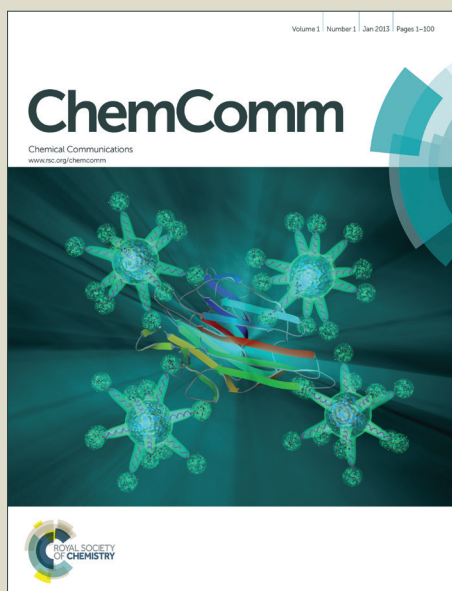


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COMMUNICATION

Selective Conversion of Glycerol to Lactic Acid with Iron Pincer Precatalysts

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A family of iron complexes of PNP pincer ligands are active catalysts for the conversion of glycerol to lactic acid with high activity and selectivity. These complexes also catalyse transfer hydrogenation reactions using glycerol as the hydrogen source.

Finding practical ways to transform biomass into more valuable products is an important current challenge.¹ One such bio-feedstock, glycerol, has received much attention as a biodiesel waste product (~10 wt.%).^{2,3} There is considerable interest in finding ways to convert this "crude glycerol", currently mostly incinerated, into value-added products.^{2,3,4} Several studies⁵ have sought to transform glycerol into lactic acid (LA), which is used extensively in the food industry and is a platform chemical for the synthesis of green solvents and biodegradable polymers.⁶ Presently, the main source of LA is bacterial fermentation of sugars. However, as a result of several drawbacks associated with this process, including complex purification procedures, low productivity, and poor scalability, it is important to find alternative methods of producing LA to meet the growing demand for this platform chemical.^{6,7}

Glycerol conversion to LA is generally carried out using heterogeneous catalysts, which often require harsh reaction conditions and give low selectivities.^{5,6} Recently, our group⁸ and Beller⁹ reported the first examples of homogeneous catalysts for the conversion of glycerol to LA (Figure 1). These complexes give significantly higher selectivity and activity than the known heterogeneous systems and can also convert crude glycerol from the biodiesel industry to LA without prior purification. However, catalysts based on sustainable first-row metals are required to make this reaction more relevant for industrial applications. We postulated that homogeneous Fe complexes with ancillary bifunctional PNP ligands (Table 2, Complexes 1-6), which have previously shown remarkable activity as catalysts for the dehydrogenation of a range of substrates, such as formic acid,¹⁰ primary and secondary alcohols¹¹ including methanol,^{12,13} and nitrogen containing heterocycles,¹⁴ could be used for glycerol dehydrogenation. Here, we describe the selective conversion of

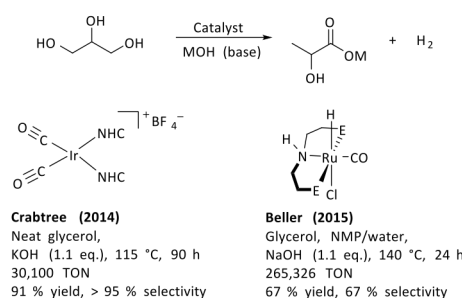


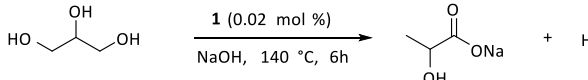
Figure 1. Previously reported homogeneous catalysts for glycerol conversion to LA. NHC = 1,3-dimethylimidazol-2-ylidene; E = PⁱPr₂.

glycerol to LA using these complexes and also show that they can be utilized for transfer hydrogenation (TH) with glycerol as the hydrogen source. This is a rare example of glycerol upgrading using a homogeneous base-metal catalyst.¹⁵

The ⁱPrPNP¹⁶ pincer borohydride complex, **1**,¹⁷ (ⁱPrPNP = bis((2-diisopropylphosphino)ethyl)amine) is a convenient entry into reactive Fe dihydrides and related species. We initially explored glycerol conversion to LA at 140 °C in several solvents using 0.02 mol % **1** and 1 eq. NaOH vs. glycerol (Table 1). Using a mixture of 1:1 N-methyl-2-pyrrolidinone (NMP)/water as the solvent, glycerol is converted to LA and H₂, as identified by ¹H NMR spectroscopy and GC, respectively (Table 1, Entry 1 and Figure S2). A turnover number (TON) of 770 was achieved after 6 h. Other solvent mixtures, as well as neat glycerol, which was used in our previous Ir system,⁸ resulted in lower activity (Table 1, Entries 2-10; Tables S1 & S4). Beller and co-workers previously utilized an NMP/water co-solvent mixture for glycerol dehydrogenation using a Ru catalyst.⁹ Interestingly, our ¹H NMR analysis of the post-catalytic reaction mixture revealed that ~60 % of the NMP undergoes ring opening to give sodium-4-N-methylaminobutanoate, **7**. This ring opening occurs in both the absence and presence of **1**, suggesting that a potential pathway is nucleophilic attack on NMP by hydroxide under the basic reaction conditions. However, **7** is not likely catalytically relevant, since addition of 200 equiv. of authentic¹⁸ **7** does not improve the activity of complex **1** in DMSO (Entry 3), and replacement of NMP/water with **7**/water gives lower activity (Table S1). The reaction is dependent on both base loading and temperature, with 140 °C and 1 eq. base being optimal, while bases weaker than hydroxide were not effective and no reaction occurs in the absence of base (Table S2).

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† Electronic Supplementary Information (ESI) available: Experimental details and selected spectra. See DOI: 10.1039/c000000x/

Table 1. Solvent screen for glycerol dehydrogenation catalyzed by **1**.


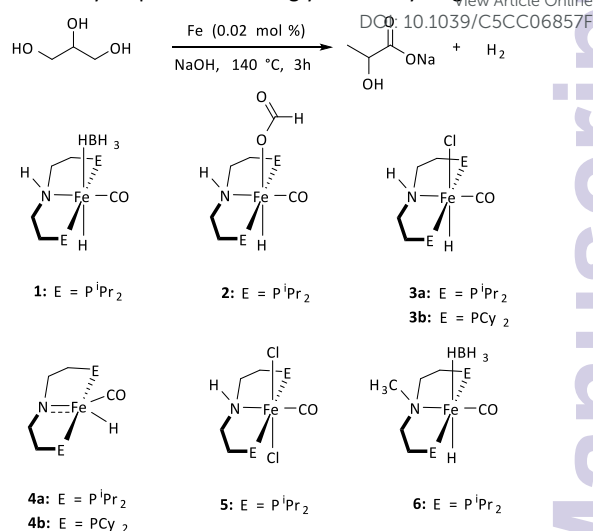
Entry	Co-solvent	TON ^a
1	NMP/water 1:1	770
2	NMP	71
3	DMSO/water 1:1 ^b	350
4	Diglyme/water 1:1	100
5	HMPA/water 1:1	55
6	Dioxane/water 1:1	30
7	Xylene/water 1:1	6
8	Propylene carbonate/water 1:1	<1
9	Water	7
10	none	3

Experiments run for 6 h at 140 °C with **1** (1.5 μmol, 0.02 mol %), glycerol (0.5 mL), co-solvent (1 mL) and NaOH (1 eq. vs. glycerol). ^aTON calculated based on yield of LA averaged over 2 experiments using ¹H NMR integration with sodium(3-trimethylsilylpropionate)2,2,3,3-d₄ as an internal standard. ^bAddition of 0.3 mmol **7** (200 equiv. vs. **1**) did not affect the yield.

Decreasing the reaction time to 3 h using **1** as the catalyst gave no change in TON, implying catalyst deactivation by this time (vide infra) (Table 2). Notably, after 3 h selectivity for LA is excellent (81 % of converted product for Table 2, entry 1; 16 % overall yield), close to that in our Ir-NHC complexes (> 95 %) and surpassing the previous Ru-PNP system (67 %). Formic acid (< 1 % of converted product; ~ 0.2% overall yield) was identified as a side product by ¹H NMR spectroscopy. However, the major class of characterized side product (18 % of converted product; 3 % overall yield) were assigned as oligoglycerols formed from glycerol etherification¹⁹ (see SI). These species form at 140 °C both in the presence and absence of catalyst and co-solvent.

We next screened a family of related Fe-PNP complexes under the optimized reaction conditions (0.02 mol % Fe; NMP/water; 1 eq. NaOH; 140 °C; 3 h; Table 2). Among the ⁱPr-PNP complexes, the formate species¹⁰ **2**⁺ and the hydrido-chloride compound¹⁷ **3a** show similar activity to **1** (Entries 2-3), with **2** giving the highest activity, 880 TON after 3 h. Complex **2** also gave superior activity in catalytic methanol dehydrogenation, attributed to its stability to decomposition in the presence of water prior to heating.¹² Consistent with this idea, the more reactive amido complex **4a**¹⁰ is less active (Entry 4) and undergoes an immediate color change upon addition of water, suggesting that initial decomposition is competing with catalysis. Finally, the dichloride precursor **5**¹⁷ shows negligible activity under the reaction conditions, implying that Fe hydrides are required to promote catalysis (Entry 5). Substitution of the phosphine R-groups from ⁱPr to the bulkier cyclohexyl¹⁷ gives considerably decreased activity (Entries 7, 8). Complex **6**,²⁰ with an N-methylated PNP ligand is much less active than its -NH analogue **1** (Entry 6), showing the importance of the bifunctional PNP ligand. The reaction does not occur with free ligand or simple Fe compounds (Entries 9-11).

Reaction profiles of the most active complexes, **1**, **2**, **3a** and **4a**, were generated by monitoring H₂ production using a gas burette (Figure 2). These complexes are initially highly active but lose activity after ~0.5 h. The decrease in H₂ production is concurrent with a loss of color of the reaction mixture, indicative of catalyst decomposition. These plots show no induction period or sigmoidal shape and are consistent with homogeneous catalysis, in agreement with prior homogeneity studies with these complexes

Table 2. Precatalyst optimization for glycerol dehydrogenation.

Entry	Complex	TON ^a	Conversion (%) ^b	Selectivity (%) ^c
1	1	770	20	81
2	2	880	24	83
3	3a	800	20	81
4	4a	560	16	79
5	5	15	<1	45
6	6	130	3	68
7	3b	290	7	70
8	4b	48	<1	55
9	ⁱ Pr(PNP) ligand	0	<1	-
10	FeCl ₂	0	<1	-
11	Fe(OTf) ₂	0	<1	-
12	None	0	<1	-

Experiments run for 3 h at 140 °C with Fe (0.02 mol %), glycerol (0.5 mL, 6.7 mmol), NMP (0.5 mL), water (0.5 mL) and NaOH (6.7 mmol). ^aTON calculated based on yield of LA averaged over 2 experiments. ^bCalculated by ¹H NMR integration using sodium(3-trimethylsilylpropionate)2,2,3,3-d₄ as an internal standard. ^cCalculated as yield of LA divided by conversion of glycerol.

(eg. quantitative poisoning^{9,10,11} kinetics^{9,10,11,14} excess ligand addition¹⁴ and Hg drop test^{10,14}). We next optimized the yield and TON using complex **1**, which is the most synthetically accessible species (Table 3). Increasing the catalyst loading from 0.02 to 0.1 mol % only slightly increases LA yield over 6 h (20 vs. 16 % yield) while decreasing the loading to 0.004 mol % gives an increased TON of 1050. This is consistent with a second order catalyst deactivation process that can outcompete catalysis at higher catalyst loading. Indeed, a similar concentration dependence was observed in methanol dehydrogenation catalysed by **4b**, and was attributed to formation of deactivation products via bimolecular pathways.¹² One strategy to minimize such deactivation is to add the precatalyst in smaller aliquots throughout the reaction.²¹ Sequential addition of 0.2 mol % **1** at five 1 h intervals (See SI page S3 for details) gives significantly higher yield (34 vs. 20 %) as well as selectivity (88 vs. 70 %) for LA. Finally, we attempted to convert a sample of crude glycerol from a biodiesel plant⁸ to LA using our optimized conditions. Activity was considerably lower (35 TON) but still above conversion without catalyst.

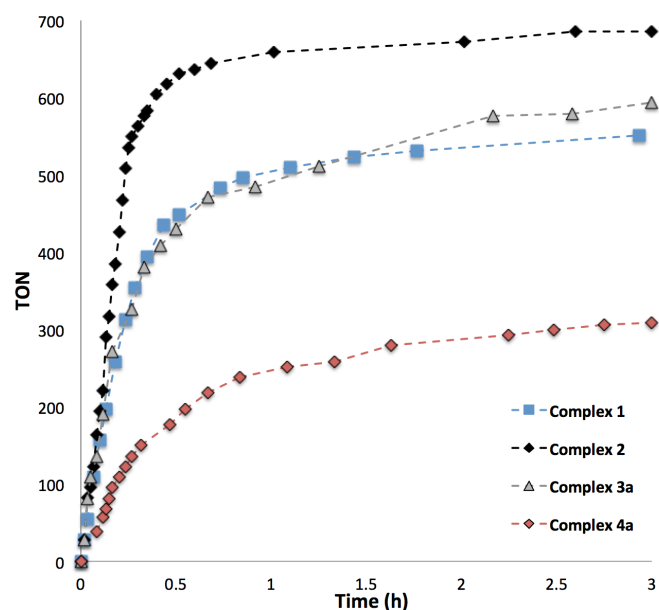


Figure 2. Reaction profiles for glycerol dehydrogenation with Fe-PNP complexes **1**, **2**, **3a**, and **4a**. Experiments run at 140 °C with Fe complex (0.02 mol %), glycerol (0.5 mL, 6.7 mmol), NMP (0.5 mL), water (0.5 mL) and NaOH (6.7 mmol). Reaction progress monitored using a gas burette (See SI for details).

Table 3. Optimization of conversion and TON with **1**.

Entry	Loading (%)	TON ^a	Conversion (%) ^b	Selectivity (%) ^c
1	0.2	90	25	80
2 ^d	0.2	150	39	88
3	0.004	1050	4	55 ^e
4 ^f	0.02	35	1	46

Experiments run for 6 h at 140 °C with **1** (0.02 mol %), glycerol (0.5 mL, 6.7 mmol), NMP (0.5 mL), water (0.5 mL) and NaOH (6.7 mmol). ^aTON calculated based on yield of LA averaged over 2 experiments. ^bCalculated by ¹H NMR integration using sodium(3-trimethylsilylpropionate)2,2,3,3-d₄ as an internal standard. ^cCalculated as yield of LA divided by conversion of glycerol. ^dCatalyst added in 5 increments during reaction. ^eDecreased selectivity is due to the fact that relatively less LA is formed compared to background base catalyzed glycerol etherification reactions. ^fCrude glycerol used instead of glycerol.

Based on our experimental results and prior studies, we propose the following mechanism for the glycerol dehydrogenation reaction (Figure 3). Complexes **1** and **2** likely access the catalytic cycle by conversion to dihydride **8**, either through base (OH⁻) assisted loss of BH₃ from **1**²² or Lewis acid (Na⁺) assisted decarboxylation of **2**.¹⁰ Complex **3** is converted to **4** through deprotonation of the amine with concomitant loss of chloride.¹⁰ The amide **4** dehydrogenates glycerol to give the dihydride complex **8** and glyceraldehyde in step (i). Subsequently, glyceraldehyde is converted to LA through a series of base catalyzed reactions, which do not require a transition metal catalyst,⁸ namely dehydration, tautomerization and an intramolecular Cannizzaro reaction, steps (ii), (iii) and (iv), respectively. Finally, LA is trapped as lactate through deprotonation, and **8** spontaneously releases H₂ to regenerate **4**.¹⁰

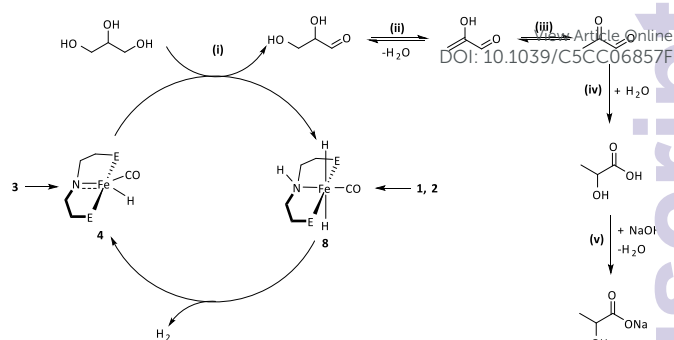


Figure 3. Proposed mechanism for glycerol conversion to LA with Fe-PNP complexes.

Given the activity of our Fe-PNP complexes for acceptorless glycerol dehydrogenation as well as the hydrogenation of several substrates,^{11,14,21} we hypothesized that they might show activity for TH²³ reactions using glycerol as the solvent and hydrogen source. TH reactions are desirable because they avoid the free H₂ used in typical hydrogenation procedures.^{23b} Additionally, there has been recent interest in using glycerol as an inexpensive solvent in organic reactions.²⁴ However, previous examples of TH using homogeneous precatalysts and glycerol use precious metals²⁵ or require high temperatures (170–230 °C).²⁶ We screened complex **1** for TH of acetophenone with glycerol at 120 °C for 22 h (Table 4). Indeed, acetophenone is reduced to 1-phenylethanol with 2.5 mol % **1** using NMP or dioxane as the co-solvent (Tables 4 & S6). The reaction is dependent on both base loading and co-solvent, with 10 equiv. KOH and NMP as co-solvent giving the best results (95 % yield, Entry 3). Yields are lower with simple Fe compounds or in the absence of a catalyst (Entries 4–5). We cannot exclude the possibility that nanoparticles are involved in the TH catalysis;^{25d,27} However, as described previously there is significant evidence that these Fe-PNP catalysts are homogeneous in several related reactions.^{10,11,14}

Table 4. TH of acetophenone using **1**.

Entry	Catalyst	Eq. KOH vs. substrate	Yield (%)
1	1	1	27
2	1	5	80
3	1	10	95
4	FeCl ₂	10	36
5	none	10	32

Experiments run for 22 h at 120 °C with Fe (2.5 mol %), glycerol (0.4 mL), NMP (0.4 mL) and KOH. ^aYield calculated based on yield of 1-phenylethanol using ¹H NMR integration with sodium(3-trimethylsilylpropionate)2,2,3,3-d₄ as an internal standard.

In conclusion, we report the first example of homogeneous glycerol conversion to LA using a base metal catalyst. Our system gives superior selectivity compared with previous heterogeneous systems, but further improvements are required to match the activity of homogeneous precious metal catalysts. In addition, we demonstrate TH of acetophenone using complex **1** and glycerol. Further work will explore the mechanisms of these transformations in more detail.

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Notes and references

[†] As part of this work **2** was characterized by X-ray crystallography (See SI). The solid state structure is consistent with a hydrogen bond between the N-

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