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c0012 CHAPTER 12

Asymmetric Reduction of Ketones to Chiral Platform Molecules

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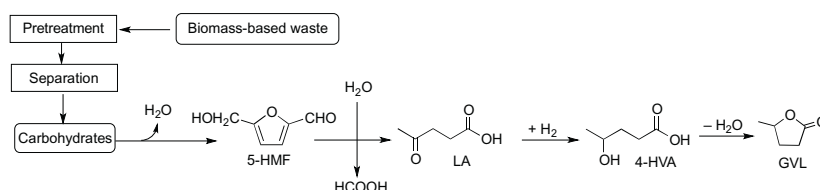
s0010 12.1 INTRODUCTION

p0010 The sustainability of our civilization exclusively depends on whether we can supply the increasing population with enough energy, food, drinking water, and carbon-based chemicals without threatening the Earth's long-term health. There is no doubt that the chemical industry, which continuously provides value-added chemicals, including biologically active compounds such as pharmaceuticals and pesticides, is also exclusively based on fossil resources. Since it is difficult to estimate the depletion of crude oil and natural gas, the utilization of renewable feedstocks for production of carbon-based end-products should be accelerated. Although, the conversion of carbon dioxide could be an elegant approach and several studies were published on its activation, no effective processes to produce organic chemicals on a large scale have been developed yet. Accordingly, selective biomass conversion as one of the most preferred alternative solutions has become a focus of interest and several novel building blocks, so-called platform chemicals, have been identified. They could either replace the currently used fossil-based chemicals or serve as renewable feedstock for their production [1]. While these bulk chemicals can be produced by biorefinery concept, several synthesis concerning biologically active compounds could utilize chiral starting materials. The optically active building blocks could easily be obtained from naturally available carbohydrates and amino acids *via* selective transformation, which do not affect their chiral center(s). However, most of the chemical reactions performed on natural resources led to the loosening of chirality and resulted in the formation of either racemic mixture or nonchiral products. Consequently, to obtain enantiopure platform molecules the chirality has to be incorporated by applying an asymmetric synthesis stage.

p0015 The main part of a biomass is present in the form of sugars, starch, cellulose, lignocellulose, and chitin. Since the main agricultural products, i.e., wheat, rice and corn, are supplied for continuously increasing food and feed production, the selection and consumption of appropriate resources have become controversial issues for sustainability [2]. Recent trends move towards the valorization of various biomass-based waste stream having very similar composition to biomass.

p0020 The acid-catalyzed dehydration and subsequent hydration reactions of C₆ sugars such as glucose and fructose lead to the formation of 5-hydroxymethyl furfural (5-HMF) and levulinic acid (LA). 5-HMF has been considered as one of the C₆-platforms and can be used for the synthesis of a wide-range of carbon-based chemicals and materials [3]. The conversion of 5-HMF resulted in an equimolar amount of LA and formic acid. The latter can also be used as a hydrogen source for the transfer hydrogenation reaction including reduction of LA. Due to its reactive functional groups, LA has been identified as a C₅-platform molecule [4]. Its various ester derivatives may be used as gasoline and biodiesel additives. While D-aminolevulinate is a known biodegradable herbicide, its calcium salt is intravenously injected as a calcium carrier [5]. Its bisphenol derivative could be a substitute of bisphenol-A in polymer manufacture [4]. The selective hydrogenation of LA to 4-hydroxyvaleric acid (4-HVA) opens the way to the facile synthesis of γ -valerolactone (GVL), which was proposed by Horváth as a sustainable liquid and the key molecule in GVL economy [6]. The simplified conversion route of carbohydrates to GVL as valorization of biomass-based waste is depicted in Scheme 12.1.

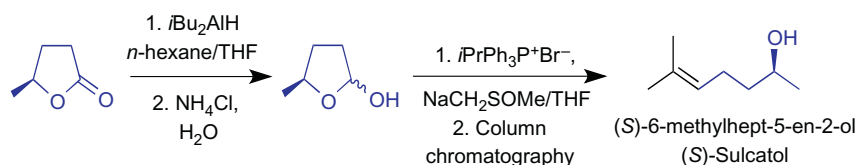
p0025 γ -valerolactone has already been used for the production of alkanes and alkenes [7], transportation fuels [8], ionic liquids [9], 1,4-pentanediol, adipic acid [10], polymers [11], illuminating liquid and lighter fluid [12], etc. Recently, it was demonstrated that GVL can be applied as an environmentally benign reaction medium for the catalytic reactions for,



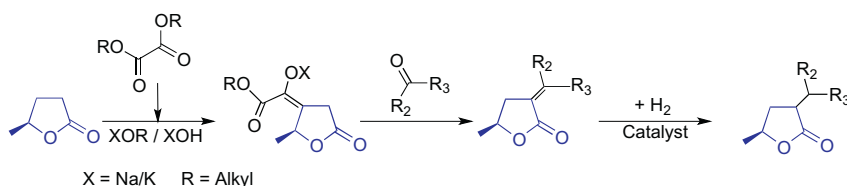
f0035 **Scheme 12.1** Production of GVL from biomass-based waste.

e.g., cross-coupling [13], hydroformylation [14], acid catalyzed dehydration of carbohydrates [16]. Due to its outstanding physical and chemical properties, GVL can be globally used as a carbon and energy source; so far no environmental concerns have been reported. Since GVL occurs naturally in fruits and fermented products such as wines and beers [15], it is nontoxic. GVL is a liquid between -31°C and $+207^{\circ}\text{C}$, has a high open cup flash point (96°C), a definite smell for easy recognition in case of need, and is miscible with water so facilitating biodegradation. It is stable in a wide range of temperatures up to 150°C [16]. Importantly, GVL does not form any measurable amount of peroxides under air, in sharp contrast to 2-methyltetrahydrofuran [17] or dialkyl ethers (diethyl ether, diisopropyl ether, etc.) making it a relatively safe molecule. Compared to commercially used industrial solvents, its vapor pressure is very low even at high temperature [18] resulting in low VOC emission.

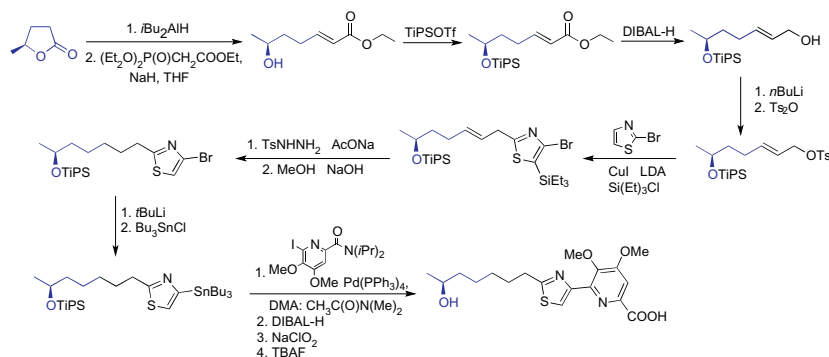
p0030 The optically active γ -lactones occur naturally [19] and can be used as chiral building blocks for the synthesis of biologically active compounds [20]. Interestingly, the optically active GVL can be found in the reaction scheme of some agricultural and pharmaceutical agents [20]. The selected examples are presented below. The aggregation pheromone Sulcatol [21] for ambrosia beetles can be synthesized in two steps from optically active γ -valerolactone (Scheme 12.2). A series of aroma compounds can also be obtained from chiral GVL via a short synthesis (Scheme 12.3).



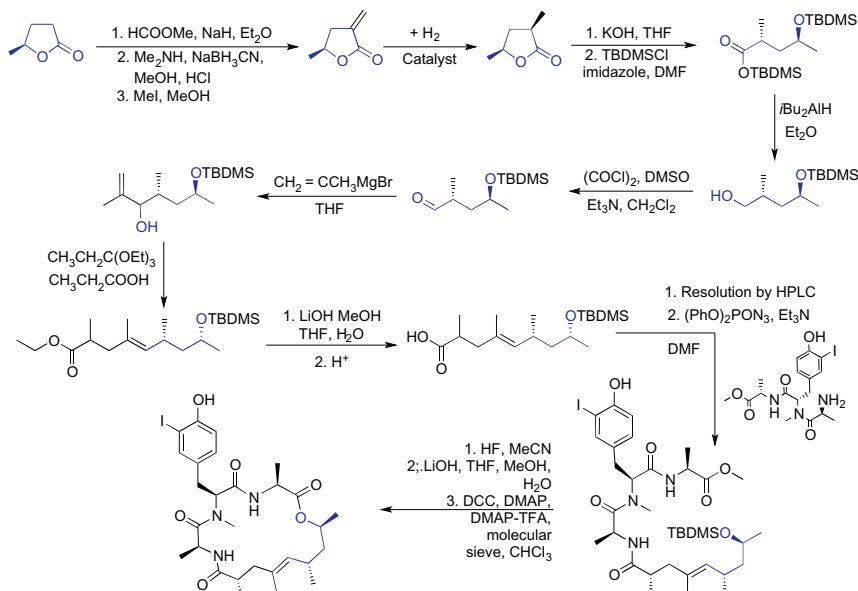
f0040 **Scheme 12.2** Synthesis of (S)-Sulcatol from (S)-GVL.



f0045 **Scheme 12.3** Synthesis of alkylated (S)-GVL.



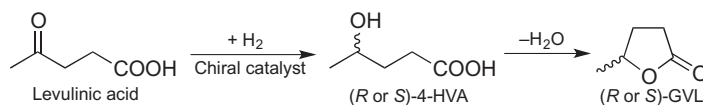
f0050 **Scheme 12.4** (S)-GVL based synthesis of (S)-WS75624S.



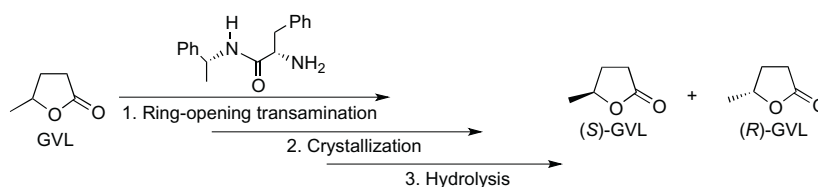
f0055 **Scheme 12.5** Synthesis of Geodiamolide, an insecticide of marine algae origin, from (S)-GVL.

p0035 Although, the synthesis of the antihypertensive WS75624B [Scheme 12.4](#) [\[22\]](#), and insecticide Geodiamolide ([Scheme 12.5](#)) [\[23\]](#) seems to be extremely complex, application of the optically active GVL in their synthesis scheme could reduce the number of corresponding synthesis steps.

p0040 Obviously, the most efficient protocol for the manufacture of GVL is the acid-catalyzed conversion of the carbohydrate content of biomass or biomass-wastes [\[7,24\]](#) to LA followed by the selective hydrogenation of



f0060 **Scheme 12.6** Enantioselective hydrogenation of LA.

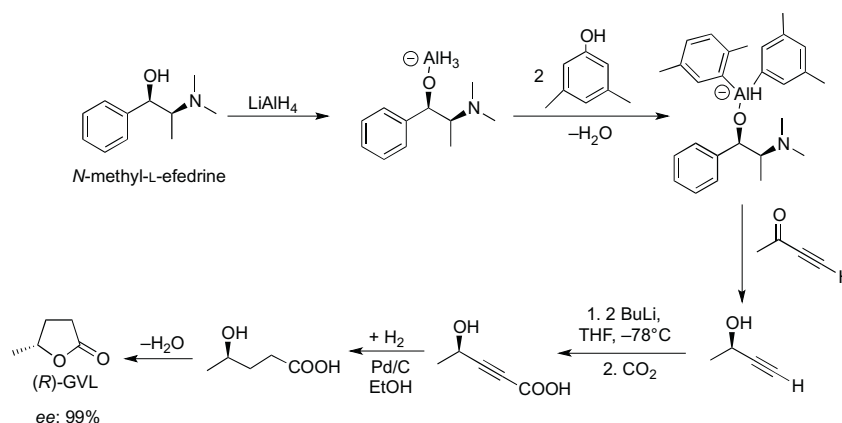


f0065 **Scheme 12.7** Resolution of GVL.

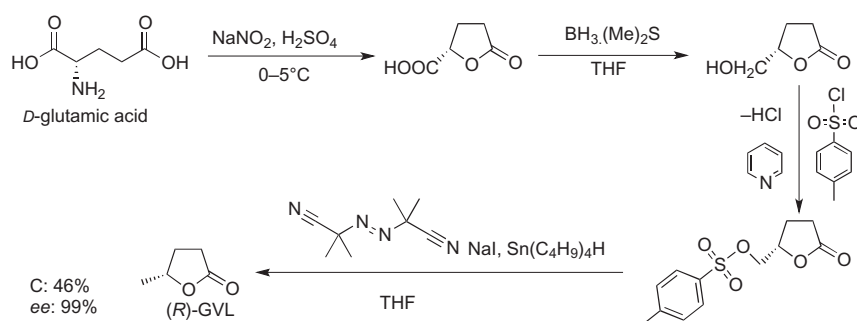
the carbonyl group of LA to 4-HVA that readily turns to GVL via intramolecular dehydration. Accordingly, several catalytic systems were developed operating under either heterogeneous [1] or homogeneous conditions [25,26]. The enantioselective hydrogenation of LA could open a new way to produce optically active 4-HVA that readily turns to optically active GVL [27] (Scheme 12.6).

p0045 The enantioselective reduction of ketones for the synthesis of optically active alcohols is of utmost importance and can be an atom-efficient protocol both on laboratory and industrial scales [28]. The most studied model substrates are different aromatic ketones, e.g., acetophenone in the enantioselective reduction of the carbonyl group. That is why novel catalyst systems have been tested on them. It was shown in several cases that enantioselectivity was dramatically influenced by the nature of the functional groups in the vicinity of the carbonyl group [28d]. Contrary to aromatic ketones, the reduction of aliphatic compounds resulted in lower yield and enantiomeric excess (*ee*) [29,30]. Concerning the production of optically active GVL, it can be obtained via enantioselective hydrogenation of LA, by using alternative synthetic routes, i.e., enzyme-catalyzed transformations, enantioselective reduction of levulinate esters. It should be noted that optical isomers of GVL were separated by resolution, as well.

p0050 To isolate two isomers of GVL, Toshima et al. proposed a process in which a L-phenylalanine derivative was used for the resolution of γ -valerolactone via its diastereomeric salt (Scheme 12.7) [31] with sufficient enantiomeric excess. It is noteworthy that the stoichiometric synthesis of enantiopure GVL was developed by Vigneron. A facile



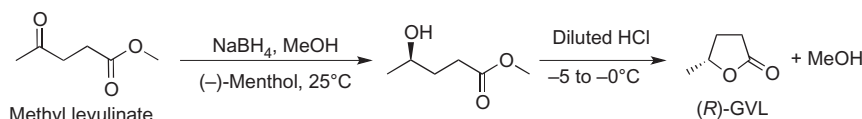
Scheme 12.8 Proposed synthesis of (R)-GVL by α -ketyl-acetylene.



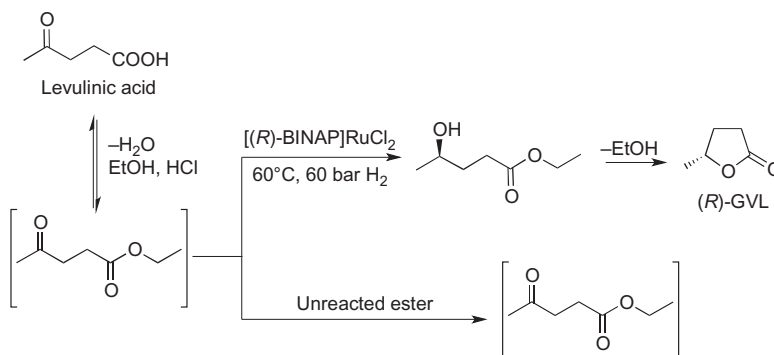
Scheme 12.9 Proposed synthesis of (R)-GVL.

enantioselective reduction of α -ketyl-acetylene was carried out by using *N*-methyl-L-efedrine for the activation of LiAlH_4 forming an optically active hydrogenation reagent. Its subsequent conversion led to the formation of the corresponding carboxylic acid. The triple bond of the latter was saturated to form (R)-4-HVA (Scheme 12.8).

Figadère and Cavé proposed the synthesis of (R)-GVL from D-glutamic acid [32]. Expectedly, due to the chirality of the natural starting material, the *ee* of the final product was remarkable (Scheme 12.9). Karnik et al. reported the synthesis of optically active γ -lactones including GVL by using (*S*)-menthyl- or (*S*)-bornyl esters of 4-carboxylates by using NaBH_4 . In the case of LA, the yield of (*S*)-GVL was moderate (61%) (Scheme 12.10) [33]. So far, a few studies were reported [34,35] on the reduction of alkyl levulinates in the presence of Ru-based catalysts to



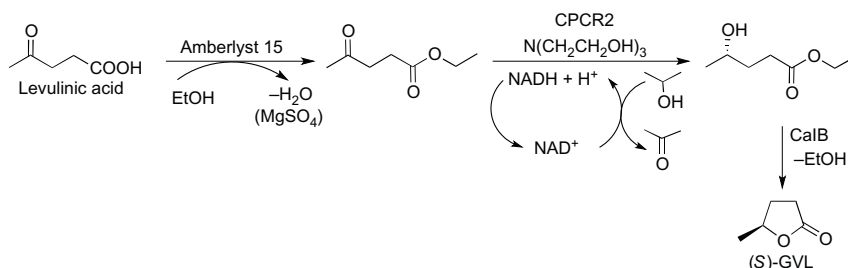
Scheme 12.10 Reduction by NaBH_4 in the presence of (-)-menthol.



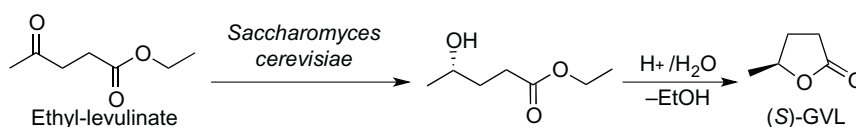
Scheme 12.11 One-pot reduction of levulinic acid to a mixture of optically active lactone and by-products.

optically active GVL. Noyori reduced methyl, ethyl, and octyl levulinates to the corresponding γ -lactones in the presence of Ru/BINAP complexes with excellent ($>90\%$) *ee*. The enantioselective hydrogenation was extended to 2-acylbenzoic esters for the synthesis of optically active phthalides [33]. Vinogradov et al. synthesized (R)-GVL from LA via ethyl levulinate (EL), which in situ formed in the reaction mixture in the presence of ethanol and HCl, by the use of Ru/BINAP catalyst in EtOH under 60 bar H_2 at 60°C [34]. The final reaction mixture contained (R)-GVL and (R)-4-hydroxyethyl levulinate and unreacted EL (Scheme 12.11).

Compared to transition metal catalyzed transformation, the selectivity of the reduction of $\text{C}=\text{O}$ bonds in the presence of enzymes was outstanding. Thus, several attempts were made to reduce γ -keto acid esters to form the corresponding optically active γ -lactones via chemoenzymatic routes. Hilterhaus et al. developed a reaction sequence to produce (S)-GVL via EL. Due to the enzymatic conversion, the *ee* and overall yields were high ($\sim 90\%$), as expected (Scheme 12.12) [36]. Jacobs et al. showed that bakers' yeast assisted the reduction of alkyl levulinates and subsequent HCl-catalyzed hydrolysis of the corresponding hydroxy esters resulted in (S)-GVL with a yield of 73% [37] (Scheme 12.13).



f0090 **Scheme 12.12** Enzymatic synthesis of (S)-GVL via ethyl levulinate.



f0095 **Scheme 12.13** Bakers' yeast assisted reduction of ethyl levulinate.

p0065 The promising aspect of the application of enantipure GVL initiated the investigation of the possibility for the asymmetric reduction of LA to optically active 4-HVA. To take into consideration the ring opening and/or closing, the stability of the chiral center of GVL was crucial for further synthetic strategies. The ring opening of GVL under acidic conditions resulted in 4-HVA, which forms GVL *via* ring closure under neutral conditions. Thus, the stability of the chiral center of GVL was investigated by using the ^{18}O isotope-labeling technique [27]. When (S)-GVL having 98.5% *ee* was reacted with 97 atom % ^{18}O water in the presence of HCl at room temperature, the in-situ ^1H -NMR verified the equilibrium reaction between GVL and 4-HVA. In order to neutralize the reaction mixture, the equimolar amount of sodium hydroxide was added, then the GVL was extracted with ethyl acetate. Based on chiral GC analysis, no change in the *ee* was observed and the GC-MS confirmed the presence of ^{18}O -GVL as well that can only be formed over ^{18}O -4-HVA (Fig. 12.1) [27].

p0070 We demonstrated that GVL can easily be prepared by selective hydrogenation of LA in the presence of bidentate phosphine-modified Ru catalysts without any added solvent with TOF of 100–21,000 h^{-1} . When racemic BINAP was used as a ligand, 98.6% conversion was obtained under 100 bar H_2 at 140°C (TOF = 6978 h^{-1}) [26c]. Consequently, the reduction of LA was achieved by using a catalyst in situ formed from Ru(acac) $_3$ and a 10-fold excess of (R)-BINAP under identical conditions. While full conversion was detected after 12 h, the *ee* was moderate (26%).

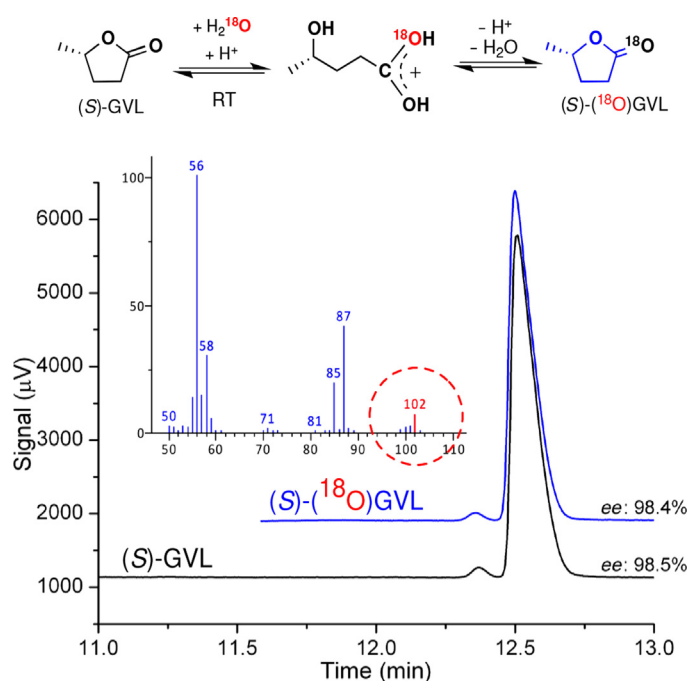


Figure 12.1 ^{18}O incorporation into the optically active GVL.

When the reaction was repeated in a 120-mL Parr high-pressure reactor, in which the reaction mixture can be intensively stirred by a propeller, a significantly higher reaction rate was observed, but the *ee* remained the same. Furthermore, it was revealed that the conversion rate had no influence on enantioselectivity (Fig. 12.2). Unexpectedly, the addition of (*R,R*)-1,2-diphenyl-ethylenediamine (*R,R*-DPEN) did not have a significant effect on the final *ee* values.

It was demonstrated that both in-situ generated and preformed transition metal complexes can be applied for selective hydrogenation; however, the latter usually showed higher activity and selectivity [28d]. Noyori et al. showed that 4-phenyl-2-butanone could be reduced with *ee* = 51% [28d] by applying a modified BINAP-based Ru/XylBINAP/(*S,S*)-DPEN catalyst. The *ee* was further increased by introducing $\text{RuCl}_2[(\text{S})\text{-XylBINAP}][(\text{R,R})\text{-DAIPEN}]$ as a catalyst. For cyclopropyl ketones, higher selectivity with opposite sense of asymmetric induction was achieved representing an outstanding *ee* (>95%) [38]. Thus, the reduction of LA in the presence of XylBINAP-modified Ru-based catalysts was performed; however, the *ee* was modest (*ee* = 11%). Similarly,

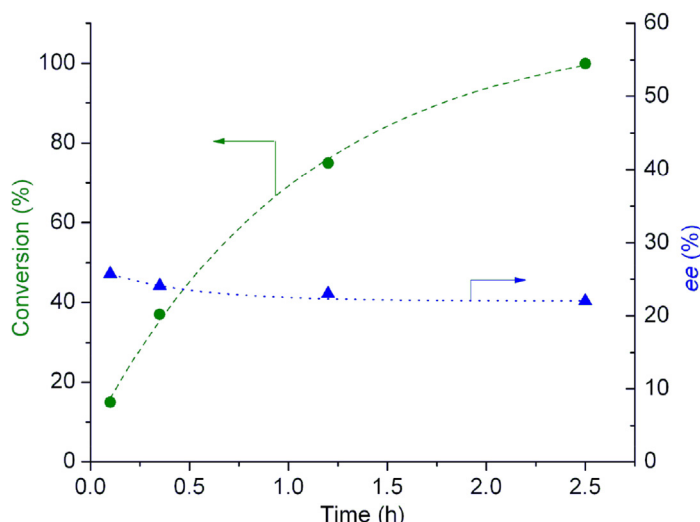
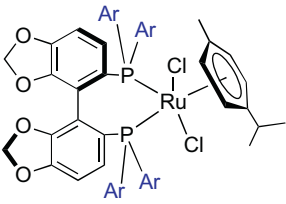
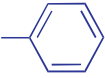
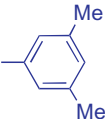
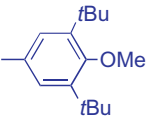
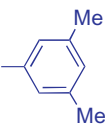
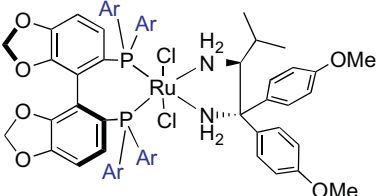
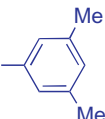
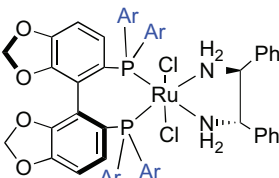
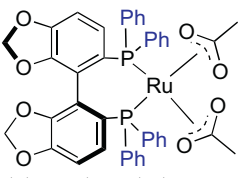
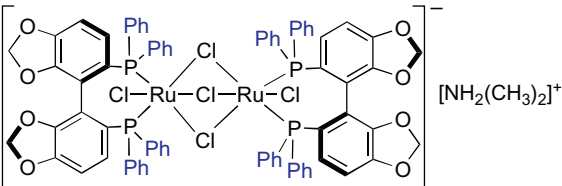


Figure 12.2 Solvent-free asymmetric reduction of LA to optically active GVL. Conditions: $[\text{Ru}] = 7.6 \times 10^{-4} \text{ mol/dm}^3$, $[(R)\text{-BINAP}] = 7.6 \times 10^{-3} \text{ mol/dm}^3$, $T = 140^\circ\text{C}$, $p = 60 \text{ bar}$, $\text{RPM} = 600$.

$ee = 13\%$ was achieved when methanol was used as a co-solvent. By using bidentate phosphine-modified Ru catalyst, both the electronic and steric effects of the bis(diarylphosphine) backbone significantly enhanced the reactivity, and improved the stereorecognition [39]. Saito et al. synthesized a new ligand family (SEGPPOS) with smaller dihedral angle representing an outstanding catalytic performance for the reduction of carbonyl compounds including aliphatic ones [40]. By using a substrate/catalyst ratio of 1000, EL was hydrogenated at 50°C for 20 h, and ethyl-4-(*R*)-hydroxypentanoate was obtained with a yield of 99% [39]. The conversion of LA to GVL in methanol, as the proposed solvent [39], was monitored by using various SEGPPOS-based Ru catalysts (Table 12.1) [27].

When mononuclear (*R*)- RuCl_2 [(*p*-cymene) (SEGPPOS)] precursor was applied complete conversion was achieved with $ee = 18\%$ (similar yields were obtained under solvent-free conditions where BINAP-based catalysts were used). When substituents on the SEGPPOS ligand were varied, a small decrease on the ee values was observed. Comparing DPEN and DAIPEN analogues of Noyori's catalyst, no significant change in the ee was detected. Similar results were observed when (*S*)- $\text{Ru}(\text{OAc})_2(\text{SEGPPOS})$ precursor was applied. However, the use of (*S*)- $[(\text{RuCl}(\text{SEGPPOS}))_2(\mu\text{-Cl})_3][\text{NH}_2(\text{CH}_3)_2]$ precursor resulted in a

Table 12.1 Conversion rates and ee values obtained for the hydrogenation of LA to GVL in the presence of various SEGPHOS-based Ru catalysts

Catalyst		Conv. (%)	ee (%)
 (R)-RuCl(<i>p</i> -cymene)(SEGPHOS)Cl types	   	100 100 95 100	18 9 13 13
 RuCl ₂ [(S)-(DM-SEGPHOS)][(S)-DAIPEN]		100	16
 RuCl ₂ [(S)-(DM-SEGPHOS)][(S,S)-DPEN]		100	12
 (S)-Ru(OAc) ₂ (SEGPHOS)		100	56
 (S)-[(RuCl(SEGPHOS)) ₂ (μ-Cl) ₃] [−] [NH ₂ Me 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.

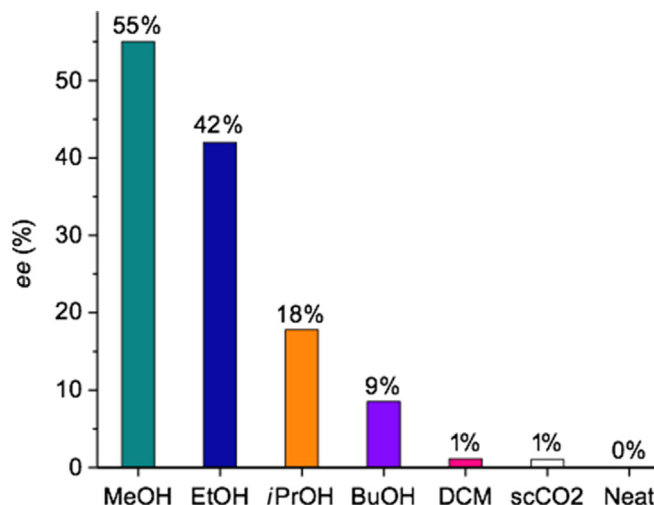


Figure 12.3 Asymmetric hydrogenation of LA to GVL in different solvents. Conditions: $[Ru] = 0.004 \text{ mol/dm}^3$, $T = 140^\circ\text{C}$, $p = 60 \text{ bar}$, $\text{RPM} = 400$. Catalyst precursor: $(S)\text{-}[(RuCl(SEGPHOS))_2(\mu\text{-Cl})_3][NH_2Me_2]$.

dramatic increase in the enantioselectivity. The reduction of LA in the presence of $(S)\text{-}[(RuCl(SEGPHOS))_2(\mu\text{-Cl})_3][NH_2Me_2]$ catalyst leads to the complete formation of $(S)\text{-GVL}$ with $ee = 56\%$, that was 4.5 and 2.5 times higher than that obtained by using Noyori's catalyst in methanol or Ru/BINAP catalyst under solvent-free conditions.

Since asymmetric induction was strongly affected by the reaction medium, alcohols, methylene chloride and supercritical CO_2 were evaluated for reduction of LA at 60 bar H_2 and 140°C . Although, complete conversion was obtained in all cases, the enantiomeric excess was in a wide range depending on the solvent (Fig. 12.3). Without any added solvent, no chiral induction occurred, and negligible values were obtained when methylene chloride or supercritical CO_2 was used. However, significantly higher ee values were obtained in alcohols, a protic reaction media, which is in accordance with the data published on the reduction of nonaromatic ketones by Saito et al. [39]. Supposedly, methanol acts as a 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 an equimolar amount of water and GVL. Accordingly, the application of a water-free solvent is inefficient.

The Ru-catalyzed asymmetric reductions are usually performed in the range of $20\text{--}40^\circ\text{C}$, although SEGPHOS-based catalysts operate at higher (65°C) temperatures. The investigation of the effect of the reaction

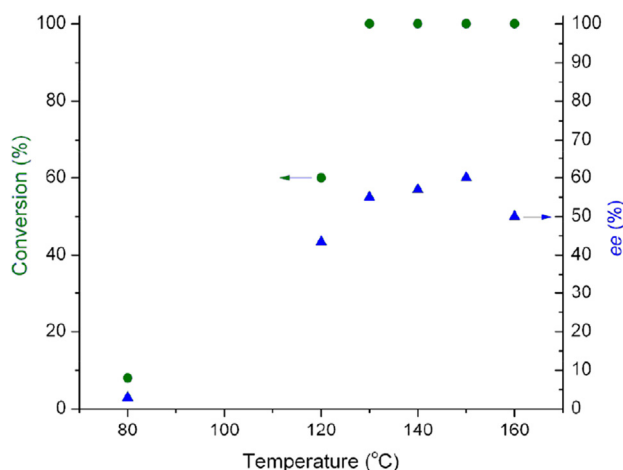


Figure 12.4 Asymmetric hydrogenation of LA to GVL at different temperatures.

temperature on the activity and selectivity of LA reduction was investigated in the range of 80–160°C. It was shown that negligible or moderate conversions were achieved below 120°C (Fig. 12.4).

Interestingly, alkyl levulinates were converted to the corresponding alcohols at 30°C [33] and 60°C [34]. When, 9.8 mmol of LA was dissolved in 1.4 mL MeOH was reduced at 80°C and 60 bar H₂ for 20 h, negligible conversion (8%) and *ee* (3%) was observed; and only a slight increase was found at 120°C. Although, full conversion was obtained over 130°C, the maximum of *ee* value (56%) was obtained at 140°C [27].

It is supposed that the reduction of LA to GVL in the presence of HCl with Ru-BINAP-HCl system undergoes via in-situ formation of EL in ethanol. When LA was reduced by catalyst (S)-[(RuCl(SEGPHOS))₂(μ-Cl)₃][NH₂(CH₃)₂] the concentration of methyl levulinate in the final reaction mixture was below detection limit. For comparison, methyl levulinate in methanol was reduced under identical conditions resulting in complete conversion and interestingly with *ee* = 27%. It 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, if LA was hydrogenated to (S)-4-hydroxyvaleric acid it was spontaneously dehydrated to (S)-GVL.

Unexpectedly, for the reduction of LA, significant improvement in enantioselectivity was detected by varying the Ru concentration. For example, when LA was hydrogenated in MeOH as co-solvent at

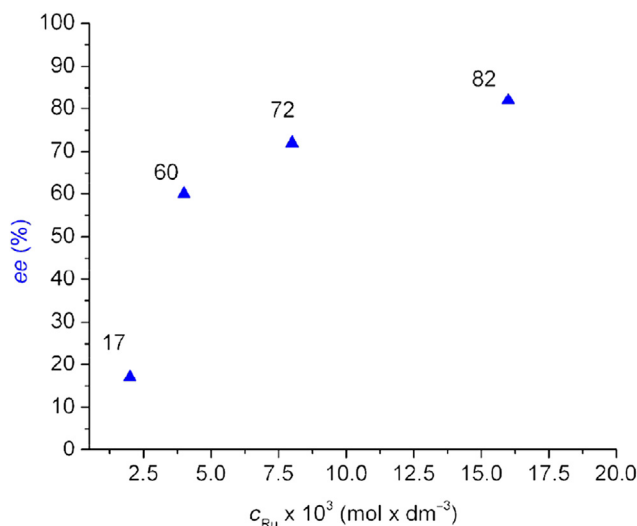
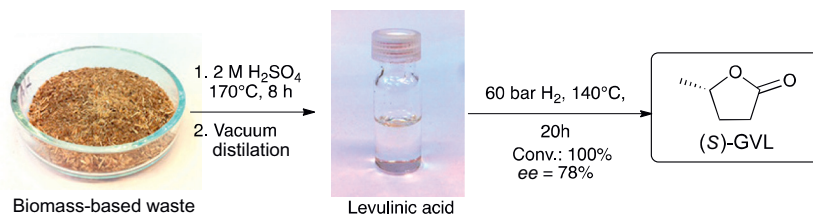


Figure 12.5 Observation of change in the enantiomeric excess with the variation of catalyst concentration.



Scheme 12.14 Conversion of biomass-based waste to (S)-GVL.

$[\text{Ru}] = 0.016 \text{ mol/dm}^3$ at 60 bar and 150°C , complete conversion was obtained with $ee = 82\%$ for (S)-GVL. This selectivity fits to the ee values obtained for dialkyl ketones; however, a further increase of the catalyst concentration had no effect on the selectivity (Fig. 12.5).

In order to demonstrate the conversion of “real” biomass-based wastes a mixture containing wheat straw, rice husk, corn straw, nut and pea-pod was treated in 2 M H_2SO_4 at 170°C for 8 h. After our published workup procedure was performed, c.1 mL of deep dark brown solution was obtained, which was subsequently purified by vacuum distillation. The hydrogenation of the colorless LA under optimized conditions resulted in complete conversion with enantioselectivity for (S)-GVL 78% [27]. Indeed, we have shown that GVL with high ee can be produced from biomass-based LA (Scheme 12.14).

s0015 12.2 CONCLUSION

p0115 We demonstrated that LA could be directly converted to optically active (S)-GVL, a proposed chiral platform molecule. It was revealed that no alkyl levulinate was necessary to obtain optically active GVL. We have shown that in the presence of a catalyst in situ generated from Ru(III)-acetylacetonate and (S)-BINAP, LA was converted to (S)-GVL with *ee* = 26% without adding any solvent and/or additive. By applying (S)-{[RuCl(SEGPHOS)]₂(μ-Cl)₃}[−][NH₂(CH₃)₂]⁺ catalyst precursor in methanol, the *ee* was increased to 82%. The conversion of “real” biomass waste to optically active GVL was also demonstrated.

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Abstract

The enantioselective reduction of prochiral substrates including C=O double bonds is fundamentally important in the synthesis of biologically active compounds. Due to the depletion of fossil-based resources, the production of these species from renewable resources is highly desired. The enantiopure γ -valerolactone was proposed as a biomass-based chiral platform molecule that can be easily obtained by the asymmetric reduction of levulinic acid and its esters. Synthetic schemes of the production of optically active γ -valerolactone are presented. The effect of catalyst composition and reaction parameters on the activity and selectivity will be discussed in detail.

Keywords: Hydrogenation; optically active; γ -valerolactone; levulinic acid; biomass conversion; enantioselective synthesis