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Photoactivated Racemization Catalyst for Dynamic Kinetic Resolution of Secondary Alcohols

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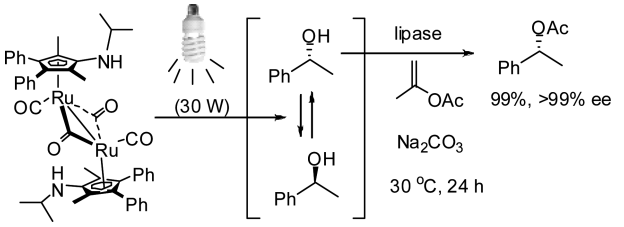

Household fluorescent light activates a diruthenium complex to generate catalytic species highly active for the racemization of secondary alcohols under ambient conditions. This catalyst system is applicable for the chemoenzymatic dynamic kinetic resolution of racemic alcohols to give optically pure acetates under mild conditions.

Enzymatic kinetic resolution is still an important and economical tool for producing optically active compounds, although it has an intrinsic drawback of yielding a maximum of 50% of the desired enantiomer.[1] Methods of racemizing the recovered and undesired enantiomers can improve the efficiency of kinetic resolution. It is more desirable that the racemization can be achieved in situ during the kinetic resolution. That is, dynamic kinetic resolution (DKR) provides single enantiomers from a racemic mixture with yields approaching 100%.[2] Thus, many researchers have focused on developing efficient chemoenzyamtic DKR, which requires racemization catalysts compatible with the conditions for enzymatic resolution.[3]

Various ruthenium complexes (**2**−**5**) have been reported as effective racemization catalysts for the chemoenzyamtic DKR of secondary alcohols since the Shvo complex (**1**) was successfully employed by Bäckvall and co-workers.[4] The DKR using **1** requires a special acyl donor such as *p*-chlorophenyl acetate, ketone additive, and a thermostable lipase at high temperature under anaerobic conditions. The use of a monomeric ruthenium complex **2** or **3**, which is highly active at room temperature, has remarkably improved the efficiency of chemoenzymatic DKR.[5] Advantageous acyl donors such as isopropenyl acetate and thermally labile enzymes such as subtilisin can be used with them for the DKR at room temperature.[6] The success of **2** led to the development of its analogues **3**−**5** displaying good racemization activities at ambient temperature. It is noticeable that the DKR with **4** or **5** can be carried out at room temperature without caution when exposed to air.[7] However, the activation step using a strong base such as potassium *t*-butoxide is required to generate active species from **2**[5,6a] and **3**.[8]

The racemization using **4** and **5** also requires inorganic bases such as potassium carbonate and potassium phosphate.[7] Here we describe an interesting finding of a highly active catalyst system for the racemization of secondary alcohols in the absence of base. In addition, this catalyst system is the first case that provides catalytic species active for the racemization of alcohols using light: (*S*)-1-phenylethanol was racemized within 10 min using 2.0 mol % of **6a** simply by illuminating household 30 W fluorescent light under ambient conditions. Delightfully, the catalytic racemization was also applicable for the chemoenzymatic DKR of secondary alcohols (Schemes 1 and 2).

The diruthenium complex **6a** was synthesized through a procedure similar to that for a *N*-phenyl analogue (**6b**).[9] Recrystallization of **6a** from a solution of dichloromethane and hexane provided crystals suitable for X-ray diffraction analysis.[10] The molecular structure of **6a** is almost same as that of **6b**, which has a Ru−Ru bond, two bridged CO, and translocated cyclopentadienyl rings.[11]

The photoinduced activity of **6a** was examined for the racemization of (*S*)-1-phenylethanol and compared with those of related ruthenium and iron complexes (Table 1). Benzene and tetrahydrofuran (THF) were better solvents than toluene and acetone (entries 1−4). Under solventless conditions, complete racemization was achieved using 0.1 mol %

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(3) (a) Pàmies, O.; Bäckvall, J. E. *Chem. Rev.* **2003**, *103*, 3247. (b) Martín-Matute, B.; Bäckvall, J. E. *Curr. Opin. Chem. Biol.* **2007**, *11*, 226. (c) Lee, J. H.; Han, K.; Kim, M.-J.; Park, J. *Eur. J. Org. Chem.* **2010**, 999.
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(10) See Supporting Information.
(11) CCDC 764257 contains the supplementary crystallographic data for **4a**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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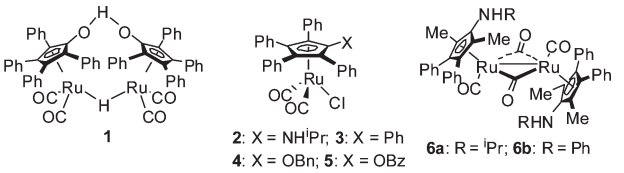
SCHEME 1. Racemization Catalyst



SCHEME 2. Synthesis of 6a and DKR of 1-Phenylethanol

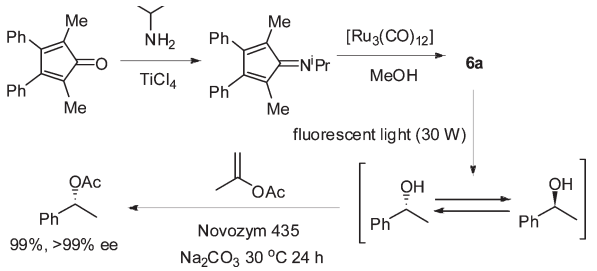
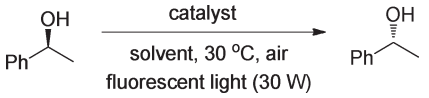


TABLE 1. Racemization of (*S*)-1-Phenylethanol[a]

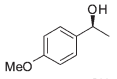
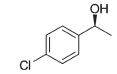
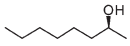


entry	catalyst	solvent	*t* (min)	ee[b](%)	yield[c](%)
1	**6a**	benzene	10	0.8	97.0
2	**6a**	THF	10	3.0	96.8
3	**6a**	toluene	10	21.2	95.6
4	**6a**	acetone	10	47.2	95.7
5	**6a**	none	360	3.9[d]	97.0
6	**6a**	benzene	1200	99.9[e]	99.9
7	**6a**	benzene	1200	89.8[f]	97.7
8	**6b**	benzene	10	89.3	96.0
9	**6b**	THF	10	2.4	96.9
10	$[Cp^*Ru(CO)_2]_2$	benzene	20	1.7	94.7
11	$[CpRu(CO)_2]_2$	benzene	720	62.5	89.7
12	$[CpFe(CO)_2]_2$	benzene	1200	98.0	97.8

[a]A solution of (*S*)-1-phenylethanol (>99% ee, 0.25 mmol) and catalyst (2.0 mol %) was illuminated with fluorescent light (30 W) at 30 °C. [b]Measured by HPLC equipped with a chiral column (Chiral OD, Daicel). [c]The intensities of 1-phenylethanol and acetophenone were measured by GC equipped with a TR-WAX column. [d](*S*)-1-Phenylethanol (>99% ee, 0.60 mL, 5.0 mmol) without solvent was reacted with **6a** (4.6 mg, 0.10 mol %). [e]The reaction was carried out in the dark. [f]The reaction was carried out in the dark at 50 °C.

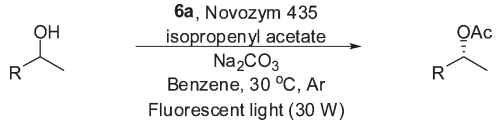
of **6a**, although it took 6 h (entry 5). In the absence of light, **6a** was inactive at 30 °C (entry 6). Thermal activation of **6a** was negligible at 50 °C in the dark (entry 7). The racemization using **6b** was much slower than that using **6a** in benzene due to its poor solubility, while the former was comparable to the latter in THF (entries 8 and 9). Pentamethylcyclopentadienylruthenium dicarbonyl dimer ($[Cp^*Ru(CO)_2]_2$) showed an activity less than a half of that of **6a** (entry 10).[12] Cyclopentadienylruthenium dicarbonyl dimer ($[CpRu(CO)_2]_2$) showed a poor activity (entry 11),[13] while its iron analogue ($[CpFe(CO)_2]_2$) was practically inactive (entry 12).[14]

TABLE 2. Racemization of Secondary Alcohols[a]

entry	alcohol	*t*	ee[b][%]	yield[c][%]
1		5 min	3.8	94.6
2		45 min	3.6	92.0
3		20 min	3.9[d]	97.7

[a]A solution of (*S*)-alcohol (>99% ee, 0.25 mmol) and **6a** (2.0 mol %) in benzene (0.80 mL) was illuminated with fluorescent light (30 W) at 30 °C. [b]Measured by HPLC equipped with a chiral column (Chiral OD, Daicel). [c]Measured by GC equipped with a TR-WAX column. [d]Determined by GC after conversion to 2-octyl acetate.

TABLE 3. Dynamic Kinetic Resolution of Secondary Alcohols[a]



entry	alcohol	*t* (h)	yield[b] (%0	ee[c] (%)
1	1-phenylethanol	24	59[d,e]	>99
2	1-phenylethanol	24	56[d,f]	>99
3	1-phenylethanol	24	96	>99
4	1-(4-methoxyphenyl)ethanol	24	90	>99
5	1-(4-chlorophenyl)ethanol	36	97	>99
6	2-octanol	24	84	97

[a]Sodium carbonate (1 equiv) and CALB (4 mg/mmol) were added into a solution of alcohol (1.00 mmol), isopropenyl acetate (1.5 equiv), and **6a** (2 mol %) in degassed benzene (3.2 mL) under argon, and the resulting mixture was illuminated with fluorescent light (30 W) at 30 °C. [b]Isolated yield. [c]Determined by GC equipped with a chiral column (*β*-DEX-TM). [d]The reaction was performed in 0.25 mmol scale, and the yield was measured by GC. [e]Without Na_2CO_3. [f]The reaction was performed exposed to air without caution.

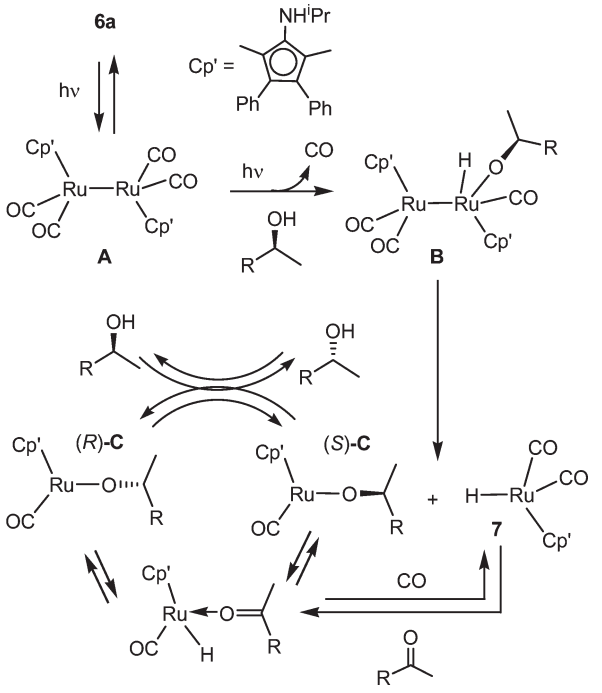
The racemization using **6a** under fluorescent light was tested for several (*S*)-alcohols (Table 2). A benzylic alcohol having an electron-donating substituent on the phenyl ring was racemized faster than that having an electron-withdrawing one (entries 1 and 2). An aliphatic alcohol, 2-octanol, was racemized a little faster than the latter (entry 3). The catalyst system was tested for the DKR of secondary alcohols (Table 3). *Candida antarctica* lipase B (CALB; trade name Novozym 435) immobilized on acrylic resin was employed for the enzymatic acylation of the alcohols. Although the DKR without base (entry 1) or in the air (entry 2) was not successful,[15] employing sodium carbonate under anaerobic conditions gave good results in the DKR of benzylic alcohols (entries 3−5) as well as in that of 2-octanol (entry 6).

Although detailed studies are required for the mechanism, a pathway for the catalytic racemization is proposed in Scheme 3 on the basis of the chemistry for the ruthenium complexes related to **6a** and the factors that affect the racemization. The photochemistry of $[CpRu(CO)_2]_2$ has been extensively studied,[16] and its photolysis at low energy (λ > 400

(12) $[Cp^*Ru(CO)_2]_2$ was prepared according to the literature procedure: King, R. B.; Iqbal, M. Z.; King, J. A. D. *J. Organomet. Chem.* **1979**, *171*, 53.
(13) $[CpRu(CO)_2]_2$ was prepared according to the literature procedure: Humphries, A. P.; Knox, S. A. R. *J. Chem. Soc., Dalton Trans.* **1975**, 1710.
(14) $[CpFe(CO)_2]_2$ was purchased from Strem Chemicals and used as received.

(15) It is known that acetic acid formed during DKR inhibits the racemization: see ref 5b.
(16) (a) Bitterwolf, T. E. *Coord. Chem. Rev.* **2000**, *419*, 206–207. (b) Bitterwolf, T. E.; Linehan, J. C.; Shade, J. E. *Organometallics* **2000**, *19*, 4915.

SCHEME 3. Proposed Pathway for the Photoinduced Racemization of Secondary Alcohols



nm) results in the homolysis of the Ru−Ru bond through the opening of the bridged form to the *trans* terminal form, as in intermediate **A**.[16a] In order to check the possibility of radical intermediates,[17] we tested the racemization of (*S*)-1-phenylethanol in the presence of radical scavengers such as 2,2,6,6-tetramethylpiperinyloxy radical (TEMPO) and 2,6-di-*tert*-butyl-4-methylphenol (BHT). In the case using TEMPO (1.0 equiv), the racemization was somewhat slower (6.7% ee after 30 min) than that without it, forming acetophenone in 30% yield. However, no effect was observed in the case using BHT (1.0% ee after 10 min). Meanwhile, the presence of CO (1 atm) stopped the racemization (92% ee after 10 min; 92% ee after 30 min).[16a] Thus, before the homolysis of the Ru−Ru bond, intermediate **A** would react with an alcohol with the dissociation of the CO ligand to give intermediate **B**. Then, the real catalytic species **C** and ruthenium hydride **7** are formed from **B**. In fact, ruthenium hydride **7** was observed in the reaction mixture during the racemization.[18,19] The interconversion between (*R*)-**C** and (*S*)-**C** can occur through reversible β-hydride elimination and insertion reaction, and the racemization is realized through the alkoxide exchange. Recently, Bäckvall and co-workers suggested an analogous ruthenium alkoxide as the key intermediate for the racemization of alcohols using **3** on the basis of density functional calculations.[20] It is notable that the illumination is not necessary after the generation of **B** or **C**.[21] The ruthenium hydride **7** can also be formed during the racemization, producing ketone as the byproduct, but the reverse reaction can possibly regenerate **C**.[5b,22]

In summary, we have found a simple and efficient catalyst system for the racemization of secondary alcohols, which consists of household fluorescent light and a diruthenium complex stable under amibient conditions. Using this catalyst system, we have demonstrated the chemoenzymatic DKR of various secondary alcohols under mild conditions.

Experimental Section

Racemization of (*S*)-1-Phenylethanol: To a solution of **6a** (4.6 mg, 2.0 mol %) in dry benzene (0.8 mL) in a 4 mL vial was added (*S*)-1-phenylethanol (>99% ee, 0.25 mmol). The reaction mixture was placed about 10 cm from a 30 W fluorescent lamp and illuminated with stirring at 30 °C. The ee value was measured by HPLC equipped with a chiral column (Chiral OD, Daicel).

Dynamic Kinetic Resolution of 1-Phenylethanol: To a 50 mL flask equipped with a grease-free high-vacuum stopcock were added **6a** (18.4 mg, 0.020 mmol) and degassed benzene (3.2 mL, 0.30 M). The flask was filled with argon and stirred for 10 min. Then, Novozym 435 (4.0 mg), Na_2CO_3 (104 mg, 1.00 mmol), 1-phenylethanol (120 μL, 1.00 mmol), and isopropenyl acetate (168 μL, 1.5 mmol) were added sequentially. The resulting red-brown suspension was placed about 10 cm from a 30 W fluorescent lamp and illuminated with stirring at 30 °C for 24 h. The reaction mixture was concentrated and purified by chromatography on a silica gel column (ethyl acetate/hexane = 1/8) to give (*R*)-1-phenylethylacetate (156 mg, 95% yield, >99% ee).

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Supporting Information Available: Experimental details. Preparation and characterization of compounds **6a**, [Cp*Ru(CO)$_2$]$_2$, and [CpRu(CO)$_2$]$_2$. X-ray analysis of complex **6a**. This material is available free of charge via the Internet at http://pubs.acs.org.

(17) Photoredox catalysis with visible light attracts much attention of organic chemists due to its efficiency and practical advantages: Zeitler, K. *Angew. Chem., Int. Ed.* **2009**, *48*, 9785–9789. and references therein.

(18) The characteristic hydride peak for **5** was observed at −9.6 ppm in the reaction mixture (C_6D_6) by ^{1}H NMR.

(19) The corresponding ruthenium chloride complex was recovered in 81% yield by the reaction with $CHCl_3$ after the racemization.

(20) Nyhlén, J.; Privalov, T.; Bäckvall, J.-E. *Chem.—Eur. J.* **2009**, *15*, 5220.

(21) The racemization continued in the dark after generating active species with fluorescent light. The racemization was almost completed after 30 min (1.0% ee) when the illunination was discontinued after 5 min (48.7% ee).

(22) Martín-Matute, B.; Edin, M.; Bogár, K.; Kaynak, F. B.; Bäckvall, J.-E. *J. Am. Chem. Soc.* **2005**, *127*, 8817–8825.