Kinetic Resolution

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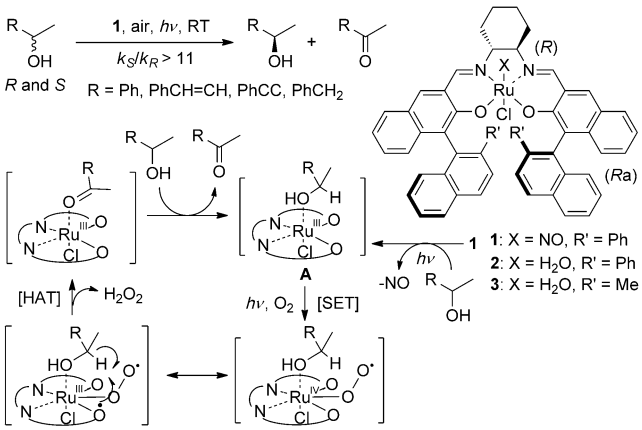
Ruthenium-Catalyzed Oxidative Kinetic Resolution of Unactivated and Activated Secondary Alcohols with Air as the Hydrogen Acceptor at Room Temperature**

*Hirotaka Mizoguchi, Tatsuya Uchida, and Tsutomu Katsuki**

Abstract: *Enantiopure alcohols are versatile building blocks for asymmetric synthesis and the kinetic resolution (KR) of racemic alcohols is a reliable method for preparing them. Although many KR methods have been developed, oxidative kinetic resolution (OKR), in which dioxygen is used as the hydrogen acceptor, is the most atom-efficient. Dioxygen is ubiquitous in air, which is abundant and safe to handle. Therefore, OKR with air has been intensively investigated and the OKR of benzylic alcohols was recently achieved by using an Ir catalyst without any adjuvant. However, the OKR of unactivated alcohols remains a challenge. An [(aqua)Ru(salen)] catalyzed OKR with air as the hydrogen acceptor was developed, in which the aqua ligand is exchanged with alcohol and the Ru complex undergoes single electron transfer to dioxygen and subsequent alcohol oxidation. This OKR can be applied without any adjuvant to activated and unactivated alcohols with good to high enantioselectivity. The unique influence of substrate inhibition on the enantioselectivity of the OKR is also described.*

The oxidative kinetic resolution (OKR) of racemic alcohols is a useful method for preparing highly enantioenriched alcohols.[1] Alcohol oxidation is a dehydrogenation reaction and requires a hydrogen acceptor. Of the various possible acceptors, dioxygen, which is ubiquitous in air, is the most atom-efficient. OKR that uses dioxygen as an acceptor has thus been extensively investigated[2,3] and not surprisingly, KR with air has also been achieved.[1a,4,5] However, except for one example, these reactions require the addition of base,[5a] heating,[5d] or photoirradiation.[4] Ikariya and coworkers have reported the highly enantioselective iridium-catalyzed OKR of secondary benzylic alcohols when using solely air at room temperature.[5b,c] However, the OKR of unactivated secondary alcohols by using air without any adjuvant at room temperature remains a challenge in asymmetric oxidation.

In 2000, we achieved the first OKR of secondary alcohols with air at room temperature under visible-light irradiation in the presence of [(ON)Ru(salen)] complex **1**.[4] Both activated and unactivated alcohols can be oxidized with good enantiomer differentiation (Scheme 1).[4a] Based on kinetics and kinetic isotope effect (KIE) studies, we proposed a mechanism



Scheme 1. The [(ON)Ru(salen)]-catalyzed aerobic OKR of secondary alcohols under irradiation and its proposed mechanism. The salen ligand is simplified for clarity.

for this oxidation[4c] in which irradiation promotes both NO-dissociation and single electron transfer (SET). We thus inferred that this alcohol oxidation would proceed without irradiation if the oxidation potential of intermediate **A** was reduced through the coordination of a donating ligand. Indeed, an achiral [Ru(salen)] complex bearing a PPh_3 ligand catalyzed alcohol oxidation in air without irradiation,[6] but its chiral derivative could not be synthesized.

To our surprise, however, it was found that pre-irradiation in air followed by vacuum-drying rendered **1** catalytically active for alcohol oxidation even in the dark (Scheme 2).[7] This result suggested that NO dissociation is reversible, that the oxidation of free NO in the reaction mixture is slow, and that irradiation is not necessarily required for SET. Therefore, we expected that alcohol-bound intermediate **A** (Scheme 2) or a corresponding water-bound complex would catalyze the OKR of secondary alcohols with air without irradiation. Herein, we describe an efficient OKR of unactivated and activated secondary alcohols with air as the hydrogen acceptor at room temperature.

[*] H. Mizoguchi
Department of Chemistry, Graduate School of Science
Kyushu University, Hakozaki, Higashi-ku, Fukuoka 812-8581 (Japan)
Dr. T. Uchida
Faculty of Arts and Science, and International Institute for Carbon-Neutral Energy Research (WPI-I2CNER), Kyushu University
Hakozaki, Higashi-ku, Fukuoka 812-8581 (Japan)
Prof. T. Katsuki
WPI-I2CNER, and Institute for Advanced Study, Kyushu University
Hakozaki, Higashi-ku, Fukuoka 812-8581 (Japan)
E-mail: katsuscc@chem.kyushu-univ.jp

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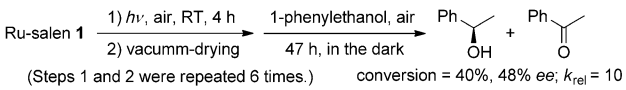
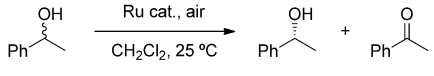


Scheme 2. Aerobic oxidation of 1-phenylethanol by using pre irradiated **1** as the catalyst in the dark.

We prepared the [(aqua)Ru-salen] complexes **2**, **3** and **4**-**8** (Figure S1 in the Supporting Information).[8,9] We first examined the oxidation of 1-phenylethanol when using **2** as the catalyst in dichloromethane under air at 25 °C without irradiation (Table 1, entry 1). As anticipated, the reaction proceeded with a good k_{rel} value ($k_{rel} = 12$), which was almost equal to that obtained with complex **1** ($k_{rel} = 11$) under irradiation,[4a] but the reaction proceeded rather slowly. Alcohol oxidation produces hydrogen peroxide that may competitively coordinate to the Ru ion and slow the desired oxidation. Under irradiation, this adverse effect may be mitigated.[10]

Table 1: Optimization of the reaction conditions.[a]



Entry	Cat.	MS X [Å][b]	Time [h]	Conv. [%][c]	*ee* [%][c,d]	$k_{rel(obs.)}$[e]
1	**2**	–	55	54.3	80.3	12
2	**2**	MS 5 Å	15	67.9	94.2	8
3	**3**	MS 5 Å	13	54.7	89.9	21
4[f]	**3**	MS 5 Å	10	53.6	89.3	23
5[g]	**3**	MS 5 Å	7	54.3	91.1	24
6[g,h]	**3**	MS 5 Å	9	55.6	94.3	25

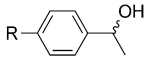
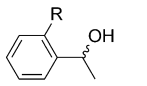
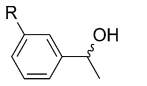
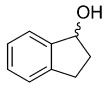
[a] Reaction conditions: CH_2Cl_2 (0.3 mL), 1-phenylethanol (0.3 mmol, 1 M), Ru complex (9 μmol, 3 mol%), bicyclohexyl (one drop, internal standard), 25 °C, air, unless otherwise noted. [b] 30 mg of MS was added. [c] Conversion and *ee* were determined by GC analysis (see the Supporting Information). [d] Configuration of the remaining isomer is *R* (see the Supporting Information). [e] Calculated by using Kagan's equation (Ref. [12a]). [f] Run in $CHCl_3$ (0.3 mL). [g] Run in $CHCl_3$ (1.0 mL). [h] Run with 2 mol% of **3**.

To enhance the reaction rate, we examined the reaction in the presence of molecular sieves (MS). The addition of MS 3 Å or 4 Å enhanced the reaction rate but significantly reduced the k_{rel} values (Table S1 in the Supporting Information, entries 2 and 3). The addition of MS 5 Å further enhanced the reaction rate without much deterioration of enantioselectivity ($k_{rel} = 8$, Table 1, entry 2).[11] The oxidation in the presence of MS 5 Å proceeded in the dark at an almost equal rate with the same k_{rel} value (8 at conv. 67.9%). Complexes **3**–**7** were examined as catalysts in the presence of MS 5 Å without irradiation (Table S1, entries 5–9). Complex **3**, which has a methyl group at position C2", produced the best k_{rel} value of 21 (Table 1, entry 3).

The rate and k_{rel} values were improved, albeit slightly, when the reaction was carried out in chloroform (Table 1, entry 4). Fortunately, we found that the reaction at a lower substrate concentration (0.3 M) proceeded more rapidly with an almost equal k_{rel} value (24; Table 1, entry 5). The catalyst loading could also be reduced to 2 mol% without reducing the selectivity (Table 1, entry 6). The oxidation with 2 mol% **3** in the dark showed the same level of selectivity ($k_{rel} = 25$ at conv. 52.5%).

Under the optimized conditions, we examined the oxidation of other alcohols (Table 2). Although the reactions of *p*-, *m*-, or *o*-substituted 1-pheneylethanols proceeded with good to high k_{rel} values, *o*-substituents generally produced better enantioselectivity than *p*- or *m*- substituents, and electron-withdrawing substituents produced better results than electron-donating substituents (Table 2, entries 1–14). The maximum k_{rel} value of 60 was observed for the oxidation of 1-(*o*-bromophenyl)ethanol (Table 2, entry 8). The oxidation of 1-(1-naphthyl)ethanol gave a k_{rel} value of 24 (Table 2, entry 15). The oxidation of allylic alcohols, (*E*)-4-phenylbut-3-en-2-ol and (*E*)-3-methylhex-3-en-2-ol, proceeded with good k_{rel} values and the best solvent for this reaction was found to be ethyl acetate (Table 2, entries 16 and 17). To our delight, this method was also successfully applied to the oxidation of secondary aliphatic alcohols (Table 2, entries 18–23),

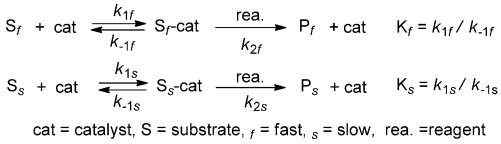
Table 2: Aerobic oxidative kinetic resolution of racemic alcohols.[a]

Entry	Substrate		Time [h]	Conv. [%][b]	ee [%][b]	$k_{rel(obs.)}$[c]
1		R = Cl	9	54.6	91.9[d]	24
2		R = Br	9	57.6	95.4[d]	21
3		R = COOMe	23	54.3	82.5[d]	16
4		R = CF_3	12	54.2	92.1[d]	26
5		R = MeO	9	59.6	83.6[d]	9
6		R = Me	7	59.6	88.5[d]	11
7		R = Cl	9	51.6	92.4[d]	46
8		R = Br	12	51.2	93.5[d]	60
9		R = MeO	24	55.4	93.1[d]	23
10		R = Me	24	53.9	94.8[d]	35
11		R = Cl	9	56.9	94.0[d]	20
12		R = Br	11	58.1	95.5[d]	20
13		R = MeO	9	65.5	98.3[d]	14
14		R = Me	11	56.9	90.3[d]	16
15		R = 1-naphthyl	15	56.2	94.7[d]	24
16[e]		R = (*E*)-	19	63.5	95.3[d]	12
17[e]		PhCH=CH	28	57.7	89.2[f]	14
		R = (*E*)-EtCH=				
		CMe				
18[g,h]		R = $PhCH_2CH_2$	25	61.4	94.3[d]	13
19[g,h]		R = cyclohexyl	24	58.2	98.3[d]	26
20[g]		R = cyclopentyl	9	52.1	86.3[d]	24
21[g,h]		R = *n*-Hexyl	11	60.9	91.5[d]	12
22[g]		R = *n*-Butyl	11	65.8	97.7[d]	12
23[g]		R = $TBSOCH_2$	15	51.2	81.5[d]	20
24			21	18.0	5.0	2
25[i]			28	66.3	95.2[j]	10

[a] Reaction conditions: $CHCl_3$ (1 mL), alcohol (0.3 mmol), **3** (6 μmol, 2 mol%), MS 5 Å (30 mg), bicyclohexyl (1 drop, internal standard), 25 °C, air, unless otherwise noted. [b] Conversion and *ee* were determined by GC analysis (see the Supporting Information). [c] Calculated by using Kagan's equation (Ref. [12a]). [d] The configuration of each slow-reacting isomer is *R* (see the Supporting Information). [e] Run with 3 mol% of **3** in EtOAc. [f] The absolute configuration is unknown. [g] Run in $ClCH_2CH_2Cl$. [h] Run with 1 mol% of **3**. [i] Run with 3 mol% of **8** in EtOAc. [j] The configuration of the slow-reacting isomer is *S* (see the Supporting Information).

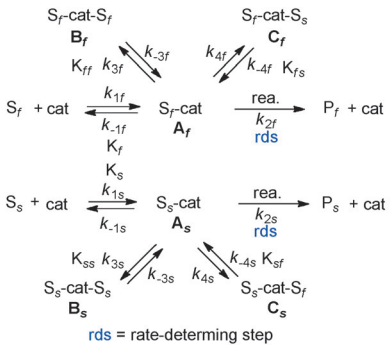
although 1,2-dichloroethane was the solvent of choice for these reactions. The oxidations of 1-cyclohexylethanol and 1-cyclopentylethanol gave high k_{rel} values of 26 and 24, and good k_{rel} values of 12 were obtained even in the oxidations of 2-octanol and 2-hexanol. However, the cyclic alcohol 1-indanol was oxidized with only a modest k_{rel} value (Table 2, entry 24). Fortunately, however, the efficiency of the KR was increased to $k_{rel} = 10$ by using complex **8**, a diastereomer of **2**, as the catalyst in ethyl acetate (Table 2, entry 25).

We further investigated the dependence of the rate on substrate concentration that was observed during the optimization of the reaction conditions (Table 1, entries 4 and 5). The rate of a catalytic reaction depends not only on catalytic activity but also on the reaction pattern. In many metal-catalyzed reactions, the catalyst and substrate (or reagent) are in equilibrium with a catalyst–substrate (or catalyst–reagent) complex, which reacts with the reagent (or substrate) to give the product [Eq. (1) and Eq. (S1) in the Supporting Information]. This type of reaction shows a first order dependence on substrate concentration and Kagan's equation[12] can be applied; however, the observed k_{rel} is not k_{2f}/k_{2s} but rather $k_{2f}K_f/k_{2s}K_s$.[13] This equation seems to agree with the reaction mechanism described in Scheme 1, as long as substrate concentration is constant.



(1)

If the catalyst has two empty coordination sites, the substrate–catalyst complex is coordinatively unsaturated, and if the product formation step is slow, active species **A** can be pre-equilibrated with catalytically inactive species (**B** and **C**), to which dioxygen cannot coordinate, and the reaction suffers substrate inhibition [Eq. (2)].[14] Since the SET step is the rate-determining step (Scheme 1),[4c] we speculated that this type of substrate inhibition would be responsible for the dependence of the rate on substrate concentration. The extent of substrate inhibition should increase with substrate concentration.



(2)

We therefore measured the rate of the oxidation of racemic 1-phenylethanol at several different concentrations

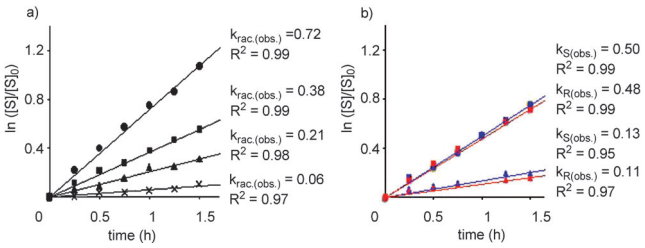
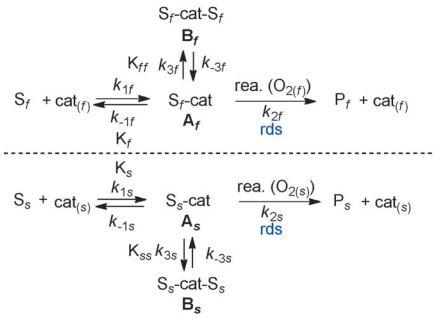


Figure 1. Initial rates of 1-phenylethanol oxidation when using **3** (6 μmol) in the presence of MS 5 Å (30 mg) in $CHCl_3$ under air at different substrate concentrations. a) Racemic 1-phenylethanol; ● $[S]_0 = 0.10$ M; ■ $[S]_0 = 0.15$ M; ▲ $[S]_0 = 0.2$ M, × $[S]_0 = 0.3$ M. (b) (*S*)- and (*R*)-1-Phenylethanols; (*S*)-isomer, blue ■ $[S]_0 = 0.15$ M; blue ▲ $[S]_0 = 0.3$ M. (*R*)-isomer, red ■ $[S]_0 = 0.15$ M; red ▲ $[S]_0 = 0.3$ M.

and observed that the oxidation rate increased at lower concentrations, (Figure 1 a, competitive experiment). The obtained result is consistent with the above speculation [Eq. (2)]: the reaction rates of the fast and slow isomers are $v_f = k_{2f}[\mathbf{A}_f][O_2]$ and $v_s = k_{2s}[\mathbf{A}_s][O_2]$ and the pre-equilibrium constants K_f and K_s are $K_f = [\mathbf{A}_f]/[S_f][cat]$ and $K_s = [\mathbf{A}_s]/[S_s][cat]$, respectively, wherein [cat] and $[O_2]$ are the same in the reactions of the fast and slow isomers. Accordingly, $v_f/v_s = k_{2f}[\mathbf{A}_f]/k_{2s}[\mathbf{A}_s] = k_{2f}K_f[S_f]/k_{2s}K_s[S_s]$.[15] The observed relative rate constant $[k_{rel}(obs.) = k_f\ (obs.)/k_s\ (obs.)]$ is $k_{2f}K_f/k_{2s}K_s$. Indeed, $k_{rel}(obs.)$ was constant during the reaction (Figure S2 in the Supporting Information). However, the reaction rate $(v_f + v_s)$ becomes slower as the substrate concentration increases because of a decrease in the concentrations of $\mathbf{A}_f$ and $\mathbf{A}_s$ owing to substrate inhibition.[15]



(3)

To further confirm the participation of pre-equilibriation in this oxidation, we then measured the reaction rate and the relative reaction rate in a noncompetitive experiment [Eq. (3) and Figure 1 b). In the noncompetitive experiment, pre-equilibration between **A** and **C** should not be possible and the influence of substrate inhibition on the reaction rate should be smaller than in the competitive experiment. This was consistent with the experimental result (Figure 1). Moreover, [cat] and $[O_2]$ are not the same in the reactions of the fast and slow isomers. The reaction rate for the fast isomer is $v_f = k_{2f}[\mathbf{A}_f][O_{2(f)}]$. Since the total catalyst concentration $[cat]_0$ is equal to the concentration of free catalyst $[cat_{(f)}]$ plus the concentrations of the substrate-bound complexes ($\mathbf{A_f}$ and $\mathbf{B_f}$): $[cat]_0 = [cat_{(f)}] + [\mathbf{A}_f] + [\mathbf{B}_f]$. Accordingly, $[\mathbf{A}_f] = [cat]_0/\{1+1/$

$K_f[S_f] + K_{ff}[S_f]\}$ (for the fast isomer) and $[\mathbf{A}_s] = [cat]_0/\{1+1/K_s[S_s] + K_{ss}[S_s]\}$ (for the slow isomer). Thus, $v_f/v_s = k_{2f}\{1+1/[S_s]K_s + [S_s]K_{ss}\}[O_{2(f)}]/k_{2s}\{1+1/[S_f]K_f + [S_f]K_{ff}\}[O_{2(s)}]$.[15] The terms $\{1 + 1/K_{f(or\ s)} + [S]K_{ff(or\ ss)}\}$ show the substrate inhibition by the fast and slow isomers, respectively. This equation indicates that the relative reaction rate (k_{2f}/k_{2s}) and the relative substrate inhibition observed for the slow- and fast-isomer reactions might cancel out. Indeed, the relative reaction rates determined by the oxidation of (*S*)- and (*R*)-1-phenylethanols was as small as 1.04–1.18, although the relative reaction rate observed in the oxidation of the racemate was 23.

The above discussion is premised on the fact that SET is the rate-determining step for the oxidation with **1** under irradiation. We thus investigated the kinetics and KIE for the alcohol oxidation when using **3** without irradiation, to ascertain whether the oxidation with **3** follows the same reaction pathway as that with **1** under irradiation (Scheme 1). The KIE values for the oxidation of benzyl alcohol when using **3** as the catalyst were determined to be 6.27 and 1.18 by using an intermolecular competitive experiment and an intermolecular noncompetitive experiment, respectively (Table S2).[16] These KIE values indicate that this oxidation process includes a hydrogen-atom transfer (HAT) step[17] but the HAT step is not the rate-determining step.[4c] On the other hand, the kinetics study showed that the oxidation is first order with respect to catalyst and oxygen.[18] These results indicate that the reactions with **1** and **3** follow an identical reaction pathway and that SET is the rate-determining step.[4c,19]

In summary, we have developed a highly efficient oxidative kinetic resolution of activated and unactivated secondary alcohols that makes use of an [(aqua)Ru(salen)] complex (**3**) as the catalyst and air as the hydrogen acceptor at room temperature. Increased substrate concentration was found to negatively affect the oxidation rate, a result ascribed to substrate inhibition based on the measurement of the relative reaction rates in competitive and noncompetitive experiments. To our knowledge, this is the first report that addresses the influence of substrate inhibition on the relative reaction rate of kinetic resolution.

Experimental Section

General procedure for the OKR of secondary alcohols: Racemic secondary alcohol (0.3 mmol), $CHCl_3$ (1.0 mL), one drop of bicyclohexyl as an internal standard for GC analysis, and MS 5 Å (30 mg) were placed in a test tube at 25 °C under air. After stirring for 30 min, **3** (5.1 mg, 6 μmol) was added to the mixture and aliquots (20 μL each) of this suspension were removed immediately after the addition, as the time-point zero sample, and then at appropriate intervals of time. Each aliquot (20 μL) was diluted with MeOH (0.6 mL) and submitted to GC analysis with a chiral column to determine the conversion and *ee* values.

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Keywords: aerobic oxidation · asymmetric catalysis · dioxygen · kinetic resolution · ruthenium

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[18] See the Supporting Information (Figures S3 and S4).
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