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Ruthenium-Catalyzed Sequential Reactions: Deracemization of Secondary Benzylic Alcohols

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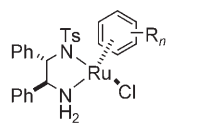
Abstract: The deracemization of secondary benzylic alcohols proceeds successfully by a two-step process with the appropriate combination of two different ruthenium complexes for catalysis in the first oxidation and second reduction steps. The sequential catalytic system provides a novel approach to obtaining optically active alcohols, including diols, in high yields with excellent enantioselectivity (up to 95% *ee*), in contrast to the conventional kinetic resolution of racemic alcohols.

Keywords: alcohols · homogeneous catalysis · oxidation · reduction · ruthenium

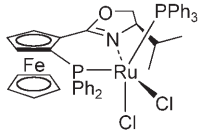
Introduction

Studies on one-pot multiple catalysis for obtaining desired products from simple starting materials are one of the current and important topics in synthetic chemistry.[1–3] Such catalysis decreases the reaction time and the loss in yield by avoiding the isolation and purification of intermediate compounds in multistep reactions. The most important and key point for success in these sequential reactions is the appropriate combination of different catalysts that do not mutually interfere in each reaction step and preferably work concurrently in all steps.

We envisaged the deracemization of secondary benzylic alcohols to the corresponding optically active alcohols by using two different types of transition-metal complexes, as the development of facile preparative methods for such alcohols is one of the important subjects in organic synthesis.[4,5] We report herein our successful result of the resolution by use of the Noyori ruthenium complex [RuCl{(*S*,*S*)-tsdpen}(η^6-arene)] (**1**; tsdpen = *N*-(*p*-toluenesulfonyl)-1,2-diphenylethylenediamine)[4a,6] and our ruthenium complex [$RuCl_2(PPh_3)$(ip-FOXAP[7])] (**2**; ip-FOXAP = isopropylferrocenyloxazolinylphosphine),[8] which are efficient catalysts for enantioselective redox reaction of ketones and alcohols.

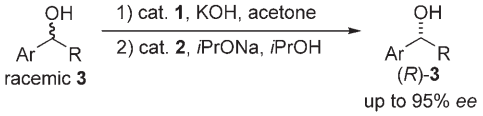


[RuCl{(*S*,*S*)-tsdpen}(η^6-arene)] (**1**)



[$RuCl_2(PPh_3)$(ip-FOXAP)] (**2**)

The present result seems to be the first successful example[9] of the deracemization of secondary benzylic alcohols by using only the chemical method (Scheme 1).[10,11]



Scheme 1. Deracemization of racemic alcohols by the chemical method.

Results and Discussion

A mixture of racemic 1-phenylethanol (**3a**) and acetone was stirred at room temperature for 15 h in the presence of catalytic amounts of [RuCl{(*S*,*S*)-tsdpen}(*p*-cymene)] (**1a**; 1 mol%) and KOH (2 mol%), then kept at room temperature for 2 h after successive addition of catalytic amounts of **2** (0.5 mol%) and *i*PrONa (2 mol%) in *i*PrOH. As a result, (*R*)-1-phenylethanol (**3a**) was recovered in 87% yield with 92% *ee* (Table 1, entry 1). A longer reaction time slightly increased the amounts of acetophenone and the aldol condensation product between acetophenone and acetone (Table 1,

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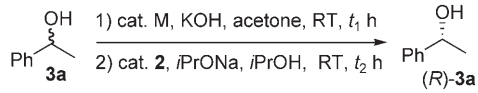
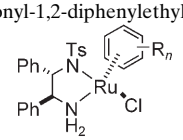
Table 1. Deracemization of alcohols **3a** catalyzed by two different transition-metal complexes (M and **2**).[a]

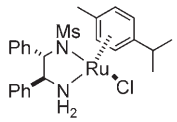


Entry	M	t_1 [h]	t_2 [h]	Recovery of **3a** [%][b]	*ee* of **3a** [%][c,d]
1	**1a**	15	2	87	92
2	**1a**	20	2	79	94
3	**1a**	15	4	77	87
4	**1b**	15	2	90	94
5	**1c**	15	2	85	94
6	**4**	15	2	82	63
7	**5**	15	2	89	32
8	**1d**	15	2	85	82

[a] Racemic **3a** (1.0 mmol) was stirred in acetone (1 mL) in the presence of M (1 mol%) and KOH (2 mol%) at room temperature for t_1 h. The mixture was then kept at room temperature for t_2 h after the addition of **2** (0.5 mol%) and *i*PrONa (5 mol%) in *i*PrOH (50 mL). [b] Determined by GLC. [c] Determined by GLC with a chiral column. [d] The absolute configuration was determined by comparison of the value of the optical rotation with that reported in the literature. msdpen = *N*-methanesulfonyl-1,2-diphenylethylenediamine.

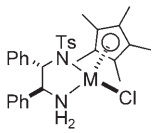


[RuCl{(*S*,*S*)-tsdpen}(η^6-*p*-cymene)] (**1a**)



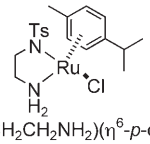
[RuCl{(*S*,*S*)-tsdpen}(η^6-mesitylene)] (**1b**)

[RuCl{(*S*,*S*)-msdpen}(η^6-*p*-cymene)] (**1c**)



[Cp*RhCl{(*S*,*S*)-tsdpen}] (**4**)

[Cp*IrCl{(*S*,*S*)-tsdpen}] (**5**)

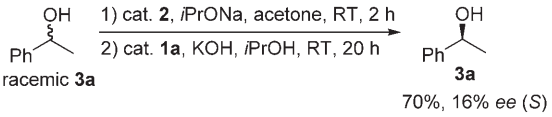


[RuCl(TsNCH$_2$CH$_2$NH$_2$)(η^6-*p*-cymene)] (**1d**)

entries 2 and 3). The use of other ruthenium complexes **1b** and **1c** in place of **1a** slightly improved the enantioselectivity (Table 1, entries 4 and 5). On the other hand, the use of rhodium and iridium complexes [Cp*MCl{(*S*,*S*)-tsdpen}] (M = Rh (**4**), Ir (**5**))[12,13] in place of **1** dramatically decreased the enantioselectivity (Table 1, entries 6 and 7). The use of a chiral ruthenium complex in the first oxidation step is necessary to achieve high enantioselectivity. In fact, the deracemization did not proceed effectively when an achiral ruthenium complex such as **1d**[14] was used as a catalyst (Table 1, entry 8). Interestingly, the deracemization of **3a** did not proceed well when the ruthenium complexes **2** and **1** were employed in reverse (Scheme 2). These results indicate that the

Abstract in Japanese:

二段階の酸化還元系に対して、二つの種類が異なるルテニウム触媒を用いることでラセミ体アルコールの動的速度論的光学分割を実現した。従来の一般的な速度論的光学分割法と比べて、本反応系は対応する光学活性アルコールを高収率かつ高エナンチオ選択的に得ることができる。

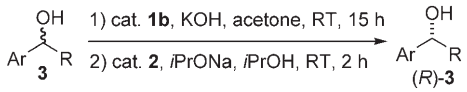


Scheme 2. Deracemization of racemic alcohols by reverse use of catalysts **1** and **2**.

appropriate use of both ruthenium complexes toward the first oxidation step and the second reduction step is an essential factor for promoting this deracemization process effectively.

Next, reactions of other 1-phenylethanols were investigated by use of catalytic amounts of **1b** and **2**. Typical results are shown in Table 2. The introduction of either electron-

Table 2. Deracemization of alcohols **3** catalyzed by both ruthenium complexes **1b** and **2**.[a]



Entry	Ar	R	Recovery of **3** [%][b]	*ee* of **3** [%][c,d]
1	Ph	Me	90 (**3a**)	94 (*R*)
2	4-MeC_6H_4	Me	92 (**3b**)	92 (*R*)
3	4-FC_6H_4	Me	82 (**3c**)	90 (*R*)
4	4-ClC_6H_4	Me	99 (**3d**)	89 (*R*)
5	4-BrC_6H_4	Me	99 (**3e**)	92 (*R*)
6[e]	4-PhC_6H_4	Me	99 (**3f**)	93 (*R*)
7[f]	3-MeC_6H_4	Me	81 (**3g**)	91 (*R*)
8	2-MeC_6H_4	Me	93 (**3h**)	2 (*R*)
9[e]	Ph	Et	88 (**3i**)	95 (*R*)
10	Ph	Et	>95 (**3i**)	88 (*R*)
11[e]	Ph	*n*Pr	85 (**3j**)	90 (*R*)
12	Ph	*n*Pr	96 (**3j**)	81 (*R*)
13[e]	Ph	*n*Bu	86 (**3k**)	94 (*R*)
14	Ph	*n*Bu	>95 (**3k**)	85 (*R*)

[a] Racemic **3** (1.0 mmol) was stirred in acetone (1 mL) in the presence of **1b** (1 mol%) and KOH (2 mol%) at room temperature for 15 h. The mixture was then kept at room temperature for 2 h after the addition of **2** (0.5 mol%) and *i*PrONa (5 mol%) in *i*PrOH (50 mL). [b] Determined by GLC. [c] Determined by GLC or HPLC with a chiral column. [d] The absolute configuration was determined by comparison of the value of the optical rotation with that reported in the literature. [e] The first oxidation step catalyzed by **1b** was carried out for 48 h. [f] The second reduction step catalyzed by **2** was carried out for 1 h.

withdrawing or electron-donating substituents such as fluoro, chloro, bromo, phenyl, and methyl at the *para* position and methyl at the *meta* position of 1-phenylethanol did not affect either the reactivity or enantioselectivity much (Table 2, entries 2–7). Unfortunately, the presence of a substituent such as methyl at the *ortho* position of 1-phenylethanol resulted in rather low enantioselectivity because the first oxidation step did not proceed smoothly (Table 2, entry 8). On the other hand, a slightly lower product yield was observed without loss of enantioselectivity when other 1-phenyl-1-alkanols were used as substrates (Table 2, entries 9–14). In all cases, a prolonged reaction time (48 h) in

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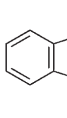
the first oxidation step slightly improved the enantioselectivity, but the amounts of the corresponding ketones and aldol condensation products increased under these reaction conditions. The use of 1-indanol as a substrate resulted in the major formation of the aldol condensation product **6** between 1-indanone and acetone. On the other hand, the reactions of secondary alcohols without an aryl group did not proceed smoothly. Interestingly, the reaction of diol **7** as a mixture of two diastereoisomers (*dl*/*meso* = 50:50) proceeded smoothly under the same reaction conditions to give (*R,R*)-**7** in 62% yield (*dl*/*meso* = 90:10) with > 99% *ee* (Scheme 3).



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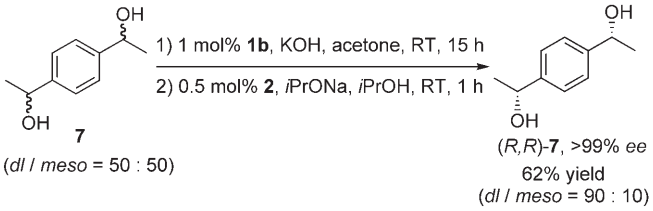
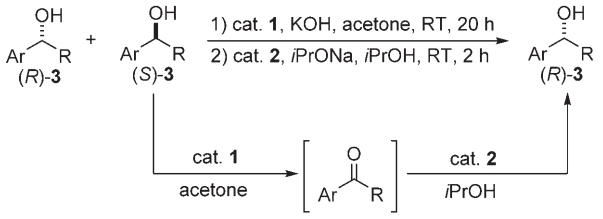


Scheme 3. Preparation of optically active diol.

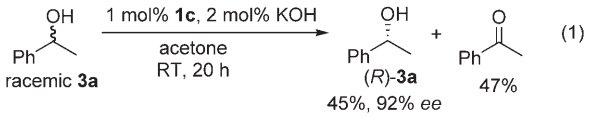
In this sequential reaction system, the ruthenium complexes **1** and **2** worked as catalysts in the oxidation and reduction steps, respectively. In the first oxidation process, only the *S* alcohol was selectively converted into the corresponding ketone, whereas in the second reduction process the ketone produced was enantioselectively reduced to the corresponding *R* alcohol (Scheme 4). In fact, we investigated

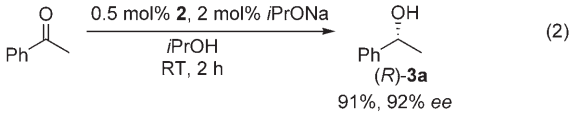


Scheme 4. Reaction pathway for deracemization of racemic alcohols.

separately the following kinetic resolution of racemic **3a** in acetone catalyzed by **1c** and reduction of acetophenone in *i*PrOH catalyzed by **2** (Equations (1) and (2)). This means that the effective inversion of the *S* alcohol in the starting racemic alcohol to the *R* isomer occurs during this asymmetric transformation, and the presence of the ruthenium complex **1** does not interfere with the subsequent reduction of the ketones produced. Notably, both ruthenium complexes play their respective roles independently in each step to realize the deracemization of secondary benzylic alcohols.

The kinetic resolution of racemic alcohols is one of the most useful chemical methods for obtaining optically active





alcohols from the starting alcohols. The drawback with kinetic resolution is that a maximum of 50% of the starting material can be used to give the product. In sharp contrast, in the novel redox reaction system, a maximum of 100% of the starting material can be used.[10,11] The sequential catalytic system herein provides a novel approach to obtaining optically active alcohols in high yields with excellent enantioselectivity, in contrast to the conventional kinetic resolution of racemic alcohols.

Conclusions

We have found that the deracemization of secondary benzylic alcohols catalyzed by two different ruthenium complexes gives the corresponding optically active alcohols in high yields with excellent enantioselectivity (up to 95% *ee*). The appropriate use of two ruthenium complexes is an essential factor in promoting this deracemization of secondary benzylic alcohols. Further investigations involving the kinetic study and the broadening of the scope of this sequential reaction system are currently in progress.

Experimental Section

A typical experimental procedure for the reaction of racemic **3e** catalyzed by **1b** and **2** is described below. KOH (1.1 mg, 0.02 mmol) and **1a** (6.2 mg, 0.010 mmol) were placed in a 50-mL flask under N_2. After the addition of racemic **3e** (201.1 mg, 1.00 mmol) in acetone (1.0 mL), the reaction mixture was kept at room temperature for 15 h. A solution of *i*PrOH (50 mL) containing *i*PrONa (0.020 mmol) and **2** (4.6 mg, 0.005 mmol) was added to the reaction mixture, which was then kept at room temperature for 2 h. For workup, aqueous HCl (1 N, 0.5 mL) was added. The solvent was concentrated under reduced pressure, then water (50 mL) was added, and the residue was extracted with diethyl ether (3 × 50 mL). The organic solution was dried over anhydrous $MgSO_4$. For isolation, the extract was concentrated under reduced pressure by an aspirator, and the residue was purified by preparative TLC (20% EtOAc/*n*-hexane) to yield (*R*)-**3e** (168.1 mg, 0.84 mmol, 84% yield, 92% *ee*) as a pale-yellow oil, which was identified by comparing its spectroscopic data with those in the literature.[15] $[\alpha]_D^{24} = +35.3$ ($c = 0.90$, $CHCl_3$); ^{1}H NMR: $\delta = 1.45$ (t, $J = 6$ Hz, 3H), 1.90 (br, 1H), 4.85 (q, $J = 6$ Hz, 1H), 7.23 (d, $J = 8$ Hz, 2H), 7.45 ppm (d, $J = 8$ Hz, 2H). The *ee* was determined by HPLC analysis with a Chiralcel OD column (eluent: hexane/2-propanol = 95/5, flow rate: 0.5 mL min^{-1}, column temperature: 25 °C, t_R: 20.53 min (*S*) and 22.30 min (*R*)).

Acknowledgements

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