Hydrogen-transfer Oxidation of Primary Alcohols Catalyzed by Iridium Complexes Bearing a Functional Pyridonate Ligand Using Isopropenyl Acetate as a Hydrogen Acceptor

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A new catalytic system for the hydrogen-transfer oxidation of alcohols catalyzed by iridium complexes bearing a functional pyridonate ligand has been developed. By using isopropenyl acetate as a hydrogen acceptor, a variety of primary alcohols were efficiently converted to the corresponding aldehydes in moderate to excellent yields.

The oxidation of alcohols to carbonyl compounds is one of the most fundamental and important reactions in synthetic organic chemistry, and it is conventionally accomplished by the use of stoichiometric amounts of harmful reagents, such as chromium reagents.¹ Recently, much effort has been devoted to catalytic oxidation using oxidants such as oxygen² and hydrogen peroxide.³ However, those oxidants often cause safety problems linked with the employment of flammable organic solvents especially in large-scale processes. Hydrogen-transfer oxidation using an organic hydrogen acceptor is a promising protocol for the green-oxidation of alcohols, because it can be performed under mild conditions and tolerates a broad range of functional groups in many cases. Oppenauer-type oxidation using acetone as a hydrogen acceptor is a well-known hydrogen-transfer oxidation of alcohols.⁴ But it usually suffers from equilibrium problem: large excess of acetone is required to obtain good yield of product.⁵ Whereas many catalytic systems using alkene,⁶ alkyne,⁷ and other organic molecules⁸ accepting hydrogen atoms in an irreversible manner have been also reported, it is important to seek a safe and easily-available hydrogen acceptor which enables environmentally benign oxidation of alcohols.

Meanwhile, we have previously reported the dehydrogenation of alcohols⁹ and cyclic amines¹⁰ which proceeds accompanying the evolution of hydrogen gas using Cp*Ir catalysts (Cp*: pentamethylcyclopentadienyl) bearing functional ligands with an α -hydroxypyridine or α -pyridonate skeleton (Figure 1). Various secondary alcohols and benzylic primary alcohols could be dehydrogenatively oxidized to ketones and benzaldehydes, respectively. However, efficient dehydrogenative oxidation of



Figure 1. Cp*Ir catalysts active for dehydrogenative reactions.

aliphatic primary alcohols into aldehydes have not been achieved yet.¹¹

In the course of our studies on the oxidation of alcohols, we examined the catalytic activity of $2a^{10}$ in dehydrogenation of 1-octanol (6a) (eq 1). Reaction using 2.0 mol% of 2a under reflux in toluene for 20 h resulted in the formation of octanal (7a) in only 26% yield. On the other hand, addition of one equivalent of isopropenyl acetate as a hydrogen acceptor effectively improved the yield of 7a to 48%. Inspired by these results, we started to investigate the hydrogen-transfer oxidation of alcohols.¹² Here, we wish to report a new system for the hydrogen-transfer oxidation of alighbatic and benzylic primary alcohols leading to aldehydes catalyzed by iridium complexes bearing a functional pyridonate ligand using isopropenyl acetate as a hydrogen acceptor.

First, we studied the oxidation of **6a** to **7a** using isopropenyl acetate as a hydrogen acceptor in the presence of various catalysts (Table 1). When the reactions were carried out in the presence of 2.0 mol% of catalysts **2a** and **2b** bearing a functional pyridonate ligand with and without a trifluoromethyl group, **7a** was obtained in 48 and 63% yields, respectively, indicating a negative effect of electron-withdrawing substituent on the catalytic activity (Entries 1 and 2). On the other hand, introduction of electron-donating groups to the functional ligand at 3- or 5-position enhanced the catalytic activity (Entries 3, 6, and 8). Thus, the highest yield of **7a** (up to 84%) was achieved by the reaction in the presence of 3.0 mol% of catalyst **2e** using three equivalents of isopropenyl acetate (Entry 7).¹³

We next examined various hydrogen acceptors (Table 2). The reactions using vinyl acetate and vinyl benzoate gave **7a** in moderate yields. However, selectivity of the reaction was relatively low in these cases (Entries 2 and 3).¹⁴ Methyl methacrylate and butyl vinyl ether both showed lower efficiency (Entries 4 and 5). The reactions using ethylene and styrene resulted in moderate yields of **7a** with relatively high selectivity (Entries 6 and 7). α -Methylstyrene and diphenylacetylene did not act as an efficient hydrogen acceptor (Entries 8 and 9). Based on these results, we concluded that isopropenyl acetate was the optimal hydrogen acceptor.

Table 1. Hydrogen-transfer oxidation of 1-octanol (**6a**) catalyzed by various Cp*Ir catalysts using isopropenyl acetate as a hydrogen acceptor^a

cai. Op				
6a CHO isopropenyl acetate (1.0 equiv) reflux in toluene, 20 h				
Entry	Catalyst	Loading/mol %	Conv ^b /%	Yield ^b /%
1	2a (R = 5-CF ₃)	2.0	51	48
2	2b (R = H)	2.0	66	63
3	2c ($R = 5$ -Me)	2.0	75	73
4 ^c	2c ($R = 5$ -Me)	3.0	87	80
5	2d (R = 4-Me)	2.0	65	61
6	2e ($R = 3$ -Me)	2.0	75	73
7 ^c	2e ($R = 3$ -Me)	3.0	91	84
8	2f(R = 3-OMe)	2.0	73	71

^aReaction was carried out with **6a** (1.0 mmol), isopropenyl acetate (1.0 mmol), and Cp*Ir catalyst (2.0 or 3.0 mol %) in toluene (18 mL) under reflux for 20 h. ^bDetermined by GC. ^cIsopropenyl acetate (3.0 mmol) was used.

Table 2. Hydrogen-transfer oxidation of 1-octanol (6a) catalyzed by 2e using various hydrogen $\mbox{acceptors}^a$

6a Catalyst 2e (2.0 mol/s) hydrogen acceptor (1.0 equiv) reflux in toluene, 20 h 7a CHO				
Entry	Hydrogen acceptor	Conv ^b /%	Yield ^b /%	
1		75	73	
2	° Co	68	40	
3	Ph	79	40	
4		39	31	
5		43	8	
6 ^c	—	40	36	
7	Ph	42	39	
8	Ph	17	15	
9	PhPh	24	21	

^aReaction was carried out with **6a** (1.0 mmol), hydrogen acceptor (1.0 mmol), and Cp*Ir catalyst **2e** (2.0 mol %) in toluene (18 mL) under reflux for 20 h. ^bDetermined by GC. ^cReaction was carried out under atmosphere of ethylene.

With the optimal catalyst and hydrogen acceptor in hand, we carried out the hydrogen-transfer oxidation of aliphatic primary alcohols (Table 3). Linear alkanols [1-octanol (**6a**), 1-decanol (**6b**), and 1-hexanol (**6c**)] were converted to the corresponding aldehydes in good yields (Entries 1–3). The reactions of cyclohexanemethanol (**6d**) and 3-phenyl-1-propanol (**6e**) proceeded in high yields (Entries 4 and 5). Phenethyl alcohol (**6f**) was also converted to phenylacetaldehyde in moderate yield, although the selectivity was lower (Entry 6).¹⁵

Table 3. Hydrogen-transfer oxidation of aliphatic primary alcohols catalyzed by $2e^a$

R	∕он	cata isoprop refl	alyst 2e enyl ace ux in tol	(3.0 mol% etate (1.0 e luene, 20 h	equiv)	RCHO
Entry		Substrat	e		Conv ^b /%	Yield ^b /%
1	\sim	\sim	~O	H (6a)	86	80
2	\sim	$\sim \sim$	\sim	`OH (6b)	80	76
3	/	$\sim \sim$	∕он	(6c)	83	76
4		\bigcirc	`ОН	(6d)	93	93
5			∕ОН	(6e)	85	85
6	[OH	(6f)	69	52

^aReaction was carried out with primary alcohol (1.0 mmol), isopropenyl acetate (1.0 mmol), and Cp*Ir catalyst **2e** (3.0 mol %) in toluene (18 mL) under reflux for 20 h. ^bDetermined by GC.

Table 4. Hydrogen-transfer oxidation of benzylic primary alcohols catalyzed by $2e^{a}$

R OH isopropenyl acetate (1.0 equiv) 80 °C in toluene, 10 h				
Entry	Substrate	Conv ^b /%	Yield ^b /%	
	R			
1	$\vec{R} = H(6g)$	98	95	
2	R = 2-Me(6h)	90	83	
3	R = 2-OMe (6i)	90	87	
4	R = 3-Me (6j)	99	92	
5	R = 3-OMe (6k)	99	94	
6	R = 4-Me(6l)	99	93	
7	R = 4-OMe (6m)	99	84 (70)	
8	R = 4-Cl(6n)	95	92	
9	$\mathbf{R} = 4\text{-Br}\left(60\right)$	93	91	
$10^{\rm c}$	$R = 4 - CF_3 (6p)$	89	87	
11	R = 4-COOMe (6q)	78	69	
12	R = 4-Ph (6r)	99	96	
13	OH (6s)	97	90	

^aReaction was carried out with primary alcohol (1.0 mmol), isopropenyl acetate (1.0 mmol), and Cp*Ir catalyst **2e** (2.0 mol%) in toluene (18 mL) at 80 °C for 10 h. ^bDetermined by GC. Yield of isolated product is indicated in parenthesis. ^cReaction was carried out under reflux.

It should be noted that the hydrogen-transfer oxidation of benzylic primary alcohols were accomplished at lower temperature in shorter time (Table 4). When the reaction of benzyl alcohol (**6g**) was carried out at 80 °C for 10 h, benzaldehyde was obtained in 95% yield (Entry 1). The reactions of benzylic alcohols **6h–6r** bearing electron-donating and electron-with-drawing substituents at the aromatic ring proceeded smoothly to give the corresponding aldehydes in good to excellent yields (Entries 2–12), demonstrating that a variety of functional groups



Scheme 1. A possible mechanism for the oxidation of primary alcohols catalyzed by **2e** using isopropenyl acetate as a hydrogen acceptor.

were tolerated. The reaction of 2-naphthalenemethanol (6s) also proceeded well.

The present catalytic system also showed high activity for the oxidation of a secondary alcohol. When the reaction of 1phenylethanol was carried out at 80 °C for 10 h, acetophenone was obtained in 97% yield (eq 2).



Although the mechanism for the present catalytic reaction is not completely clear yet, a possible one is shown in Scheme 1. The first step of the reaction would involve the activation of an alcohol by the cooperative reaction of iridium and the functional ligand with the hydroxy group to afford an alkoxo iridium species **A**. β -Hydrogen elimination of the alkoxo moiety in **A** would occur to give an aldehyde and a hydrido iridium species **B**.¹⁶ Then, insertion of isopropenyl acetate into the iridiumhydride bond would occur to give an alkyl iridium species **C**. β -Acetate elimination¹⁷ accompanied by the release of propene would occur to afford iridium acetate species **D**. Finally, reaction of iridium acetate moiety with the hydroxy proton on the functional ligand would occur to release acetic acid, regenerating the iridium pyridonate species.

In order to confirm the mechanism proposed above, we conducted the reaction of 4-methylbenzyl alcohol using 1-phenylvinyl benzoate as a hydrogen acceptor (eq 3). When the reaction was carried out at 80 °C for 10 h, 4-methylbenzaldehyde was obtained in 77% yield, along with benzoic acid (62%) and styrene (44%).¹⁸ This result strongly supports the proposed mechanism.

$$\begin{array}{c} p\text{-Tol} \frown OH \\ 0 \\ Ph \\ 0 \\ Ph \\ 0 \\ \end{array} \xrightarrow{} \begin{array}{c} catalyst \ \textbf{2e} \ (2.0 \text{ mol}\%) \\ \hline 80 \ ^{\circ}\text{C} \text{ in toluene, 10 h} \end{array} \xrightarrow{} \begin{array}{c} p\text{-Tol}\text{CHO} \ 77\% \\ \hline Ph \\ OOH \ 62\% \end{array} (3) \\ \begin{array}{c} + \\ Ph \\ \hline Ph \\ \end{array} \xrightarrow{} \begin{array}{c} 0 \\ + \\ Ph \\ \end{array} \xrightarrow{} \begin{array}{c} + \\ Ph \\ OOH \ 62\% \end{array} (3)$$

In summary, we have developed a new system for hydrogentransfer oxidation of various primary alcohols catalyzed by iridium complexes bearing a functional pyridonate ligand using isopropenyl acetate as a hydrogen acceptor.¹⁹

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- 13 Formation of a small amount of octyl acetate, which would be formed by acetylation of 1-octanol, was also observed.
- 14 Overoxidation product (octanoic acid) was not observed. Relatively large amount of octyl acetate was formed in the reaction using vinyl acetate as a hydrogen acceptor (Table 2, Entry 2).
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- 18 Formation of 13% of ethylbenzene, which would be formed by transfer hydrogenation of styrene, was also observed, because styrene proved to be a good hydrogen acceptor (Table 2, Entry 7). On the other hand, 1-phenylethyl benzoate, which might be formed by simple transfer hydrogenation of olefinic moiety in 1-phenylvinyl benzoate, was not detected.
- Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/ index.html.