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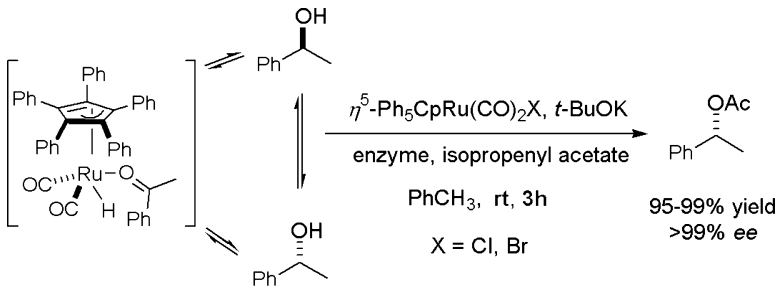

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Combined Ruthenium(II) and Lipase Catalysis for Efficient Dynamic Kinetic Resolution of Secondary Alcohols. Insight into the Racemization Mechanism

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Abstract: Pentaphenylcyclopentadienyl ruthenium complexes (**3**) are excellent catalysts for the racemization of secondary alcohols at ambient temperature. The combination of this process with enzymatic resolution of the alcohols results in a highly efficient synthesis of enantiomerically pure acetates at room temperature with short reaction times for most substrates. This new reaction was applied to a wide range of functionalized alcohols including heteroaromatic alcohols, and for many of the latter, enantiopure acetates were efficiently prepared for the first time via dynamic kinetic resolution (DKR). Different substituted cyclopentadienyl ruthenium complexes were prepared and studied as catalysts for racemization of alcohols. Pentaaryl-substituted cyclopentadienyl complexes were found to be highly efficient catalysts for the racemization. Substitution of one of the aryl groups by an alkyl group considerably slows down the racemization process. A study of the racemization of (*S*)-1-phenylethanol catalyzed by ruthenium hydride η^5-$Ph_5CpRu(CO)_2H$ (**8**) indicates that the racemization takes place within the coordination sphere of the ruthenium catalyst. This conclusion was supported by the lack of ketone exchange in the racemization of (*S*)-1-phenylethanol performed in the presence of *p*-tolyl methyl ketone (1 equiv), which gave <1% of 1-(*p*-tolyl)ethanol. The structures of ruthenium chloride and iodide complexes **3a** and **3c** and of ruthenium hydride complex **8** were confirmed by X-ray analysis.

Introduction

Due to the chiral nature of all living organisms, there is an ever increasing demand for enantiomerically pure compounds, primarily for use as pharmaceuticals, but also for use as flavor and aroma chemicals, agricultural chemicals and specialty materials. Great achievements in catalytic asymmetric synthetic transformations using transition metals, enzymes and organocatalysts have been reported in recent years.[1] However, despite the fact that in nine of the top ten drugs produced, the active ingredients are chiral,[2] resolution of racemic mixtures is still the most common way to prepare enantiomerically pure compounds on an industrial scale.[3] Immobilized lipases are robust biocatalysts for kinetic resolution (KR) of esters in water and of alcohols in organic solvents.[4] Enzymatic KRs are often very efficient in terms of selectivity, but suffer, as all resolutions, from being limited to a maximum theoretical yield of 50%. Strategies to increase the yield are therefore of great importance. In situ racemization of the slow-reacting enantiomer leads to deracemization by dynamic kinetic resolution (DKR) and makes possible a 100% yield. Secondary alcohols can be racemized via transition metal-catalyzed hydrogen transfer reactions.[5] In recent years chemoenzymatic DKR of secondary alcohols (Scheme 1) has been a rapidly evolving field of research.[6,7,8]

Various rhodium, iridium and ruthenium complexes are known to catalyze rapid racemization of alcohols,[5a,c,9,10] but only few have proved compatible with an enzymatic reaction. The

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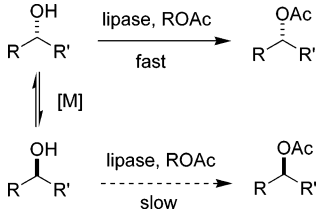
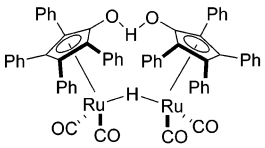
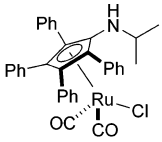
Scheme 1. Chemoenzymatic DKR of Secondary Alcohols



first example was reported by Williams who combined a rhodium catalyst and a lipase to obtain a DKR of secondary alcohols with moderate efficiency.[9] In 1997 we reported[11] an efficient DKR for the synthesis of enantiopure secondary alcohols by use of ruthenium catalyst **1**[12] in combination with an immobilized lipase. This method has also been applied to the DKR of different functionalized alcohols[13−18] that are useful building blocks in enantioselective synthesis. Kim and Park have also employed catalyst **1** in the DKR of secondary alcohols[19] and in the asymmetric transformation of ketones and enol acetates to chiral acetates.[20] In general, good yields and enantioselectivities were obtained. A drawback with precatalyst **1** is that it needs activation at slightly elevated temperature; hence, only thermostable enzymes can be used in the process. Also, the addition of an appropriate hydrogen source is often needed to prevent ketone formation, and *p*-chlorophenyl acetate is required as a specifically designed acyl donor for good yields.



1



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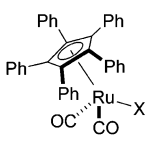

3a X = Cl
3b X = Br
3c X = I

Recently, Kim and Park reported that ruthenium precatalyst **2** racemizes alcohols within 30 min at room temperature.[21] However, when combined with an enzyme (lipase) in DKR at room temperature very long reaction times (1.3 to 7 days) were required, although the enzymatic KR takes only a few hours.

Recently, we communicated a highly efficient metal- and enzyme-catalyzed DKR of alcohols at room temperature.[22] This is the fastest DKR of alcohols hitherto obtained by the combination of metal and enzyme catalysts. Racemization was effected by a new class of very potent hydrogen transfer catalysts (**3a**−**b**). Evidence for the intermediacy of a ruthenium alkoxide complex was also provided. Various mechanisms have been proposed for Ru-catalyzed hydrogen transfer involving alcohols and ketones,[23] a transformation involved in the Ru-catalyzed racemization of secondary alcohols. In some of those mechanisms the substrate is coordinated to the Ru center prior to hydrogen transfer,[5c,24] whereas in other mechanisms the substrate is hydrogenated/dehydrogenated outside the coordination sphere of the Ru.[25,26] In some instances, it is difficult to determine whether hydrogen transfer occurs inside or outside the coordination sphere of the metal.[27,28]

In this full account on mild and efficient DKR, a broad substrate scope is demonstrated. Various heterocyclic alcohols have successfully been deracemized for the first time by the use of ruthenium catalyst **3a** and an enzyme. Some examples of potential applications are also given. A new and efficient method for the preparation of ruthenium halide complexes **3a**−**c**, **5** and **6** has been developed. We have also prepared a ruthenium hydride complex and studied its possible intermediacy in the racemization mechanism. Furthermore, evidence is presented that supports a mechanism in which the racemization of the alcohol takes place within the coordination sphere of the Ru atom. X-ray characterizations of the ruthenium precatalysts **3a**, **3c** and of ruthenium hydride **8** are provided.

Results and Discussion

Synthesis of the Ruthenium Complexes. In our preliminary work ruthenium complexes **3a** and **3b** were prepared by reaction of C_5Ph_5X (X = Cl, Br[29]) with $[Ru_3(CO)_{12}]$ in toluene under reflux.[22] However, with this procedure the iodide complex (**3c**) was not accessible since C_5Ph_5I could not be successfully prepared. Therefore, we decided to develop a new method for the synthesis of ruthenium halide complexes **3** (Scheme 2).

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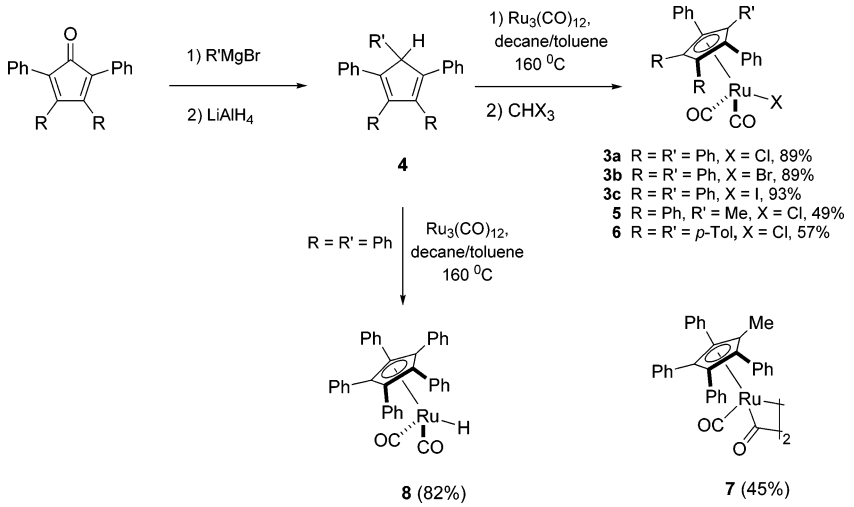
Scheme 2. Synthesis of Ruthenium Complexes



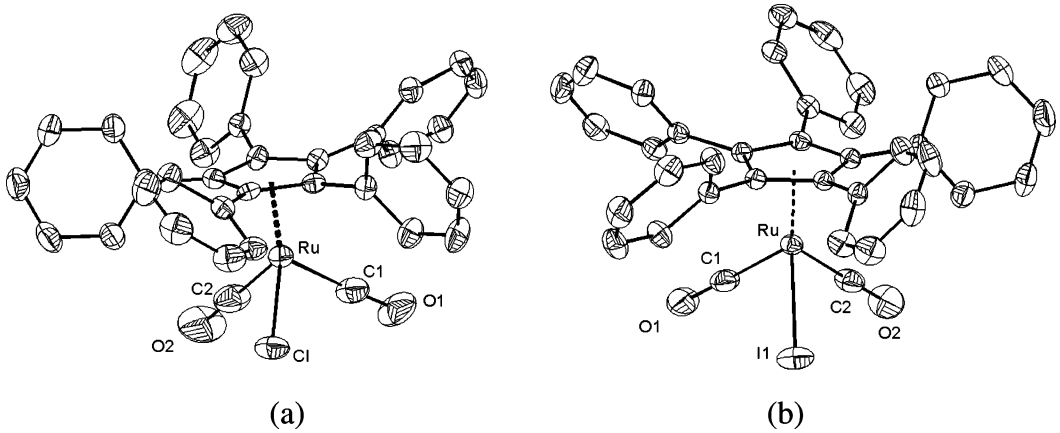


Figure 1. (a) X-ray crystal Structure of **3a**:[32] Thermal ellipsoids are drawn at 50% probability. Selected bond lengths (Å): Ru(B)−C(1B) 1.878(5), Ru(B)−C(2B) 1.888(5), Ru(B)−Cl(B) 2.3982(11). Selected angles (deg): C(1B)−Ru(B)−C(2B) 88.9(2), C(1B)−Ru(B)−Cl(B) 89.59(14), C(2B)−R(B)−Cl(B) 87.71 (17). (b) X-ray crystal Structure of **3c**: Thermal ellipsoids are drawn at 50% probability. Selected bond lengths (Å): Ru(1)−C(1) 1.866(4), Ru(1)−C(2) 1.879(4), Ru(1)−I(1) 2.7230(4). Selected angles (deg): C(1)−Ru-C(2) 90.61(18), C(1)−Ru-I(1) 84.23(12), C(2)−Ru-I(1) 85.55 (13).

Reaction of R′MgBr (R′ = Ph, *p*-Tol) with substituted cyclopentadienones followed by in situ reduction of the magnesium alkoxide with $LiAlH_4$ afforded tetrasubstituted cyclopentadienes **4** in high yields.[30] Oxidative addition of **4** to Ru(0) afforded, after treatment with excess of haloform, Ru-complexes **3a**−**c**, **5** and **6** in good to excellent yields. In the case of complex **5**, a significant amount of a new complex was obtained (45%). Due to the extremely low solubility of this new complex, the structure could not be confirmed by NMR, but two strong bands at 1960 and 1767 cm^{-1} in the IR spectrum clearly indicate the presence of nonbridging and bridging CO ligands. It was assigned as dimer **7**.[31] The structures of complexes **3a** and **3c** were confirmed by X-ray diffraction analysis (Figure 1).[32]

Ruthenium hydride η^5-$Ph_5CpRu(CO)_2H$ (**8**) was prepared in 82% yield by oxidative addition of **4** (R = R′ = Ph) to Ru(0) (Scheme 2). Thus, in a sealed tube a mixture of cyclopentadiene **4** (R = R′ = Ph) and [$Ru_3(CO)_{12}$] was stirred in decane/toluene (2:1) for 2.5 days at 160 °C. While cooling the tube, a precipitate fell out, which was collected by filtration. The ^1H NMR of this complex showed a hydride resonance at −9.4 in toluene-d_8 suggesting structure **8**. The structure was confirmed by X-ray diffraction analysis (Figure 2) and elemental analysis. The five Ru−Cp carbons bond lengths are very similar, providing evidence for η^5-coordination of the cyclopentadienyl ligand. The

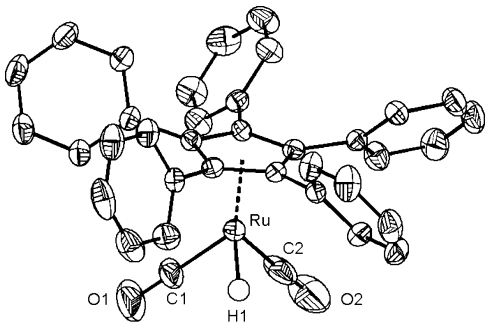


Figure 2. X-ray crystal Structure of **8**. Thermal ellipsoids are drawn at 50% probability. Selected bond lengths (Å): Ru(1)−C(1) 1.795(5), Ru(1)−C(2) 1.811(5), Ru(1)−Cp carbons: Ru(1)−C(3) 2.270(3), Ru(1)−C(4) 2.268(3), Ru(1)−C(5) 2.267(3), Ru(1)−C(6) 2.251(3), Ru(1)−C(7) 2.286(3). Selected angles (deg): C(1)−Ru(1)−C(2) 89.3(2).

(30) A slightly modified method was employed for the synthesis of **4** (R = Ph, R′ = Me). See Supporting Information for details.
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(32) Complete details of the X-ray analysis are given in the crystal structure analysis report in the Supporting Information.

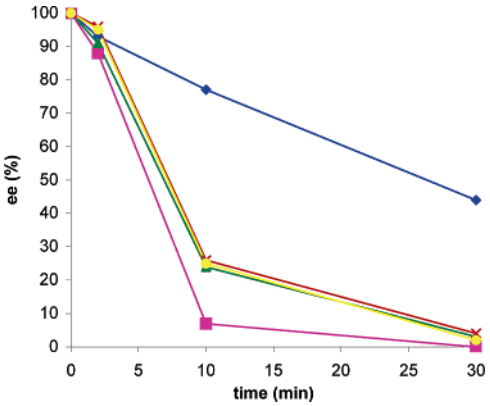
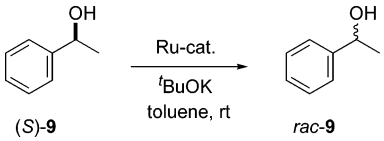


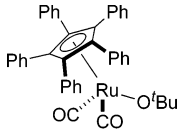
Figure 3. Racemization of (*S*)-**9** (0.5 M in toluene) catalyzed by: **3a** (▲), **3b** (●), **3c** (×), **5** (◆), **6** (■), after treatment with *t*-BuOK. Catalyst concentration: 0.0025 M.

Scheme 3. Racemization of (*S*)-1-Phenylethanol



two Ru−CO bond lengths (1.795, 1.811 Å) are slightly shorter than those in ruthenium chloride **3a** (1.878, 1.888 Å) and in ruthenium iodide **3c** (1.866, 1.879 Å).

Racemization of (*S*)-1-Phenylethanol. With five catalysts in hand we studied the racemization of (*S*)-1-phenylethanol ((*S*)-**9**) at room temperature (Scheme 3). In our previous communication we reported the efficient activation of Ru-halide complexes by *t*-BuOK, and we identified the formation of Ru-alkoxide complex **10** as the key intermediate.[22]



10

To compare the catalytic activity of ruthenium complexes **3a**−**c**, **5** and **6**, the corresponding ruthenium alkoxides were generated by treatment of the catalyst (0.5 mol %) with *t*-BuOK (1 mol %) in toluene, and after 6 min (*S*)-**9** was added. The results are presented in Figure 3. The racemization rate is affected by the substituents on the Cp ring. In general, pentaaryl-substituted catalysts rapidly racemized (*S*)-**9**.[33] The substitution of only one of the phenyl groups by a methyl group slowed considerable the rate of racemization. The racemization is not significantly affected by the nature of the halide atom, indicating that the active intermediate formed from complexes **3a**−**c** in the catalytic cycle might be the same.

Dynamic Kinetic Resolution of Secondary Alcohols. Although several metal complexes are known to catalyze fast racemization of alcohols, their combination with an enzyme-catalyzed kinetic resolution is not always straightforward. For example, the metal catalyst may interfere with the enzyme to give poor resolution or the enzyme may slow or inhibit racemization by the metal catalyst. Another problem often

Scheme 4. DKR of 1-Phenylethanol Catalyzed by *Candida antarctica* Lipase B and a Ruthenium Catalyst

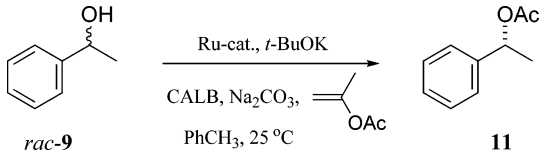


Table 1. Dynamic Kinetic Resolution of 1-Phenylethanol[a]

entry	Ru-catalyst	time (h)	%yield[b]	% ee[b]
1	**3a**	3	95 (92)[c]	>99
2	**3b**	3	98	>99
3	**3c**	3	60	93
4	**3c**	7.5	66	93
5[d]	**3c**	3	86	35
6	**5**	3	58	99
7	**5**	18	75	99

[a] Unless otherwise noted, Ru-catalyst (5 mol %), CALB (6 mg), Na_2CO_3 (1 mmol) and *t*-BuOK (5 mol %) were stirred in toluene (2 mL) for 6 min before adding **9** (1 mmol). After 4 min, isopropenyl acetate (1.5 mmol) was added and the mixture was stirred under an argon atmosphere. [b] Determined by chiral GC. [c] Isolated yield. [d] 6 mol % of *t*-BuOK.

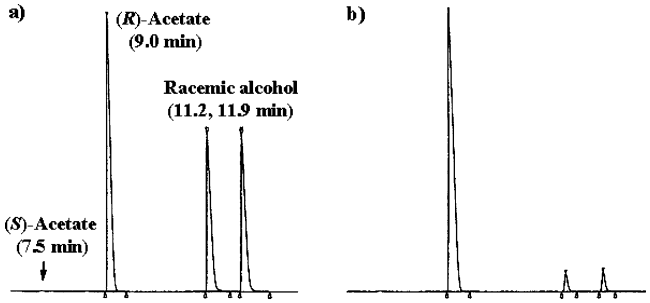


Figure 4. GC chromatogram of DKR of 1-phenylethanol (**9**) catalyzed by ruthenium complex **3b**: (a) 42% conversion, (b) 91% conversion.

encountered is that the base used to activate the metal catalyst can catalyze direct chemical esterification of the alcohol by the acyl donor, and this pathway leads to racemic product. We tested complexes **3a**−**c** and **5** in the DKR of 1-phenylethanol (*rac*-**9**) as a model substrate (Scheme 4, Table 1). For the kinetic resolution we have employed *Candida antarctica* lipase B (CALB)[34,35] as the enzyme and isopropenyl acetate as the acyl donor. The reactions were run at ambient temperature.

Complexes **3a**,**b** both gave excellent results and afforded enantiopure acetate **11** in high yields within 3 h (Table 1, entries 1 and 2). The combination of catalysts **3a**,**b** with the enzyme is so efficient that the starting alcohol **9** stays racemic throughout the reaction (Figure 4). Surprisingly, iodide complex **3c** gave after 3 h only 60% of acetate **11** and in only 93% ee (Table 1, entry 3). A plausible explanation is that due to the higher solubility of KI compared to KBr and KCl, the generation of the ruthenium *tert*-butoxide complex **10** becomes reversible. This leads to the presence of ruthenium iodide complex **3c** and *t*-BuOK, and the latter can catalyze chemical acylation of the alcohol, resulting in a lower enantiopurity of acetate **11**. The yield does not increase with time, and after 7.5 h only 66% (93% ee) of acetate product was obtained (entry 4). Increasing the added amount of *t*-BuOK to 6 mol % resulted in an increase of chemically acylated product (entry 5). As expected from

(33) The racemization is even faster when only 1 mL of toluene is employed: Csjernyik, G.; Bogár, K.; Bäckvall, J.-E. *Tetrahedron Lett.* **2004**, *45*, 6799−6802.

(34) Immobilized and commercially available as Novozym-435.
(35) To control the water activity, the enzyme was stored in a sealed container with a saturated solution of LiCl for a minimum of 24 h.

Figure 3, catalyst **5** did not give good results under DKR conditions (entries 6 and 7).

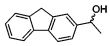
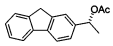
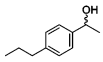
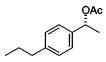
Due to the more straightforward syntheses of complexes **3a**,**b** and their high efficiency as racemization catalysts, we decided to investigate the combination of these catalysts with different enzymes to study the scope and limitations of the metal- and bio-catalyzed DKR of a variety of secondary alcohols. The catalyst was activated by a catalytic amount of *t*-BuOK in the presence of the enzyme and Na_2CO_3. The required amount of the base depends on the amount of enzyme employed and on the substrates. Therefore, it was optimized for each entry. The enzymatic resolution of most substrates was efficiently catalyzed by CALB. The amount of enzyme employed depends on each substrate, too. For a successful DKR, the resolution rate should not exceed the racemization rate too much, to avoid depletion of the resolved enantiomer; this could result in an ee decrease of the ester product. A great advantage of this system is that isopropenyl acetate can be employed as the acyl donor, and therefore the only byproduct is acetone, which can be easily removed after the reaction. It is interesting to note that acetone is not interfering with this catalyst, indicating that the intermediate ketone from dehydrogenation of the alcohol stays coordinated to the metal (vide infra). The results from the DKR of secondary alcohols are summarized in Table 2. In general, secondary alcohols bearing an aromatic group are readily transformed to enantiopure acetates in excellent yields and with short reaction times. Similar to 1-phenylethanol (Table 2, entries 1 and 2), the 2-naphthyl derivative (entry 3) is transformed to enantiopure acetate in only 3 h in excellent yield. The more sterically hindered 1-naphthyl derivative required longer reaction times (entry 4). Longer reaction times were also needed for 2-fluorenyl- and biphenyl-substituted alcohols (entries 5 and 6). In these cases the need for longer reaction times is most probably due to low solubility of the alcohols under the reaction conditions. The kinetic resolution of the ethyl carbinol in entry 7, as shown in separate experiments, is very slow, but with the use of 40 mg of enzyme per mmol of alcohol under DKR conditions, the product was obtained in 92% yield and >99% ee after 17 h. We also studied the effect on the DKR of the variation in the electronic properties of the alcohols. Aromatic alcohols bearing an electron-donating group on the ring were successfully converted to the acetates (entries 8 and 9). Substrates with electron-withdrawing groups on the phenyl ring gave almost quantitative yields of enantiopure acetates in all cases (entries 10−14); however, longer reaction times were required. For substrates bearing a coordinating group (entries 11 and 12) a possible explanation is that coordination of these N-containing groups to the ruthenium center slows down the reaction rate. However, this explanation seems to be less likely since electron-deficient substrates not bearing a coordinating group also required longer reaction times (entries 13 and 14). Therefore, the rates of some of the steps in the catalytic cycle might be also slowed (vide infra).

The results obtained for aliphatic substrates should be of importance since these alcohols are not readily accessible via asymmetric reduction. Synthesis of enantiomerically pure aromatic alcohols has been successfully accomplished via stereoselective hydrogenation of ketones and through transfer hydrogenation reactions but the corresponding aliphatic substrates proceed with lower selectivity.[36−38] However, with our metal- and enzyme-catalyzed DKR procedure we have been able to successfully obtain very high selectivity for a variety of aliphatic substrates. Thus, cyclohexylmethylcarbinol (entry 15) gave enantiopure acetate in quantitative yield. We were pleased to find that 2-octanol afforded the corresponding acetate in excellent yield and >98% ee (entry 16).[39] DKR of 4-phenyl-2-butanol afforded the acetate in high yield and good enantioselectivity (entry 17). Whereas CALB shows an excellent selectivity ($E > 200$) and activity (only 0.5 mg of enzyme were employed) for this substrate, the selectivity for 1-phenyl-2-propanol is not so high ($E = 70$). Furthermore, the kinetic resolution is rather slow (only 30% conversion to acetate after 2.5 h using 15 mg of enzyme/mmol of alcohol). However, the use of 40 mg of enzyme/mmol of alcohol under DKR conditions afforded quantitative conversion to the acetate in 91% ee in only 6 h (entry 18). The DKR of 1-phenoxypropan-2-ol is of practical interest since this alcohol is a useful intermediate for bactericides,[40] and also for the synthesis of hemilabile bidentate ligands. The racemization of this substrate is rather slow, but the acetate was obtained in excellent yield in >92% ee (entry 19).

We have also now tested a series of heteroaromatic substrates. Interestingly, excellent results were obtained with the piperidine derivative (entry 20). Also, benzofuran, furan, thiophene, and 4-pyridine-substituted alcohols gave excellent yields and high ee (96 to >99) (entries 21−24). 1-(2-Furyl)ethanol and its derivatives are important building blocks for the synthesis of carbohydrates, macrospelides H, G,[41a] and A, B,[41b] and pheromones and alkaloids.[41c−d] Also some functionalized alcohols were subjected to DKR (entries 25−26).[14,16] A great advantage of these alcohols is that they can be further transformed into more complex molecules. β-Chloro alcohols are important building blocks for the synthesis of chiral epoxides and amino alcohols. This kind of substrates can be also resolved to enantiopure acetates at room temperature. Thus, 2-chloro-1-phenylethyl acetate was obtained in high yield and excellent ee (entry 25). β-Hydroxy nitriles are also versatile building blocks. For example, they are useful precursors for γ-amino alcohols. The DKR of 3-hydroxy-3-phenylpropanenitrile (entry 26) was complete in only 6 h. High temperatures and larger amounts of enzyme are needed due to the slow racemization and slow KR. This DKR product can also easily be further manipulated into

(36) Review on metal-catalyzed hydrogenation of ketones: Noyori, R.; Ohkuma, T. *Angew. Chem., Int. Ed.* **2001**, *40*, 40−73.
(37) Reviews on asymmetric transfer hydrogenation of ketones: (a) Palmer, M. J.; Wills, M. *Tetraherdron: Asymmetry* **1999**, *10*, 2045−2061. (b) Wills, M.; Palmer, M.; Smith, A.; Kenny, J.; Walsgrove, T. *Molecules* **2000**, *5*, 4−18.
(38) For reduction of 2-alkanones, see: Sarvary, I.; Almqvist, F.; Frejd, T. *Chem. Eur. J.* **2001**, *7*, 2158−2166.
(39) Reduction of 2-hexanone using catalytic hydrogenation gives 96% yield of the alcohol in 75% ee, and reduction of 2-nonanone gives the alcohol in 100% yield, 1% ee. See ref 36.
(40) Naoaki, T.; Kenji, K.; Yoshihiko, Y.; Kenji, I.; Junzo, H. Enzymatic manufacture of (*R*)-2-hydroxy-1-phenoxypropanes from phenoxyacetones. (Kanefaguchi Chemical Industry Co., Ltd., Japan). Jpn. Kokai Tokkyo Koho 5, 2000.
(41) (a) Kobayashi, Y.; Wang, Y.-G. *Tetrahedron Lett.* **2002**, *43*, 4381−4384. (b) Kobayashi, Y.; Kumar, G. B.; Kurachi, T.; Acharya, H. P.; Yamazaki, T.; Kitazume, T. *J. Org. Chem.* **2001**, *66*, 2011−2018. (c) Samojski, A.; Grynkiewicz, G. *Total Synthesis of Natural Products*; ApSimon, J., Ed.; Wiley: New York, 1984; Vol. 6, pp 141−235. (d) See also: Stampfer, W.; Edegger, K.; Kosjek, B.; Faber, K.; Kroutil, W. *Adv. Synth. Catal.* **2004**, *346*, 57−62.
(42) Kamal, A.; Khanna, G. B. R.; Ramu, R. *Tetrahedron: Asymmetry* **2002**, *13*, 2039−2051.
(43) DKR of allylic alcohols at room temperature has been previously reported, but longer reaction times (48 h) were needed: Lee, D.; Huh, E. A.; Kim, M.-J.; Jung, H. M.; Koh, J. H.; Park, J. *Org. Lett.* **2000**, *2*, 2377−2379.

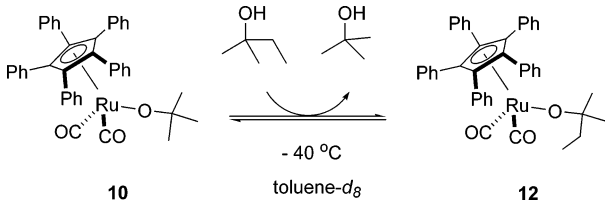
Table 2. Dynamic Kinetic Resolution Various Alcohols[a]

Entry	Alcohol	*t*-BuOK (mol%)	Time (h)	Product	% Yield[b,c]	% ee[b]	Entry	Alcohol	*t*-BuOK (mol%)	Time (h)	Product	% Yield[b,c]	% ee[b]
1[d]		5	3		98	>99	16[j]		7	20		93	>98
2		5	3		95 (92)	>99	17[k]		5	12		91	96
3		6.25	3		93	>99	18[h]		8	6		99	91
4[e]		5	24		>97 (97)	>99	19[j]		5	24		>98 (96)	>92
5[f]		5	24		>97[g] (97)	>99[g]	20		5	5		>99	99
6		5	24		>96[g] (96)	>99[g]	21		7	6		98(92)	96
7[h]		8	17		92 (90)	>99	22[m]		8	6		93	96
8		7.5	6		96 (94)	>99	23		5	6		>98 (98)	>99
9		5	6		96 (95)	99	24[n]		5	20		97(96)	99
10		5	6		93 (91)	>99	25[o]		10	13		83[l]	>99
11		5	20		99 (97)	>99	26[p]		8	6		85[l,q]	97
12		5	20		98 (95)	>99	27		6	18		89[r]	>99
13		5	24		>98 (98)	>99	28[s]		5	5		97[l] (94)	>97[g]
14		5	72		98 (97)	>99	29[t]		5	72		92 (90)	98
15		7	17		98[l]	>99	30[a,u]		6	10		94 (90)	>99 (97% de)

[a] Unless otherwise noted, Ru-catalyst **3a** (5 mol %), CALB (6 mg), Na_2CO_3 (1 mmol) and *t*-BuOK were stirred in toluene (2 mL) for 6 min before adding the alcohol (1 mmol). After 4 min, isopropenyl acetate (1.5 mmol) was added and the mixture was stirred under an argon atmosphere at ambient temperature. [b] Unless otherwise noted, determined by chiral GC. [c] Isolated yield in parentheses. [d] **3b**: 4 mol %. [e] 3 mL of toluene. [f] CALB: 12 mg, 5 mL of toluene and 40 °C. [g] Determined by chiral HPLC. [h] CALB: 40 mg. [i] Yield determined by ^{1}H NMR spectroscopy. [j] CALB: 2 mg. [k] CALB: 0.5 mg. [l] CALB: 1 mg, 40 °C. [m] The THF from the *t*-BuOK solution was not evaporated. [n] 50 °C. [o] The THF from the *t*-BuOK solution was not evaporated; enzyme: PS−C "Amano II", 100 mg. [p] CALB: 100 mg, 100 °C. [q] 9% of cinnamonitrile was also produced. [r] 11% of 4-phenyl-2-butanone was also formed. [s] 35 °C. [t] CALB: 1 mg. [u] 3 equiv of isopropenyl acetate.

important antidepressants, such as fluoxetine, tomoexetine and norfluoxetine.[42] Allylic alcohols are also important building blocks that can be transformed to a wide range of more complex molecules. The enantiopure acetate was obtained in 89% yield (>99% ee) (entry 27).[43] Another potential application is shown in entry 28. The starting amino alcohol can be easily obtained from dibenzylamine. Deprotection after DKR can provide (*R*)-1-amino-2-propanol efficiently and economically (Acros).

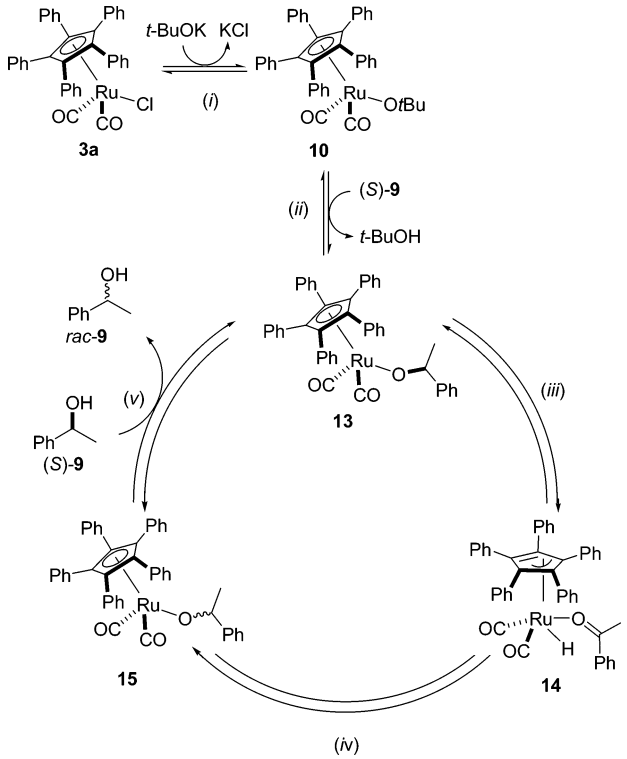
Scheme 5. Alkoxide Exchange Reaction



Sulcatol acetate (entry 29) can also be easily obtained via DKR. Sulcatol is a male-produced pheromone with important biological activity, such as insect pest control.[44] Besides, it can be readily transformed to pityol, an important pest attractant.[45] Finally, diols can also be transformed to enantiopure diacetates in excellent yield, enantioselectivity, and diastereoselectivity (entry 30).

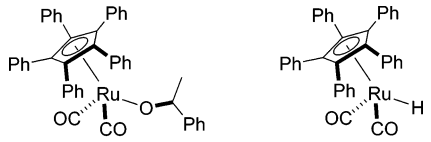
Mechanism of the Ruthenium-Catalyzed Racemization. The first step in the catalytic cycle is the activation of the ruthenium halide complex. In our previous communication[22] we reported the formation of a ruthenium *tert*-alkoxide (**10**)[46] by reaction of ruthenium chloride **3a** with *t*-BuOK. We observed the formation of complex **10** by mixing complex **3a** with a slight excess of *t*-BuOK in deuterated toluene. The NMR resonances of **10** differ from those of **3a**, *t*-BuOK, and *t*-BuOH in deuterated toluene. The formation of this intermediate was also supported by a strong color change of the reaction mixture from yellow to red. Furthermore, when (*S*)-**9** was added to the NMR tube containing alkoxide **10**, racemization immediately occurred.[47] It was suggested that in the next step, complex **10** reacts with (*S*)-**9** in a ligand exchange reaction to give a new alkoxide. We decided to investigate this alkoxide ligand exchange reaction in more detail. Since a secondary alcohol undergoes rapid α-CH bond cleavage (leading to racemization), a tertiary alcohol must be used in the exchange studies. Therefore, to study the alkoxide exchange, *tert*-alkoxide complex **10** was allowed to react with another tertiary alcohol, *tert*-amyl alcohol. Complex **3a** was mixed with *t*-BuOK in an NMR tube in toluene-d_8 at room temperature. Once complex **10** had been formed, the NMR tube was cooled in a liquid nitrogen bath. Then, *tert*-amyl alcohol (3 equiv) was added. After less than 10 min at −40 °C the formation of a new complex (**12**) was observed by ^{13}C NMR spectroscopy (about 20%).[48] When only 1 equiv of *tert*-amyl alcohol was employed, the equilibrium was established also very fast (within minutes) at 10 °C (Scheme 5). The ^{13}C resonances in deuterated toluene of the new *tert*-amyl alkoxide complex are very similar but clearly distinguishable from those of complex **10**.[49] The mechanism of the alkoxide exchange reaction remains unclear. There are two principal mechanisms for ligand substitution reactions, one dissociative and the other associative. A dissociative pathway would lead to the formation of free

Scheme 6. Mechanism of Racemization



alkoxide, which in the presence of isopropenyl acetate is expected to result in classical chemical acylation in the DKR. However, under DKR reaction conditions enantiopure acetates are obtained, indicating that free alkoxide is not produced. An associative pathway would require a η^5 to η^3 ring slippage.[50] Further studies to establish the detailed mechanism of this alkoxide exchange are required and are currently underway in our laboratory.

Reaction of (*S*)-**9** with alkoxide **10** would give the enantiopure Ru-complex **13** via a ligand exchange process (step *ii* in Scheme 6). Complex **13** can undergo β-hydride elimination and form a ruthenium hydride complex (**8**) and the oxidized product, acetophenone.



To find out if ruthenium hydride **8** is an active catalytic intermediate, the racemization of (*S*)-**9** catalyzed by 5 mol % of ruthenium hydride **8** was studied.[51] Since **8** needs to transfer the hydride to a ketone, 5 mol % of acetophenone was added to the reaction mixture. The racemization was followed by chiral

(44) (a) Byrne, K. J.; Swigar, A. A.; Silverstein, R. M.; Borden, J. H.; Stokkink, E. *J. Insect Physiol.* **1974**, *20*, 1895−1900. (b) For a recent synthesis of (*R*)-sulcatol and (2*S*,5*R*)-pityol see: Chen, S.-L.; Hu, Q.-Y.; Loh, T.-P. *Org. Lett.* **2004**, *6*, 3365−3367.

(45) See for example: Trudel, R.; Guertin, C.; de Groot, P. *J. Appl. Entomol.* **2004**, *128*, 403−406.

(46) Ru-alkoxide complexes: (a) ref 28 (b) Loren, S. D.; Campion, B. K.; Heyn, R. H.; Tilley, T. D.; Bursten, B. E.; Luth, K. W. *J. Am. Chem. Soc.* **1989**, *111*, 4712−4718. (b) Re-alkoxide complex: Saura-Llamas, I.; Gladysz, J. A. *J. Am. Chem. Soc.* **1992**, *114*, 2136−2144. (c) Ru-alcohol complex: See ref 27a. (d) W-alcohol and Mo-alcohol complexes: Bullock, R. M. *Chem. Eur. J.* **2004**, *10*, 2366−2374 and references therein.

(47) The mixture was analyzed by chiral GC.

(48) See ^{13}C NMR spectra in Supporting Information.

(49) See Experimental Section for details.

(50) The possible pathways for alkoxide exchange include: (i) ring slippage, (ii) alkoxide loss, (iii) CO loss, (iv) alkoxide attack at CO followed by alkoxide loss.

(51) As shown in Figure 3, the racemization of (*S*)-**9** catalyzed by complexes **3a**−**c** can be performed by the use of only 0.5 mol % of catalyst with short reaction times. In sharp contrast, the racemization of (*S*)-**9** catalyzed by 1 mol % of ruthenium hydride **8** (in the presence of 1 mol % acetophenone) required very long reaction times (1.5 days). Only when 5 mol % of ruthenium hydride **8** was used (in the presence of 5 mol % of acetophenone) could shorter reaction times be realized but still with an induction period of 2.5 h (Figure 5).

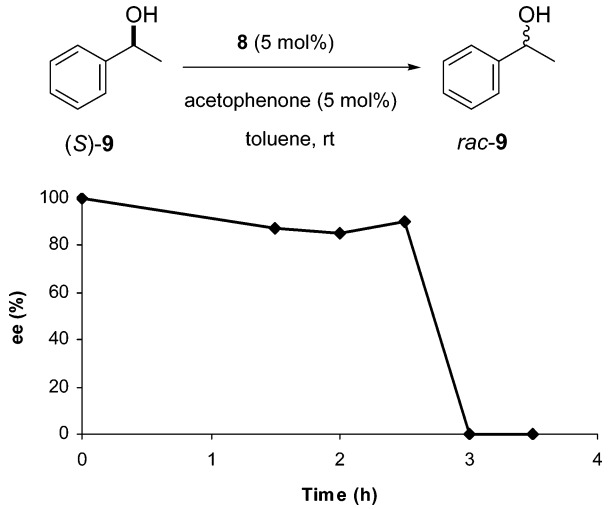
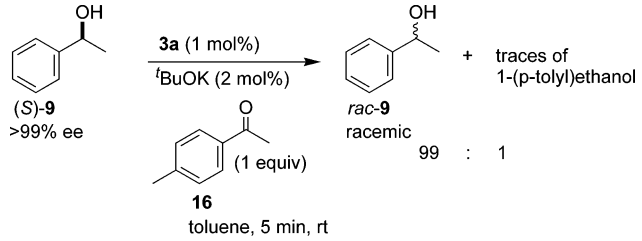


Figure 5. Racemization of (*S*)-1-phenylethanol catalyzed by η^5-ruthenium hydride **8**.

GC. As shown in Figure 5, ruthenium hydride complex **8** can catalyze the racemization of secondary alcohols, but with a long induction period of 2.5 h. After this induction period the racemization takes off and is complete after an additional 30 min. This result indicates that the reaction of the ruthenium hydride with acetophenone is rather slow.[52] However, once a small amount of the active species (the alkoxide) is formed, the racemization of (*S*)-**9** proceeds very fast. During the first 2 h the reaction mixture remains yellowish (Ru hydride **8** is a light brown powder), and then it turns orange and finally dark red. The red color is a clear indication of formation of Ru-alkoxides (ruthenium *tert*-butoxide complex **10** in toluene is a red solution).

Our results imply that, although ruthenium hydride intermediates are most likely involved in the racemization of secondary alcohols, the ruthenium η^5-hydride **8** is not an abundant species in the catalytic process. A proposed mechanism for the catalytic cycle is shown in Scheme 6. The first step is the formation of *tert*-alkoxide **10** by reaction of the ruthenium halide with *t*-BuOK (Scheme 6, step *i*). A very fast ligand-exchange reaction of **10** with the substrate would give enantiopure alkoxide complex **13** (step *ii*), which undergoes β-hydride elimination via a $\eta^5 \rightarrow \eta^3$ ring slippage (step *iii*) to give hydride ketone complex **14**. Thus we propose that the ketone stays coordinated to the ruthenium center (**14**). This explains why there is no interference between the acetone (produced from isopropenyl acetate) and the ruthenium hydride intermediate. To keep an 18-electron system, we propose that a $\eta^5 \rightarrow \eta^3$ ring slippage is required in the β-elimination, i.e. transformation **13** → **14**. Another possibility involves CO dissociation instead of ring slippage, but this seems less likely since high temperatures are usually required to dissociate CO from the coordination sphere of the ruthenium center.[53,54]

Scheme 7. Crossover Experiment: Racemization of (*S*)-1-Phenylethanol in the Presence of 1 Equiv of *p*-Tolyl Methyl Ketone (**16**)



In the ketohydride complex **14** with σ-bonded oxygen there is free rotation around the ruthenium oxygen bond, and the hydride addition (i.e. insertion) can take place from either face of the prochiral ketone. The readdition of the hydride (**14** → **15**) most likely occurs via slippage to π-coordinated ketone (not shown) followed by insertion.[55] Insertion of the ketone into the Ru−H bond produces the racemic alkoxide complex **15** (step *iv*). Alkoxide exchange with (*S*)-**9** releases racemic alcohol (*rac*-**9**) and regenerates intermediate **13**.

To obtain further insight into the mechanism of the racemization, the racemization of (*S*)-**9** was carried out in the presence of 1 equiv of tolyl methyl ketone (**16**) (Scheme 7). The reaction was carried out at room temperature in toluene with 1 mol % of catalyst **3a**, which was activated by 2 mol % of *t*-BuOK. After 5 min complete racemization of (*S*)-**9** to *rac*-**9** had occurred, but only 1% of the added ketone had been converted to alcohol (1-(*p*-tolyl)ethanol) (about 1% of acetophenone was also observed). These results show that, at room temperature, the ketone obtained from the alcohol stays in the coordination sphere of the Ru atom during racemization and does not exchange with free ketone. This observation is best explained by the intermediacy of a η^3-ruthenium hydride ketone complex after β-hydride elimination.[56]

In conclusion, we have studied the scope and limitation of the DKR catalyzed by ruthenium complexes **3** in combination with different lipases. A wide range of secondary alcohols, including aliphatic and heteroaromatic alcohols, have been deracemized to give the corresponding acetates in excellent yields and enantioselectivities via DKR. The DKR of important intermediates in the synthesis of some products of biological interest has been accomplished, showing the applicability of this process. Also, a new convenient method for the preparation of $(\eta^5\text{-}R_5Cp)Ru(CO)_2X$ (R = Ph, Me, *p*-Tol, X = Cl, Br, I) complexes in good yields was developed. We have studied the mechanism of the racemization of secondary alcohols catalyzed by Ru complexes and proven the intermediacy of Ru alkoxides. The most likely pathway for racemization involves β-elimination from an alkoxide complex to give a hydride ketone complex that undergoes reversible insertion. Interestingly, the ketone stays coordinated during the racemization and does not leave the coordination sphere. Study of the racemization catalyzed by η^5-Ph_5C_5 ruthenium hydride **8** indicates that the latter complex is not an abundant catalytic species in the racemization.

(52) In accordance, related 18-electron hydride [2,5-Me_2-3,4-Ph_2(η^5-C_4CNHPh)]-$Ru(CO)_2H$ reacts very slowly with benzaldehyde: Casey, C. P.; Vos, T. E.; Singer, S. W.; Guzei, I. A. *Organometallics* **2002**, *21*, 5038−5046.

(53) (a) Guari, Y.; Sabo-Etienne, S.; Chaudret, B. *J. Am. Chem. Soc.* **1998**, *120*, 4228−4229. (b) Guari, Y.; Sabo-Etienne, S.; Chaudret, B. *Eur J. Inorg. Chem.* **1999**, 1047−1055.

(54) Other conceivable mechanisms are hydride migration to the cyclopentadienyl ring and hydride migration to CO to give a formyl intermediate. We are currently investigating the mechanism of this remarkable C−H bond cleavage in our laboratories.

(55) If the ketone from β-elimination were only π-bonded no racemization could take place, since the hydride would readd to the same enantioface from which it was eliminated.

(56) An interesting question is why the ring slippage readily occurs for the alkoxide in β-elimination and not for the hydride in its reaction with a ketone. This is probably due to that the ketone is not nucleophilic enough to induce a ring slip. In the alkoxide the C−H can interact with ruthenium and induce a push of electrons to favor the ring slip.

Experimental Section

General Procedure for Racemization of (*S*)-1-Phenylethanol ((*S*)-9) Catalyzed by Ruthenium Halide Complexes. To a Schlenk type flask containing Ru complex **3a** (3.2 mg, 0.005 mmol) in toluene (2 mL) was added a solution of *t*-BuOK (0.5 M in THF; 20 μL, 0.01 mmol) under an argon atmosphere. After 6 min, (*S*)-1-phenylethanol (120 μL, 1 mmol) was added. Samples of the reaction mixture were collected under a rigorous argon atmosphere and analyzed by chiral GC. After 30 min, chiral GC analysis showed complete racemization of 1-phenylethanol.

General Procedure for DKR of Secondary Alcohols. Dynamic kinetic resolution of 1-phenylethanol: A solution of *t*-BuOK (0.5 M in THF; 100 μL, 0.05 mmol) was added to a 10 mL Schlenk flask. The THF was carefully removed under vacuum and the flask filled with argon. CALB (6 mg), Na_2CO_3 (106 mg, 1 mmol) and Ru-catalyst **3a** (25 mg, 0.04 mmol) were quickly added. The Schlenk flask was evacuated and filled with argon. Toluene (2 mL) was added, and the mixture was stirred for 6 min. Then 1-phenylethanol (120 μL, 1 mmol) was added, and after 4 min, isopropenyl acetate (165 μL, 1.5 mmol) was added. After being stirred for 3 h at ambient temperature, the reaction mixture was filtered and concentrated. Purification by column chromatography (SiO_2; pentane/diethyl ether 98:2) afforded (*R*)-1-phenylethanol acetate as a colorless oil (151 mg, 92% yield, >99% ee).

Formation of (η^5-Ph_5Cp)$Ru(CO)_2(O^tBu)$ (10) and Reaction with *tert*-Amyl Alcohol: (η^5-Ph_5Cp)$Ru(CO)_2$(*t*Pentoxide) (12). A solution of *t*-BuOK in THF (82 μL, 0.04 mmol; 0.5M) was added to an NMR tube. The THF was evaporated under reduced pressure. Then (η^5-Ph_5Cp)$Ru(CO)_2Cl$ (**3a**) (20 mg, 0.03 mmol) was placed in the NMR tube. The tube was evacuated and filled with argon before adding toluene-d_8 (0.5 mL). The tube was shaken vigorously, and a fine new precipitate of KCl was formed and allowed to settle. The quantitative formation of complex **10** was observed by ^{13}C NMR spectroscopy: ^{13}C NMR (toluene-d_8, 75 MHz, ambient temperature) δ 202.80, 132.72, 131.24, 128.06, 127.81, 108.75, 73.11, 34.28. The NMR tube was cooled in a liquid nitrogen bath. Then *tert*-amyl alcohol (100 μL, 0.092 mmol; 0.914 M in toluene-d_8) was added. At −40 °C the formation of complex **12** was observed by ^{13}C NMR in less than 10 min (about 20%). When only 1 equiv of *tert*-amyl alcohol was employed, the equilibrium was very fast established at 10 °C. **12**: ^{13}C NMR (toluene-d_8, 75 MHz, −15 °C) (selected peaks) δ 202.78, 108.51, 74.53, 39.11, 32.33, 10.20. The resonances of the *tert*-pentoxide ligand differ from those of *tert*-pentanol in toluene-d_8 (70.10, 36.59, 28.81, 8.64). The resonances of the five equivalent carbons of the cyclopentadienyl ring and of the CO ligand are also clearly distinguishable from those of *tert*-butoxide complex **10** under the same conditions [(toluene-d_8, 75 MHz; −15 °C) δ 202.86, 108.20].[48]

Racemization of (*S*)-1-Phenylethanol (9) Catalyzed by $Ph_5CpRu(CO)_2H$ (8) in the Presence of Acetophenone. A solution of (*S*)-**9** (122 mg, 1 mmol) and acetophenone (6 mg, 0.05 mmol) in toluene (2 mL) was added to a flame-dried flask containing ruthenium hydride complex **8** (30 mg, 0.05 mmol) under an argon atmosphere. The mixture was stirred at room temperature. Aliquots were analyzed by chiral GC. The results are presented in Figure 5.

Racemization of (*S*)-1-Phenylethanol (9) in the Presence of 1 Equiv of p-Tolyl Methyl Ketone (16). Potassium *tert*-butoxide (0.5 M in THF, 0.02 mmol, 40 μL) was added at room temperature to a solution of catalyst **3a** (0.01 mmol, 6.4 mg) in toluene (2 mL), and the flask was flushed with argon. After stirring for 6 min, *p*-methylacetophenone (1.0 mmol, 0.135 mL) and (*S*)-1-phenylethanol (1.0 mmol, 0.120 mL) were added successively. Aliquots were analyzed by chiral GC. After 5 min, complete racemization of (*S*)-**9** to *rac*-**9** had occurred and only 1% of the added ketone had been converted to alcohol (1-(*p*-tolyl)ethanol) (about 1% of acetophenone was also observed).

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Supporting Information Available: Experimental details and analysis of new secondary alcohols and acetates. Preparation and characterization of compounds **3**−**8** and **12**. X-ray analysis of complexes **3a**, **3c** and **8**. This material is available free of charge via the Internet at http://pubs.acs.org.

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