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New efficient ruthenium catalysts for racemization of alcohols at room temperature

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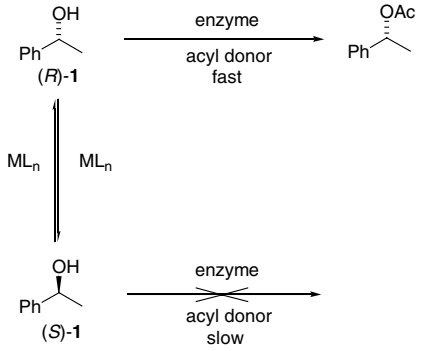
Abstract—(η^5-Pentaphenylcyclopentadienyl)RuCl(CO)$_2$ was found to catalyze efficiently the racemization of chiral alcohols such as (*S*)-1-phenylethanol, (*S*)-1-phenylpropan-2-ol, (*S*)-4-phenylbutan-2-ol and (*S*)-4-methoxy-1-phenylethanol at room temperature in the presence of a base. The catalytic activity of three other Ru(II) complexes was also investigated. The effects of halide and solvent were studied as well.

Racemization of organic compounds is an important process that has attracted considerable attention recently in connection with the preparation of enantiomerically pure compounds.[1] Separation of enantiomers in racemates via resolution, crystallization or chiral chromatography is still the most common way of obtaining enantiomerically pure compounds in the industry. With this technique, however, the yield of one enantiomer cannot exceed 50% and the other enantiomer is not used. However, by racemization the unwanted enantiomer can be brought back into the process. An important application of racemization is in combination with kinetic resolution and this is exemplified for enzymatic resolution of alcohols in Scheme 1.[2] If racemization can be achieved in situ during the enzymatic resolution it leads to an asymmetric transformation of the second kind (Scheme 1). This process has been termed dynamic kinetic resolution (DKR).



Scheme 1. Dynamic kinetic resolution (DKR) of alcohols.

A number of Rh, Ir and Ru complexes are known to racemize alcohols under relatively mild reaction conditions.[1b,3–6] These racemization reactions proceed via hydrogen transfer from the chiral alcohol to the corresponding ketone, which is generated in situ in catalytic amounts. The hydrogen transfer reaction proceeds via metal hydride intermediates and two principally different mechanisms have been proposed for Rh, Ir and Ru catalysis.[6] One mechanism involves monohydride intermediates and the other proceeds via dihydride intermediates. Another mechanistic dichotomy is that the hydrogen transfer with monohydrides can occur with or without coordination of the ketone.[7]

Although many transition metal complexes are known to racemize alcohols, only a few of these have been successfully employed in chemoenzymatic DKR. For example the dimeric ruthenium complex **2**[2,8] and more recently the amino analogue **3**[9] have been found to be compatible with the enzyme and the acyl donor in DKR (Fig. 1). Also, other ruthenium catalysts have been used to some extent.[10,11]

A common feature with catalysts **2** and **3** is that they are sterically hindered. Both **2** and **3** have four phenyl groups on the cyclopentadienyl ring. In addition to causing steric bulk, the phenyl groups may influence

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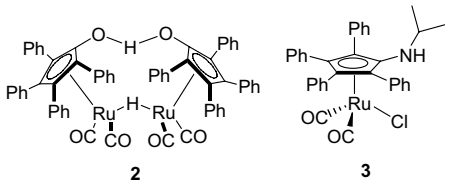
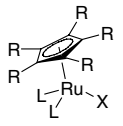


Figure 1.

the electronic properties of the complex. Complexes **2** and **3** also have CO ligands, which are electron-withdrawing ligands. To estimate the effect of the sterically hindered cyclopentadienyls and the electron-withdrawing effect by the ligands, it was of interest to study ruthenium complexes **4**–**8** as racemization catalysts for alcohols.



4 R=H, L=PPh_3, X=Cl
5 R=CH_3, L=PPh_3, X=Cl
6 R=H, L=CO, X=Cl
7 R=CH_3, L=CO, X=Cl
8a R=Ph, L=CO, X=Cl
8b R=Ph, L=CO, X=Br
8c R=Ph, L=CO, X=I

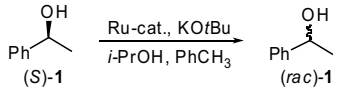
Complexes **4**–**5**[12] and **6**–**8**[13] were prepared by published literature methods.

The rate of racemization of (*S*)-1-phenyl ethanol with complexes **4**–**8** as the catalyst in toluene was studied (Scheme 2). The active catalyst from the cyclopentadienyl ruthenium chlorides is the corresponding ruthenium hydride (X = H).

These hydrides were generated in situ from the reaction of the appropriate ruthenium complex **4**–**8** with isopropanol and 1 equiv of base. Thus, treatment of 1 mol% of phosphine complex **4** with 1 mol% of potassium *t*-butoxide in the presence of isopropanol in toluene at room temperature followed by the addition of (*S*)-1-phenylethanol and stirring at room temperature for 6 h resulted in complete racemization. The half time ($t_{1/2}$) for the racemization was 2 h.[14] In an analogous experiment the pentamethyl substituted ruthenium catalyst **5** racemized (*S*)-1-phenylethanol in 5 h with a $t_{1/2}$ of 2 h.

On applying the same reaction conditions to **6** the enantiopurity of (*S*)-1-phenylethanol did not change even after prolonged reaction time.

Carbonyl complexes **7** and **8a** were also applied to the racemization of (*S*)-1-phenylethanol. Rapid racemization of (*S*)-1-phenylethanol occurred with only 0.5 mol% catalyst and with excellent substrate recovery



Scheme 2. Racemization of secondary alcohols.

Table 1. Solvent effect on the racemization with **8a**[a]

Entry	Solvent	Ee of **1** (%)
1	Cyclohexane	0.2
2	*t*-BuOMe	33
3[b]	Diisopropyl ether	61
4	$PhCH_3$	0.0

[a] 0.5 mol% of **8a**, 0.5 mol% of KO*t*Bu, 5 μL of *i*PrOH, 1 mL of solvent, 193 μL of decane, at rt, for 30 min, under argon.
[b] 1.5 mL.

(>98%). Complete racemization was achieved in 45 and 10 min, respectively. The half times of the racemizations were approximately 2.2 min for **7** and <2 min for **8a**.

The racemization protocol was performed in different solvents and the results are summarized in Table 1.

Apolar solvent such as cyclohexane and toluene (Table 1, entries 1, 4) proved to be ideal for the racemization process. Complete racemizations were obtained within 30 min in these solvents, whereas in *tert*-butyl-methyl ether (entry 2) there was still a 33% enantiomeric excess after 30 min and racemization was only complete after 1 h. Moreover, in diisopropyl ether (entry 3) the rate of racemization dropped significantly, and a prolonged reaction time was required to reach complete racemization (4.5 h). Due to the low solubility of the active ruthenium catalyst the amount of diisopropyl ether was increased from 1 to 1.5 mL.

The rate dependence on the halide for the racemization was studied for catalyst precursors **8** (Fig. 2). The rate of the racemization was only slightly effected by the different catalyst precursors used **8a** (X = Cl), **8b** (X = Br), **8c** (X = I), and all three catalyst had completely racemized the alcohol after 15 min. The chloride gave the best result and full racemization was obtained within 10 min. Therefore, we decided to use chloride **8a** in the racemi-

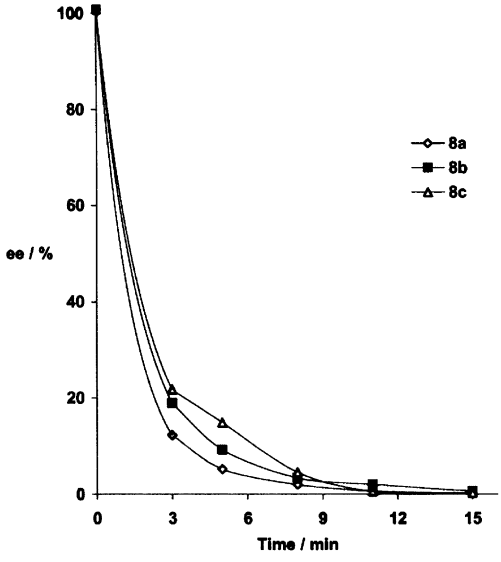
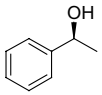
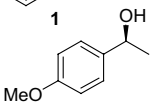
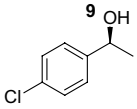
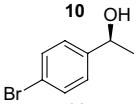
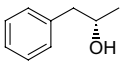
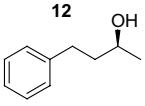
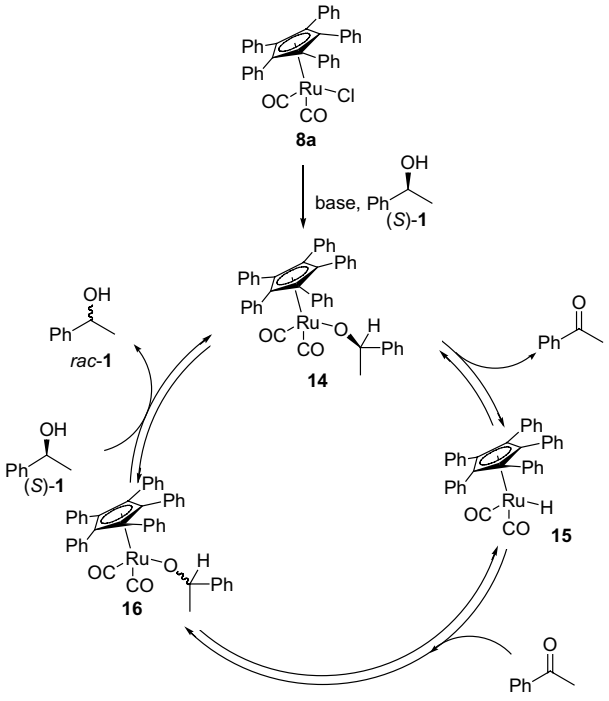


Figure 2. Racemization of (*S*)-**1** at room temperature in toluene catalyzed by **8a**–**c** (0.5 mol%).

Table 2. Racemization of secondary alcohols with **8a**[a]

Entry	Substrate	$Time_{rac}$ (min)	$t_{1/2}$ (min)
1	 **1**	10	<2
2	 **9**	75	13
3	 **10**	n.r	—
4	 **11**	n.r.	—
5[b]	 **12**	45	7
6	 **13**	90	18

[a] 0.5 mol% of **8a**, 0.5 mol% of KO*t*Bu, 5 μL of *i*PrOH and 1 mL of PhMe at rt under argon.
[b] 2 mol% of **8a**.



Scheme 3. The mechanism of the racemization.

zation studies of some different alcohols. Some additional alcohols were subjected to the racemization protocol with **8a** as catalyst. The acquired results are summarized in Table 2.

The enantiopurity of (*S*)-4-methoxy-1-phenylethanol (**9**) was diminished completely within 75 min using **8a** as catalyst and resulted in 50% racemization after 13 min (Table 2, entry 2). Unfortunately, the racemization of 4-bromo or 4-chloro substituted (*S*)-1-phenylethanol (**10** and **11**) did not occur (entries 3 and 4). It has previously been demonstrated that ruthenium hydride species can readily dehalogenate aryl chlorides.[15] However, (*S*)-1-phenyl-2-propanol (**12**) and (*S*)-4-phenyl-2-butanol (**13**) were completely racemized within 45 and 90 min, respectively (entries 5 and 6). The half time of the racemization were 7 min for (*S*)-1-phenyl-2-propanol and 18 min for (*S*)-4-phenyl-2-butanol.

Several ruthenium-catalyzed transfer-hydrogenation protocols have been established over the past decade.[7,16–18] The ruthenium-mediated transfer hydrogenation of alcohols consists of two reaction steps: dehydrogenation of the alcohol followed by the addition of the hydrogens to a susceptible hydrogen acceptor. Therefore, the ruthenium-catalyzed racemization of alcohols falls into the category of redox racemization. The racemization is accomplished by the successive oxidation (dehydrogenation) to the corresponding ketone, followed by readdition of the abstracted hydrogens to the ketone formed yielding the racemic alcohol.

The mechanism of the racemization is given in Scheme 3. Reaction of the catalyst precursor with the alcohol in the presence of base generates a ruthenium alkoxide complex (**14**), which undergoes a spontaneous β-hydride elimination to give the active hydride catalyst **15**.[19] Insertion of the ketone into the ruthenium hydride bond of **15** produces the racemic alkoxide complex **16**. Exchange of the racemic alkoxide in **16** with alcohol (*S*)-**1** releases *rac*-**1** and regenerates **14**.[6] Control experiments revealed the necessity of the added base. Omitting the base resulted in complete suppression of the racemization and the enantiopure (*S*)-1-phenylethanol was recovered in 100% yield.

In conclusion, (*S*)-1-phenylethanol was successfully racemized with **8a** or **7** as catalyst at room temperature with half times of about 2 min or less. With these catalysts the catalytic loading was kept low, only 0.5 mol% being required to achieve complete racemization with excellent substrate recovery (>98%). Also, 4-methoxy-(*S*)-1-phenylethanol, (*S*)-1-phenyl-2-propanol and (*S*)-4-phenyl-2-butanol were racemized with excellent substrate recovery with **8a** as catalyst. However, the extension of the racemization protocol to halogen substituted secondary alcohols was unsuccessful probably due to dehalogenation.

Acknowledgement

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19. In the kinetic experiments small amounts of isopropanol was used to obtain the active catalyst where the chloride has been removed. The substrate alcohol was then added to the catalyst and this procedure enabled a more accurate determination of the true reaction time.