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# Zinc Oxide-Catalyzed Dehydrogenation of Primary Alcohols into Carboxylic Acids

Fabrizio Monda and Robert Madsen*[a]

**Abstract:** Zinc oxide has been developed as a catalyst for the dehydrogenation of primary alcohols into carboxylic acids and hydrogen gas. The reaction is performed in mesitylene solution in the presence of potassium hydroxide followed by workup with hydrochloric acid. The transformation can be applied to both benzylic and aliphatic primary alcohols and the catalytically active species was shown to be a homogeneous compound by a hot filtration test. Dialkylzinc and strongly basic zinc salts also catalyze the dehydrogenation with similar results. The mechanism is believed to involve the formation of a zinc alkoxide which degrades into the aldehyde and a zinc hydride. The latter reacts with the alcohol to form hydrogen gas and regenerating the zinc alkoxide. The degradation of a zinc alkoxide into the aldehyde upon heating was confirmed experimentally. The aldehyde can then undergo a Cannizzaro reaction or a Tishchenko reaction which in the presence of hydroxide leads to the carboxylic acid.

## Introduction

The acceptorless dehydrogenation of alcohols has gained much attention for the synthesis of imines, esters, amides, carboxylic acids, heterocycles and aldol products.[1] The reactions only produce hydrogen gas as a co-product and does not require any stoichiometric oxidants. The most widely used catalysts have been complexes based on the platinum group metals such as ruthenium and iridium.[1] More recently, different iron, cobalt and manganese complexes have also been shown to catalyze the dehydrogenations.[2] In addition, nickel, copper and molybdenum catalysts have been employed in several special cases.[3] Zinc, however, has gained very little interest for catalyzing the acceptorless dehydrogenation of alcohols.

Due to its poor redox properties zinc catalysis is often viewed as being limited to Lewis acid mediated reactions. Zinc exists in oxidation states 0 and +2 and only in the latter is it possible to form complexes with ligands. However, in recent years an increasing number of zinc(II)-catalyzed oxidations with hydroperoxides and reductions with hydride sources have been developed.[4] The last category includes hydrosilylation of ketones, esters, imides and amides with silanes[5] as well as hydrogenation of ketones and imines with hydrogen gas.[6] Most of the transformations are believed to proceed through the formation of zinc(II) hydrides[7] which are known to be able to reduce C=O and C=N bonds.

A few dehydrogenations with the release of hydrogen gas have also been described with zinc(II) catalysts. Zinc triflate catalyzes the borylation and silylation of terminal alkynes with boranes and silanes,[8] respectively, as well as the *N*-silylation of indoles with silanes.[9] Zinc oxide catalyzes the dehydrogenation of alcohols in the gas phase at temperatures around 400 °C and the reaction is often accompanied by a competing dehydration reaction.[10] In addition, heating a mixture of a primary alcohol, a zinc salt and sodium hydroxide to 210 – 260 °C under neat conditions has been reported to afford a mixture of the corresponding ester and carboxylic acid in moderate yields.[11] The transformation is believed to proceed through a Tishchenko reaction[12] of the intermediate aldehyde to give the ester. Thus, it appears that zinc(II) species are able to mediate the necessary molecular pathways for releasing hydrogen gas and it is therefore conceivable that they will also catalyze alcohol dehydrogenations at more moderate temperatures in solution.

Herein, we describe the development of a zinc(II)-catalyzed protocol for the dehydrogenation of primary alcohols into carboxylic acids. Zinc oxide was shown to be the preferred catalyst and with a price of only $1/kg it constitutes by far the most inexpensive catalyst for alcohol dehydrogenation in solution.[1-3] The acceptorless dehydrogenative synthesis of carboxylic acids from alcohols has previously been described with a 0.1 – 5% loading of ruthenium,[13] iridium,[14] palladium,[15] rhodium,[16] silver[17] and nickel[18] catalysts at reflux temperature in water, toluene or mesitylene solution. The dehydrogenative protocol constitutes a benign alternative to alcohol oxidation to carboxylic acid which is usually performed with a stoichiometric metal oxide or by a catalytic procedure with a stoichiometric co-oxidant.[19]

## Results and Discussion

The transformation was discovered while attempting to use zinc metal as a reducing agent for other Earth-abundant metals in the presence of water and hydroxide. We have previously performed a dehydrogenative self-condensation of 1-phenylethanol into 3-methyl-1,3-diphenylpropan-1-one with a ruthenium catalyst.[20] The reaction is carried out at reflux temperature with one equiv. of potassium hydroxide. Several inexpensive metals[2] were investigated as new catalysts for this transformation with different ligands and zinc metal as a reducing agent. However, it was quickly realized that zinc was responsible for the conversion into the product. In fact, reacting the alcohol with 0.25 equiv. of Zn in mesitylene solution gave 45% yield of the ketone product with some unreacted alcohol remaining (Scheme 1). Zinc metal is known to react with water in organic solvents and produce

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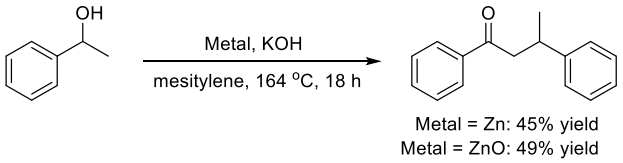
zinc oxide upon heating.[21] Therefore, we speculated that the actual catalyst was zinc oxide which was confirmed by repeating the reaction with this salt to give the ketone in 49% yield. Again, unreacted alcohol was responsible for the moderate yield and it was not possible to further optimize the reaction. Instead, it was decided to investigate the transformation with a primary alcohol which would presumably be more reactive.

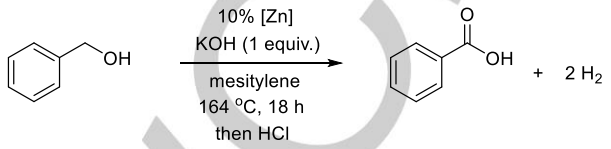



**Scheme 1.** ZnO-catalyzed self-condensation of 1-phenylethanol.

Indeed, reacting benzyl alcohol with 10% of zinc oxide and one equiv. of potassium hydroxide in refluxing mesitylene now furnished the carboxylic acid in 58% isolated yield after workup by acidification (Table 1, entry 1). However, full conversion of the alcohol was still not obtained and a number of experiments were therefore performed to improve the transformation. Replacing zinc oxide with zinc metal gave a very similar outcome (entry 2) while poor results were obtained with lithium hydroxide and sodium hydroxide as the base (entries 3 and 4). Additives also gave a lower yield (entries 5 and 6) while the reaction with *p*-cymene as the solvent furnished the acid in 73% yield (entry 7). The improved yield in the latter case is most likely due to the higher reaction temperature since no conversion of the alcohol was obtained upon refluxing the reactants in toluene or diglyme. As a result, it was decided to continue the optimization in mesitylene solution.

Several other zinc sources were also investigated and interestingly $Et_2Zn$, $Me_2Zn$, $Zn(HMDS)_2$ and $Zn(OMe)_2$ all gave yields similar to zinc oxide and with a slightly higher alcohol conversion (entries 8–11). This indicates that the catalytically active species is the same in all cases regardless of the zinc source. Therefore, the optimization continued with the inexpensive zinc oxide catalyst. The morphology of this oxide had no influence on the outcome, but when a zinc oxide dispersion in water was employed, the reaction stalled (entry 12). This could suggest that water had a detrimental influence on the dehydrogenation and explain the cumbersome reaction in Scheme 1 where water is formed as a byproduct. In fact, commercial samples of potassium hydroxide contains 0.35 – 0.55 equiv. of water per equiv. of hydroxide and a new protocol was therefore devised to decrease the amount of water in the reaction. First, potassium hydroxide was mixed with zinc oxide and the mixture heated to 170 °C under vacuum for 1 h. This produced a molten slurry to which benzyl alcohol and mesitylene were added. After stirring the mixture at reflux for 18 h the acid was now isolated in 72% yield with an improved conversion of the alcohol (entry 13). To ensure complete conversion of benzyl alcohol, the amounts of zinc oxide and potassium hydroxide were increased to 20% and 2 equiv., respectively, which now afforded 91% yield of benzoic acid (entry 14). Notably, essentially the same yield was obtained with 20% of $Zn(OMe)_2$ (entry 15). Control experiments revealed that zinc oxide and potassium hydroxide were both vital for the transformation (entries 16 and 17). Thus, an optimized protocol has been developed for the acceptorless dehydrogenation of alcohols into carboxylic acids by using zinc oxide and potassium hydroxide in refluxing mesitylene (entry 14).

**Table 1.** Optimization of zinc-catalyzed dehydrogenation.[a]



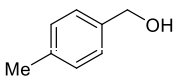
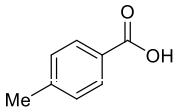
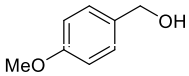
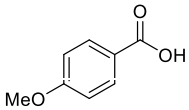
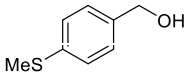
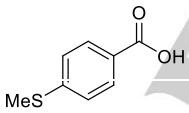
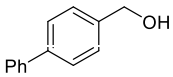
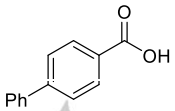
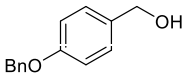
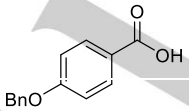
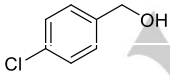
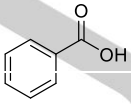
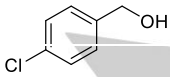
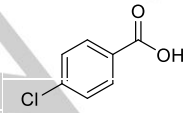
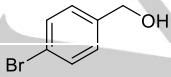
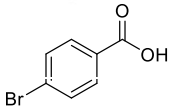
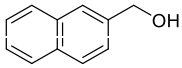
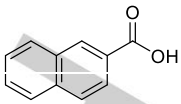

| Entry | [Zn] | Conversion [%][b] | Yield [%][c] |
|---|---|---|---|
| 1 | ZnO | 78 | 58 |
| 2 | Zn | 62 | 58 |
| 3[d] | ZnO | 0 | 0 |
| 4[e] | ZnO | 62 | 18 |
| 5[f] | ZnO | 40 | 32 |
| 6[g] | ZnO | 47 | 27 |
| 7[h] | ZnO | 99 | 73 |
| 8 | $Et_2Zn$ | 91 | 54 |
| 9 | $Me_2Zn$ | 86 | 56 |
| 10 | $Zn(HMDS)_2$ | 76 | 51 |
| 11 | $Zn(OMe)_2$ | 97 | 62 |
| 12 | ZnO[i] | 14 | 0 |
| 13[j] | ZnO | 89 | 72 |
| **14[j,k,l]** | **ZnO** | **99** | **91** |
| 15[j,k,l] | $Zn(OMe)_2$ | 99 | 90 |
| 16[l] | - | 18 | 0 |
| 17[k,m] | ZnO | 0 | 0 |

[a] Reaction conditions: Benzyl alcohol (2 mmol), [Zn] (0.2 mmol), KOH (2 mmol), mesitylene (3 mL), reflux, 18 h. [b] Determined by GC. [c] Isolated yield. [d] With LiOH instead of KOH. [e] With NaOH instead of KOH. [f] With 1 equiv. of LiCl as additive. [g] With 1 equiv. of KF as additive. [h] In *p*-cymene at 177 °C. [i] 20 wt.% dispersion in water. [j] [Zn] and KOH premixed at 170 °C for 1 h. [k] With 20% of [Zn]. [l] With 2. equiv. of KOH. [m] Without KOH.

The procedure was now applied to a variety of primary alcohols to explore the substrate scope and limitations of the reaction. First, several other benzylic alcohols were subjected to the dehydrogenation (Table 2). *p*-Methylbenzyl alcohol afforded *p*-toluic acid in 85% isolated yield (entry 1) while the *p*-methoxy

analogue gave *p*-anisic acid in 79% yield (entry 2). Almost the same outcome was obtained with *p*-methylthiobenzyl alcohol illustrating the compatibility of a thio ether with the transformation (entry 3). *p*-Phenyl- and *p*-benzyloxybenzyl alcohol furnished the corresponding acids in 62 and 91% yield, respectively (entries 4 and 5). When *p*-chlorobenzyl alcohol was submitted to the optimized conditions complete dechlorination occurred and benzoic acid was isolated in 76% yield (entry 6). To prevent the dehalogenation the reaction temperature was lowered to 150 °C which now allowed *p*-chlorobenzoic acid to be isolated in 47% yield (entry 7). *p*-Bromobenzyl alcohol also underwent complete dehalogenation in refluxing mesitylene, but at 150 °C *p*-bromobenzoic acid could be obtained in 42% yield (entry 8). The naphthalene substrate 2-naphthylmethanol afforded the corresponding 2-naphthoic acid in 70% yield (entry 9). 2,4,6-Trimethylbenzyl alcohol, on the other hand, did not react in the transformation (result not shown) illustrating the steric effect of the two *ortho* methyl groups.

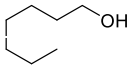
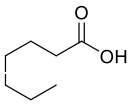
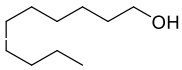
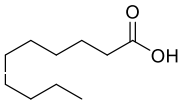
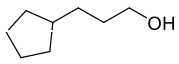
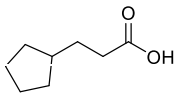
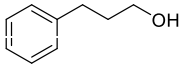
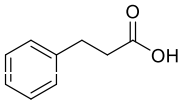
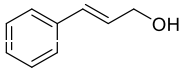
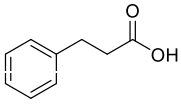
**Table 2.** Zinc-catalyzed dehydrogenation of benzylic alcohols.[a]

| Entry | Substrate | Product | Yield [%][b] |
|---|---|---|---|
| 1 |  |  | 85 |
| 2 |  |  | 79 |
| 3 |  |  | 78 |
| 4 |  |  | 62 |
| 5 |  |  | 91 |
| 6 |  |  | 76 |
| 7[c] |  |  | 47 |
| 8[c] |  |  | 42 |
| 9 |  |  | 70 |

[a] Reaction conditions: ZnO (0.4 mmol) and KOH (4 mmol) at 170 °C for 1 h then add benzylic alcohol (2 mmol) and mesitylene (3 mL) and heat to 164 °C for 18 h. [b] Isolated yield. [c] Reaction temperature 150 °C.

The transformation could also be applied to aliphatic primary alcohols although a slower conversion was observed and a longer reaction time of 36 h was necessary (Table 3). Under these conditions, heptan-1-ol and decan-1-ol afforded the corresponding acids in 79 and 82% yield, respectively (entries 1 and 2). 3-Cyclopentyl- and 3-phenylpropan-1-ol gave the 3-substituted propanoic acids in 74 and 69% yield (entries 3 and 4). Cinnamyl alcohol also furnished 3-phenylpropanoic acid due to a simultaneous reduction of the olefin (entry 5). Cyclohex-3-enylmethanol, on the contrary, gave rise to a partial migration of the olefin and yielded a 2:1 mixture of cyclohex-3-enecarboxylic acid and cyclohex-1-enecarboxylic acid (entry 6). The bulky substrate 1-adamantanemethanol could be converted to the acid as well which was isolated in 67% yield (entry 7). Full or almost full conversion of the starting material was observed with all the aliphatic alcohols.

**Table 3.** Zinc-catalyzed dehydrogenation of aliphatic alcohols.[a]

| Entry | Substrate | Product | Yield [%][b] |
|---|---|---|---|
| 1 |  |  | 79 |
| 2 |  |  | 82 |
| 3 |  |  | 74 |
| 4 |  |  | 69 |
| 5 |  |  | 75 |

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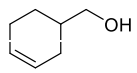
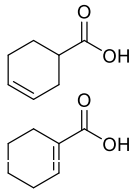
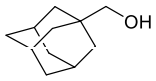
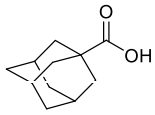
| 6 |  |  | 78[c] |
| 7 |  |  | 67 |

[a] Reaction conditions: ZnO (0.4 mmol) and KOH (4 mmol) at 170 °C for 1 h then add aliphatic alcohol (2 mmol) and mesitylene (3 mL) and heat to 164 °C for 36 h. [b] Isolated yield. [c] Isolated as a 2:1 mixture of cyclohex-3-ene- and cyclohex-1-enecarboxylic acid.

If the amount of potassium hydroxide was lowered, the aliphatic alcohols produced a mixture of the carboxylic acid and the corresponding Guerbet alcohol[22] (by self-coupling through an aldol pathway). As an example, heptan-1-ol furnished 51% of heptanoic acid and 46% of the Guerbet alcohol (2-pentylnonan-1-ol) with one equiv. of potassium hydroxide while the yields were 6% and 50%, respectively, with 30% of the base. The formation of heptanoic acid is due to a faster dehydrogenation of heptan-1-ol than of the more hindered Guerbet alcohol. However, it was never possible to optimize the Guerbet coupling to give more than a moderate yield and this reaction was therefore not further developed.

The evolution of hydrogen gas was measured from the reaction with zinc oxide in *p*-cymene (Table 1, entry 7). A total of 61 mL (2.5 mmol) was collected corresponding to approximately 2 equiv. of gas in a reaction with an yield of 73%. The gas was shown to be $H_2$ which confirms that the transformation takes place by an acceptorless dehydrogenative pathway. Interestingly, the measurement showed that the reaction had almost gone to completion after about 6 h (Figure 1).

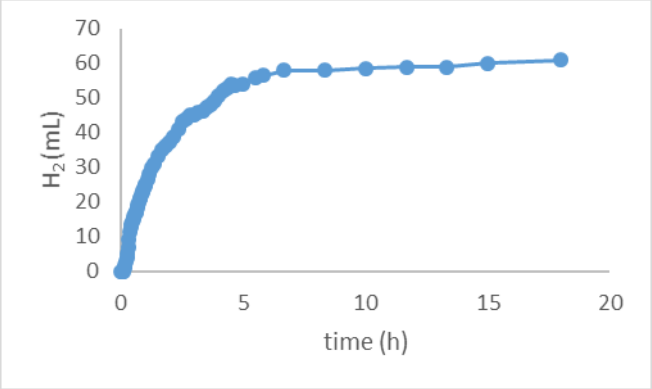



**Figure 1.** Development of hydrogen gas over time. Conditions: BnOH (1 mmol), ZnO (0.2 mmol), KOH (2 mmol), *p*-cymene (3 mL), 177 °C.

Zinc oxide was submitted to trace metal analysis by inductively coupled plasma mass spectrometry (ICP-MS) to exclude other elements known to perform alcohol dehydrogenation.[23] Fortunately, none of these metals were observed beyond their detection limits of typically 1 ppm and the transformation is therefore not believed to be catalyzed by trace metal residues in zinc oxide.

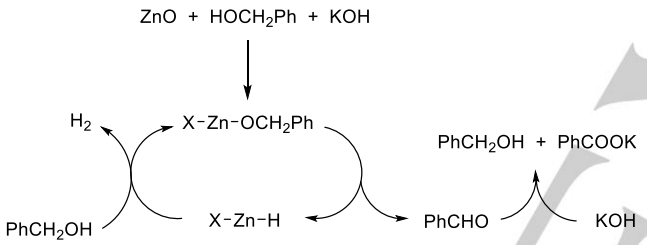
The catalytically active species is not known and several experiments were performed in order to gain more information about the actual catalyst. First, the reaction in Table 1, entry 14 was repeated with 50 μL of mercury added from the beginning or after 2, 4 or 6 h. None of these mercury poisoning experiments had any significant influence on the yield of benzoic acid and zinc nanoparticles can therefore be excluded as the actual catalyst.[17]

Next, it was decided to perform a hot filtration test since the reaction mixture of zinc oxide and potassium hydroxide is heterogeneous, but the actual catalyst could be a homogeneous species. Thus, an experiment was performed as in Table 1, entry 1, but after 35 min with about 15 – 20% alcohol conversion the mixture was filtered through a nylon syringe filter (0.22 μm pore size) to afford a clear filtrate. This solution was then refluxed for an additional 18 h to give 59% alcohol conversion and 45% yield of benzoic acid. This result indicates that a homogeneous species is formed and is responsible for the catalytic conversion. Accordingly, it is unlikely that the transformation takes place on the surface of zinc oxide as has been proposed in the gas phase dehydrogenation based on kinetic and spectroscopic measurements.[24] A control experiment was performed where zinc oxide and potassium hydroxide were refluxed in mesitylene for 35 min (without adding the alcohol) and then subjected to the same hot filtration. The alcohol was then added to the clear filtrate and the solution refluxed for 18 h. This second hot filtration experiment gave no conversion of the alcohol at all which shows that the alcohol is involved in the formation of the homogeneous species and this cannot alone be formed from zinc oxide and potassium hydroxide.

As a result, the homogeneous species is most likely a zinc alkoxide which would also explain why the transformation can be catalyzed by a variety of other zinc(II) species to give similar results as with zinc oxide. There is to the best of our knowledge no evidence in the literature for a classical β-hydride elimination pathway with zinc alkoxides to form zinc hydrides.[25] The enzyme alcohol dehydrogenase reacts by hydride elimination from a zinc alkoxide, but the hydride is transferred to $NAD^+$.[26] This, however, does not rule out that a zinc hydride can be formed at elevated temperature and especially if the carbonyl compound is removed from the mixture. An experiment was therefore conducted where 48 mmol of benzyl alcohol was reacted with 6 mmol of $Et_2Zn$ at 0 °C under an inert atmosphere. The mixture was then slowly heated to 185 °C over 15 h with a distillation head attached. During this time, 4 mmol of a 5:3 mixture of benzyl alcohol and benzaldehyde distilled off from the reaction. This experiment shows that a zinc alkoxide can in fact be decomposed to form the aldehyde (and most likely the corresponding zinc hydride). A very interesting observation was

made when the residue from the distillation was analyzed by NMR. This showed a 1:1 mixture of benzyl alcohol and benzyl benzoate showing that a large amount of benzaldehyde was actually formed in the experiment, but had reacted further to the ester through a Tishchenko reaction. A recent study showed that zinc metal catalyzes the Tishchenko reaction where zinc alkoxides are believed to be the active catalyst formed in situ.[27]

Consequently, we consider the most likely mechanism to involve a zinc alkoxide and a zinc hydride (Scheme 2). The zinc alkoxide is first generated from zinc oxide and the alcohol and then degrades into the aldehyde and the zinc hydride. The latter deprotonates the alcohol to regenerate the alkoxide in a reaction that is known to occur readily.[28] The exact pathway for the conversion of the zinc alkoxide in to the zinc hydride can only be speculated upon. The classical β-hydride elimination is one possibility if X in Scheme 2 is a vacant coordination site. Another possibility is an outer-sphere bifunctional pathway if X is an alcohol. [(HOCH$_2$Ph)Zn–OCH$_2$Ph)] would then be cleaved into [(PhCH$_2$O···HOCH$_2$Ph)Zn] followed by transfer of the benzylic hydride to the metal through a six-membered transition state. This bifunctional pathway has been calculated for hydride eliminations in NH–metal–alkoxide complexes of osmium, ruthenium and iron[29] as well as for the Shvo catalyst.[30]




**Scheme 2.** Proposed mechanism.

In the case of benzaldehyde, the liberated aldehyde can undergo a Cannizzaro reaction with hydroxide to afford a 1:1 mixture of the carboxylate and the alcohol. We have previously shown that the Cannizzaro reaction occurs easily under these conditions.[13d] This was also confirmed when a mixture of benzaldehyde, potassium hydroxide and zinc oxide was heated to reflux in mesitylene. Complete conversion of benzaldehyde was observed after only 30 min and an almost equal mixture of benzoic acid (55%) and benzyl alcohol (43%) was formed. With aliphatic alcohols the Tishchenko reaction can account for the further oxidation to the carboxylic acid level. Several experiments were performed with heptanal, zinc oxide and potassium hydroxide, but even at slow addition only aldol condensation was observed. However, when heptan-1-ol was also included in the reaction, heptanoic acid was now obtained which is presumably due to a zinc alkoxide-mediated Tishchenko reaction followed by ester hydrolysis. In one experiment 1 mmol of heptanal was added over 1 h to a mixture of zinc oxide, potassium hydroxide and 1 mmol of heptan-1-ol in refluxing mesitylene followed by heating for an additional 1 h. This gave complete conversion of the alcohol and the aldehyde and produced 1 mmol of heptanoic acid together with several aldol products especially 2-pentylnon-2-en-1-ol. The large amount of acid after only 2 h cannot be formed from the alcohol alone, but shows the involvement of a further reaction from the aldehyde. The intermediate ester, although, could not be detected under these conditions and is presumably hydrolyzed rapidly. It is beyond the scope of this study to discuss the mechanism of the Tishchenko reaction in detail, but it should be noted that this transformation in some cases is accelerated by the presence of an alcohol where a bifunctional pathway with the formation of a metal hydride may be involved.[29a,30]

## Conclusions

In summary, zinc oxide has been developed as a catalyst for the acceptorless dehydrogenation of primary alcohols into carboxylic acids. The transformation can be applied to both benzylic and aliphatic alcohols where the former reacts faster than the latter. The catalytically active species is homogeneous and is believed to be the corresponding zinc alkoxide. Degradation of the alkoxide into the aldehyde was confirmed experimentally and explains the dehydrogenation with the release of hydrogen gas. The aldehyde can then undergo a disproportionation by either a Cannizzaro reaction or a Tishchenko reaction to afford a mixture of the carboxylic acid and the starting alcohol in the presence of hydroxide.

## Experimental Section

**General procedure for carboxylic acid synthesis:** Zinc oxide (32.60 mg, 0.4 mmol) and potassium hydroxide (224.4 mg, 4 mmol) were placed in an oven-dried tube, which was placed in a Radley carousel. The flask was subjected to vacuum and then filled with nitrogen gas (repeated three times). Vacuum was applied again and the carousel heated to 170 °C for 1 h. Subsequently, the tube was refilled with nitrogen gas. Anhydrous and degassed mesitylene (3 mL) was added and the mixture heated to reflux. Alcohol (2 mmol) and tetradecane (0.1 mL as internal standard) were added by syringe, and the reaction was refluxed with stirring under a flow of nitrogen for 18 h (benzylic alcohols) or 36 h (aliphatic alcohols). The mixture was cooled to room temperature and diethyl ether (5 mL) was added. The white precipitate was filtered off and washed with diethyl ether (10 mL). The precipitate was dissolved in water (5 mL) and acidified to pH 1 with 16% aqueous hydrochloric acid. The aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over sodium sulfate and concentrated in vacuo to give the corresponding acid as a pure compound.

## Acknowledgements

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**Keywords:** alcohols • carboxylic acids • dehydrogenation • synthetic methods • zinc


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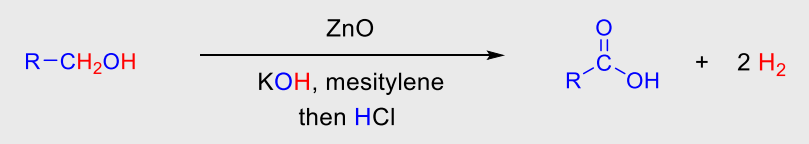


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**Zinc Oxide-Catalyzed Dehydrogenation of Primary Alcohols into Carboxylic Acids**

**Catalysis at a bargain:** Zinc oxide catalyzes the dehydrogenation of primary alcohols into carboxylic acids with the release of hydrogen gas. It constitutes the most inexpensive catalyst for the acceptorless alcohol dehydrogenation in solution where the catalytically active species most likely is a zinc alkoxide.

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