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ARTICLE

Direct asymmetric reduction of levulinic acid to gamma-valerolactone: synthesis of a chiral platform molecule

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József M. Tukacs,[a] Bálint Fridrich,[a] Gábor Dibó,[b] Edit Székely[a] and László T. Mika[a,*]

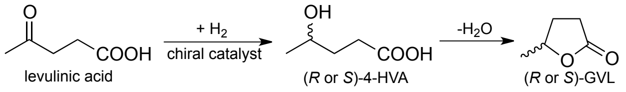
Levulinic acid was directly converted to optically active (*S*)-gamma-valerolactone, a proposed biomass-based chiral platform molecule. By using SEGPHOS ligand-modified ruthenium catalyst in methanol as co-solvent, eventually, 100% chemoselectivity, and 82% enantioselectivity were achieved. The effect of catalyst composition and reaction parameters on the activity and selectivity were investigated in details. The conversion of a "real" biomass derived levulinic acid to optically active GVL without decreasing the enantioselectivty was also demonstrated.

Introduction

Currently, one of the most pressing challenges for the chemical industry is the gradual replacement of fossil resources with renewable ones. Since it is difficult to estimate the exact reserves of fossil resources, which provides more than 95% of our carbon based chemicals, the development of novel strategies to provide carbon-based building blocks should be accelerated. The selective biomass transformation, as one of most preferred solution, offers several alternative production of value-added chemicals and has led to the identification of key platform molecules *e.g.* 5-hydroxymethyl furfural,[1] levulinic acid (LA),[2] and γ-valerolactone (GVL),[3] which could replace the currently used fossil-based building blocks or serve as a "green" and renewable feedstock for their production. Due to its outstanding physical and chemical properties, Horváth *et al*. have first suggested GVL as a sustainable liquid.[3] Later, it was shown that GVL can be used for the production of fuels,[4] fuel additives,[3] alkanes,[5] and fine chemicals.[6] In addition, GVL was also utilized as a green solvent for the conversion of carbohydrates to LA and subsequently to GVL.[7]

Obviously, the most efficient protocol for the manufacture of GVL is the conversion of the carbohydrate content of biomass[7b,8] including cellulose[9] and/or biomass wastes[10] to LA followed by the selective hydrogenation of LA to 4-hydroxyvaleric acid (4-HVA) by using either heterogeneous[11] or homogeneous catalysis.[6f,12,13] Recently, several catalytic systems have been reported for the conversion of LA to GVL. However, the asymmetric reduction of LA to optically active 4-HVA, which subsequently turns to optically active GVL *via* ring closure dehydration (Scheme 1) has not been reported yet. The one-pot conversion of LA to optically active GVL could result in a green process representing the elegant approach of biomass waste valorization to a value-added chiral building block.

Optically active γ-lactones occur naturally[14] and can be used as chiral building blocks for the synthesis of several biologically active compounds.[15] The optically active GVL can be found in the synthetic schemes of several agricultural or pharmaceutical compounds[16] *e.g.* the aggregation pheromone Sulcatol,[17] the antihypertensive WS75624B,[18] the antileukemic Steganacin,[19] and the insecticide Geodiamolide (Fig. 1).[20]



Scheme 1

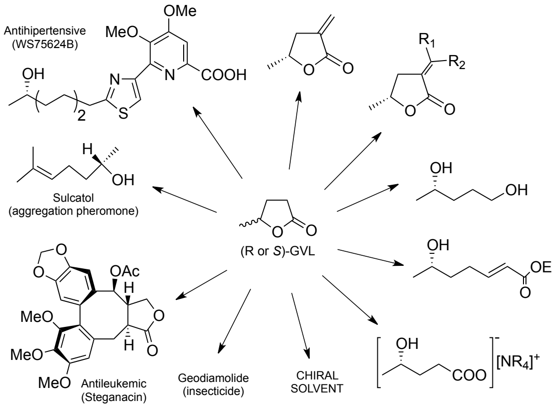


Fig. 1 Selected application of optically pure GVL.

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[a] Department of Chemical and Environmental Process Engineering, Budapest University of Technology and Economics, Budapest, Hungary Fax: +36 1 463 3197; L. T. Mika: Tel.: +36 1 463 1263, e-mail: laszlo.t.mika@mail.bme.hu.

[b] János Selye University, Faculty of Education, Department of Chemistry, Bratislavská str. 3322, Komárno SK-94501, Slovakia.

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Accordingly, we propose here that the enantiopure GVL can be used as a promising chiral starting material for the synthesis of fine chemicals and other valuable intermediates *i.e.* chiral pentane-1,4-diol, 5-methyl-3-methylenedihydrofuran-2(3*H*)-one and its derivatives, unsaturated esters, and ionic liquids *etc*. (Fig. 1). Since chiral solvents are of utmost importance in chiral recognition,[21] due to its good solvating properties, the optically active GVL could serve as a renewable and non-toxic chiral reaction media in asymmetric synthesis, as well. It was demonstrated that chiral ionic liquids were successfully applied in asymmetric synthesis.[22] GVL can easily be converted to ILs,[6a,b] the application of chiral 4-hydroxyvalerate-based ionic liquids are also proposed as a chiral reaction media is proposed, as well.

The enantioselective reduction of prochiral substrates including ketones is of utmost importance for the synthesis of optically pure substances both on laboratory and industrial scale, as well.[23] Although, several catalyst systems have been developed for the asymmetric reduction of the carbonyl group, most of them were tested on aromatic ketones *e.g.* acetophenone. It was revealed that the enantioselectivity could be dramatically influenced by the functional groups in the vicinity of the carbonyl group.[23d] Compared to the reduction of aromatic substrates, reduction of aliphatic ketones resulted in slightly lower yield and small *ee* value.[24,25] Several methods have been developed for the reduction of the carbonyl group of γ-oxo carboxylates; however, to our best knowledge, no direct asymmetric hydrogenation of the free carboxylic acid has been reported yet.

Karnik *et al.* reported the stoichiometric synthesis of optically active γ-lactones from (*S*)-menthyl or (*S*)-bornyl esters of 4-carboxylates by using $NaBH_4$, however, the yield of (*S*)-GVL was moderate.[26] Hilterhaus *et al.* suggested a chemoenzymatic reaction sequence to produce (*S*)-GVL *via* ethyl levulinate (EL). Expectedly, due to the enzymatic conversion, the *ee* values and overall yields were high (~90%).[27] So far, a few studies on the reduction of alkyl levulinates in the presence of Ru-based catalysts to optically active GVL were published.[28,29] Vinogradov *et al.* reported the Ru/BINAP-catalyzed asymmetric hydrogenation of LA by applying HCl in ethanol under 60 bar H_2 at 60 °C.[29a] It was also shown that, instead of the reduction of LA, the *in situ* formed EL was reduced. Jacobs *et al.* demonstrated that the bakers' yeast assisted reduction of alkyl levulinates and subsequent HCl-catalyzed hydrolysis of the corresponding hydroxy esters resulted in (*S*)-GVL with a yield of 73%.[30] It is important to note that the ester hydrolysis step requires mineral acid. Noteworthily, HCl is released from the reaction to the atmosphere resulting in serious environmental concerns or rather, the aqueous HCl is extremely corrosive.

We report here the direct conversion of levulinic acid to optically active γ-valerolactone *via* asymmetric hydrogenation using various Ru-based catalyst systems.

Results and discussion

Firstly, concerning the ring opening and/or closing, the stability of the chiral center of GVL is a crucial point for further synthetic schemes. The ring opening of GVL under acidic conditions leads to the formation of 4-HVA. Subsequently, 4-HVA forms GVL *via* ring closure under neutral condition. Accordingly, the stability of the chiral center of GVL is of utmost importance and was investigated by using ^{18}O-labelling technique as follows: 0.3 mmol of (*S*)-GVL having 98.5% *ee* was treated with 2.7 mmol of $H_2{}^{18}O$ (97 atom % ^{18}O) in the presence of 1 mmol HCl at room temperature. The *in situ* NMR showed peaks at 176.6 ppm in ^{13}C-NMR, and 1.2 ppm (3H, d, J = 5.9 Hz), 1.6 ppm (2H, m), 3.75 ppm (1H, s, J = 5.9 Hz) in ^{1}H-NMR spectra. These data proved the equilibrium reaction between GVL and [4-HVA]. To neutralize the solution, equimolar amount of sodium hydroxide was added to the reaction mixture after 1 h. The incorporation of ^{18}O-isotope into the (*S*)-GVL was verified by GC-MS. Chiral GC analysis of ^{18}O-labelled GVL established that the ring opening and reclosing had no effect on the enantiopurity of (*S*)-GVL, as expected (Fig. 2).

It was demonstrated, that LA was efficiently converted to GVL in the presence of bidentate phosphine-modified Ru catalysts without any added solvent and TOF = 100–21000 h^{-1} values were obtained. In the case of BINAP ligand, 98.6% conversion was achieved with TOF = 6978 h^{-1}.[12c] Firstly, reduction of LA (1 mL, 9.85 mmol) was attempted by using a catalyst *in situ* formed from $Ru(acac)_3$ (1.56 μmol) and (*R*)-BINAP (15.6 μmol) under 60 bar H_2, at 140 °C and 500 rpm. After 12 h, full conversion was obtained with *ee* = 26%. The reaction was repeated in a 120-mL Parr high-pressure reactor (equipped with a propeller stirrer) loaded with 30 mL (293.02 mmol) of LA, 0.023 mmol of $Ru(acac)_3$ and 10-fold excess (0.233 mmol) of (*R*)-BINAP under identical conditions to monitor the possible change of *ee* with increasing conversion (Fig. 3). By using the propeller stirrer, the rate of hydrogen transfer from gas to liquid phase was significantly higher. Thus, the reaction time required for full conversion of LA to GVL was decreased to 2.5 h, however, it was perceived that the *ee* value was almost the same (*ee* = 23%). To conclude, the *ee*

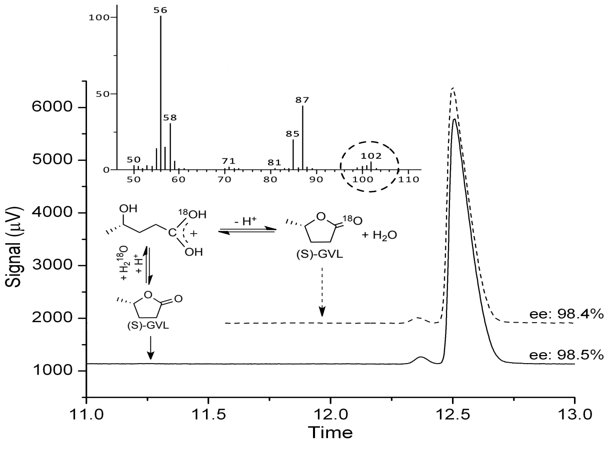


Fig. 2 Chromatograms of (*S*)-GVL before and after ring opening, and MS spectrum of ^{18}O (*S*)-GVL.

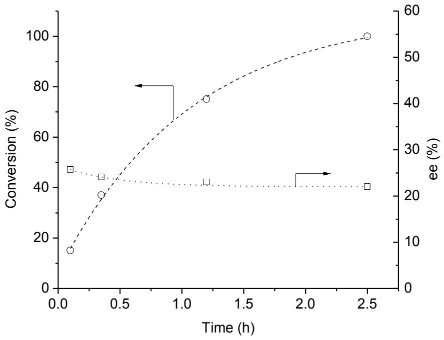


Fig. 3 Solvent free asymmetric reduction of LA to optically active GVL. Conditions: [Ru] = 7.6×10^{-4} mol dm $^{-3}$, [(*R*)-BINAP] = 7.6×10^{-3} mol dm $^{-3}$, T = 140 °C, p = 60 bar, RPM = 600

Table 1 Conversion rates and ee values obtained for the hydrogenation of LA to GVL in the presence of various SEGPHOS-based Ru catalysts.

Entry	Catalyst	Conv (%)	*ee*
1	(*R*)-$RuCl_2$[(*p*-cymene)(SEGPHOS)]	100	18
2	(*R*)-$RuCl_2$[(*p*-cymene)(DM-SEGPHOS)]	100	9
3	(*R*)-$RuCl_2$[(*p*-cymene)(DTMB-SEGPHOS)]	95	13
4	$RuCl_2$[(*S*)-(DM-SEGPHOS)][(*S,S*)-DPEN]	100	16
5	$RuCl_2$[(*S*)-(DM-SEGPHOS)][(*S*)-DAIPEN]	100	13
6	$Ru(OAc)_2$((*S*)-SEGPHOS)	100	12
7	(*S*)-[(RuCl(SEGPHOS))$_2$(μ-Cl)$_3$][NH_2Me_2]	100	56

Reaction conditions: 1 mL (9.8 mmol) LA in 1.4 mL MeOH, T = 140 °C, t = 20 h, p = 60 bar, catalyst: 0.004 mmol, S/C = 2400.

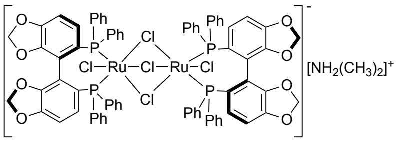


Fig. 4. (*S*)-[(RuCl(SEGPHOS))$_2$(μ-Cl)$_3$][NH_2Me_2] catalyst (**3**)

values were not affected by the conversion rate. Moreover, addition of (*R,R*)-1,2-diphenyl-1,2-diaminoethane (*R,R*-DPEN) neither had significant effect on the final *ee* values. When 9.85 mmol of LA was reduced in the presence of 0.001 mmol $Ru(acac)_3$, 0.01 mmol (*R*)-BINAP, and 0.02 mmol of (*R,R*-DPEN), similarly 26.4 % *ee* was obtained under identical conditions. Although the *ee* value was moderate, to our best knowledge, so far the solvent-free asymmetric reduction of levulinic acid to optically active GVL has not been reported yet.

It was established that *in situ* generated and preformed complexes can be used for the reduction, however, the latter showed higher activity and selectivity.[23d] Noyori *et al.* demonstrated that dialkyl ketones *e.g.* 4-phenylbutan-2-one was reduced with *ee* = 51%[23d] by applying XylBINAP/(*S,S*)-DPEN-modified Ru catalyst (**1**) (ESI Fig. S1**)**. Significantly higher selectivity with opposite sense of asymmetric induction was achieved for the $RuCl_2$[(*S*)-XylBINAP][(*R,R*)-DAIPEN] (**2**) (ESI Fig. S1**)** catalyzed reduction of cyclopropyl ketones.[31] Accordingly, we performed the reduction of LA in the presence of **1** and **2**. Firstly, in the absence of catalyst no conversion was detected demonstrating the inactivity of the high-pressure Hastelloy-C reactor. When LA was used as substrate and solvent without any additive, all substrates were converted to GVL using **1**. However, the enantioselectivity was modest (*ee* = 11%). Similarly, *ee* = 13% was achieved when methanol was used as a co-solvent (ESI† Table S1, entries 1-2). Importantly, the composition of the reaction mixture was continuously changing from LA to LA/GVL/H_2O and finally a GVL/H_2O mixture was obtained. When different alcohols were used as co-solvents, either with or without a base, the *ee* was not influenced significantly (ESI† Table S1, entries 4–10). Although, by replacing DPEN to DAIPEN, higher enantioselectivity was proposed,[23d] however, in our hand no further increase could be achieved (ESI† Table S1, entry 4).

By using bidentate phophine-modified Ru catalyst, both the electronic and steric effects of the bis(diarylphosphine) backbone significantly enhanced the reactivity, and improved the stereorecognition.[32] Recently, Saito *et al.* introduced a new ligand family (SEGPHOS) with smaller dihedral angle representing an outstanding catalytic performance for the reduction of carbonyl compounds.[33] By using a substrate/catalyst ratio of 1000, ethyl levulinate was hydrogenated at 50 °C for 20 h, and ethyl 4(*R*)-hydroxypentanoate was obtained with a yield of 99%.[33b] The conversion of LA to GVL in methanol, as the preferred solvent,[33b] was screened and further improved by using various SEGPHOS-based Ru catalysts (Table 1). When mononuclear (*R*)-$RuCl_2$[(*p*-cymene)(SEGPHOS)] precursor was applied, full conversion was achieved with *ee* = 18 % (similar yields were obtained under solvent-free conditions where BINAP-based catalysts were used). When various substituents on the SEGPHOS ligand were used, a small decrease on the *ee* values was observed (Table 1, entries 1–3). Comparing DPEN and DAIPEN analogues of Noyori's catalyst, no significant change in the *ee* was detected (Table 1, entries 4–5); similar results were observed when (*S*)-$Ru(OAc)_2$(SEGPHOS) precursor was applied. However, the use of (*S*)-[(RuCl(SEGPHOS))$_2$(μ-Cl)$_3$][$NH_2(CH_3)_2$] (**3**) (Fig. 4) precursor resulted in a dramatic increase in the enantioselectivity. The reduction of 9.8 mmol of LA in the presence of 0.004 mmol **3** leads to the complete formation of (*S*)-GVL with of *ee* = 56% (Table 1, entry 7), that was 4.5 and 2.5 times higher than that obtained by the use of Noyori's catalyst in methanol or Ru/BINAP catalyst under solvent-free condition.

Since the asymmetric induction could be strongly affected by the solvent, we screened the conversion of LA (9.8 mmol) to GVL by using various alcohols, methylene chloride and supercritical CO_2 at 60 bar H_2 and 140 °C. Although, full conversion was obtained in all cases, the enantiomeric excess varied in a wide range depending on the solvent (Fig. 5). Without any added solvent, no chiral induction occurred, and negligible values were obtained when methylene chloride or supercritical carbon-dioxide was used. However, significantly higher enantioselectivities were obtained in alcohols, a protic reaction media, in accord with literature data concerning the reduction of non-aromatic ketones (Saito *et al*).[33] Hydrogenation of 9.8 mmol LA in 1.4 mL methanol resulted in *ee* = 56% (Fig. 5). When 9.8 mmol of LA was reduced in 0.7 mL methanol in the presence of 0.004 mmol of **3**, the *ee* decreased to 43%. By using 3 mL methanol, the *ee* was 53%. Supposedly, methanol acts as co-solvent and may have an effect on the formation and stabilization of the catalytically active species. Importantly, the ring closure of 4-hydroxypentanoic acid resulted in the formation of equimolar amount of water and GVL. Accordingly, the application of a water-free solvent is inefficient, however the initial water content may have an effect on the *ee*. When, the reaction was performed in 96% ethanol, a slight decrease of *ee* (37%) was found.

Subsequently, the effect of the reaction temperature on the activity and selectivity was investigated (Fig. 6). The Ru-catalyzed asymmetric reductions are usually performed in a range of 20–40 °C, although, the SEGPHOS-based catalysts operate at higher (65 °C) temperature. Noteworthily, hydrogenation of LA was unsuccessful below 80 °C by homogeneous Ru catalyst, and minimum 140 °C was necessary to get reduction product.[12a] Interestingly, ethyl and methyl levulinate was converted to the corresponding alcohols at 30 °C[28] and 60 °C,[29] respectively. When, 9.8 mmol LA in 1.4 mL MeOH was reduced, negligible conversion (8%) and *ee* (3%) was observed at 80 °C and 60 bar H_2 for 20 h; and only a slight increase was observed at 120 °C. Although, full conversion was obtained over 130 °C, the maximum *ee* value was 56% at 140 °C (Scheme 2, (a)).

Supposedly, the reduction of LA to GVL in the presence of HCl with Ru-BINAP-HCl system undergoes via *in situ* formation of ethyl levulinate in ethanol. Although no *in situ* spectroscopic data were included, ethyl levulinate, ethyl 4-hydroxyvalerate and GVL were detected in the product mixture.[29a] When LA was reduced by catalyst **1**, the concentration of methyl levulinate in the final reaction mixture was below the detection limit. For comparison, methyl levulinate (9.8 mmol) in methanol (1.4 mL) was reduced under identical conditions resulting in full conversion and with *ee* = 27% *cf.* Scheme 2 (b) which is significantly lower than the value obtained for LA (56%). In addition, the methyl levulinate was reduced at lower temperature. Although, the *in situ* equilibrium formation of methyl levulinate from methanol and LA cannot be completely excluded, however if LA was hydrogenated to (*S*)-4-hydroxyvaleric acid it will spontaneously dehydrate to (*S*)-GVL. Unexpectedly, for the reduction of LA, significant improvement in enantioselectivity was detected by varying the Ru concentration between 0.002–0.016 mol dm^{-3} (Fig. 7.). For example, 9.8 mmol LA was hydrogenated in 1.4 mL of methanol as co-solvent at [Ru] = 0.016 mol dm^{-3} at 60 bar and 150 °C, full conversion was obtained with *ee* = 82% for (*S*)-GVL. This selectivity fits to the *ee* values obtained for dialkyl ketones, however further increase of the amount of catalyst had no effect on the selectivity.

The use of "real" biomass based levulinic acid to chiral γ-valerolactone is fundamentally important to show and establish that no "chemical" (product or side product) formed, which could interfere with chiral induction of the catalyst. In order to investigate the catalyst's applicability, firstly D-

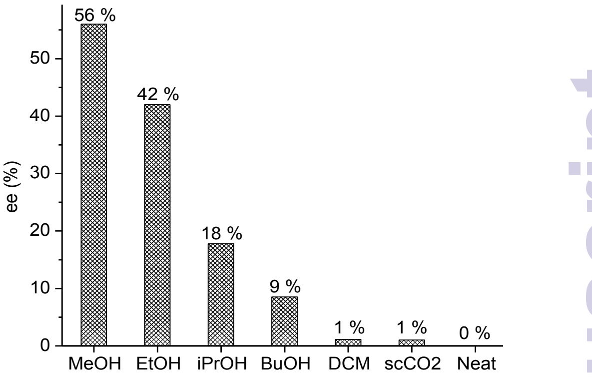


Fig. 5 Asymmetric hydrogenation of LA to GVL in different solvents. Conditions: [Ru] = 0.004 mol dm $^{-3}$, *T* = 140 °C, *p* = 60 bar, RPM = 400

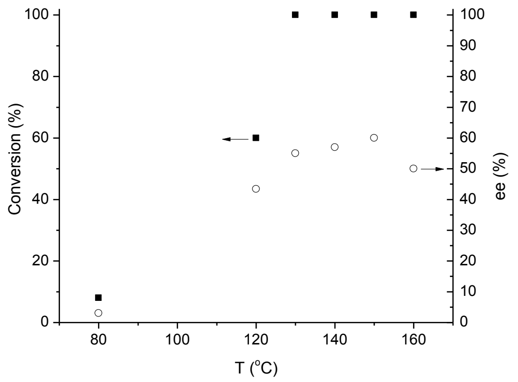
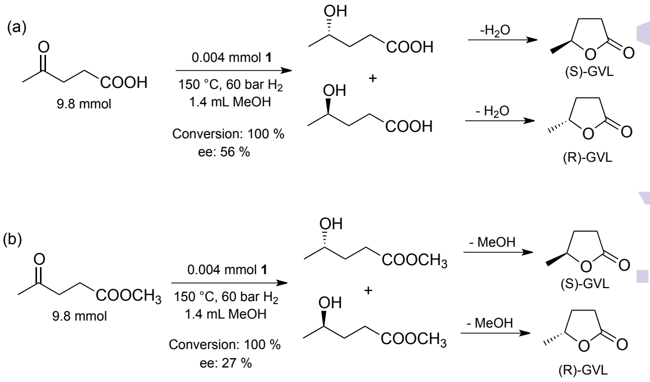


Fig. 6 Asymmetric hydrogenation of LA to GVL at different temperatures. Conditions: 9.8 mmol LA in 1.4 mL MeOH, [Ru] = 0.004 mol dm^{-3}, p_{H2} = 60 bar, RPM = 400



Scheme 2 Reduction of LA and methyl levulinate.

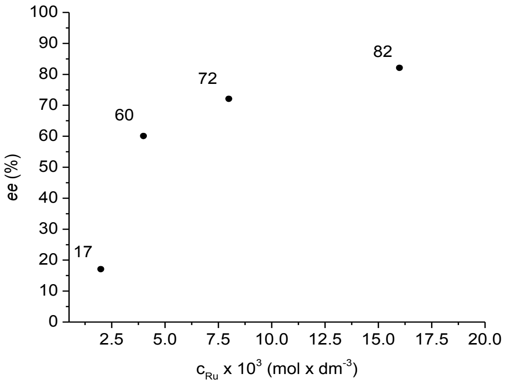


Fig. 7 Influence of catalyst concentration on *ee*. Reaction conditions: 9.8 mmol LA in 1.4 mL MeOH, p_{H2} = 60 bar, *T* = 150 °C, RPM = 400

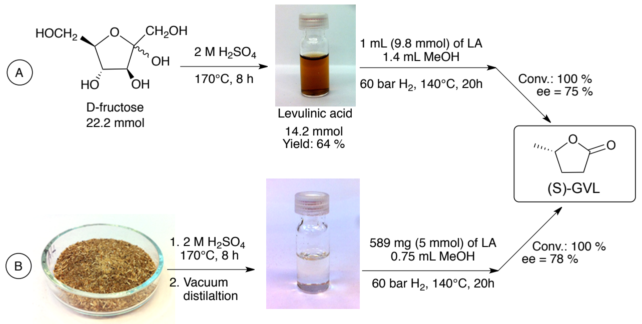
fructose (4 g, 22.2 mmol) was converted to LA under optimized conditions.[8b] As result: 1.65 g of LA was isolated as a light brown and viscous liquid. 1 mL of this product was mixed with 1.4 mL of methanol and subsequently hydrogenated by using **3** at 60 bar H_2 and 150 °C. Quantitative formation of GVL was achieved with *ee* = 78 % after 20 h (Scheme 3. A). Finally, to demonstrate the conversion of a "real" biomass waste containing wheat straw, rice husk, corn straw, nut and pea-pod was treated as follows: 3 g of dried biomass waste was heated in 2 M H_2SO_4 at 170 °C for 8 h. After our published workup procedure was performed,[8b] *c.a.* 1 mL of deep dark brow solution was obtained. After vacuum distillation 560 mg of LA was isolated as colorless liquid (Yield: 18 %). It was subsequently reduced under optimized conditions (0.75 mL MeOH, 0.009 mmol **3**, 60 bar H_2, 150°C) resulting in 100% conversion of LA with enantioselectivity for (*S*)-GVL 80 % (Scheme 3. B). Indeed, GVL with high enantiomeric excess can be produced from biomass based levulinic acid under optimized conditions.

The reproducibility of the experiments were confirmed by repeating the reduction of LA (9.8 mmol) at 60 bar H_2 and 140 °C (Table 1, entry 7). Complete conversion was achieved after 20 h with *ee* = 55.2%. When LA (9.8 mmol) in 1.4 mL of methanol was reduced by using **3** ([Ru] = 0.016 mol dm^{-3}) under 60 bar of H_2 at 150 °C, full conversion with *ee* = 83% was achieved. After removal of methanol and H_2O by vacuum distillation 712 mg of colorless (S)-GVL was obtained. Isolated yield: 62.4% (*ee* = 83%).

Experimental

Levulinic acid, catalyst precursors, (*S*)-GVL, were purchased from Sigma-Aldrich Ltd., Budapest, Hungary and used as received. Solvents were obtained from Molar Chemicals Ltd., Budapest, Hungary and used without further purification (ESI†).

Hydrogenation reactions were performed in a magnetically stirred 25 mL high-pressure Hastelloy-C reactor (Parr Inst, IL USA) equipped with manometer, safety relief and magnetic stirring bar using external heating. In a hydrogenation experiment using *in situ* generated Ru-based catalysts, the high-pressure reactor was charged with 1.14 g (1 mL, 9.8 mmol) levulinic acid, 1.4 mL methanol, 0.62 mg (0.00156 mmol) ruthenium(III)-acetylacetonate and 10 eq (0.0156 mmol) of the corresponding chiral phosphine ligand. In the case of pre-prepared Ru-based catalyst, the reactor was charged with 1.14 g (1 mL, 9.8 mmol) levulinic acid, 1.46 mL methanol, and 0.0048 mmol ruthenium-based chiral complex resulting in a colorful solution. In both cases, the reaction mixture was pressurized up to the desired pressure and heated to the given temperature. After completing the reaction, the reactor was cooled down to ambient temperature, and stirring was stopped. The conversion was determined by ^{1}H-NMR spectroscopy by the signals of methyl protons of levulinic acid (δ: 2.11 ppm, s, 3H) and GVL (δ: 1.41 ppm, d, 3H). The NMR measurements were performed on a Bruker-Avance 250 MHz instrument. The enantiomeric excess (*ee*) was determined on an HP-CHIRAL-20B capillary column (30 m × 0.25 mm × 0.25 μm) with a Finigan Trace GC Ultra (Thermo Electron Corporation) using H_2 as a carrier gas. For the analysis, 10 μL of the reaction mixture was dissolved in 1 mL methanol.



Scheme 3 Conversion of D-fructose (A) and mixed biomass waste (B) to (S)-GVL

Conclusions

We demonstrated that levulinic acid could be directly converted to optically active (*S*)-GVL, a proposed chiral platform molecule. In contrast to previously published procedures, no alkyl levulinate was necessary to synthesize optically active GVL. It was revealed that in the presence of a catalyst *in situ* generated from Ru(III)-acetylacetonate and (*S*)-BINAP, levulinic acid was converted to (*S*)-GVL with *ee* = 26% without adding any solvent and/or additive. By applying (*S*)-$\{[RuCl(SEGPHOS)]_2(\mu\text{-}Cl)_3\}^-[NH_2(CH_3)_2]^+$ catalyst precursor in methanol, the enantiomeric excess was increased resulting in enantioselectivity of 82%. The conversion of "real" biomass waste to optically active GVL was also demonstrated.

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Direct asymmetric reduction of levulinic acid to □amma-valerolactone: synthesis of a chiral platform molecule

József M. Tukacs,[a] Bálint Fridrich,[a] Gábor Dibó,[b] Edit Székely[a] and László T. Mika*[a]

[a]Budapest University of Technology and Economics, Department of Chemical and Environmental Process Engineering, Budafoki str. 8., Budapest, Hungary, H-1111. Tel: +361463 1263, e-mail: laszlo.t.mika@mail.bme.hu
[b] János Selye University, Faculty of Education, Department of Chemistry, Bratislavská str. 3322, Komárno SK-94501, Slovakia.

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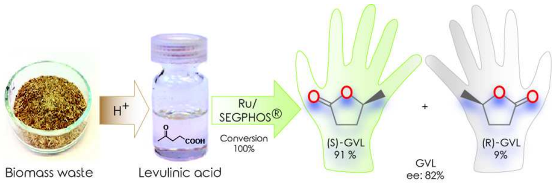

Biomass-originated levulinic acid was directly converted to optically active (*S*)-gamma-valerolactone, a proposed biomass-based chiral platform molecule.