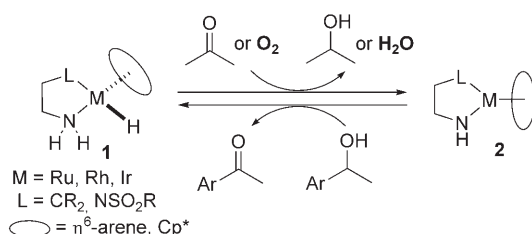


Aerobic Oxidative Kinetic Resolution of Racemic Secondary Alcohols with Chiral Bifunctional Amido Complexes**

Sachiko Arita, Takashi Koike, Yoshihito Kayaki, and Takao Ikariya*

Catalytic hydrogen transfer between alcohols and ketones offers a great opportunity to explore an attractive molecular transformation because of its low cost and operational simplicity.^[1] We have developed chiral bifunctional Ru, Rh, and Ir hydride complexes—[RuH(Tsdpn)(η^6 -arene)] and [Cp*MH(Tsdpn)] (TsDPEN: *N*-(*p*-toluenesulfonyl)-1,2-diphenylethylenediamine, Cp* = 1,2,3,4,5-pentamethylcyclopentadienyl, M = Rh, Ir) as practical catalysts for the asymmetric transfer hydrogenation of ketones.^[1a-d,2] The amine–hydrido complex has a sufficiently acidic NH proton to activate ketones, leading to the amido complex along with the formation of the reduction products. The resulting amido complex readily dehydrogenates alcohols to regenerate the amine–hydrido complex (Scheme 1). Because of its intrinsic

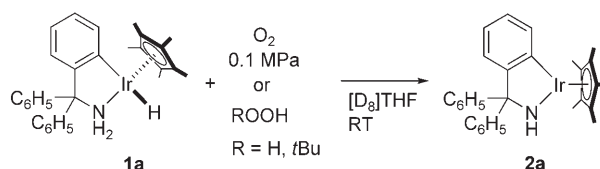


Scheme 1. Hydrogen transfer with bifunctional molecular catalysts.

reversible nature, both forward and reverse reactions can be utilized as the reduction of ketones and oxidation of alcohols, respectively. However, the dehydrogenative oxidation reaction with the related amine/amido catalysts has been investigated less, mainly because of the lack of appropriate hydrogen acceptors, except for ketones for the kinetic resolution of racemic alcohols,^[3] intramolecular redox isomerization,^[4] and other oxidative transformations.^[5] We have extended a conceptually new hydrogen-transfer protocol with bifunctional catalysts and found that molecular oxygen readily reacts with the amine–hydrido complex leading to

the amido complex. Based on the present new finding,^[6] we could successfully apply the aerobic oxidation to the kinetic resolution of racemic secondary alcohols with chiral bifunctional Ir, Rh, and Ru catalysts, in which O₂ serves as a hydrogen acceptor.

The newly developed {Cp*Ir} hydride complex **1a**^[7] bearing a C–N chelate primary amine ligand prepared from triphenylmethylamine reacts rapidly with O₂ or air under mild conditions to give the corresponding amido complex **2a** (Scheme 2). Monitoring a solution of **1a** in [D₈]THF under air



Scheme 2. Reaction of **1a** with oxidants including O₂, H₂O₂, and *t*BuOOH.

at room temperature by ¹H NMR spectroscopy showed a rapid decrease in the intensity of a hydride signal at $\delta = -13.12$ ppm and an increase in the characteristic signal due to the NH moiety of **2a** at $\delta = 8.37$ ppm, indicating the smooth conversion to the amido complex (70 % yield based on **1a**) by the action of O₂.

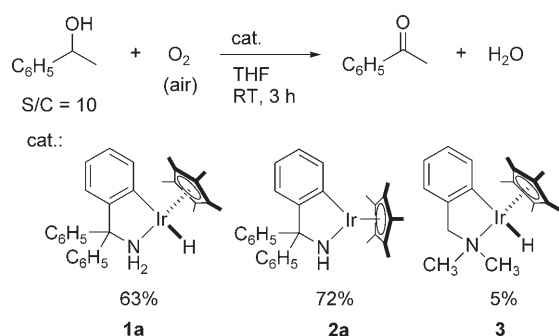
Other oxidants like hydroperoxides also promoted the transformation to **2a**. The reaction of **1a** with an equimolar amount of H₂O₂ in [D₈]THF for 24 h gave **2a** in 95 % yield in addition to a detectable amount of H₂O. The O–O bond cleavage of peroxides with the hydrido complex **1a** was also clearly demonstrated in the treatment of *t*BuOOH, which afforded **2a** and *t*BuOH (26 % yield). Although the precise mechanism of the formation of **2a** from **1a** in the presence of O₂ has remained unclear, these findings as well as recently reported results^[6] imply that the reaction of **1a** with O₂ might proceed through O₂ insertion into the metal–hydride bond^[8] to form an amine–hydroperoxo complex, followed by the release of **2a** and H₂O₂.^[9] The H₂O₂ product then reacts with **1a** to provide **2a** and water.

Encouraged by the rapid conversion of **1a** with O₂ into **2a**, we next examined the catalytic aerobic dehydrogenative oxidation of 1-phenylethanol with Ir complexes bearing C–N chelate ligands; representative results are shown in Scheme 3. Exposure of a THF solution containing 1-phenylethanol and **1a** (S/C = 10:1) to air at room temperature gave acetophenone in 63 % yield after 3 h.^[10] Comparable catalyst performance was observed for the reaction with the amido complex

[*] S. Arita, Dr. T. Koike, Dr. Y. Kayaki, Prof. Dr. T. Ikariya
Department of Applied Chemistry
Graduate School of Science and Engineering
Tokyo Institute of Technology
2-12-1 O-okayama, Meguro-ku, Tokyo 152-8552 (Japan)
Fax: (+81) 3-5734-2637
E-mail: tikariya@apc.titech.ac.jp

[**] This work was financially supported by a Grant-in-Aid from the Ministry of Education, Culture, Sports, Science and Technology (Japan) (No. 18065007) and partially supported by The 21st Century COE and G-COE Programs.

Supporting information for this article is available on the WWW under <http://www.angewandte.org> or from the author.



Scheme 3. Aerobic oxidation of 1-phenylethanol using C–N chelate complexes.

2a. Notably, the hydrido complex **3** bearing an *N,N*-dimethylamino group did not catalyze the oxidation under otherwise identical conditions, indicating that the metal/NH units possibly participate in the activation of O₂ to facilitate transformation to the amido complex.

This aerobic oxidation of alcohols is more appealing when applied to the kinetic resolution of racemic secondary alcohols with chiral amido catalysts.^[11,12] The efficiency is significantly influenced by the redox properties of the alcohols and the reaction conditions as well as the chiral catalyst performance.

When a THF solution of racemic 1-phenylethanol (1.0 M) and the chiral Ir complex **2b** derived from (*R*)-1-naphthylethylamine (S/C = 10) was treated with air at 30 °C for 4 h, (*R*)-1-phenylethanol was recovered with a 48 % yield and 14 % *ee* (entry 1, Table 1). The same reaction but at higher dilution (0.1 M substrate) led to a marked increase in the *ee* value, up to 42 % (entry 2, Table 1). Noticeably, the use of the chiral amido Ir complex bearing an *N*-sulfonylated diamine ligand, [Cp*Ir((*S,S*)-Tsdpen)] (**2c**),^[2] significantly improved the enantioselectivity, and (*R*)-1-phenylethanol was recovered in 39 % yield and 86 % *ee* with a *k_t/k_s* ratio^[13] of 9, although a prolonged reaction time was necessary for completion (entry 3, Table 1). Further improvement in the stereochemical outcome of the reaction was possible when the reaction with [Cp*Ir((*S,S*)-Msdpen)] (**2d**) (Ms = methanesulfonyl) was carried out

under dilute conditions. The desired *R* alcohol with 98 % *ee* was recovered in 48 % yield and the *k_t/k_s* value was up to 90 (entry 5, Table 1). A 1-phenylethanol derivative having an electron-donating CH₃O group at the *para* position was efficiently resolved with catalyst **2d** (entry 6, Table 1). Similarly, the *R* enantiomers with > 99 % *ee* and with 46–50 % yields were readily obtainable from the reactions of 1-indanol and 1-tetralol at ambient temperature (entries 7 and 8, Table 1).

The reaction with the binary catalyst system including [Cp*IrCl((*S,S*)-Tscyn)] (**4**) (TsCYDN = *N*-(*p*-toluenesulfonyl)-1,2-cyclohexanediamine) and *t*BuOK proceeded equally well to provide (*R*)-1-phenylethanol with an excellent *ee* value of 98 % in 45 % recovered yield (entry 9, Table 1). Additionally, the added base did not promote any harmful

Table 1: Aerobic oxidative kinetic resolution of secondary alcohols.^[a]

Entry	Alcohol	Conc. [M]	Cat.	<i>t</i> [h]	Unreacted alcohol recov. [%] ^[b]	<i>ee</i> [%] ^[c]	<i>k_t/k_s</i> ^[d]
1		1.0	2b	4	48	14	1.5
2		0.1	2b	75	48	42	3.3
3		1.0	2c	24	39	86	9.1
4		1.0	2d	22	44	84	12.6
5		0.2	2d	38	48	98	91.3
6		0.2	2d	19	38	98	17.2
7		0.1	2d	6	50	> 99	> 100
8		0.1	2d	6.5	46	> 99	77.6
9		1.0	4 ^[e]	24	45	98	40.8
10		1.0	5 ^[e]	3.5	46	93	28.9
11		1.0	6 ^[e]	12	78	23	12.3

[a] Reaction conditions: The reaction was carried out with a solution of alcohol (1.1 mmol) in THF and a substrate/catalyst ratio of 10 under air. [b] Recovered starting material; determined by GC using duren as an internal standard. [c] Determined by HPLC on a Daicel Chiralcel OD column. [d] $\ln[1-C]/\ln[1-C(1-ee)]$. [e] *t*BuOK (1.5 equiv) was added.

side reactions as observed in our previous work.^[3a] The resolution with the chiral amido Rh catalyst generated analogously from [Cp*RhCl((S,S)-Tsdpen)] (**5**) and the base proceeded faster to completion, providing the desired chiral alcohols with 93% *ee* (entry 10, Table 1), while the related chiral Ru complex, [RuCl((S,S)-Tsdpen)(*p*-cymene)] (**6**) gave unsatisfactory results (entry 11, Table 1).

In summary, we found facile hydrogen transfer from the amine-hydrido complex to the oxygen molecule, generating the corresponding amido complex. Based on the finding that O₂ is a promising hydrogen acceptor, we successfully demonstrated the first example of aerobic oxidative kinetic resolution of racemic secondary alcohols with well-defined bifunctional catalysts, providing chiral alcohols with up to 99% *ee*. The present aerobic oxidative transformation with the bifunctional catalysts is a clean process that proceeds under mild conditions with high efficiency and minimal organic waste. Further efforts to improve the rate of the reaction and to clarify the mechanism for the hydrogen transfer to oxygen and to expand further the scope of the aerobic oxidation are now underway.

Experimental Section

General procedure for the aerobic kinetic resolution of secondary alcohols: A 20-mL Schlenk flask was charged with the catalysts (0.11 mmol), durene (0.024 mg, 1.1 mmol; an internal standard), and THF (1.1 mL) under Ar atmosphere. After the secondary alcohols (1.1 mmol) had been introduced, the flask was evacuated and filled with air. The reactions were carried out at 30°C under an air balloon and monitored by gas chromatography and HPLC to determine the conversion and *ee* values. The methods utilized for the determination of enantiomeric excesses are summarized in Table S1 in the Supporting Information.

Received: December 21, 2007

Published online: February 22, 2008

Keywords: alcohols · homogeneous catalysis · iridium · kinetic resolution · oxidation

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