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# Oxidative Kinetic Resolution of Racemic Alcohols Catalyzed by Chiral Ferrocenyloxazolinylphosphine−Ruthenium Complexes

Yoshiaki Nishibayashi, Akiyoshi Yamauchi, Gen Onodera, and Sakae Uemura*

*Department of Energy and Hydrocarbon Chemistry, Graduate School of Engineering, Kyoto University, Yoshida, Sakyo-ku, Kyoto 606-8501, Japan*

*uemura@scl.kyoto-u.ac.jp*

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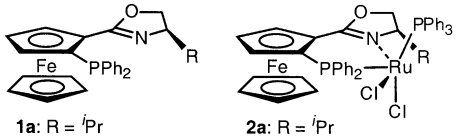
Oxidative kinetic resolution of racemic secondary alcohols by using acetone as a hydrogen acceptor in the presence of a catalytic amount of [$RuCl_2(PPh_3)$(ferrocenyloxazolinylphosphine)] (**2**) proceeds effectively to recover the corresponding alcohols in high yields with an excellent enantioselectivity. When 1-indanol is employed as a racemic alcohol, the oxidation proceeds quite smoothly even in the presence of 0.0025 mol % of the catalyst **2** to give an optically active 1-indanol in good yield with high enantioselectivity (up to 94% ee), where turnover frequency (TOF) exceeds 80 000 $h^{-1}$. From a practical viewpoint, the kinetic resolution is investigated in a large scale, optically pure (*S*)-1-indanol (75 g, 56% yield, >99% ee) being obtained from racemic 1-indanol (134 g) by employing this kinetic resolution method twice.

## Introduction

The oxidation of alcohols is one of the most common and well-studied reactions in organic chemistry.[1] Highly efficient and selective oxidative methods of alcohols to the corresponding ketones, aldehydes, and carboxylic acids have been developed.[2] We have also found the selective palladium-catalyzed oxidation of alcohols with molecular oxygen as an oxidant.[3] Application of these oxidation methods to kinetic resolution of racemic alcohols might give optically active alcohols together with carbonyl compounds. However, there are only a few successful examples of catalytic enantioselective methods for this purpose,[4] in sharp contrast to so-far well-known excellent catalytic enantioselective methods for epoxidation,[5] dihydroxylation,[6] and aziridination,[7] all involving oxidation processes.

Since the first preparation of optically active *f*errocenyl*oxa*zolinyl*p*hosphines (Chart 1; **1**; we abbreviate these to FOXAP) by us in 1995,[8,9] we have developed many enantioselective reactions catalyzed by various transition

**CHART 1**




**1a**: R = $^i$Pr
**1b**: R = Ph
FOXAP (**1**)

**2a**: R = $^i$Pr
**2b**: R = Ph
[$RuCl_2(PPh_3)$(FOXAP)] (**2**)

* Corresponding author.

(1) For examples, see: (a) Sheldon, R. A.; Kochi, J. K. *Metal-Catalyzed Oxidations of Organic Compounds*; Academic Press: New York, 1984. (b) Hudlicky, M. *Oxidations in Organic Chemistry*; ACS Monograph Series 186; American Chemical Society: Washington, DC, 1990.

(2) Selected examples, see: (a) Markó, I. E.; Giles, P. R.; Tsukazaki, M.; Brown, S. M.; Urch, C. J. *Science* **1996**, *274*, 2044. (b) Sato, K.; Aoki, M.; Takagi, J. Noyori, R. *J. Am. Chem. Soc.* **1997**, *119*, 12386. (c) Markó, I. E.; Giles, P. R.; Tsukazaki, M.; Chelle-Regnaut, I.; Urch, C. J.; Brown, S. M. *J. Am. Chem. Soc.* **1997**, *119*, 12661. (d) Hanyu, A.; Takezawa, E.; Sakaguchi, S.; Ishii, Y. *Tetrahedron Lett.* **1998**, *39*, 5557. (e) Brink, G.-J.; Arends, I. W. C. E.; Sheldon, R. A. *Science* **2000**, *287*, 1636. (f) Dijksman, A.; Marino-González, A.; Payeras, A. M.; Arends, I. W. C. E.; Sheldon, R. A. *J. Am. Chem. Soc.* **2001**, *123*, 6826. (g) Son, Y.-C.; Makwana, V. D.; Howell, A. R.; Suib, S. L. *Angew. Chem., Int. Ed.* **2001**, *40*, 4280. (h) Mori, K.; Yamaguchi, K.; Hara, T.; Mizugaki, T.; Ebitani, K.; Kaneda, K. *J. Am. Chem. Soc.* **2002**, *124*, 11572. (i) Yamaguchi, K.; Mizuno, N. *Angew. Chem., Int. Ed.* **2002**, *41*, 4538.

(3) (a) Nishimura, T,; Onoue, T.; Ohe, K.; Uemura, S. *J. Org. Chem.* **1999**, *64*, 6750. (b) Nishimura, T.; Maeda, Y.; Kakiuchi, N.; Uemura, S. *J. Chem. Soc., Perkin Trans.* 1 **2000**, 4301. (c) Kakiuchi, N.; Nishimura, T.; Inoue, M.; Uemura, S. *Bull. Chem. Soc. Jpn.* **2001**, *74*, 165. (d) Kakiuchi, N.; Maeda, Y.; Nishimura, T.; Uemura, S. *J. Org. Chem.* **2001**, *66*, 6620.

(4) (a) Hashiguchi, S.; Fujii, A.; Haack, K.-J.; Matsumura, K.; Ikariya, T.; Noyori, R. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 288. (b) Masutani, K.; Uchida, T.; Irie, R.; Katsuki, T. *Tetrahedron Lett.* **2000**, *41*, 5119. (c) Jensen, D. R.; Pugsley, J. S.; Sigman, M. S. *J. Am. Chem. Soc.* **2001**, *123*, 7475. (d) Ferreira, E. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2001**, *123*, 7725. (e) Sun, W.; Wang, H.; Xia, W. C.; Li, J.; Zhao, P. *Angew. Chem., Int. Ed.* **2003**, *42*, 1042. (f) Rychnovsky, S. D.; McLernon, T. L.; Rajapakse, H. *J. Org. Chem.* **1996**, *61*, 1194.

(5) For examples, see: (a) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974. (b) Hanson, R. M.; Sharpless, K. B. *J. Org. Chem.* **1986**, *51*, 1922. (c) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765.

(6) For examples, see: (a) Hentges, S. G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 4263. (b) Jacobsen, E. N.; Markó, I.; Mungall, W. S.; Schröder, G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 1968.

(7) For examples, see: (a) Evans, D. A.; Woerpel, K. A.; Hinman, M. M.; Faul, M. M. *J. Am. Chem. Soc.* **1991**, *113*, 726. (b) Li, Z.; Conser, K. R.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1993**, *115*, 5326. (c) Nishioka, H. Katsuki, T. *Tetrahedron Lett.* **1996**, *37*, 9245.

(8) (a) Nishibayashi, Y.; Uemura, S. *Synlett* **1995**, 79. (b) Nishibayashi, Y.; Segawa, K.; Arikawa, Y.; Ohe, K.; Hidai, M.; Uemura, S. *J. Organomet. Chem.* **1997**, *545*−*546*, 381 and references therein. (c) Borman, S. *Chem. Eng. News* **1996**, July 22, 38. (d) A ferrocenyloxazolinylphosphine (**1a**) is commercially available from Wako Pure Chemical Industries (Japan) as ip-FOXAP (*f*errocenyl*oxa*zolinyl*p*hosphine).

(9) The first preparation of optically active ferrocenyloxazolinylphosphines was independently reported by our group[8a] and Richards et al.[9a] (a) Richards, C. J.; Damalidis, T.; Hibbs, D. E.; Hurshouse, M. B. *Synlett* **1995**, 74. (b) Richards, C. J.; Mulvaney, A. W. *Tetrahedron: Asymmetry* **1996**, *7*, 1419. Independently, Sammakia et al. reported the diastereoselective lithiation of oxazolinylferrocenes.[9c−e] (c) Sammakia, T.; Latham, H. A.; Schaad, D. R. *J. Org. Chem.* **1995**, *60*, 10. (d) Sammakia, T.; Latham, H. A. *J. Org. Chem.* **1995**, *60*, 6002. (e) Sammakia, T.; Latham, H. A. *J. Org. Chem.* **1996**, *61*, 1629.

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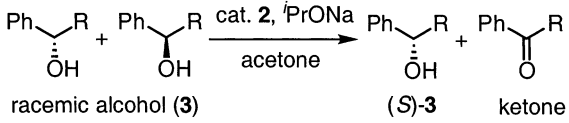
metal complexes having FOXAP as chiral ligands. Rh- and Ir-catalyzed asymmetric hydrosilylation of prochiral ketones has been found to afford the corresponding chiral alcohols after acid hydrolysis.[10] It is noteworthy that the chiral alcohols of the opposite configuration were produced from the same ketones by changing Rh to Ir.[10] The chiral FOXAP has been found to be effective ligands for the Ir-catalyzed asymmetric hydrosilylation of prochiral imines to give secondary amines with high enantioselectivities.[11] In addition, we have prepared the ruthenium complexes having FOXAP and investigated the asymmetric Ru-catalyzed hydrosilylation of prochiral ketones, imines, and ketoximes to give the corresponding chiral secondary alcohols, secondary amines, and primary amines with high enantioselectivities, respectively.[12,13] Optically active FOXAP has been found to work effectively as chiral ligands in Ni-catalyzed cross-coupling reactions of allylic compounds with arylboronic acids and Grignard reagents, which are known to behave as hard nucleophiles, to give the expected coupling products in good yields with a high enantioselectivity.[14,15] More recently, we disclosed the kinetic resolution of racemic alcohols via Pd-catalyzed enantioselective acylation using CO and organobismuth compound, although the enantioselectivities of the produced esters were moderate.[16]

In our continuing study, we have found the enantioselective redox reaction of ketones and alcohols catalyzed by [$RuCl_2(PPh_3)$(FOXAP)] (Chart 1; **2**).[17,18] In the presence of a catalytic amount of **2**, transfer hydrogenation of prochiral ketones proceeded effectively to give the corresponding chiral alcohols with an extremely high enantioselectivity (up to 99.9% ee), while asymmetric oxidation of racemic secondary alcohols occurred to lead to the kinetic resolution of the alcohols with similar high enantioselectivity.[17a] It is noted that the chiral alcohols of the opposite configuration were obtained by using this redox reaction in the presence of **2a**. For example, (*R*)-1-phenylethanol (**3a**) was produced in the transfer hydrogenation of acetophenone with $^i$PrOH. On the other hand, (*S*)-1-phenylethanol (**3a**) was recovered in kinetic resolution of racemic **3a** with acetone. In the latter oxidation system, acetone worked as an oxidant of alcohols in the presence of **2**. This preliminary result prompted us to investigate this oxidative kinetic resolution in more detail, because acetone is considered to be one of the most appreciable oxidant from economical and environmental viewpoints. In this paper, we will describe the detailed results of the **2**-catalyzed oxidative kinetic resolution of racemic secondary alcohols in acetone.

**SCHEME 1**




## Results and Discussion

Treatment of racemic 1-phenylethanol (**3a**) (1 mmol) in the presence of a catalytic amount of **2a** (0.25 mol %) and $^i$PrONa (1.00 mol %) in anhydrous acetone (10 mL) at 50 °C for 30 min afforded a mixture of 1-phenylethanol (53% yield with 93% ee) and acetophenone (47% yield) (Scheme 1; Table 1, run 1). The absolute configuration of the recovered 1-phenylethanol is *S*, and the turnover frequency (TOF) was 400 $h^{-1}$. In the absence of $^i$PrONa, no reaction occurred at all. The reaction proceeded even at room temperature, but the efficiency of the kinetic resolution was lower than that of the reaction at 50 °C. The ratio of substrate and catalyst (S/C) could be increased up to 1200, and thus, the reaction using **3a** (3 mmol) at 50 °C for 30 min gave chiral **3a** (53% yield with 97% ee) and acetophenone (47% yield) (Table 1, run 4). The TOF in this reaction was 1200 $h^{-1}$. However, when S/C ratio was increased to 1600, only moderate enantioselectivity of the recovered **3a** was obtained (Table 1, run 5), indicating that the S/C is one of the important factors to achieve the high efficiency of the kinetic resolution. In the oxidation of **3a** at 50 °C for 150 min under the same reaction conditions using **2b** as a catalyst, the unreacted alcohol was obtained in 48% yield with 95% ee (*S*) together with acetophenone in 52% yield (Table 1, run 2). The oxidation using **2b** proceeded more slowly than that using **2a**.

Asymmetric oxidation of a variety of secondary alcohols proceeded with high enantioselectivity. Typical results are also shown in Table 1. Reactions of racemic benzylic alcohols such as 1-phenyl-1-propanol (**3b**), 1-phenyl-1-butanol (**3c**), 1-phenyl-1-pentanol (**3d**), 1-phenyl-1-hexanol (**3e**), and 1-phenyl-1-heptanol (**3f**) were investigated at 50 °C for 30 min (Table 1, runs 6−11). In all cases, the corresponding unreacted alcohols were recovered in high yields with an excellent enantioselectivity. Interestingly, the reaction of 2-methyl-1-phenyl-1-propanol (**3g**) did not proceed at all (Table 1, run 12). On the other hand, the reaction of cyclopropylphenylmethanol (**3h**) proceeded smoothly, but moderate enantioselectivity of the recovered alcohol was observed (Table 1, run 13).

Next, reactions of phenylethanol derivatives were investigated under the same conditions as above (S/C = 1000). Typical results are shown in Table 2. Introduction of a *p*-halogeno or *p*-methyl substituent to the aromatic ring of phenylethanol slightly decreased the reactivity and selectivity (Table 2, runs 1−4). In contrast, introduction of a *p*-methoxy substituent to the aromatic ring of

(10) (a) Nishibayashi, Y.; Segawa, K.; Ohe, K.; Uemura, S. *Organometallics* **1995**, *14*, 5486. (b) Nishibayashi, Y.; Segawa, K.; Takada, H.; Ohe, K.; Uemura, S. *Chem. Commun.* **1996**, 847.

(11) Takei, I.; Nishibayashi, Y.; Arikawa, Y.; Uemura, S.; Hidai, M. *Organometallics* **1999**, *18*, 2271.

(12) Nishibayashi, Y.; Takei, I.; Uemura, S.; Hidai, M. *Organometallics* **1998**, *17*, 3420.

(13) Takei, I.; Nishibayashi, Y.; Ishii, Y.; Mizobe, Y.; Uemura, S.; Hidai, M. *Chem. Commun.* **2001**, 2360.

(14) Chung, K.-G.; Miyake, Y.; Uemura, S. *J. Chem. Soc., Perkin Trans. 1* **2000**, 15.

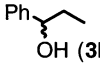
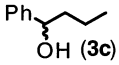
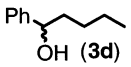
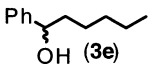
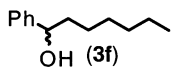
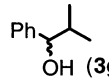
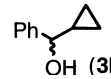
(15) Chung, K.-G.; Miyake, Y.; Uemura, S. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2725.

(16) (a) Miyake, Y.; Iwata, T.; Chung, K.-G.; Nishibayashi, Y.; Uemura, S. *Chem. Commun.* **2001**, 2584. (b) Iwata, T.; Miyake, Y.; Nishibayashi, Y.; Uemura, S. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1548.

(17) (a) Nishibayashi, Y.; Takei, I.; Uemura, S.; Hidai, M. *Organometallics* **1999**, *18*, 2291. (b) Arikawa, Y.; Ueoka, M.; Matoba, K.; Nishibayashi, Y.; Hidai, M.; Uemura, S. *J. Organomet. Chem.* **1999**, *572*, 163.

(18) Sammakia et al. previously reported the asymmetric transfer hydrogenation of alkyl aryl ketones using the catalyst prepared in situ from $RuCl_2(PPh_3)_3$ and an oxazolinylferrocenylphosphine at 80 °C for 1 h. The NMR study of the reaction of $RuCl_2(PPh_3)_3$ and [2-(4′-phenyloxazolin-2′-yl)ferrocenyl]diphenylphosphine showed that the produced catalyst consisted of two diastereomers in an approximately 5:1 ratio. For example, acetophenone was reduced by using this catalyst with up to 94% ee: Sammakia, T.; Stangeland, E. L. *J. Org. Chem.* **1997**, *62*, 6104−6105.

**TABLE 1. Kinetic Resolution of Racemic *sec*-Alcohols Catalyzed by 2[a]**

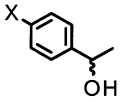
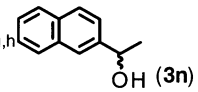
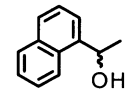
| run | alcohol | S/C | time (min) | unreacted alcohol | | |
|---|---|---|---|---|---|---|
| | | | | recov-[b] ery (%) | ee (%)[c] /(*S*) | $k_f$ / $k_s$[d] |
| 1 |  (**3a**) | 400 | 30 | 53 | 93 | 71 |
| 2[e] | | 400 | 150 | 48 | 95 | 56 |
| 3 | | 800 | 30 | 50 | 94 | 115 |
| 4 | | 1,200 | 30 | 53 | 97 | 183 |
| 5 | | 1,600 | 60 | 63 | 55 | 7 |
| 6 |  (**3b**) | 400 | 30 | 52 | 92 | 65 |
| 7 | | 1,000 | 40 | 47 | 92 | 32 |
| 8 |  (**3c**) | 400 | 30 | 53 | 95 | 104 |
| 9 |  (**3d**) | 400 | 30 | 50 | 92 | 79 |
| 10 |  (**3e**) | 400 | 40 | 48 | 94 | 50 |
| 11 |  (**3f**) | 400 | 40 | 41 | 95 | 17 |
| 12 |  (**3g**) | 400 | 30 | 100 | 0 | – |
| 13 |  (**3h**) | 400 | 30 | 50 | 43[f] | 4 |

[a] All reactions of racemic alcohol **3** were carried out in the presence of **2a** (0.0025 mmol) and $^i$PrONa (0.010 mmol) in acetone (10 mL) at 50 °C. [b] Determined by GLC. [c] Determined by GLC with chiral capillary column. [d] The ratio was estimated based on the final conversion and enantiomeric purity of the recovered alcohol. [e] Complex **2b** was used in place of **2a**. [f] Determined by HPLC chiral capillary column.

phenylethanol greatly increased the reactivity without affecting a high enantioselectivity (Table 2, run 5). In this case, the reaction was complete within 5 min. The oxidative kinetic resolution of 1-(1-naphthyl)-1-ethanol (**3o**) did not proceed smoothly in contrast to that of 1-(2-naphthyl)-1-ethanol (**3n**) (Table 2, runs 6 and 7).

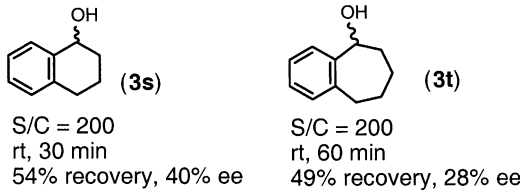
Interestingly, oxidative kinetic resolution of 1-indanol proceeded quite rapidly. Typical results are shown in Table 3. In sharp contrast to the reaction of phenylethanol derivatives, 1-indanol (**3p**) was oxidized to 1-indanone even at 0 °C within 10 min (Table 3, run 1). The absolute configuration of the recovered 1-indanol is *S*. The result of this high-speed oxidation prompted us to investigate the reactivity of 1-indanol in detail. When the S/C is 40 000 at 50 °C for 15 min, **3p** was recovered in 42% yield with 94% ee (*S*) (Table 3, run 6). The TOF of this reaction exceeded 80 000 $h^{-1}$. Even at S/C = 80,000, **3p** was oxidized in the presence of **2a** at 50 °C for 40 min, and **3p** was recovered in 51% yield with 84% ee (Table 3, run 7). Reactions of indanol derivatives such as 6-methoxy-1-indanol (**3q**) and 6-methyl-1-indanol (**3r**) proceeded

**TABLE 2. Kinetic Resolution of Racemic Phenylethanol Derivatives Catalyzed by 2a[a]**

| run | alcohol | time (min) | unreacted alcohol | | |
|---|---|---|---|---|---|
| | | | recov-[b] ery (%) | ee (%)[c] /(*S*) | $k_f$ / $k_s$[d] |
| 1 |  X = F (**3i**) | 35 | 38 | 91 | 11 |
| 2 | X = Cl (**3j**) | 40 | 44 | 98 | 34 |
| 3 | X = Br (**3k**) | 45 | 49 | 85 | 27 |
| 4 | X = Me (**3l**) | 60 | 43[e] | 99[f] | 35 |
| 5 | X = OMe (**3m**) | 5 | 31 | 98[f] | 10 |
| 6[g,h] |  (**3n**) | 60 | 52 | 70[f] | 11 |
| 7[h] |  (**3o**) | 120 | 66 | 53[f] | 4 |

[a] All reactions of racemic alcohol (**3**; 2.50 mmol) were carried out in the presence of **2a** (0.0025 mmol) and $^i$PrONa (0.010 mmol) in acetone (10 mL) at 50 °C (S/C = 1000). [b] Determined by GLC. [c] Determined by GLC with chiral capillary column. [d] The ratio was estimated based on the final conversion and enantiomeric purity of the recovered alcohol. [e] Isolated yield. [f] Determined by HPLC with chiral capillary column. [g] At room temperature. [h] S/C = 200.

**CHART 2**

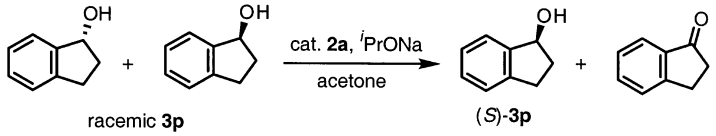



smoothly and the corresponding unreacted 1-indanol derivatives were recovered in good yields with high enantioselectivity (Table 3, runs 8 and 9). However, oxidative kinetic resolution of other cyclic alcohols such as 1,2,3,4-tetrahydro-1-naphthol (**3s**) and 6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-ol (**3t**) did not proceed so selectively under the same reaction conditions (Chart 2).

Recently, Noyori and co-workers developed clean and effective oxidation method of a variety of alcohols with hydrogen peroxide in the presence of tungsten catalyst.[2b] The TON value, defined as mols of product per mol of catalyst, approached 179 000 (1-phenylethanol). More recently, Kaneda and co-workers reported a highly efficient palladium-catalyzed aerobic oxidation of alcohols, where TON value approached 236 000 (1-phenylethanol).[2h] Both oxidation processes are quite efficient and synthetically useful methods to obtain the corresponding carbonyl compounds. On the other hand, the highly efficient oxidative kinetic resolution of racemic alcohols is strictly limited to the Noyori's system. In this system, the enantioselective ruthenium-catalyzed kinetic resolution of racemic or meso alcohols has been achieved, where S/C is up to 500 and TOF is up to 100 $h^{-1}$.[4a] It is noteworthy that our method presented here is the so-far known most efficient oxidative kinetic resolution of racemic alcohols, where S/C is up to 80 000.

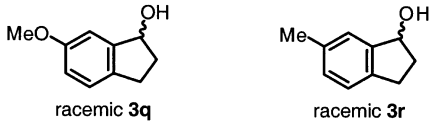
To obtain the information on the reaction mechanism, we examined the reactivities of (*S*)- and (*R*)-**3p** in this oxidation process. At first, we compared the initial rates of oxidation and racemization of (*S*)- and (*R*)-**3p**. Time

**TABLE 3. Kinetic Resolution of Racemic 1-Indanol (3p) Catalyzed by 2a[a]**




| run | 1-indanol (mmol) | **2a** (mmol) | S/C | $^i$PrONa (mmol) | acetone (mL) | $T$ (°C) | time (min) | unreacted 1-indanol recovery[b] (%) | unreacted 1-indanol ee[c] (%)/(*S*) | $k_f/k_s$[d] |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 1 | 0.005 | 200 | 0.02 | 10 | 0 | 10 | 45 | 97 | 36 |
| 2 | 5 | 0.005 | 1000 | 0.02 | 50 | rt | 40 | 45 | 97 | 36 |
| 3 | 25 | 0.005 | 5000 | 0.02 | 50 | rt | 155 | 50 | 98 | >200 |
| 4 | 25 | 0.0025 | 10 000 | 0.01 | 25 | 30 | 30 | 33 | 99 | 14 |
| 5 | 50 | 0.0025 | 20 000 | 0.01 | 25 | 50 | 7 | 39 | 94 | 13 |
| 6 | 100 | 0.0025 | 40 000 | 0.01 | 25 | 50 | 15 | 42 | 94 | 18 |
| 7 | 200 | 0.0025 | 80 000 | 0.01 | 25 | 50 | 40 | 51 | 84 | 28 |
| 8[e] | 25 | 0.0025 | 10 000 | 0.01 | 25 | 30 | 12 | 30 | 94 | 7 |
| 9[f] | 25 | 0.0025 | 10 000 | 0.01 | 25 | 30 | 12 | 34 | 99 | 15 |

[a] All reactions of racemic 1-indanol (**3p**) were carried out in the presence of **2a** and $^i$PrONa in acetone. [b] Determined by GLC. [c] Determined by GLC with chiral capillary column. [d] The ratio was estimated based on the final conversion and enantiomeric purity of the recovered alcohol. [e] 6-Methoxy-1-indanol (**3q**) was used in place of **3p**. [f] 6-Methyl-1-indanol (**3r**) was used in place of **3p**.



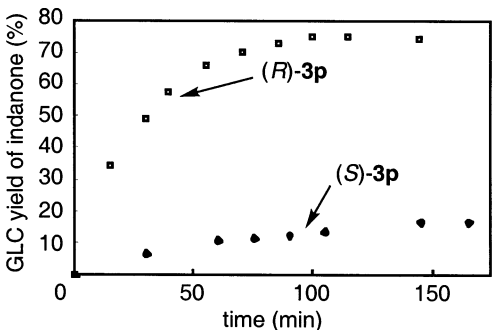




**FIGURE 1.** Time profile of the oxidation of (*R*)- and (*S*)-1-indanol (**3p**) (0.50 mmol) in the presence of **2a** (0.5 mol %) and $^i$PrONa (2.0 mol %) in acetone (25 mL) at 0 °C.

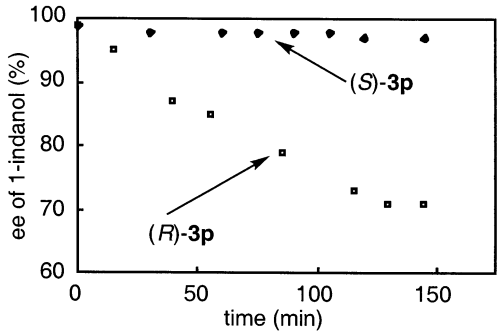



**FIGURE 2.** Time profile of the racemization of (*R*)- and (*S*)-1-indanol (**3p**) (0.50 mmol) in the presence of **2a** (0.5 mol %) and $^i$PrONa (2.0 mol %) in acetone (25 mL) at 0 °C.

profile of the oxidation of indanols in the presence of **2a** and $^i$PrONa is shown in Figure 1. The result indicated that the oxidation of (*R*)-**3p** is ca. 15 times faster than that of (*S*)-**3p**. The difference of the reaction rate was consistent with the selectivity factor ($k_f/k_s$) shown in Table 3, which was estimated from the recovered yield and enantiomeric excess of the recovered 1-indanol.[19] Time profile of the racemization of optically active **3p** in the presence of **2a** and $^i$PrONa is shown in Figure 2. No racemization of (*S*)-**3p** occurred, while (*R*)-**3p** slowly racemized. These results indicate that dynamic kinetic resolution of racemic **3p** is possible by using this oxidation system. Namely, optically active (*S*)-**3p** might be obtained in >50% yield from racemic **3p**.

Next, the role of $^i$PrONa to the oxidation was investigated. Bäckvall and co-workers recently reported that the role of base in $RuCl_2(PPh_3)_3$-catalyzed hydrogen transfer is to generate a highly reactive catalyst $RuH_2(PPh_3)_3$ from the dichloride via two consecutive alkoxide displacement-$\beta$-elimination sequences.[20] A similar displacement of chloride to hydride should occur in our asymmetric oxidation (Scheme 2). In addition, the use of an excess amount of $^i$PrONa increased the rate of the oxidation as shown in Figure 3. The oxidation in the presence of a large excess amount of $^i$PrONa (8 equiv to the catalyst) proceeds ca. 4 times faster than that in the presence of a slight excess amount of $^i$PrONa (4 equiv to the catalyst), and yet the use of an excess amount of $^i$PrONa does not influence the enantioselectivity of the recovered alcohol. This result indicates that an excess amount of $^i$PrONa such as 4 equiv to the catalyst is essential to achieve the highly efficient oxidation of alcohols.

(19) The efficiency of the kinetic resolution is characterized by $k_f/k_s$, the selectivity factor = (rate of fast-reacting enantiomer)/(rate of slow-reacting enantiomer); For a review, see: Noyori, R.; Tokunaga, M.; Kitamura, M. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 36 and references therein. When the recovered yields of alcohols are estimated to be a few % high, the selectivity factors are also estimated to be quite high. Thus, the simple calculation for run 3 in Table 3 affords the $k_f/k_s$ value of 458. To avoid misunderstanding, such extremely high value was expressed as >200.

(20) Aranyos, A.; Csjernyik, G.; Szabó, K. J.; Bäckvall, J.-E. *Chem. Commun.* **1999**, 351.

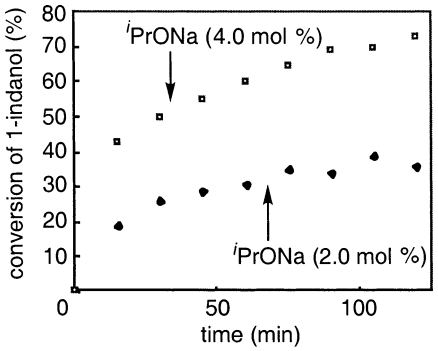
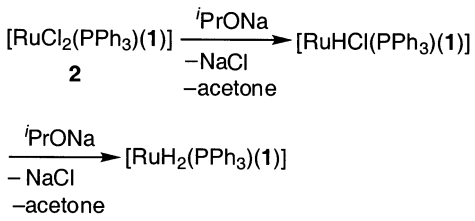
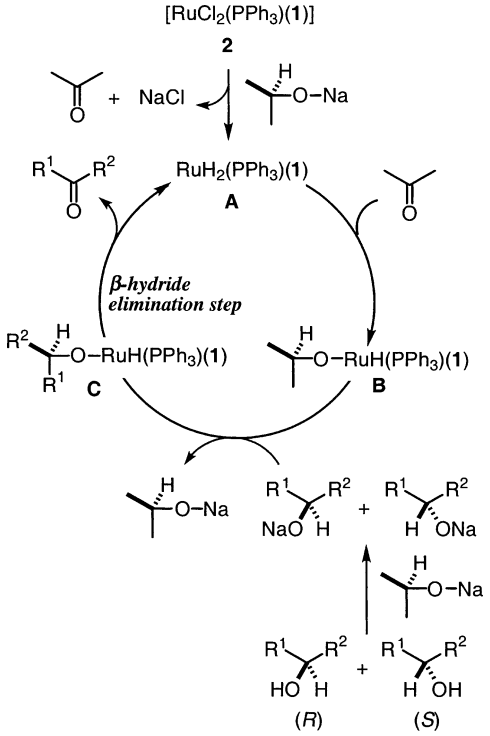



**FIGURE 3.** Time profile of the oxidation of 1-indanol (**3p**) (0.50 mmol) in the presence of **2a** (0.5 mol %) and $^{i}$PrONa in acetone (25 mL) at 0 °C.

**SCHEME 2**




**SCHEME 3**




The plausible reaction pathway of the oxidative kinetic resolution is shown in Scheme 3. At first, two chlorides in the complex **2** are removed in two consecutive alkoxide displacement-$\beta$-elimination sequences to form the active Ru−dihydride complex (**A**). The complex **A** reacts with acetone to give the Ru−hydride−2-propoxide complex (**B**). The replacement of the propoxide on **B** with the more reactive (*R*)-alcohol affords the Ru−hydride−alkoxide complex (**C**) together with 2-propanol. In the presence of an excess amount of $^{i}$PrONa, the formation of more reactive alkoxides, which are prepared from the deprotonation of alcohols with $^{i}$PrONa, makes this replacement step more facile. Finally, the $\beta$-hydride elimination from **C** leads to the formation of the starting Ru−dihydride complex **A** and a ketone. Thus, unreacted (*S*)-alcohol is recovered with a high enantioselectivity. Substantial isotope effect ($k_H/k_D = 4$) was observed when the oxidation of racemic 1-indanol and that of 1-indan-1-$d_1$-ol was carried out in the presence of **2** and $^{i}$PrONa at 0 °C. This result clearly indicates that the C−H bond breaking at the benzylic position of the alcohol ($\beta$-hydride elimination step) is involved in the rate-determining step.

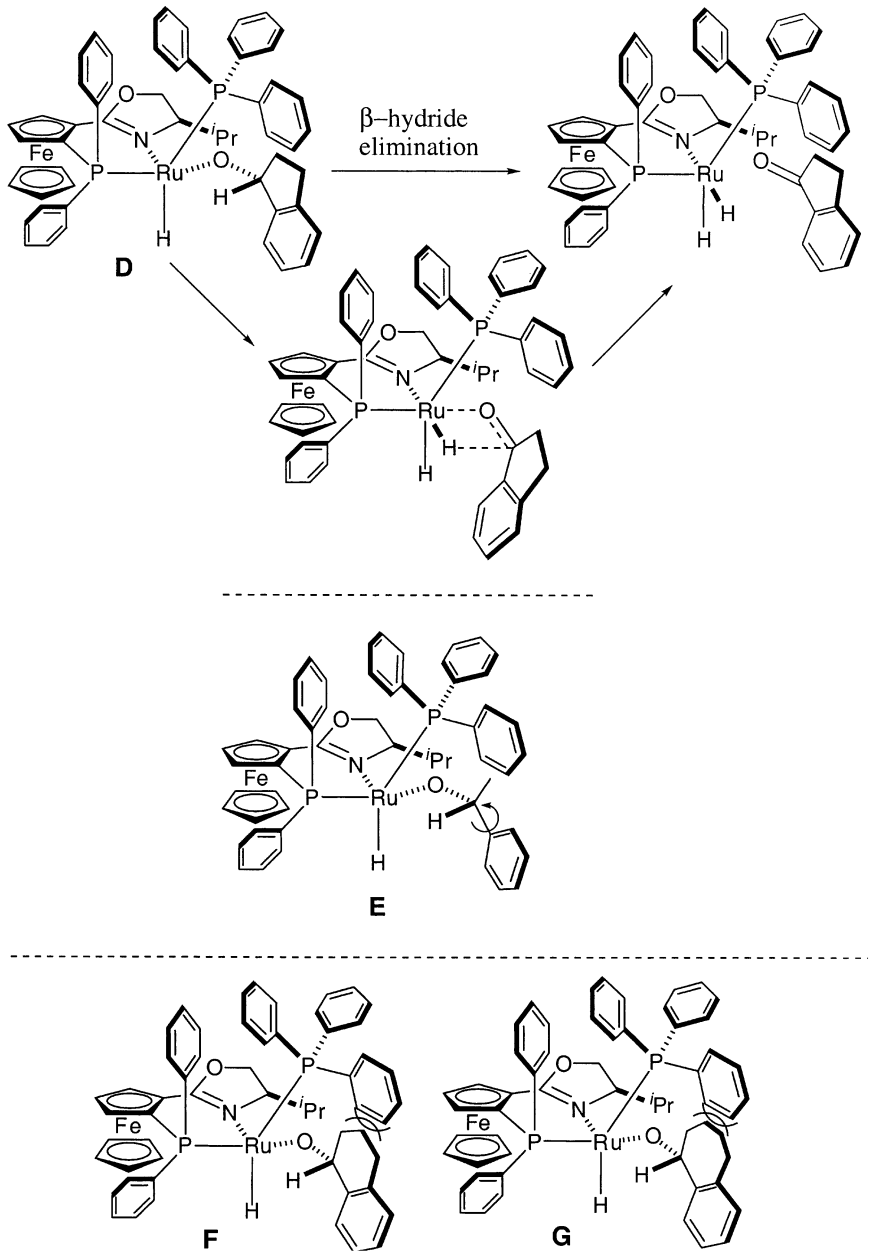
To account for the high efficiency of the oxidation of (*R*)-1-indanol **3p**, we propose a transition-state model shown in Scheme 4. Thus, the formation of 1-indanone, which has a rigidly conjugated system in the same plane derived from carbon−oxygen double bond in carbonyl moiety and carbon−carbon double bond in the benzene ring, is considered to be a driving force to promote a facile $\beta$-hydride elimination in the Ru−hydride−1-indanoxide complex (**D**). This is in sharp contrast to that in the Ru−hydride−1-phenylethoxide complex (**E**) to form acetophenone, which does not have such a rigidly conjugated system as in the case of 1-indanone. On the other hand, the kinetic resolution of other cyclic alcohols such as 1,2,3,4-tetrahydro-1-naphthol (**3s**) and 6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-ol (**3t**) did not proceed so selectively as shown in Chart 2. In these cases, the steric repulsion between cyclic moieties on **3s** and **3t** and phenyl group on the ligand in the Ru−hydride complexes (**F** and **G**) might prevent the formation of a favorable transition state which gives a high selectivity.

Finally, oxidative kinetic resolution of racemic 1-indanol (**3p**) was investigated in a large scale from a practical viewpoint (Scheme 5). When a mixture of **3p** (134 g, 1.00 mol), **2a** (22.8 mg, 0.025 mmol), and $^{i}$PrONa (8.2 mg, 0.10 mmol) in acetone (250 mL) was heated at 50 °C for 15 min, optically active (*S*)-1-indanol **3p** (52 g, 0.39 mol) was obtained with >99% ee after recrystallization (Scheme 5). Quantitative reduction of the recovered ketone provides an opportunity for the preparation of optically active alcohol in >50% overall yield from a racemic alcohol by employing sequentially this oxidative kinetic resolution method. Actually, the second oxidative kinetic resolution of the recovered **3p** gave the optically active (*S*)-1-indanol (23 g, 0.17 mol). Thus, the optically active (*S*)-**3p** (75 g, 0.56 mol) was obtained in 56% overall yield with >99% ee. The oxidative kinetic resolution of racemic alcohols described in this paper provides a practically useful method for optically active alcohols with high enantioselectivity.

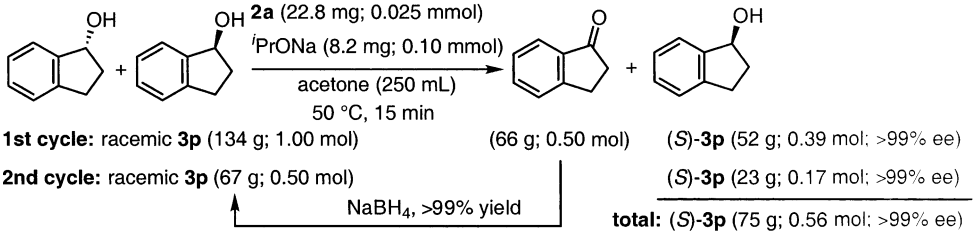
## Conclusion

We have found that oxidative kinetic resolution of racemic secondary alcohols using acetone as a hydrogenacceptor in the presence of a catalytic amount of [$RuCl_2$($PPh_3$)(FOXAP)] (**2**) proceeded quite effectively to recover the corresponding alcohols in high yields with an excellent enantioselectivity. A variety of alcohols such as 1-phenylethanol derivatives are available for this oxidative kinetic resolution. Especially, oxidative kinetic resolution of 1-indanol proceeded quite rapidly. The TOF of

**SCHEME 4**




**SCHEME 5**




this oxidation exceeded 80 000 $h^{-1}$ and TON value approached 40 000. The method presented in this paper provides a practically useful method for the preparation of optically active alcohols with a high enantioselectivity.

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**Supporting Information Available:** Experimental procedures for oxidative kinetic resolution of racemic alcohols. This material is available free of charge via the Internet at http://pubs.acs.org.

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