Oxidation

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Catalytic Fehling's Reaction: An Efficient Aerobic Oxidation of Aldehyde Catalyzed by Copper in Water

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Abstract: *The first example of homogeneous copper-catalyzed aerobic oxidation of aldehydes is reported. This method utilizes atmospheric oxygen as the sole oxidant, proceeds under extremely mild aqueous conditions, and covers a wide range of various functionalized aldehydes. Chromatography is generally not necessary for product purification.*

Oxidation of aldehydes into carboxylic acids is a very important biological process in nature.[1] One of the most representative examples is the oxidation of acetaldehyde into acetic acid in liver cells, with aldehyde dehydrogenase as the catalyst and oxygen as the sole oxidant, at 37 °C in water.[1b] Despite being prone to oxidation, most aldehydes are generally stable and inert towards autoxidation. Even in modern industry and academia, catalytic oxidations of aldehydes into carboxylic acids still remain scarce. Most synthetic processes still rely on oxidations which require stoichiometric amounts of highly hazardous oxidants such as dichromate[2]/permanganate,[3] periodate reagent,[4] oxone,[5] etc. Notably, among all the classical methods for aldehyde oxidation, the Fehling's reaction[6] and Tollens' reaction[7] are extremely useful because of their extraordinarily wide substrate scopes and high reaction efficiencies. The Achilles' heel of these methods, however, is that they still require stoichiometric amounts of either copper or silver reagents and generate stoichiometric amounts of metal waste, as there are expensive and wasteful.

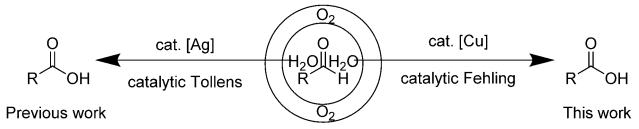

Figure 1. Catalytic aerobic oxidation of aldehydes.

Inspired by the efficient and clean biological oxidation of aldehydes into carboxylic acids in nature, we aim to develop efficient chemical oxidations of aldehydes into acids, oxidations which are efficient, run under extremely mild reaction conditions in water, and use only atmospheric oxygen gas (or air; atmospheric pressure) as the sole oxidant, thus mimicking nature. Recently, we succeeded in a Tollens-type reaction, which instead of requiring a stoichiometric amount of silver in the classic reaction, only requires a catalytic amount of silver using oxygen as the sole oxidant in aqueous conditions (Figure 1).[8] However, since silver is a precious yet toxic metal and one of the seriously endangered elements in the next 100 years,[9] it would be highly desirable to develop a similar catalytic reaction by using a more earth-abundant metal as the catalyst. Despite other recent innovations, the requirement of scarce and expensive noble metals as catalysts still persists as a major limitation.[10] Herein, we report the first example of copper-catalyzed aerobic oxidation of aldehydes in water, a catalytic Fehling reaction, which proceeds by a different mechanism compared to the well-established dinuclear copper-oxygen-bridge mechanism for dioxygen activation,[11] thus representing a potentially new type of aerobic oxidation pathway.

We began our investigation by examining the oxidation of benzaldehyde (**1a**) under aqueous reaction conditions using various copper catalysts (Table 1). Oxygen gas was simply flushed into the reaction tube and sealed (without using a balloon). With the catalyst generated from $CuCl_2$ and 2,2′-bipyridine (bipy), a widely-used ligand for aerobic oxidation, at the reaction temperature of the classic Fehling's reaction (100 °C) we observed 5% yield, by ^{1}H-NMR spectroscopy, of the desired carboxylic acid (entry 1). With the same ligand, CuCl was also tested but showed inferior catalytic activity in this case (entry 2). Surprisingly, lowering the reaction temperature to 50 °C increased the yield to 13% (entry 3), which may be due to the increased contact between O_2 (in the gas phase) and the catalyst. Using $CuBr_2$ together with the same ligand decreased the product yield to 3% (entry 4), and the use of CuO completely stopped the reaction (entry 5). With $Cu(OAc)_2$ the yield was boosted to 68% (entry 6), whereas the use of $[Cu(acac)_2]$ gave a nearly quantitative yield of benzoic acid (**2a**; entry 7) and only 50% yield was obtained in the absence of the ligand (entry 8). However, the same reaction condition did not work with a more functionalized aldehyde, piperonal (**1b**; entry 9). Switching the ligand to phosphine ligands did not show any improvement (entries 10 and 11). With IMes, an N-heterocyclic carbene (NHC) ligand, 20% yield of the oxidation product, piperonylic acid (**2b**), was obtained (entry 12). Using the more sterically hindered IPr ligand reduced the yield to 11% (entry 13). With the more electron-rich SIMes, a dramatic yield increase to 80% was observed (entry 14), while SIPr gave 41% yield (entry 15). Halving the catalyst loading to 5 mol% barely affected the reaction, with 77% yield of the isolated **2b** being obtained (entry 16). The purification process did not require chromatography, but only acidification and liquid–liquid extraction.

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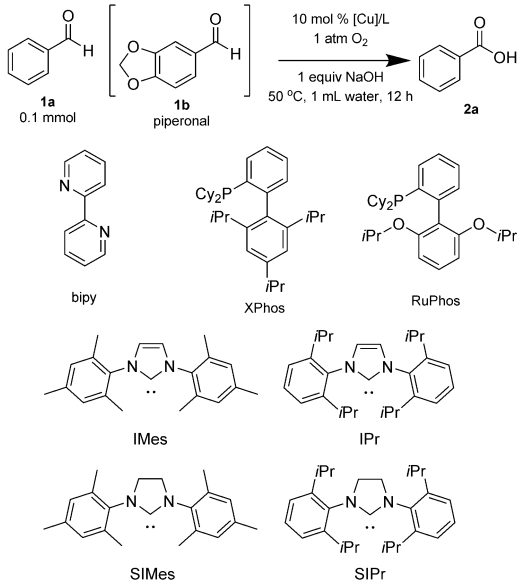
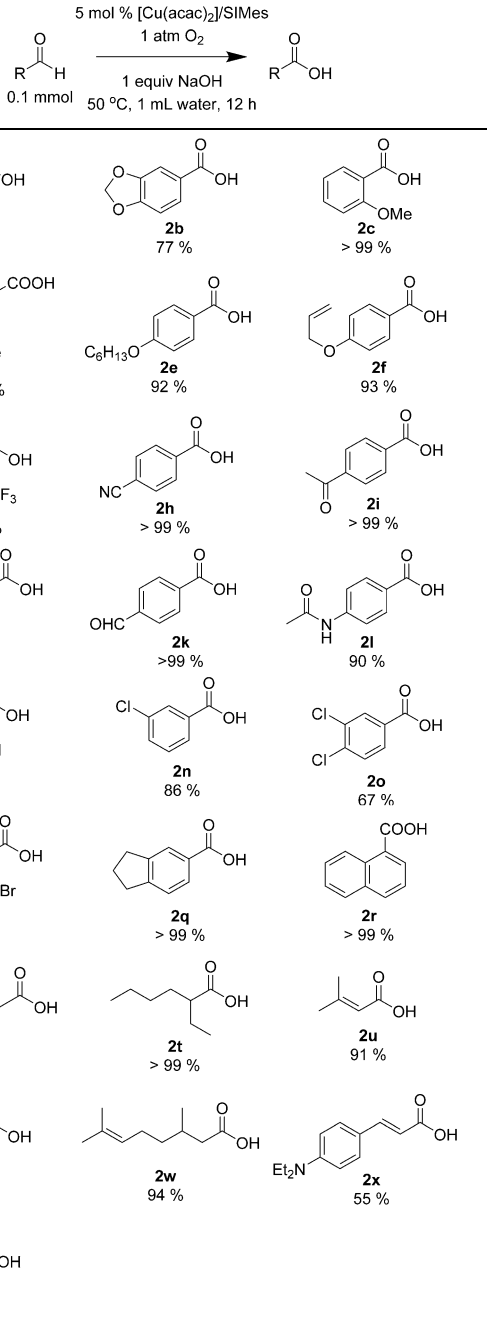
Table 1: Optimization of reaction conditions.



Entry	[Cu]/L[a]	Yield [%][b]	Entry	[Cu]/L[a]	Yield [%][b]
1	$CuCl_2$/bipy[c]	5	10	[Cu(acac)$_2$]/XPhos[d]	n.r.
2	CuCl/bipy	1	11	[Cu(acac)$_2$]/RuPhos[d]	n.r.
3	$CuCl_2$/bipy	13	12	[Cu(acac)$_2$]/IMes[d]	50
4	$CuBr_2$/bipy	3	13	[Cu(acac)$_2$]/IPr[d]	33
5	CuO/bipy	n.r.	14	[Cu(acac)$_2$]/SIMes[d]	80
6	Cu(OAc)$_2$/bipy	68	15	Cu(acac)$_2$/SIPr[d]	41
7	[Cu(acac)$_2$]/bipy	99	16	[Cu(acac)$_2$]SIMes[d,e]	78 (77)[f]
8	[Cu(acac)$_2$]/–	50	17	–/IMes[d]	n.r.
9	[Cu(acac)$_2$]/bipy[d]	n.r.	18	[Cu(acac)$_2$]/SIMes[d,g]	n.r.

[a] The copper catalyst was generated prior to the oxidation by mixing the copper salt with the ligand under argon in acetonitrile. [Cu(acac)$_2$]/NHC-type catalyst can be generated either by mixing [Cu(acac)$_2$] salt with the corresponding imidazolium salt in acetonitrile under argon for 24 h, or treating the imidazolium salt with *n*BuLi under argon in THF then adding [Cu(acac)$_2$] salt. Either protocol worked as the results were unaffected. [b] Yields were determined by NMR spectroscopy using 1,3,5-mesitylene as the internal standard. [c] This reaction was performed at 100 °C. [d] This reaction was performed using piperonal as the starting material. [e] This reaction was performed with a 5 mol% catalyst loading. [f] Yield of isolated product. [g] [Cu(acac)$_2$] and SIMes were directly introduced to the reaction without premixing. acac = acetylacetonate, n.r. = no reaction.

Table 2: Investigation of substrate scope.[a]



[a] All reactions were conducted under the standard reaction procedure (details available in the Supporting Information): Aldehyde (0.1 mmol), Cu catalyst (0.005 mmol, 5 mol%), and NaOH (0.1 mmol, 1 equiv) were mixed in 1 mL water under non-pressurized oxygen with stirring at 50 °C for 12 h. Yields are those of the isolated products.

In the absence of a copper salt, no reaction was observed (entry 17). Furthermore, if the copper salt and NHC were directly introduced to the reaction without premixing, no reaction was observed (entry 18).

With the optimized reaction conditions in hand, the scope and functional-group compatibility of this methodology was then tested with various functionalized aldehydes (Table 2). Besides **1a** and **1b** giving quantitative and 77% yields, respectively (**2a** and **2b**), electron-rich *o*-anisaldehyde and 3,4,5-trimethoxybenzaldehyde provided quantitative product yields (**2c** and **2d**). Other electron-rich aldehydes such as the hydrophobic 4-hexyloxybenzaldehyde and 4-allyloxybenzaldehyde gave 92 and 93% yields, respectively (**2e** and **2f**). Most aromatic aldehydes bearing electron-withdrawing groups such as α,α,α-trifluoro-*o*-tolualdehyde, 4-cyanobenzaldehyde, and 4-acetylbenzaldehyde all gave quantitative yields (**2g**–**i**), with the exception of 4-nitrobenzaldehyde giving 62% yield (**2j**). As another example of electron-poor aromatic aldehydes, oxidation of terephthalaldehyde resulted

in the oxidation of only one aldehyde group in the aromatic ring (**2k**), possibly because of the high solubility of **2k** in basic aqueous solution, thus preventing the interaction of **2k** with the hydrophobic catalyst. Other aldehydes containing a carbonyl moiety, such as 4-acetaminobenzaldehyde, gave an excellent 90% yield (**2l**). Halogen-substituted aldehydes such as 2-chlorobenzaldehyde, 3-chlorobenzaldehyde, 3,4-dichlorobenzaldehyde, and 2-bromo-5-fluorobenzaldehyde gave 90%, 86%, 67%, and 97% yields, respectively (**2m–p**), thus demonstrating tolerance of the reaction towards halogens. Fused-ring aldehydes such as 5-indancarboxyaldehyde and 1-naphthaldehyde gave quantitative oxidations (**2q** and **2r**). Simple aliphatic aldehydes such as octanal and 2-ethylhexanal all gave quantitative yields (**2s** and **2t**). Unsaturated aldehydes also worked excellently (**2u–x**), with the exception of **2x** giving a moderate yield of 55%, possibly because of the reduced electrophilicity of the carbonyl resulting from the high electron-donation of *p*-diethylamino group. Importantly, 2-hydroxylpentanal also gave quantitative oxidation without the need for hydroxy protection (**2z**).

Heterocyclic aromatic aldehydes such as 2-furaldehyde and 2-thiophenecarboxyaldehyde also gave essentially quantitative yields of oxidation products (Figure 2a, **4a** and **4b**). Finally, a gram-scale test was conducted with 10 mg of catalyst using 1 mL benzaldehyde in a more concentrated basic aqueous solution for a prolonged reaction time. The reaction gave 71% yield of isolated analytically pure benzoic acid (Figure 2b).

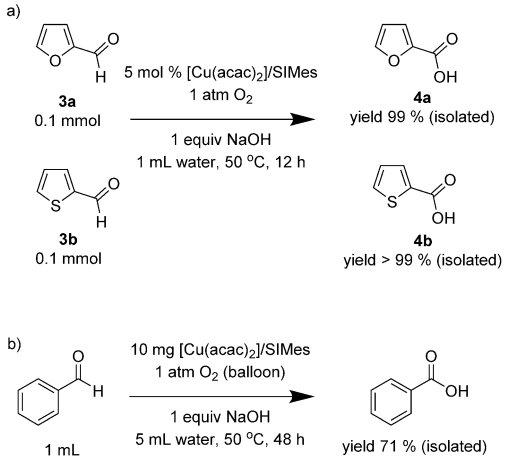


Figure 2. Other notable examples of substrate scope.

To obtain some mechanistic insight into the reaction, an X-ray diffraction experiment[12] showed that the catalyst was composed of $[Cu(acac)_2]$ and a NHC/Cu^{I}Cl complex, which was also confirmed with authentic NHC/Cu^{I}Cl synthesized according to the literature.[13] When 5 mol% NHC/Cu^{I}Cl alone was used as the catalyst, the aerobic oxidation of **1b** under standard conditions gave 55% yield, whereas all the starting material was recovered with $[Cu(acac)_2]$ alone as a catalyst (Figure 3a). When a mixture of 2.5 mol% of $[Cu(acac)_2]$ and 2.5 mol% of the NHC/Cu^{I}Cl was used as catalyst, a slightly increased yield of 73% was obtained. Using

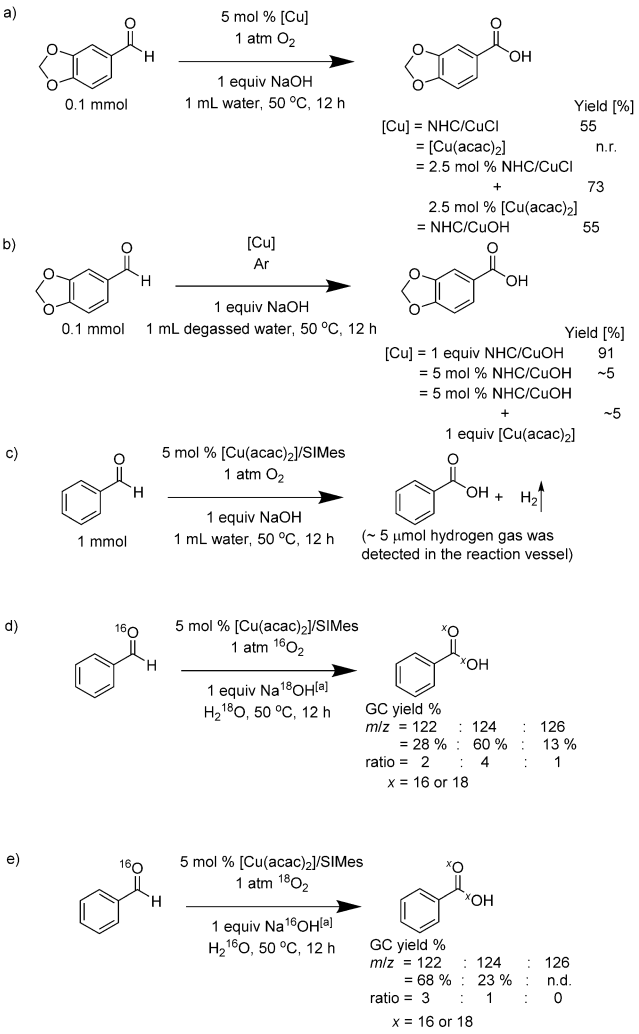


Figure 3. Investigation of reaction mechanism. [a] Na^{18}OH was generated by reacting NaH with $H_2{}^{18}O$.

NHC/Cu^{I}OH, generated in situ from NHC/Cu^{I}Cl and KOH,[14] as catalyst also gave 55% yield. Furthermore, when NHC/Cu^{I}OH was used stoichiometrically under inert atmosphere, 91% of the **1b** was converted into **2b**, while only 5% yield was obtained with 5 mol% NHC/Cu^{I}OH (Figure 3b). To preclude the possibility of $[Cu(acac)_2]$ serving as an oxidant,[15] the combination of 5 mol% NHC/Cu^{I}OH and a stoichiometric amount of $[Cu(acac)_2]$ under inert atmosphere was also tested, but only gave 5% yield (Figure 3b), thus confirming that NHC/Cu^{I}OH is the active catalyst while $[Cu(acac)_2]$ serves as an additive. Next, heat-conductivity GC analysis of the head space of the sealed reaction vial showed a considerable amount of H_2 (Figure 3c), whereas no hydrogen was detected when the oxidation did not occur. An isotope-labelling experiment using Na^{18}OH and $H_2{}^{18}O$ instead of normal NaOH and water was also conducted (Figure 3d): the GC-MS analysis showed *m*/*z* 122 ($m+0$), 124 ($m+2$), and 126 ($m+4$) peaks with integral ratio of 2:4:1, while an extremely low $m+2$ peak, and no $m+4$ peak were observed with standard oxidation conditions using NaOH and water. Further isotope experiments (Figure 3e) using normal

NaOH/water and $^{18}O_2$ resulted in a consistent ratio of 3:1 for m/z 122($m+0$) and 124($m+2$), and no m/z 126($m+4$) product was detected.

Based on these experimental results, a tentative mechanism was proposed for the catalytic Fehling's reaction (Figure 4). First, NHC/Cu^{I}Cl (**A**) reacts with an hydroxide

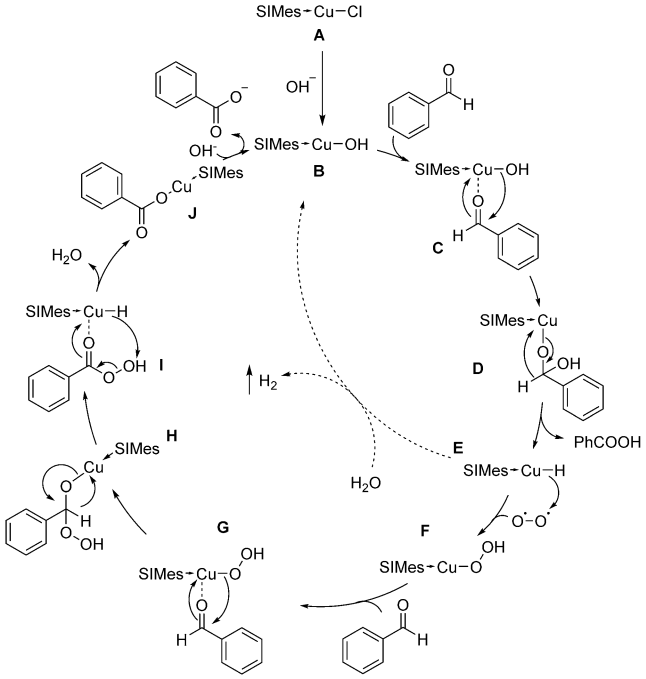


Figure 4. Proposed mechanism for the catalytic Fehling reaction.

anion to give a NHC/Cu^{I}OH species as the active catalyst **B**, which coordinates with the carbonyl group to give **C**. The hydroxide ion then attacks the carbonyl of the aldehyde to give the tetrahedral intermediate **D**, which undergoes β-hydride elimination[16] to give the copper(I) hydride species **E**, possibly being responsible for the minor H_2 generation by a minor cycle of hydrolysis. The copper(I) hydride then reacts with a molecule of dioxygen to generate a hydroperoxide copper species **F**, which then coordinates with another aldehyde carbonyl group to give **G**. Nucleophilic attack by the hydroperoxide in **G** gives the tetrahedral intermediate **H**. Hydride abstraction generates the intermediate **I**, which is followed by an intramolecular reduction of the peroxide by the hydride to give the carboxylate product **J**. Finally, substitution of the carboxylate in **J** by a hydroxide anion releases the product and regenerates the active catalyst **B**.

In conclusion, we have developed the first catalytic version of the well-known classic Fehling's reaction, which only consumes oxygen (under atmospheric pressure) as the sole oxidant, in water. The method is functional-group tolerant and demonstrates wide substrate scope. Further studies on the mechanism and synthetic applications of this catalytic reaction are in progress.

Experimental Section

General procedure for the oxidation of aldehydes: A reaction vessel, charged with [Cu(acac)$_2$]/SIMes catalyst (4.7 mg, 0.005 mmol, 5 mol%) and sodium hydroxide (4 mg, 0.1 mmol, 1 equiv) was gently flushed with oxygen of ordinary purity using either a balloon or gas valve. Then distilled water (1 mL) was added to the vessel. The reaction mixture was then warmed up to 50 °C before the aldehyde (0.1 mmol, 1 equiv) was added. The reaction vessel was then sealed and kept at 50 °C for 12 h. After this, the reaction mixture was washed with methylene chloride (DCM) three times with a total DCM volume of 10 mL, and the pH of the aqueous phase was then adjusted to 2 with 0.1M HCl. The aqueous phase was then extracted with ethyl ether 3 times with a total ether volume of 10 mL and the combined ether phase was dried over anhydrous sodium sulfate and evaporated in vacuo to obtain the carboxylic acid product.

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Keywords: copper · homogeneous catalysis · oxidation · reaction mechanisms

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