
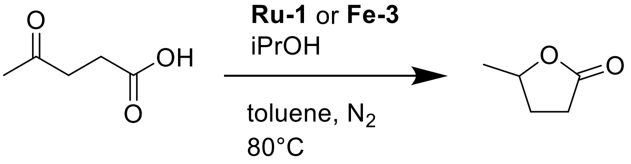


Figure 2. Kinetic profiles for transfer hydrogenation of LA catalyzed by **Ru-1** with isopropanol in toluene (IPA / Toluene ratio = 4:5 v/v). GVL yields were determined by GC-fid analysis, and calibrated against hexadecane external standard.



Scheme 7. Transfer hydrogenation of LA to GVL.

While turn-overs up to 430 could be achieved with **Ru-1**, the activity of **Fe-3** was still limited for transfer hydrogenation of LA. These results prompted us to investigate the kinetic profiles of the corresponding reactions (Scheme 7). Continuous activity was observed for **Ru-1** up to 24 hours, with the catalyst loading ranging from 1% to 0.1% (Figure 2). Turn-over frequencies (TOF) of 9.57 h^{-1} and 18.98 h^{-1} were found for the reactions with 1.0% and 0.25% of **Ru-1**, respectively, during the first 8 hours. The GVL yields obtained after 24 hours did not match with these TOFs, while complete conversion was not achieved either. From these observations it could not be deduced whether the diminished activity and incomplete conversion were the result of catalyst deactivation or a different cause. Therefore, another two experiments using 0.1% **Ru-1** with 25 and 2.5 equivalents of IPA to LA, respectively, were monitored for 32 hours. The kinetic plots of these reactions show considerably equal TOFs of 31.32 h^{-1} and 32.97 h^{-1} initially. However, during the time lapse of 24 – 32 hours, the TOF decreased to 7.82 h^{-1} for the reaction with 25 equivalents of IPA, while a negligible change in TOF to 30.03 h^{-1} was observed in the presence of 2.5 equivalents of IPA. The outcome of these kinetic studies suggests that dilution of the catalytic system (i.e. using 25 equivalents of IPA instead of 2.5 equivalents) is a stronger factor to catalyst inhibition rather than approaching LA and/or IPA depletion over the course of the reaction.

On the other hand, the reactions catalyzed by **Fe-3** showed initially a much lower average TOF of 1.1 h^{-1} during the first 4 hours of the reaction than for **Ru-1** (Figure 3). After 4 hours reaction time the catalytic activity started to decrease as a result of catalyst deactivation, which was further indicated by gradual color changing from yellow to red, and evidenced by the final GVL yields observed after 24 hours. The catalyst lifetime in the reaction also appeared to be independent of the catalyst loading. Hence, **Fe-3** is not suitable for the transfer hydrogenation of LA, in contrast to **Ru-1.**

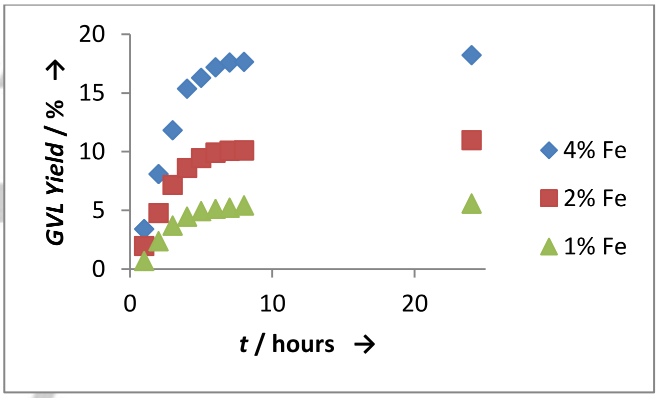


Figure 3. Kinetic profile for transfer hydrogenation of LA catalyzed by **Fe-3** with 25 equivalents of isopropanol in toluene (IPA / Toluene ratio = 4:5 v/v). GVL yields were determined by GC-fid analysis, and calibrated against hexadecane external standard.

In order to both enhance the catalytic performance of **Fe-3**, and to make this chemistry more industrially attractive in terms of solvent-to-substrate ratio, we then decided to investigate the use of H_2 as hydrogen source. The catalytic mechanism of H_2-mediated LA hydrogenation is similar to that of transfer hydrogenation with IPA, as depicted in Figure 6, albeit the catalyst regeneration proceeds slightly different (Supporting Information). An important advantage of using H_2 over transfer hydrogenation is that the reaction is not limited to (mixtures of) IPA or FA as solvent, and does not consume the solvent either. Hence, a selection of various solvents was incorporated in the conversion of LA to GVL under 60 bar H_2 for 20 hours, with a substrate concentration of 10 v% (Scheme 8). The typical reaction temperature of 100°C was selected, since Dai *et al.* demonstrated optimal catalytic performance with **Fe-2** under such condition, but severe catalyst inhibition at elevated temperature.[33]

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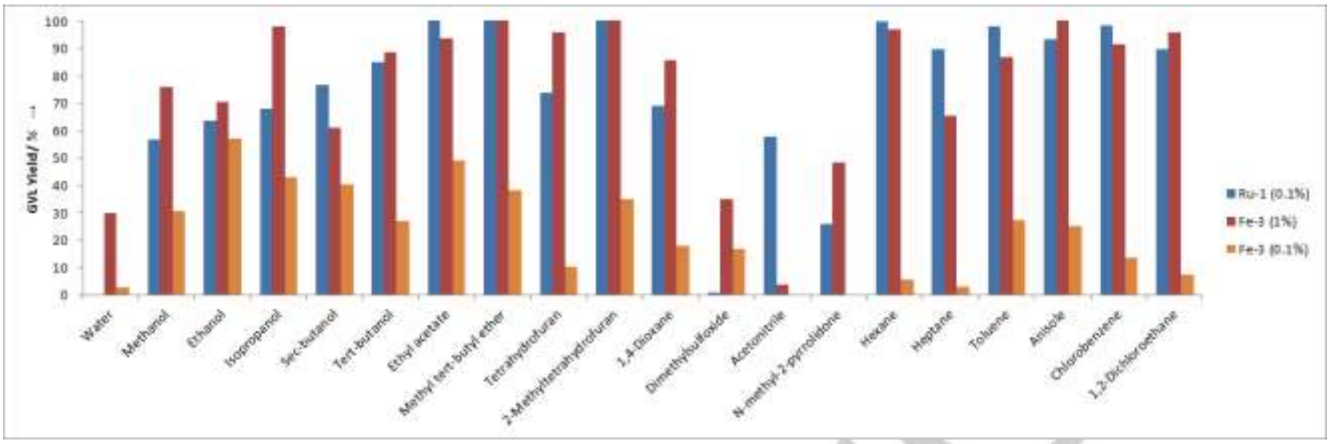
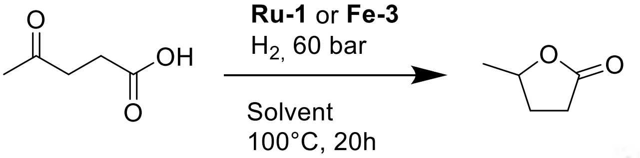


Figure 4. Solvent screening for the catalytic hydrogenation of LA to GVL. The catalyst loadings are expressed in mol% metal atoms to the substrate for both **Ru-1** and **Fe-3**. 100 μL LA was dissolved in 900 μL solvent. All GVL yields were determined by GC-fid analysis, and calibrated against hexadecane external standard.



Scheme 8. H_2-hydrogenation of LA to GVL.

Ru-1 and **Fe-3** with catalyst loadings of 0.1% and 1%, respectively, were employed in the combinatorial screening (Figure 4). The results for 0.1% of **Ru-1** always show moderate to complete conversion of LA with exception of the apparent anti-solvents: water and DMSO. Several side products were observed as well in different abundancies, though always below a combined 8% yield, depending on the applied solvent. These were identified as 1,4-pentanediol, 2-methyltetrahydrofuran and levulinate esters. However, the reactions in toluene and 1,2-dichloroethane produced GVL with a selectivity over 99%.

To our delight, the performance of 1% catalyst loading of **Fe-3** was tremendously improved with respect to the transfer hydrogenation results. GVL yields exceeding 80% were notably achieved by using solvents such as alcohols, ethers, hydrocarbons, and chlorinated compounds. Upon decreasing the catalyst loading of **Fe-3** to 0.1%, the finer solvent affinities were exposed. Notably, aromatics and alcohols were identified as the optimal solvents for **Ru-1** and **Fe-3**, respectively. Herein, the highest activity observed for **Fe-3** rendered 570 turn-overs, and was obtained in ethanol. Based on the incomplete LA conversions by **Fe-3** at 0.1% catalyst loading, we interpret the found activity of **Fe-3** in ethanol as its highest turn-over number possible for the LA hydrogenation. However, several solvents (i.e. ethyl acetate, methyl tert-butyl ether, 2-methyl-tetrahydrofuran, hexane, and chlorobenzene) in combination with **Ru-1** do achieve complete LA conversion at 0.1% catalyst loading, which indicates that even higher turn-over numbers for **Ru-1** are likely possible.

Regarding **Fe-3**, its activity for LA hydrogenation under 60 bar H_2 pressure is slightly lower in comparison with the transfer hydrogenation example of Dai *et al.*, for which a maximal turn-over of 610 was found. However, it must be strictly remarked that Dai *et al.* obtained this result by employing EL as substrate, which does not have the free carboxylic acid functionality.

Next, the screening combinations of **Ru-1** and **Fe-3** at 0.1% catalyst loading, with respect to the metal concentrations, in toluene were selected for upscale experiments in a 100 ml autoclave, and were monitored for 7 hours (Figure 5). The optimal result for 0.1% **Fe-3**, i.e. in ethanol, was reproduced and monitored as well. The resulting kinetic reaction plots reveal that **Ru-1** achieves complete conversion after 7 hours. On the other hand, the final GVL yields, achieved by **Fe-3** in toluene and ethanol, equal 19.7% and 41.6%, respectively. These values are significantly lower than the GVL yields observed in the corresponding solvent screening experiments, which were run for 20 hours. Since the kinetic reaction plots of **Fe-3** do not show a significant decrease of reactivity over time, it is evident that **Fe-3** requires a reaction time longer than 7 hours in order to achieve its maximum yield.

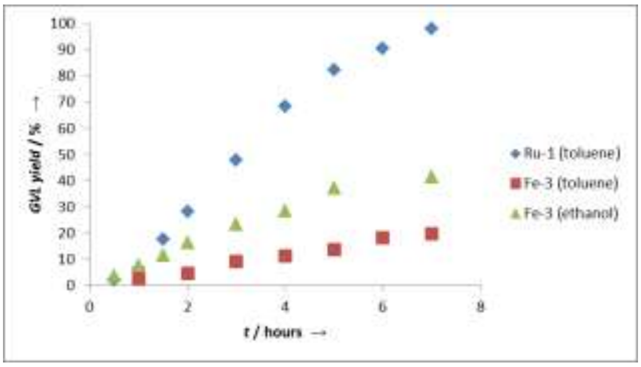


Figure 5. Kinetic reaction profiles for catalytic H_2-hydrogenation of LA in a specific solvent (i.e. toluene or ethanol). The catalyst loadings count 0.1 mol% metal atoms to the substrate for both **Ru-1** and **Fe-3**. GVL yields were determined by GC-fid analysis, and calibrated against hexadecane external standard.

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However, the GVL yields observed in the screening are merely an approximate 1.4 times higher than the final yields derived from the autoclave experiments, while the reaction time was nearly 3 times longer. Based on these facts, we infer that deactivation of **Fe-3** is still inevitable despite the improved conditions for its use as catalyst in this reaction. Thus, our results demonstrate that **Fe-3** can achieve an appreciable catalytic activity under the optimized conditions and careful choice of solvent, but is ultimately outcompeted by **Ru-1** in the hydrogenation of LA to GVL.

Conclusions

In summary, we have established selective hydrogenation of LA to GVL by employing homogeneous ruthenium and iron catalysts with IPA as well as H_2 as hydrogen donors. While catalytic activity for Shvo's catalyst (**Ru-1**) was readily achieved, Knölker's complex (**Fe-1**) did not render any turn-overs initially. The activating agent for **Fe-1** (i.e. Me_3NO) was found to interfere with LA, which prevented *in situ* activation. This problem was circumvented by pre-activating **Fe-1** into the corresponding dicarbonyl mono-acetonitrile derivative (**Fe-3**). Hence, we demonstrated the first example of 'Knölker-catalyzed' hydrogenation of non-esterified LA. Kinetic reaction profiles for transfer hydrogenation with IPA showed **Ru-1** to outcompete **Fe-3** in terms of activity as well as catalyst lifetime. However, under H_2 pressure the catalytic performance of **Fe-3** was notably improved within certain dependence of the solvent. Kinetic studies conducted under H_2 pressure have demonstrated that **Fe-3** can now yield GVL in the same order of magnitude within the same reaction time, although its catalytic performance and stability remains inferior to that of **Ru-1**.

Experimental Section

Materials & Methods:
Levulinic acid, trimethylamine-oxide, and N-methyl-N-trimethylsilyl-trifluoro acetamide were purchased from Sigma Aldrich. All other chemicals were purchased from miscellaneous sources. Complex syntheses of **Ru-1**, **Fe-1**, and **Fe-3** were performed in accordance with the corresponding literature procedures.[44,39] Standard Schlenk techniques were applied for preparations involving inert atmosphere and/or vacuum. All solvents used in catalytic reactions were degassed by bubbling through with nitrogen gas for 30 minutes, and were optionally stored under inert atmosphere before use. Unless otherwise stated, all commercial chemicals were used without further purification. NMR spectra were recorded on a Bruker Avance AV 300 spectrometer (300 MHz) at 298 K. Infra-red spectra were recorded on a Shimadzu Miracle 10 FT-IR spectrometer in the range of 450−4000 cm^{-1}. GC measurements were performed by using a Shimadzu 2010 Plus gas chromatograph equipped with a Supelco SLB-5 column (length = 30 m, internal diameter = 0.32 mm, and film thickness = 0.50 mm), and with a flame ionization detector. GC method: 80 °C, 4 min; 15 °C min^{-1} to 225 °C; 30 °C min^{-1} to 300, and 300 °C, 1 min.

General syntheses of catalysts:
*Shvo's catalyst (**Ru-1**)* [46]*:*
A solution of $Ru_3(CO)_{12}$ and 3.0 equivalents of 2,3,4,5-tetraphenylcyclopentadienone in dry toluene was refluxed for 3 days under a nitrogen atmosphere. The resulting mixture was concentrated *in vacuo*, and separated by column chromatography on silica using hexane/ethyl acetate (100:0 to 70:30) as eluent. A pale yellow solid corresponding to the monomeric (2,3,4,5-tetraphenylcyclopentadienone) ruthenium tricarbonyl complex was obtained, and refluxed in isopropanol under a nitrogen atmosphere for 3 hours in order to furnish the actual catalyst (77% yield). Spectroscopic NMR and IR analysis was in accordance with literature data.

*Knölker's catalyst (**Fe-1**)* [41]*:*
A solution of $Fe_3(CO)_{12}$ and 3 equivalents of 1,8-bis(trimethylsilyl)octa-1,7-diyne in dry toluene was refluxed for 3 days under a nitrogen atmosphere. The resulting mixture was concentrated *in vacuo*, and separated by column chromatography on silica using hexane/ethyl acetate (100:0 to 70:30) as eluent (85% yield). Spectroscopic NMR and IR analysis was in accordance with literature data.

*Pre-activated iron dicarbonyl mono-acetonitrile complex (**Fe-3**)* [41]*:*
The parent (1,3-bis(trimethylsilyl)-4,5,6,7-tetrahydro-2H-inden-2-one)iron tricarbonyl complex, **Fe-1**, was dissolved in dry acetonitrile under a nitrogen atmosphere. A solution of 1.5 equivalents trimethylamine-*N*-oxide in dry acetonitrile was added, and the resulting mixture was stirred for 3 hours at room temperature and in darkness. A precipitate was readily afforded, and further induced by storage at -20°C. The precipitate was isolated by decantation and washing with cold diethyl ether (90% yield). Spectroscopic NMR and IR analysis was in accordance with literature data.

General procedures for catalytic experiments:
Transfer hydrogenation:
The catalyst was loaded into an oven-dried Schlenk flask equipped with a reflux cooler, and the system was purged with three vacuum/nitrogen cycles. The degassed solvent and other reagents were brought into one liquid phase, which was then added under outflow of nitrogen. The Schlenk flask was immersed into a pre-heated oil bath and reacted in accordance with the indicated conditions. Optionally, samples for kinetic studies were collected by using a syringe with a long needle under outflow of nitrogen.

H_2 hydrogenation:
High throughput screening reactions were performed by using a custom apparatus; the Premex A96 reactor. Reaction samples were prepared by loading the catalyst and a stirring magnet in designated 5 mL crimp-cap vials from *Agilent Technology*, which were placed inside a Schlenk flask subsequently, and were purged with three vacuum/nitrogen cycles. The degassed solvent (900 μL) and LA (100 μL) were brought into one liquid phase, which was then added under outflow of nitrogen. The vials were capped under outflow of nitrogen with aluminum crimp caps equipped with a PTFE septum. The vials were placed into the reactor, which pierced each septum with a needle for gas regulation upon closure. The reactor was purged with 3x 10 bar nitrogen and with 3x 10 bar H_2. Subsequently, the reactor was loaded with 50 bar cold pressure of H_2, and was heated to 100°C (pressure increased to 60 bar) for 20 hours.

For kinetic experiments, a 100 mL autoclave equipped with a sampling outlet was charged with the reaction components (i.e. 0.050 mmol catalyst, 45 mL solvent, 50.0 mmol LA), and was purged with 5x 3 bar nitrogen pressure and with 3x 10 bar H_2 pressure. Next, the desired H_2 pressure was selected, mechanical stirring at 700 rpm was initiated, and the autoclave was heated up to 100°C within 4 minutes.

Analysis:
GC samples were prepared by dissolving aliquots of the reaction mixtures with known concentrations in 1.00 mL of a stock solution of 0.1 v% hexadecane (external standard) in DCM. An excess of 25 – 100 μL of N-methyl-N-trimethylsilyl-trifluoro acetamide was added for derivatization of unreacted LA; complete derivatization was always confirmed by the absence of the signal for free LA in the GC analyses. GVL concentrations were calibrated against hexadecane for quantification.

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Keywords: comparative screening • homogeneous catalysis • hydrogenation • levulinic acid • pre-activation

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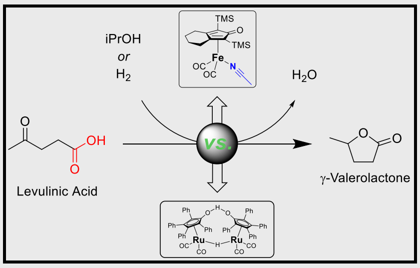
FULL PAPER

LA to GVL with Ru vs. Fe:
The (transfer) hydrogenation of non-esterified levulinic acid to γ-valerolactone using isopropanol or hydrogen gas was established with the Shvo catalyst and a modified Knölker-type catalyst. This reaction was further optimized and investigated in a comparative way regarding the structurally related ruthenium and iron catalysts.



*C. A. M. R. van Slagmaat, S. M. A. De Wildeman**

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A Comparative Study of Structurally Related Homogeneous Ruthenium and Iron Catalysts for the Hydrogenation of Levulinic Acid to γ-Valerolactone

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