Dynamic Kinetic Resolution

Highly Compatible Metal and Enzyme Catalysts for Efficient Dynamic Kinetic Resolution of Alcohols at Ambient Temperature**

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The demand for chiral compounds as single enantiomers has increased dramatically in recent years, driven by the pharmaceutical industry and also by other applications, such as

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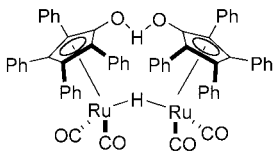
[**] We are grateful for financial support from the Swedish Research Council, the Swedish Foundation for Strategic Research, and the Ministerio de Educación y Ciencia of Spain.

Supporting information for this article (NMR data for **3a** and **5g**) is available on the WWW under http://www.angewandte.org or from the author.

 DOI: 10.1002/anie.200461416

agrochemicals, flavors, fragrances, and materials. Dynamic kinetic resolution (DKR) is a powerful tool to transform a racemic mixture into one enantiomer.[1] This strategy overcomes the limitation of the maximum 50% yield in a kinetic resolution (KR) by combining it with an in situ racemization of the substrate. Recently the coupling of enzymes and transition metals for the DKR of alcohols has attracted considerable attention.[2,3] In these reactions, in situ racemization by a metal occurs during the enzymatic resolution. The first example was reported by Williams and co-workers who used a rhodium catalyst and a lipase to obtain a DKR of secondary alcohols with moderate efficiency.[4] In 1997 our group reported[5] an efficient DKR process for the synthesis of enantiopure secondary alcohols by the use of ruthenium catalyst **1**[6] in combination with an immobilized lipase. This



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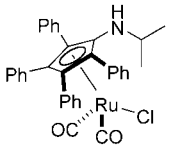

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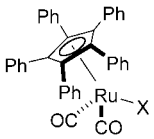


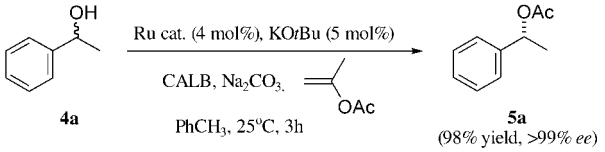
3a: X = Cl
3b: X = Br
3c: X = I

method has also been applied to the DKR of different functionalized alcohols, such as hydroxyacid derivatives,[7] hydroxynitriles,[8] azidoalcohols,[9] haloalcohols,[10] hydroxyphosphonates,[11] and diols.[12] Kim, Park, and co-workers have also employed catalyst **1** in the DKR of protected hydroxyacids, diols, and hydroxyaldehydes,[13] and in the asymmetric transformation of ketones and enol acetates to chiral acetates.[14] In general, good yields and enantioselectivities were attained. However, complex **1** suffers from some drawbacks: it is activated at high temperature and therefore a thermally stable enzyme is required. Also, the addition of an appropriate hydrogen source is needed in some cases to prevent ketone formation.

Various ruthenium, rhodium, and iridium complexes are known to catalyze fast racemization of alcohols.[2c,4,5,15,16] Unfortunately, almost all of these catalysts do not work in the DKR of alcohols when combined with the enzyme. Recently, Kim, Park, and co-workers reported that ruthenium catalyst **2** racemizes alcohols within 30 min at room temperature.[17] However, when combined with an enzyme (lipase) in DKR at room temperature, very long reaction times (1.3–7 days) were required, in spite of the fact that the enzymatic reaction (in KR) takes only a few hours.

Very recently we found that complexes **3a–c** catalyze the racemization of chiral alcohols highly efficiently at room temperature after being activated by KO*t*Bu.[18] For example, **3a** (0.5 mol%) racemized (*S*)-1-phenylethanol within 10 min and resulted in 50% racemization after less than 2 min.

Initial attempts to combine catalyst **3a** (or **3b**) with an enzymatic resolution were unsuccessful and gave either no DKR or led to very long reaction times for the DKR (several days). This was frustrating, as the isolated reactions (racemization and enzymatic resolution) are very fast. Finally, after some fine-tuning and optimization, we were able to find reaction conditions under which the DKR process has almost the same rate as the kinetic resolution. Herein we report a DKR process (Scheme 1) that is more than two orders of



Scheme 1. DKR of 1-phenylethanol.

magnitude faster than our previous procedures[2,5] and one order of magnitude faster than the hitherto fastest procedure reported.[17] We also provide evidence for the intermediacy of a ruthenium alkoxide complex.

In one experiment a solution of 1-phenylethanol (**4a**) in toluene (0.3 M) was added to a mixture of KO*t*Bu and ruthenium complex **3b**, under an argon atmosphere. After stirring for 5 min, Na_2CO_3, *Candida antarctica* lipase B (CALB[19]), and isopropenyl acetate were added. After 4 h, only 55% yield of enantiopure (*R*)-1-phenylethanol acetate (**5a**) was obtained (Table 1, entry 1).[20] Surprisingly, when the

Table 1: Dynamic kinetic resolution of 1-phenylethanol.[a]

Entry	Ru catalyst	*t* [h]	Yield [%][b]	*ee* [%][b]
1[c]	**3b**	4	55	>99
2[d]	**3b**	4	99 (97)[e]	>99
3	**3b**	3	98	>99
4	**3a**	3	95 (92)[e]	>99
5[f]	**3b**	15	60	>99

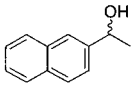
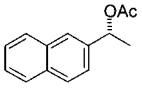
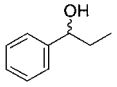
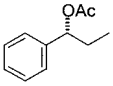
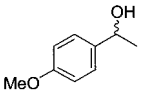
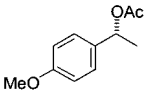
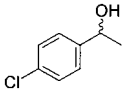
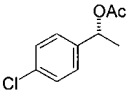
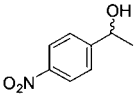
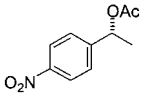
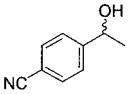
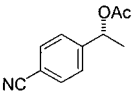
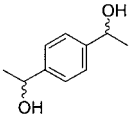
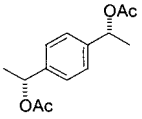
[a] Unless otherwise noted, Ru catalyst (4 mol%) and KO*t*Bu (5 mol%) were stirred in toluene (2 mL) for 6 min before adding **4a** (1 mmol). After 4 min CALB (6 mg), Na_2CO_3 (1 mmol), and isopropenyl acetate (1.5 mmol) were added and the mixture was stirred under an argon atmosphere. [b] Determined by chiral GC. [c] A solution of **4a** in toluene (3.3 mL) was added to a mixture of Ru catalyst and KO*t*Bu. [d] Toluene: 3.3 mL. [e] Yield of isolated product. [f] Under an air atmosphere.

mixture of KO*t*Bu and complex **3b** was stirred for 6 min in toluene before adding the alcohol **4a**, acetate **5a** was obtained in 99% yield with >99% *ee* in 4 h (Table 1, entry 2). When the concentration of **4a** was increased to 0.5 M, **5a** was obtained after only 3 h in 98% yield (>99% *ee*) (Table 1, entry 3). Similar results were obtained with catalyst **3a** under the same reaction conditions (Table 1, entry 4). It was observed that the system is very sensitive to molecular oxygen; thus when the reaction was run under an air atmosphere, only 60% yield was attained after 15 h (Table 1, entry 5).

To study the scope of the reaction, a variety of substrates were tested with the reaction conditions used in Table 1, entry 4.[21] For most substrates we obtained the best results when employing 5 mol% of **3a**. The amount of KO*t*Bu needed depends on the substrate and on the amount of CALB employed;[22] therefore it was optimized for each entry. The

results are summarized in Table 2. Similarly to **5a** (Table 2, entries 1 and 2), the naphthyl derivative **5b** was obtained in 93% yield after 3 h (Table 2, entry 3). The ethyl carbinol **4c** reacts slower with the enzyme and required the use of 40 mg of CALB and 8 mol% of KO*t*Bu. Although a longer reaction time is needed (17 h), **5c** was obtained in high yield and enantioselectivity (92%, >99% *ee*) (Table 2, entry 4). Electron-rich alcohol **4d** did not significantly change the rate or selectivity of the reaction and gave enantiomerically pure **5d** in 96% yield after 6 h (Table 2, entry 5). Similarly, electron-withdrawing groups on the phenyl ring gave enantiopure acetates in excellent yields. Thus, **5e** was obtained in 93% yield in 6 h (Table 2, entry 6). Despite the prolonged reaction times needed for alcohols **4f** and **4g**, this is the first time that acetates **5f** and **5g** are obtained through DKR (Table 2, entries 7 and 8). A plausible explanation that accounts for the need for longer reaction times is that the nitrogen-containing substituents on the substrates slow down the reaction rate by coordination to the ruthenium center. Excellent selectivity and yield were also obtained with the aliphatic substrate **4h** (Table 2, entry 9). DKR of diol **6** is also possible when using 5 mol% of catalyst **3a** at room temperature, although 72 h were needed to attain 93% yield. However, at 50°C enantiopure diacetate **7** was obtained after 10 h in 94% yield (Table 2, entry 10).

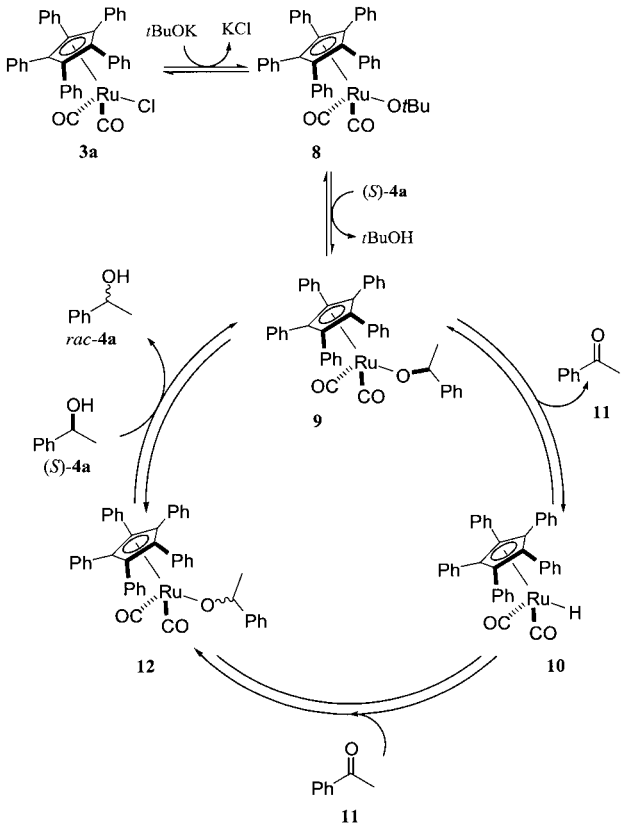
Table 2: DKR of various alcohols.[a]

Entry	Alcohol		KO*t*Bu (mol%)	*t* [h]	Product		Yield [%][b,c]	*ee* [%][b]
1[d]		**4a**	5	3		**5a**	98	>99
2		**4a**	5	3		**5a**	95 (92)	>99
3		**4b**	6.25	3		**5b**	93	>99
4[e]		**4c**	8	17		**5c**	92 (90)	>99
5		**4d**	7.5	6		**5d**	96 (94)	>99
6		**4e**	5	6		**5e**	93 (91)	>99
7		**4f**	5	20		**5f**	99 (97)	>99
8		**4g**	5	20		**5g**	98 (95)	>99
9		**4h**	7	17		**5h**	98[f]	>99
10[g]		**6**	6	10		**7**	94 (90)	>99 (99:1 d.r.)

[a] Unless otherwise noted, Ru catalyst **3a** (5 mol%), CALB (6 mg), Na_2CO_3 (1 mmol), and KO*t*Bu were stirred in toluene (2 mL) at room temperature for 6 min before adding the alcohol (1 mmol). After 4 min, isopropenyl acetate (1.5 mmol) was added and the mixture was stirred at room temperature under an argon atmosphere. [b] Determined by chiral GC. [c] Yield of isolated product in parenthesis. [d] **3b**: 4 mol%. [e] CALB: 40 mg. [f] Yield determined by ^{1}H NMR spectroscopy. [g] 50°C.

The necessity for premixing complex **3a** (or **3b**) with KO*t*Bu in toluene suggests that a new ruthenium complex is formed and this is supported by a color change from yellow to dark red within a few minutes. This intermediate is most likely ruthenium alkoxide **8**, which is crucial for initiating the racemization under DKR conditions. The formation of intermediate **8** is inhibited or slowed down when the substrate alcohol is present in the reaction mixture. A ligand-exchange reaction of **8** with the substrate gives alkoxide **9**, which undergoes β-hydride elimination and forms ruthenium hydride **10** and the oxidized product **11**. Insertion of the ketone into the Ru–H bond produces the racemic alkoxide complex **12**. Alkoxide exchange with *S* alcohol releases *rac* alcohol and regenerates intermediate **9** (Scheme 2).

Alcohol complexes of tungsten, rhenium, and molybdenum have previously been prepared.[23] Recently, Casey et al. observed a Ru–alcohol complex by NMR spectroscopy.[24] Unfortunately, attempts to prepare the alkoxide complex by deprotonation with a base were unsuccessful.[24] The postulated ruthenium alkoxide complex **8** in Scheme 2, would be easy to observe as it cannot undergo β-hydride elimination. When complex **3a** and KO*t*Bu were mixed in [D_8]toluene in an NMR tube and shaken vigorously, a fine new precipitate of KCl was formed that was allowed to settle. The quantitative formation of a new ruthenium complex was observed by ^{13}C NMR spectroscopy. The resonance of the five equivalent quaternary carbons of the cyclopentadienyl ring of **8** is shifted to higher frequency ($\delta = 108.8$ ppm) than that of **3a** ($\delta = 107.1$ ppm) in [D_8]toluene. Similar changes are observed for the resonance of the CO ligands ($\delta = 202.8$ ppm in **8** and 198.0 ppm in **3a**). The resonances of the *tert*-butoxide ligand are also observed ($\delta = 34.3$ and 73.1 ppm), and differ from those of *t*BuOH ($\delta = 31.3$ and 68.2 ppm) and of KO*t*Bu ($\delta = 37.6$ and 66.5 ppm) in [D_8]toluene. Furthermore, when an



Scheme 2. Proposed mechanism for the racemization.

excess of 1-phenylethanol (**4a**) was added to the NMR tube, the formation of acetophenone (**11**) was immediately observed.

In summary, we have developed a highly efficient DKR of secondary alcohols at room temperature that for the first time provides enantiopure products in high yields in very short reaction times. Furthermore, isopropenyl acetate can be employed as the acyl donor, which makes the purification of the products very easy. We have also proven the intermediacy of Ru alkoxides in this process. This mild procedure makes it possible to use sensitive and/or less-thermostable enzymes in future applications.

Experimental Section

Complexes **3a** and **3b** were prepared as described in the literature.[18,25] Toluene was dried over CaH_2 overnight, distilled under argon, and stored over 4-Å molecular sieves. Isopropenyl acetate was washed with saturated K_2CO_3, dried with $CaCl_2$, and distilled under argon. ^{1}H NMR and ^{13}C NMR spectra of acetates were in good agreement with the data previously reported in the literature.[26]

Dynamic kinetic resolution of 1-phenylethanol (**4a**): A solution of KO*t*Bu (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 was filled with argon. CALB[19] (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.[27] 1-Phenylethanol (**4a**) (120 μL, 1 mmol) was then 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/Et_2O 98:2) afforded (*R*)-1-phenylethanol acetate (**5a**) as a colorless oil (151 mg, 92% yield, >99% *ee*).

Received: July 23, 2004

Keywords: enantioselectivity · enzyme catalysis · kinetic resolution · reaction mechanisms · ruthenium

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[19] Immobilized and commercially available as Novozym-435.
[20] Under the same reaction conditions, (2-naphthyl)-1-ethanol gave (2-naphthyl)-1-ethanol acetate in 100% yield but 0% *ee*.
[21] To avoid opening of the reaction vessel, the order of addition of reagents was changed slightly: Toluene was added to a mixture

of KO*t*Bu, Ru complex, CALB, and Na_2CO_3. After 6 min the alcohol was added and the mixture was stirred for 4 min. Finally, isopropenyl acetate was added.

[22] 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. An excess of KO*t*Bu is needed to consume the water in the reaction mixture. To test this hypothesis, DKR of **4a** was carried out under the same reaction conditions as in Table 1, entry 4, but employing 40 mg of CALB instead of 6 mg. Acetate **5a** was obtained in only 57% yield after 3 h.

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[27] Stirring for 10 min gave essentially the same result but stirring for 1.5 h gave less-reproducible results.

