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Ligand-Promoted Dehydrogenation of Alcohols Catalyzed by Cp*Ir Complexes. A New Catalytic System for Oxidant-Free Oxidation of Alcohols

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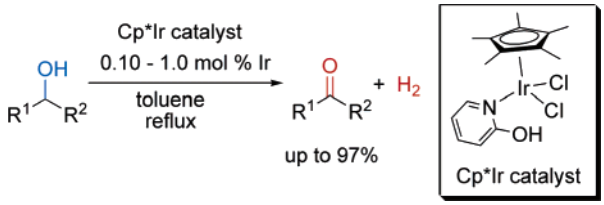
ABSTRACT



An efficient catalytic system for oxidant-free oxidation of alcohols has been developed. A new Cp*Ir catalyst bearing a 2-hydroxypyridine ligand has been designed on the concept of "ligand-promoted dehydrogenation". Various secondary alcohols can be dehydrogenatively oxidized to ketones under neutral conditions with high turnover numbers by using the new Cp*Ir catalyst.

The oxidation of alcohols to carbonyl compounds is one of the most fundamental and important reactions in synthetic organic chemistry, and it is quite important to develop a mild and less toxic oxidation system. Recently, much effort have been devoted to the transition-metal-catalyzed oxidation of alcohols using environmentally friendly oxidants such as oxygen,[1] hydrogen peroxide,[2] or acetone.[3] However, from the viewpoint of atom efficiency and safety of the reaction, an oxidant-free reaction to give carbonyl products should be ideal.

Although several oxidant-free (dehydrogenative) systems for the oxidation of alcohols using ruthenium and rhodium catalyst have been reported,[4−6] most of them require acidic or basic reaction conditions and turnover numbers of the catalyst are not so high. It has been generally recognized that the most critical step in the catalytic dehydrogenative oxidation of alcohols would be the release of dihydrogen

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(5) Heterogeneous catalytic systems for the oxidant-free oxidation of alcohols have been also reported. (a) Choi, J. H.; Kim, N.; Shin, Y. J.; Park, J. *Tetrahedron Lett.* **2004**, *45*, 4607. (b) Kim, W.-H.; Park, I. S.; Park, J. *Org. Lett.* **2006**, *8*, 2543.

(6) Closely related dehydrogenative esterification of alcohols has been recently reported: (a) Zhao, J.; Hartwig, J. F. *Organometallics* **2005**, *24*, 2441. (b) Zhang, J.; Leitus, G.; Ben-David, Y.; Milstein, D. *J. Am. Chem. Soc.* **2005**, *127*, 10840.

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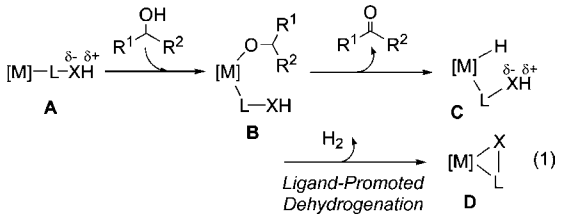
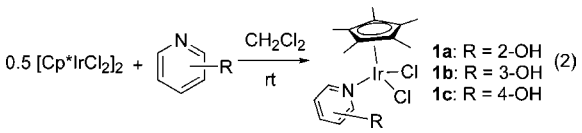
from metal hydride intermediate generated by β-elimination of an metal alkoxide to regenerate a catalytically active species. When a metal complex **A** ligated with a ligand bearing a protic functional group could be employed, a metal hydride **C** should be formed via metal alkoxide **B** (eq 1). Then, an intramolecular reaction of the hydride on the metal with the protic hydrogen on the ligand could readily take place to facilitate the release of dihydrogen. The resulting hydride-free metallacycle **D** would react with an alcohol to reproduce **B**.



Considering the above working hypothesis, we have started to design the metal catalyst suitable for dehydrogenative oxidant-free oxidation of alcohols. In this paper, we wish to report a new and efficient system for the oxidant-free oxidation of secondary alcohols to give ketones catalyzed by a Cp* (pentamethylcyclopentadienyl)iridium complex having 2-hydroxypyridine ligand. With this catalytic system, the reaction can be conducted under neutral conditions, and high turnover numbers up to 2000 have been achieved.

Cp*Ir catalysts used in this study were prepared as illustrated in eq 2. Treatment of $[Cp^*IrCl_2]_2$ with hydroxypyridine derivatives in dichloromethane at room temperature gave complexes **1a**−**c**. Single-crystal X-ray analyses of **1a**−**c** demonstrate that hydroxypyridine ligands are coordinated to the iridium center in monodentate κN fashion (Figure 1 Figures S1 and S2, Supporting Information).

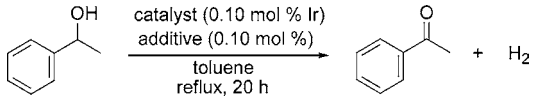


With these new Cp*Ir hydroxypyridine complexes in hand, we next examined their catalytic activity for the oxidant-free oxidation of alcohols. At first, the reactions of 1-phenylethanol to give acetophenone under various conditions were investigated (Table 1). When the reaction was carried out in the presence of **1a** (0.10 mol % of Ir) under reflux in toluene for 20 h, acetophenone was formed in 70% yield selectively (conversion of 1-phenylethanol was 70%) (entry 1).[7] Other Cp*Ir catalysts having a 3- or 4-hydroxypyridine ligand (**1b** and **1c**) or Cp*Ir(pyridine)Cl_2 showed lower catalytic activity than **1a**, indicating the hydroxyl substituent at the 2-position was indispensable for high catalytic performance (entries 2−4). The reaction using $[Cp^*IrCl_2]_2$ as a catalyst under neutral, basic (K_2CO_3), or acidic (phenol) conditions were also examined, but the yields of acetophenone were low (entries 5−7). The highest turnover number (2120) was accomplished when the reaction was carried out under reflux in xylene for 100 h with catalyst **1a** (0.025 mol % of Ir) (entry 8).

To evaluate the scope of this system, the oxidation reactions of various secondary alcohols were undertaken (Table 2). The reactions of 1-arylethanols with electron-

(7) Evolution of dihydrogen was confirmed by the analysis of gas phase using a hydrogen sensor, although quantitative analysis was not carried out.

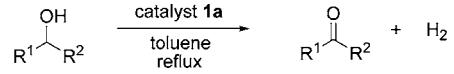
Table 1. Oxidant-Free Oxidation of 1-Phenylethanol Catalyzed by Cp*Ir Complexes under Various Conditions[a]

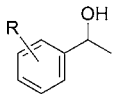


entry	catalyst	additive	convn[b] (%)	yield[b] (%)	TON
1	**1a**	none	70	70	700
2	**1b**	none	10	10	100
3	**1c**	none	13	13	130
4	Cp*Ir(pyridine)Cl_2	none	10	9	90
5	$[Cp^*IrCl_2]_2$	none	20	17	170
6	$[Cp^*IrCl_2]_2$	K_2CO_3	22	22	220
7	$[Cp^*IrCl_2]_2$	phenol	14	13	130
8[c]	**1a**	none	54	53	2120

[a] The reaction was carried out with 1-phenylethanol (20 mmol), catalyst (0.10 mol % of Ir), and additive (0.10 mol %) in toluene (6 mL) under reflux for 20 h. [b] Determined by GC. [c] The reaction was carried out with 1-phenylethanol (40 mmol) and **1a** (0.025 mol % of Ir) in xylene (6 mL) under reflux for 100 h.

Table 2. Oxidant-Free Oxidation of Various Secondary Alcohols Catalyzed by **1a**[a]



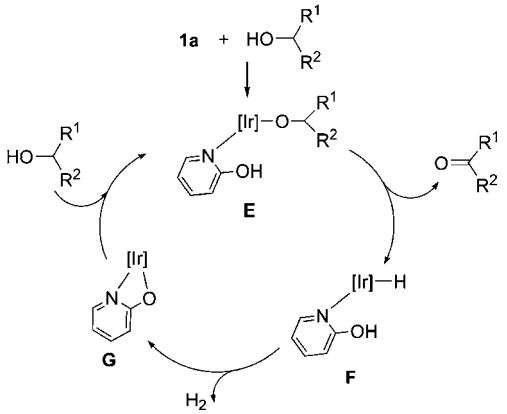
entry	substrate	cat. [mol % Ir]	time [h]	yield [%][b]
				
1	R = H	0.20	20	95
2	R = 4-Me	0.20	20	82
3	R = 4-OMe	0.20	20	94
4	R = 4-Cl	0.20	20	81
5	R = 4-Br	0.20	50	82
6	R = 4-NO_2	0.33	50	86
7	R = 2-Me	0.20	20	89
8	R = 3-Me	0.20	20	75
9[c]	1-(2-furyl)ethanol	1.0	50	76[d]
10	1-phenylpropan-1-ol	0.20	20	92
11	cyclohexanol	1.0	50	85[d]
12	cycloheptanol	0.20	20	92[d]
13	1-indanol	0.20	20	97
14	1-tetralol	1.0	50	86
15	2-octanol	0.33	50	93[d]

[a] The reaction was carried out with alcohol (1.0−5.0 mmol) and catalyst **1a** (0.20−1.0 mol % of Ir) in toluene (2−6 mL) under reflux. [b] Isolated yield. [c] The reaction was carried out in the presence of K_2CO_3 (1.0 mol %). [d] Determined by GC.

donating and withdrawing substituents at the aromatic ring proceeded to give corresponding ketones in good to excellent yields with high turnover numbers (entries 1−8). The oxidation of acid-sensitive 1-(2-furyl)ethanol was possible to give 2-acetylfuran in good yield by the reaction in the presence of a catalytic amount of K_2CO_3 (entry 9). Other aromatic, aliphatic, and cyclic secondary alcohols were also applicable to this system (entries 10−15). Unfortunately, primary alcohols were not efficiently oxidized by this system; the reaction of benzyl alcohol catalyzed by **1a** (1.0 mol %) for 20 h gave benzaldehyde in 24% yield.

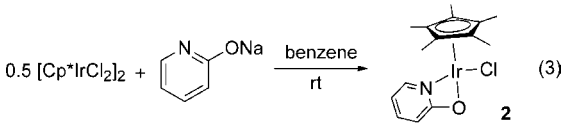
A possible mechanism for the present reaction is shown in Scheme 1. The first step of the reaction would involve

Scheme 1. Possible Mechanism for the Oxidant-Free Oxidation of Alcohols Catalyzed by **1a**



the formation of an alkoxo iridium intermediate **E** by the reaction of **1a** with alcohol. β-Hydrogen elimination of **E** would occur to give the ketone product and an iridium hydride species **F**. Then, the reaction of the hydride on iridium with the hydroxyl proton on the ligand would occur to release dihydrogen accompanied by the formation of 2-hydroxypyridinate chelated intermediate **G**, which would be subjected to the addition of alcohol to regenerate **E**. The much lower catalytic activities of the complexes **1b** and **1c** could be in accordance with the supposed mechanism.

To verify this mechanism, 2-hydroxypyridinate-chelated iridium complex corresponding to **G** was prepared, and its catalytic activity was examined. The treatment of $[Cp^*IrCl_2]_2$ with sodium 2-hydroxypyridinate in benzene gave **2** (eq 3).



The structure of **2** was confirmed by X-ray diffraction study (Figure 1).[8] The complex **2** exhibited a high catalytic

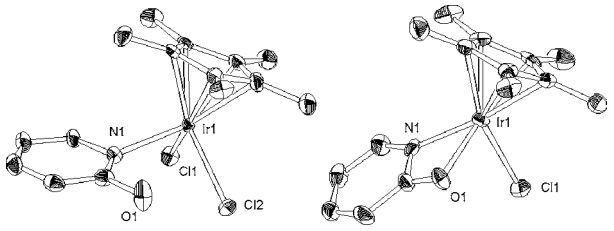
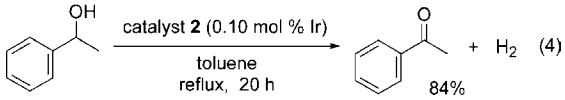


Figure 1. ORTEP drawings of **1a** (left) and **2** (right) with 50% thermal probability ellipsoids. Hydrogen atoms are omitted for clarity.

activity comparable to **1a** in the oxidation of 1-phenylethanol (eq 4), indicating its importance as a catalytic active species. Additionally, when the oxidation of 1-phenylethanol was carried out using **1a** as a catalyst (2.0 mol % of Ir) in a *sealed* NMR tube, the formation of dihydrogen besides acetophenone was confirmed by ^{1}H NMR analysis (δ 4.46).[9]



In summary, we have accomplished the design and the synthesis of new Cp*Ir complexes bearing hydroxypyridine ligands and developed a new efficient catalytic system for oxidant-free oxidation of alcohols, which can be conducted under neutral conditions with high turnover numbers. We have also disclosed that the protic functional group on the ligand promotes the release of dihydrogen from the metal hydride intermediate and that 2-hydroxypyridine chelated Cp*Ir complex acts as a highly active catalyst, supporting the proposed catalytic cycle.

Supporting Information Available: General experimental procedure, characterization data of the catalysts and products, and X-ray crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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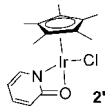
(8) X-ray study indicated a contribution of another resonance form of pyridonate **2′**, which is also supported by the result of $^{13}C\{^1H\}$ NMR analysis.



(9) The reaction was carried out using 1-phenylethanol (0.75 mmol) and **1a** (2.0 mol % of Ir) in benzene-d_6 at 130 °C for 3 h in a sealed NMR tube. In the ^{1}H NMR analysis, a signal of H_2 was observed at δ 4.46 besides the signals of acetophenone (7%) and 1-phenylethanol (93%).