Air-Stable Racemization Catalyst for Dynamic Kinetic Resolution of Secondary Alcohols at Room Temperature

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Air-Stable Racemization Catalyst for Dynamic Kinetic Resolution of Secondary Alcohols at Room Temperature

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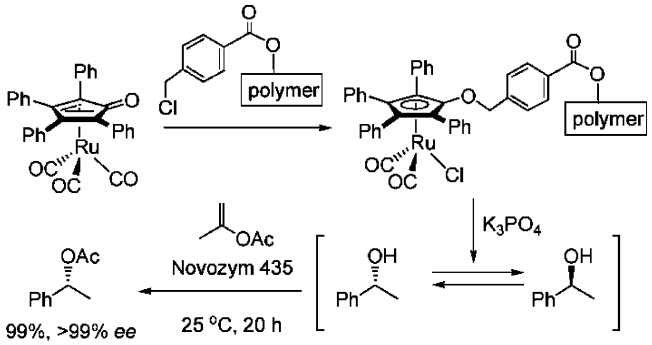
ABSTRACT



A novel racemization catalyst was synthesized for the dynamic kinetic resolution (DKR) of alcohols with a lipase at room temperature in the air. Furthermore, a polymer-supported derivative was also synthesized and tested as a recyclable catalyst for the aerobic DKR of alcohols.

Methods for preparing optically pure compounds are of great importance in pharmaceutical, agrochemical, and other fine chemical industries. One of the most popular methods is the kinetic resolution (KR) of racemic mixtures by enzymes such as lipases and esterases.[1] However, the KR has an intrinsic limitation; the yield of a desired enantiomer is less than 50%. Dynamic kinetic resolution (DKR), in which in situ racemization of unwanted enantiomers is coupled with KR, is an attractive method to overcome the limitation.[2] Several groups have reported transition-metal racemization catalysts that are compatible with the enzymatic systems for the DKR.[3] Our group has reported a ruthenium catalyst (**1**) that can be combined with lipase or subtilisin to convert racemic secondary alcohols into the corresponding optically pure acetates in (*R*)- or (*S*)-forms at room temperature (Figure 1).[4] Recently, a more active racemization catalyst (**2**) has been reported by Bäckvall et al.; the DKR of secondary alcohols can be completed in 3 h at room temperature.[5] However, all of the transition-metal racemization catalysts reported so far require anaerobic conditions due to their air

(1) (a) Waldmann, K. D. H. *Enzyme Catalysis in Organic Synthesis: A Comprehensive Handbook*, 2nd ed.; Waldmann, K. D. H., Ed.; Wiley-VCH: Weinheim, 2002; Vols. I−III. (b) Faber, K. In *Biotransformations in Organic Chemistry*, 4th ed.; Springer: Berlin, 2000.

(2) (a) Faber, K. *Chem. Eur. J.* **2001**, *7*, 5005. (b) Caddick, S.; Jenkins, K. *Chem. Soc. Rev.* **1996**, 447. (c) Noyori, R.; Tokunaga, M.; Kitamura, K. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 36. (d) Ward, R. S. *Tetrahedron: Asymmetry* **1995**, *6*, 1475.

(3) (a) Pàmies, O.; Bäckvall, J.-E. *Trends Biotechnol.* **2004**, *22*, 130. (b) Pàmies, O.; Bäckvall, J.-E. *Chem. Rev.* **2003**, *103*, 3247. (c) Kim, M.-J.; Ahn, Y.; Park, J. *Bull. Kor. Chem. Soc.* **2005**, *26*, 515. (d) Kim, M.-J.; Ahn, Y.; Park, J. *Curr. Opin. Chem. Biol.* **2002**, *13*, 578. (e) Gihani, M. T. E.; Williams, J. M. J. *Curr. Opin. Chem. Biol.* **1999**, *3*, 11. (f) Dijksman, A.; Elzinga, J. M.; Li, Y.-X.; Arends, I. W. C. E.; Sheldon, R. A. *Tetrahedron: Asymmetry* **2000**, *13*, 879. (g) Reetz, M. T.; Schimossek, K. *Chimia* **1996**, *50*, 668.

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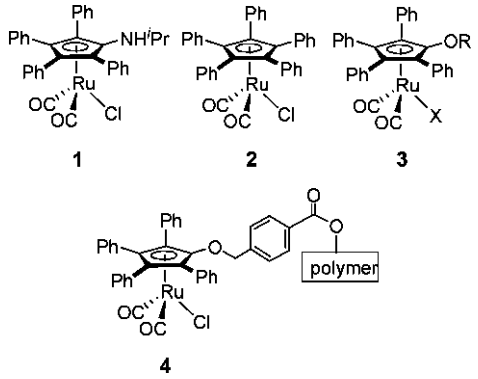
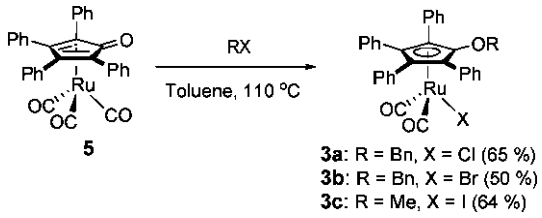


Figure 1. Racemization catalysts.

sensitivity during DKR and, therefore, are not reusable.[6] Herein, we report an air-stable and recyclable racemization catalyst (**3**) that is applicable to alcohol DKR at room temperature. We also report a heterogeneous version (**4**) of **3** for more efficient recovery and reuse.

On the basis of the known synthetic method for a methoxycyclopentadienyl ruthenium complex (**3c**),[7] benzyloxy derivatives (**3a** and **3b**) were prepared by the reaction of $[Ph_4(\eta^4\text{-}C_4CO)]Ru(CO)_3$ (**5**) with benzyl chloride and with benzyl bromide,[8] respectively (Scheme 1).

Scheme 1. Synthesis of *O*-Alkyl(tetraphenyl)cyclopentadienyl Ruthenium Complexes **3**



The ruthenium complexes were tested for the racemization of (*S*)-1-phenylethanol under various conditions (Table 1). The choice of a proper base was crucial; potassium phosphate displayed satisfactory performance, while potassium *tert*-butoxide decomposed the ruthenium complexes. Notably, contrary to known transition-metal-catalyzed racemizations,

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

entry	catalyst	base	atmosphere	% ee[b,c]
1	**3a**	*t*-BuOK	argon	45 (59)
2	**3a**	K_2CO_3	argon	25 (64)
3	**3a**	K_3PO_4	argon	0 (65)
4	**3a**	K_3PO_4	air	0 (73)
5	**3a**	K_3PO_4	O_2 (1 atm)	3 (67)
6	**3b**	K_3PO_4	air	13 (77)
7	**3c**	K_3PO_4	air	10 (51)

[a] (*S*)-1-Phenylethanol (>99% ee, 0.25 mmol) dissolved in toluene (0.80 mL) was added to a flask containing **3** (4.0 mol %) and base (1.0 equiv) and stirred at 25 °C for 2.5 h. [b] Measured by HPLC equipped with a chiral column (Chiralcel OD, Daicel). [c] Numbers in parentheses show the % ee of 1-phenylethanol after 30 min.

the racemization of (*S*)-1-phenylethanol was completed in 2.5 h with 4 mol % of **3a** at room temperature *in the air* (entry 4). The racemization was possible even under an oxygen atmosphere (entry 5). The chloride derivative (**3a**) was better than the bromide (**3b**) or the iodide (**3c**) (entries 4, 6, and 7) in the air.

The DKR of racemic 1-phenylethanol was carried out with the ruthenium complexes **3a**−**c** to find the optimum conditions (Table 2). Toluene was a better solvent than polar ones

Table 2. Dynamic Kinetic Resolution of 1-Phenylethanol[a]

entry	catalyst (mol %)	atmosphere	solvent	yield[b] (%)	% ee[c]
1	**3a** (4.0)	argon	acetone	55	>99
2	**3a** (4.0)	argon	EtOAc	57	>99
3	**3a** (4.0)	argon	toluene	>99	>99
4	**3a** (1.0)	argon	toluene	85	>99
5	**3a** (4.0)	air	toluene	>99	>99
6	**3b** (4.0)	air	toluene	67	>99
7	**3c** (4.0)	air	toluene	57	>99

[a] 1-Phenylethanol (1.0 mmol) dissolved in a solvent (3 mL) was added to a flask containing **3**, K_3PO_4 (1.0 mmol), Novozym 435 (8 mg), and isopropenyl acetate (1.5 mmol) at 25 °C. [b] Measured by GC after 20 h. [c] Measured by GC equipped with a chiral column (BETA DEX 120, Supelco).

such as acetone and ethyl acetate (EtOAc). As in the racemization, **3a** was the best catalyst and active in the air.

The synthetic method for **3** was applied to the preparation of a polymer-bound derivative (**4**) (Scheme 2). Hydroxylmethyl polystyrene (**6**) was reacted with 4-(chloromethyl)-benzoyl chloride to attach chlorobenzyl groups.[9] Heating a mixture of the resulting polymer **7** and $[Ph_4(\eta^4\text{-}C_4CO)]Ru(CO)_3$ (**5**) gave the polymer-supported catalyst **4**.[10] Then, the reusability of **4** was tested in the DKR of 1-phenylethanol under conditions similar to those for entry 5 of Table 2: first run, >99%, >99% ee; second run, >99%, >99% ee; third

(4) (a) Choi, J. H.; Choi, Y. K.; Kim, Y. H.; Park, E. S.; Kim, E. J.; Kim, M.-J.; Park, J. *J. Org. Chem.* **2004**, *69*, 1972. (b) Kim, M.-J.; Chung, Y. I.; Choi, Y. K.; Lee, H. K.; Kim, D.; Park, J. *J. Am. Chem. Soc.* **2003**, *125*, 11494. (c) Choi, J. H.; Kim, Y. H.; Nam, S. H.; Shin, S. T.; Kim, M.-J.; Park, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 2373.

(5) (a) Martín-Matute, B.; Edin, M.; Bogár, K.; Kaynak, F. B.; Bäckvall, J.-E. *J. Am. Chem. Soc.* **2005**, *127*, 8817. (b) Martín-Matute, B.; Edin, M.; Bogár, K.; Bäckvall, J.-E. *Angew. Chem., Int. Ed.* **2004**, *43*, 6535.

(6) The complexes **1** and **2** were active in the air for the racemization of (*S*)-1-phenylethanol in the presence of K_3PO_4. However, the DKR of (*S*)-1-phenylethanol with them gave (*R*)-1-phenylethyl acetate in 67% and 58% yield, respectively, after 20 h under the aerobic conditions.

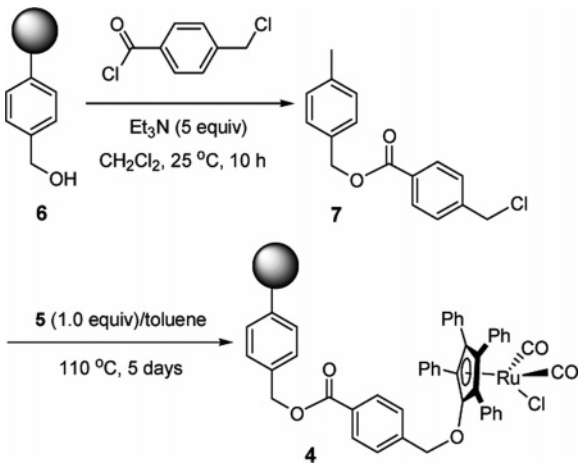
(7) Schneider, B.; Goldberg, I.; Reshef, D.; Stein, Z.; Shvo, Y. *J. Organomet. Chem.* **1999**, *588*, 92.

(8) See the Supporting Information.

(9) Hydroxymethyl polystyrene (100−200 mesh, 1% divinylbenzene; substitution: 1.13 mmol/g) was purchased from Novabiochem.

(10) The resulting polymer (3.37 wt % Ru) was characterized by IR. See the Supporting Information.

Scheme 2. Synthesis of a Polymer-Bound Racemization Catalyst



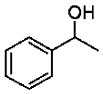
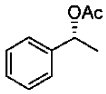
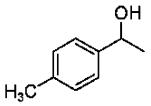
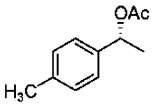
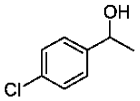
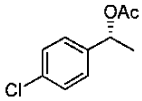
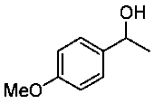
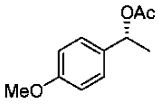
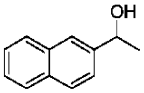
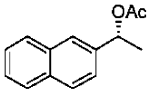
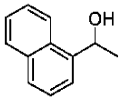
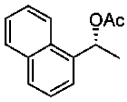
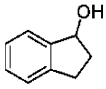
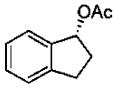
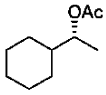
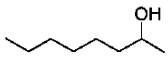
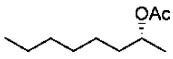
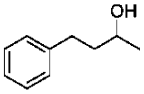
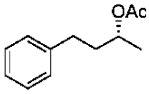
run, 95%, >99% ee; fourth run, 36%, >99% ee.[11] In the fourth run, the reaction mixture became a thick suspension. Meanwhile, the optical purity of the unreacted 1-phenylethanol was 39% ee. These observations indicate that inefficient stirring and/or decreased enzyme activity is the major cause of the drastic yield drop.

On the basis of the results from the DKR of 1-phenylethanol, the scope of our catalysts **3a** and **4** was investigated in the DKR of various secondary alcohols (Table 3). Our catalyst systems displayed high efficiency toward benzylic alcohols (entries 1−12) as well as aliphatic ones (entries 13−21). The catalytic activity of **4** was practically same as that of **3a**. Electronic effect on the reaction rate for the benzylic alcohols was not significant. 1-Phenylethanol, 1-(4-methylphenyl)ethanol, and 1-(4-chlorophenyl)ethanol were resolved completely in 20 h, while 1-(4-methoxyphenyl)-ethanol required a little longer reaction time (30 h) (entry 7). Naphthyl derivatives also gave excellent results in yield and enantioselectivity (entries 8−11). The DKR of 1-indanol was less enantioselective than those of other benzylic alcohols (entry 12). An excellent result in enantioselectivity and yield was obtained for 1-cyclohexylethanol, although a longer reaction time (72 h) is needed (entry 13). However, heating at 50 °C increased the reaction rate satisfactorily (entries 14−15). For linear aliphatic alcohols such as 2-octanol and 4-phenyl-2-butanol, reducing the amount of the lipase to suppress the acylation of (*S*)-isomer as well as heating (50 °C) were needed for satisfactory results in both yield and enantioselectivity (entries 16−21).

NMR experiments were carried out to get clues to explain the racemization. Interestingly, except for the resonances for **3a** and 1-phenylethanol, there were no resonances that show the formation of new species such as a ruthenium hydride, a ruthenium alkoxide, and acetophenone in the ^{1}H and ^{13}C NMR spectra of a toluene-d_8 solution containing **3a**, potas-

(11) When the DKR was completed, the reaction mixture was extracted with hexane five times. The residue was dried under vacuum and stored for reuse.

Table 3. DKR of Secondary Alcohols[a]

entry	substrate	product	catalyst	yield (%)[b,c]	ee[d] (%)
1			**3**	>99 (98)	>99
2			**4**	>99 (98)	>99
3			**3**	>99 (98)	>99
4			**4**	>99 (98)	>99
5			**3**	99.0 (99)	>99
6			**4**	>99 (98)	>99
7			**3**	94[e] (92)	>99
8			**3**	>99 (98)	>99[f]
9			**4**	>99 (98)	>99[f]
10			**3**	>99 (98)	>99[f]
11			**4**	>99 (98)	>99[f]
12			**3**	94[e] (91)	88[f]
13			**3**	98[g]	>99
14			**3**	94[h]	>99
15			**4**	95[h]	>99
16			**3**	62[g]	89
17			**3**	98[h]	79
18			**3**	94[h,i]	97
19			**4**	94[h,i]	97
20			**3**	85[h,i]	83
21			**4**	86[h,i]	92

[a] A mixture of alcohol (1.0 mmol), **3a** (4 mol %), K_3PO_4 (1.0 mmol), Novozym 435 (8 mg), and isopropenyl acetate (1.5 mmol) in toluene (3 mL) was stirred at 25 °C for 20 h. [b] Determined by GC. [c] Numbers in parentheses show isolated yields. [d] Determined by GC equipped with a chiral column (BETA DEX 120, Supelco). [e] After 30 h. [f] Determined by HPLC equipped with a chiral column (chiralcel OD, Daicel). [g] After 72 h. [h] After 20 h at 50 °C. [i] The amount of Novozym 435 was reduced to 4 mg.

sium phosphate, and 1-phenylethanol.[8] An explanation would be that an equilibrium between the ruthenium chloride **3a** and active species is far shifted toward **3a**.

In summary, we have demonstrated for the first time that a chemoenzymatic alcohol DKR in the air is possible by the combination of a readily preparable ruthenium catalyst and an immobilized lipase. Furthermore, a heterogeneous derivative has been synthesized by coupling a ruthenium tricarbonyl complex (**5**) and a polymer containing (chloromethyl)benzoyl moieties. Our synthetic method for the ruthenium catalysts can be modified to develop more practical catalyst systems for alcohol DKR.

Acknowledgment. We are grateful for the financial supports from the Korean Ministry of Science and Technology through KISTEP (NRL program) and KOSEF (the Center for Integrated Molecular System) and the Korean Ministry of Education through KRF (the BK21 program).

Supporting Information Available: Synthetic procedures for **3a**,**b**, **4**, and **7** and the NMR spectra of a mixture of **3a**, K_3PO_4, and 1-phenylethanol). This material is available free of charge via the Internet at http://pubs.acs.org.

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