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Dehydrogenative Oxidation of Primary and Secondary Alcohols Catalyzed by a Cp*Ir Complex Having a Functional C,N-Chelate Ligand

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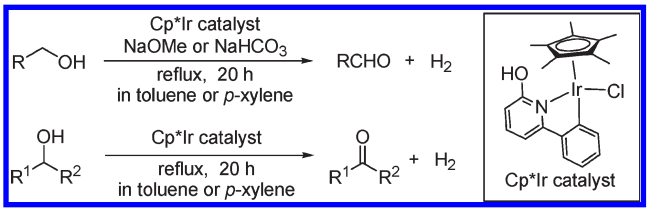
ABSTRACT



A new catalytic system for the dehydrogenative oxidation of alcohols using a Cp*Ir complex having a functional C,N-chelate ligand has been developed. With this catalytic system, both primary and secondary alcohols were efficiently converted to aldehydes and ketones, respectively. Mechanistic investigations of this catalytic system have revealed that the catalytically active species is a hydrido iridium complex with a functional C,N-chelate ligand.

The oxidation of alcohols to carbonyl compounds is one of the most fundamental and important transformations in synthetic organic chemistry. To develop an environmentally benign system, much effort has been devoted to the studies on the transition-metal-catalyzed oxidation of alcohols using less-toxic oxidants such as oxygen,[1] hydrogen peroxide,[2] or acetone.[3] However, an oxidant-free reaction to give carbonyl products via dehydrogenative oxidation accompanied by the release of hydrogen gas must be superior from the viewpoint of atom economy.[4] Several systems for the dehydrogenative oxidation of secondary alcohols to ketones using ruthenium[5] and iridium[6] catalysts have been developed.[7] In contrast, there

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(1) (a) Markó, I. E.; Giles, P. R.; Tsukazaki, M.; Brown, S. M.; Urch, C. J. *Science* **1996**, *274*, 2044. (b) Sheldon, R. A.; Arends, I. W. C. E.; ten Brink, G.-J.; Dijksman, A. *Acc. Chem. Res.* **2002**, *35*, 774. (c) Csjernyik, G.; Éll, A. H.; Fadini, L.; Pugin, B.; Bäckvall, J.-E. *J. Org. Chem.* **2002**, *67*, 1657. (d) Sigman, M. S.; Jensen, D. R. *Acc. Chem. Res.* **2006**, *39*, 221. (e) Schultz, M. J.; Sigman, M. S. *Tetrahedron* **2006**, *62*, 8227. (f) Jiang, B.; Feng, Y.; Ison, E. A. *J. Am. Chem. Soc.* **2008**, *130*, 14462.

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(3) (a) Almeida, M. L. S.; Beller, M.; Wang, G.-Z.; Bäckvall, J.-E. *Chem.—Eur. J.* **1996**, *2*, 1533. (b) Fujita, K.; Furukawa, S.; Yamaguchi, R. *J. Organomet. Chem.* **2002**, *649*, 289. (c) Hanasaka, F.; Fujita, K.; Yamaguchi, R. *Organometallics* **2005**, *24*, 3422. (d) Coleman, M. G.; Brown, A. N.; Bolton, B. A.; Guan, H. *Adv. Synth. Catal.* **2010**, *352*, 967. (e) Moyer, S. A.; Funk, T. W. *Tetrahedron Lett.* **2010**, *51*, 5430.

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(5) (a) Dobson, A.; Robinson, S. D. *J. Organomet. Chem.* **1975**, *87*, C52. (b) Dobson, A.; Robinson, S. D. *Inorg. Chem.* **1977**, *16*, 137. (c) Ligthart, G. B. W. L.; Meijer, R. H.; Donners, M. P. J.; Meuldijk, J.; Vekemans, J. A. J. M.; Hulshof, L. A. *Tetrahedron Lett.* **2003**, *44*, 1507. (d) Zhang, J.; Gandelman, M.; Shimon, L. J. W.; Rozenberg, H.; Milstein, D. *Organometallics* **2004**, *23*, 4026. (e) Adair, G. R. A.; Williams, J. M. J. *Tetrahedron Lett.* **2005**, *46*, 8233. (f) van Buijtenen, J.; Meuldijk, J.; Vekemans, J. A. J. M.; Hulshof, L. A.; Kooijman, H.; Spek, A. L. *Organometallics* **2006**, *25*, 873.

(6) (a) Fujita, K.; Tanino, N.; Yamaguchi, R. *Org. Lett.* **2007**, *9*, 109. (b) Royer, A. M.; Rauchfuss, T. B.; Wilson, S. R. *Inorg. Chem.* **2008**, *47*, 395. (c) Royer, A. M.; Rauchfuss, T. B.; Gray, D. L. *Organometallics* **2010**, *29*, 6763.

(7) Transition-metal-catalyzed hydrogen production from alcohols has been also reported. (a) Morton, D.; Cole-Hamilton, D. J. *J. Chem. Soc., Chem. Commun.* **1987**, 248. (b) Morton, D.; Cole-Hamilton, D. J. *J. Chem. Soc., Chem. Commun.* **1988**, 1154. (c) Morton, D.; Cole-Hamilton, D. J.; Utuk, I. D.; Paneque-Sosa, M.; Lopez-Poveda, M. *J. Chem. Soc., Dalton Trans.* **1989**, 489. (d) Junge, H.; Beller, M. *Tetrahedron Lett.* **2005**, *46*, 1031. (e) Junge, H.; Loges, B.; Beller, M. *Chem. Commun.* **2007**, 522.

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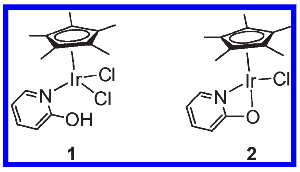
have been no homogeneous systems which efficiently catalyze the dehydrogenation of primary alcohols to aldehydes.[8,9]

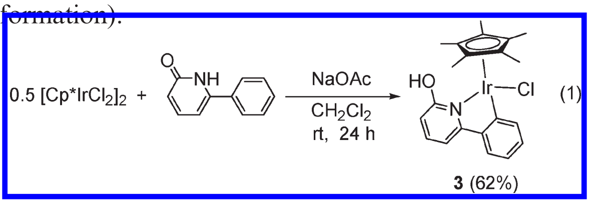
We have recently reported the dehydrogenative oxidation of alcohols catalyzed by Cp*Ir complexes **1** having 2-hydroxypyridine as a functional ligand, in which N, O-chelated complex **2** could act as a catalytically active species.[6a] Use of the catalyst achieved extremely high turnover numbers up to 2000 in the oxidation of secondary alcohols. However, such catalysts did not exhibit a high activity for the reaction of primary alcohols (vide infra).



1 **2**

Here, we report a new catalytic system for the dehydrogenative oxidation of alcohols using a Cp*Ir complex having a functional C,N-chelate ligand. Both primary and secondary alcohols were efficiently converted to aldehydes and ketones, respectively. Mechanistic studies of this catalytic system are also demonstrated.

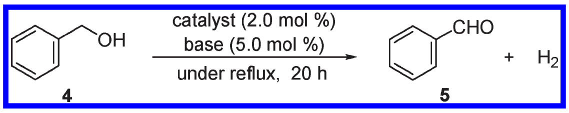
The Cp*Ir catalyst used in this study was prepared as illustrated in eq 1. The reaction of $[Cp^*IrCl_2]_2$ with 6-phenyl-2-pyridone in the presence of NaOAc (1.3 equiv) in dichloromethane at room temperature gave a C,N-chelated complex **3** in 62% yield via coordination of the nitrogen atom in the pyridine ring followed by orthometalation at the phenyl group.[10] The complex **3** was obtained as a stable yellow powder, and its structure was elucidated by spectroscopic data and single-crystal X-ray analysis (see the Supporting Information).



3 (62%) (1)

The catalytic performance of **3** for the dehydrogenative oxidation of primary alcohols was investigated.

Table 1. Dehydrogenative Oxidation of Benzyl Alcohol (**4**) under Various Conditions[a]



4 **5**

entry	catalyst	base	solvent	conv[b](%)	yield[b] (%)
1	**3**	none	toluene	59	59
2	**3**	Na_2CO_3	toluene	66	62
3	**3**	K_2CO_3	toluene	77	75
4	**3**	$NaHCO_3$	toluene	86	84
5	**3**	NaOMe	toluene	91	90
6	**3**	NaO*t*Bu	toluene	81	66
7	**3**	$NaHCO_3$	*p*-xylene	91	88
8	**6**	NaOMe	toluene	8	8
9	**1**	none	toluene	63	63
10	**1**	NaOMe	toluene	31	30
11	**2**	none	toluene	52	50
12	**2**	NaOMe	toluene	17	17

[a] The reaction was carried out with **4** (1.0 mmol), catalyst (2.0 mol %), and base (5.0 mol %) in toluene (18 mL) under reflux for 20 h. [b] Detemined by GC.

First, reactions of benzyl alcohol (**4**) under various conditions were conducted in order to find optimum conditions (Table 1). When the solution of **4** in toluene was refluxed for 20 h in the presence of **3** (2.0 mol %), benzaldehyde (**5**) was selectively formed in 59% yield (entry 1).[11] The yield of **5** was improved by the addition of a base. When the reactions were carried out in the presence of Na_2CO_3, K_2CO_3, $NaHCO_3$, and NaOMe, the yields of **5** were improved up to 62%, 75%, 84%, and 90%, respectively (entries 2–5).[12] The best result was obtained by using NaOMe (entry 5), while the reaction using NaO*t*Bu resulted in a lower selectivity for **5** (entry 6). A high yield of **5** (88%) was also achieved by the reaction using $NaHCO_3$ as a base under reflux in *p*-xylene (entry 7).[13] The hydroxy group in the C,N-chelate ligand was indispensable to attain high catalytic activity: when the reaction was carried out using Cp*IrCl[2-(2-pyridyl)phenyl]Cl (**6**)[10,14] as the catalyst, **5** was formed in only 8% yield (entry 8). Other Cp*Ir catalysts **1** and **2**, those exhibited high activity for the dehydrogenative oxidation of

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[8] Robinson has reported the dehydrogenation of primary alcohols catalyzed by $Ru(OCOCF_3)(CO)(PPh_3)_2$ in refs 5a and 5b. However, quantitative study with respect to the fate of the alcohols was not demonstrated. Additionally, Hulshof noted in ref 5c that dehydrogenative oxidation of primary alcohols catalyzed by the same ruthenium complex resulted in low conversions and selectivities.

[9] Heterogeneously catalyzed systems for the dehydrogenative 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. (c) Mitsudome, T.; Mikami, Y.; Funai, H.; Mizugaki, T.; Jitsukawa, K.; Kaneda, K. *Angew. Chem., Int. Ed.* **2008**, *47*, 138. (d) Mitsudome, T.; Mikami, Y.; Ebata, K.; Mizugaki, T.; Jitsukawa, K.; Kaneda, K. *Chem. Commun.* **2008**, 4804. (e) Shimizu, K.; Sugino, K.; Sawabe, K.; Satsuma, A. *Chem.—Eur. J.* **2009**, *15*, 2341.

[10] Synthesis of a C,N-chelated complex by the reaction of $[Cp^*IrCl_2]_2$ with 2-phenylpyridine in the presence of NaOAc has been reported. (a) Scheeren, C.; Maasarani, F.; Hijazi, A.; Djukic, J.-P.; Pfeffer, M.; Zarić, S. D.; Le Goff, X.-F.; Ricard, L. *Organometallics* **2007**, *26*, 3336. (b) Li, L.; Brennessel, W. W.; Jones, W. D. *J. Am. Chem. Soc.* **2008**, *130*, 12414. (c) Boutadla, Y.; Al-Duaji, O.; Davies, D. L.; Griffith, G. A.; Singh, K. *Organometallics* **2009**, *28*, 433.

[11] Evolution of the hydrogen gas was confirmed by an analysis of the gas phase using a hydrogen sensor.

[12] We have also carried out the reaction of **4** by using equimolar amounts of **3** (2.0 mol %) and NaOMe (2.0 mol %) under reflux in toluene for 20 h, resulting in a lower yield (70%) of **5**.

[13] The addition of $NaHCO_3$ as a base gave the best result for the reaction under *p*-xylene reflux. The addition of NaOMe lowered the yield of **5** to 58%.

[14] The catalytic activity of complex **6** has been recently reported. (a) Hull, J. F.; Balcells, D.; Blakemore, J. D.; Incarvito, C. D.; Eisenstein, O.; Brudvig, G. W.; Crabtree, R. H. *J. Am. Chem. Soc.* **2009**, *131*, 8730. (b) Blakemore, J. D.; Schley, N. D.; Balcells, D.; Hull, J. F.; Olack, G. W.; Incarvito, C. D.; Eisenstein, O.; Brudvig, G. W.; Crabtree, R. H. *J. Am. Chem. Soc.* **2010**, *132*, 16017.

secondary alcohols,[6a] showed lower activity than **3** in the reaction of **4** (entries 9–12)

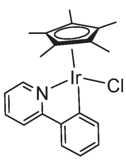

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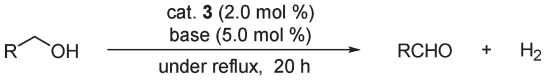
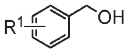
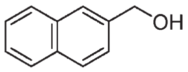
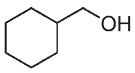
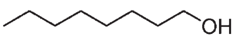
Table 2. Dehydrogenative Oxidation of Various Primary Alcohols Catalyzed by **3**[a]

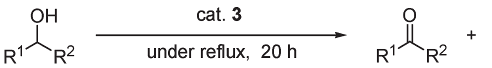


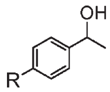
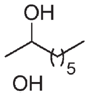
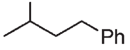
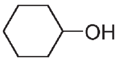
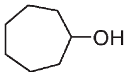
entry	primary alcohol	condition	conv[b] (%)	yield[b] (%)
				
1	R^1 = H	**A**	91	90
2	R^1 = *o*-Me	**A**	83	79
3	R^1 = *o*-Me	**B**	100	95
4	R^1 = *m*-Me	**A**	85	82
5	R^1 = *p*-Me	**A**	93	93
6	R^1 = *m*-OMe	**A**	83	78
7	R^1 = *p*-OMe	**A**	100	95 (92)
8	R^1 = 3,5-OMe	**A**		(40)
9	R^1 = 3,5-OMe	**B**		(77)
10	R^1 = *p*-Ph	**A**	85	82 (80)
11	R^1 = *p*-Cl	**A**	74	73
12	R^1 = *p*-Cl	**B**	82	79
13	R^1 = *p*-Br	**A**	62	57
14	R^1 = *p*-Br	**B**	76	71 (63)
15	R^1 = *p*-CF_3	**A**	42	37
16	R^1 = *p*-CF_3	**B**	54	51
17	R^1 = *p*-CO_2Me	**A**	48	42
18	R^1 = *p*-CO_2Me	**B**	67	60
19		**A**		(78)
20		**A**	26	18
21[c]		**B**	74	62
22		**A**	40	34
23[c]		**B**	65	46

[a] Condition **A**: The reaction was carried out with primary alcohol (1.0 mmol), catalyst **3** (2.0 mol %), and NaOMe (5.0 mol %) in toluene (18 mL) under reflux for 20 h. Condition **B**: The reaction was carried out with primary alcohol (1.0 mmol), catalyst **3** (2.0 mol %), and $NaHCO_3$ (5.0 mol %) in *p*-xylene (18 mL) under reflux for 20 h. [b] Determined by GC. The value in parentheses is isolated yield. [c] 5.0 mol % of catalyst **3** was used.

Having the optimum conditions **A** and **B** (**A**: reflux in toluene with NaOMe, **B**: reflux in *p*-xylene with $NaHCO_3$) in hand, we next investigated the dehydrogenative oxidation of various primary alcohols catalyzed by **3** (Table 2). The reactions of benzylic alcohols with electron-donating and -withdrawing substituents at the aromatic ring proceeded to give corresponding aldehydes in moderate to excellent yields (entries 1–18). Most of the electron-rich benzylic alcohols could be converted to aldehydes in high yields by the reactions under condition **A**. When the yield of the aldehyde under condition **A** was unsatisfactory, the reaction under condition **B** was conducted to improve the yield of aldehyde (entries 3 and 9). Reactions of electron-poor benzylic alcohols were relatively slow: thus, condition **B** was applied to obtain better results (entries 11–18). The present catalytic system was also applicable to aliphatic primary alcohols, although the yields of corresponding aldehydes were moderate (entries 20–23). When the reactions of cyclohexanemethanol and 1-octanol were carried out under condition **B** using 5.0 mol % of **3**, cyclohexanecarbaldehyde and octanal were formed in 62% and 46% yield, respectively (entries 21 and 23).

Table 3. Dehydrogenative Oxidation of Various Secondary Alcohols Catalyzed by **3**[a]



entry	secondary alcohol	cat. **3** (mol %)	solvent	conv[b] (%)	yield[b] (%)
					
1	R = H	0.10	*p*-xylene	96	96
2	R = Me	0.10	toluene	100	100
3	R = OMe	0.10	*p*-xylene	100	100
4	R = Cl	0.20	*p*-xylene	100	100
5	R = NO_2	0.40	*p*-xylene	100	100
6		0.20	*p*-xylene	93	92
7		0.40	*p*-xylene	97	97
8		0.50	*p*-xylene	100	100
9		0.20	*p*-xylene	100	100

[a] The reaction was carried out with secondary alcohol (1.5–15 mmol) and catalyst **3** (0.10–0.50 mol %) in toluene or *p*-xylene (0.50–5.0 M solution) under reflux for 20 h. [b] Determined by GC.

Reactions of secondary alcohols proceeded to give ketones with much lower catalyst loadings (0.10–0.50 mol %) without the addition of base (Table 3).[11,15] 1-Arylethanols with electron-donating and -withdrawing substituents proceeded to give corresponding ketones in excellent yields with complete selectivity (entries 1–5). Aliphatic secondary alcohols including cyclic alcohols were also converted to ketones in excellent yields (entries 6–9).

A possible mechanism for the present dehydrogenative oxidation is shown in Scheme 1. The first step of the reaction would involve the formation of an alkoxo iridium species **7** by the reaction of **3** with an alcohol

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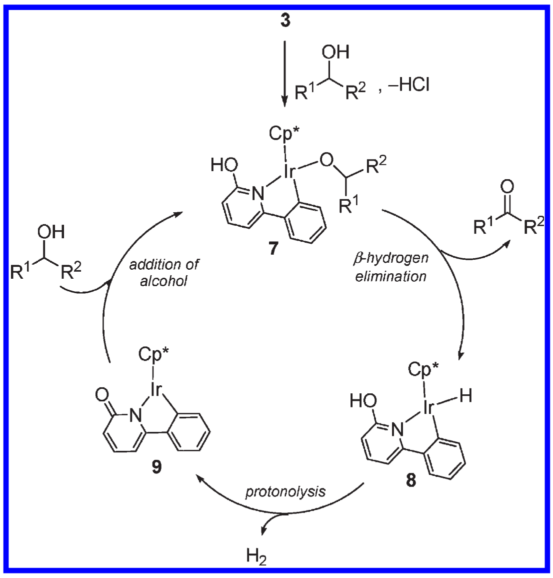
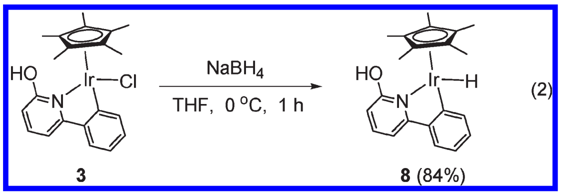
(15) Generated hydrogen gas could be used for the hydrogenation of an alkene (1-decene). Details are shown in the Supporting Information.

with liberation of hydrogen chloride, which would be accelerated by the addition of a base. *β*-Hydrogen elimination of **7** would occur to give the dehydrogenated product and a hydrido iridium complex **8**. Then, protonolysis of the iridium hydride with the hydroxy proton in the C,N-chelate ligand would occur to release hydrogen gas accompanied by the formation of an unsaturated pyridonate complex **9**. Addition of the alcohol to **9** would regenerate species **7**.

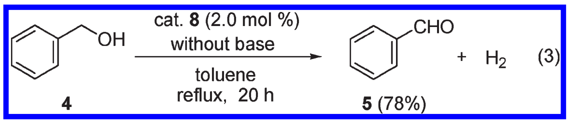
Scheme 1. A Possible Mechanism for the Dehydrogenative Oxidation of Alcohols Catalyzed by **3**



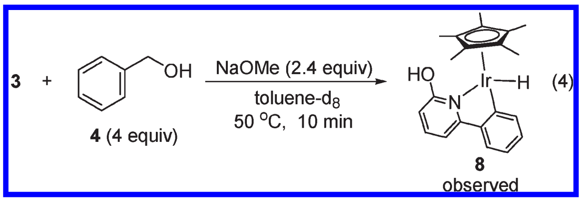
The hydrido complex **8** mentioned above was actually prepared by the reaction of **3** with $NaBH_4$ in THF at 0 °C for 1 h in 84% yield (eq 2). Complex **8** was obtained as a relatively unstable pale-yellow powder. The structure of **8** was determined by spectroscopic data (see the Supporting Information).



To verify the proposed mechanism, the catalytic activity of **8** was examined. When the reaction of **4** was carried out in toluene under reflux for 20 h in the presence of **8** (2.0 mol %) without a base, **5** was formed in 78% yield (eq 3),[16] indicating its importance as a catalytically active species.



Furthermore, the formation of the hydrido complex **8** in the early stage of the dehydrogenative reaction was confirmed by NMR study. ^{1}H NMR analysis of the substoichiometric reaction of **3** with **4** (4 equiv) and NaOMe (2.4 equiv) in toluene-d_8 at 50 °C for 10 min revealed the formation of **8** (eq 4),[17] strongly supporting the proposed mechanism (see the Supporting Information).



In summary, we have developed a new Cp*Ir catalyst having a functional C,N-chelate ligand, which exhibited a high activity for the dehydrogenative oxidation of both primary and secondary alcohols. A variety of primary and secondary alcohols were converted to aldehydes and ketones accompanied by the release of hydrogen gas. The mechanistic investigations have revealed that the catalytically active species is a hydrido iridium complex with a functional C,N-chelate ligand.

Acknowledgment. This work was supported by KAKENHI (No. 19750075). We also thank Johnson Matthey, Inc. for a generous loan of iridium trichloride.

Note Added in Proof. Very recently, dehydrogenative oxidation of primary and secondary benzylic alcohols catalyzed by homogeneous triazolylidene ruthenium complexes was reported. Prades, A.; Peris, E.; Albrecht, M. *Organometallics* **2011**, *30*, 1162.

Supporting Information Available. General experimental procedure, characterization data of the catalysts and products, and X-ray crystallographic data for **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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[16] The yield of **5** in the reaction of **4** catalyzed by **8** (78%) was higher than that catalyzed by **3** without a base (59%), but lower than that catalyzed by **3** with NaOMe (90%). Instability of the hydrido complex **8** would cause the lower yield of **5** compared to the reaction catalyzed by stable complex **3** with NaOMe.

[17] In addition to the hydrido complex **8**, the formation of **5** was confirmed by ^{1}H NMR analysis.