JOC*Article*

Ruthenium- and Enzyme-Catalyzed Dynamic Kinetic Asymmetric Transformation of 1,4-Diols: Synthesis of γ-Hydroxy Ketones

Belén Martín-Matute and Jan-E. Bäckvall*

Department of Organic Chemistry, Arrhenius Laboratory, Stockholm University, SE-106 91 Stockholm, Sweden

jeb@organ.su.se

Received August 25, 2004

Enzymatic kinetic resolution of unsymmetrical 1,4-diols in combination with a ruthenium-catalyzed hydrogen transfer process led to a dynamic kinetic asymmetric transformation (DYKAT) of the least hindered alcohol. Oxidation of the second hydroxy group takes place under the reaction conditions leading to the formation of γ-acetoxy ketones in high enantiomeric purity.

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 chemistry.[1] In particular, the resolution of racemic compounds by enzyme-catalyzed reactions has become a powerful tool in organic chemistry.[2] However, for the production of a single enantiomer, kinetic resolution has a maximum theoretical yield of 50%. By applying dynamic kinetic resolution (DKR)[3,4] this limitation can be overcome since the unreactive enantiomer is continuously racemized and the product can be obtained in 100% yield. In the past few years we[3a−c,5] and others[3d,e,g,6] have applied DKR to the preparation of different functionalized alcohols that are important building blocks for the synthesis of high-value compounds.

The synthesis of γ-hydroxy ketones as precursors of versatile building blocks, such as tetrahydrofurans[7] and dihydrofurans,[8] is well established. These compounds are also useful in biodegradable polymers and perfumes.[9]

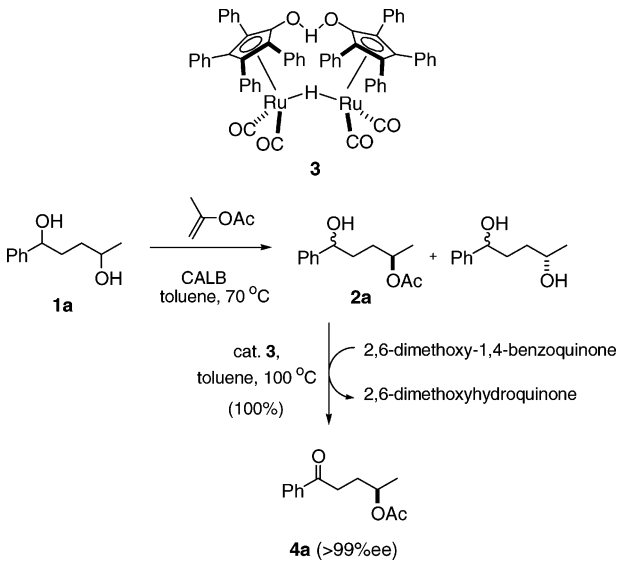
Some approaches for the preparation of enantiopure γ-hydroxy ketones have been reported. These procedures include the use of chiral catalysts,[9,10] the use of chiral epoxides,[11] and the kinetic resolution of γ-hydroxy ketones.[11] To the best of our knowledge, only one study dealing with the lipase-catalyzed kinetic resolution of γ-hydroxy ketones has been reported.[11] The efficiency of the kinetic resolution for acyclic γ-hydroxy ketones is rather low, and the highest ee value obtained was 42%. The low efficiency of the kinetic resolution of γ-hydroxy ketones prompted us to develop an alternative dynamic process for the preparation of enantioenriched γ-hydroxy ketones. As part of our ongoing program on the combined enzyme- and transition metal-catalyzed DKR some procedures for diols have been recently reported.[12,13] All diols tested were transformed into diacetates in excellent enantiomeric excess. We have now taken advantage of the very efficient enzymatic resolution of 1,4-diols and combined it with a Ru-catalyzed hydrogen transfer process leading to a dynamic kinetic asymmetric transformation (DYKAT)[13,14] providing chiral γ-acetoxy ketones. In this process, 1,4-diols, containing one large (R_L) and one small (R_S) group, are transformed to enantiomerically enriched γ-acetoxy ketones (Scheme 1).

(1) (a) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; John Wiley & Sons: New York, 1994.
(2) (a) Faber, K. *Biotransformations in Organic Chemistry*; Springer-Verlag: Berlin, Germany, 2000. (b) *Enzyme Catalysis in Organic Synthesis*: *A Comprehensive Handbook*; Drauz, D., Waldmann, H., Eds.; Wiley-VCH: Weinheim, Germany, 2002; Vol. 2. (c) Kazlauskas, R. J.; Bornscheuer, U. T. *Hydrolases in Organic Synthesis*; Wiley-VCH: Weinheim, Germany, 1999.
(3) For reviews on DKR, see: (a) Pàmies, O.; Bäckvall, J.-E. *Trends Biotechnol.* **2004**, *22*, 130−135. (b) Pàmies, O.; Bäckvall, J.-E. *Chem. Rev.* **2003**, *103*, 3247−3262. (c) Huerta, F. F.; Minidis, A. B. E.; Bäckvall, J.-E. *Chem. Soc. Rev.* **2001**, *30*, 321−331. (d) Kim, M.-J.; Ahn, Y.; Park, J. *Curr. Opin. Biotechnol*. **2002**, *13*, 578−587. Kim, M.-J.; Ahn, Y.; Park, J. *Curr. Opin. Biotechnol.* **2003**, *14*, 131. (e) El Gihani, M. T.; Williams, J. M. J. *Curr. Opin. Chem. Biol*. **1999**, *3*, 11−15. (f) Stürmer, R. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1173−1174. (g) Reetz, M. T.; Schimossek, K. *Chimia* **1996**, *50*, 668−669. (h) Noyori, R.; Tokunaga, M.; Kitamura, M. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 36−56. (i) Ward, R. S. *Tetrahedron*: *Asymmetry* **1995**, *6*, 1475−1490.
(4) For dynamic thermodynamic resolutions see: Beak, P.; Anderson, D. R.; Curtis, M. D.; Laumer, J. M.; Pippel, D. J.; Weisenburger, G. A. *Acc. Chem. Res.* **2000**, *33*, 715−727.
(5) Martín-Matute, B.; Edin, M.; Bogár, K.; Bäckvall, J.-E. *Angew. Chem., Int. Ed.* **2004**, in press.
(6) (a) Choi, J. H.; Kim, Y.-H.; Nam, S. H.; Shin, S. T.; Kim, M.-J.; Park, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 2373−2376. (b) Choi, J. H.; Choi, Y. K.; Kim, Y. H.; Park, E. S.; Kim, E. J.; Kim, M.-J.; Park, J. *J. Org. Chem.* **2004**, *69*, 1972−1977.
(7) Harmange, J. C.; Figadère, B. *Tetrahedron*: *Asymmetry,* **1993**, *4*, 1711−1754.
(8) See, for example: (a) Shao, X.; Tamm, C. *Tetrahedron Lett.* **1991**, *32*, 2891−2892. (b) Reissig, H.-U.; Holzinger, H.; Glomsda, G. *Tetrahedron* **1989**, *45*, 3139−3150. (c) Roussis, V.; Gloer, K. B.; Wiemer, D. F. *J. Org. Chem.* **1988**, *53*, 2011−2015.
(9) Seiji, W.; Shigeru, M.; Kidenori, K. European Patent Appl. 18, 1997.
(10) (a) Corey, E. J.; Link, J. O. *Tetrahedron Lett.* **1989**, *30*, 6275−6278. (b) Watanabe, M.; Soai, K. *J. Chem. Soc., Perkin Trans. 1* **1994**, 837−842.
(11) Crotti, P.; Bussolo, V. D.; Favero, V.; Minutolo, F.; Pineschi, M. *Tetrahedron*: *Asymmetry,* **1996**, *7*, 1347−1356.
(12) Persson, B. A.; Huerta, F. F.; Bäckvall, J.-E. *J. Org. Chem.* **1999**, *64*, 5237−5240.
(13) Edin, M.; Steinreiber, J.; Bäckvall, J.-E. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5761−5766.
(14) Trost, B. M. *Chem. Pharm. Bull.* **2002**, *50*, 1−14.

10.1021/jo048511h CCC: $27.50
Published on Web 11/11/2004

SCHEME 1. Dynamic Kinetic Asymmetric Transformation of 1,4-Diols to γ-Acetoxy Ketones ($R_L \neq$ Me, Et, R_S = Me)

SCHEME 2. Two-Step Procedure for the Synthesis of Enantiomerically Pure γ-Acetoxy Ketones



Results and Discussion

For an unsymmetrical 1,4-diol with a large and a small group only one of the alcohol groups (the least sterically hindered) will be accessible to the enzyme. Treatment of 1-phenyl-1,4-pentanediol (**1a**) with isopropenyl acetate in the presence of *Candida antarctica* lipase B (CALB) in toluene at 70 °C afforded diol monoacetate **2a** in 45% yield.[15] After purification by chromatography (38% isolated yield) oxidation[16] of **2a** in the presence of Shvo's catalyst (**3**)[17] and 2,6-dimethoxy-1,4-benzoquinone afforded the known γ-acetoxy ketone **4a**[11] enantiomerically pure (>99% ee) (Scheme 2). This result prompted us to develop conditions for a one-pot synthesis of compounds **4** starting from the diols precursors.

In the very first attempts to combine the DYKAT of the least hindered alcohol and the oxidation of the inner alcohol, we used CALB, isopropenyl acetate, and Shvo's ruthenium catalyst **3**. Subjecting diol **1b** (R = *i*-Pr) to the reaction conditions at 70 °C with use of 5 mol % of catalyst **3** led to consumption of all the starting material after 12 h. Surprisingly, 57% of acetoxy ketone **4b** was obtained in 90% ee and the remainder of the converted starting material was diketone **5b** (Scheme 3).

Before turning to other substrates, studies were undertaken to improve the synthesis of γ-acetoxy ketones in one pot (Table 1). The yield was improved by using freshly distilled isopropenyl acetate, but in this case **4b** was obtained in lower ee (compare entries 1 and 2, Table 1). By increasing the amount of freshly distilled acyl donor the yield improved and the ee remained the same (compare entries 2 and 3, Table 1). When 20 equiv of isopropenyl acetate were employed the ee was improved to 89% and **4b** was obtained in good yield (entry 4, Table 1). Running the reaction in the presence of 40 equiv of acyl donor did not increase either the ee or the yield (entry 5, Table 1). The reaction was also tried in different solvents. Thus, in cyclohexane at 65 °C **4b** was obtained in 81% yield (71% ee) (entry 6, Table 1). Using *tert*-butyl methyl ether as the solvent at 65 °C did not improve the process (entry 7, Table 1). Increasing the amount of enzyme to 60 mg per mmol of diol gave **4b** in high yield but low ee (entry 8, Table 1). When *p*-chlorophenyl acetate was employed as acyl donor, **4b** was obtained in 93% yield and 86% ee. However, prolonged reaction times were needed (entry 9, Table 1). The use of *Pseudomonas cepacia* lipase (PS-C "Amano II") gave only decomposition products (entry 10, Table 1). Diol **1a** gave acetoxy ketone **4a** by using CALB and 10 equiv of isopropenyl acetate (entry 11, Table 1).

SCHEME 3. One-Pot Procedure for the Synthesis of γ-Acetoxy Ketones

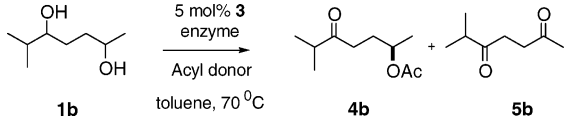
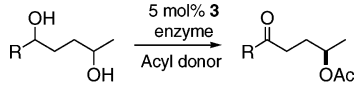


TABLE 1. DYKAT of 1,4-Diols[a]



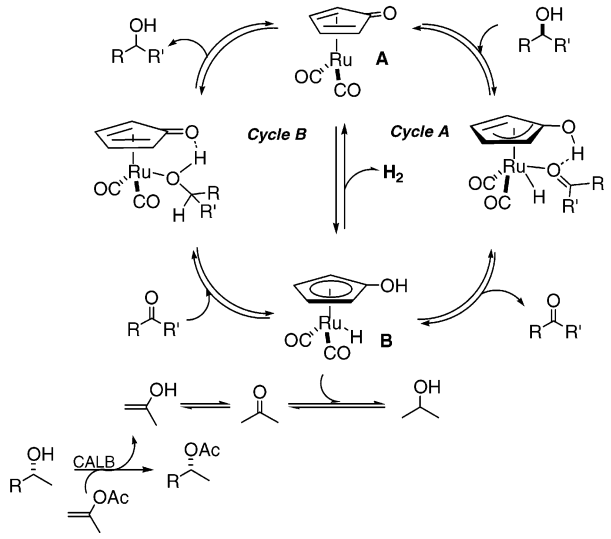
entry	substrate	acyl donor (equiv)	enzyme (mg/mmol)[b]	yield of **4** (%)[c]	ee (%)[d]
1	**1b**	3	CALB (30)	57 (53)[e]	90
2[f]	**1b**	3	CALB (30)	75	75
3[f]	**1b**	10	CALB (30)	84	75
4[f]	**1b**	20	CALB (30)	77	89
5[f]	**1b**	40	CALB (30)	71	83
6[f,g]	**1b**	20	CALB (30)	81	71
7[f,h]	**1b**	20	CALB (30)	76	75
8	**1b**	20	CALB (60)	90	51
9[i]	**1b**	3[j]	CALB (30)	93	86
10	**1b**	20	PS-C "Amano II"		
11	**1a**	10	CALB (60)	63[e]	83

[a] Conditions unless otherwise noted: 0.14 mmol of **1**, CALB, isopropenyl acetate and 5 mol % of **3** in 0.5 mL of toluene at 70 °C for 12 h. [b] Milligrams of enzyme per millimole of diol. [c] % yield measured by GC. [d] Enantiomeric excess determined by GC. [e] Isolated yield. [f] Freshly distilled isopropenyl acetate. [g] In cyclohexane at 65°C. [h] In *tert*-butyl methyl ether at 65°C. [i] Reaction time was 4 days. [j] *p*-Chlorophenyl acetate as acyl donor.

Scope and Limitations of the DYKAT. To study the scope of the reaction, a variety of substrates were resolved (Table 2). Aliphatic substrates were tested by using the best reaction conditions of Table 1. Thus, substrates **1b**,**c** gave the corresponding γ-hydroxy ketones **4b**,**c** in good yields and high enantiomeric excess (entries 2−4, Table 2). Substrate **1d** was also converted to the corresponding acetoxy ketone in a high yield but with low enantiomeric excess. A plausible explanation is that the readdition of hydrogen to the inner ketone might simply be very slow because of steric hindrance

(15) Yield determined by ^{1}H NMR.
(16) Csjernyik, G.; Éll, A. H.; Fadini, L.; Pugin, B.; Bäckvall, J.-E. *J. Org. Chem.* **2002**, *67*, 1657−1662.
(17) Menasche, N.; Shvo. Y. *Organometallics* **1991**, *10*, 3885−3891.

SCHEME 4. Proposed Mechanism for the Easy [Ru]-Catalyzed Oxidation of the Inner Alcohol[a]



[a] The phenyl groups on the ring are omitted for clarity.

giving rise to the formation of a significant amount of hydroxy ketone, and as observed before,[11] the enantioselectivity of CALB for this kind of substrates is rather low (vide infra). For aromatic substrates 2.5 mol % of Shvo's catalyst gave good results, and the use of 8 mg of CALB per mmol of diol and 10 equiv of isopropenyl acetate gave the best ee. Electron-donating groups on the phenyl ring significantly decreased the enantioselectivity (entry 10, Table 2), which is a result of the high redox potential of phenyl ketones/benzylic alcohols with electron-donating groups in the 4-position.[18] Running the reaction under a hydrogen gas (1 bar) atmosphere[19] gave the same result. Electron-withdrawing groups on the ring do not have a significant effect on the outcome of the reaction.

Mechanistic Considerations. The least sterically hindered alcohol function is acylated under DYKAT conditions. This acylation leads to acetate formation in strict agreement with Kazlauskas' rule.[20] The second alcohol function, the most hindered, cannot lead to the acylated product because both substituents at the stereocenter are too big to be placed in the small pocket of the enzyme. However, under the reaction conditions, the most hindered alcohol is easily oxidized to the ketone. In this transformation there is a hydrogen loss process. Two explanations can account for this ruthenium-mediated oxidation (Scheme 4). Catalyst **3** is activated by heat to ruthenium species **A** (16 electrons) and **B** (18 electrons). The alcohol function reacts with complex **A** giving rise to the oxidized product and complex **B** (cycle A, Scheme 4). This process is in principle reversible, thus the ketone can react with species **B** and the alcohol is obtained. However, if this ruthenium-mediated reduction is slow (cycle B, Scheme 4), complex **B** can lose hydrogen

TABLE 2. DYKAT of a Variety of 1,4-Diols[a]

1a-i 4a-i

entry	R	CALB[b]	acyl donor (equiv)[c]	time (h)	product	yield[d] (%)	ee[e] (%)
1[f,g]	Ph	8	10	20	**4a**	75 (69)[h]	84
2	*i*-Pr	30	20	18	**4b**	77	89
3	*i*-Pr	30	3[i]	96	**4b**	93 (89)[h]	86
4	Cy	30	20	17	**4c**	73	90
5	pentyl	30	20	16	**4d**	82 (77)[h]	48
6	benzyl	30	20	17	**4e**	70	74
7[f,g]	2-naphthyl	15	10	18	**4f**	82	79
8[f,g]	*p*-Br	8	10	24	**4g**	81	88
9[f,g]	*p*-F	8	10	36	**4h**	75 (72)[h]	86
10[f,g]	*p*-OMe	8	10	8	**4i**	96[h]	21

[a] Conditions unless otherwise noted: 0.43 mmol of **1**, CALB, isopropenyl acetate and 5 mol % of **3** in 1.5 mL of toluene at 70 °C. [b] Milligrams of enzyme per millimole of diol. [c] Freshly distilled isopropenyl acetate. [d] % yield measured by GC. [e] Enantiomeric excess determined by GC. [f] Reaction run in 3 mL of toluene. [g] 2.5 mol % of **3**. [h] Isolated yield. [i] *p*-Chlorophenyl acetate as the acyl donor.

and be converted to ruthenium-species **A**.[21] As a consequence, the ketone would be accumulated in the reaction mixture. The second explanation that can account for this oxidation has to do with the acyl donor. Since isopropenyl acetate was employed as the acyl donor, acetone will be formed from the tautomerization of the corresponding enol formed after the acylation reaction. Probably acetone is reduced faster than the oxidized substrate, and, once again, the ketone would be accumulated in the system. To test this hypothesis two control experiments were carried out. In the first one a mixture of 1-phenylethanol and 2.5 mol % of **3** in toluene was stirred at 70 °C. After 15 h 6% of acetophenone had been formed. In the second experiment, a mixture of 1-phenylethanol and 2.3 mol % of **3** in a mixture of toluene/acetone (4:1) was stirred at 70 °C. After 15 h 97% of acetophenone had been formed.[22] These results strongly suggest that the oxidation of the inner alcohol in the diols occurs mainly via hydrogen transfer to acetone and to a lesser extent via loss of molecular hydrogen from the catalyst.

Despite the excellent enantiomeric excess reported in dynamic kinetic asymmetric transformation of symmetrical 1,4-diols[12] it was of interest to measure the selectivity of CALB for unsymmetrical 1,4-diols. The *E* value (enantiomeric ratio)[23] is applied only to enantiomers. In this case, this does not apply since the starting substrate is a mixture of rac-/diastereomeric diols. However, it was found that the stereochemistry of the inner alcohol does not affect the enzyme-catalyzed acylation of the least hindered alcohol (Scheme 5). Therefore, the selectivity of the enzyme was tested for different dia-

(18) Electronic effects in ruthenium-catalyzed asymmetric transfer hydrogenation reactions: (a) Hashiguchi, S.; Fujii, A.; Takehara, J.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 7562−7563. (b) Jiang, Y.; Jiang, Q.; Zhu, G.; Zhang, X. *Tetrahedron Lett.* **1997**, *38*, 215−218.

(19) Pàmies, O.; Bäckvall, J.-E. *J. Org. Chem.* **2002**, *67*, 1261−1265.

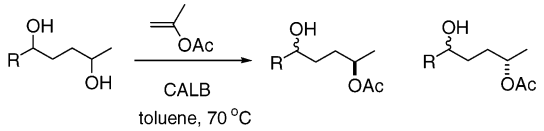
(20) Kazlauskas, R. J.; Weissfloch, A. N. E.; Rappaport, A. T.; Cuccia, L. A. *J. Org. Chem.* **1991**, *56*, 2656−2665.

(21) (a) Casey, C. P.; Vos, T. E.; Singer, S. W.; Guzei, I. A. *Organometallics* **2002**, *21*, 5038−5046. (b) Choi, J. H.; Kim, N.; Shin, Y. J.; Park, J. H.; Park. J. *Tetrahedron Lett.* **2004**, *45*, 4607−4610.

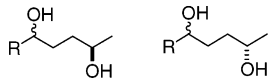
(22) For oxidations employing acetone as the hydrogen acceptor see: Almeida, M. L. S.; Beller, M.; Wang, G.-Z.; Bäckvall, J.-E. *Chem. Eur. J.* **1996**, *2*, 1533−1536.

(23) (a) Chen, C.-S.; Fujimoto, Y.; Girdaukas, G.; Sih, G. C. J. *J. Am. Chem. Soc.* **1982**, *104*, 7294−7299. (b) Chem, C.-S.; Wu, S.-H.; Girdaukas, G.; Sih, C. J. *J. Am. Chem. Soc.* **1987**, *109*, 2812−2817.

SCHEME 5. Enzyme-Catalyzed Kinetic Asymmetric Transformation of Diastereomeric Mixtures of Unsymmetrical 1,4-Diols



1a R = Ph, **1b** R = *i*-Pr **2**-(2*R*), de ≈ 0 **2**-(2*S*), de ≈ 0



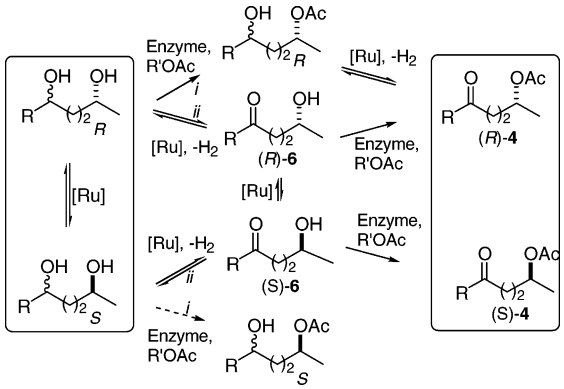
1-(2*R*), de ≈ 0 **1**-(2*S*), de ≈ 0

TABLE 3. CALB-Catalyzed Acylation of Rac-/Diastereomeric Mixtures of 1,4-Diols[a]

substrate	yield of **2** (%)[b]	**2**-(2*R*):**2**-(2*S*)[c]	**1**-(2*R*):**1**-(2*S*)[c]	pseudo-*E*
1a	27	>99:<1	32.5:67.5	285
1b	35	>99:<1	22:78	350

[a] Conditions: 0.68 mmol of **1**, CALB (30 mg/mmol of diol), freshly distilled isopropenyl acetate (20 equiv) in 2 mL of toluene at 70 °C for 1 h. [b] % yield measured by NMR. [c] Ratio determined on diacetate by GC.

SCHEME 6. Reaction Intermediates



stereomeric substrates and the measured kinetic parameter was called the pseudo-*E* value (Table 3).

Despite the excellent pseudo-*E* value measured for substrates **1a** and **1b**, under DYKAT conditions acetate **2a** could be obtained in only 84% ee and **2b** in 90% ee. Scheme 6 shows the two different pathways leading to the products. If the kinetic asymmetric transformation takes place before the oxidation of the inner alcohol (path i) one might expect to obtain, after the oxidation, the enantiomerically pure product based on the pseudo-*E* values measured. However, if the oxidation of the inner alcohol takes place before the enzyme-catalyzed reaction (path ii), hydroxy ketones are formed and, as pointed out before,[11] the kinetic resolution of acyclic γ-hydroxy ketones has been shown to proceed in low enantioselectivity.

It was therefore of interest to determine the relative rate of the CALB-catalyzed acylation of (4*R*)- and (4*S*)-4-hydroxy-1-phenyl-1-pentanone (**6a**) under the reaction conditions employed for our system. Thus, reaction of racemate **6a** in the presence of CALB and isopropenyl acetate (20 equiv) gave acetoxy ketone **4a** (12%)[24] in 35% ee after 10 min. This gave an *E* value of 2.2 for the kinetic resolution of **6a** (Scheme 7).

SCHEME 7. Kinetic Resolution of Hydroxy Ketone 6

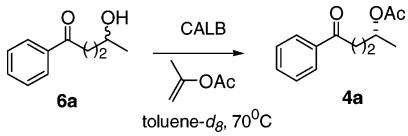
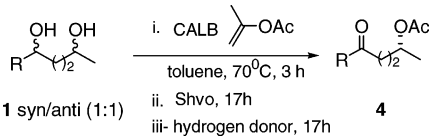


TABLE 4. Sequential KAT/DYKAT[a]



			ii		iii	
entry	product	R	yield[b] (%)	ee[c]	yield[d] (%)	ee[c]
1	**4c**	Cy	65	90	66	89
2	**4d**	pentyl	60	99	63	99
3	**4e**	Bn	56	99	58	93
4	**4f**	2-naphthyl	49[d]	90	nd	nd

[a] Conditions unless otherwise noted: (i) 0.43 mmol of **1**, CALB (30 mg/mmol of diol), isopropenyl acetate (10 equiv) in 1.5 mL of toluene at 70 °C under argon for 3 h; (ii) 5 mol % of **3** for 12 h; (iii) under hydrogen gas (1 bar) for an additional 12 h. [b] Yield measured by GC. [c] Enantiomeric excess determined by GC. [d] Isolated yield.

To minimize the oxidation of the inner alcohol at the very early stage of the DYKAT, and therefore avoid path ii (Scheme 6), a different procedure was investigated. Thus, diols **1c**−**f** were first treated with the enzyme and the acyl donor in a kinetic asymmetric transformation (KAT). After 3 h the Ru catalyst was added. This sequential KAT/DYKAT led to the products in moderate yields but in good to excellent ee. Several attempts to increase the efficiency of the process by reducing the amount of diketone formed as byproduct have been carried out. The use of hydrogen gas (1 bar)[19] after running the reaction for 17 h in the presence of Shvo's catalyst slightly improved the yield, but the ee dropped for some substrates (Table 4).

Conclusion

We have taken advantage of the higher selectivity of CALB for 1,4-diols than for γ-hydroxy ketones to develop a new dynamic kinetic asymmetric transformation. This process allows a one-pot transformation of 1,4-diols into enantiomerically enriched γ-acetoxy ketones. Despite the fact that CALB is among the most enantioselective lipases toward secondary alcohols, the efficiency of the kinetic resolution of 4-hydroxy-1-phenyl-1-pentanone (**6a**) catalyzed by this enzyme is rather low. The interaction of CALB with 1,4-diols and γ-hydroxy ketones is currently being investigated in our laboratories.

Experimental Section

General Procedure for the Synthesis of 1,4-Diols: 1-Phenyl-1,4-pentanediol (1a).[25,26] A solution of 3-butyn-2-ol (1.5 g, 21.4 mmol) in THF (60 mL) was cooled to −50 °C.

(24) Yield of **4a** determined by ^{1}H NMR.

MeLi (28 mL, 44.94 mmol; 1.6 M in Et_2O) was added slowly. The mixture was stirred at the same temperature for 2 h and then benzaldehyde (2.5 g, 23.54 mmol) was added. The reaction mixture was slowly allowed to reach 0 °C and stirred overnight at room temperature. After extractive workup (NH_4Cl/EtOAc) 1-phenyl-2-pentyn-1,4-diol (3.77 g, 100%) was obtained as a yellowish oil. 1-Phenyl-2-pentyn-1,4-diol (1.5 g, 8.5 mmol), PtO_2 (150 mg, 0.68 mmol), and methanol (40 mL) together with a magnetic stirrer bar were placed in an autoclave. The autoclave was evacuated and then charged with hydrogen. The hydrogen pressure was adjusted to 100 psi. After being stirred for 12 h the solution was filtered and the solvent was evaporated. Purification by chromatography (SiO_2, 2:1 pentane/EtOAc) yielded **1a** (780 mg, 51%) as a colorless thick oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35−7.24 (m, 5H), 4.74−4.68 (m, 1H), 3.87 (quint, J = 6.2 Hz, 1H, one isomer), 3.84 (quint, J = 6.2 Hz, 1H, one isomer), 2.95−2.0 (br s, 2H), 1.91−1.79 (m, 2H), 1.65−1.43 (m, 2H), 1.19 (d, J = 5.7 Hz, 3H, one isomer), 1.18 (d, J = 6.2 Hz, 3H, one isomer); ^{13}C NMR (100 MHz, $CDCl_3$; DEPT) δ 144.8 (C), 144.7 (C), 128.4 (2 × CH), 127.5 (CH), 127.5 (CH), 125.8 (CH), 125.8 (CH), 74.8 (CH), 74.4 (CH), 68.2 (CH), 67.9 (CH), 36.0 (CH_2), 35.9 (CH_2), 35.2 (CH_2), 35.1 (CH_2), 23.7 (CH_3), 23.5 (CH_3).

(25) Skattebøl, L.; Y. Stenstrøm, Y. *Acta Chem. Scand.* **1995**, *49*, 543−545.
(26) Bäckvall, J.-E.; Byström, S. E.; Nordberg, R. E. *J. Org. Chem.* **1984**, *49*, 4619−4631.

General Procedure for the DYKAT of 1,4-Diols: 1-Phenyl-4-(acetyloxy)-1-pentanone (4a).[11] In a typical experiment a solution of the diol (**1a**) (77 mg, 0.43 mmol) in toluene (1.5 mL) was added to a mixture of CALB (3.5 mg) and **3** (0.012 mmol, 13 mg) in a Schlenk-type flask under argon atmosphere. Then isopropenyl acetate (4.3 mmol, 430 mg) was added. The mixture was stirred at 70 °C for 20 h under Ar. After filtration through Celite and purification by chromatography (SiO_2, 20:1 pentane/EtOAc) **4a** (65 mg, 69%) was obtained as a colorless thick oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97−7.90 (m, 2H), 7.56 (tt, J = 7.4, 1.4 Hz, 1H), 7.49−7.43 (m, 2H), 5.00 (sext, J = 6.3 Hz, 1H), 3.11−2.93 (m, 2H), 2.00 (s, 3H), 2.05−1.97 (m, 2H), 1.28 (d, J = 6.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$; DEPT) δ 199.3 (C), 170.7 (C), 136.8 (C), 133.1 (CH), 128.6 (CH), 128.0 (CH), 70.4 (CH), 34.5 (CH_2), 30.2 (CH_2), 21.3 (CH_3), 20.1 (CH_3).

Acknowledgment. Financial support from the Swedish Foundation for Strategic Research, the Swedish Research Council, and the Spanish Ministerio de Educación y Ciencia is gratefully acknowledged.

Supporting Information Available: General experimental procedure and spectral data and ^{1}H and ^{13}C NMR spectra of compounds **1a**−**i**, **3**, and **4a**−**i**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO048511H