Ruthenium- and Enzyme-Catalyzed Dynamic Kinetic Resolution of Secondary Alcohols

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Abstract: Enzymatic resolution of secondary alcohols under substrate racemizing conditions was studied using an immobilized lipase from *Candida antarctica* in the presence of a ruthenium catalyst. A specifically designed acyl donor, 4-chlorophenyl acetate, was found to be compatible with both catalysts and resulted in an efficient dynamic kinetic resolution. Studies of the reaction in different solvents showed that nonpolar solvents gave the best results. With this process, a variety of racemic secondary alcohols were transformed to the corresponding enantiomerically pure acetates, making efficient use of all starting material. In most cases, the reaction proceeded with >99% ee and in good yield.

Introduction

During the last two decades, the synthesis of enantiomerically pure, or enriched, compounds has emerged into one of the most important fields of organic synthesis.[1] In particular, catalytic asymmetric synthesis, including both metal- and enzyme-catalyzed reactions, has been a highly active area of research. In enzyme-catalyzed transformations, the development of reactions in nonaqueous media constitutes a major breakthrough which has increased their use by nonspecialists.[2] Today, kinetic resolution of racemic substrates by enzyme catalysis has become a standard reaction in organic synthesis.[3] In particular, a variety of efficient processes for lipase-catalyzed hydrolysis of esters and acylation of alcohols are available.[3,4]

A kinetic resolution is generally defined as a process where the two enantiomers of a racemic mixture are transformed to products at different rates. Thus, in an efficient enzymatic resolution, one of the enantiomers of the racemate is selectively transformed to product, whereas the other is left behind (Figure 1).[5] One obvious limitation with this type of enzymatic resolution is that the maximum theoretical yield is limited to 50%. There are several ways to overcome this problem: (1) the use of meso compounds or prochiral substrates;[3f] (2) stereoinversion of the remaining enantiomer[6f] (e.g., Mitsunobu reaction of remaining alcohol in Figure 1); and (3) dynamic kinetic resolution (DKR).[6,7] In DKR, the substrate is continuously isomerized during the resolution process, and this leads to efficient use of all starting material (Scheme 1). In such a process, one can theoretically obtain 100% yield of one enantiomer. Furthermore, provided that the rate of the equilibration of the substrate enantiomers is about the same as or higher than the rate of removal of one enantiomer from the system ($k_{rac} \geq k_R$ or k_S), DKR will lead to higher enantiomeric ratios of the product.[7] Several examples of efficient dynamic enzy-

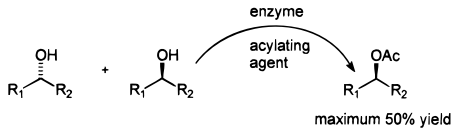
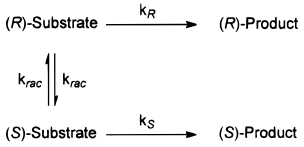


Figure 1. Enzymatic resolution of a secondary alcohol.

Scheme 1



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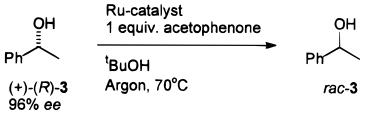
Scheme 2. Ruthenium-Catalyzed Racemization of (+)-(*R*)-**3**[a]



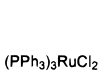
[a] Reaction conditions: 2 mol % **1**, 10 mol % NaOH, 4 h, or 2 mol % **2**, 24 h.

matic resolution have been reported,[6−8] and recently the use of transition metals for substrate racemization has attracted some interest.[6e,9]

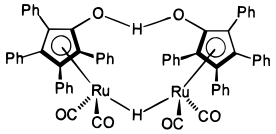
We have been involved in the combination of enzyme and transition metal catalysis,[9c,10] and in a preliminary communication we recently reported on an efficient enzymatic resolution of 1-phenylethanol and 1-indanol coupled with ruthenium-catalyzed racemization of the substrate.[9c] One problem with the latter procedure was that 1 equiv of the corresponding ketone (acetophenone and indanone, respectively) was required for a good result. We have now overcome this problem, and here we give a full account of our new results and discuss the scope and limitations of the reaction.

Results and Discussion

During our studies on ruthenium-catalyzed hydrogen-transfer reactions employing catalyst **1** and **2**,[11−13] we had observed that alcohols undergo fast isomerization at the α-carbon leading to racemization or epimerization.[14] With the aim of developing a DKR of alcohols, we studied the isomerization of (+)-(*R*)-**3** with catalysts **1** and **2** (Scheme 2). Both of the catalysts were able to catalyze the complete racemization of (+)-(*R*)-**3**, **1** with a higher rate than **2**.[15] Although **1** is faster than **2**, it requires the presence of NaOH, which may interfere with the enzyme.

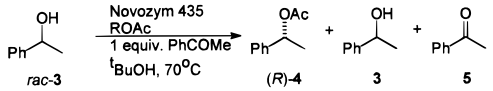


1



2

Scheme 3



The ruthenium-catalyzed racemization of (+)-(*R*)-**3** was then combined with an enzyme-catalyzed transesterification using *Candida antarctica* component B lipase[16] supported on acrylic resin (commercially available under the trade name Novozym 435). This enzyme has been successfully employed in esterifications,[17] transesterifications,[18] and hydrolysis,[19] perhydrolysis,[20] and aminolysis[21] of esters. It has been shown to possess a very high thermostability, tolerating temperatures as high as 70−80 °C,[17] which makes this enzyme most suitable for our purposes. The use of catalyst **1** in combination with the enzyme and different acyl donors gave poor results with decreased activity of the enzyme, and furthermore, the rapid racemization with this catalyst could not be reproduced in the presence of the enzyme. On the other hand, combination of catalyst **2** with the enzyme and the acyl donor worked better. Using vinyl acetate as the acyl donor,[22] a complete conversion of the alcohol was achieved within 17 h. However, only 50% yield of the acetate was obtained, and the rest was oxidized starting material (Scheme 3 and Table 1, entry 1). The use of isopropenyl acetate, from which acetone is formed in the acylation step, showed the same phenomenon but to a lower extent than for vinyl acetate. In this case, 72% of the substrate was converted to (*R*)-1-phenylethyl acetate ((*R*)-**4**), and the remaining 28% was oxidized (Table 1, entry 2).

To avoid the problem with the oxidation associated with alkenyl acetates as acyl donors, we turned our attention to other

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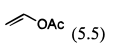
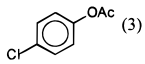
Table 1. Enzymatic Resolution of 1-Phenylethanol (*rac*-**3**) Coupled with Ruthenium-Catalyzed Racemization Employing Catalyst **2**[a]

Entry	ROAc (equiv.)	Time (h)	(*R*)-**4** : **3** : **5**[b]	% ee of (*R*)-**4**
1	 (5.5)	17	50 : 0 : 50	>99[c]
2	 (5)	24	72 : 0 : 28	>99[d]
3[e]	 (3)	87	100 : 0 : 0	>99[d]
			92% isol. yield of (*R*)-**4**	

[a] The reactions were performed on a 2 mmol scale with 2 mol % of complex **2**, 1 equiv of acetophenone, 50 mg of Novozym 435, and the acyl donor (ROAc) in 5 mL of t-BuOH at 70 °C under argon atmosphere. [b] The conversion and ratio of products were determined by ^{1}H NMR and GC. The relative amount of formed acetophenone (**5**) has been corrected for the amount of added acetophenone. [c] The ee was determined on (*R*)-**4** using chiral HPLC on a Chiralcel OD-H column using 5% i-PrOH in hexane, 0.5 mL/min. [d] The ee was determined on the alcohol corresponding to (*R*)-**4** (*i.e.*, (+)-(*R*)-**3**) by chiral HPLC using the same conditions as for the acetate. [e] The reaction was run on half the scale as above (1 mmol).

types of activated esters. Activated esters, such as trichloroethyl esters[2b] and trifluoroethyl esters,[23] have been used in transesterifications, and they shift the equilibrium of the enzyme-catalyzed acyl transfer toward acylated product. For our purposes, however, esters with protons in the α-position to the oxygen are not suitable since the alcohol released will interfere with the ruthenium catalyst (vide infra). Aryl esters were therefore considered as acyl donors, and these esters should also be more reactive than alkyl esters and therefore favor acylation to an aliphatic alcohol. An additional advantage with these esters, e.g., aryl acetates, is that the reactivity can be tuned with electron-withdrawing (or electron-donating) substituents. Attempts to use phenyl acetate as the acyl donor showed that this ester was not active enough in the transesterification. Electron-withdrawing groups on the aryl ring increased the reactivity, and 4-chlorophenyl acetate was found to be an excellent acyl donor in the ruthenium- and enzyme-catalyzed DKR of *rac*-**3** using enzyme Novozym 435 (N-435) and catalyst **2** (Table 1, entry 3). It is interesting to note that the selectivity of the enzyme is excellent irrespective of which acyl donor was used, and the ee was >99% for all three acyl donors employed.

Before turning to other substrates, studies were undertaken to improve the process and make it more general. The addition of 1 equiv of the corresponding ketone to the alcohol was an obvious drawback and would put severe limitations on the procedure, especially when performing the reaction on more sophisticated substrates. However, by gradually decreasing the amount of ketone, the yield of (*R*)-**4** went down and the amount of oxidized starting material increased, suggesting that there was a hydrogen-consuming process taking place, possibly involving the enzyme. The addition of 1 equiv of ketone would prevent this side reaction by keeping a constant and high concentration of the corresponding ketone in the reaction mixture. Since the substrate structure requirement for the enzyme is limited to a relatively small group next to the alcohol function, we thought that benzophenone could work as a hydrogen acceptor in the catalytic cycle. This would provide a general ketone to be used with any substrate, since the intermediate benzhydrol formed would be too sterically demanding for the enzyme and would finally redeliver its hydrogens back to the substrate ketone. This worked to some extent,[24] but as the results without ketone were similar, we decided to omit any ketone when turning to other substrates.

Table 2. Enzymatic Resolution of 1-Phenylethanol (*rac*-**3**) Coupled with Ruthenium-Catalyzed Racemization Employing Catalyst **2** in Various Solvents[a]

entry	solvent	time (h)	conv[b] (%)	(*R*)-**4**:**5**[b]	ee of (*R*)-**4**[c] (%)
1	t-BuOH	20	97	61:39	
		40	>99	67:33	>99
2	*n*-hexane	20	99	83:17	
		40	>99	87:13	>99
3	toluene	20	>99	81:19	
		40	>99	86:14	>99
4	*n*-Bu_2O	20	>99	82:18	
		40	>99	86:14	>99
5	THF	20	98	65:35	>99
6	1,4-dioxane	20	99	72:28	>99

[a] The reactions were performed on a 1 mmol scale with 2 mol % of complex **2**, 30 mg of Novozym 435, 1.0 equiv of benzophenone, and 3.0 equiv of acyl donor (4-Cl−PhOAc) in 2.5 mL of solvent at 70 °C under argon atmosphere. [b] The conversion and ratio of products were determined by ^{1}H NMR and GC. [c] The ee was determined on the alcohol corresponding to (*R*)-**4** (*i.e.*, (+)-(*R*)-**3**) by chiral HPLC on a Chiralcel OD-H column using 5% i-PrOH in hexane, 0.5 mL/min.

The resolution of **3** catalyzed by **2** (2 mol %) and Novozym 435 using 3 equiv of 4-chlorophenyl acetate was then examined using a variety of solvents.[25] As shown in Table 2, full conversion was obtained within 20 h for all of the solvents tested, where nonpolar solvents such as toluene and hexane gave the best results; t-BuOH was the slowest among the solvents tested. The selectivity of the enzyme, however, did not vary significantly in any of the solvents. Significant amounts of acetophenone **5** were formed as a byproduct in all cases, again t-BuOH being the poorest solvent. Toluene was finally chosen as the solvent for further studies.

To study the scope of the reaction, a variety of substrates were resolved using the same reaction conditions as in Table 1 but employing toluene as the solvent and without added ketone. The results are summarized in Table 3. The phenylethanol (**3**) gave the acetate **4** in 80% yield with >99% ee. The fused ring systems, indanol and dehydronaphthol (**6** and **8**, entries 2 and 3), afforded the acetates in high selectivities and in good yields. The 4-bromo-substituted derivative **10** did not significantly change the rate or selectivity of the reaction and gave enantiomerically pure **11** in 78% yield. However, a methoxy substituent in the 4-position (**12**, entry 5) had a negative effect on the efficiency of the process, and the corresponding acetate (**13**) was obtained in only 60% yield and 91% ee. In this reaction, large amounts of oxidized ketone were formed, which is a result of the high reduction potential of benzylic alcohols with electron-donating groups in the 4-position.[26,27] Slightly longer reaction times were required for the 1-naphthyl derivative **14**

(23) Hennen, W. J.; Sweers, H. M.; Wang, Y.-F.; Wong, C.-H. *J. Org. Chem.* **1988**, *53*, 4939.

(24) Using 1 equiv of benzophenone gave a high initial formation of acetophenone which dropped during the course of the reaction, indicating that benzophenone indeed worked as a hydrogen mediator. After 24 h, the product composition was acetate/acetophenone 87:13, and that without added ketone was 85:15. Adding hydrogen gas (5 mL) and closing the system had no effect.

(25) For other solvent studies using Novozym 435, see refs 17a, 18f, and 18i.

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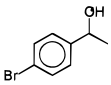
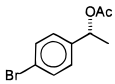
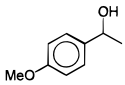
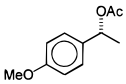
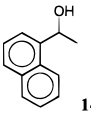
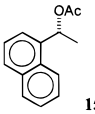
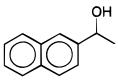
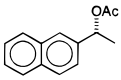
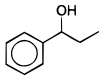
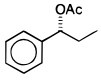
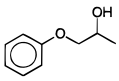
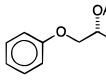
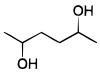
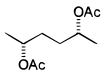
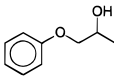
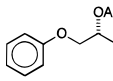
Table 3. Enzymatic Resolution of Secondary Alcohols Coupled with Ruthenium-Catalyzed Racemization Employing Catalyst **2**[a]

Entry	Substrate	Product	Time/h	%Yield[b]	%ee[c]
1	 **3**	 **4**	46	80[d]	>99
2	 **6**	 **7**	48	77[d]	>99
3	 **8**	 **9**	48	65	>99
4	 **10**	 **11**	44	78[d]	>99
5	 **12**	 **13**	48	60[d]	91
6	 **14**	 **15**	72	69	99[e]
7	 **16**	 **17**	48	79	>99
8	 **18**	 **19**	46	80[d]	98
9	 **20**	 **21**	46	88	>99
10	 **22**	 **23**	48	79[d]	>99[e]
11	 **24**	 **25**	24[f]	80	>97[g]
12[h]	 **26**	 **27**	48	63	>99[e,i]
13[j]	 **28**	 **29**	24[f]	68	79[k]

[a] The reactions were performed on a 2 mmol scale with 2 mol % of complex **2**, 60 mg of Novozym 435, and 3 equiv of acyl donor (4-Cl-PhOAc) in 5 mL of toluene at 70 °C under argon atmosphere. [b] Isolated yield. [c] Unless otherwise noted, the ee was determined on the alcohol corresponding to the acetate formed, by using chiral HPLC on a Chiralcel OD-H column. [d] Products were contaminated with 4-Cl-PhOAc after flash chromatography. Yields were calculated from ^{1}H NMR spectrum. [e] The ee was determined on the 2-chlorobenzoic acid ester of the alcohol corresponding to the acetate formed, by using chiral HPLC on a Chiralcel OD-H column. [f] The reaction was run with half the amount of solvent. Under the general conditions, the reaction time was 68 h. [g] The ee was determined on the alcohol corresponding to the acetate formed, by using chiral GC on a CP-Chirasil Dex CB. [h] The reaction was performed on a 1 mmol scale with 4 mol % of complex **2**, 60 mg of Novozym 435, and 3 equiv of acyl donor (4-Cl-PhOAc) in 3 mL of toluene at 70 °C under argon atmosphere. [i] *R,R*/*meso* 86:14. [j] Half the amount of enzyme (30 mg) and double the amount (4 mol %) of complex **2** were used (see text). [k] The ee was determined on the acetate by using chiral HPLC on a Chiralcel OD-H column.

(entry 6). Only 73% conversion was obtained after 48 h, finally giving the product in 69% yield after 72 h. About 20% was oxidized byproduct (16% isolated). The other naphthyl derivative, (2-naphthyl)-1-ethanol (**16**), showed behavior similar to that of 1-phenylethanol (**3**), both in terms of reaction time and yield (entry 7).[28] The result from alcohol **18** demonstrates that going from methyl to ethyl carbinol makes no significant change in either yield or selectivity, giving acetate **19** in 80% yield and 98% ee.[29] The best substrate in terms of yield was phenoxypropanol (**20**), which afforded acetate **21** in 88% isolated yield (entry 9). *High selectivities and good yields were also obtained with the aliphatic substrates* ***22***, ***24***, *and* ***26*** *(entries 10*−*12).* It is interesting to note that these alcohol derivatives are difficult to obtain in high ee from asymmetric reduction of the corresponding ketone. For example, the highest reported enantioselectivity in the reduction of 2-octanone is 79% ee.[30] DKR of two chiral centers in the same molecule is exemplified by diol **26**, which gave diacetate **27** with >99% ee (entry 12). This compound is an important synthetic building block for the transformation into enantiomerically pure 2,5-dimethylpyrrolidine via a two-step procedure.[31] The introduction of small functional groups next to the alcohol is tolerated, as demonstrated by the α-chloro-substituted alcohol **28** (entry 13).[32] This would allow further functionalization of the products and increase the synthetic utility of the process. Acetate **29**, for example, can easily be converted into the corresponding amino alcohol by a two-step procedure.[33] The initial experiment using the conditions of entry 11 gave acetate **29** in 71% yield but only 58% ee, indicating that the racemization was too slow compared to acylation. Increasing the amount of catalyst **2** and at the same time decreasing the amount of enzyme gave acetate **29** in 68% yield and 79% ee.

The separation of product from unreacted acyl donor, 4-chlorophenyl acetate, was in some cases difficult. This problem was solved to some extent by performing a selective hydrolysis of 4-chlorophenyl acetate in the presence of the product acetate. This was accomplished by treating the mixture with a saturated solution of $NaHCO_3$ in methanol and carefully monitoring the reaction by GC. Kinetic experiments showed that the rate of hydrolysis of 4-chlorophenyl acetate was nearly 200 times faster than that of acetate **4**, which was used as the model substrate, allowing a more than 95% recovery of the product.

Another way around this problem would be to design other types of acyl donors that could be more easily separated from the products. We therefore prepared some substituted aryl acetates, 4-NO_2, 2-CO_2H, and 4-CO_2H, and tested them under the conditions of entry 1, Table 3. The carboxylic derivatives gave very poor results, which undoubtedly could be ascribed to the acid functionality. The 4-NO_2 derivative gave a 60% yield of acetate, which should be compared with 76% using 4-chlorophenyl acetate.

We were also interested in whether the number of halogens attached to the phenyl acetate would influence the rate of the acylation step. This would give the possibility to match the rate of the enzyme-catalyzed acylation with the racemization of a given alcohol. A variety of mono-, di-, and trichloro-substituted phenyl acetates was prepared and compared using 1-phenyl-

(28) A big difference in rate between 1-naphthylethanol (**14**) and 2-naphthylethanol (**16**) has been observed in ruthenium-catalyzed asymmetric transfer hydrogenation reactions. See ref 26a.

(29) Substrates with larger groups (e.g., isopropyl) next to the alcohol function are too sterically demanding for this particular enzyme; see ref 18e.

(30) Almquist, F.; Torstensson, L.; Gudmundsson, A.; Frejd, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 376.

(31) Short, R. P.; Kennedy, R. M.; Masamune, S. *J. Org. Chem.* **1989**, *54*, 1755.

(32) Closely related substrates gave low *E* values when using *Candida antarctica* in hydrolysis of the corresponding butanoic esters; see ref 19b.

(33) Ader, U.; Schneider, M. P. *Tetrahedron: Asymmetry* **1992**, *3*, 205.

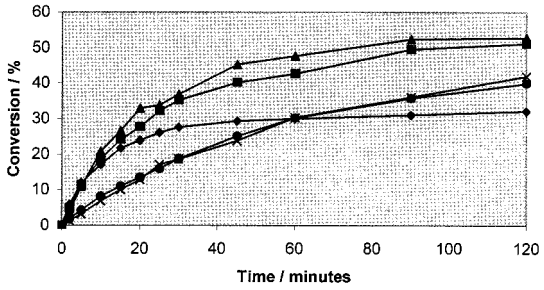
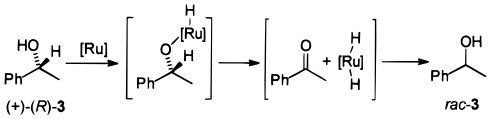


Figure 2. Novozym 435-catalyzed acylation of 1-phenylethanol (**3**), in toluene at 30 °C, using chloro-substituted phenyl acetates (PA) as acyl donors: (▲) 2,4-dichloro-PA; (■) 4-chloro-PA; (◆) PA; (●) 2,4,6-trichloro-PA; (×) 2,4,5- trichloro-PA.

Scheme 4



ethanol (**3**) and N-435 in toluene at 30 °C. The results are summarized in Figure 2. The mono- and disubstituted derivatives were comparable in rate, with the latter being somewhat faster. The initial rate of the nonsubstituted phenyl acetate was similar but reached equilibrium at ca. 30% conversion, where it stopped even after prolonged reaction times. Interestingly, the initial rates of the trisubstituted analogues were by far the slowest, although 50% conversion was reached after extended reaction times (not shown in Figure 2). This difference in rate may be explained by the size of these compounds and the steric restrictions of the enzyme, which counterbalance the good activation of these compounds.

Mechanistic Considerations

The mechanism of the ruthenium-catalyzed hydrogen-transfer reaction has been studied in some detail.[11−13,34,35] The reaction proceeds through a base-mediated hydrogen abstraction from a hydrogen donor, in our case the substrate itself, forming an intermediate ruthenium alkoxy species. Abstraction of the α-proton gives the intermediate ketone and a ruthenium hydride complex. Subsequent readdition of the hydrogens to the ketone completes the catalytic cycle to give the racemized substrate (Scheme 4).

The problems with oxidized starting material when using vinyl and isopropenyl acetates as acyl donors (Table 1) could be explained by this mechanism. When the acyl part of these acyl donors is transferred to the substrate, the remaining vinyl alcohol is rapidly tautomerized into the corresponding carbonyl compound, acetaldehyde and acetone, respectively. Both of these can compete with the intermediate ketone of the substrate as hydrogen acceptors in the catalytic cycle and thereby consume the hydrides on ruthenium, resulting in an overall oxidation of the starting material.[36] The formation of 2-propanol when using isopropenyl acetate as acyl donor was also confirmed by GC analysis. By using an activated aryl acetate, this problem was completely avoided. The reason for this is that the phenol released contains neither α-protons nor keto functionality; hydrogens cannot be abstracted or added to it, and therefore it does not interfere with the ruthenium catalyst.

The somewhat long reaction times (>40 h) are mainly a result of the rate-determining racemization. This could, according to Scheme 1, lead to partial acylation of the wrong isomer, giving ee values below the reported >99%. However, the high preference (*E* value often >200)[18] for *C. antarctica* to acylate only the *R*-isomer compensates for this. The case of 2-octanol (entry 11) also shows that the reaction times can be shortened from 68 to 24 h simply by concentrating the reactions from 0.4 to 0.8 M (in substrate). Since most examples in Table 3 were run at 0.4 M, the reaction times can be brought down by carrying out the reactions at a higher concentration.

Conclusion

We have demonstrated that it is possible to combine transition metal and enzyme catalysis to obtain dynamic kinetic resolution of alcohols. In situ isomerization of the substrate alcohol by a ruthenium catalyst and enzymatic acylation with a specifically designed acyl donor resulted in full transformation of the racemic alcohol to enantiomerically pure acetate. The yields and selectivities were consistently high, and in most cases ee's were >99%.

Experimental Section

General. Solvents for extraction and chromatography were technical grade and distilled: pentane, hexane, and ethyl acetate (EtOAc). GC columns used were Rescom SE54 and Chrompack CP-Chiracil-Dex CB.

All reactions were performed under dry nitrogen or argon atmosphere in oven-dried (140 °C) glassware, except for those reactions utilizing water as a solvent, which were run in air. Brine refers to a saturated solution of NaCl. Novozym 435 (*C. antarctica* lipase B; 8200 units/g) was a generous gift from Novo Nordisk A/S, Denmark. Substrates **3**, **6**, **8**, **10**, **12**, **14**, **16**, **18**, **22**, and **24** were commercially available and used without further purification. 2,5-Hexanediol (**26**) was prepared by $NaBH_4$ reduction of commercially available 2,5-hexanedione using standard techniques. 1-Phenoxy-2-propanol[37] (**20**) and 1-phenoxy-3-chloro-2-propanol[38] (**28**) were prepared according to literature procedures.

$[Ru_2(CO)_4(\mu\text{-}H)(C_4Ph_4COHOCC_4Ph_4)]$ (2). A modified synthesis of this catalyst was used.[13,39] In step 1, $Ru_3(CO)_{12}$ (1.205 g, 1.885 mmol) and tetraphenylcyclopentadienone (2.899 g, 7.54 mmol) in mesitylene (18 mL) was heated to reflux under argon for 24 h. The mixture was cooled to room temperature, flushed with argon several times, and heated to reflux for an additional 6 h. The solvent was distilled off under reduced pressure, and the crude, dark red mixture was separated on silica (CH_2Cl_2) to yield $Ru(CO)_3(\eta^4\text{-}Ph_4C_4CO)$ (2.018 g, 63%).

In step 2, the product from the first step was dissolved in acetone (120 mL). Saturated Na_2CO_3 (aqueous, 60 mL) was added, and the mixture was stirred under argon at ambient temperature for 1.5 h. The brown-orange mixture changed to bright orange during the course of the reaction. Saturated NH_4Cl (aqueous, 150 mL) was added, and the acetone was removed in vacuo. The aqueous solution was extracted with CH_2Cl_2 (3 × 100 mL), and the combined organic phases were dried ($MgSO_4$). The solvent was evaporated, and the orange residue was purified on a short silica column. Hexane was used until the red fraction had moved about 2−3 cm on the column, and then hexane/CH_2Cl_2 (gradient 50:50 to 0:100) was used to yield the title compound (1.336 g, 69%).

(34) (a) Morton, D.; Cole-Hamilton, D. J. *J. Chem. Soc., Chem. Commun.* **1988**, 1154. (b) Osakada, K.; Kim, Y. J.; Tanaka, M.; Ishiguro, S. I.; Yamamoto, A. *Organometallics* **1991**, *10*, 197. (c) Sasson, Y.; Blum, J. *J. Org. Chem.* **1975**, *40*, 1887. (d) Dobson, A.; Robinson, S. D. *Inorg. Chem.* **1977**, *16*, 137. (e) Shinoda, S.; Itagaki, H.; Saito, Y. *J. Chem. Soc., Chem. Commun.* **1985**, 860.

(35) (a) Shvo, Y.; Blum, Y. *Isr. J. Chem.* **1984**, *24*, 144. (b) Blum, Y.; Czarkie, D.; Stein, Z.; Shvo, Y. *Organometallics* **1985**, *4*, 1459. (c) Shvo, Y.; Czarkie, D.; Rahamin, Y. *J. Am. Chem. Soc.* **1986**, *108*, 7400. (d) Abed, M.; Goldberg, I.; Stein, Z.; Shvo, Y. *Organometallics* **1988**, *7*, 2054.

(36) The ethanol or 2-propanol formed is then acylated by the enzyme, and the process becomes irreversible.

(37) Waagen, V.; Partali, V.; Hollingsaeter, I.; Huang, M. S. S.; Anthonsen, T. *Acta Chem. Scand.* **1994**, *48*, 506.

(38) Stephenson, O. *J. Chem. Soc.* **1954**, 1571. See also ref 19b.

(39) Beller, M. Unpublished results from these laboratories.

4-Chlorophenyl Acetate. Acetyl chloride (2.4 mL, 33 mmol) was added dropwise to a solution of 4-chlorophenol (3.86 g, 30.0 mmol), Et_3N (9.11 g, 90 mmol), and DMAP (73 mg, 0.6 mmol) in CH_2Cl_2 (60 mL). The reaction mixture was stirred at room temperature for 16 h. The solution was washed with 1 M HCl (3 × 50 mL), and the combined aqueous phases were extracted with ether (3 × 50 mL). The combined organic phases were washed with saturated Na_2CO_3 (aqueous, 30 mL) and brine (20 mL) and dried over $MgSO_4$. The solvent was evaporated, and the crude mixture was purified on silica using MPLC (EtOAc/pentane gradient) to yield 4-chlorophenyl acetate (4.423 g, 86%). ^{1}H NMR: δ 2.35 (3 H, s, CH_3), 7.04 (2 H, dm, J = 7.9 Hz, ArH) 7.36 (2 H, dm, J = 7.9 Hz, ArH). ^{13}C NMR: δ 21.0, 122.9, 129.4, 131.2, 149.1, 169.2.

General Procedure for the Ruthenium- and Enzyme-Coupled Resolution of Secondary Alcohols. Catalyst [$Ru_2(CO)_4(\mu$-H)(C_4Ph_4-$COHOCC_4Ph_4$] (**2**) (43 mg, 0.04 mmol) and Novozym 435 (60 mg) were placed in a two-necked flask with a condenser, and the atmosphere was changed to argon. Argon was bubbled through a solution of racemic 1-phenylethanol (**3**, 244 mg, 2 mmol) and 4-chlorophenyl acetate (1.02 g, 6 mmol) in toluene (5 mL), followed by transfer to the ruthenium catalyst and enzyme. The reaction was stirred under argon for 46 h at 70 °C. The reaction mixture was filtered and separated on silica (ether/pentane 2:98) to yield (*R*)-1-phenylethyl acetate (**4**, 135 mg, 80%).[40] The acetate was hydrolyzed by treatment with K_2CO_3 (276 mg, 2 mmol) in methanol/water (4:1), 16 h at room temperature. The methanol was evaporated, and the aqueous phase was extracted with Et_2O (3 × 50 mL). The combined organic phases were washed with brine, dried over Na_2SO_4, and reduced in vacuo. The residue was purified on a short silica column (Et_2O/pentane 10:90). The ee of the alcohol was determined with chiral HPLC on a Chiralcel OD-H column, using 5% 2-propanol in hexane, 0.5 mL/min: ee > 99.5% racemic 1-phenylethanol (**3**) used as reference.

The ^{1}H NMR and ^{13}C NMR spectra of each compound were in good agreement with the data previously reported in the literature.[41] Compounds **11**, **23**, and **27** are known in the literature, but no NMR spectra were given. We therefore provide their NMR spectra as Supporting Information.

Selective Hydrolysis of 4-Chlorophenyl Acetate. The following procedure is representative: 0.648 g of a mixture of 1,2,3,4-tetrahydro-1-naphthyl acetate (**9**) and 4-chlorophenyl acetate in 15 mL of a 4:1 mixture of methanol and saturated $NaHCO_3$ (aqueous) was stirred at room temperature. The reaction was followed by GC. After 2.5 h, the methanol was evaporated and the aqueous phase extracted with Et_2O (3 × 30 mL). The combined organic phases were washed with 2 M NaOH and brine and finally dried over Na_2SO_4. The solvent was removed in vacuo and the residue chromatographed through a short plug of SiO_2 (pentane/Et_2O 9:1) to give 0.246 g of pure 1,2,3,4-tetrahydro-1-naphthyl acetate (**8**) (65% yield overall from racemic **8**). This was then hydrolyzed according to the general procedure before ee determination.

Acknowledgment. Financial support from the Swedish Natural Science Research Council, the Swedish Research Council for Engineering Sciences, and the Swedish Foundation for Strategic Research is gratefully acknowledged.

Supporting Information Available: Additional experimental procedures and NMR data for **11**, **23**, and **27** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA983819+

(40) The separation of 1-phenylethyl acetate (**4**) and 4-chlorophenyl acetate is difficult, and in most cases only unreacted 1-phenylethanol (**3**) was separated in this purification. The hydrolysis was performed on the mixture of (*R*)-1-phenylethyl acetate and 4-chlorophenyl acetate, and the (*R*)-1-phenylethanol was isolated in the purification after the hydrolysis step.

(41) NMR data can be found in the following references. **4:** Bianchi, D.; Cesti, P.; Battistel, E. *J. Org. Chem.* **1988**, *53*, 5531. **7:** Pincock, J. A.; Wedge, P. J. *J. Org. Chem.* **1995**, *60*, 4067. **9:** Boyd, D. R.; Sharma, N. D.; Kerley, N. A.; McMordie, R. A. S.; Sheldrake, G. N.; Williams, P.; Dalton, H. *J. Chem. Soc, Perkin Trans. 1* **1996**, *1*, 67. **13:** Brown, S. M.; Davies, S. G.; de Sousa, J. A. A. *Tetrahedron: Asymmetry* **1993**, *4*, 813. **15:** Pirkle, W. H.; Hauske, J. R. *J. Org. Chem.* **1976**, *41*, 801. **17:** Legros, J. Y.; Toffano, M.; Fiaud, J. C. *Tetrahedron* **1995**, *51*, 3235. **19:** Rao, B. R.; Nambudiry, M. E. N. *Synth. Commun.* **1991**, *21*, 1721. **21:** Funahashi, K. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1488. **25:** See ref 22b. **29:** Iqbal, J.; Srivastava, R. R. *Tetrahedron* **1991**, *47*, 3155.