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# Base-Free Iridium-Catalyzed Hydrogenation of Esters and Lactones

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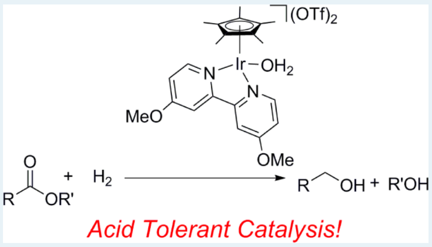
*Supporting Information*

**ABSTRACT:** Half-sandwich iridium bipyridine complexes catalyze the hydrogenation of esters and lactones under base-free conditions. The reactions proceed with a variety of ester and lactone substrates. Mechanistic studies implicate a pathway involving rate-limiting hydride transfer to the substrate at high pressures of $H_2$ (≥50 bar).



**KEYWORDS:** *ester, hydrogenation, acid, homogeneous catalysis, iridium*

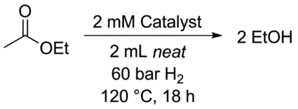
Resonance-stabilized carbonyls are challenging to reduce due to the low electrophilicity of the carbonyl carbon.[1] As a result, strongly basic stoichiometric reductants such as lithium aluminum hydride are commonly employed to effect the reduction of esters to alcohols.[2] The utilization of dihydrogen as the reductant would serve as an attractive, mild alternative. Recent advances in this area have demonstrated the feasibility of transition-metal-catalyzed ester hydrogenation. However, the vast majority of these catalysts require the addition of basic additives (most commonly alkoxide bases) to activate the catalyst, or contain a basic site within the catalyst, which can pose limitations with respect to functional group compatibility.[1,3−9] To date, only a single catalyst system has been reported to hydrogenate esters under neutral or acidic conditions without prior activation of the catalyst.[10−14] New ester hydrogenation catalysts that can operate in the absence of base would be a valuable complement to existing systems, as they would allow for mild reduction in the presence of base-sensitive functionalities.

In addition to synthetic applications, esters have been utilized as intermediates in strategies for carbon recycling. Specifically, formate esters serve as intermediates in a cascade hydrogenation pathway from carbon dioxide to methanol.[15] In this system, the generation of the formate ester takes place under acidic conditions and is thus poorly compatible with base-driven ester hydrogenation catalysts. This provides further motivation for the development of acid-tolerant ester hydrogenation catalysts.

This communication describes the use of an iridium catalyst, $[Cp^*Ir(bpy\text{-}OMe)OH_2][OTf]_2$ (**1**), ($Cp^*$ = pentamethylcyclopentadienide, bpy-OMe = 4,4′-dimethoxy-2,2′-bipyridine, OTf = trifluoromethanesulfonate)[16,17] for the hydrogenation of esters and lactones without added base. In many cases, the addition of a Lewis acid was found to enhance the TONs with this catalyst. The optimization, substrate scope, and mechanistic investigations of ester hydrogenation reactions catalyzed by **1** are also described.[17]

Our initial studies focused on the use of catalyst **1** for the hydrogenation of ethyl acetate. Heating a 2 mM solution of **1** in neat ethyl acetate under 60 bar $H_2$ for 18 h in the absence of any additives affords ethanol with a TON of 363 ± 46 (Table 1).[17] Catalysts **2**[18] and **3**,[17] which are sterically similar to **1**, but contain different 4,4′-substituents on the bipyridine ligands (Figure 1) were also examined. The highest turnover numbers were obtained using **1**, which contains electron-donating methoxy substituents. An analogous trend was observed in the hydrogenation of carboxylic acids with this series of catalysts, suggesting that the reactions may be mechanistically similar.[17]

**Table 1. Catalyst Screen for Ethyl Acetate Hydrogenation[a]**



| catalyst | TON |
|---|---|
| **1** | 363 ± 46 |
| **2** | 309 ± 47 |
| **3** | 116 ± 7 |

[a] 4 μmol catalyst in 2 mL of ethyl acetate (20.4 mmol), 60 bar $H_2$, 18 h at 120 °C. Average of 3 trials with standard deviation. Theoretical maximum TON under these conditions = 5100. Small amounts of diethyl ether (~10%) are also observed.

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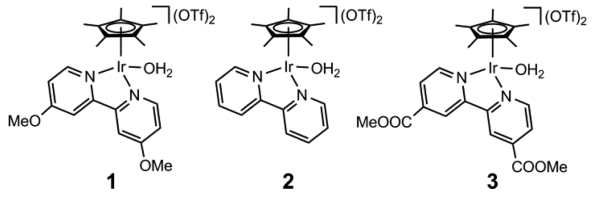


**Figure 1.** Ester hydrogenation catalysts.

Mechanistic investigations of the hydrogenation of ethyl acetate with catalyst **1** were undertaken.[19] The reactions were conducted in neat ethyl acetate, and the % conversion and TON were determined after 18 h of heating at 120 °C.[20] The rate of hydrogenation of ethyl acetate exhibits a linear dependence on catalyst concentration (Figure 2A), and saturation behavior is observed with respect to hydrogen pressure (Figure 2B). Saturation is reached at approximately 50 bar $H_2$, and a linear dependence on $H_2$ pressure is observed up to approximately 17 bar (Figure 2B).[21] The dependence on substrate concentration was determined utilizing hexyl formate as the substrate (for ease in measurement of the concentrations of reactant and products) in 1,2-dimethoxyethane (DME). The reactions were run for 4 h at 100 °C under 60 bar $H_2$.[20] Under these conditions, a linear dependence on substrate concentration was observed (Figure 2C).

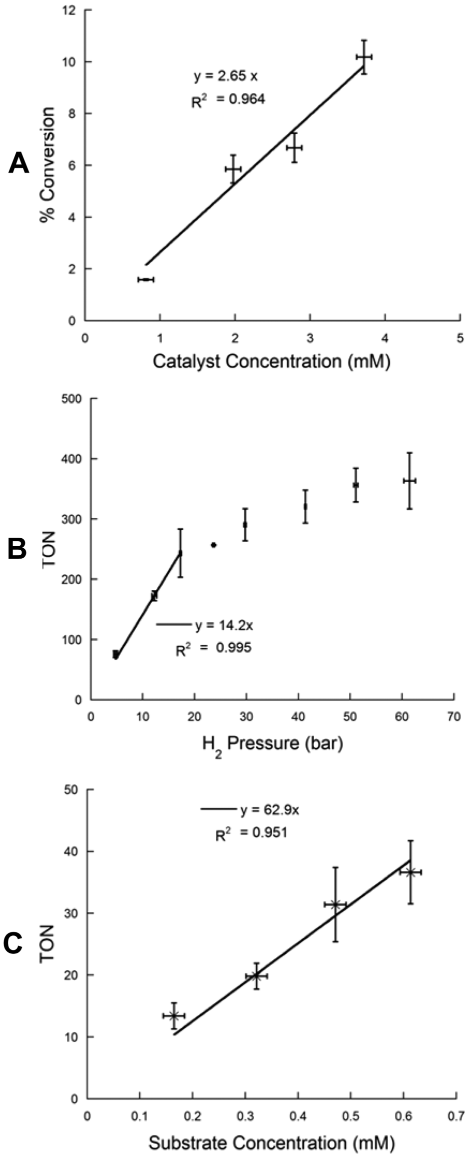
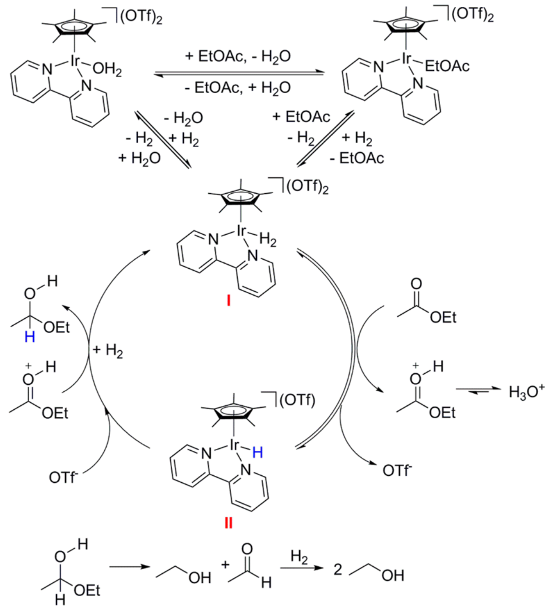


**Figure 2.** Dependence of **1**-catalyzed hydrogenation of esters on catalyst concentration (A), $H_2$ pressure (B), and substrate concentration (C). (A) 2 mL of ethyl acetate (20.4 mmol), 30 bar $H_2$, 120 °C, 18 h. (B) 4 μmol of **1** in 2 mL of ethyl acetate (20.4 mmol), 120 °C, 18 h. (C) Substrate: hexyl formate; 4 μmol of **1** in DME, 60 bar $H_2$, 100 °C, 4 h.

These data are consistent with the ionic hydrogenation mechanism proposed in Scheme 1.[22,23] Initial addition of $H_2$ to the solvento complex Cp*Ir(bpy) (solv)$^{2+}$ (solv = ester or $H_2O$) reversibly forms the iridium dihydrogen complex (**I**). In neat reactions, the dihydrogen complex is then deprotonated by substrate to generate the corresponding iridium hydride (**II**) along with the protonated ester. This hydride attacks the protonated substrate to generate a hemiacetal intermediate, which then eliminates one equivalent of alcohol to generate a transient aldehyde. The aldehyde is significantly more electrophilic than the parent ester and undergoes rapid hydrogenation to form the alcohol product. When the reactions are run in DME, the solvent likely acts as a proton shuttle to protonate the ester substrate prior to nucleophilic attack.

**Scheme 1. Proposed Mechanism for Ester Hydrogenation**

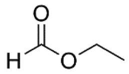
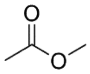
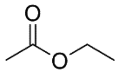


The first-order dependence on $H_2$ pressure below 17 bar is consistent with turnover-limiting formation of the dihydrogen complex (**I**). The saturation observed at higher hydrogen pressures suggests a change to turnover-limiting hydride transfer. Notably, a similar mechanism (and change in turnover limiting step) was proposed previously for the **1**-catalyzed hydrogenation of carboxylic acids.[17]

The scope of this transformation was next investigated. A series of esters and lactones were evaluated using catalyst **1** and 30 bar of $H_2$ in both neat substrate and in DME solvent. Quantitative analysis of TON was carried out using either $^1H$ NMR spectroscopy or gas chromatography.[19] Under neat conditions, the reaction was examined in the presence and absence of the Lewis acid $Sc(OTf)_3$.[19] On the basis of the mechanism proposed in Scheme 1, we hypothesized that a Lewis acid should accelerate the hydrogenation reaction by activating the ester substrate for nucleophilic attack, as seen previously in the hydrogenation of carboxylic acids catalyzed by **1**.[17]

The hydrogenation of esters **E1−E3** was first conducted under neat conditions using 2 mM **1** and 30 bar $H_2$ at 100 °C for 16 h. In all cases, significant quantities of hydrogenation products were observed, with the TON ranging from 106 to 341 (Table 2). The addition of 20 mM $Sc(OTf)_3$ resulted in a marked improvement in TON. This effect is most dramatic with ethyl formate (**E1**), where the TON increases from 341 to 1317 upon the addition of $Sc(OTf)_3$.[24]

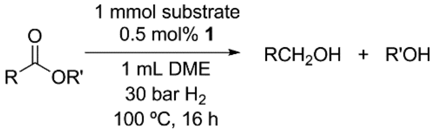
**Table 2. Ester Hydrogenation under Neat Conditions**[a]

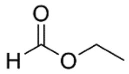
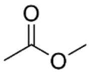
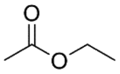
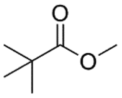
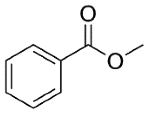
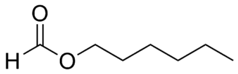
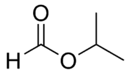
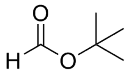
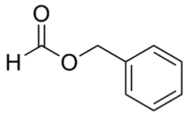
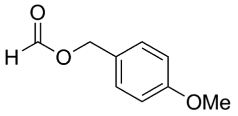
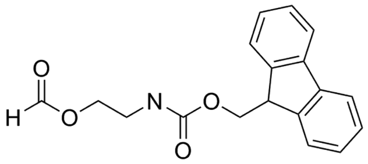
| | Substrate | TON | TON with $Sc(OTf)_3$[b] |
|---|---|---|---|
| E1 |  | 341 ± 25 | 1317 ± 37 |
| E2 |  | 305 ± 38 | 346 ± 28 |
| E3 |  | 106 ± 16 | 200 ± 23 |

[a] Average of at least 3 trials with standard deviation. Conditions: 4 μmol of **1** in 2 mL of substrate (E1, 24.8 mmol; E2, 24.4 mmol; E3, 20.4 mmol), 30 bar $H_2$, 100 °C, 16 h. Theoretical maximum TON under these conditions = E1, 6200; E2, 6300; E3, 5100. [b] with 40 μmol $Sc(OTf)_3$.

The hydrogenation of ester substrates **E1−E11** was next evaluated in DME (Table 3). These reactions were conducted using 1 mmol of substrate in 1 mL of solvent under 30 bar $H_2$ at 100 °C for 16 h using 0.5 mol % of **1**. These conditions enabled a clear comparison between different substrates because the reactions generally proceeded to moderate conversion. The reactivity was found to be strongly sensitive to the size of the carbonyl substituent. For example, ethyl formate afforded nearly quantitative conversion (TON = 173), whereas the more sterically encumbered substrate ethyl acetate showed much lower reactivity (TON = 27). Substrates bearing even larger carbonyl substituents such as *tert*-butyl and phenyl (**E4, E5**) afforded very low conversion under these conditions. Hydride transfer is likely prohibitively slow in these systems due to the steric demands of the substrate.

**Table 3. Ester Hydrogenation in DME Solvent**[a]



| | Substrate | TON |
|---|---|---|
| E1 |  | 173 ± 30 |
| E2 |  | 24 ± 6 |
| E3 |  | 27 ± 5 |
| E4 |  | 0 ± 0 |
| E5 |  | 2 ± 1 |
| E6 |  | 89 ± 5 |
| E7 |  | 94 ± 15 |
| E8 |  | 115 ± 5 |
| E9 |  | 101 ± 12 |
| E10 |  | 114 ± 2 |
| E11 |  | 107 ± 14[b] |

[a] 1 mmol substrate, 0.5 mol % **1**, 1 mL of DME, 30 bar $H_2$, 100 °C, 16 h. Yields represent an average of 3 trials ± standard deviation. [b] Reaction run in 2 mL DME. Average of 2 trials.

On the basis of the high reactivity of ethyl formate, the reactions of a series of other formate esters were examined.[19] Formate esters bearing alkyl ester substituents (**E6−E11**) afforded methanol with TONs ranging from 89 to 115.[25] Interestingly, these reactions were relatively insensitive to the size and functionality of the alkoxy component of the ester substrate. For example, *t*-butylformate (**E8**) and the FMOC-protected amine **E11** underwent hydrogenation with comparable TON and no apparent deprotection of the amine functionality (115 and 107, respectively).

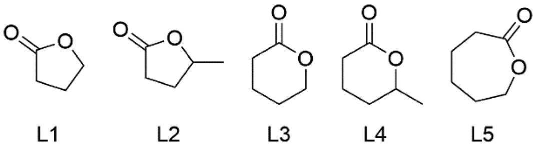
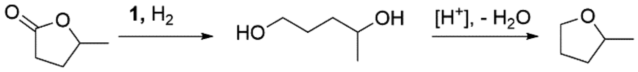


**Figure 3.** Lactone substrates.

A variety of lactones (Figure 3, **L1−L5**) were also examined as substrates for hydrogenation with catalyst **1**. As shown in Scheme 2, the initial product of lactone hydrogenation is a diol. However, in the presence of catalyst **1**, this diol intermediate undergoes rapid dehydration to afford cyclic ethers as the major product. This is noticeably different from the previously reported Ru/Triphos catalyst system for lactone hydrogenation, which affords the diol as the final product in the absence of added acid.[10−13]

**Scheme 2. Hydrogenation of L2**



The results for the hydrogenation of the 5-membered lactones γ-butyrolactone (**L1**) and γ-valerolactone (**L2**) are shown in Table 4. In neat lactone, the addition of $Sc(OTf)_3$ was found to enhance reactivity.[17] In contrast, in DME solvent, the Lewis acid cocatalyst had minimal impact on TON. This may be due to competitive coordination of the Lewis acid to DME.

**Table 4. Hydrogenation of L1 and L2 with 1**

| solvent | time (h) | additive | TON[a] | |
|---|---|---|---|---|
| | | | **L1** | **L2** |
| neat[b] | 16 | none | 291 ± 7 | 76 ± 5 |
| neat[b] | 16 | $Sc(OTf)_3$[c] | 410 ± 53 | 200 ± 19 |
| neat[b] | 65 | none | 487 ± 16 | 166 ± 54 |
| DME[d] | 16 | none | 33 ± 4 | 27 ± 5 |
| DME[d] | 16 | $Sc(OTf)_3$[e] | 23 ± 6 | 19 ± 3 |
| DME[d] | 65 | none | 69 ± 4 | 78 ± 6 |

[a] TON for cyclic ether product, average of 3 trials, standard deviation in parentheses. [b] 2 mL of substrate, 4 μmol **1**, 30 bar $H_2$, 100 °C. [c] 40 μmol of $Sc(OTf)_3$. [d] 1 mmol substrate, 0.5 mol % **1**, 1 mL DME, 30 bar $H_2$, 100 °C. [e] 0.5 mol % $Sc(OTf)_3$

The presence of the methyl group in **L2** led to significantly diminished TON in the neat reactions. This is consistent with the observation that steric bulk around the carbonyl component of the ester diminishes reactivity under neat conditions (**E2** vs **E3**, Table 2).

For the 6- and 7-membered ring lactones **L3**−**L5**, we observe rapid conversion of starting material to a mixture of products by NMR spectroscopy. However, only traces of the expected diol and cyclic ether products were detected (as confirmed by independent synthesis).[19] Instead, ESI-MS revealed product masses consistent with the formation of oligoesters (see Supporting Information). This suggests that ring-opening polymerization occurs more rapidly than hydrogenation for these substrates.[26,27] Analogous byproducts were not observed for **L1** or **L2**.

In conclusion, we have demonstrated that **1** catalyzes the base-free hydrogenation of a variety of esters and lactones. This catalyst is particularly effective for the hydrogenation of formate esters, a substrate class that has been utilized as an intermediate along an acid-assisted path from $CO_2$ to methanol.[15] Notably, the presence of Lewis acid $Sc(OTf)_3$ was not detrimental to catalyst activity. Indeed, for reactions carried out in neat substrate, this additive led to enhanced TONs. Mechanistic investigations are consistent with a reaction pathway involving turnover-limiting hydride transfer at high pressures of $H_2$. Consistent with this mechanism, the catalyst is very sensitive to the size of the carbonyl substituent. Overall, this system offers a valuable complement to previously developed, base-assisted catalysts for the hydrogenation of esters.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.6b00263.

Experimental details and procedures, ESI-MS data, time-course studies(PDF)

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### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

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(19) For full experimental details, see Supporting Information.
(20) At this time point, reaction progress is within the linear initial rate regime allowing for direct comparison across concentrations. See Supporting Information for further details.
(21) In contrast, the **2**-catalyzed hydrogenation of glacial acetic acid reaches saturation at approximately 25 bar $H_2$ (ref 8).
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(24) Preliminary experiments run at lower $H_2$ pressure (10 bar) showed no added effect of $Sc(OTf)_3$ on yield, suggesting that hydride transfer is not turnover-limiting in this regime.

(25) The second product of the reaction is the corresponding alcohol (i.e., 1-hexanol from hexyl formate). Only in the cases of benzyl formate (**E9**) and *p*-methoxybenzyl formate (**E10**) was an additional product, the respective dibenzyl ether, observed in measurable quantities. The ether byproduct is likely formed via an acid-catalyzed condensation reaction.

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