Asymmetric Synthesis

DOI: 10.1002/anie.200503765

A Dynamic Kinetic Resolution of Allyl Alcohols by the Combined Use of Lipases and $[VO(OSiPh_3)_3]$**

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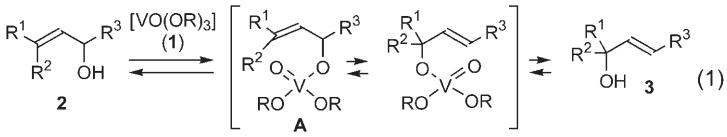
The lipase-catalyzed dynamic kinetic resolution (DKR) of racemic alcohols has drawn increasing attention over the last few years. The DKR protocol combines the lipase-catalyzed kinetic resolution (KR) of racemic alcohols[1] with an in situ racemization of the less reactive enantiomers, thus producing optically enriched esters in up to quantitative yields,[2–4] whereas the original KR has the inherent limitation of 50% product yield at best. In previously reported DKRs, ruthenium complexes were used as effective catalysts to bring about the racemization of optically active alcohols through oxidation/reduction reactions. Similarly, the combined use of lipases with other transition-metal-based racemization catalysts has the potential to produce diverse DKR methods. However, although some rhodium, iridium, ruthenium, and aluminum complexes are known to catalyze the racemization of alcohols,[5] only a few have proven to be compatible with enzymatic reactions.[5a,6]

Optically enriched allyl alcohols and their derivatives are especially important as useful intermediates in the synthesis of natural and non-natural compounds.[7] Therefore, their asymmetric synthesis has been extensively investigated, with much of the attention focused on the transition-metal-catalyzed KR and DKR of allyl alcohols and their esters[8,9] and the asymmetric reduction of enones.[10,11] From the viewpoint of the synthetic utility of the allyl alcohols as well as the extension of the lipase-catalyzed DKR methodology, we report herein a very different DKR of allylic alcohols by the combination of lipases with $[VO(OSiPh_3)_3]$.[12]

It has been known for more than three decades that the oxovanadium(v) compounds, $[VO(OR)_3]$ (**1**), catalyze the interconversion of allylic alcohols (**2** and **3**) through the formation of the allyl vanadates **A** [Eq. (1)].[13]

However, because the reactions are usually performed at high temperatures (150–170 °C) and afford thermodynamic

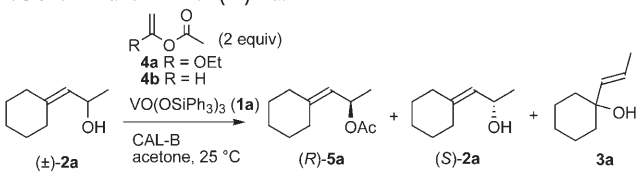


(1)

mixtures of two regioisomers (**2** and **3**), this isomerization has found limited application.[14,15] If these vanadium-catalyzed isomerization reactions could be combined with the lipase-catalyzed KR, a new DKR method would be established by virtue of the high enantio- and chemoselective abilities of the lipases.[16] To examine the feasibility of this idea, a lipase-catalyzed KR of (±)-**2a** was examined first without and then with a catalytic amount of the stable compound, $[VO(OSiPh_3)_3]$ (**1a**).

First, after screening a number of commercially available lipases and organic solvents, we found that ordinary KR took place effectively. For instance, *Candida antarctica* lipase fr.B (CAL-B, Roche Diagnostics) and the acyl donor ethoxyvinyl acetate[17] (**4a**, 2 equiv) in acetone at 25 °C for 21 h completed the resolution to give (*R*)-**5a** (92% *ee*, 51% yield) and (*S*)-**2a** (97% *ee*, 49% yield) (Table 1, entry 1).

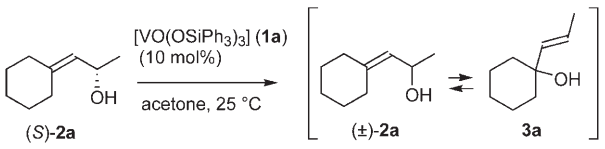
Table 1: KR and DKR of (±)-**2a**.[a]



Entry	4	1a [mol%]	t [h]	(R)-5a[b] ee [%]	(R)-5a[b] Yield [%]	(S)-2a[b] ee [%]	(S)-2a[b] Yield [%]	3a Yield [%]
1	**4a**	–	21	92	51[c]	97	49[c]	–
2	**4a**	10	16	99	66[d]	5	5[d]	29[d]
3	**4a**	10	60	98	95[c]	–	trace	< 5[d]
4	**4b**	10	72	93	89[c]	–	< 5[d]	6[d]

[a] The reaction was carried out as stated in the text. [b] The optical purities of **2a** and **5a** were determined by GC with a chiral column, TCI Chiraldex G-TA. The absolute stereochemistry of the recovered **2a** was determined to be *S* by the modified Mosher method, and thereby that of **5a** to be *R*. [c] Yield of isolated product after SiO_2-column chromatography. [d] Yield based on ^1H NMR spectroscopic data.

Next, **1a** in acetone was found to effect 1,3-transposition at 25 °C. The reaction of (*S*)-**2a** (98% *ee*) with **1a** (10 mol%) reached thermodynamic equilibrium after about 12 h to give a mixture of (±)-**2a** and **3a** (15:85), while the racemization of (*S*)-**2a** proceeded [Eq. (2)] (Figure 1).



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[**] This work was supported by Grants-in-Aid for Scientific Research (S and C) from the Ministry of Education, Culture, Sports, Science, and Technology, Japan. We thank Roche Diagnostics K. K., Japan and Amano Enzyme Inc., Japan for the generous gift of the lipases.

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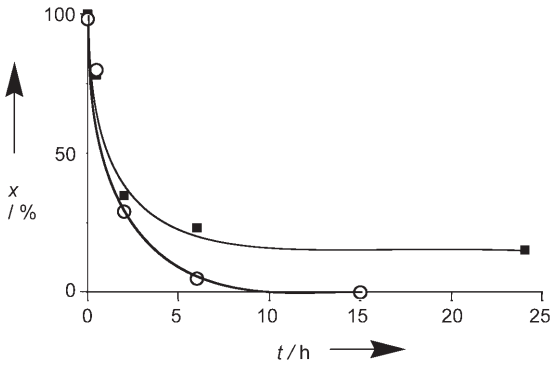
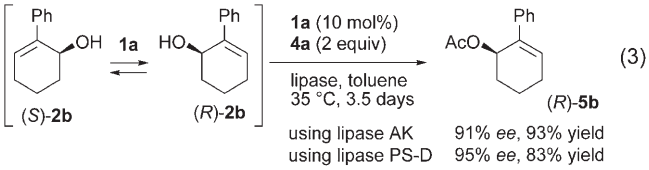


Figure 1. Time course of the isomerization of (*S*)-**2a** (98% *ee*) catalyzed by **1a** in acetone at 25°C. ■ Mol ratio **2a**/(**2a** + **3a**), ○ optical purity of (*S*)-**2a**.

We then investigated the DKR of **2a** by the combined use of CAL-B and **1a**. A mixture of **2a, 4a** (2 equiv), **1a** (10 mol%), and CAL-B was stirred in anhydrous acetone at 25°C. After 16 h, a mixture of (*R*)-**5a** (99 *ee*, 66% yield), (*S*)-**2a** (5% *ee*, 5% yield), and **3a** (29% yield) was obtained (Table 1, entry 2). These results indicated that the lipase and **1a** had little adverse affect on each other. Prolonged stirring for 2.5 days resulted in the conversion of **3a** into (*R*)-**5a** (98% *ee*, 95% yield) (Table 1, entry 3). The use of vinyl acetate (**4b**, 2 equiv), currently the most popular acyl donor, also brought about a similar DKR that produced (*R*)-**5a** (93% *ee*, 89% yield) after 3 days (Table 1, entry 4), although its optical and chemical yields were slightly lower than those obtained using **4a** (Table 1, entry 3). In these reactions, the formation of the acetate of the tertiary alcohol **3a** was not observed, which was expected from the high chemoselectivity of the lipase-catalyzed reactions.[16]

The preparation of the ester (*R*)-**5a** from the tertiary alcohol **3a** is a unique feature of this DKR protocol. The alcohol, which is readily available by the alkynylation of cyclohexanone followed by reduction,[18] can be converted into (*R*)-**5a** (99% *ee*, 91% yield) under the same conditions as entry 3 of Table 1 (Scheme 1).[19]

This DKR method was also effective for the cyclic allylic alcohol (±)-**2b**. In this case, both *Pseudomonas fluorescens* lipase (AK, Amano Enzyme) and *Burkholderia cepacia* lipase immobilized on diatomaceous earth (PS-D, Amano Enzyme) in toluene was suitable for ordinary KR, and DKR using these lipases with **1a** produced (*R*)-**5b** (91–95% *ee*) in 83–93% yield [Eq. (3)].[20,21] Although a related DKR of the



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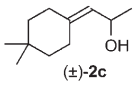
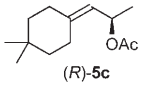
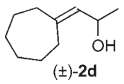
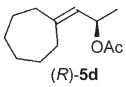
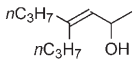
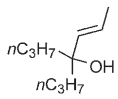
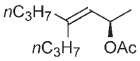
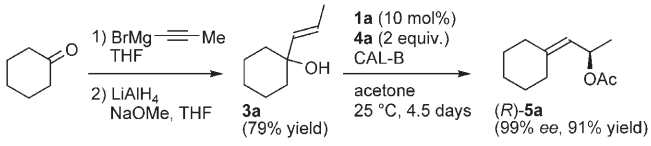
racemic acetate (±)-**5b**, in which the lipase-catalyzed hydrolysis and the palladium(II)-catalyzed racemization were combined to yield optically enriched **2b** (96% *ee*, 81% yield), was previously reported, the reaction took 19 days for completion.[22]

The DKR protocol was successfully applied to other racemic secondary alcohols (±)-**2c–g** as well as the tertiary alcohol **3e** with either **4a** or **4b** (Table 2). All reactions were carried out at around room temperature to produce the esters

Table 2: DKR of (±)-**2** and **3** to give (*R*)-**5**.[a]

Entry	Alcohol	4	Lipase	Solvent	*T* [°C]	*t* [days]	5[b]	*ee* [%]	Yield [%]
1	 (±)-**2c**	**4a**	CAL-B	acetone	25	2	 (*R*)-**5c**	97[c]	88
2		**4b**	CAL-B	acetone	25	2		98[c]	94
3	 (±)-**2d**	**4a**	CAL-B	acetone	10	2	 (*R*)-**5d**	97[c]	88
4		**4b**	CAL-B	acetone	10	2		98[c]	80
5	 (±)-**2e**	**4a**	CAL-B	acetone	25	3		99[d]	91
6		**4b**	CAL-B	acetone	25	3		99[d]	85
7	 **3e**	**4a**	CAL-B	acetone	25	4	 (*R*)-**5e**	98[d]	93
8		**4b**	CAL-B	acetone	25	4		99[d]	93
9	 (±)-**2f**: R = Ph	**4a**	PS-D	toluene	35	2	 (*R*)-**5f** R = Ph	97[e]	91
10		**4b**	PS-D	toluene	35	2		99[e]	96
11	(±)-**2g** R = C≡CSiMe$_3$	**4a**	PS-D	toluene	35	4	(*R*)-**5g**: R = C≡CSiMe$_3$	91[c]	81

[a] The reaction was carried out as stated in the text. [b] Yield of isolated product after SiO_2-column chromatography. [c] Optical purity was determined by HPLC with a Daicel Chiralcel OD-H column (for **5c** and **5g**) or a Daicel Chiralpak AD-H column (for **5d**), after conversion into the corresponding alcohol **2**. [d] Optical purity was determined by GC with a chiral column, TCI Chiraldex G-TA, after conversion into the corresponding alcohol **2e**. [e] Optical purity was determined by HPLC with a Daicel Chiralcel OD-H column.



Scheme 1. Preparation of **3a** and its conversion into (*R*)-**5a** by DKR.

(*R*)-**5c–g** with 91–99% *ee* in 80–96% yields, which demonstrates the similar high efficacy of both **4a** and **4b**. The use of ethoxyvinyl esters, in particular, will enable us to apply the DKR method to the domino-type reactions that we recently developed.[3,17] Among the products, (*R*)-**5g** was reported to be a key synthetic intermediate of medicinally important

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compounds.[23] It was previously prepared by the ordinary KR of (±)-**2g** to give (*R*)-**5g** and (*S*)-**2g**, followed by Mitsunobu reaction of the mixture. Although the enantioselectivity of the KR was excellent (99% *ee* for both products), the Mitsunobu inversion suffered partial racemization to give (*R*)-**5g** with 88% *ee*.[23a] Our DKR method produced (*R*)-**5g** (91% *ee*, 81% yield) directly (Table 2, entry 11).

In conclusion, we have shown that the combination of the oxovanadium compound **1a** with lipases produces a novel DKR process with excellent enantiomer resolution and chemical yields. The 1,3-transposition of allyl alcohols was catalyzed by **1a** and resulted in a thermodynamic equilibrium of two regioisomers, which underwent highly enantio- and chemoselective esterification under the action of the lipases. Because the **1a**-catalyzed 1,3-transposition reactions are not very sensitive to oxygen and moisture, this DKR method offers the advantage of a facile experimental procedure without the need for special apparatus.[24] Furthermore, it features a unique preparation of optically active esters of secondary alcohols from the corresponding ketones via the readily available tertiary alcohols; this synthesis is not attainable by existing DKRs with ruthenium complexes.

Experimental Section

Typical procedure: (±)-**2a** (50 mg, 0.36 mmol), **4a** (93 mg, 0.71 mmol), **1a** (32 mg, 0.036 mmol), CAL-B (150 mg), and anhydrous acetone (4 mL) were added to a round-bottomed flask. The flask was sealed and the reaction mixture was stirred at 25 °C for 2.5 days. The reaction mixture was then filtered and concentrated in vacuo. The residue was purified by flash column chromatography on SiO_2 (hexane/Et_2O, 20:1 to 2:1) to give (*R*)-**5a** as a colorless oil (62 mg, 95% yield, 98% *ee* (GC analysis with TCI chiraldex G-TA)). $[\alpha]_D^{20} = +35.0$ ($c = 0.96$, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.26$ (d, $J = 7.0$ Hz, 3H), 1.48–1.58 (m, 6H), 2.02 (s, 3H), 2.06–2.09 (m, 2H), 2.18–2.23 (m, 2H), 5.11 (br d, $J = 9.0$ Hz, 1H), 5.63 ppm (qd, $J = 7.0$, 9.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 21.3$, 21.5, 26.6, 27.7, 28.4, 29.4, 36.8, 67.4, 121.5, 144.1, 170.5 ppm; IR (KBr): $\nu = 1715\ cm^{-1}$; elemental analysis: calcd (%): C 72.49, H 9.95; found: C 72.26, H 9.89.

Received: October 24, 2005
Revised: January 13, 2006
Published online: March 17, 2006

Keywords: allyl alcohols · asymmetric synthesis · dynamic kinetic resolution · lipases · vanadium

[1] For recent reviews, see: a) S. M. Roberts, *J. Chem. Soc. Perkin Trans. 1* **2001**, 1475–1499; b) T. Ema, *Curr. Org. Chem.* **2004**, *8*, 1009–1025; c) A. Ghanem, H. Y. Aboul-Enein, *Chirality* **2005**, *17*, 1–15; d) E. Garcia-Urdiales, I. Alfonso, V. Gotor, *Chem. Rev.* **2005**, *105*, 313–354.

[2] For reviews, see: a) O. Pàmies, J.-E. Bäckvall, *Chem. Rev.* **2003**, *103*, 3247–3261; b) N. J. Turner, *Curr. Opin. Chem. Biol.* **2004**, *8*, 114–119; c) M.-J. Kim, Y. Ahn, J. Park, *Bull. Korean Chem. Soc.* **2005**, *26*, 515–522.

[3] S. Akai, K. Tanimoto, Y. Kita, *Angew. Chem.* **2004**, *116*, 1431–1434; *Angew. Chem. Int. Ed.* **2004**, *43*, 1407–1410.

[4] For some recent improvements and applications of the lipase–ruthenium(II)-catalyzed DKRs, see: a) J. H. Choi, Y. K. Choi, Y. H. Kim, E. S. Park, E. J. Kim, M.-J. Kim, J. Park, *J. Org. Chem.* **2004**, *69*, 1972–1977; b) M. Edin, J. Steinreiber, J.-E. Bäckvall, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5761–5766; c) B. Martin-Matute, M. Edin, K. Bogár, F. B. Kaynak, J.-E. Bäckvall, *J. Am. Chem. Soc.* **2005**, *127*, 8817–8825; d) P. Kielbasinski, M. Rachwalski, M. Mikolajczyk, M. A. H. Moelands, B. Zwanenburg, F. P. J. T. Rutjes, *Tetrahedron: Asymmetry* **2005**, *16*, 2157–2160; e) G. K. M. Verzijl, J. G. de Vries, Q. B. Broxterman, *Tetrahedron: Asymmetry* **2005**, *16*, 1603–1610.

[5] a) P. M. Dinh, J. A. Howarth, A. R. Hudnott, J. M. J. Williams, W. Harris, *Tetrahedron Lett.* **1996**, *37*, 7623–7626; b) O. Pàmies, J.-E. Bäckvall, *Chem. Eur. J.* **2001**, *7*, 5052–5058; c) M. Ito, A. Osaku, S. Kitahara, M. Hirakawa, T. Ikariya, *Tetrahedron Lett.* **2003**, *44*, 7521–7523; d) S. Wuyts, D. E. de Vos, F. Verpoort, D. Depla, R. de Gryse, P. A. Jacobs, *J. Catal.* **2003**, *219*, 417–424.

[6] For a related DKR of racemic secondary amines with palladium(0) on carbon as a racemization catalyst, see: M. T. Reetz, K. Schimossek, *Chimia* **1996**, *50*, 668–669; see also: Y. K. Choi, M. J. Kim, Y. Ahn, M.-J. Kim, *Org. Lett.* **2001**, *3*, 4099–4101.

[7] For examples, see: R. M. Hanson, *Org. React.* **2002**, *60*, 1–156.

[8] For a recent review, see: E. Vedejs, M. Jure, *Angew. Chem.* **2005**, *117*, 4040–4069; *Angew. Chem. Int. Ed.* **2005**, *44*, 3974–4001.

[9] For recent examples, see: B. J. Lüssem, H.-J. Gais, *J. Am. Chem. Soc.* **2003**, *125*, 6066–6067; H.-J. Gais, O. Bondarev, R. Hetzer, *Tetrahedron Lett.* **2005**, *46*, 6279–6283.

[10] For typical reviews, see: R. Noyori, T. Ohkuma, *Angew. Chem.* **2001**, *113*, 40–75; *Angew. Chem. Int. Ed.* **2001**, *40*, 40–73; S. Itsuno, *Org. React.* **1998**, *52*, 395–576.

[11] For other recent examples based on different methodologies, see: H. Li, P. J. Walsh, *J. Am. Chem. Soc.* **2004**, *126*, 6538–6539; S. F. Kirsch, L. E. Overman, *J. Am. Chem. Soc.* **2005**, *127*, 2866–2867.

[12] The first preparation of **1a** was reported independently by two groups: a) N. F. Orlov, B. N. Dolgov, M. G. Voronkov, *Dokl. Akad. Nauk SSSR* **1958**, *122*, 246–249; b) F. E. Granchelli, G. B. Walker, US 2863891, **1958** [*Chem. Abstr.* **1959**, *53*, 50997]; for a precise preparation of **1a**, see: c) B. M. Trost, C. Jonasson, *Angew. Chem.* **2003**, *115*, 2109–2112; *Angew. Chem. Int. Ed.* **2003**, *42*, 2063–2066.

[13] a) P. Chabardes, E. Kuntz, J. Varagnat, *Tetrahedron* **1977**, *33*, 1775–1783; for a review, see: b) S. Bellemin-Laponnaz, J.-P. Le Ny, *C. R. Chim.* **2002**, *5*, 217–224.

[14] The related isomerization of propargyl and allenyl alcohols has found synthetic use for producing conjugated carbonyl compounds after irreversible enol–keto transformation (for an example, see: C. Tode, Y. Yamano, M. Ito, *J. Chem. Soc. Perkin Trans. 1* **2001**, 3338–3345) and was applied to the aldol reaction of the intermediate vanadium enolates.[12c]

[15] The vanadium catalyst prepared in situ from $[VO(acac)_2]$ and $Me_3SiOOSiMe_3$ caused isomerization at room temperature: S. Matsubara, T. Okazoe, K. Oshima, K. Takai, H. Nozaki, *Bull. Chem. Soc. Jpn.* **1985**, *58*, 844–849.

[16] The lipase-catalyzed reactions of tertiary alcohols are usually slow, probably due to steric hindrance: U. T. Bornscheuer, R. J. Kazlauskas, *Hydrolases in Organic Synthesis: Regio- and Stereoselective Biotransformations*, Wiley-VCH, Weinheim, **1999**, p. 95.

[17] For a review, see: Y. Kita, S. Akai, *Chem. Rec.* **2004**, *4*, 363–372; for a recent example, see: S. Akai, K. Tanimoto, Y. Kanao, S. Ohmura, Y. Kita, *Chem. Commun.* **2005**, 2369–2371.

[18] For the *E*-selective reduction of alkynes with $LiAlH_4$/NaOMe, see: I. Fleming, N. K. Terrett, *J. Organomet. Chem.* **1984**, *264*, 99–118.

[19] The reaction of **3a** with **1a** (10 mol%) in acetone at 25 °C reached equilibrium after about 6 h to afford a mixture of **2a** and **3a** (15:85).

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[20] The optical purity was determined by HPLC with a Daicel Chiralpak AD-H column; $[\alpha]_D^{22} = +169$ ($c = 1.0$, $CHCl_3$) (lit: $[\alpha]_D^{25} = -157$ ($c = 0.57$, $CHCl_3$) for (*S*)-**5b** with 96% *ee*).[21]
[21] M. Frohn, X. Zhou, J.-R. Zhang, Y. Tang, Y. Shi, *J. Am. Chem. Soc.* **1999**, *121*, 7718–7719.
[22] J. V. Allen, M. J. Williams, *Tetrahedron Lett.* **1996**, *37*, 1859–1862.
[23] a) S. Takano, M. Suzuki, K. Ogasawara, *Tetrahedron: Asymmetry* **1993**, *4*, 1043–1046; b) M. M. Kabat, J. Kiegiel, N. Cohen, K. Toth, P. M. Wovkulich, M. R. Uskoković, *J. Org. Chem.* **1996**, *61*, 118–124.
[24] The ruthenium-catalyzed racemization reported so far needed strict anaerobic conditions because the interfusion of oxygen often caused the formation of significant amounts of side products, that is, ketones.[2–4] However, just before submitting this Communication, a novel ruthenium complex was reported to produce the DKR of alcohols with a lipase in air (N. Kim, S.-B. Ko, M. S. Kwon, M.-J. Kim, J. Park, *Org. Lett.* **2005**, *7*, 4523–4526).

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