Final report on project entitled
"Application of gamma-valerolactone as a green solvent in catalysis"

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1. Introduction

The gradual replacement of fossil resources of chemical industry including solvents with renewable alternatives is one of the most pressing challenge of mankind. Biomass could be an ideal replacement as it is one of the most abundant carbon resources and globally available on the Earth. The rapidly accelerating research on biomass conversion has led to the identification of novel platform molecules[1] *e.g.* levulinic acid (LA),[2] and γ-valerolactone (GVL),[3] which could either replace the currently used fossil-based chemicals or serve as renewable feedstock for their production.

The solvents are intrinsic part of many chemical reactions and the "solvent friendly chemical thinking" has evolved due to many advantages in laboratory operations including the simple regulation of temperatures, moderation of exothermic reactions, dissolution of solids to get molecules in a common phase, facilitation of mixing, *etc.*[4] Consequently, the industrial activities involving solvents are resulting in the release of 10-15 million tons of solvents into the atmosphere annually, some of which are leading to serious environmental concerns and economic issues. Accordingly, the replacement of conventional, fossil-based organic solvents with green solvents having low vapour pressure even at high temperature, low or no toxicity, low flammability and limited negative impacts on the environment is a crucial part in the development of greener and cleaner chemical technologies.[5]

Thus, the main objective of my proposal was to demonstrate that GVL could be a key component of environmentally benign and renewable reaction media for catalysis by selected homogeneous catalytic transformations. The proof of concept is depicted on Fig. 1.

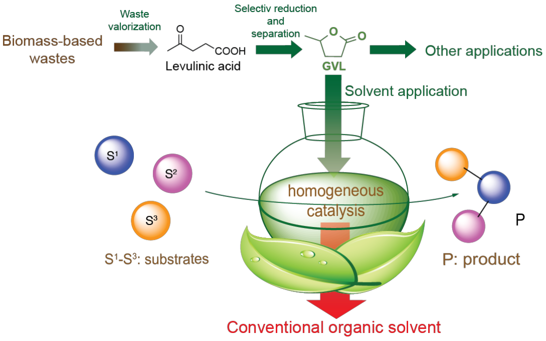


Fig. 1 Application of GVL as a biomass-based solvent

According to the proof of concept, the research activity was focused on the production of gamma-valerolactone (GVL) from biomass including conversion of lignocellulosic wastes to levulinic acid, conversion of levulinic acid to GVL, investigation of separation and purification of GVL, optimization of synthesis of enantiopure GVL as well as application of GVL as a reaction media for selected homogeneous transition metal-catalyzed reactions i.e. hydroformylation, aminocarbonylation, hydrogenation, and metathesis. The determination of vapor-liquid equilibria of GVL–water, GVL and C_1-C_3 alcohols as potential by-products of its synthesis, and GVL–formic acid was also completed.

2. Results

2.1 Synthesis and separation of γ-valerolactone

The efficient conversion of various lignocellulosic waste streams to levulinic acid and subsequently to GVL could open an economically viable process to produce this biomass-based solvent. Therefore, we investigated the acid catalyzed conversion of selected biomass wastes to levulinic acid as extension of original workplan. It was demonstrated that cheap and readily available wastes could be valorized to levulinic acid in the presence of sulfuric acid at 170 °C. The yields were in the range of 10–25 wt% depending on the type of waste. When MW dielectric and conventional heating were compared, no differences in the yields were detected. However, the reaction time could be reduced to 1/16th when MW technique was applied. The influence of the water content of the sample, which could be crucial for drying processes on the levulinic acid formation, was also investigated revealing that it had no significant effect on the final yields. Thus, it can be concluded that the high energy demand pretreatment process can be eliminated from the process.[6] The investigation of sulfuric acid recycling revealed that it could either be reused after extracting the product or before extraction. By reusing sulfuric acid in the process, the amount of waste and therefore the E-factor can be reduced from 20.5 to 2.3.[7] The production of initial platform chemicals from biomass was overviewed in detailed, as well.[1]

Since GVL has a chiral center, it can either be used as a chiral building block in synthetic schemes or applied as a chiral reaction media. It was shown that LA could be efficiently converted to optically active (*S*)-GVL. In contrast to previously published procedures, no alkyl levulinate was necessary for its synthesis as we showed that in the presence of a catalyst *in situ* generated from $Ru(acac)_3$ and (*S*)-BINAP, LA could be converted to (*S*)-GVL with *ee* of 26% without any co-solvent and additive. Although the *ee* for this case was moderate, to our best knowledge, so far it is the first example of co-solvent-free asymmetric hydrogenation of C=O-double bond. The investigation of a series of preformed Ru-based chiral catalyst including BINAP- and SEGPHOS-modified ones revealed that by applying (*S*)-$\{[RuCl(SEGPHOS)]_2(\mu\text{-}Cl)_3\}^-[NH_2(CH_3)_2]^+$ catalyst precursor using methanol as a co-solvent, the *ee* could be increased to 82% without carbon-containing by-product formation under 60 bar H_2 at 140 °C. Since the transformation of biomass-based wastes to value-added chemicals is of utmost importance, the conversion of both fructose as a model source and "real" biomass waste containing wheat straw, rice husk, corn straw, etc. to optically active GVL was also demonstrated without any decrease in enantioselectivity (Fig. 2).[8]

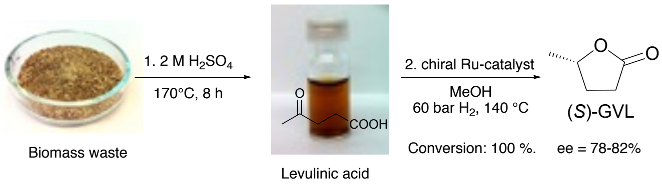


Fig. 2 Synthesis of (S)-GVL from biomass waste

Concerning the ring opening and/or closing, the stability of GVL including its chiral center is a crucial point for further synthetic schemes. Accordingly, the stability of the chiral center of GVL was investigated by using ^{18}O-labelling technique revealing that the ring opening and reclosing had no effect on the enantiopurity of (*S*)-GVL. The pH value and reaction temperature also could have influence on the stability. Therefore, we monitored the stability in the range of pH = 1 – 13 and temperature of 25 – 100 °C. The chiral GC analysis established that the ring opening and re-closing did not affect the enantiopurity, which was unchanged respecting the analysis error of chiral GC analysis.[8,9,10]

Since GVL can be obtained from levulinic acid or alkyl levulinates, the final reaction mixtures could contain equimolar amount of water or corresponding alcohol. When formic acid is used as a hydrogen donor, its present in the final mixture could also be considered. The water content of the solvent could reduce the activity or even damage the transition metal-based catalysts. Thus, we investigated in details of the vapor-liquid equilibria of GVL–H_2O, GVL–MeOH, GVL–EtOH, GVL–2-propanol, and GVL–formic acid binary systems, as an extension of work plan. It has been shown that GVL can easily be separated from these by-products by vacuum distillation without formation of azeotropic mixtures. The Antoine-constants of GVL, and binary interaction parameters for Wilson, NRTL, and UNIQUAC activity coefficient models, which can be used for designing of separation units were determined.[11–13]

2.2 Application of γ-valerolactone as a solvent for homogeneous catalysis

2.2.1 Hydroformylation

The hydroformylation of olefins has become one of the most important industrial homogeneous catalytic processes. Due to the high pharmacological importance of 2-arylpropanals, the Pt- and Rh-catalyzed enantioselective hydroformylation of styrene as a model reaction utilizing GVL a non-toxic, dipolar, aprotic, renewable reaction media was investigated. Initially, the formation of bidentate phosphine ligands (BDPP, BINAP, JOSIPHOS, SEGPHOS)- modified Pt-complexes in GVL was monitored by ^{31}P-NMR spectroscopy. It was established that GVL can be a good solvent for characterization of transition metal complexes.

The *in situ* generated Pt-diphosphine-tin(II)chloride catalyst systems were utilized for hydroformlyation of styrene. In general, slightly higher activities and regioselectivities towards branched aldehyde (2-phenylpropanal) were obtained in toluene as a reference solvent. However, higher chemoselectivities towards aldehydes (up to 98%) in GVL were obtained at lower temperatures (Fig. 3). The application of GVL proved to be also advantageous regarding enantioselectivity: although moderate enantioselectivities were obtained in both solvents, in most cases higher *ee* values were detected in GVL. When chiral phosphine ((S,S)-BDPP, (R)-BINAP, (R)-QUINAP, (R,R)-DIOP, (R_c),(S_p)-JOSIPHOS, (S)-SEGPHOS, modified Rh-catalysts were applied for hydroformylation of styrene, remarkable chemo- (>99%) and regioselectivities (>99%) were observed in GVL compared to toluene; however, the activities were lower (Fig. 3). Similar results were obtained for the oxo-synthesis of α-methylstyrene, dimethyl itaconate, and (*R*)-limonene as model substrates. The BDPP-modified Rh-catalyst was recycled for three consecutive cycles; however, a decrease in its activity was detected. The investigation of the influence of chiral GVL as a reaction environment on activity and selectivity revealed that chiral solvent has no effect on the enantioselectivity.[14,15]

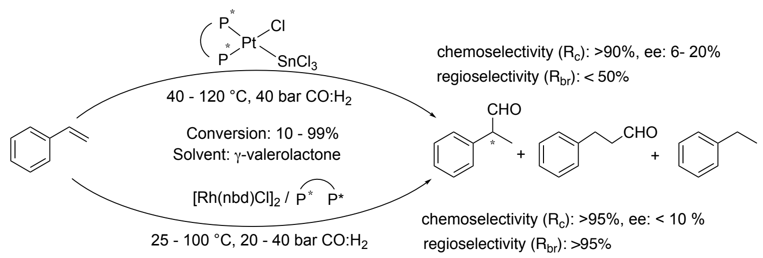


Fig. 3 Asymmetric hydroformylation in GVL

Beyond the asymmetric hydroformylation, the unmodified Co-based system was also monitored revealing that GVL can be applied as reaction media for hydroformylation of terminal C_6, C_8, and C_{10} olefins to the corresponding aldehydes with full conversion under 100 bar of CO:H_2 = 1:1 at [Co] = 58 mmol/L 120 °C for 1 h. The *normal* to *iso* ratios varied between 2 and 3 depending on the substrate. The PPh_3-modified Rh-based system using [Rh] = 0.4 mmol/L and P/Rh = 6.7 also resulted in complete conversion of both hexane and decane; however, the n:i ratios were unexpectedly (ca. 4) low.

2.2.2 Hydrogenation

The selective reduction of furfural is an industrially applied catalytic transformation to produce furfuryl alcohol. Furfuryl alcohol is important building block of polymers, thermostatic resins, adhesives etc. Since the heterogeneous copper-chromite catalyst, operating in either gas or liquid phase has high toxicity and negative environmental impacts, the development of an environmental benign selective catalyst could open a greener way for furfuryl-alcohol production. Accordingly, we attempted to reduce furfural as a biomass-derived, industrially important aldehyde in GVL as a green solvent. It was shown that the reduction could be performed by catalyst in situ formed from $Ru(acac)_3$ and $Ph_2P(CH_2)_4PPh_2$ under 100 bar H_2 at 140 °C with complete conversion and >99.9% selectivity towards furfuryl alcohol. During optimization of the reaction, it was revealed that the solvent could be completely eliminated from the reaction mixture. By subsequent optimization, a solvent and additive-free $Ru/Ph_2P(CH_2)_4PPh_2$-catalyzed hydrogenation of furfural to furfuryl alcohol was developed exhibiting turnover frequency of 6273 h^{-1}. So far, to our best knowledge, no solvent-free selective homogeneous reduction of FAL to FOL has been reported yet.[16]

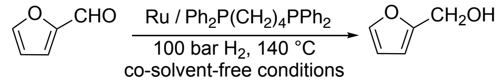


Fig. 4 Hydrogenation of furfural to furfuryl-alcohol

The hydrogenation of α,β-unsaturated carbonyl compounds was performed by the use of *trans*-chalcone as a model substrate in GVL. The effects of various catalyst precursors ($Ru(Cl)_2(PPh3)_3$, [Rh(cod)2][BF_4], $RhClPPh_3$ etc.), pressure (10–60 bar), reaction temperature (50-90 °C), type of the ligand (PPh_3, $Ph_2P(CH2)_nPPh_2$ n=2–6) and its ratio to the metal on the activity and selectivity were optimized. It was established that the C,C-double bond can be selectively reduced by the use of catalyst *in situ* generated from $[Rh(cod)_2][BF_4]$ and PPh_3, under 50 bar H_2 with >90% conversion at 60 °C for 5 h. The optimal P/Rh ratio was determined as of 3 at substrate/Rh = 2500, which is in excellent agreement with "classical" olefin hydrogenation conditions. The application of bidentate ligands dramatically reduced the catalytic activity. To monitor the effect of various groups attached to C=C bond on the hydrogenation rate, a series of (C_6H_5(C=O)CH=CH-(*m*-R-C_6H_4), where R = -OMe, -F, -Cl, NO_2, -Me, -CF_3, -*t*Bu) chalcones were synthesized by Claisen-Schmidt condensation and subjected to hydrogenation (Fig. 4). It was shown that the presence of electron donating group accelerates the reaction rate. The optimized conditions were successfully utilized for other unsaturated compounds i.e. cynnamaldehyde and its derivatives, dimethyl-itaconate etc. showing similarly high selectivities (> 99%). However, the reaction rate was significantly affected by the substrates' structure.[17,18]

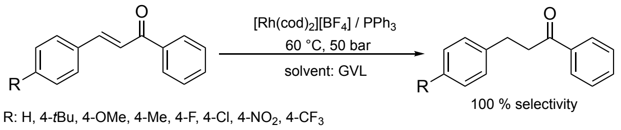


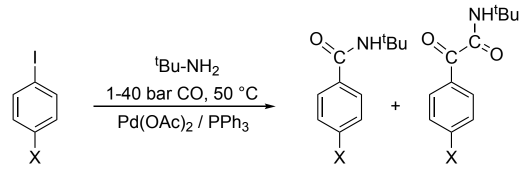
Fig. 4 Hydrogenation chalcone and its derivatives in GVL

Transfer hydrogenation of aldehydes and ketones providing an environmentally benign alternative to produce alcohols were performed by using various Shvo type catalysts. A series of $\{[2,5\text{-}(C_6H_5)\text{-}3,4\text{-}(R)_2(\eta^5\text{-}C_4CO)]_2H\}Ru_2(CO)_4(\mu\text{-}H)]\}$ catalyst (R: 1 or 2, -CH_3, -C_2H_4, -F, -Cl, -Br, -CF_3, -OCH_3)) were prepared and tested for reduction of acetophenone and its derivatives as model reactions in the presence of various H-donors (HCOOH, HCOONa, HCOOK etc.). It was revealed that acetophenone and its derivatives can be reduced to corresponding 1-phenylethanol at substrate/Ru ratio = 600–1000 in GVL at 80-95 °C for 8 h. The highest activity was detected when formic acid was used as hydrogen source in the presence of $\{[2,5\text{-}Ph_2\text{-}3,4\text{-}(p\text{-}MeOPh)_2(\eta^5\text{-}C_4CO)]_2H\}Ru_2(CO)_4(\mu\text{-}H)$ catalyst at substrate/Ru ratio = 800 and 95 °C. The catalyst systems can be used for selective reduction of other carbonyl compounds such as cynnamaldehyde, benzophenone, ethyl-levulinate, methyl-levulinate, chalcones, and furfural.[18]

GVL was proposed as reaction medium for asymmetric hydrogenation reactions. Although high activities were detected for asymmetric reduction acetophenone and its derivatives, the enantioselectivities remained rather low. Therefore, neither GVL nor chiral GVL could be used for these purposes.

2.2.3 Aminocarbonyaltion

Because the GVL was found to be inappropriate solvent for asymmetric hydrogenation reactions, a new subsequent application was investigated. We proposed that GVL as a renewable, non-toxic reaction medium having negligible vapor pressure could be used for homogeneous Pd-catalyzed aminocarbonylation reactions. Iodobenzene as a model substrate and its 4-substituted derivatives were converted to the corresponding 2-ketocarboxamides with high conversion and chemoselectivity in GVL. The effect of carbon monoxide pressure and reaction temperature on the conversion and selectivities were studied in the range of 1–50 bar and 25–100 °C, respectively. The highest conversion and selectivity was achieved at 25 bar and 50 °C for iodobenzene in GVL for 24 h.[19]



X = H (a), NH$_2$ (b), OH (c), *t*Bu (d), CH$_3$ (e), *i*Pr (f), Ph (g), F (h), Cl (i) Br (j), COOCH$_3$ (k), C(O)CH$_3$ (l), CF$_3$ (m), CN (n), NO$_2$ (o)

Fig. 5 Aminocarbonylation of iodoaromatic compounds in GVL

2.2.4 Metathesis

The investigation of metathesis reactions was first focused on ring opening metathesis polymerization of norbornene and cyclooctenol in the presence of Grubbs II. catalyst at room temperature. GVL was compared to CD_2Cl_2 as a reference conventional solvent. The *in situ* NMR investigation revealed that GVL could be considered as appropriate solvent for metathesis; however, a ca. 50% decrease in the reaction rate was detected. The polymer was easily precipitated from both reaction media. The investigation of other metathesis reactions is still in progress.

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