Selective Reduction of Carboxylic Acids to Alcohols in the Presence of Alcohols by a Dual Bulky Transition-Metal Complex/Lewis Acid Catalyst

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ABSTRACT: Here, we report a molecular method for the generally applicable reduction of mono- and dicarboxylic acids that selectively furnishes a diverse variety of alcohols, including mono- and diols. One of the inherent drawbacks of the direct hydrogenation of carboxylic acids to alcohols is the in situ formation of the corresponding esters via condensation of the carboxylic acids with the produced alcohols. Especially, the hydrogenation of polycarboxylic acids frequently suffers from the formation of a complex mixture of oligomeric esters. This issue was successfully overcome by the combined use of a dual catalyst that consists of a bulky (PNNP)iridium complex and a Lewis acid. Owing to the steric bulk and robustness of the iridium catalyst, the main role of the Lewis acid is to independently catalyze the esterification, albeit the cooperative activation of (a resting state of) the iridium catalyst by the Lewis acid also seems to be implied.

KEYWORDS: carboxylic acid, hydrogenation, iridium catalyst, Lewis acid, tandem catalysis, alcohols, diols, polyols

INTRODUCTION

Mono- and polycarboxylic acids (mono- and poly-CAs) are ubiquitous in nature and represent a large repository of platform chemical precursors. Several reports have shown that CAs can be derived from biomass-based resources such as lignin and hemicellulose using green and economically feasible methods. Likewise, many different methods for producing dicarboxylic acids (di-CAs) from biomass have been developed. Although the produced CAs are valuable by themselves, their corresponding terminal alcohols (ALs) are more interesting as platform chemicals, as they may find useful applications in the production of polymers and as fuel additives to improve the octane number. Moreover, terminal ALs are in general synthetically more useful than the parent CAs. Thus, the transformation of CAs into terminal ALs represents—not least financially—an attractive method to add value to inexpensive chemicals to generate useful fine chemicals. However, the transformation of poly-CAs into terminal poly-ALs is highly challenging due to the high thermodynamic stability imposed by their high oxidation states and the low solubility of poly-CAs in organic solvents, which is due to complex hydrogen-bonding networks formed by their multiple CA moieties.

In this context, the hydrogenation of CAs is among the most promising and clean methods for producing ALs on a large scale because water is the only byproduct. However, the in situ formation of the corresponding esters via the condensation of the product alcohols with their parent CAs is, unfortunately, an inherent drawback in the direct hydrogenation of CAs. For instance, when acetic acid is hydrogenated, ethyl acetate is found to be the major or sole product, except for one rare example. The hydrogenation of poly-CAs frequently suffers from the generation of a complex mixture of oligomeric esters, thereby decreasing the selectivity and productivity toward the desired alcohols. Our group has recently developed a (PNNP)iridium [((PNNP)Ir] pre-catalyst that does not require activation by a base such as NaH for a cascade of orthogonal steps to yield 1,4-diols from di-CAs, that is, to form anhydrides from di-CAs with a four-carbon (C4) main chain and hydrogenation of the resulting γ-butyrolactones. This system is highly effective for this cascade, and due to the robust structure imposed by the tetradeinate PNNP ligand, the catalyst remains active in the presence of a wide range of functional groups, maintaining its structural integrity for long reaction times even under harsh temperature and hydrogen-pressure conditions. Experimental

Received: September 24, 2021
Revised: December 14, 2021
and theoretical insights based on our results, and those of Gusev, indicate that this class of precatalysts, which comprise bipyridyl methylene (bpyCH2) or pyridyl methylene (pyCH2) units in the ligand framework, operates in many instances via Noyori’s metal–ligand bifunctional (MLB) mechanism. This implies that the substrate does not need to directly coordinate to the metal center for the reduction to occur. Consequently, undesirable side reactions and/or substrate/product inhibition such as the coordination of extra organic entities to the metal center and decay of the catalyst structure are effectively avoided using the essentially coordinatively saturated (PNNP)Ir catalyst. However, this catalyst is virtually inactive for the direct hydrogenation of mono-CAs under the reaction conditions we have tested thus far.

As part of our continuous endeavors to reduce highly oxidized carbons of renewable resources using molecular catalysts, we report here that a (PNNP)Ir complex can catalyze the apparent hydrogenation of di-CAs with n carbon atoms (Cn: n ≠ 4) in their main chain, as well as mono-CAs, in the presence of alcohol and a catalytic amount of a Lewis acid, such as ZrCl4, HfCl4, or AlCl3. This protocol facilitates the hydrogenation of CAs by substantially altering the reactivity compared to that of the hydrogenation reaction in the absence of alcohol (Figure 1c). The otherwise unavoidable issue of esterification of 1a, followed by the hydrogenation of the resulting ester (ES) in the presence of an alcohol such as 1-BuOH (2 equiv relative to 1a) and NaH (6 mol %). After a relatively long reaction time of 76 h, 2a was obtained in high yields (entry 1) in the absence of a Lewis acid. The extreme sluggishness of the reaction can be explained reasonably by slow esterification in conjunction with catalyst deactivation in the presence of free CA (vide infra). To speed up the transformation, we screened several Lewis-acidic additives to accelerate the esterification step and thus the entire transformation. The presence of Lewis-acidic additives greatly increased the overall reaction rate (entries 2–7). HfCl4(THF)2 and ZrCl4(THF)2, which have previously been demonstrated to be some of the most promising catalysts for CA–AL condensation, as well as AlCl3, were highly active, furnishing 2a in a quantitative 1H NMR yield (isolated yield: 87%) within 28 h. Notably, the hydrogenation activity was maintained in the presence of all the tested additives, demonstrating the structural robustness of IrPCY2, which operates separately from the additives. Ultimately, non-hygroscopic ZrCl4(THF)2 was chosen as the additive for this study due to its ease of handling. Unlike in our previous study, the necessity of a

**RESULTS AND DISCUSSION**

We started this study by investigating whether our (PNNP)Ir catalyst IrPCY2 (1 mol %; Table 1) can catalyze the esterification of 1a, followed by the hydrogenation of the resulting ester (ES) in the presence of an alcohol such as 1-BuOH (2 equiv relative to 1a) and NaH (6 mol %). After a relatively long reaction time of 76 h, 2a was obtained in high yields (entry 1) in the absence of a Lewis acid. The extreme sluggishness of the reaction can be explained reasonably by slow esterification in conjunction with catalyst deactivation in the presence of free CA (vide infra). To speed up the transformation, we screened several Lewis-acidic additives to accelerate the esterification step and thus the entire transformation. The presence of Lewis-acidic additives greatly increased the overall reaction rate (entries 2–7). HfCl4(THF)2 and ZrCl4(THF)2, which have previously been demonstrated to be some of the most promising catalysts for CA–AL condensation, as well as AlCl3, were highly active, furnishing 2a in a quantitative 1H NMR yield (isolated yield: 87%) within 28 h. Notably, the hydrogenation activity was maintained in the presence of all the tested additives, demonstrating the structural robustness of IrPCY2, which operates separately from the additives. Ultimately, non-hygroscopic ZrCl4(THF)2 was chosen as the additive for this study due to its ease of handling. Unlike in our previous study, the necessity of a
catalytic amount of base (NaH) was demonstrated in a control experiment (entry 8), which confirmed negligible hydrogenation activity in its absence. The use of other AL additives instead of 1-BuOH (EtOH, 2-ProH, 1-hexanol, and 1-octanol) resulted in either a negative effect or negligible improvement (Table S1). Particularly, when conventionally less reactive alcohols for esterification such as t-BuOH were utilized, extremely sluggish esterification was observed; thus, 1-BuOH was ultimately chosen due to its low boiling point (118 °C at 1 atm), which is favorable for the separation of the desired ALs from 1-BuOH. Alkali metal effects10,28 were also examined as follows: with LiH, esterification was completed but activity for hydrogenation was not obtained10 over 40 h of reaction time, whereas both KH and KO t-Bu gave similar results to give 2a in 90% yield with ES (~5%) (Table S2). Other (PNNP)Ir derivatives, in which the Cy group, was replaced with Et, i-Pr, Ph or Py were also tested, but their effectiveness was comparable to or lower than that of IrPCY2 (Table S6), which highlights the importance of the steric demand of the Ir catalyst.

After shortening the reaction time, we investigated the substrate scope of mono-CAs (Scheme 1). Biorelevant aliphatic fatty CAs, such as lauric acid (1b) and stearic acid (1c), were smoothly hydrogenated to the corresponding ALs, which were isolated in high yields. Notably, the notoriously challenging substrate acetic acid (1d) could be hydrogenated to EtOH with high selectivity, without the significant formation of ethyl acetate. Benzoic acid (1e), one of the least reactive CAs toward hydrogenation,6,9,11b proved challenging to hydrogenate under the optimized conditions due to its sluggish esterification, presumably a result of its steric hindrance and electronic nature.14 However, this issue was resolved by employing MeOH as the sole solvent, which furnished benzyl alcohol (2e) in 94% yield. In contrast to some of the previously reported Ru complexes for the catalytic hydrogenation of unactivated esters which exhibited low stability and/or reactivity in MeOH or toluene,10 our system displayed high activity in these solvents. Compared to other reported systems for mono-CA hydrogenation,9,11,12,14,22 we achieved comparable or improved conversion and selectivity at a lower catalyst loading or shorter reaction time.

After establishing a protocol for the hydrogenation of mono-CAs, we investigated the hydrogenation of more challenging, bio-renewable di-CAs (1f–1k, C_{n−m} and C_{n+m}) with even or odd numbers of carbon atoms (Scheme 2). The odd-even effect on the physical properties (e.g., crystallinity) of di-CAs (C_{n−m}) are long-standing concerns and may also have a strong influence on their solubility during hydrogenation.29 The catalytic hydrogenation of di-CAs using homogeneous catalysts is completely absent in the literature, except succinic acid and other C_{n−m}-di-CA derivatives, which easily form intramolecular anhydrides.12,14,18 Heterogeneous systems for the hydrogenation of di-CAs tend to rely on harsh conditions and/or exhibit unsatisfactory selectivity.16,18 Surprisingly, using our system, all the tested long-chain di-CAs, none of which easily undergo intramolecular cyclization to give the anhydride, could be hydrogenated to produce their corresponding terminal diols in high to near-quantitative yields. The global market for brassylic acid (C_{13}, 1k) is expanding rapidly; this substrate successfully produced diol 2k in 96% yield.50 Glutaric (1f) and adipic acid (1g) could not be hydrogenated effectively using the 1-BuOH/toluene solvent system; however, the hydrogenation proceeded successfully in MeOH. To the best of our knowledge, none of these ALs are accessible using conventional homogeneous systems for CA hydrogenation. Additionally, we have made significant improvements concerning the substrate scope, mild reaction conditions, and selectivity compared to previously reported heterogeneous systems for the hydrogenation of di-CAs.16–18

![Scheme 2. Hydrogenation of Di-CAs](https://doi.org/10.1021/acscatal.1c04392)

To further demonstrate the versatility of our system, we investigated the sequential esterification/hydrogenation of biorelevant oxalic (1l) and glycolic acids (1m)13 to yield ethylene glycol (2l) (Scheme 3). 1l is one of the most challenging substrates, as it undergoes facile decomposition via decarboxylation. The hydrogenation of these substrates is highly promising in terms of a sustainable method for the production of one of the monomers of polyethylene terephthalate (PET) (2l) from biorenewable 1l. However, due to their inherent instability, reports of the direct double

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**Scheme 1. Hydrogenation of Mono-CAs**

![Scheme 1](https://doi.org/10.1021/acscatal.1c04392)

1f−1k: [IrPCY2]0 = 5−10 mM; yields of isolated, purified products. Yields of esters (in parentheses) were determined by 1H NMR using mesitylene as an internal standard. A small amount of ester derived from the condensation of the product AL with 1 was observed in some entries. [IrPCY2]: 1 mol %. 6Average of three runs, the yield of esters <12% in all three runs, and the yield were determined by 1H NMR spectroscopy using mesitylene as an internal standard. 7MeOH as a solvent; [IrPCY2]0 = 3.3 mM; yield of esters not determined.

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**Scheme 2. Hydrogenation of Di-CAs**

![Scheme 2](https://doi.org/10.1021/acscatal.1c04392)

In 90% yield with ES (<1%); yields shown are isolated yields, yields of esters shown in parenthesis were determined by 1H NMR using mesitylene as an internal standard. A small amount of ester derived from the condensation of the product AL with 1 was observed in some entries. 6[IrPCY2]: 1 mol %. 6Average of three runs, the yield of esters <12% in all three runs, and the yield were determined by 1H NMR spectroscopy using mesitylene as an internal standard. 7MeOH as a solvent; [IrPCY2]0 = 3.3 mM; yield of esters not determined.
reduction of both CA groups of 1l, which complements the
electrochemical mono-reduction of 1l to 1m31 and oxalate
hydrogenation to 2l,32 are virtually absent from the literature
except for a few systems, all of which are characterized by a low
selectivity toward 2l.33,34 By conducting the esterification at
low temperatures, followed by hydrogenation in a one-pot
fashion, these substrates were selectively hydrogenated to yield
2l, efficiently circumventing the issues of the decomposition
and in situ formation of polyesters, which are usually
associated with these substrates.

The mechanistic aspects of our system were investigated
using kinetic studies and electrospray ionization mass
spectrometry (ESI-MS) measurements. The kinetic study
was conducted using IrPCY2 in the absence and presence of
a Lewis-acidic additive and 1a (Figure 2). During the first 29 h
of the reaction without a Lewis acid, esterification predomi-
nates and only small amounts of the alcohol 2a are formed;
this product distribution remains mostly constant until ~64 h.
Surprisingly, between 64 and 72 h, all the formed ES are
hydrogenated rapidly to the targeted 2a. Notably, a tiny
amount of 1a was detected even at a reaction time of 64 h,
suggesting that significant hydrogenation activity cannot be
achieved until the esterification step is driven to completion. In
contrast, alcohol 2a was produced sluggishly during the
first 16 h in the presence of ZrCl4(THF)2, but the reduction to
2a suddenly accelerated at ~16 h, just after the complete
conversion of 1a (~99%) was confirmed by 1H NMR
spectroscopy. Thus, the use of ZrCl4(THF)2 seems to
significantly accelerate both the esterification of CA and the
hydrogenation of the formed ES.

A possible explanation for the low activity for the
hydrogenation during the esterification step is that the Ir
catalyst is significantly deactivated by the strong coordination
at low temperatures, followed by hydrogenation in a one-pot
fashion, these substrates were selectively hydrogenated to yield
2l, efficiently circumventing the issues of the decomposition

Figure 2. Kinetic studies (time-dependent yield) of the hydrogenation of 1a conducted: without ZrCl4(THF)2, and with 1 h of preactivation (Supporting Information S5) to form the catalyst (1a: ◇; ES: △; 2a: ○); with ZrCl4(THF)2 but without preactivation (1a: ■; ES: ▲; 2a: ●); ES: mixture of butyl 3-phenylpropanoate and 3-phenylpropyl 3-phenylpropanoate.
Table 2. ESI-MS Measurements of the Crude Mixture of Hydrogenation of 1a at Different Reaction Times$^a$

| Time (h) | Major species | Mass (found) | Yield (%) | ES (%) |
|----------|---------------|--------------|-----------|--------|
| 3 h      | ![image](1) | 778.4170     | 2a, 9%    | ES, 74% |
| 14 h     | ![image](2) | 928.4848     | 2a, 17%   | ES, 70% |
| 28 h     | ![image](3) | 931.5097     | 2a, 99%   | ES, <1% |

$^a$[(IrPCY2)$_0$]$_0$ = 5 mM; yield of 2a and ES determined by $^1$H NMR spectroscopy using mesitylene as an internal standard. Major species detected in the ESI-MS are shown. $^b$Mixture of butyl 3-phenylpropanoate and 3-phenylpropyl 3-phenylpropanoate.

1a-coordinated Ir species (2 or 4) were detected. Interestingly, the complete hydrogenation of the bipyridine backbone was observed in all entries, which supports previous claims that the active species for the hydrogenation is formed by the reduction of the ligand by H$_2$. Notably, even after 28 h, where a near-quantitative yield of 2a is obtained, the main species detected using ESI-MS is CA-coordinated Ir catalyst 4. These species thus seem to be relatively stable, that is, they exist in the reaction mixture even when the esterification is close to completion. The insufficient activity toward hydrogenation in the presence of a large amount of CA is likely because CA-coordinated Ir species are less active or inactive for ES hydrogenation. However, it is also noteworthy that even though 1a remained in the reaction mixture (Figure 2; t = 0–16 h), the apparent hydrogenation of 1a to 2a was moderately accelerated in the presence of the Lewis acid. This result suggests that a low concentration of 1a does not completely deactivate the (PNPN)Ir catalyst for ES hydrogenation. This is entirely different from the hydrogenation of the C$_2$-di-CA (e.g., succinic acid) in the absence of a Lewis acid in our previous system, in which the hydrogenation of the γ-butyrolactone intermediate did not start until the conversion of succinic acid reached ∼99%.

In the present case, when no Lewis acid was used, even after an apparent ∼99% conversion of CA (1a) was achieved (t ≈ 29 h), the reduction of ES to 2a unexpectedly did not start for a long period of time (Figure 2; t = 29–64 h). In a sharp contrast, the ZrCl$_4$(THF)$_2$-assisted hydrogenation of ES to 2a accelerated immediately and significantly (Figure 2; t = 16–24 h) after 1a had almost disappeared, whereby the average rate for the formation of 2a (10%/h) is higher than that in the absence of the Lewis acid (7%/h; t = 64–72 h). Thus, ZrCl$_4$(THF)$_2$ may play another important role as the Lewis-acidic activator: abstracting/attracting the carboxylate ligand from the Ir center of the less active/inactive complexes (e.g., 2 or 4), thereby shifting the ligand association–dissociation equilibrium to the more active forms (e.g., 1, 3, or 5). In a nutshell, the less active Ir catalyst was restored to a more active form in the presence of the Lewis acid. The carboxylate anion (RCO$_2^-$) abstracted from the Ir center could help dually activate H$_2$ with an action of the cationic Ir center, as frequently proposed theoretically that transition-metal alkoxides could function similarly for the activation of H$_2$ by forming a contact (hydrogen-bonded) ion pair [RO]$^-$...[HN−M]$^+$ (M = Ir, Ru, Os) as the onium salt.

Based on our experimental results and mechanistic studies, we would like to propose a reasonable catalytic cycle (Figure 3a). The main role of the Lewis-acidic additive is to catalyze the esterification, which is followed by ES hydrogenation by the IrPCY2-derived catalyst. Considering the extensive experimental and theoretical studies by Dub, Gusev, and Schaub for the catalytic hydrogenation of esters, in addition to our previous results, including ESI-MS studies, it seems more likely that H$_2$ is donated to the ES through the revised Noyori’s MLB mechanism [with the N–X (X = H or Na, Figure 3) bond of X–N–M-type complexes (M = e.g., Ru) kept intact throughout the catalytic cycle], although the original Noyori’s MLB mechanism that involves the simultaneous donation of a nitrogen-bound proton and an Ir-bound hydride from 5x to RCO$_2$R to generate RCHO, ROH, and 3 (non-innocent N–H bond) could not be fully ruled out. Species 3, which is off-cycle in the revised mechanistic scenario, could also follow one of two possible pathways. In the presence of free CA, coordination of one molecule of CA to 3 yields another off-cycle species 4, which is less active/inactive for ES hydrogenation but may be activated by ZrCl$_4$ (Figure 3b). In the absence of CA, enough concentration of the active species 5x (X = H or Na) is on-cycle and could hydrogenate ES most efficiently, while 3 may have a chance to heterolytically cleave H$_2$ to form 5x (assisted by RCO$_2$Na as a base, Figure 3c). We conclude that the key to obtaining high activity for hydrogenation using our system is to eliminate free CA in the reaction mixture, and thus the binding of CA to the Ir center, by driving the esterification step to completion. In addition, the interplay between the Lewis acid and (a resting state of) the Ir catalyst was found to be crucial for substantially accelerating the apparent hydrogenation of CAs.

CONCLUSIONS

We have shown that the hydrogenation of carboxylic acids (CAs) through in situ esterification is a highly efficient method
for the selective production of ALs from biomass-derived resources. Our system exhibits substantially improved selectivity of heterogeneous catalysis and activity of homogeneous catalysts at a significantly lower catalyst loading compared to most state-of-the-art catalytic reduction systems for the one-pot direct transformation of CAs into the ALs. The cascade catalytic approach to the hydrogenation of CAs led to an unprecedented substrate scope, including several di-CAs, which, to the best of our knowledge, have not yet been hydrogenated. Side reactions are negligible in our system, likely due to the limited interaction between IrPCY2 and the substrate/product, and most products were furnished in high to quantitative yields. Considering all these advantages, we are convinced that this study will serve as a major stepping stone for the development of economically relevant homogeneous systems for the direct reduction of both mono- and poly-CAs to ALs.

Figure 3. (a) Proposed catalytic cycle for ester hydrogenation, which is assumed to proceed in the absence of RCO₂H. In the presence of RCO₂H, R’O− and RCH₂O− would uniformly abstract the acidic CA proton to yield RCO₂−; X = H or Na; P = Cy2P. (b) Possible activation of 4 to 5x. (c) Possible activation of 3 to 5x.
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**NOTE ADDED AFTER ASAP PUBLICATION**

Due to a production error, this paper was published ASAP on January 23, 2022, with formatting errors in Tables 1 and 2, Schemes 1 and 3, and Figure 3. The corrected version was reposted on January 25, 2022.