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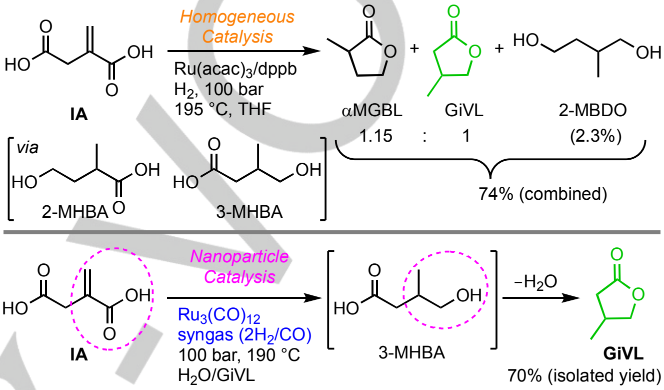
Regioselective Hydrogenation of Itaconic Acid to γ-Isovalerolactone by Transition-Metal Nanoparticle Catalysts

Ravikumar R. Gowda* and Eugene Y.-X. Chen*[a]

Abstract: Current methods for hydrogenation of bio-derived itaconic acid (IA) lead to a mixture of isomeric lactone products. Here we report that *in situ* generated transition-metal nanoparticles (TM-NPs), via thermolysis of TM(0) (Ru, Fe, W, Cr) carbonyls, in particular Ru-NPs, catalyze regioselective hydrogenation of IA by syngas ($2H_2$:CO) into γ-isovalerolactone (GiVL) in ~70% isolated yield. Key sustainability features of this new route include: a one-pot direct transformation of bio-renewable IA into value-added GiVL selectively, use of inexpensive and renewable syngas in aqueous solution, and development of a supported recyclable NP catalyst system, Al_2O_3-Ru-NPs.

Biomass-derived γ-valerolactone (GVL) or γ-methyl-γ-butyrolactone has been hailed as an "ideal" sustainable liquid for the chemical industry in the production of carbon-based consumer products and energy, thanks to its various desirable physical and chemical properties.[1-4] GVL is not only a potential fuel or green solvent but also a feedstock of monomer γ-methyl-α-methylene-γ-butyrolactone[5] for the production of acrylic bioplastic.[6] Biomass platform chemical levulinic acid (LA)[1f],[7] has been the widely adopted feedstock for the production of GVL[8] via homogeneous[9] and heterogeneous[10] hydrogenation catalysis. Both the relatively high cost of LA (with a bulk price of ~$8/kg) and an energy-intensive conversion of it to GVL in an industrial process[5] render GVL as an expensive renewable carbon source (currently priced at $254/0.5 kg for the 99% purity). As a constitutional isomer of GVL, γ-isovalerolactone (GiVL) or β-methyl-γ-butyrolactone exhibits similar physical and chemical properties to those of GVL and, therefore, it can be considered as an alternative to GVL. More importantly, GiVL could offer the following two key advantages over GVL. First, compared to the GVL's feedstock LA, the GiVL's feedstock IA is about 4 times cheaper. Annually about 80 kilotons of IA are produced worldwide in a high-yielding fermentation process (0.72 g/g from glucose), with titers of up to 86 g/L and a bulk price of ~$2/kg.[7g],[11] Owing to the high potential of IA, the production capacity is expected to grow by 5.5% every year,[12] and the predicted market for IA for 2020 is estimated to be ~200 kilotons.[13] Second, GiVL leads to superior bioplastics in contrast with those derived from GVL, as evidenced by our work that showed the monomer derived from GiVL, namely β-methyl-α-methylene-γ-butyrolactone ($_{\beta}$MMBL), forms bioplastic poly($_{\beta}$MMBL) with considerably enhanced materials properties over the bioplastic based on the GVL-derived monomer $_{\gamma}$MMBL.[6],[14] However, the catalytic method for the direct regioselective reduction of IA to GiVL is currently unknown.



Scheme 1. Non-selective reduction of IA by homogeneous molecular Ru catalyst and molecular H_2 in THF vs. regioselective reduction of IA to GiVL by Ru-NP catalyst and syngas in aqueous solution.

Few studies have been reported on the hydrogenation of IA to value-added chemicals. The double bond in IA readily undergoes hydrogenation to 2-methylsuccinic acid (2-MSA) under mild conditions.[15] Beyond this stage, the reduction of the carboxylic acid with molecular dihydrogen is usually performed under high temperature and high pressure, due to the low reactivity of the carboxylic group. In this context, hydrogenation/lactonization of IA by a homogeneous, molecular catalyst system based on $Ru(acac)_3$/dppb in dry THF at 195 °C under 100 bar H_2 pressure for 20 h resulted in a mixture of isomeric lactones, α-methyl-γ-butyrolactone ($_{\alpha}$MGBL) and GiVL in a 1.15:1 ratio, plus over-reduction product 2-methylbutane-1,4-diol (2-MBDO), in a 74% combined yield (Scheme 1). Separation of these two regio-isomeric lactones is practically infeasible.[9c],[16] Similarly, the reduction of itaconic anhydride by heterogeneous Raney nickel catalyst[17] and the reduction of IA by Ru-NPs supported on titania or ruthenium on carbon have been reported to produce a lactone mixture.[18] Other catalysts, such as Pd/C[19] and Pd–0.5ReOx/C,[20] have also been employed for hydrogenation of IA, but they all led to formation of a mixture of lactones. In 2014, we reported the regioselective synthesis of GiVL from IA, but it was a multi-step synthesis and used stoichiometric reagents under low temperature. [21]

Based on the above overview, it is evident that the economical and sustainable one-pot conversion of IA to GiVL via catalyzed regioselective reduction and lactonization is currently lacking. Here we report that such desired transformation can be accomplished by the direct regioselective hydrogenation/lactonization of IA to GiVL using TM-NP catalysts with syngas ($2H_2$:CO) in water or water/GiVL solution (Scheme 1).

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As we found earlier that TM-NPs derived from group 6 carbonyl complexes, including $Fe_3(CO)_{12}$, $Cr(CO)_6$ and $W(CO)_6$, are highly effective catalysts for the selective transfer hydrogenation of LA to GVL in up to 93% isolated yield,[22] we first screened these TM-NPs as potential catalysts for the conversion of IA to GiVL. Under syngas ($2H_2/CO$) pressure of 1250 psi and 225 °C conditions, these group 6 TM-NPs were found to be active for this transformation, but the isolated GiVL yield was extremely low (from 5 to 12%, Table S1). Considering the effectiveness of Ru-based molecular catalysts for converting IA to a mixture of two isomeric lactones,[9c] we reasoned that Ru-NPs could be an appropriate catalyst for establishing the effective one-pot regioselective conversion of IA to GiVL if strategies and conditions could be identified for the required regioselectivity. In this context, we hypothesized that, if the carboxylic acid group that is conjugated with the external C=C double could be hydrogenated *selectively* and *concertedly* while leaving the unconjugated carboxylic acid group intact, then the resulting reduction intermediate, 3-methyl-4-hydroxybutanoic acid (3-MHBA), can be readily lactonized into the desired regioselective product GiVL (Scheme 1).

Guided by this hypothesis, we next investigated the hydrogenation/lactonization of IA by syngas with $Ru_3(CO)_{12}$ as the pre-catalyst under varied syngas pressure and H_2/CO ratios, catalyst loading, reaction temperature and time, as well as single and mixed solvent conditions, the selected results of which are summarized in Table 1. At 190 °C, the degradation temperature of the NP precursor to ensure complete thermal degradation to NPs,[23] the reaction with 0.3 mol% loading of $Ru_3(CO)_{12}$ in water for 36 h produced GiVL with an isolated yield increasing gradually from 0 to 15% as the H_2/CO pressure increased from 600 to 1950 psi (entries 1-4, Fig. S1). Keeping the pressure at 1950 psi, increasing the temperature from 190 °C to 250 °C enhanced the yield to 20% in 16 h (entry 5); the yield was further enhanced to 30% by increasing the Ru loading to 1.0 mol% (entry 6) and to 36% by increasing both the Ru loading to 1.0 mol% and the temperature to 282 °C (entry 7). Worth noting here is that when the reaction was performed at 150 °C, a temperature below the pre-catalyst decomposition threshold, no GiVL was obtained (entries 8 and 13). The GiVL yield was also affected by the reaction time as expected (entry 6 vs. 9; 10 vs. 11). Switching the solvent from water to THF reduced only the double bond to form 2-methylsuccinic acid (MSA) as the exclusive product (entry 12). On the other hand, the use of GiVL as a co-solvent with water in a 1:1 H_2O:GiVL ratio enabled the best isolated GiVL yield up to 70% upon some optimization efforts by adjusting the pre-catalyst loading from 0.4 to 1.3 mol% (entries 14-16, Fig. S2). The complete conversion of IA has been observed for all the experimental runs in the Table 1. The product distribution of IA hydrogenation under Table 1 conditions mainly consisted GiVL and MSA. All IA hydrogenation runs produced MSA as the major byproduct, and Table S2 summarizes detailed resultant product distributions. A small amount of αMGBL (2-5%) was also detected as a minor byproduct for runs 5-7 (Table S2). We also tested other NP catalyst systems such as Au-NPs supported on *m*-ZrO_2, which was reported to be selective in converting IA to GiVL (one data point by GC);[24] however, in our hands Au/*m*-ZrO_2 led to formation of a mixture of lactones $_{\alpha}$MGBL and GiVL.

To probe the origin of the observed regioselectivity in the reduction of IA to GiVL by the current Ru-NP catalyst system, we performed the following control experiments. First, the control reaction with H_2 (1000 psi, 190 °C, 36 h) instead of syngas ($2H_2/CO$) afforded a mixture of four products containing $_{\alpha}$MGBL, GiVL, 2-methyl-4-hydroxybutanoic acid (2-MHBA), and 3-MHBA (Fig. S3), highlighting the important role of CO in the regioselectivity of this hydrogenation. Second, changing the H_2:CO ratio in syngas to 3:1 also resulted in formation of a mixture of the above four products, while both 1:5 and 1:1 ratio gave a mixture of $_{\alpha}$MGBL, GiVL, and MSA (Figs. S4-5), indicating that 2:1 H_2:CO ratio is optimal for achieving the regioselectivity. Third, the hydrogenation of mesaconic acid (IA isomer with an internal double bond conjugated with both carboxylic groups, Scheme S1) and citraconic acid (*cis* isomer of mesaconic acid, Scheme S2) carried out under the identical conditions used for the IA hydrogenation afforded a mixture of $_{\alpha}$MGBL, GiVL, and MSA (Figs. S6-7). These results provide strong support for the hypothesis that, under the current conditions, IA is regioselectively reduced through concerted hydrogenation of the conjugated external C=C double bond and the carboxylic acid group. In contrast, mesaconic acid and citraconic acid–where both carboxylic acid groups are in conjugation with the internal C=C double bond—are not selective for reduction of only one carboxylic group. Fourth, subjecting the independently synthesized methyl-4-hydroxy-3-methylbutanoate (Fig. S8) to the current hydrogenation conditions led to formation of GiVL (Fig. S9) and subjecting the MSA to the current hydrogenation conditions led to negligible conversion and complete recovery of MSA post hydrogenation (Fig. S10) provided additional evidence for the involvement of intermediate 3-MHBA in the regioselective reduction of IA to GiVL, as depicted in Scheme 1.

Table 1. Selected results for conversion of IA to GiVL by Ru carbonyls via thermolysis. [a]

entry	pre-catalyst	catalyst loading [mol%]	solvent	syngas [psi at RT]	temp [°C]	time [h]	GiVL [%] [b]
1 [c]	$Ru_3(CO)_{12}$	0.3	H_2O	600	190	36	0
2	$Ru_3(CO)_{12}$	0.3	H_2O	1000	190	36	5 ± 1
3	$Ru_3(CO)_{12}$	0.3	H_2O	1500	190	36	10 ± 2
4	$Ru_3(CO)_{12}$	0.3	H_2O	1950	190	36	15 ± 2
5	$Ru_3(CO)_{12}$	0.3	H_2O	1950	250	16	20 ± 2
6	$Ru_3(CO)_{12}$	1.0	H_2O	1950	250	16	30 ± 2
7	$Ru_3(CO)_{12}$	1.0	H_2O	1950	282	16	36 ± 2
8 [c]	$Ru_3(CO)_{12}$	1.3	H_2O	1950	150	16	0
9	$Ru_3(CO)_{12}$	1.3	H_2O	1950	250	3	0
10	$Ru_3(CO)_{12}$	1.3	H_2O	1950	190	16	6 ± 2
11	$Ru_3(CO)_{12}$	1.3	H_2O	1950	190	38	18 ± 2
12	$Ru_3(CO)_{12}$	1.3	THF	1500	190	36	0

13 [c]	$Ru_3(CO)_{12}$	0.4	H_2O/GiVL	1500	150	12	0
14	$Ru_3(CO)_{12}$	0.4	H_2O/GiVL	1500	190	36	55 ± 2
15	$Ru_3(CO)_{12}$	1.0	H_2O/GiVL	1500	190	36	63 ± 2
16	$Ru_3(CO)_{12}$	1.3	H_2O/GiVL	1500	190	36	70 ± 2
17 [d]	$Ru(acac)_3$	0.2	H_2O	1950	195	36	0

[a] Conditions: 0.50 g of IA in 5.00 mL solvent. For entries 13-16, a 1:1 mixture of water and GiVL was used as solvent. [b] Isolated yield averaged based on duplicates (representative ^{1}H and ^{13}CNMR spectra of the isolated GiVL was provided in Figs S11-12). [c] 2-methylsuccinic acid formed exclusively with complete conversion of IA. [d] 2 mol % 1,4-bis(diphenylphosphino)butane was used as ligand.

In-situ generated TM-NPs were shown to be responsible for the LA-to-GVL conversion,[22] and glucose-to-5-hydroxymethylfurfural conversion[25] when the $Co_2(CO)_8$ and $Cr(CO)_6$ carbonyl complexes were employed, respectively. TM-carbonyl complexes are also known to rapidly decompose into their corresponding TM-NPs in the presence of an ionic liquid such as 1-butyl-3-methylimidazolium tetrafluoroborate ($[BMIm]BF_4$) under microwave irradiation.[26] To gain evidence for the *in-situ* generated Ru-NPs from the current hydrogenation system with $Ru_3(CO)_{12}$, we selected one of the post reaction samples obtained from the hydrogenation (entry 4, Table 1) for scanning transmission electron microscopic (STEM) analysis. The STEM images of the reaction sample withdrawn from the solution at the end of the IA conversion clearly revealed monodisperse Ru-NPs with an average size of NPs(100) of 2.4 ± 0.6 nm (Figure 1), while the STEM images of the control sample withdrawn before setting up the reaction (thermolysis of the carbonyl precursor), recorded under identical STEM conditions of the post-reaction sample, revealed the absence of Ru-NPs. These results are in line with the formation of the Ru-NPs during the reaction and not due to the STEM electron beam induction.[27] Moreover, EDS (Energy-dispersive X-ray spectroscopy) spectrum of Ru-NPs (Fig. S13) of the post IA hydrogenation reaction sample employing $Ru_3(CO)_{12}$ (entry 4, Table 1) revealed no oxygen associated with Ru or ruthenium oxide formation. In the current nanocatalysis for the IA hydrogenation/lactonization, the stabilization of Ru-NPs is likely provided by electrostatic repulsion derived from solvent (H_2O) induced NPs' surface polarization,[28] and Ru-NPs stabilized by solvent molecules are known in the literature. [29] In addition, a control experiment of IA hydrogenation with the homogeneous ruthenium(III) acetylacetonate $[Ru(acac)_3]$ catalyst system[9c],[16] revealed no GiVL formation (entry 17, Table 1). Hence, all the current evidence suggests *in-situ* generated Ru-NPs are responsible for the catalysis brought about in the hydrogenation of IA to GiVL by $Ru_3(CO)_{12}$.

To address the recyclability of supported Ru-NP catalysts, we preformed Ru-NPs derived from $Ru_3(CO)_{12}$ and stabilized by poly(vinylpyrrolidone) (PVP) with an average molecular weight of 40.0 kgmol^{-1}, Al_2O_3, and ZrO_2. Scheme S3 summarizes the conditions for the preparation of PVP-Ru-NPs. Al_2O_3-Ru-NPs, and ZrO_2-Ru-NPs were prepared using the same conditions. The TEM or STEM images of PVP-Ru-NPs (Fig. S14), Al_2O_3-Ru-NPs (Fig. S15), and ZrO_2-Ru-NPs (Fig. S16) confirmed the formation of the corresponding NPs with an average size of NPs(100) = 7.4 ± 2.6 nm, 2.8 ± 0.5 nm, and 3.7 ± 1.5 nm for PVP-Ru-NPs, Al_2O_3-Ru-NPs, and ZrO_2-Ru-NPs, respectively. The optimized conditions of IA-to-GiVL conversion with such supported Ru-NPs at loadings of 1.0 – 2.0 mol% was summarized in Table S3. Among these three supported Ru-NP catalysts, Al_2O_3-Ru-NPs gave the best performance in water, achieving >99% conversion of IA and 68% isolated GiVL yield under 1400 psi H_2/CO pressure at 215 °C (entry 5, Table S3). The GiVL yield can be further enhanced to 71% (entry 6, Table S3) with the H_2O/GiVL mixture as the solvent at a lower temperature of 150 °C (note the NPs were preformed and stabilized before the reaction). Thus, the conditions for achieving the highest GiVL yield of 71% were used for testing the catalyst recyclability, with the recovered Al_2O_3-Ru-NPs being reused for next IA hydrogenation under the same conditions. Note that the recovered Al_2O_3-Ru-NPs were thermally activated before being reused for the next IA hydrogenation cycle. The corresponding TEM of the first recovered NPs indicated an average size of NPs(100) = 2.9 ± 0.7 nm (Fig. S17), which is similar to the preformed Al_2O_3-Ru-NPs. As depicted in Fig. S18, Al_2O_3-Ru-NPs showed constant IA conversions of ~99% but with a slight drop in the isolated GiVL yield from 62 to 54% throughout each of the five cycles.

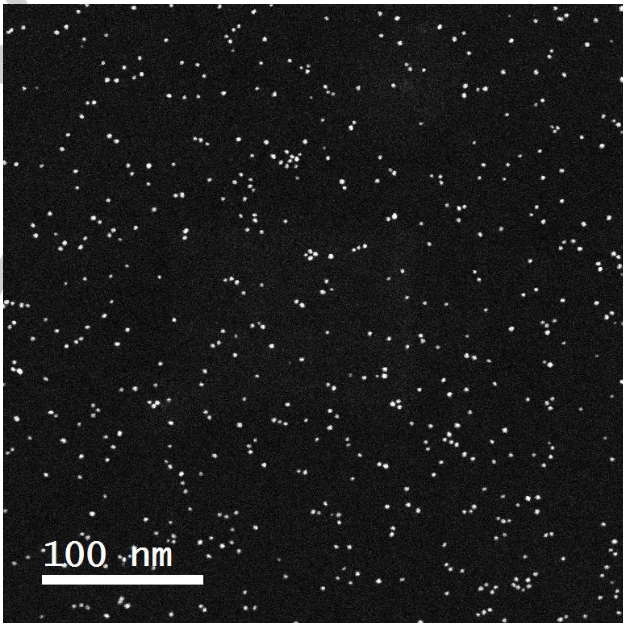

Figure 1. STEM image of Ru-NPs obtained using the post IA-to-GiVL reaction sample employing $Ru_3(CO)_{12}$ (entry 4, Table 1). The NPs(100) average size is 2.4 ± 0.6 nm.

In summary, we have developed a direct, one-pot regioselective conversion of bio-based IA into value-added GiVL in ~70% isolated yield via regioselective hydrogenation/lactonization of IA with $Ru_3(CO)_{12}$ and syngas ($2H_2$:CO) in water or a water/GiVL mixture. The results obtained from multiple experiments and controls showed that *in-situ* generated Ru-NPs are responsible for the regioselective catalysis, while the presence of CO and the H_2/CO ratio of syngas as well as the chemical structure of IA are also critical for achieving regioselectivity. Based on the evidence gathered by this study, it is postulated that when the carboxylic acid group conjugated to the external C=C double in IA is hydrogenated *selectively* (leaving the other carboxylic acid group intact) and *concertedly* (together with the C=C double bond) to form intermediate 3-MHBA, the desired regioselectivity is achieved. On the other hand, catalysts, substrates, and conditions that lead to hydrogenation of the double bond first, namely via MSA intermediate, promote a non-regioselective transformation, resulting in a mixture of isomeric lactones and often other species. Supporting the preformed Ru-NPs on polymer or oxide surfaces such as Al_2O_3 led to stabilized and supported Ru-NPs with good recyclability.

Experimental Section

The Supporting Information contains experimental details, as well as Tables and Figures referred to in the text.

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Keywords: itaconic acid • γ-isovalerolactone • syngas • hydrogenation • nanoparticle catalyst

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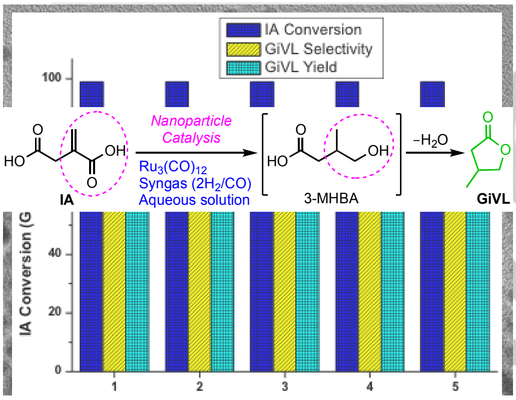
Layout 1:

COMMUNICATION

Nano-Bio: *In situ* generated transition-metal nanoparticles (Ru-NPs) catalyze regioselective hydrogenation of IA by syngas ($2H_2$:CO) into GiVL in ~70% isolated yield. Key sustainability features of this new route include: a one-pot direct transformation of bio-renewable IA into value-added GiVL selectively, use of inexpensive and renewable syngas in aqueous solution, and development of a supported recyclable NP catalyst system, Al_2O_3-Ru-NPs.



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Regioselective Hydrogenation of Itaconic Acid to γ-Isovalerolactone by Transition-Metal Nanoparticle Catalysts