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Hydrogenation of Carboxylic Acids Catalyzed by Half-Sandwich Complexes of Iridium and Rhodium

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Supporting Information

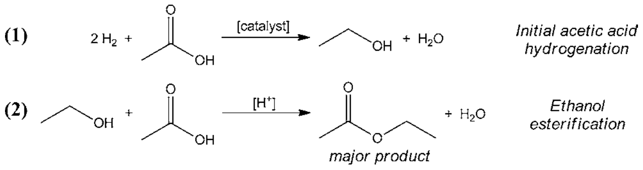
ABSTRACT: A series of half-sandwich Ir and Rh compounds are demonstrated to be competent catalysts for the hydrogenation of carboxylic acids under relatively mild conditions. Of the structurally diverse group of catalysts tested for activity, a Cp*Ir complex supported by an electron-releasing 2,2′-bipyridine ligand was the most active. Higher activity was achieved with employment of Brønsted or Lewis acid promoters. Mechanistic studies suggest a possible reaction pathway involving activated carboxylic acid substrates. The hydrogenation reaction was shown to be general to a variety of aliphatic acids.

Reduction of carboxylic acids to alcohols is a fundamental transformation in organic chemistry. Traditionally, this reaction has been carried out using stoichiometric quantities of strong reducing agents such as lithium aluminum hydride or lithium triethylborohydride.[1] The use of stoichiometric amounts of strong reductants is undesirable due to issues of reagent compatibility and the poor atom economy of the overall transformation.

An attractive alternative would be the direct hydrogenation of the carboxylic acid by dihydrogen. Unfortunately, carboxylic acids are among the most difficult carbonyl substrates to hydrogenate due to the low electrophilicity of the carbonyl carbon.[2] Recently, a biocatalytic route was reported to catalyze acid hydrogenation under mild conditions.[3] However, only two homogeneous, transition-metal based systems for acid hydrogenation have been reported, both of which operate under relatively forcing conditions (≥160 °C, ≥100 atm H_2).[4−9]

We recently reported that formic acid can be reduced to methanol via an apparent transfer hydrogenation mechanism in which formic acid acts as both the hydrogen donor and acceptor.[10] Mechanistic studies suggested that catalyst [Cp*Ir(bpy)(OH_2)][OTf]$_2$ (bpy = 2,2′-bipyridine, OTf = trifluoromethanesulfonate) (**1**) was converted to [Cp*Ir(bpy)(H)][OTf] (**2**) during turnover; hydride transfer from **2** to protonated formic acid appears to be an important step in the reaction. Hydride **2** has also been implicated in hydrogenation reactions using H_2 directly, notably in the hydrogenation of CO_2 to formic acid.[11] It seemed likely, therefore, that replacement of formic acid by H_2 might facilitate hydrogenation of a wide range of carboxylic acid substrates while avoiding competitive decomposition pathways. We report that **1** and related homogeneous catalysts hydrogenate aliphatic carboxylic acids under the mildest conditions yet reported.

Scheme 1. Reductive Coupling Reaction Sequence



We began our investigation of direct hydrogenation of carboxylic acids by **1** utilizing acetic acid as substrate.[12] Glacial acetic acid solutions containing 2 mM **1** were pressurized with 30 atm H_2 and heated to 120 °C. After 65 h, ethyl acetate was observed to be the major product by gas chromatography (approximately 42:1 ethyl acetate/ethanol vs dioxane internal standard), as outlined in Scheme 1. Reactions in glacial acetic acid consistently produced reductively coupled ester products with high selectivity (>95%). No additional products are observed under these conditions.

Mechanistic studies were undertaken to understand and optimize the reaction. Relative reaction rates were assessed from the turnover number[13] (TON) after 65 h (up to 30% conversion). Measurements at relatively low conversion are required to avoid rate effects due to inhibition by water (*vide infra*).[14] Direct temperature dependence was observed with the TON increasing from 73 at 60 °C to 425 at 120 °C after 65 h.[15] Unfortunately, at temperatures above 120 °C, deposition of iridium black on the reactor liners and irreproducible rates demonstrated catalyst decomposition. The heterogeneous decomposition products were tested and found to be inactive for catalyzing the hydrogenation reaction.[15]

The rate of hydrogenative coupling of acetic acid was found to be first order in both substrate and catalyst at 120 °C, and saturation behavior was observed with respect to the pressure of H_2 (Figure S6, Figure 1). Addition of water to the reaction dramatically slowed the rate. In 8.7 M acetic acid only 26 turnovers occurred after 65 h. Conversely, in the presence of added HBF_4[16] (8.7 M acetic acid in a 1:1 (w:w) H_2O/HBF_4 solution), the rate increased markedly to 1338 turnovers after 65 h, as shown in Figure 1. Under higher concentrations of water and protons the distribution of products began to shift; diethyl ether was now observed as a minor product, and more ethanol was present (8:13:1 ratio of EtOH:EtOAc:Et_2O). This is unsurprising, as esterification to ethyl acetate should be less

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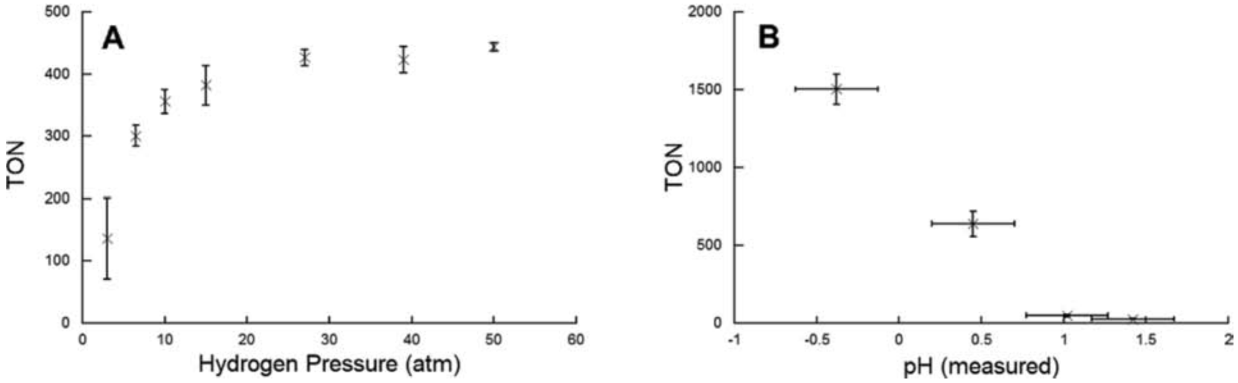
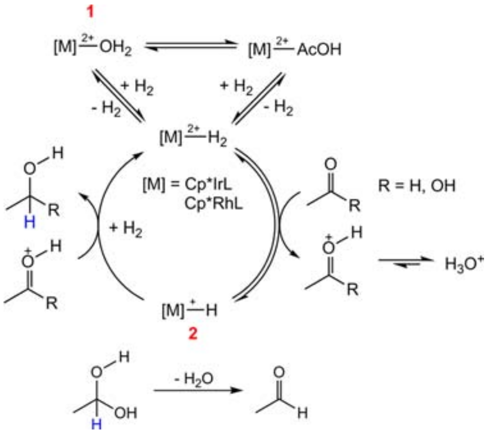


Figure 1. Dependence of the hydrogenation of acetic acid by **1** on H_2 pressure and pH. (A) 2 mM 1, 2 mL glacial AcOH, 120 °C, 65 h. (B) 2 mM 1, 2 mL 8.7 M AcOH (aq) at given pH[16] (adjusted with HBF_4), 120 °C, 65 h.

Scheme 2



favored in the presence of excess water. The diethyl ether is presumably formed through an acid-catalyzed dehydrative homocoupling of ethanol.

A reaction mechanism consistent with the above data is shown in Scheme 2. An initial equilibrium between aqua complex **1**, acetic acid complex [Cp*Ir(bpy)(HOAc)][OTf]$_2$, and dihydrogen complex [Cp*Ir(bpy)(H_2)][OTf]$_2$ is established.[15] Such dihydrogen complexes are highly acidic,[17] so rapid deprotonation to form **2** would be expected. This pre-equilibrium is consistent with the observed H_2 saturation kinetics. At sufficiently high pressure, formation of the dihydrogen complex is favored, leading to rapid formation of **2** and rate-limiting hydride transfer that does not depend on H_2 pressure. After protonation of acetic acid, **2** transfers a hydride to the activated acetic acid molecule, producing acetaldehyde, and then rejoins the equilibria between dicationic Ir species. The proposal that the reaction involves protonated acetic acid is consistent with our observations involving aqueous dilution; the concentration of protonated acetic acid drops significantly in the presence of water which is more basic ($pK_a(H_3O^+ (aq)) = -1.7$,[18] $pK_a(CH_3CO_2H_2^+ (aq)) = -6.1$).[19] Further, addition of strong acid accelerates the reaction.

The acetaldehyde produced after one hydrogenation cycle would then be converted to ethanol following a similar mechanism. No aldehydes (or aldehyde hydrates) were observed, consistent with previous reports of rapid (transfer) hydrogenation of aldehydes under even milder conditions.[20] Depending on conditions, the initial hydrogenation product, ethanol, can undergo either Fischer esterification with the acetic acid solvent to generate the hydrogenative coupling product ethyl acetate (major product) or acid-catalyzed homocoupling to generate diethyl ether (minor product).

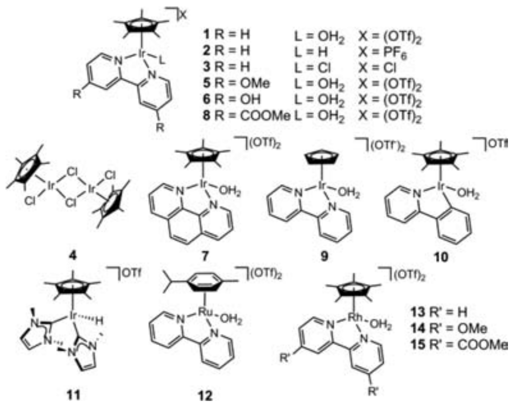


Figure 2. Precatalysts screened for AcOH hydrogenation.[12]

A variety of homogeneous metal catalysts for the hydrogenolysis of esters under mild conditions have been reported.[2,21−23] In separate experiments, methoxy-substituted catalyst **5** (Figure 2) was also demonstrated to be competent for hydrogenolysis of ethyl acetate at a rate comparable to that of acetic acid hydrogenation under similar conditions.[15] Thus, at the low conversions of acetic acid used in our kinetic studies, hydrogenolysis of the ester product is not expected to be a significant contributor.

To probe the intermediacy of iridium monohydride complex **2**, the previously reported hydride was prepared[12] and employed as the precatalyst. Interestingly, the reaction rate under standard conditions was much slower when **2** was used instead of **1**. We hypothesized that complex **1** effectively acts as a strong acid, as [Cp*Ir(bpy)(H_2)]$^{2+}$ quickly releases H^+ into solution to generate hydride **2** (Scheme 2). Accordingly, reactions catalyzed by a combination of **2** and HOTf (1 μL, 3 equiv) gave similar rates to reactions catalyzed by **1**.[15] These results confirm the viability of complex **2** as an intermediate in the hydrogenation reaction.

The known iridium chloride complex [Cp*Ir(bpy)Cl][Cl][12] (**3**) notably shows no catalytic activity for acetic acid hydrogenation. This result is in contrast to the case of formic acid disproportionation where complex **3** was shown to be a competent catalyst.[10] The relatively nonpolar glacial acetic acid solvent (ε = 6.1[24]) may inhibit chloride dissociation and prevent formation of the key hydride intermediate. The

Table 1. Comparison of Acetic Acid Hydrogenation Catalysts[a,b]

Cat.	TON ± dev.	Cat.	TON ± dev.
1	425 ± 8	**8**[e]	9
2	41 ± 12	**9**[e]	40
2[c]	503 ± 34	**12**[e]	21
5	777 ± 15	**13**	96 ± 5
5[d]	1637 ± 25	**14**	56 ± 1
6	615 ± 50	**15**	125 ± 23
7	389 ± 56	none	trace

[a]For results of all catalysts shown in Figure 2, see Table S1 in the SI. [b]Average of three trials with calculated standard deviation; 2 mM catalyst in glacial acetic acid, 27 atm H_2, 120 °C, 65 h. [c]5 mM HOTf. [d]16 mM $Sc(OTf)_3$ added. [e]Average of two trials.

chloride-bridged dimer $[Cp^*IrCl_2]_2$[12] (**4**) was also tested, but only traces of product and large amounts of Ir black were observed.

The above mechanistic studies suggest that, under sufficient H_2 pressure, hydride transfer is involved in the rate-limiting step. Thus, increasing the hydricity of this intermediate should increase the rate of reaction. A series of structurally related catalysts with varying electronic properties were therefore investigated (Figure 2). All catalysts were tested for activity in glacial acetic acid at 120 °C under 27 atm H_2 (above the H_2 saturation pressure for **1**), mild conditions compared to those of related previous literature reports.[4−9] The results are summarized in Table 1. Methoxy-substituted catalyst **5**, and hydroxy-substituted catalyst **6**[12] (Figure 2) showed markedly increased reaction rates when compared to bpy itself, consistent with our hypothesis that hydride donor ability is an important factor. Phenanthroline complex **7** showed activity nearly identical to that of **1**. In contrast, catalyst **8** featured electron-withdrawing methyl ester groups and showed no activity. Replacing Cp* with the unsubstituted Cp ligand (**9**) also led to a decrease in rate. No decomposition to Ir black was observed in any of these reactions.

Noticing that electron-rich complexes were better catalysts, we sought other viable catalysts supported by strong donor ligands. The reported[12] phenylpyridine complex **10** and bis(*N*-heterocyclic carbene) complex **11** seemed promising, but these complexes showed little activity at 120 °C, and a large amount of iridium black was observed to form in these reactions.

Half-sandwich complexes of alternative metals were also explored as catalysts for this reaction.[12] First, an analogous half-sandwich Ru complex, **12**, was investigated. While similar complexes are highly active toward asymmetric hydrogenation of ketones,[25−28] **12** showed no activity for acetic acid hydrogenation. In contrast, the Rh complex **13**, $[Cp^*Rh(bpy)(OH_2)][OTf]_2$, was found to be a competent precatalyst for this reaction, albeit at a rate slower than that of its iridium analogue. $[Cp^*Rh(bpy\text{-}OMe)(OH_2)][OTf]_2$, **14**, and $[Cp^*Rh(bpy\text{-}COOMe)(OH_2)][OTf]_2$, **15**, were also found to be active precatalysts. Surprisingly, Rh and Ir exhibit opposite trends in terms of how the ligand-donating ability affects the reactivity of the catalyst. Rh catalyst **14**, with electron-donating methoxy groups, showed the lowest activity while catalyst **15**, with electron-withdrawing ester groups, exhibited the highest activity (Table S1 in the SI).

This difference between Rh and Ir may be explained by a change in the resting state in the mechanism proposed in Scheme 2. For both metals, more strongly donating ligands should render the dihydrogen complex less acidic.[29,30] For Ir, the saturation kinetics of Figure 1A suggest that above ∼30 atm H_2 the limiting step involves hydride transfer, which would be accelerated by more strongly donating ligands that render hydride **2** a stronger H^- donor. For Rh catalyst **13**, saturation kinetics were not observed up to a H_2 pressure of 50 atm (Figure S7 in the SI).[15] In this case, formation of the Rh−H complex is likely involved in the rate law. The aforementioned slowing of catalytic rates with more donating ligands could then be attributed to a lowering of the concentration of the Rh dihydrogen species or inhibiting the proton loss from the Rh dihydrogen complex.

The rate of formation of the metal hydride species will depend on the pre-equilibrium between the solvento and dihydrogen complexes. Efforts to observe ligand effects on the position of the pre-equilibrium, and thus the effect on catalytic rate, are currently underway. Consistent with our mechanistic proposal, preliminary data using complex **1** show two observable species in solution under H_2 pressures below saturation: the solvento complex and a second species formed reversibly upon addition of H_2 (Figure S10 in the SI).

As mentioned previously, our mechanistic proposal suggests that, at pressures where the reaction rate is independent of $[H_2]$, hydride transfer to a protonated substrate is rate limiting. We have already seen that increasing the proton concentration increases the reaction rate. By analogy, Lewis acid activation of the carbonyl could be expected to accelerate the reaction. Indeed, addition of NaOTf, $Zn(OTf)_2$, or $Sc(OTf)_3$ resulted in a rate enhancement over reactions lacking these promoters (for a full list of screened Lewis acids see Table S2 in SI). A specific interaction of the Lewis acid with the carbonyl is implied by the complete suppression of the acid effect when 15-crown-5 was added to a reaction containing NaOTf. Under these conditions, turnover returned to the level observed in the absence of Lewis acids.

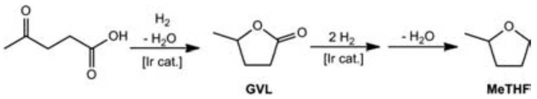
We also investigated hydrogenation of other carboxylic acids. An experiment involving catalyst **1** in a mixture of 3 M formic acid (aq) and 3 M acetic acid (aq) yielded only methanol and methyl ester products, suggesting that carboxylic acids with shorter aliphatic carbon chains react more rapidly (consistent with previous observations).[4] Indeed, using our most active catalyst **5**, propionic acid and butyric acid were each hydrogenated in 3:1 H_2O/HBF_4 at diminished rates compared to acetic acid (Table 2). Reaction selectivity also changes from

Table 2. Comparing Reactivity of Aliphatic Carboxylic Acids

Substrate	Aqueous TON ± dev.[a]	AcOH selectivity[b] (%)
acetic acid	68 ± 3	100
propionic acid	37 ± 1	87
butyric acid	21 ± 3	91

[a]3.5 mmol substrate and 4 μmol **5** in 2 mL 3:1 (v:v) H_2O/HBF_4, 30 atm H_2, 120 °C, 18 h (three runs per substrate). [b]2 mM **5**, 20 mM NaOTf in 2 mL 1:1 (mol:mol) AcOH/substrate, 30 atm H_2, 120 °C, 18 h (three runs per mixture). Selectivity calculated from the ratio of hydrogenated acetic acid to hydrogenated substrate.

Scheme 3



2.5:1 ester/alcohol for acetic acid to 1:2 ester/alcohol for propionic and butyric acids. The observed decrease in reactivity is consistent with our proposed mechanism; as the size of the carboxylic acid increases from C_1 to C_4, the carboxylate carbon would be expected to become more electron-rich and thus less susceptible to nucleophilic attack from the iridium hydride. The magnitude of the electronic effect would likely diminish with increasing aliphatic chain size, but this could not be directly verified due to substrate solubility.[31] The relative rates of aliphatic carboxylic acid hydrogenation were further probed through competition experiments. Equimolar mixtures of acetic acid and C_3 or C_4 acids were subjected to 30 atm H_2 in the presence of 2 mM **5** and 20 mM NaOTf for 18 h at 120 °C. The trend in relative rates of hydrogenation observed in this experiment reflected the activity previously observed as displayed in the ratio of observed hydrogenation products (Table 2). Under these conditions, acetic acid was reduced with 6-fold selectivity over propionic acid and 10-fold selectivity relative to butyric acid.

Finally, hydrogenation of levulinic acid was examined in order to make direct comparisons to the system recently reported by Leitner.[7,8] Using an *in situ* generated Ru trisphosphine catalyst (0.1 mol % catalyst in 1,4-dioxane, 100 atm H_2, 160 °C, 18 h), they reported 95% yield of 1,4-pentanediol (PDO), 3% γ-valerolactone (GVL, Scheme 3), and no 2-methyltetrahydrofuran (MeTHF).[7] With the addition of 1 mol % *p*-toluenesulfonic acid, the products shifted to 1% PDO, 58% GVL, and 39% MeTHF.[32] At a lower temperature and pressure with catalyst **5** (0.08 mol % catalyst, 8 mol % HOTf, 30 atm H_2, 120 °C, 18 h in 1,2-dimethoxyethane), we observed complete consumption of levulinic acid, a 90% yield of partially reduced GVL, and a small amount (10% yield) of fully reduced MeTHF. Notably, no dehydration products were observed in our system.

In conclusion, we have demonstrated a novel system for catalytic hydrogenation of a variety of carboxylic acids. The proposed reaction mechanism (based on experimental evidence) guided optimization of the reaction, including the use of Lewis acid additives. The optimized catalyst system exhibits activity similar to those of previously published systems under significantly milder conditions. Extension of this reactivity is currently under investigation.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Full experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(12) Full synthetic details for new and previously reported catalysts are available in the SI.

(13) Turnover number is based on combined yield of all hydrogenation products. Ethanol and ethyl acetate yield one turnover. Diethyl ether yields two turnovers.

(14) Turnover frequencies after 18 h were similar to turnover frequencies after 65 h (catalyst **5**: Table 1 and Table S2, SI).

(15) See SI for further details.

(16) The ionic strength at this acid concentration is too high for accurate pH measurement. These are meant as qualitative pH values.

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(31) Preliminary experiments investigating fluorinated alcoholic or ethereal solvents met with difficulties due to solvent decomposition and/or esterification with the carboxylic acid starting material. For example, in the case of 1,2-dimethoxyethane, large amounts of methyl ester were observed.

(32) When a sulfonic acid containing ionic liquid rather than *p*-toluenesulfonic acid was added to the reaction mixture, 87% yield of MeTHF was obtained in addition to 1% PDO and 5% GVL.