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A Prolific Catalyst for Selective Conversion of Neat Glycerol to Lactic Acid

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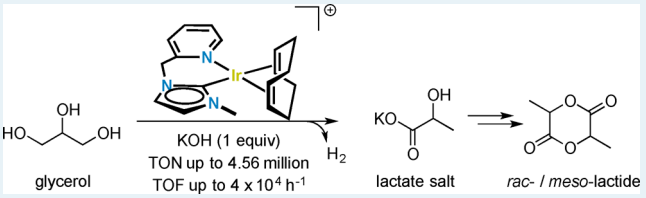
Supporting Information

ABSTRACT: We report the synthesis and reactivity of a very robust iridium catalyst for glycerol to lactate conversion. The high reactivity and selectivity of this catalyst enable a sequence for the conversion of biodiesel waste stream to lactide monomers for the preparation of poly(lactic acid). Furthermore, experimental data collected with this system provide a general understanding of its reactive mechanism.



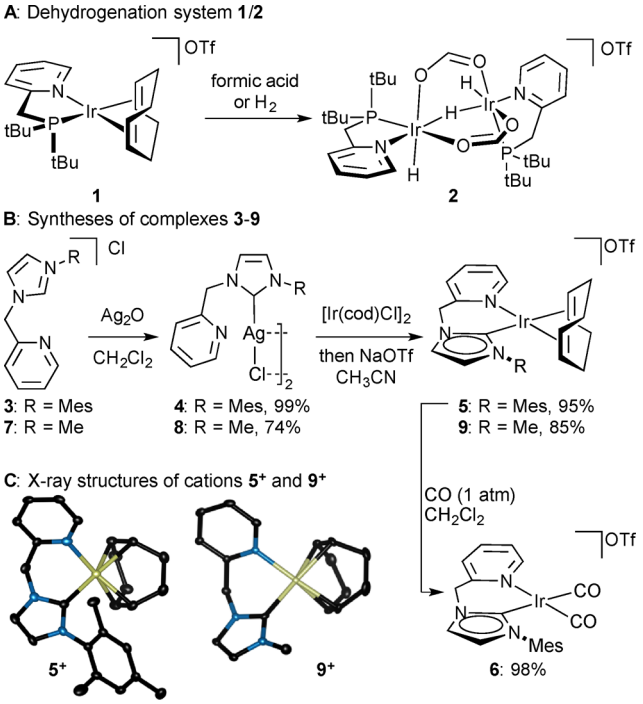
KEYWORDS: *glycerol, lactic acid, iridium, dehydrogenation, biodiesel*

Glycerol is a byproduct of biodiesel production and of other fine chemical syntheses, such as those of perfumes, fragrances, and pharmaceuticals.[1] Currently the biodiesel industry in the United States produces 2.0 billion gallons of glycerol each year,[2] with an increase projected in the future.[3] Because glycerol constitutes about 10% of the weight of crude biodiesel, the utilization of this "waste" is an opportunity for new technology.[4] Significant effort has been invested in catalytic conversion of glycerol to value-added products.[5] Selective dehydrogenation of glycerol to lactic acid is particularly appealing, because lactic acid is both a valuable feedstock for organic synthesis and a precursor for poly(lactic acid) (PLA), a biodegradable polymer. The market demand of PLA is estimated at 150 000 tons by 2017 and 400 000 tons by 2022.[6] Moreover, when such conversions are conducted by acceptorless dehydrogenation, the byproduct H_2 is a readily separable energy carrier that has value as such. In these regards, homogeneous conversion of glycerol to lactic acid has shown promising reactivity and good selectivity.[7]

Here we report the most robust and selective catalyst to date for the conversion of glycerol and new insights into its reactive mechanism. Our system enables high conversion of neat glycerol, even if isolated crude from biodiesel production, to sodium lactate with >99% selectivity. We also show that lactic acid can be easily isolated from our reaction mixture and then converted to *rac*- and *meso*-lactides, the precursors for PLA synthesis.

Our entry into glycerol dehydrogenation stemmed from our diiridium catalyst (**2**) for formic acid dehydrogenation (Scheme 1a).[9] In this prior study, we found that **2** forms from monomer **1** and that the (pyridyl)methylphosphine ligand plays a vital part in enabling dimer formation and catalyst longevity: other P−N and C−N ligands did not efficiently dimerize or display the reactivity of **1**/**2**. We further observed that once dimerized, complex **2** had little dehydrogenation reactivity with substrates other than formic acid. On these bases, we designed complexes **5** and **9** (Scheme 1bc), which feature bidentate (pyridyl)methylcarbene ligands that apparently inhibit an analogous dimerization and enable more general dehydration reactivity.

Scheme 1. (A) Formic Acid Dehydrogenation System 1/2, (B) Syntheses, and (C) Molecular Structures[8] of Novel Iridium Complexes[a]



[a]Ellipsoids drawn at the 50% probability level.

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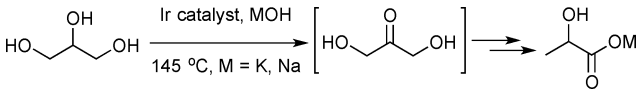
Table 1. Dehydrogenation of Neat Glycerol to Lactic Acid[a]



entry	catalyst (ppm)	temp (°C)	time	base (mol %)	TON	conversion
1	20 (**5**)	145	3 day	25	12964	25.9%
2[b]	0.1 (**5**)	145	8 days	25	1057172	10.5%
3	20 (**5**)	145	6 days	50	14901	29.8% (22%)[c,d]
4	20 (**5**)	145	6 days	100	17285	34.6%
5	100 (**5**)	180	1 h	1	119	1.2%
6	100 (**5**)	180	1.5 h	10	1162	11.6%
7	20 (**5**)	180	10 h	10	5215	10.4%
8	20 (**5**)	180	15 h	25	13113	26.2%
9	20 (**5**)	180	15 h	50	15894	31.9%
10[e]	200 (**5**)	145	5 days	50	1909	38.2%
11[e]	200 (**5**)	145	5 days	100	3445	68.9%
12	20 (**6**)	145	6 days	50	7490	15.0%
13	20 (**6**)	145	6 days	100	10785	21.6%
14	20 (**9**)	145	3 days	50	25015	50.0% (37%)[c]
15	20 (**9**)	145	3 days	100	37083	74.2% (54.0%)[c]
16[b]	0.1 (**9**)	145	32 days	100	4557487	45.6%
17[e,g]	20 (**9**)	145	7 days	100	40889	81.7% (55.6%)[c]
18[f,g]	140 (**9**)	145	7 days	100	45010	90.0% (61.2%)[c]

[a]Typical reaction conditions are 5 mL of glycerol, Ir catalyst, and base (KOH/NaOH weighed and mixed in air). Reaction progress was monitored by gas evolution. [b]The reaction started with 100 mL glycerol and was active when quenched. [c]Isolated yield. [d]73% based on conversion. [e]The volume of glycerol is 2 mL in this reaction. [f]9.3 g of glycerol isolated from biodiesel transesterification was used. [g]NaOH is used in place of KOH.

Heating compound **5** in air with KOH and glycerol results in the selective formation of H_2 and lactate (>95%, Table 1) with *no other products detectable*. For example, in a particular run, we observe absence of common side products in glycerol oxidation, such as ethelene glycol, proplene glycol, and 1,3-propane diol by NMR; GC data corroborate the absence of any nonproduct signals (see Supporting Information). The robustness of the catalyst is evident from an experiment in which we observe over 1 million turnovers in 8 days (entry 2). This TON is higher than any other homogeneous system reported to date. For example, maximum reported turnover number (TON) for the Crabtree (Ir)[7a] and Beller (Ru)[7b] systems are 30 100 and 256 326, respectively. In a case of a polymeric iridium catalyst, the maximum TON is 124 000.[7c] Further, our system is robust at higher temperatures: at 180 °C the reaction time is shortened from days to hours (entries 5−9). We think that the greater stability and longevity of catalyst **9** is due, in part, to the bidentate architecture of the (pyridyl)carbene. This appears to inhibit ligand scrambling processes, which are observed in the Crabtree system.[7a]

Because these reactions are free of solvent, the medium is very viscous, and the hydroxide base is a partially dissolved suspension. Upon completion, the reaction mixture comprises mostly lactate salt. Thus, the reaction reaches a solid, unstirrable state at its end, when H_2 ceases to evolve. At this point, the reaction system is no longer a fluid. The reaction rate slows after ca. 25−30% conversion. We expect that this is a result of the very high viscosity of the reaction mixture limiting mixing and heat flow, rather than chemical deactivation of the catalyst itself. Accordingly, higher catalyst loading will affect higher conversion (compare entries 4 and 11).

While **5** is very robust, we sought a faster and more efficient catalyst. Unlike Crabtree's iridium systems,[7a] our CO-coordinated catalyst precursor (**6**) shows a mild *decrease* in catalytic reactivity relative to **5** (compare Table 1, entries 4 and 13). We find, however, that the less sterically hindered pyridine-carbene complex **9** enables more rapid reactions than **5**. For example, in a typical run with a catalyst loading as low as 20 ppm, over 80% of glycerol can be converted to lactate (entries 17, 18). This conversion is higher than any other homogeneous catalyst in neat glycerol. In a particular run, **9** remains reactive over 32 days delivering a total *TON of over 4.5 million* (Table 1, entry 14). The catalysis is fast at 145 °C, with a turnover frequency (TOF) of up to $4 \times 10^4\ h^{-1}$ in the first hour, and the reaction also takes place at as low as 110 °C, with a TOF up to 190 h^{-1} in the first hour. By switching the base to NaOH, the reaction eudiometry kinetic profile appeared a little slower yet steadier through a higher conversion; furthermore, the sodium salt enables more facile product isolation (vide infra).

While our reaction mixtures are suspensions because of the sparing solubility of the hydroxide base, we find that that dehydrogenation catalysis is most likely homogeneous on the basis of (1) physical appearance, (2) clean kinetics, and (3) tolerance of liquid mercury. Quantitative poisoning results are less useful with this reaction:[7,10] surprisingly, 1,10-phenanthroline, a popular catalyst poison that quantitatively deactivates **2** in formic acid dehydrogenation, was found to have no significant impact on the reaction kinetics, even when present in large excess (35 equiv to [Ir]). We thus find that **9** is tolerant of nitrogen-containing compounds. Triphenylphosphine, another strong poison for homogeneous iridium catalysts, was also used in our glycerol dehydrogenation reaction. With a substoichiometric amount of the poison (0.5 equiv to [Ir]), the reaction rate is within error of the parent. With 600 equiv of triphenylphosphine to catalyst, the reaction stopped after ca. 3% conversion, 1500 TON.

Key to the value of this contribution is the ability to convert crude output from biodiesel production to value added material. Along these lines, we have demonstrated the conversion of soybean oil to fatty acid methyl esters (FAMEs, a biodiesel

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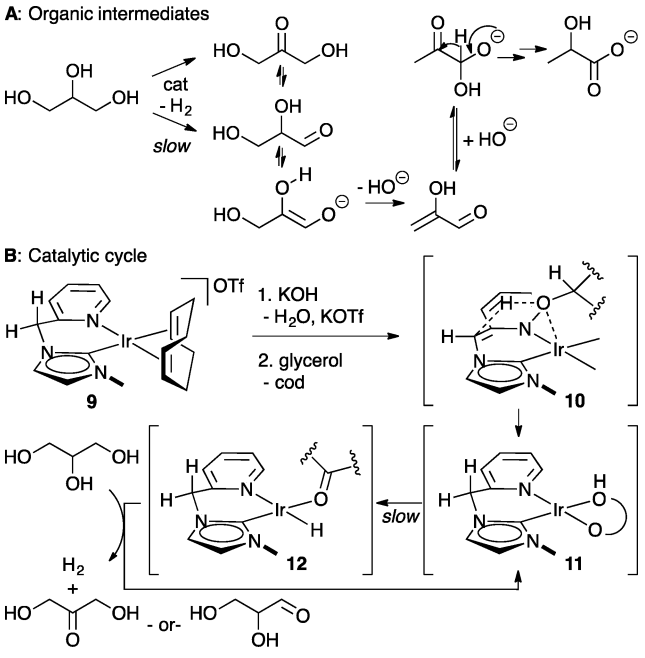
component) and crude glycerol, then further conversion of the resulting crude glycerol to lactate salt. Thus, we treated 100 mL (93.2 g) of Wesson soy bean oil with sodium methoxide and successfully isolated 100 mL of FAMEs and 9.3 g glycerol, the latter with >95% NMR purity. With no purification other than solvent removal, this glycerol was catalytically converted to an isolated aliquot of 5.6 g of lactic acid.

Of further importance to the utility of this technology is a facile route to convert the crude lactate salt to *rac*- and *meso*-lactide monomers for use in poly(lactic acid) synthesis. We have achieved this using a simple pH extraction followed by known transformations for lactide preparation (see Supporting Information). Thus, lactic acid can be thermally oligomerized directly from our concentrated extract to yield a prepolymer, which can then be treated with SnO to convert the material to crude *rac*- and *meso*-lactide mixture. Recrystallization of the lactide mixture successfully afforded *rac*-lactide with high purity and a yield of 69% from crude lactic acid, with a small fraction of *meso*-lactide available from the mother liquor.

Beyond glycerol conversion, we find that **9** is a catalyst for general alcohol dehydrogenation. For example, we can effect methanol dehydrogenation in a refluxing alkaline solution of 25% aqueous methanol. From the reaction solution, we evolve hydrogen with 461 turnovers of H_2 in 12 h and isolate a crystal $Na_2CO_3{\cdot}NaHCO_3{\cdot}H_2O$ as the byproduct.

Although we do not yet have a complete understanding of the mechanism of our reaction, we do have a working model (Scheme 2). The fate of the organic species is known:[11] an initial,

Scheme 2. Mechanistic Model for Catalytic Glycerol Dehydrogenation with 9



rate-determining dehydrogenation of either of the alcohol positions of glycerol enables facile dehydration and rearrangement according to Scheme 2a. We know that catalytic oxidation is the slow step in this sequence for us because we see no organic species other than glycerol and lactate >1% by NMR under the catalytic conditions. In addition, conversion of glyceraldehyde to lactate is known to be rapid at temperatures as low as 25 °C in alkali media.[12]

More interesting to us is the mechanism of the catalytic oxidation cycle (Scheme 2b). We propose that the active catalytic species is monomeric: unlike species **1**, species **5** and **9** do not undergo dimerization in the presence of buffered formic acid and lack **1**'s reactivity in formic acid dehydrogenation. Particularly, under comparable conditions (140 ppm [Ir], 280 ppm base in 2 mL HCO_2H, 3.5 h), a **1**-catalyzed reaction undergoes >97% conversion of formic acid, whereas the conversion is below 3% when **5** or **9** is used. Conversely, **1** does not lead to efficient glycerol to lactate conversion under the conditions used in Table 1. In a representative example, when 200 ppm **1** is heated with glycerol and hydroxide, lactate is formed with <5% conversion at the point that catalyst turnover ceases.

Unfortunately, study of this mechanism is frustrated by a complicated network of exchangeable protons and rapidly substituting labile oxygen ligands. We believe that catalysis initiates from **9** by solvent displacement of **9**'s cyclooctadiene ligand, which we observe to be rapid, even at room temperature. We then believe that our ligand is deprotonated to make a charge-neutral complex. This deprotonated form of **9** is deeply purple in color, which is observed at room temperature only when **9** is treated with base in the absence of glycerol.[13] If **9** is treated with base in the presence of glycerol, the red solution of **9** assumes a light yellow color, which is characteristic of our working catalyst. We therefore expect that the deprotonated catalyst cleaves glycerol's O−H bond cooperatively, rather than by simple proton transfer, because we observe that **9** is more acidic than glycerol. One possibility for this O−H cleavage is illustrated as **10**. We think that the catalyst rests as a mixture of coordination adducts of deprotonated glycerol, which are sketched as **11**.

We used dehydrogenation of 1-phenylethanol as simplified model to probe reaction kinetics. The turnover-limiting step of catalysis appears to be β-hydride elimination from an iridium alkoxide such as **11**. Three key data points support this finding: (1) we observe a first-order dependence on the concentration of the alcohol substrate, which is inconsistent with rate-determining H−H bond formation or H_2 loss. (2) We find an insignificant $KIE_{OH/OD}$ of 1.1(1), which is inconsistent with kinetic relevance of any transition state involving O−H cleavage or H−H formation. (3) A more electron-rich substrate, 1-(4-methoxyphenyl)ethanol, dehydrogenates with a rate ca. 3 times faster than 1-phenethylethanol. This indicates a negative (electrophilic) Hammett reaction parameter, which is better fit to β-hydride elimination than H−H bond formation or ligand substitution as a turnover-limiting step.[14]

We do not know which hydroxyl group of glycerol is oxidized: in two parallel experiments in which aqueous solutions of ^{i}PrOH and ^{n}PrOH are dehydrogenated with **9** and base, we see rates that are identical within error. Either of these β-hydride elimination reactions should form an iridium hydride, which is sketched as **12** in Scheme 2. Hydrogen is likely released from hydride **12** by protonation with an alcohol O−H group. While we see no evidence for an iridium hydride under the catalytic conditions, we can observe a diversity of iridium hydride species at room temperature when **9** is treated with a stoichiometric portion of isopropanol in alkaline solution. We therefore find that an iridium hydride is a plausible intermediate, although not a resting state of catalysis.

In conclusion, we present here a high-utility technique for the conversion of crude glycerol to value-added lactides based on the oxidative conversion of glycerol to lactate. This oxidation utilizes a structurally novel iridium catalyst supported by a bidentate

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(pyridylmethyl)imidazolium carbene ligand. The new catalyst system enables unprecedented efficiency, longevity, and conversion in the oxidation of glycerol to lactic acid and thus enables a very practical alternative to fermentation compared to those currently available for lactic acid preparation. The reactive mechanism of this new system is proposed on the basis of experimental evidence: oxidation involves turnover-limiting β-hydride elimination to form dihydroxyacetone, which is converted rapidly to lactate. Investigations of the broader utility of **9** and its mechanism for alcohol dehydrogenation are underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.5b02732. CDCC #1438246 (**5**) and #1438247 (**9**) contain supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Experimental procedures, graphical, and tabular characterization information (PDF)
X-ray data for **5** (CIF)
X-ray data for **9** (CIF)
The carbonate product of methanol dehydrogenation, as described in the SI (CIF)

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Notes

The authors declare no competing financial interest.

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