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Effective dehydrogenation of 2-pyridylmethanol derivatives catalyzed by an iron complex†

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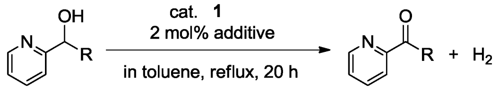
An unprecedented iron complex-catalyzed dehydrogenation of alcohols was achieved using $CpFe(CO)_2Cl$ with a base or CpFe(CO)(Py)(Ph) as a catalyst without sacrificing the hydrogen acceptors. This reaction effectively (up to TON 67 000) converted 2-pyridylmethanol derivatives to the corresponding ketones or aldehydes. The mechanistic study is also discussed.

Oxidation of alcohols to ketones or aldehydes is one of the most important reactions with practical applications in organic synthesis. Traditionally, stoichiometric amounts of harmful oxidants such as chromium compounds have been used for oxidation.[1,2] Many methods of transition metal-catalyzed oxidation of alcohols have been developed because of environmental concern, using a stoichiometric amount of oxygen,[3] hydrogen peroxide,[4] alkenes[5] and acetone[6] as less harmful hydrogen acceptors that are sacrificed. However, from the atom efficiency viewpoint, the use of stoichiometric amounts of oxidants is undesirable. On the other hand, oxidant-free dehydrogenation is not only an environmentally benign reaction, but can also save the cost and time because stoichiometric amounts of by-products are not generated, thus avoiding the need for a removal process. Furthermore, such reactions generate hydrogen gas and thus have a potential to become a promising hydrogen source.[7,8] Several systems capable of acceptorless dehydrogenation of alcohols have been developed using rhodium,[9] ruthenium,[10] and iridium[11,12] catalysts; however, all these catalysts are highly toxic and precious transition metals. To the best of our knowledge, iron or other non-precious metal-based catalysts for oxidant-free or acceptorless dehydrogenation of alcohols have not been reported to date. Herein, we report an unprecedented iron-catalyzed dehydrogenation of alcohols in the absence of hydrogen acceptors. In particular, this system could effectively convert the 2-pyridylmethanol derivatives to the corresponding ketones or aldehydes. The catalytic cycle was envisioned based on the results obtained from stoichiometric and catalytic reactions of the iron precursors and isolated intermediates.

Firstly, various combinations of alcohols and iron complexes were examined, and $CpFe(CO)_2Cl$ (**1**)[13] showed catalytic activity for the oxidation of 2-pyridylmethanol derivatives to the corresponding dehydrogenated products. The reaction of 2-pyridylmethanol (96 μL, 1.0 mmol) with **1** (2.1 mg, 10 μmol, corresponding to 1 mol% based on alcohol) in toluene (20 mL) at reflux temperature for 20 h afforded 2-pyridinecarboxaldehyde in 18% yield (Table 1, entry 1). The catalytic activity of **1** was enhanced by the addition of 2 mol% of NaH based on the alcohol (entry 2). Other 2-pyridylmethanol derivatives were also dehydrogenated under the same reaction conditions (entries 3 and 4).

Table 1 Acceptorless dehydrogenation of 2-pyridylmethanol derivatives catalyzed by an iron complex[a]



Entry	R	Additive	Cat. (mol%)	Yield[b] (%) (TON)
1	H	None	**1** (1)	18 (18)
2	H	NaH	**1** (1)	35 (35)[c]
3	Me	NaH	**1** (1)	62 (62)[d]
4	Ph	NaH	**1** (1)	100 (100)
5[e]	Ph	NaH	**1** (1)	8 (8)
6	Ph	NaH	**2** (1)	Trace (–)
7	Ph	NaH	**3** (1)	Trace (–)
8	Ph	NaH	**4** (1)	Trace (–)
9	Ph	NaH	**5** (1)	Trace (–)
10	Ph	NaH	**6** (1)	Trace (–)
11[f]	Ph	NaH	**1** (0.1)	100 (1000)
11[f]	Ph	NaH	**1** (0.01)	87 (8700)
13[g]	Ph	NaH	**1** (0.001)	67 (67 000)

[a] The reaction was carried out with alcohol (1.0 mmol), catalyst (1.0 mol%), and additive (2.0 mol%) in toluene (20 mL) under reflux for 20 h, except for entries 11–13. [b] Isolated yields of ketone/aldehyde products. [c] Yield is 48% based on the ^1H NMR data. [d] Yield is 65% based on the ^1H NMR data. [e] Heated at 100 °C. [f] Only the ratio of alcohol to catalyst was changed. [g] The reaction was carried out with alcohol (1.0 mmol), catalyst (0.001 mol%), and additive (1.0 mol%) in toluene (1 mL) under reflux for 20 h.

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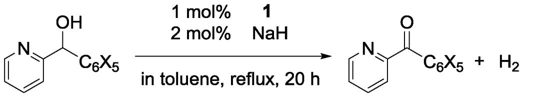
In particular, 2-pyridylbenzylalcohol was quantitatively converted to 2-benzoylpyridine. The yield dramatically decreased when the reaction was performed at 100 °C (entry 5). Similar reactions were carried out using other iron complexes ($FeCl_2$ (**2**), $FeCl_3$ (**3**), $Fe(OTf)_2$ (**4**), $Fe(BF_4)_2/6H_2O$ (**5**) and $Fe(CO)_5$ (**6**)). However, they displayed no catalytic activity toward the dehydrogenation of 2-pyridylbenzylalcohol (entries 6–10). The dehydrogenation could also be achieved even when the amount of catalyst **1** was reduced from 1 to 0.001 mol% (entries 11–13). The highest turnover number (TON) achieved was 67 000 (entry 13), and it is the highest value achieved so far using a transition metal catalyst in the dehydrogenation of alcohols.[10k] The conversions were determined by the isolated yield of the dehydrogenated products (ketones/aldehydes).

Next, we checked the applicability of various related alcohols for the dehydrogenation reaction catalyzed by **1**, and the results are shown in Table 2. Various *para*-substituted phenyl derivatives were effectively converted into the corresponding ketones (entries 1–4), with both electron-donating (entries 1 and 2) and electron-withdrawing (entries 3 and 4) substituents on the phenyl rings. CF_3 or five F groups on the phenyl ring (entries 5 and 7) gave low conversion yields. An *ortho*-disubstituted phenyl derivative did not diminish the catalytic activity (entry 6). It should be noted that the NMe_2, Cl, and F groups in the *para* positions of the phenyl rings did not diminish the catalytic activity of **1**. In stark contrast, the compounds listed in Chart 1 did not undergo dehydrogenation. 3-Pyridylmethanol and 4-pyridylmethanol did not undergo dehydrogenation, indicating that the 2-pyridyl moiety of the 2-pyridylmethanol derivatives is important for the catalytic dehydrogenation, presumably because the chelation of this moiety to the iron of the catalyst makes a stable five-membered ring. This is supported by the fact that 1-octanol and $Ph_2CH(OH)$ did not undergo the iron-catalyzed dehydrogenation reaction. The nitrogen atom in the 2-pyridyl group is important for the iron-catalyzed dehydrogenation because 2-franylmethanol and 2-thiophenylmethanol did not undergo dehydrogenation. 2-Dimethylaminoethanol also did not undergo dehydrogenation, indicating that the nitrogen atom in the aromatic ring (2-pyridyl) is important due to steric and/or electronic reasons.

Table 2 Acceptorless dehydrogenation of various 2-pyridylmethanol derivatives catalyzed by an iron complex[a]



Entry	C_6X_5	Yield[b,c] (%)
1	C_6H_4Me-4	99 (100)
2	$C_6H_4NMe_2$-4	96 (100)
3	C_6H_4Cl-4	98 (100)
4	C_6H_4F-4	92 (97)
5	$C_6H_4CF_3$-4	42 (43)
6	$C_6H_2Me_3$-2, 4, 6	99 (100)
7	C_6F_5	15 (23)

[a] The reaction was carried out with alcohol (1.0 mmol), catalyst (1.0 mol%), and NaH (2.0 mol%) in toluene (20 mL) under reflux for 20 h. [b] Isolated yields. [c] Yields based upon ^1H NMR in parentheses.

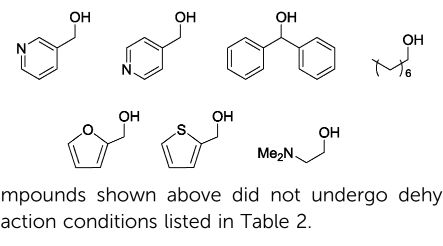
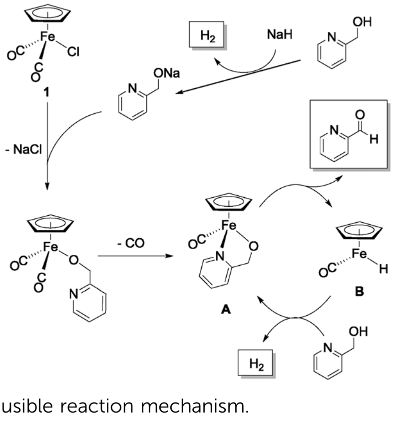


Chart 1 Compounds shown above did not undergo dehydrogenation under the reaction conditions listed in Table 2.

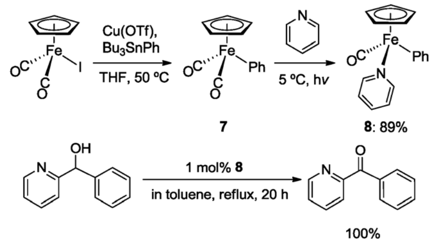
Notably, after the completion of the reaction and removal of the volatile materials, the products (pure ketones) could be easily obtained by simple filtration of the reaction mixtures without any further purification.

Herein, we propose a catalytic cycle for the dehydrogenation of 2-pyridylmethanol derivatives catalyzed by **1** and NaH (Scheme 1). Firstly, the alcohol reacts with the co-catalyst NaH to give the corresponding sodium alkoxide, which then reacts with **1** to give the iron alkoxide complex. Next, the nitrogen atom in the attached pyridine moiety displaces one of the CO ligands to give **A**. Dissociation of the pyridine portion of **A** takes place,[14] and the subsequent β-hydride elimination produces the iron hydride complex (**B**) and 2-pyridinecarboxyaldehyde. Finally, the oxidative addition of the O–H bond of 2-pyridinylmethanol (or coordination of the pyridine moiety of 2-pyridylmethanol) followed by the H_2 reductive elimination (or the coupling of hydride of **B** and proton of the hydroxy group) produce **A** to complete the catalytic cycle.

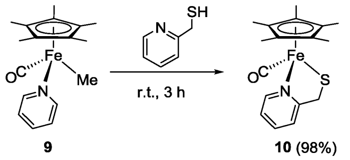
The main cycle in Scheme 1 consists of **A** and **B**, and NaH converts the starting alcohol into the corresponding alkoxide in order to activate **1**. The use of NaH should be avoided because NaH is a strong base, in order to make the catalytic system applicable to a more wide range of applications. After several trials, we finally found that **8** serves as a good precursor of the reactive 16e species, CpFe(CO)Ph, because the pyridine moiety of **8** might readily dissociate from the iron center compared to the CO moiety of **1** (Scheme 2). Complex **8** was isolated in 89% yield upon the photo-irradiation of **7**[15] in the presence of pyridine. Complex **8** was characterized by NMR spectroscopy, EA and X-ray diffraction study.[16] Complex **8** exhibited excellent catalytic activity for the dehydrogenation of 2-pyridylbenzylalcohol even without the presence of a base (NaH). The results show that the catalytic cycle shown in Scheme 1 is reasonable. To obtain further evidence to support the proposed reaction pathway, the stoichiometric



Scheme 1 Plausible reaction mechanism.



Scheme 2 Formation of complex **8** and its reactivity.



Scheme 3 Preparation of intermediate **10** and its catalytic activity.

reaction of **8** with 2-pyridylmethanol was carried out at room temperature.

In the ^{1}H NMR spectrum, the expected intermediate could not be observed; however, the corresponding product, 2-pyridinecarboxaldehyde, was slowly formed even at room temperature, indicating that the intermediate was too unstable to be isolated. Therefore, the reaction of a more stable iron analogue having a η^5-C_5Me_5 group, (η^5-C_5Me_5)Fe(CO)(Py)(Me) (**9**),[17] with 2-pyridylmethane thiol was carried out at room temperature. After the work-up of the reaction mixture, the expected thioalkoxy complex **10**, (η^5-C_5Me_5)Fe(CO)($PyCH_2S$), was isolated in 98% yield, and characterized by ^{1}H NMR, ^{13}C NMR, and elemental analysis (Scheme 3). Although **10** showed a catalytic activity for the dehydrogenation of 2-pyridylbenzylalcohol even without the presence of a base (NaH) similar to that of **8**, the corresponding ketone was obtained in only 36% yield because of the stabilization of **10** by the η^5-C_5Me_5 ligand and the strong S–Fe bond compared to the O–Fe bond of **A**. The formation of **10** and its catalytic activity toward the dehydrogenation of 2-pyridylbenzylalcohol are consistent with our proposed catalytic cycle.

In conclusion, we demonstrated the first iron-catalyzed dehydrogenation of alcohols (hydrogen production). This reaction works only for the 2-pyridylmethanol derivatives. The highest TON achieved was 67 000 using a combination of **1** and NaH, as the catalysts for the dehydrogenation reaction. Precursor **8** exhibited a similar catalytic activity even in the absence of NaH. The mechanistic study supported the proposed reaction pathway.

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