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Reinvestigating Catalytic Alcohol Dehydrogenation with an Iridium Dihydroxybipyridine Catalyst

Wenzhi Yao, Alexa R. DeRegnaucourt, Emily D. Shrewsbury, Kylie H. Loadholt, Weerachai Silprakob, Fengrui Qu, Timothy P. Brewster,* and Elizabeth T. Papish*

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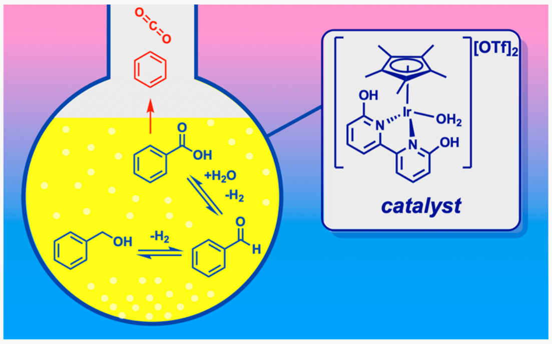
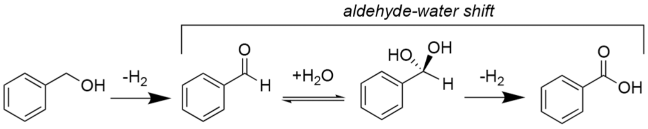


ABSTRACT: The examined catalyst $[Cp^*Ir(H_2O)(6,6'\text{-dhbp})]^{2+}$ (**1**; 6,6′-dhbp = 6,6′-dihydroxy-2,2′-bipyridine) was reported in 2012 as a highly efficient (92% conversion) and selective catalyst for the conversion of benzyl alcohol to benzaldehyde as the sole product via acceptorless dehydrogenation. We report herein that the observed conversion and selectivity data are not accurate but may have resulted, in part, from other products being produced that are not easily detected. Specifically, benzoic acid is formed as a byproduct via the disproportionation of benzaldehyde, but at high temperatures, most of the benzoic acid produced is converted *in situ* to benzene and carbon dioxide. While we can explain the observed selectivity, we cannot explain the observed conversion to products. In our hands, we observed 15% conversion to products under the original conditions. Other alcohol substrates were also examined and gave lower conversion to products and decreased selectivity in comparison with the original report. Acceptorless alcohol dehydrogenation to generate aldehydes is a potentially transformative technology which can allow chemists to replace stoichiometric oxidants that produce waste with efficient catalysts that only generate H_2 gas as a byproduct. Thus, clarification of the 2012 report to indicate what conditions can lead to high efficiency and selectivity is a worthy topic of discussion in the literature.

■ INTRODUCTION

Catalytic acceptorless alcohol dehydrogenation is an environmentally friendly method for converting alcohols into aldehydes (Scheme 1).[1−5] This method has the potential to replace stoichiometric methods that use an oxidizing agent (e.g., PCC) and generate waste products. Stronger oxidants (e.g., CrO_3) are known to overoxidize alcohols and produce the carboxylic acid product rather than the desired aldehyde. Therefore, the report from Fujita et al. in 2012 describing catalytic and selective alcohol dehydrogenation to form exclusively aldehyde in high yields was an exciting development.[6] While various catalysts were tested, the best catalyst employed in their report was $[Cp^*Ir(H_2O)(6,6'\text{-dhbp})]^{2+}$ (**1**; 6,6′-dhbp = 6,6′-dihydroxy-2,2′-bipyridine), which at 1.5 mol % was able to give a 92% yield of pure benzaldehyde (100% selectivity) after 20 h of reflux in water.

Scheme 1. Acceptorless Alcohol Dehydrogenation as Shown with Benzyl Alcohol to Generate an Aldehyde and/or a Carboxylic Acid as the Product[a]



[a]After aldehyde formation, the aldehyde−water shift (AWS) reaction is shown.

However, in 2014 a report by Brewster, Cundari, Heinekey, et al. described the aldehyde−water shift reaction for converting various aldehydes into the corresponding carboxylic acids.[7] This study included **1** as a catalyst with propionaldehyde as the substrate (the corresponding reaction with benzaldehyde was not reported for this catalyst). In their report, carboxylic acid could be obtained from aldehyde via two unique routes. The aldehyde−water shift (AWS) reaction is shown in Scheme 1 and converts water plus aldehyde to 1 equiv of carboxylic acid plus 1 equiv of H_2. Alternatively, a disproportionation reaction (Scheme 2) can convert 2 equiv of benzaldehyde to benzoic acid (or benzoate) and benzyl alcohol. Under basic conditions, the uncatalyzed Cannizzaro reaction (Scheme 2a) can occur.[8] With an iridium catalyst (e.g. **1**) and neutral or acidic conditions, a metal-catalyzed

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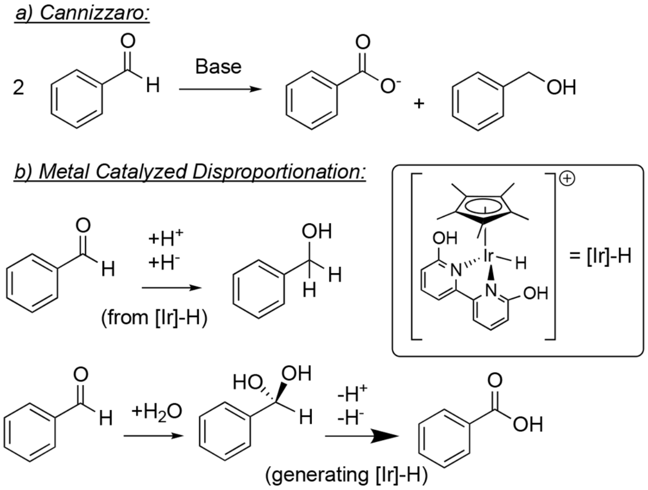
Scheme 2. (a) The Cannizzaro Reaction Differs from AWS in That It Does Not Generate Hydrogen and It Generates Alcohol as a Byproduct and (b) Metal-Catalyzed Disproportionation Reaction Converts 2 equiv of Benzaldehyde to Benzoic Acid and Benzyl Alcohol

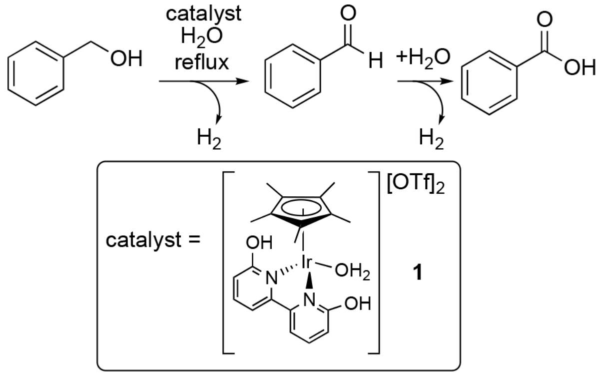


disproportionation reaction is more likely to occur via [Ir]−H formed *in situ* (Scheme 2b). With 0.8 mol % of **1**, aqueous propionaldehyde was converted to the carboxylic acid in 51% yield with the reactivity being primarily due to disproportionation (96%) with a small amount (4%) of AWS reactivity observed.[7] Since the focus of this paper was on obtaining carboxylic acid in good yields without alcohol byproduct formation, other catalysts were pursued that favored AWS reactivity, including $[Cp^*Ir(OH_2)bipy]^{2+}$ (**2**) and $[(\eta^6\text{-p-cymene})Ru(OH_2)(bipy)]^{2+}$, and these catalysts showed an ability to convert benzaldehyde to benzoic acid with a selectivity for carboxylic acid as high as 95% (via 95% AWS, though often with low conversion).[7,9,10] Other groups have pursued other catalysts (using mostly Ru) for AWS and closely related reactivity.[11−13] Though the reaction conditions differed slightly, given that both the Heinekey and Fujita papers had benzaldehyde in a flask (as either a starting material or a product) with a catalyst **1** or similar in aqueous solution, it seemed highly unlikely to us that both papers could be simultaneously consistent. This means that either the benzaldehyde is inert and can be generated without further reactivity (the Fujita results) or the benzaldehyde can produce benzoic acid (the Heinekey results). We report herein that the observed selectivity for oxidative dehydrogenation of benzyl alcohol with **1** is sensitive to temperature, and at higher temperatures an apparent selectivity for benzaldehyde is observed, yet at lower temperatures significant quantities of benzoic acid are formed (Scheme 3).

■ RESULTS AND DISCUSSION

This study began as part of a CHEM 413 Advanced Inorganic Chemistry Lab experiment for senior undergraduate students at the University of Alabama during 2017−2018. As part of a laboratory assignment, students attempted to reproduce the benzyl alcohol dehydrogenation with iridium catalysts as reported by Fujita et al.[6] The students were provided with $[Cp^*IrCl(6,6'\text{-dhbp})]Cl$ (**1-Cl**) that was synthesized in the Papish research group and is known to form **1** *in situ* by exchange of chloride for water.[14] However, in addition to the observation of benzaldehyde formation, significant quantities of benzoic acid were observed by ^1H NMR. This was further corroborated by the observation of a pH drop during the reaction, which is attributable to the formation of benzoic acid.

Scheme 3. Dehydrogenation of Benzyl Alcohol to Form both Benzaldehyde and Benzoic Acid



Following the CHEM 413 experiments in the Fall of 2018, we began efforts to reproduce Fujita's results[6] in the Papish group research laboratory during 2019. We synthesized $[Cp^*Ir(H_2O)(6,6'\text{-dhbp})][OTf]_2$ (**1**) in the prescribed manner,[6] characterized it fully, found that it matched literature data as described in the Supporting Information, and used it in experiments to rule out any influence of chloride with **1-Cl**. In our experience, catalyst **1** (synthesized in the Papish group[6,15]) at 1.5 mol % when it is heated at 110 °C with benzyl alcohol in aqueous solution under nitrogen produces benzaldehyde (∼97.6% of converted material) and benzoic acid (∼2.4% of converted material) (entry 4, Table 1). These values in Table 1 represent an apparent selectivity, since we did not trap any volatile products (*vide infra*). This reaction also shows a pH drop from 3.2 at the start of the reaction to 3.0 at the end of the reaction. However, our percent conversion is somewhat variable, averaging around 18%, far less than the 92% reported in the literature by Fujita.[6] Anticipating that contamination of the inert reaction atmosphere by room air may be causing the oxidation of substrate, we attempted this same reaction in air (entry 5) and observed no significant difference in the results. In an effort to further check our results, we reached out to Brewster, the lead author of the Heinekey study (now at the University of Memphis), for independent verification. Qualitatively similar results were obtained with the catalyst synthesized and tested by the Brewster group (the catalyst synthesized in the Brewster laboratory has also been fully characterized, as described in the Supporting Information). Furthermore, the catalyst made by one group was shared with the other for catalytic trials and similarly consistent results were obtained.[16]

These results stand in contrast to Fujita's observations (entry 1) and prompted us to contact Profs. Fujita and Yamaguchi for clarification on the experimental procedure. We obtained a response which indicated that it was important for the reaction to be run at 130 °C for a vigorous reflux reaction under argon but that it was otherwise fairly insensitive to the conditions. This prompted us to study the reaction at 130 °C under nitrogen (entry 6) or argon (entry 7). Qualitatively, these two trials gave similar results in terms of conversion (7−15%) and selectivity (95−98% aldehyde formed). In all of these trials in Table 1, both GC and ^1H NMR analyses show

Table 1. Catalytic Dehydrogenation of Benzyl Alcohol with **1** in Water under Various Conditions[a]

entry	source	*T* of oil bath (°C)	atmosphere	**1** (mol %)	conversn (%)	sel (%) aldehyde	sel (%) acid
1	Fujita[6]	130	Ar	1.5	92	100	0
2	this work[c]	80	N_2	1.5	6(1)	88(13)[d]	12(13)[d]
3	this work[c]	95	N_2	1.5	10(4)	95(5)	5(5)
4	this work[b]	110	N_2	1.5	17.7(3)	97.6(3)	2.4(3)
5	this work[b]	110	air	1.5	14(2)	97.5(2)	2.5(2)
6	this work[c]	130	N_2	1.5	7(3)	95(6)[d]	5(6)[d]
7	this work[b]	130	Ar	1.5	14.6(2)	98.2(4)	1.8(4)
8	this work[b]	130	Ar	10	37(1)	99.1(1)	0.9(1)

[a] All reactions were carried out with 0.25 mmol of benzyl alcohol and **1** (at the catalyst loading shown in the fifth column) in water for 20 h. All yields were determined via GC analysis with biphenyl as an internal standard. Reactions were conducted under the atmosphere indicated in the fourth column. We note that % conversion is defined here as 100 × ((moles of aldehyde) + (moles of acid))/(moles of benzyl alcohol). [b] These reactions were performed at the University of Alabama (UA) in triplicate, and a majority of these entries have been verified by either another student at UA or co-workers at the University of Memphis. [c] These reactions were performed at the University of Memphis (UM) in triplicate, and a majority of these entries have been verified by co-workers at UA. [d] These selectivity measurements had high estimated standard deviations.

Table 2. Catalytic Dehydrogenation of Various Substrates with **1** in Water[a]

entry	catalyst (loading (mol %))	substrate	conversn (%) Fujita,[6,b]	conversn (%) this work	sel (%) aldehyde	sel (%) acid
1	**1** (2)	4-chlorobenzyl alcohol	92	2.0(2)	>99(1)[c]	<1(1)[c]
2	**1** (2)	4-bromobenzyl alcohol	93	3(1)	75(2)[c]	25(2)[c]
3	**1** (1.5)	4-methoxybenzyl alcohol	93	21(6)	91(5)	9(5)
4	**1** (1.5)	4-methylbenzyl alcohol	94	27(3)	97(1)	3(1)
5	**1** (2)	cyclohexanol	80	8(3)[d]	NA[d]	NA[d]
6	**1** (1)	1-phenylethanol	92	15(4)[d,e]	NA[d]	NA[d]
7	**2** (0.5)	benzyl alcohol	25	7(2)	>99(1)	<1(1)

[a] All reactions were carried out with 0.25 mmol of substrate and catalyst in water for 20 h. All yields were determined via GC analysis with biphenyl as an internal standard. Reactions were done with vigorous reflux conditions (oil bath at 130 °C) and under Ar as done by the Fujita group. Catalyst loadings were selected to match those in the Fujita report for the selected substrate. We note that % conversion is defined here as 100 × ((moles of aldehyde) + (moles of acid))/(moles of benzyl alcohol). [b] Fujita et al. report 100% selectivity for the aldehyde and 0% selectivity for the acid with all substrates.[6] [c] The selectivity is difficult to measure accurately for these entries with low percent conversion. [d] Carboxylic acids and aldehydes are not possible products for the oxidation of secondary alcohols. Here, the ketone is the sole product and the selectivity is not applicable. [e] This value was confirmed by ^{1}H NMR analysis, showing a mixture of acetophenone (minor component) and 1-phenylethanol (major component). ^{1}H NMR analysis of the methyl peaks showed 7% conversion, in agreement with 10% conversion by GC analysis for this trial. GC analysis is expected to give greater precision.

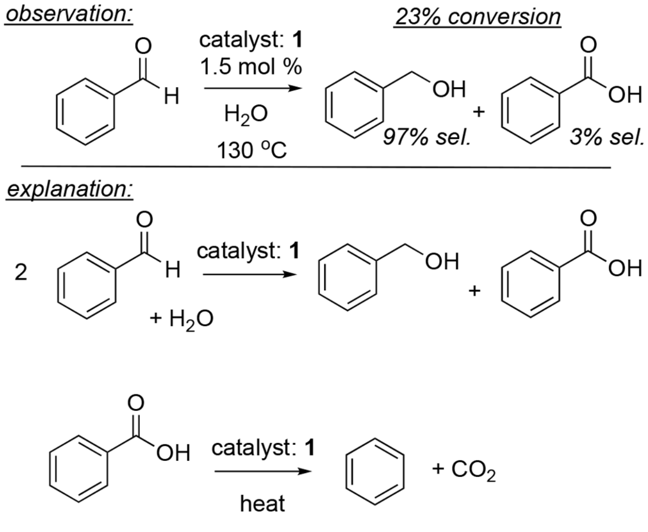
that the major isolated species is leftover unreacted benzyl alcohol (82−93%). We also explored the influence of using lower temperatures for the reaction (entries 2 and 3), and we observed a similar percent conversion and worse selectivity at 80 °C. Furthermore, hypothesizing that increased catalyst loading may allow us to achieve the Fujita results, we performed the reaction at a higher catalyst loading (10 mol %, entry 8). However, the improved conversion of 37% is still less than the Fujita results, and the selectivity is similar (99.1% aldehyde). *In no instance were we able to reproduce the published combination of conversion and selectivity.*

We also tested other substrates to determine if our results were unique to benzyl alcohol (Table 2). Fujita reported that the oxidative dehydrogenation of 4-R-benzyl alcohols with catalyst **1** results in complete selectivity for the corresponding aldehyde with isolated yields of 92−94% (entries 1−4). Our results (under conditions identical with those in Fujita's paper for each substrate) show low conversion (2−3%) with halide substitution and more moderate conversion (21 and 27%) with methyl and methoxy substitution, respectively (entries 1−4). These trials showed apparent selectivity for the aldehyde in some cases (entries 1 and 4) but also significant formation of the corresponding carboxylic acid (9 and 25%) for some substrates (entries 2 and 3). The remaining quantitatively measured material was the starting benzyllic alcohol (73−97% depending on substrate). Fujita also reported that catalyst **1** facilitated the oxidative dehydrogenation of secondary alcohols to the corresponding ketones in high yields: for example, cyclohexanol and 1-phenylethanol produced ketones in 80 and 92% yields, respectively. In contrast, we observed conversion to products of 8 and 15%, respectively, when we used the same conditions (entries 5 and 6; the remaining quantitated material is recovered unreacted secondary alcohol).

Furthermore, we prepared another catalyst from Fujita's paper to determine if our results were unique to catalyst **1**. The catalyst $[Cp^*Ir(OH_2)bipy](OTf)_2$ (**2**; 0.5 mol %) was reported for the oxidative dehydrogenation of benzyl alcohol with 25% conversion.[6] In contrast, we obtained 7% conversion with freshly prepared, analytically pure catalyst under the reported conditions (entry 7). Overall, it appears that our results are not unique to a particular substrate or catalyst. It is unlikely that our results stem from an impurity in the catalyst or the substrates. All substrates were purchased from commercial sources, and ^{1}H NMR analysis shows that the substrates are >99% pure. The catalysts were synthesized as previously reported and characterized by NMR spectroscopy, single-crystal X-ray diffraction for **1** (which matches the prior structure[6]), and elemental analysis to eliminate the possibility of trace impurities.[6,14] Full synthetic details and characterization data are given in the Supporting Information.

The results in Table 1 suggest that at higher temperatures less benzoic acid is being isolated at the end of the reaction. Initially, this seems counterintuitive because Scheme 1 shows that forming benzaldehyde releases 1 equiv of H_2 but forming benzoic acid releases 2 equiv of H_2. Thus, one would expect acid production to be both enthalpically *and entropically* favorable. Increased temperature should only increase amounts of benzoic acid by providing a driving force for gas release, and these steps should be irreversible with hydrogen escaping via the bubbler. These results prompted us to look at the aldehyde reactivity directly by using benzaldehyde as a substrate with 1.5 mol % of **1** in water at 130 °C. This reaction led to 23% conversion, with the observed selectivity producing 97% benzyl alcohol and 3% benzoic acid (Table S1). These results can only be explained by a disproportionation reaction (Scheme 2), or a combination of disproportionation and AWS, which is followed by decomposition of benzoic acid, most likely to form benzene and CO_2 (Scheme 4). Prior to this discovery we had not specifically looked for benzene in our GC analysis of the product mixtures. Under vigorous reflux conditions at 130 °C it is possible that benzene could have escaped the reaction flask, and thus, our detection. Furthermore, the percent recovery of organic material was never 100%, suggesting that some mass loss due to product decomposition during the dehydrogenation reaction was possible.

Scheme 4. Heating Benzaldehyde in Water with Catalyst 1 Leading to Benzyl Alcohol as the Major Product and Benzoic Acid as the Minor Product[a]



[a]This can be explained by a disproportionation followed by decomposition of benzoic acid.

With this knowledge in hand after obtaining the results in Scheme 4, the Papish laboratory performed the reaction of benzyl alcohol with catalyst **1** (1.5 mol %) in water in a sealed tube at 130 °C for 20 h. After the reaction mixture was cooled to room temperature, an extraction was performed with $CDCl_3$. ^1H NMR data suggested, and GC analysis confirmed, the presence of benzene. As a second verification, the Brewster laboratory also sought out the production of benzene (see the Supporting Information). A set of reactions were run in Schlenk flasks capped with septa under a positive pressure of inert gas (the standard Fujita setup) at 120 °C for 24 h. Reaction mixtures were diluted with isopropyl alcohol and injected into a GC/FID for analysis. Crucially, benzene was observed in this open-system reaction *and* the product distribution (alcohol:aldehyde:acid) was consistent with all the reactions undertaken above. Thus, it is highly likely that benzene was produced in earlier trials.

Other possible explanations for the discrepancy between our work and that of Fujita were also probed but were found not to be supported by experimental evidence. The Fujita paper does not mention the pH of the reaction mixture, but correspondence with the author confirms that the pH was not regulated and distilled, unbuffered water was used for the reaction. Furthermore, Fujita has informed us that the reaction is not sensitive to trace contaminants, and we have observed similar results upon using ultrapure unbuffered water for this reaction. Thus, one can presume that the pH used for the reaction by Fujita is 3.2 (which is the pH we observed in entries 2−7 of Table 1), which results from the acidic properties of catalyst **1**. In fact, the pH observed comes close to that predicted from the average pK_a values of 4.1 for the diprotic acid **1**.[17] Given that the properties of a catalyst can change as it is deprotonated,[14,15,18−21] we used catalyst **1** with added base to achieve pH 7−10 at the start of the reaction to see if we could obtain results closer to those observed by Fujita et al. (entry 1, Table 1). As shown in Table S2 in the Supporting Information, these experiments did not significantly change the percent conversion (3−5%) or the selectivity (∼97% selectivity for benzaldehyde with ∼3% benzoic acid). We also observe that the pH drops significantly during these reactions (ending at pH 4 and 5 when starting at pH 7 and 10, respectively), presumably due to the formation of benzoic acid.

Catalyst instability or sensitivity to a trace contaminant[22−24] is frequently blamed when catalytic results in the literature cannot be reproduced. However, as noted above, an increased loading of catalyst **1** (Table 1, entry 8) to compensate for purported catalyst decomposition does not result in quantitative conversion to the products. Notably, this catalyst is stable and long-lived in aqueous solution, as demonstrated by published studies of **1** (as the sulfate salt) and **1-Cl** (which produces **1** *in situ*) catalyzing CO_2 hydrogenation with base (pH 8.5) in aqueous solution over 18 h.[17,20] The continued catalytic output over the course of the reaction time frame[17] and UV−vis analysis of the catalyst at the end of the reaction[20] both demonstrate stability. Similarly, catalysts **1** and **1-Cl** are stable in acidic aqueous solution (pH 1.9) when they are used for formic acid dehydrogenation.[20,25] Thus, it appears that this catalyst is stable but not particularly active for acceptorless dehydrogenation of benzyl alcohol, which is a very different reaction vs CO_2 hydrogenation (and the reverse reaction) from both a thermodynamic and kinetic perspective.

■ CONCLUSIONS

Fujita's 2012 paper has been cited over 250 times as of August 2020. Over 100 of these citations use iridium, but only 31 (12 from Fujita et al.) use catalyst **1** or a close derivative. Many papers use **1** (or attempt to use **1**) for other reactions or use significantly different substrates or solvents, which precludes a comparison with Fujita's results,[26−28] but a few papers are relevant here. Do et al. reported that **1** (2 mol %) in aqueous solution was *not able* to dehydrogenate benzyl alcohol (and several other substrates used by Fujita et al.) to form the corresponding aldehyde, but this result may be attributed to the low temperature (40 °C) used.[29] Bruijnincx et al. used catalyst **1** in 1:1 water and dioxane with base present at T = 130 °C to first cleave the C−C bond in lignin models and then disproportionate the resulting aldehyde to form both alcohol and carboxylic acid.[30] For this multistep reaction, yields of the corresponding carboxylic acid were as high as 33% for the product 3,4-dimethoxybenzoic acid.[30] Various conditions were used in this paper, but in no case was high conversion to products accompanied by the exclusive formation of only the aldehyde product. More frequently, high conversion to products resulted in the formation of approximately equal parts alcohol, aldehyde, and carboxylic acid. However, significant differences in the solvent, the base present (Na_2CO_3), and the substrate could play some role in the different results observed by Bruijnincx vs Fujita. Similar to Bruijnincx's work, other catalysts using Ir, Ru, and other metals also convert alcohols to carboxylic acids by a mechanism similar to that shown in Schemes 1 and 2.[31−33] In another paper that cites Fujita et al., Li et al. report that *o*-aminobenzyl alcohols underwent dehydrogenative oxidation with **1** to form an aldehyde, which then underwent an intermolecular cyclization reaction that precluded carboxylic acid formation.[34] Though the authors assert that initial acceptorless dehydrogenation of the benzylic alcohol is crucial to the reaction, little mechanistic support was provided. Additionally, stoichiometric KOH was included in this reaction, suggesting that the Cannizzaro reaction should occur if the benzaldehyde derivative is formed in appreciable amounts. Thus, this report is largely distinct from the Fujita report. In summary, we were unable to find any literature that directly reproduces or confirms the Fujita conclusions, but several papers do indirectly call into question the validity of the Fujita paper and are more in line with our observations.

Now that we have established that carboxylic acid formation is supported by literature precedent, we can discuss the decarboxylation reaction. Complex **1** and closely related iridium complexes have been previously demonstrated to function as highly active catalysts for formic acid decomposition to form CO_2 and H_2.[20,25,35] Thus, it is not surprising that this catalyst can perform a similar reaction with benzoic acid. The release of CO_2 and formation of benzene could become more competitive as the reaction temperature is increased due to the driving force required for this reaction. Thus, it is possible that, under Fujita's conditions, 100% selectivity may have been observed for the aldehyde due to decomposition of benzoic acid, as illustrated in Scheme 4. In our hands, at lower temperatures (80 and 95 °C) we obtain more benzoic acid and apparently worse selectivity.

Our overall aim in this work has been to clarify the literature record and find conditions that can lead to efficient catalytic activity in the acceptorless dehydrogenation of substrates with catalyst **1**. Despite our explanation of the observed selectivity, we do not have an explanation for the discrepancies we find in our results vs Fujita's results with respect to percent conversion. While percent conversions can vary in our hands, we observe ∼15% conversion with benzyl alcohol as the substrate at 130 °C. Thus, the literature and our results herein support that (1) aldehydes are generally not inert and can react further to form carboxylic acids, (2) catalyst **1** does not universally give quantitative conversion to the aldehyde (or ketone) for dehydrogenation reactions and the results depend on the temperature and the exact substrates used, and (3) catalyst **1** appears to be stable,[17,20,25] but we cannot definitively rule out the possibility that **1** is sensitive to a trace contaminant. Catalytic reactions in general are known to be sensitive to conditions and trace contaminants that can enhance or be detrimental to catalysis.[22−24] Thus, it is of the utmost importance that all experimental details and sources of reagents be reported for new catalytic methods. Any experimental details that can lead to higher percent conversion would be useful for this important reaction, which allows a stoichiometric oxidant to be replaced with a green and potentially recyclable catalyst for the acceptorless dehydrogenation of substrates.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.organomet.0c00398.

> Experimental details on the synthesis of the catalyst **1** and its characterization data, further details on the catalytic studies and characterization of the products formed, and GC method details (PDF)

Accession Codes

CCDC 2025971 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Authors

Timothy P. Brewster − *Department of Chemistry, University of Memphis, Memphis, Tennessee 38152, United States;* orcid.org/0000-0002-7654-4106; Email: tbrwster@memphis.edu

Elizabeth T. Papish − *Department of Chemistry and Biochemistry, University of Alabama, Tuscaloosa, Alabama 35487, United States;* orcid.org/0000-0002-7937-8019; Email: etpapish@ua.edu

Authors

Wenzhi Yao − *Department of Chemistry and Biochemistry, University of Alabama, Tuscaloosa, Alabama 35487, United States;* orcid.org/0000-0002-4874-0169

Alexa R. DeRegnaucourt − *Department of Chemistry and Biochemistry, University of Alabama, Tuscaloosa, Alabama 35487, United States*

Emily D. Shrewsbury − *Department of Chemistry and Biochemistry, University of Alabama, Tuscaloosa, Alabama 35487, United States*

Kylie H. Loadholt − *Department of Chemistry, University of Memphis, Memphis, Tennessee 38152, United States*

Weerachai Silprakob − *Department of Chemistry and Biochemistry, University of Alabama, Tuscaloosa, Alabama 35487, United States*

Fengrui Qu − *Department of Chemistry and Biochemistry, University of Alabama, Tuscaloosa, Alabama 35487, United States;* orcid.org/0000-0002-9975-2573

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.organomet.0c00398

Notes

The authors declare no competing financial interest.

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