Transfer Hydrogenation from Glycerol: Activity and Recyclability of Iridium and Ruthenium Sulfonate-Functionalized N-heterocyclic Carbene Catalysts

*Arturo Azua, Matt Finn, Hannah Yi, Ana Beatriz Dantas, Adelina Voutchkova-Kostal**

Department of Chemistry, The George Washington University, 800 22nd St NW, Washington, DC 20052.

KEYWORDS: transfer hydrogenation, reductive amination, N-heterocyclic carbene, ruthenium, iridium, recycling

SYNOPSIS Comparison of activity, selectivity and recyclability of Ir and Ru NHC-based catalysts for transfer hydrogenation of carbonyls, imines and olefins from glycerol.

Abstract

Three ruthenium(II) and two iridium(III) N-heterocyclic carbene (NHC) complexes functionalized with sulfonates are compared with respect to their activity and selectivity for the transfer hydrogenation of imines, aldehydes, ketones and olefins using neat glycerol as hydrogen donor and solvent. Four of the five catalysts likely proceed through a monohydride mechanism, and are more active for TH of imines than aldehydes, ketones and olefins. The fifth catalyst likely proceeds through a dihydride mechanism, and is found to be more active for carbonyls than imines and olefins. Lactic acid is observed as the only detectable byproduct from glycerol. Quantitative

poisoning experiments with 1,10-phenanthroline suggest a predominant catalytically active species is a ligated homogeneous complex with weak binding to the poison. The potential for catalyst recycling is explored: the ruthenium NHC catalysts with chelating ligands are found to be more robust and recyclable relative to the iridium catalysts and the ruthenium mono-NHC catalyst. The reason is traced to the relative rate of degradation of the catalyst in the presence of glycerol and KOH but no substrate. This degradation is only observed when glycerol is used, as replacing glycerol with isopropanol allows the ruthenium catalyst to be fully recyclable.

INTRODUCTION

Transfer hydrogenation (TH) continues to be a key reaction of interest for the fine chemical and pharmaceutical industries as a safer and milder alternative to hydrogenation of multiple bonds with flammable hydrogen gas.[1] TH involves the transfer of a hydride and proton from a donor to an acceptor molecule that is reduced.[2] The most common donors are isopropanol and formic acid, while acceptors include C=O, C=N, N=O and C=C bonds. Compared to reduction of C=O bonds by TH, the reduction of C=N and C=C bonds is typically more challenging due to lower polarization of the double bond in both cases.[3-4]

One of the frontiers of TH catalysis is the expansion to renewable, cheap and minimally hazardous hydrogen donors. In the search for hydrogen donors and solvents that meet green chemistry criteria, glycerol is a promising candidate due to: (i) its low cost and abundance as a byproduct from biodiesel processing, and (ii) its physical and solvation properties (high dielectric constant, high boiling point and ability to solvate salts, acids, bases, metal complexes, and organics).[5-6] Glycerol is also compatible with microwave heating,[7] which is an attractive method for reducing reaction time and improving selectivity.[8] Lastly, glycerol is non-toxic and fully biodegradable, which make it an attractive candidate for industrial applications.

Using glycerol as hydrogen donor in TH reactions could also provide a route to glycerol valorization, as long as the catalytic process has high selectivity for a single glycerol byproduct.[9] The common dehydrogenation product of glycerol at low temperature is dihydroxyacetone (DHA), but DHA is typically not obtained in appreciable yield in TH reactions as it is not stable under basic conditions.[10-14] Some alternative glycerol by-products of TH that have been experimentally identified include acetals and ketals,[15-16] as well as lactic acid,[17-19] especially at temperatures above 200°C.

The most exploited transition metal catalysts for TH are based on Ru, Ir and Rh; complexes of these metals exhibit high activity for a broad range of substrates. A wide variety of ligand architectures have been reported for TH catalysts with these metals, but *N*-heterocyclic carbenes (NHC) are arguably the best candidates for affording high thermal stability and tunability of the steric and electronic properties of the metal.[20-21] Numerous Rh, Ir and Ru-NHC complexes that have been shown to catalyze TH of carbonyls, olefins, imines and nitroarenes from isopropanol with high efficiency. Based on considerations of activity, metal cost and catalyst stability, Ir(III) and Ru(II) NHC complexes appear most attractive candidates: Ir(III) NHCs have been reported to reach TOFs of 50 000 h^{-1} for TH of from isopropanol to ketones,[22] while Ru(II) NHC pincer (CNC) have been shown to reach TOFs of 126 000 for a similar reaction.[23]

Catalysts that are expected to operate in highly polar media, such as glycerol, should have appreciable solubility in such solvents. Ir and Ru-NHC complexes with hydrocarbon N-substituents are typically not very soluble in glycerol. However, this solubility can be greatly improved by installing ionizable N- substituents on the NHCs. In particular, sulfonate groups have shown promise for affording stable, water-soluble NHC complexes.[24-26] Two examples of sulfonate NHC complexes of Ir and one of Ru have been applied to TH reactions in glycerol for

aldehydes, ketones and olefins, and shown promising activity.[10-11] The key reports of TH reactions from glycerol catalyzed by homogeneous Ir(I), Ir(III), Ru(II) and Rh(III) catalysts are summarized in Table 1 and reviewed by Diaz-Alverez.[27] These reports suggest that the activity and robustness of Ir(III) and Ru(II) NHC complexes often exceed those of other reported catalysts, but the trade-offs are not well elucidated.[28-32] Interested in identifying highly active and robust homogeneous catalysts for TH from glycerol that can serve as potential precursors for supported recyclable catalysts, we set out to optimize and compare activity and of the most promising Ir(III) and Ru(II) NHC sulfonate catalysts for TH of imines, ketones, aldehydes and olefins. To the best of our knowledge this is the first report of TH of imines from glycerol. We also provide new insights into the role of degradation products and the potential for recyclability of the catalysts.

Table 1. Summary of literature reports of TH from glycerol using homogeneous catalysts.

Catalyst	*Substrates*	*Conditions*	*Ref.*
Iron PNP complex	Acetophenone (one example)	2.5 mol% Fe cat, 22 h at 120 °C, NMP co-solvent and 10 eq KOH	Hazari [33]
$Ir(NHC)_2I_2OAc$ $Ir(abNHC)_2I_2OAc$ (*p*-cyam)Ru(NHC)(CO_3)	Ketones Aldehydes Olefins	2.5 mol% Ir, co-solvents such as DMSO accelerate reaction	Peris [10]
$Ir(NHC)_2I_2OAc$ $Ir(abNHC)_2I_2OAc$ (cod)Ir(NHC) Cl Ir(III)Cp*NHC	Ketones Aldehydes	2.5 mol% Ir, microwave/ultrasound, 120 °C; formation of nanoparticles observed for Ir catalyst;	Peris [11]
[Ir(diene)(bpy)X]	Ketones Aldehydes	1 mol% Ir, 1h at 100 °C; characterized DHA as by-product in low yields	Crotti [34-35]

$[Ru(p\text{-cumene})Cl_2]_2$	Aldehydes Olefins Nitro compounds	Microwave-accelerated reaction, 70 °C.	Wolfson [14, 36-38]
Rh(III) and Ir(III) organochalcogen ligands	Ketones Aldehydes	0.5 – 1.0 mol%, 120 °C in water (1 eq glycerol); Hg and PPh_3 do not impede reactions	Singh[30, 32, 39]

EXPERIMENTAL SECTION

General Considerations

The syntheses of the catalysts were carried out under nitrogen using standard Schlenk technique, unless otherwise stated. Anhydrous solvents were dried using a solvent purification system (SPS MBraun) or 4Å molecular sieves. Glycerol (>99%, Alfa Aesar) was dried over activated 4Å molecular sieves. NMR spectra were recorded on an Agilent NMR spectrometer operating at 400 MHz. Microwave-assisted reactions were performed in sealed vessels with a CEM Discover microwave. UV-Visible spectroscopy was performed using a Jasco V770 spectrophotometer. PXRD measurements were performed using a Rigaku MiniFlex II X-Ray defractometer. Transmission Electron Microscope (TEM) images were taken on Talos F200X under 200kV FEG with Ceta 16M camera. Elemental maps were obtained using a built-in Silicon Drift Detector (Super-X EDS Detector). Elemental composition was determined by ICP-AES using a Shimadzu 9820 instrument. DLS

Catalyst synthesis

The ligands for catalysts ***1*** - ***5*** (methylenebis-[N,N′(propanesulfonate) imidazolium],[40] 1,1′-methylenebis [(2,2′-methyl)(3,3′-propanesulfonate)imidazolium,[24] CNC-(propanesulfonate[41] and N,N′-(methyl)(propanesulfonate)imidazolium[42]) were prepared via literature procedures. Compounds ***1***, ***4*** and ***5*** were prepared from corresponding imidazolium ligand, base and $[RuCl_2(\eta^6\text{-p-cymene})]_2$ under reflux conditions in acetonitrile. Catalysts ***2*** and ***3*** were synthesized from

$[Ir(cod)Cl]_2$ (cod=1,5-cyclooctadiene), the corresponding imidazolium salt, potassium iodide and sodium acetate in refluxing methanol. Catalysts ***2, 3*** and ***5*** were first reported by Peris et al,[42-43] while ***1*** and ***4*** were reported by Hermann et al.[44] The five catalysts in Figure 1 were prepared via a modification of the reported protocols (see ESI Scheme 1-2).

Catalytic reductive amination

In a typical experiment, 0.50 mmol of amine, 0.55 mmol of aldehyde, 0.25 mmol of potassium hydroxide, 5.0 mL of glycerol and 0.50 g of 4Å molecular sieves were heated in a sealed microwave vial for 1 hour to 150 °C while stirring. The catalyst (***1*** – ***5,*** 1 mol%, 0.005 mmol) was then added in a glycerol solution (0.5 mL) and the reaction was heated again to 140 °C in the sealed microwave vial for an additional 2 hours using 200 W power. After cooling, the vials were opened and an internal standard was added (anisole). The organics were extracted with EtOAc after addition of 5 mL water, and dried *in vacuo*. Yields were determined from ^{1}H NMR using anisole as internal standard.

Catalytic transfer hydrogenation of aldehydes, ketones and olefins

In a typical experiment, 0.50 mmol of substrate, 0.25 mmol of potassium hydroxide, 0.01 mmol of catalyst ***1-5*** (2 mol %), and 2 mL of glycerol were added to microwave vial, sealed, and heated to the temperature and time indicated in Tables 4 – 5. The vials were opened after cooling and internal standard was added (anisole). The organics were extracted with EtOAc after addition of 5 mL water, and dried *in vacuo*. Yields were determined from ^{1}H NMR using anisole as internal standard.

RESULTS AND DISCUSSION

Catalysts ***2, 3*** and ***5*** (Figure 1) were selected based on previous reports of activity for TH.[10-11, 25] Catalysts ***1*** and ***4*** have not previously been reported as TH catalysts from glycerol to the best of our knowledge, and provide useful comparisons of ligand effects. Catalyst ***5*** was also examined because it has been reported as being highly recyclable under aqueous reaction conditions in allylic alcohol isomeroizations.[42]

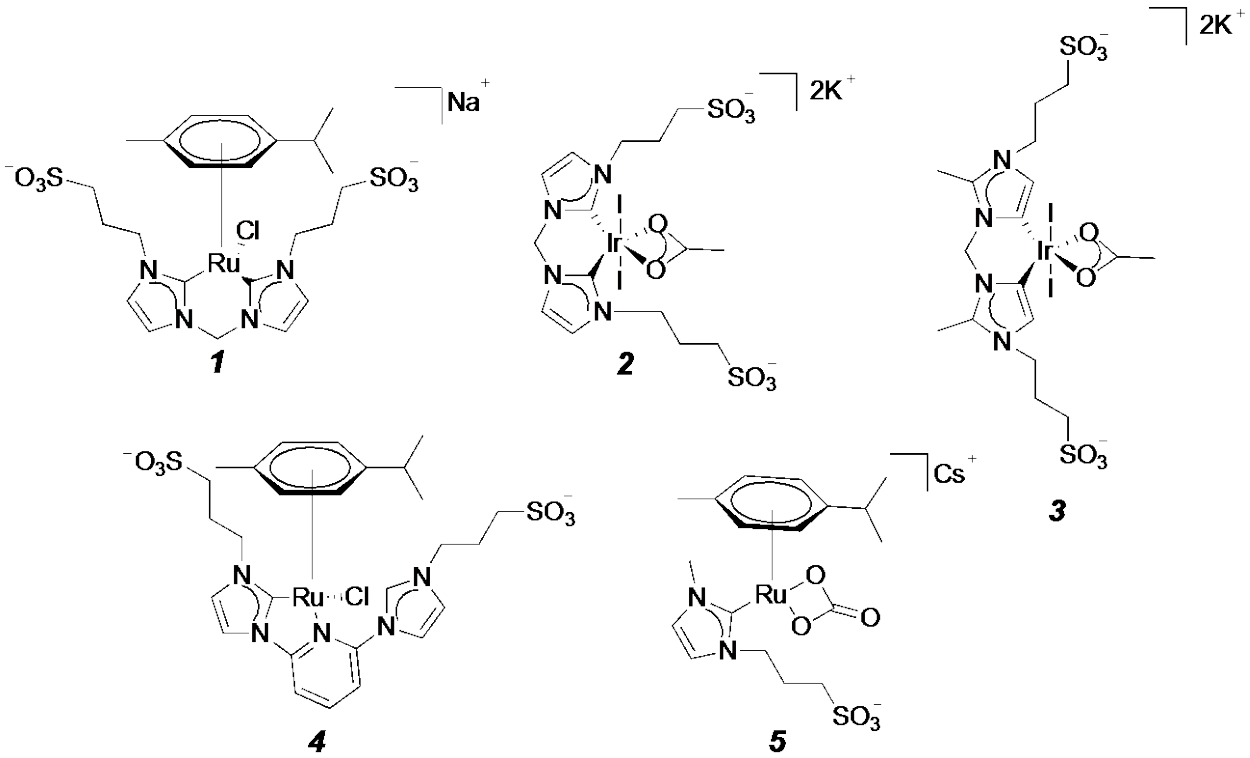


Figure 1. Iridium and ruthenium NHC catalysts for transfer hydrogenation from glycerol.

Imine transfer hydrogenation from glycerol

The activity of catalysts ***1*** - ***5*** for transfer hydrogenation of *in-situ* prepared imines from glycerol using aniline and benzaldehyde as model substrates are compared in Table 2. In a typical experiment, the aldehyde, amine, potassium hydroxide, glycerol and molecular sieves were first

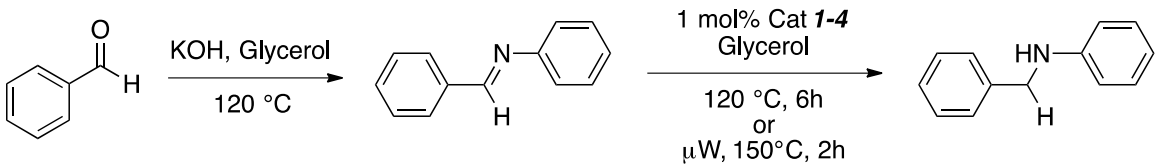
heated to 120 °C for 2 h to form the imine (Step 1). This condensation step could also be carried out using microwave heating for a shorter time (1 hr, 150 °C). The catalyst was then added in a glycerol solution and the mixture heated either conventionally or in the microwave (Step 2). If the catalyst is added at the beginning of the reaction instead, the amine yield is lower due to competitive reduction of the aldehyde.

The two iridium catalysts (***2*** and ***3***) outperformed the three ruthenium complexes (***1***, ***4*** and ***5***), and catalyst ***1*** was significantly less active than ***4***, while ***5*** had no appreciable activity. Catalyst ***3*** was the most active (quantitative yield with microwave irradiation in 2 h), which translates to 49 turnovers per hour. Although this turnover frequency is orders of magnitude lower than that of the most active reported Ir catalyst for TH of imines from isopropanol (50 000 h^{-1}),[22] it shows promising activity considering the challenging hydrogen donor. Catalyst ***2*** was slightly less active than ***3***, affording 85% amine over the same period. The higher activity of the abnormal bis-NHC Ir(III) compound (***3***) can be attributed to its more electron-rich (and thus more nucleophilic) iridium hydride intermediate that results from beta-hydride elimination of glycerol. Assuming that the iridium catalysts go through the accepted "hydridic" mechanism[11, 22] and insertion is the rate-determining step, the higher nucleophilicity of the Ir-H would favor insertion of the electrophilic imine, increasing activity.[11] By the same logic, the lower activity of catalyst ***5*** vs ***1*** could be attributed to less electron-rich ruthenium hydride compared to that of the bis-NHC Ru complex.

The proportional increase in activity afforded by microwave heating is consistent with that observed by Peris et al for the TH of carbonyl compounds and olefins in glycerol,[11] and likely arises from the improved mass transfer (dispersion) of reactants and base in the polar and viscous glycerol solvent. The yield increase for catalyst ***4*** with microwave irradiation was most significant (17% vs 77%). This enhancement could be attributed to the highly polar zwitterionic character of

the complex, which results in enhanced absorbance of microwave irradiation. Optimal yields were obtained when the microwave power was limited to 200 W, which resulted in a more gradual heating of the reaction and more prolonged low-power irradiation. Use of temperatures lower than 150 °C, even with prolonged reaction times, resulted in lower amine yields.

Table 2. Activity of catalysts ***1*** - ***5*** for transfer hydrogenation of imines with glycerol.



Cat	Yield %	
	Conventional	*Microwave*
1	18	38
2	61	85
3	74	99
4	17	77
5	<5	<5

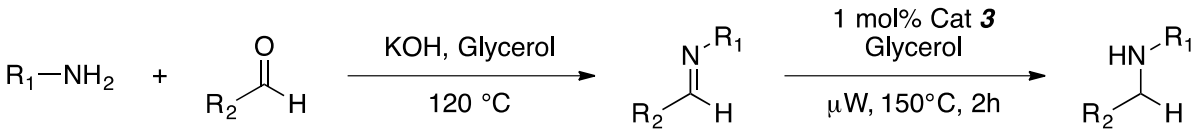
Reaction conditions: 0.50 mmol aniline, 0.50 mmol benzaldehyde, 0.25 mmol KOH, 5mL glycerol (120 ºC for 2 hours conventional or 1 hr at 150 ºC in the microwave, for Step 1); subsequent addition of 1 mol% catalyst added and microwave heating (2 hours, 150 ºC). Yields obtained by NMR using anisole as internal standard.

Use of bases other than KOH resulted in lower product yields. To our surprise, control reactions of a pre-formed imine without base surprisingly afforded some product: 47% for catalyst ***3*** and 63% for catalyst ***4*** respectively under microwave conditions. In comparison, Ir bis-NHC catalysts with alkyl wingtips have been reported to be almost inactive without base.[22] Involvement of the sulfonate as an internal base was considered. Aryl-sulfonate and alky-sulfonate functionalized NHC complexes require an external base for coupling reactions (Suzuki and Heck olefinations),

anticipated based on the low *p*Ka of the sulfonate.[45] However, a base-free alcohol aminations using an NHC-methylsulfonate ligand on Ru and Ir,[46] and a base-free allylic alcohol isomerization using ruthenium NHC-propylsulfonate Ru complex have also been observed.[42] In light of these disparate prior examples, we suggest that the activity observed in the absence of base implicates sulfonate involvement, but further mechanistic studies would be needed to interrogate the base-free catalytic cycle.

The substrate scope with catalyst ***3*** under optimized microwave heating conditions was expanded to a series of *in-situ* prepared imines shown in Table 3. The yields of the TH of the imine from glycerol (Step 2) were nearly quantitative for substrates in entries 3 - 5. Benzyl(2-phenylpropylidene)amine (entry 1), heptyl(phenylmethylidene)amine (entry 2), and 4-chloropheny(benzylidene)amine (entry 6) afforded 61%, 72% and 78% yield respectively. This reactivity trend is comparable with that observed for TH of imines from isopropanol.[47] The lower activity of 4-chlorophenyl(benzylidene)amine (TOF 39 h^{-1}) compared to phenyl(benzylidene)amine (TOF 49 h^{-1}) shows that electron-richer imines are more reactive for transfer hydrogenation. Lower yields were observed for imines having an α-H at the N-alkyl substituent (entries 1 and 2), which is likely due to with competitive isomerization.[48] Isomerization product was observed only for benzyl(2-phenylpropylidene) amine (entry 1). This is consistent with the higher relative stability of the isomerized imine, which is conjugated with the aromatic ring. For heptyl(phenylmethylidene)amine and benzyl(2-phenylpropylidene) amine coordination and insertion might also be hindered by the increased steric hindrance arising from the methyl group and the conformational degrees of freedom of the *n*-heptyl chain.

Table 3. Substrate scope of reductive amination from glycerol using catalyst ***3***.



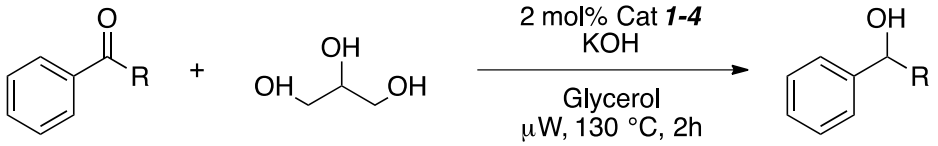
			Step 1		Step 2		
Entry	**R_1**	**R_2**	**Time (h)**	**Yield %**	**Time (h)**	**Yield %**	**TOF**
1	Benzyl	2-phenylpropionaldehyde	2	99	6	61	10
2	Heptyl	Phenyl	2	95	2	72	36
3	Benzyl	Phenyl	0.5	100	1	99	99
4	Phenyl	Benzyl	2	100	2	97	48
5	Phenyl	Phenyl	3	80	1	98	49
6	4-chloro phenyl	Benzyl	3	75	2	78	39

Reaction conditions: 0.50 mmol amine, 0.50 mmol aldehyde, 0.25mmol KOH, 5 mL glycerol (120 ^{o}C for hours, for Step 1); subsequent addition of 1 mol% catalyst added and microwave heating (μW) for time indicated at 140 °C. Yields obtained by NMR using anisole as internal standard.

Transfer hydrogenation of carbonyls

The five catalysts were compared for activity and selectivity in the TH of aldehydes and ketones under microwave conditions, as shown in Table 4.

Table 4. Activity of catalysts ***1*** - ***5*** for transfer hydrogenation of benzaldehyde and acetophenone from glycerol.



Entry	Cat	% Yield	
		R=H	R=Me
1	***1***	88	85
2	***2***	80	40
3	***3***	98	46
4	***4***	79	30
5	***5***	73	47

Reaction conditions: 0.50 mmol substrate, 2 mol% catalyst, 0.25 mmol KOH, 2 mL glycerol, 140 °C, 2 h microwave heating (μW). Yields obtained by NMR using anisole as internal standard.

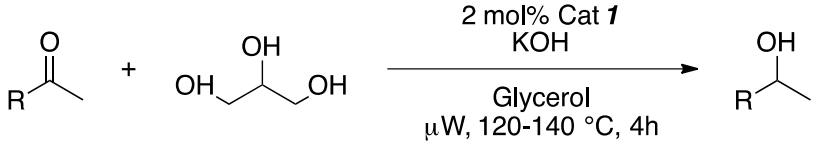
Complexes ***1*** - ***5*** were all active precatalysts for the TH of benzaldehyde from glycerol under microwave conditions (yields in range of 73 - 98%, Table 4). Optimization of catalytic activity was attempted by varying the concentrations of reagents and reaction temperature (120 – 150 °C). The optimal ratio of glycerol to substrate was found to be 2 mL:0.50 mmol. The temperature selected was based on the lowest that afforded quantitative yields for at least one catalyst in 2 hours. Maximum TOF for benzaldehyde TH were 49 h^{-1} with catalyst ***3,*** and the same for acetophenone with catalyst ***1***. For comparison, Peris et al. have reported maximum TOF of 40 h^{-1} for benzaldehyde and 32 h^{-1} for acetophenone using catalyst ***3***.

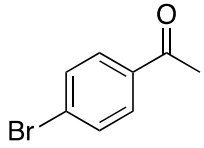
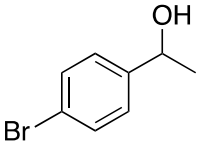
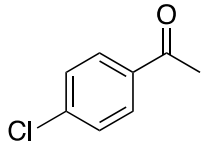
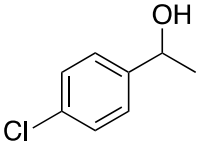
TH of acetophenone from glycerol was facilitated most efficiently by catalyst ***1***, the Ru bis-NHC complex, (Table 1, entry 1). Catalysts ***5*** and ***3*** were the next in activity trends, but with a large margin, affording 47% and 46% alcohol from acetophenone respectively, followed by ***2*** and ***4*** as the least active of the series. The ranking of catalysts by activity for benzaldehyde TH from glycerol is ***3*** > ***1*** > ***2*** ~ ***4*** > ***5***, while that of acetophenone from glycerol: ***1*** > ***5*** ~ ***3*** > ***2*** > ***4***. As

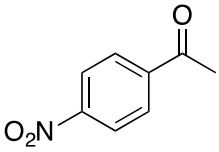
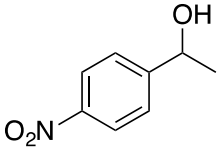
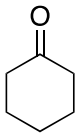
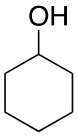
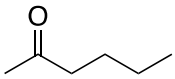
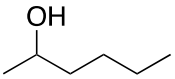
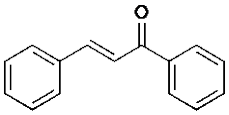
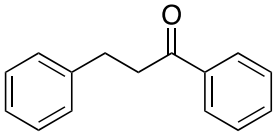
expected the catalysts are more active for benzaldehyde than acetophenone, although the difference in the case of catalyst ***1*** is marginal.

The substrate scope for ketone TH of ***1***, the most active catalyst, was briefly investigated, as this complex has not been previously reported for TH from glycerol (Table 5). Aromatic ketones with different substituents allow us to relate the effect of the polarization of the carbonyl to the catalytic activity. Electron-withdrawing substituents are expected to enhance the polarization (and thus electrophilicity) of the carbonyl, which in turn enhances rate of insertion.[49] Consistent with this expectation, halogen substituents were found to have a mild activating effect on the ketone reactivity for TH. The more strongly electron-withdrawing nitro group has a significant enhancing effect on the rate of TH. Thus, in the case of C=O the reactivity trend is consistent with a stepwise TH mechanism with a rate-determining insertion step. Notably, these substituents were not affected during the TH process, suggesting that competitive oxidative addition of Ar-X is slow in comparison to the TH.

Table 5. Ketone substrate scope for TH from glycerol using catalyst ***1***.



Entry	Substrate	Temp (°C)	Product	%Yield
1		130		82
2		130		89

3		130		92
4		130		10
5		140		22
6		120		<99

Reaction conditions: 0.50 mmol substrate, 2 mol% ***1***, 0.25 mmol KOH, 2 mL glycerol, 4h, microwave heating (μW) with temperature as indicated. Yields obtained by NMR using anisole as internal standard;

Alkyl substituted methyl ketones were significantly less active than acetophenone derivatives (entries 4-5). The lower yields are consistent with the less electrophilic carbonyl groups. Given the interest in the selectivity of TH of α,β-unsaturated carbonyls we also examined the activity of all five catalysts with 1,3-diphenylpropan-1-one. The reaction afforded the ketone in quantitative yields by all catalysts, underscoring the high reactivity of the conjugated system.

Transfer hydrogenation of olefins

To test the applicability of these catalysts to TH of olefins from glycerol we employed conjugated and isolated alkenes – namely, styrene, cyclooctadiene and cyclooctene. The only olefin that afforded significant product formation was styrene, which afford 50% yield with catalyst ***3*** in 4 hours at 150 °C under microwave irradiation. Cyclooctadiene afforded only isomerization products (1,4- and 1,3-dienes), consistent with previous reports with isopropanol as

hydrogen donor.[22] The lower activity of olefins compared to carbonyls and imines is consistent with the stronger binding of the olefin to the metal and the lower electrophilicity of the C=C bond compared to C=O and C=N.

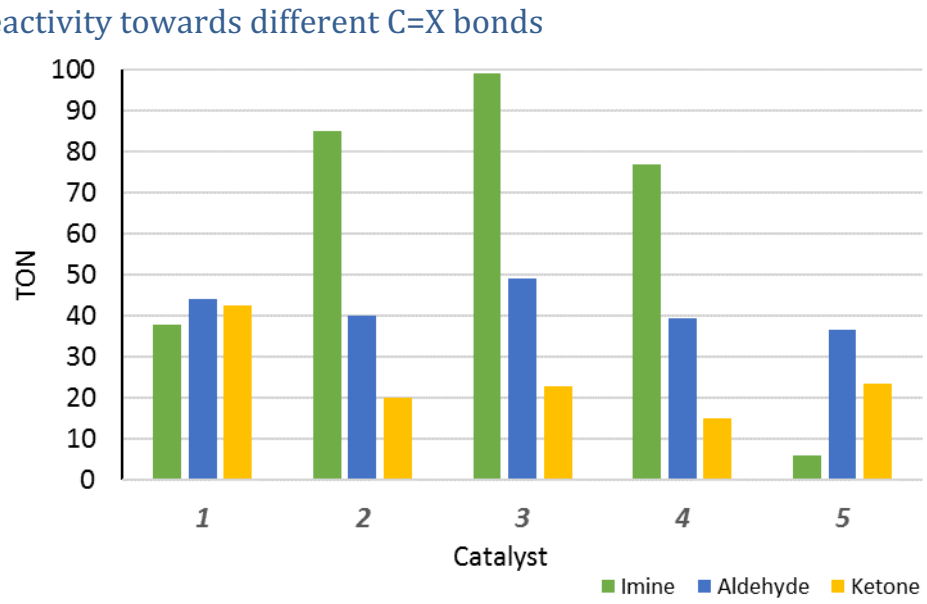


Figure 2. Bar chart showing turnover numbers afforded by catalysts ***1*** **-** ***5*** for TH of benzylphenyl imine (imine), benzaldehyde (aldehyde) and acetophenone (ketone). Reaction conditions please refer to Tables 2 and 4.

The reactivity of the catalysts for imines, aldehydes and ketones is compared in Figure 2 based on total turnover numbers. The reactivity order for aldehydes, ketones and imines with Ru catalysts operating by ligand-metal bifunctional outer-sphere mechanisms has been shown to correlate with the polarization of the double bond of the substrate, resulting in the reactivity order aldehydes > ketones > imines.[50] Iridium catalysts operating by inner sphere mechanism have also shown the same trend.[3b,12] Consistent with this observation, imines often require harsher reaction conditions than ketones and aldehydes.[50] In contrast to this general trend, we find that for four of the five catalysts imines were more reactive than aldehydes, which are more reactive than ketones. This observation may suggest that the catalytic cycle for TH of imines with glycerol may

have a different rate-determining step than that with carbonyls: whereas insertion step is likely rate-determining for carbonyls (consistent with observed electronic trends in substrates), substrate coordination might be rate-determining for imine TH from glycerol in the present case. Further kinetic and computational studies to elucidate these mechanistic differences are currently underway.

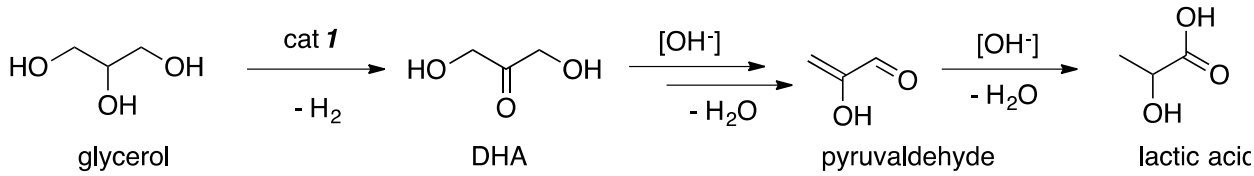
The large disparity in reactivity with catalyst ***5*** is also apparent. Catalyst ***5*** should be capable of a dihydride mechanism, which may influence its selectivity. However, it is not immediately apparent whether the dihydride mechanism would indeed be the lowest energy pathway with glycerol as the hydride donor, and how the substrate selectivity would be influenced by the mechanism. Further DFT and experimental studies are underway to elucidate these mechanisms with glycerol as hydride donor.

Glycerol by-products

Prior reports of TH from glycerol suggested formation of dihydroxyacetone (DHA). However, in most cases the DHA is not experimentally observed, as it is expected to decompose under basic conditions.[11-13] Crotti et al and Bajaj et al report formation of acetals and ketals either with Ir-Cp* as catalyst[15] or with no catalyst under microwave conditions.[16] For the reactions reported herein we did not observe formation of acetals or ketals, save for small amounts when the substrate was cyclohexanone. Analysis of acetophenone TH reactions with catalyst ***1*** by HPLC identified lactic acid as only product in a ~2:1 ratio with respect to the ketone substrate. When the reaction was carried out in the absence of substrate, lactic acid was still observed, suggesting that ***1*** facilitate dehydrogenation of glycerol without an acceptor. This finding is not surprising, given recent reports demonstarting activity of Ir bis-NHC complexes and iron PNP pincer complexes in catalyzing the selective conversion of glycerol to lactic acid via acceptorless dehydrogenation.[33, 51] Lactic acid is likely formed from DHA, which undergoes base-catalyzed dehydration to form

pyruvaldehyde and subsequent intramolecular Cannizaro reaction to form lactic acid (Scheme 1). No additional oxidation or reduction products of viable intermediates were observed.

Scheme 1. Formation of lactic acid through dehydrogenation of glycerol under basic condtions.



Homogeneous vs heterogeneous

Given that formation of nanoparticles is not uncommon under the reaction conditions, we examined the reaction mixtures at the end of the reactions using dynamic light scattering (DLS). The size distributions of colloidal particles were determined based on number (rather than intensity) measurements. The mean particle sizes for catalysts ***1*** – ***5*** were 141 ± 18 nm), 28 ± 5 nm, 34 ± 4 nm, 52 ± 5 nm and 91 ± 9 nm respectively. We noted that upon standing these particles, not surprisingly, agglomerate to larger clusters. Control measurements taken at the beginning of the reaction showed no detectable particles. The presence of particulates does not necessarily signify presence of metal nanoparticles, but it raises sufficient suspicion that nanoparticles do form during the course of the reaction, and if they do, they may be the most active catalytic species.

To characterize the remaining material after extraction of organics, the reaction mixtures of the catalysts with acetophenone were centrifuged, solids collected and washed extensively. The resulting materials were analyzed by TEM, UV-visible spectroscopy, PXRD and LC-MS. HRTEM with EDX of the reactions with catalysts ***2*** and ***3*** showed formation of dispersed spherical iridium-containing particles, which when isolated and dispersed in water showed a UV-visible absorbance maximum of 261 nm for both catalysts (Figure S1). Although consistent with prior reports of UV-

visible features of iridium nanoparticles,[11] the ligand architecture on the nanoparticle surface may modify these features, thus rendering this comparison not conclusive. Similar TEMs could not be obtained for the Ru catalysts, which was likely because the solids collected were not predominantly derived from the catalyst, based on elemental Ru content.

Probing the catalytically active specie is far from trivial due to complex equilibria between the heterogenized and homogeneous catalysts, as well as potential existence of multiple catalytic cycles. Of the available techniques we selected quantitative poisoning with 1,10-phenanthroline, which has been applied to Rh[52] and Ru[53] in distinguishing single metal species from metal clusters and metal nanoparticles. Quantitative poisoning is based on the relationship between relative rate and number of equivalents of a poison vs catalyst.[54] This relationship for catalyst ***1*** showed a slightly sigmoidal shape. Finke et al have suggested that sigmoidal behavior can best be explained using a weak binding model shown in equation 1 below,

$$Relative\ Rate = \frac{1}{1+K'_{assoc}(1,10-phenanthroline)^{m'}_{initial}} \qquad \text{(eq 1)}$$

where K'_{assoc} is the binding constant of catalyst to 1,10-phenanthroline and m' is the molar ratio of 1,10-phenanthroline that can bind to each metal. The weak binding is not unusual, as the binding affinities of poisons to catalysts can vary based on ligand and metal center. The two parameters can be solved by fitting the experimental relative rate data to the equation above. A nonlinear least-squares fit using eq 1 of the experimental poisoning data for ***1*** yields a good fit to the data (R^2 = 0.993) and affords K'_{assoc} = 4532 M^{-1} and m′ = 0.91± 0.12 respectively (Figure 3). Overall if we approximate the value of m′ to 1, the results are consistent with the presence of homogeneous catalytically active species to which 1 equivalent of phenanthroline binds. The value of m' slightly below 1 though does not allow us to exclude the possible presence of some nanoparticulates with

catalytic competence. The molecular complexes may be in equilibrium with nanoparticles, further complicating the dynamic behavior of the system and the direct interpretation of the result.

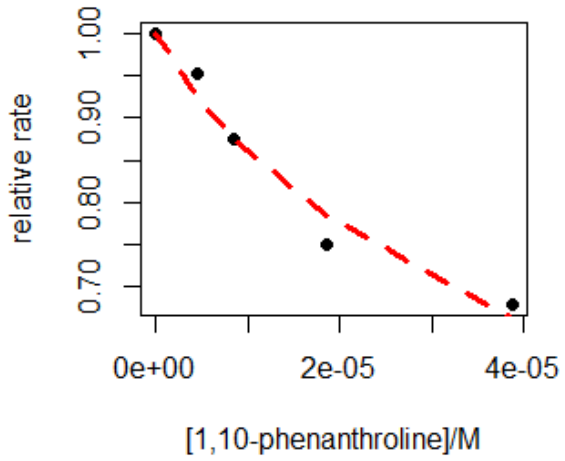


Figure 3. The relative rate vs 1,10-phenanthroline concentration vs relative rate of acetophenone transfer hydrogenation reaction with glycerol and catalyst ***1***. The data is fitted to eq 1 (solid line), R^2 =0.995, with resultant K'_{assoc} = 4532 M^{-1} and $m' = 0.91 \pm 0.12$.

We also carried out a classical test to probe whether the catalytic cycle involves Ir(0) or Ru(0) intermediates: mercury poisoning test. Mercury amalgamates Pt group metal nanoparticles, including Ir and Ru, thus in theory inhibiting reactions that go through zero oxidation state intermediates,[55] but this test is often inconclusive for metals other than Pd and Pt. [56] The tests were performed on TH of acetophenone from glycerol with one Ir catalyst (***3***) and one Ru catalyst (***1***). Addition of mercury afforded <10% inhibition of product formation in both cases, suggesting that the intermediates of the predominant catalytic cycles are predominantly ligated complexes. This result is consistent with that from the quantitative poisoning of catalyst ***1***.

Recycling of catalysts in TH of ketones

The use of Pt group metals as homogeneous catalysts can only be sustainable if the catalysts are reusable. Given that the hydrophilic nature of these catalysts allows extraction of the organic substrates and products from the reaction mixture, we examined the fate and recyclability of the five catalysts after TH of acetophenone. The organics were extracted readily, and the remaining glycerol solution reused with addition of new substrate and KOH. The resulting yields are compared to those obtained from the first cycle of each catalyst in Figure 4. The chelated Ru catalysts (***1*** and ***4***) retain greater fractions of their activity (52% and 71% respectively) when compared to the chelated iridium catalysts ***2*** and ***3*** and the ruthenium mono-NHC catalyst ***5***. Interestingly, ***5*** has been previously reported to be readily recyclable for base-free allylic alcohol isomerization.[42]

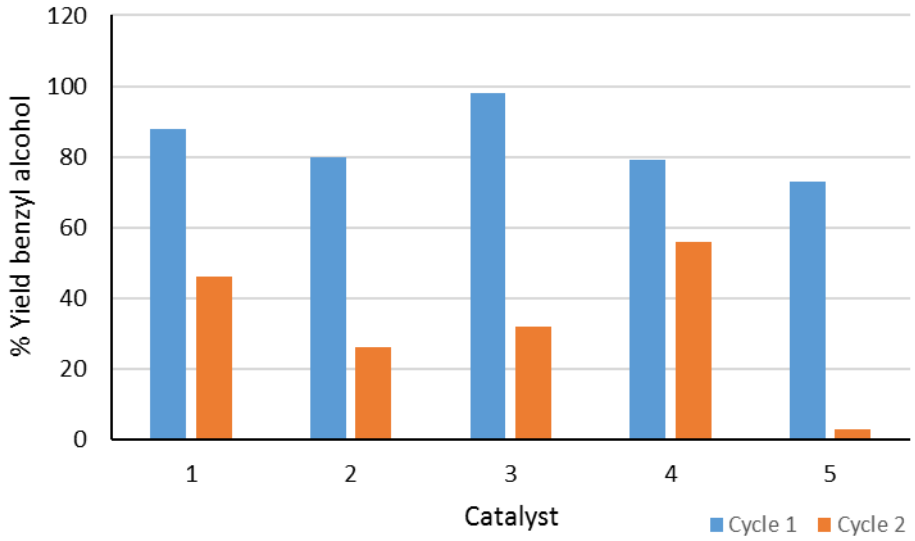


Figure 4. Activity of catalysts ***1*** - ***5*** for transfer hydrogenation of benzaldehyde and acetophenone from glycerol. Reaction conditions: 0.50 mmol substrate, 2 mol% catalyst, 0.25 mmol KOH, 2 mL glycerol, 140 °C, 2 h. Yields obtained by NMR using anisole as internal standard.

We hypothesized that the low recyclability of the catalysts is associated with the presence of glycerol and base. To test this hypothesis, we used catalyst ***1*** to carry out TH of benzaldehyde in isopropanol instead of glycerol, which afforded full conversion in 2 hours. After drying the reactions *in vacuo* and extracting the organics, the catalysts were reused for a second cycle successfully to afford full conversion in the same time period. The kinetic competence of the catalyst in the second cycle was comparable within experimental error to that in cycle 1. This result was consistent with our hypothesis that glycerol and strong base cause decomposition and hinder recyclablility.

To further investigate the degradation of the catalysts in the presence of glycerol and base, and elucidate why Ir catalysts (***2*** and ***3)*** may lose greater fraction of activity than Ru catalysts (***1*** and ***4)*** we carried out NMR experiments. Incubation of catalysts ***1*** (Ru) and ***2*** (Ir) with glycerol and KOH resulted in rapid formation of a hydide for ***2*** (observed as a singlet at -13 ppm), but no apparent change for catalyst ***1***. In fact, the hydride resonance was not observed for ***1*** until the reaction was heated to 100 °C for 1h (-23.4 ppm, ESI Figures S3 and S4). Some *p*-cymene dissociation was also observed at this time. These observations suggest that glycerol coordination and β-hydride elimination occur significantly faster from the more electron-rich Ir (***2***) than the Ru (***1***), which is not surprising given that the Ir center is more electron-rich than that of the Ru in ***2***.

However, the more reactive catalyst ***2*** was also observed to degrade significantly faster than ***1***. For ***2***, ligand degradation, signaled by splitting of resonances associated with the methylenes in the N-C*H*$_2$-N bridge and wingtips, was observed immediately after addition of KOH at room temperature, while for ***1*** it was not until the reaction was heated to 100 °C for over an hour. At this time the NHC ligand of ***1*** was observed to dissociate based in the disappearance of the 175 ppm ^{13}C resonance associated with the NHC C-2, coordinated to Ru (Figure S5). These observations,

together with the complete recyclability observed with isopropanol, suggest that in catalyst degradation is triggered by KOH and glycerol in the absence of substrate. Although both catalysts show degradation, the Ir catalyst ***2*** degrades significantly more rapidly than Ru catalyst ***1***. The resulting degraded mixtures were inactive for TH of benzaldehyde.

CONCLUSIONS

The catalytic transfer hydrogenation (TH) from glycerol has a prominent place in the green chemistry synthetic toolbox, especially if it can be facilitated by recyclable catalysts. Building on prior research efforts that have shown the feasibility of glycerol as a hydrogen source for the reduction of organic substrates, we report optimized protocols for the TH of imines, aldehydes, ketones and to a lesser extent, olefins, using iridium and ruthenium *N*-heterocyclic carbene complexes with sulfonate *N*-wingtips. Microwave heating is significantly more effective than conventional heating for these transformations, likely due to its beneficial effect of improving mass transfer. The commonly encountered trend for difficulty of substrate reduction in TH from isopropanol follows the sequence: aldehydes < ketones < imines << olefins. However, we find deviations from this trend for TH from glycerol using catalyst suspected of acting via a monohydridic route (***1*** - ***4***) – in this case imines are more readily reduced than carbonyls. On the other hand, catalyst ***5***, which is suspected to proceed through a dihydridic mechanism, follows the aforementioned expected trend. The reactions afford lactic acid as the only observed glycerol byproduct.

Under catalytic conditions in the absence of substrate we observe catalyst degradation when glycerol is used as the hydrogen source, but significantly slower degradation with isopropoanol as hydrogen source. Thus, while catalyst recycling is possible with isopropanol, with glycerol the five catalysts can be reused with retention of only maximum ~70% of original activity.

NMR experiments demonstrate that degradation in the absence of substrate is triggered by addition of KOH and glycerol, and is significantly faster for Ir catalyst (***3***) in comparison to the Ru catalyst (***1***). The two ruthenium catalysts with chelated NHC ligands (***1*** and ***4***) outperformed the iridium bis(NHC) catalysts and the ruthenium mono-NHC catalyst in a second use cycle, suggesting that Ru complexes with chelating NHC ligands may be more promising candidates as recyclable catalysts. Data from quantitative poisoning experiments using 1,10-phenanthroline fitted to a non-linear model reveal that the poison is weakly binding to Ru and approximately one molecule of poison binds per Ru. Overall, the quantitative poisoning and mercury poisoning experiments suggest a predominantly homogeneous catalytically active species for catalyst ***1***.

Supporting Information.

The following files are available free of charge.

Schematic routes to ligand and complex synthesis, UV-Visible characterizations of used catalysts, and spectroscopic characterization of catalysis products. (PDF)

AUTHOR INFORMATION

Corresponding Author

*Adelina Voutchkova-Kostal: avoutchkova@gwu.edu

Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Funding Sources

We thank NSF for funding through NSF CAREER award.

ACKNOWLEDGMENT

The authors thank GWU Materials institute and GWU Imaging and Nanofabrication Core for facilities use.

REFERENCES

1. Wang, D.; Astruc, D., The Golden Age of Transfer Hydrogenation. *Chemical reviews* **2015,** *115* (13), 6621-6686.
2. Knoevenagel, E.; Bergdolt, B., Ueber das Verhalten des Δ2.5-Dihydroterephtalsäuredimethylesters bei höheren Temperaturen und in Gegenwart von Palladiummohr. *Berichte der deutschen chemischen Gesellschaft* **1903,** *36* (3), 2857-2860.
3. Ashley, J. M.; Farnaby, J. H.; Hazari, N.; Kim, K. E.; Luzik, E. D., Jr.; Meehan, R. E.; Meyer, E. B.; Schley, N. D.; Schmeier, T. J.; Tailor, A. N., Axially chiral dimeric Ir and Rh complexes bridged by flexible NHC ligands. *Inorganica Chimica Acta* **2012,** *380*, 399-410.f
4. Gnanamgari, D.; Moores, A.; Rajaseelan, E.; Crabtree, R. H., Transfer Hydrogenation of Imines and Alkenes and Direct Reductive Amination of Aldehydes Catalyzed by Triazole-Derived Iridium(I) Carbene Complexes. *Organometallics* **2007,** *26* (5), 1226-1230.
5. Diaz-Alvarez, A. E.; Francos, J.; Lastra-Barreira, B.; Crochet, P.; Cadierno, V., Glycerol and derived solvents: new sustainable reaction media for organic synthesis. *Chemical Communications* **2011,** *47* (22), 6208-6227.
6. Gu, Y. L.; Jerome, F., Glycerol as a sustainable solvent for green chemistry. *Green Chemistry* **2010,** *12* (7), 1127-1138.
7. Cintas, P.; Tagliapietra, S.; Gaudino, E. C.; Palmisano, G.; Cravotto, G., Glycerol: a solvent and a building block of choice for microwave and ultrasound irradiation procedures. *Green Chemistry* **2014,** *16* (3), 1056-1065.
8. Varma, R. S., Green Chemistry with Microwave Energy. In *Innovations in Green Chemistry and Green Engineering: Selected Entries from the Encyclopedia of Sustainability Science and Technology*, Anastas, T. P.; Zimmerman, B. J., Eds. Springer New York: New York, NY, 2013; pp 115-156.
9. Pagliaro, M.; Ciriminna, R.; Kimura, H.; Rossi, M.; Della Pina, C., From glycerol to value-added products. *Angewandte Chemie-International Edition* **2007,** *46* (24), 4434-4440.
10. Azua, A.; Mata, J. A.; Peris, E., Iridium NHC Based Catalysts for Transfer Hydrogenation Processes Using Glycerol as Solvent and Hydrogen Donor. *Organometallics* **2011,** *30* (20), 5532-5536.
11. Azua, A.; Mata, J. A.; Peris, E.; Lamaty, F.; Martinez, J.; Colacino, E., Alternative Energy Input for Transfer Hydrogenation using Iridium NHC Based Catalysts in Glycerol as Hydrogen Donor and Solvent. *Organometallics* **2012,** *31* (10), 3911-3919.
12. Farnetti, E.; Kaspar, J.; Crotti, C., A novel glycerol valorization route: chemoselective dehydrogenation catalyzed by iridium derivatives. *Green Chemistry* **2009,** *11* (5), 704-709.
13. Crotti, C.; Kaspar, J.; Farnetti, E., Dehydrogenation of glycerol to dihydroxyacetone catalyzed by iridium complexes with P-N ligands. *Green Chemistry* **2010,** *12* (7), 1295-1300.

14. Wolfson, A.; Dlugy, C.; Shotland, Y.; Tavor, D., Glycerol as solvent and hydrogen donor in transfer hydrogenation-dehydrogenation reactions. *Tetrahedron Letters* **2009,** *50* (43), 5951-5953.
15. Crotti, C.; Farnetti, E.; Guidolin, N., Alternative intermediates for glycerol valorization: iridium-catalyzed formation of acetals and ketals. *Green Chemistry* **2010,** *12* (12), 2225-2231.
16. Pawar, R. R.; Jadhav, S. V.; Bajaj, H. C., Microwave-assisted rapid valorization of glycerol towards acetals and ketals. *Chem Eng J* **2014,** *235*, 61-66.
17. Shen, Z.; Zhang, Y. L.; Jin, F. M., The alcohol-mediated reduction of CO2 and NaHCO3 into formate: a hydrogen transfer reduction of NaHCO3 with glycerine under alkaline hydrothermal conditions. *Rsc Advances* **2012,** *2* (3), 797-801.
18. Su, J.; Yang, L. S.; Yang, X. K.; Lu, M.; Luo, B.; Lin, H. F., Simultaneously Converting Carbonate/Bicarbonate and Biomass to Value-added Carboxylic Acid Salts by Aqueous-phase Hydrogen Transfer. *Acs Sustain Chem Eng* **2015,** *3* (1), 195-203.
19. Dibenedetto, A.; Stufano, P.; Nocito, F.; Aresta, M., Ru-II-Mediated Hydrogen Transfer from Aqueous Glycerol to CO2: From Waste to Value-Added Products. *Chemsuschem* **2011,** *4* (9), 1311-1315.
20. Eduardo, P.; Robert, H. C., Recent homogeneous catalytic applications of chelate and pincer N-heterocyclic carbenes. *Coordination Chemistry Reviews* **2004,** *248*, 2239-2246.
21. Jantke, D.; Cokoja, M.; Pothig, A.; Herrmann, W. A.; Kuhn, F. E., Synthesis and Characterization of Highly Water Soluble Ruthenium(II) and Osmium(II) Complexes Bearing Chelating Sulfonated N-Heterocyclic Carbene Ligands. *Organometallics* **2013,** *32* (3), 741-744.
22. Albrecht, M.; Miecznikowski, J.; Samuel, A.; Faller, J. W.; Crabtree, R. H., Chelated Iridium(III) Bis-carbene Complexes as Air-Stable Catalysts for Transfer Hydrogenation. *Organometallics* **2002,** *21* (17), 3596-3604.
23. Poyatos, M.; Mata, J. A.; Falomir, E.; Crabtree, R. H.; Peris, E., New ruthenium(II) CNC-pincer bis(carbene) complexes: Synthesis and catalytic activity. *Organometallics* **2003,** *22* (5), 1110-1114.
24. Azua, A.; Sanz, S.; Peris, E., Water-Soluble Ir-III N-Heterocyclic Carbene Based Catalysts for the Reduction of CO2 to Formate by Transfer Hydrogenation and the Deuteration of Aryl Amines in Water. *Chemistry-a European Journal* **2011,** *17* (14), 3963-3967.
25. Sanz, S.; Azua, A.; Peris, E., '(eta(6)-arene)Ru(bis-NHC)' complexes for the reduction of CO2 to formate with hydrogen and by transfer hydrogenation with iPrOH. *Dalton Transactions* **2010,** *39* (27), 6339-6343.
26. Sanz, S.; Benitez, M.; Peris, E., A New Approach to the Reduction of Carbon Dioxide: CO2 Reduction to Formate by Transfer Hydrogenation in iPrOH. *Organometallics* **2010,** *29* (1), 275-277.
27. Díaz-Álvarez, E. A.; Cadierno, V., Glycerol: A promising Green Solvent and Reducing Agent for Metal-Catalyzed Transfer Hydrogenation Reactions and Nanoparticles Formation. *Applied Sciences* **2013,** *3* (1).
28. Cadierno, V.; Crochet, P.; Francos, J.; García-Garrido, S. E.; Gimeno, J.; Nebra, N., Ruthenium-catalyzed redox isomerization/transfer hydrogenation in organic and aqueous media: A one-pot tandem process for the reduction of allylic alcohols. *Green Chemistry* **2009,** *11* (12), 1992.
29. Cadierno, V.; Francos, J.; Gimeno, J., Ruthenium-catalyzed reduction of allylic alcohols: An efficient isomerization/transfer hydrogenation tandem process. *Green Chemistry* **2007,** (11), 1992-2000.

30. Sharma, A. K.; Joshi, H.; Sharma, K. N.; Gupta, P. L., 2-Propanol vs Glycerol as Hydrogen Source in Catalytic Activation of Transfer Hydrogenation with (η6-Benzene)ruthenium(II) Complexes of Unsymmetrical Bidentate Chalcogen Ligands. *Organometallics* **2014,** *33* (13), 3629-3639.
31. Prakash, O.; Sharma, K. N.; Joshi, H.; Gupta, P. L., Half-Sandwich Rhodium/Iridium(III) Complexes Designed with Cp* and 1,2-Bis(phenylchalcogenomethyl)benzene as Catalysts for Transfer Hydrogenation in Glycerol. *Organometallics* **2014,** *33* (10), 2535-2543.
32. Prakash, O.; Joshi, H.; Sharma, K.; Gupta, P.; Singh, A. K., Transfer Hydrogenation (pH Independent) of Ketones and Aldehydes in Water with Glycerol: Ru, Rh, and Ir Catalysts with a COOH Group near the Metal on a (Phenylthio) methyl-2-pyridine Scaffold. *Organometallics* **2014,** *33* (14), 3804-3812.
33. Sharninghausen, L. S.; Mercado, B. Q.; Crabtree, R. H.; Hazari, N., Selective conversion of glycerol to lactic acid with iron pincer precatalysts. *Chemical Communications* **2015,** *51* (90), 16201-16204.
34. Farnetti, E.; Kašpar, J.; Crotti, C., A novel glycerol valorization route: chemoselective dehydrogenation catalyzed by iridium derivatives. *Green Chemistry* **2009,** *11* (5), 704.
35. Crotti, C.; Kašpar, J.; Farnetti, E., Dehydrogenation of glycerol to dihydroxyacetone catalyzed by iridium complexes with P–N ligands. *Green Chemistry* **2010,** *12* (7), 1295.
36. Tavor, D.; Popov, S.; Dlugy, C.; Wolfson, A., Catalytic transfer-hydrogenations of olefins in glycerol. *Organic Communication* **2010**.
37. Tavor, D.; Sheviev, O.; Dlugy, C.; Wolfson, A., Transfer hydrogenations of benzaldehyde using glycerol as solvent and hydrogen source. *Canadian Journal of Chemistry* **2010,** *88* (4), 305-308.
38. Wolfson, A.; Abu-Zaed, H.; Tavor, D., Transfer hydrogenation of a carbonyl compound in glycerol based solvent mixtures. *Organic Communications* **2016**.
39. Prakash, O.; Sharma, K. N.; Joshi, H.; Gupta, P. L., Half-Sandwich Rhodium/Iridium (III) Complexes Designed with Cp* and 1, 2-Bis (phenylchalcogenomethyl) benzene as Catalysts for Transfer Hydrogenation in …. ... **2014**.
40. Azua, A.; Sanz, S.; Peris, E., Water-Soluble IrIII N-Heterocyclic Carbene Based Catalysts for the Reduction of CO2 to Formate by Transfer Hydrogenation and the Deuteration of Aryl Amines in Water. *Chemistry – A European Journal* **2011,** *17* (14), 3963-3967.
41. Godoy, F.; Segarra, C.; Poyatos, M.; Peris, E., Palladium Catalysts with Sulfonate-Functionalized-NHC Ligands for Suzuki-Miyaura Cross-Coupling Reactions in Water. *Organometallics* **2011,** *30* (4), 684-688.
42. Azua, A.; Sanz, S.; Peris, E., Sulfonate-Functionalized NHC-Based Ruthenium Catalysts for the Isomerization of Allylic Alcohols in Water. Recyclability Studies. *Organometallics* **2010,** *29* (16), 3661-3664.
43. Azua, A.; Sanz, S.; Peris, E., Water-soluble IrIII N-heterocyclic carbene based catalysts for the reduction of CO2 to formate by transfer hydrogenation and the deuteration of aryl amines in water. *Chemistry (Weinheim an der Bergstrasse, Germany)* **2011,** *17* (14), 3963-3967.
44. Jantke, D.; Cokoja, M.; Pöthig, A.; Herrmann, W. A., Synthesis and characterization of highly water soluble ruthenium (II) and osmium (II) complexes bearing chelating sulfonated N-heterocyclic carbene ligands. *Organometallics* **2013,** *32* (3), 741-744.
45. Schaper, L.-A.; Hock, S. J.; Herrmann, W. A.; Kühn, F. E., Synthesis and Application of Water-Soluble NHC Transition-Metal Complexes. *Angewandte Chemie International Edition* **2013,** *52* (1), 270-289.

46. Rajaraman, A.; Sahoo, A. R.; Hild, F.; Fischmeister, C.; Achard, M.; Bruneau, C., Ruthenium(ii) and iridium(iii) complexes featuring NHC-sulfonate chelate. *Dalton Transactions* **2015,** *44* (40), 17467-17472.
47. Dinakar, G.; Audrey, M.; Edward, R.; Robert, H. C., Transfer Hydrogenation of Imines and Alkenes and Direct Reductive Amination of Aldehydes Catalyzed by Triazole-Derived Iridium(I) Carbene Complexes. *Organometallics* **2007,** *26* (5), 12261230.
48. Samec, J. S. M.; Bäckvall, J.-E., Ruthenium-Catalyzed Transfer Hydrogenation of Imines by Propan-2-ol in Benzene. *Chemistry – A European Journal* **2002,** *8* (13), 2955-2961.
49. Dub, P. A.; Gordon, J. C., The mechanism of enantioselective ketone reduction with Noyori and Noyori-Ikariya bifunctional catalysts. *Dalton T* **2016,** *45* (16), 6756-6781.
50. Shende, V. S.; Deshpande, S. H.; Shingote, S. K.; Joseph, A.; Kelkar, A. A., Asymmetric Transfer Hydrogenation of Imines in Water by Varying the Ratio of Formic Acid to Triethylamine. *Organic Letters* **2015,** *17* (12), 2878-2881.
51. Fang, L.; Jia, Y.; Mishra, V.; Chaparro, C.; Vlasko-Vlasov, V. K.; Koshelev, A. E.; Welp, U.; Crabtree, G. W.; Zhu, S.; Zhigadlo, N. D.; Katrych, S.; Karpinski, J.; Kwok, W. K., Huge critical current density and tailored superconducting anisotropy in SmFeAsO0.8F0.15 by low-density columnar-defect incorporation. *Nature Communications* **2013,** *4*.
52. Bayram, E.; Linehan, J. C.; Fulton, J. L.; Szymczak, N. K.; Finke, R. G., Determination of the Dominant Catalyst Derived from the Classic [RhCp*Cl2]2 Precatalyst System: Is it Single-Metal Rh1Cp*-Based, Subnanometer Rh4 Cluster-Based, or Rh(0)n Nanoparticle-Based Cyclohexene Hydrogenation Catalysis at Room Temperature and Mild Pressures? *ACS Catalysis* **2015,** *5* (6), 3876-3886.
53. Hagen, C. M.; Vieille-Petit, L.; Laurenczy, G.; Süss-Fink, G.; Finke, R. G., Supramolecular Triruthenium Cluster-Based Benzene Hydrogenation Catalysis: Fact or Fiction? *Organometallics* **2005,** *24* (8), 1819-1831.
54. Bayram, E.; Finke, R. G., Quantitative 1,10-Phenanthroline Catalyst-Poisoning Kinetic Studies of Rh(0) Nanoparticle and Rh4 Cluster Benzene Hydrogenation Catalysts: Estimates of the Poison Kassociation Binding Constants, of the Equivalents of Poison Bound and of the Number of Catalytically Active Sites for Each Catalyst. *ACS Catalysis* **2012,** *2* (9), 1967-1975.
55. Anton, D. R.; Crabtree, R. H., Dibenzo[a,E]Cyclooctatetraene in a Proposed Test for Heterogeneity in Catalysts Formed from Soluble Platinum Group Metal-Complexes. *Organometallics* **1983,** *2* (7), 855-859.
56. Crabtree, R. H., Resolving Heterogeneity Problems and Impurity Artifacts in Operationally Homogeneous Transition Metal Catalysts. *Chemical Reviews* **2012,** *112* (3), 1536-1554.