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Dynamic Kinetic Resolution of Allylic Alcohols Mediated by Ruthenium- and Lipase-Based Catalysts

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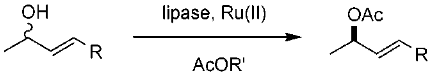
ABSTRACT

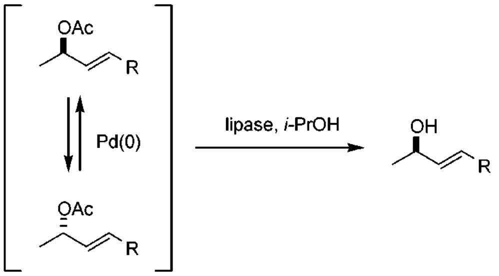


An enzyme–metal combo reaction has been developed for the dynamic kinetic resolution of allylic alcohols in which racemic substrates are transformed by a lipase and a ruthenium complex in the presence of an acyl donor to allylic acetates of high optical purity in over 80% yield.

We and others are developing enzyme/metal combo reactions (EMCRs) as a new methodology for the synthesis of homochiral compounds.[1,2] In this Letter, we describe an EMCR for the dynamic kinetic resolution (DKR) of allylic alcohols in which racemic substrates are enantioselectively acetylated by a lipase with the in situ racemization of unreacted substrates by a ruthenium complex to give allylic acetates of high optical purity in over 80% yields.

Chiral allylic alcohols and acetates in optically pure forms are useful synthons which can be transformed to a wide range of more complex molecules.[3] Among the methods currently available for the synthesis of the allylic compounds, two of the most practical are the kinetic resolutions of racemic allylic alcohols by asymmetric epoxidation[3a] and by enzymatic acylation.[4] However, these procedures suffer from a disadvantage that the theoretical maximum yield is limited to 50%. This problem can be overcome if an efficient DKR procedure is developed.[5] We recently reported an EMCR for the DKR of racemic allylic acetates in which racemic substrates were converted by a lipase in the presence of a palladium complex to single enantiomers of allylic alcohols[1a,2c] (Scheme 1).

Scheme 1. EMCR for the DKR of Allylic Acetates



Subsequently, we became interested in an EMCR for the reverse reaction as a useful alternative for the synthesis of homochiral allylic acetates.

Previously, ruthenium complexes **1** and **2** were proved to be efficient racemization catalysts for the DKRs of simple secondary alcohols.[1b,2d−e] These ruthenium catalysts, however, were not appropriate as racemization catalysts for the

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[1] (a) Choi, Y.-K.; Suh, J. H.; Lee, D.; Lim, I.; Jung, J. Y.; Kim, M.-J. *J. Org. Chem.* **1999**, *64*, 8423. (b) Koh, J. H.; Jung, H. M.; Kim, M.-J.; Park, J. *Tetrahedron Lett.* **1999**, *40*, 6281. (c) Jung, H. M.; Koh, J. H.; Kim, M.-J.; Park, J. *Org. Lett.* **2000**, *2*, 409. (d) Jung, H. M.; Koh, J. H.; Kim, M.-J.; Park, J. Submitted.

[2] (a) Dinh, P. M.; Howarth, J. A.; Hudnott, A. R.; Williams, J. M. J.; Harris, W. *Tetrahedron Lett.* **1996**, *37*, 7623. (b) Reetz, M. T.; Schimossek, K. *Chimia* **1996**, *50*, 668. (c) Allen, J. V.; Williams, J. M. J. *Tetrahedron Lett.* **1996**, *37*, 1859. (d) Persson, B. A.; Larsson, A. L. E.; Ray, M. L.; Bäckvall, J.-E. *J. Am. Chem. Soc.* **1999**, *121*, 1645. (e) Huerta, F. F.; Laxmi, Y. R. S.; Bäckvall, J.-E. *Org. Lett.* **2000**, *2*, 1037.

[3] (a) Johnson, R. A.; Sharpless, K. B. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: Oxford, 1991; Vol. 7, p 389. (b) Jonson, R. A.; Sharpless, K. B. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: New York, 1993; Chapter 4. (c) Heck, R. F. *Palladium Reagents in Organic Synthesis*; Academic: London, 1985; Chapter 5. (d) Tsuji, J. *Palladium Reagents and Catalysts*; John Wiley & Sons: Chichester, 1997; Chapter 4.

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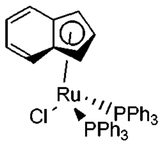
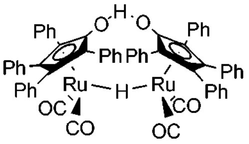
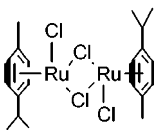
DKR of allylic alcohols since they were practically inactive at ambient temperature and catalyzed mainly the isomerization of substrates to saturated ketones at elevated temperature.[6] We found that commercially available (*p*-cymene)-ruthenium(II) complex **3** and its hydride analogue **4**[7] were excellent racemization catalysts for the DKR of allylic alcohols even at room temperature.[8]



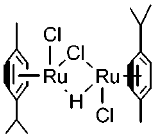
1



2



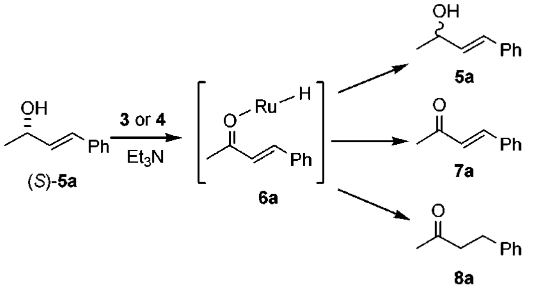
3



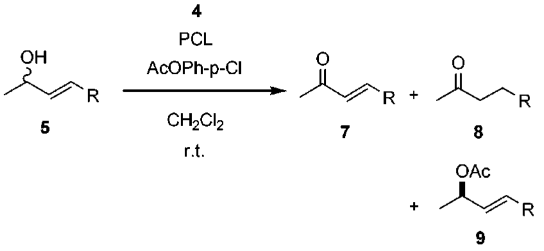
4

For example, (*S*)-**5a** (>99% ee) was racemized completely within 5 h in the presence of 4 mol % of **3** or **4** and a weak base (1.0 equiv of Et_3N) in methylene chloride at room temperature (Scheme 2). Undesirable side products (**7a** and **8a**) were formed in modest amounts: combined yields were 25% with **3** and 18% with **4**. Here, the racemization could take place in two ways: (1) by epimerization via **6a** (for clarity, other ligands omitted) and (2) by transfer hydrogenation of oxidized product **7a**.

Scheme 2. Ru-Catalyzed Racemization of Chiral Allylic Alcohol

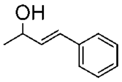
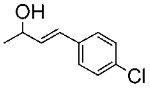
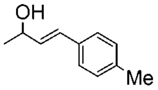
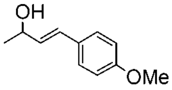
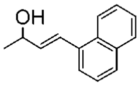
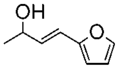
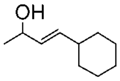
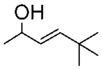
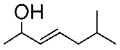
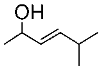
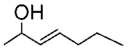


Scheme 3. EMCR for the DKR of Allylic Alcohols



For DKR studies, 11 allylic alcohols **5a**–**k** were chosen as the substrates, the immobilized lipase from *Pseudomonas cepacia* (PCL)[9] as the catalyst for the enantioselective acylation of the racemic substrates, and **4** as the racemization catalyst[10] (Scheme 3). In typical procedures, the reactions

Table 1. Dynamic Kinetic Resolution of Allylic Alcohols

substrate		conv. %[a]	yield, %[a]	ee, %[b]
	**5a**	>99	84 (83)	>99
	**5b**	>99	91(88)	99
	**5c**	>99	88(86)	>99
	**5d**	>99	85(81)	99
	**5e**	94	86(83)	>99
	**5f**	>99	92(86)	99
	**5g**	97	90(84)	95
	**5h**	>99	85(83)	>99
	**5i**	>99	91(84)	>99
	**5j**	>99	87(83)	>99
	**5k**	>99	86(83)	95

[a] On the basis of ^1H NMR analysis. The isolated yields are given in parentheses. The acetylated products were contaminated by a substantial amount of *p*-chlorophenyl acetate, which can be removed through mild selective hydrolysis.[2d] [b] On the basis of analyses by HPLC and capillary GC using a chiral column. Analytical conditions: **9a**–**g**, HPLC, Whelk-O1, hexane/2-propanol = 95/5 or 99/1 (**9e**), flow rate = 1.0 mL/min, UV 254 (**9a**–**d**), 248 (**9e**), 296 (**9f**), 270 (**9g**) nm; **9h**,**i**, hydrolyzed to **5h**,**i** and then determined in the benzoate form, HPLC, Whelk-O1, hexane/2-propanol = 98/2, UV 254 nm; **9j**,**k**, GC, Chiraldex B-PH, injection temperature 110 °C, detection temperature 130 °C, flow rate = 1.0 mL/min.

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(4) (a) Wong, C.-H.; Whitesides, G. M. *Enzymes in Synthetic Organic Chemistry*; Pergamon: Oxford, 1994; Chapter 2. (b) Burgess, K.; Jennings, L. D. *J. Am. Chem. Soc.* **1991**, *113*, 6129. (c) Burgess, K.; Jennings, L. D. *J. Org. Chem.* **1990**, *55*, 1138. (d) Burgess, K.; Cassidy, J.; Henderson, I. *J. Org. Chem.* **1991**, *56*, 2050.

(5) Ward, R. S. *Tetrahedron: Asymmetry* **1995**, *6*, 1475.

(6) For the ruthenium-catalyzed isomerization of allylic alcohols to saturated ketones, see: (a) Trost, B. M.; Kulawiec, R. J. *J. Am. Chem. Soc.* **1993**, *115*, 2027. (b) Bäckvall, J.-E.; Andreasson, U. *Tetrahedron Lett.* **1993**, *34*, 5459.

(7) It was readily prepared by the reaction of **3** with 2-propanol in the presence of Et_3N in methylene chloride at room temperature under argon. The crude products obtained after solvent removal were used without further purification. Bennett, M. A.; Ennett, J. P. *Organometallics* **1984**, *3*, 1365.

(8) Catalysts **3** and **4** with triethylamine were also effective as the racemization catalysts for the DKR of simple secondary alcohols at higher temperature: Hyun Min Jung, Jeong Hwan Koh, Mahn-Joo Kim, and Jaiwook Park, unpublished results.

were carried out at room temperature with substrate (0.1−0.2 g, 0.5−1.4 mmol), *p*-chlorophenyl acetate (1.5−1.7 equiv) as an acyl donor, PCL (150 mg/mmol), **4** (4 mol %), and triethylamine (1 equiv) in methylene chloride (2−4 mL). The DKR of **5a** is described as a representative procedure. A suspension containing **5a** (200 mg, 1.35 mmol), **4** (31 mg, 0.054 mmol), PCL (200 mg), *p*-ClPhOAc (34 mg, 2.0 mmol), and Et_3N (0.19 mL, 1.3 mmol) in dry methylene chloride (4 mL) was stirred at room temperature (20−25 °C) under an argon atmosphere. After 48 h, the enzymes were filtered out and the filtrate was concentrated and analyzed by ^{1}H NMR spectroscopy, indicating that all of substrate was converted to **7a** (9%), **8a** (7%), and **9a** (84%). The mixture was subjected to flash chromatography to provide (*R*)-**9a** (213 mg, 1.12 mmol, 83%, >99% ee). This product contained a substantial amount of *p*-chlorophenyl acetate, which can be readily removed by selective hydrolysis.[2d]

All of the results are described in Table 1. Both aromatic (**5a**−**f**) and aliphatic substrates (**5g**−**k**) were resolved equally well to provide (*R*)-enantiomeric products.[11] The isolated yield ranged from 81 to 88% and the enantiomeric excess (ee) reached 99% or greater in most cases except the DKRs of **5g** and **5k**, in which the enantiomeric excess was slightly lower (95%) presumably due to the lower enantioselectivity of the lipase toward the substrates. The amounts of byproducts (**7** and **8**) varied (7−16%) and, in several cases (DKRs of **5b**, **5e**−**g**, and **5j**), were substantially less than expected on the basis of results from the racemization of (*S*)-**5a**. All of these observations clearly indicate that the DKR of racemic allylic alcohols has been achieved successfully.

We thus have developed an enzyme/metal combo reaction using a lipase and a ruthenium complex for the one-pot transformation of racemic allylic alcohols to homochiral allylic acetates. It is practical and straightforward. The catalysts employed are readily available and the reactions proceed at room temperature. The reaction followed by mild hydrolysis also provides a useful route to homochiral allylic alcohols.[12] Further studies to broaden the scope of this EMCR methodology are underway in this laboratory.

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[9] PCL immobilized on ceramic particles (trade name, Lipase PS-C (type II), Amano, Japan.

[10] This was chosen favorably over **3** to minimize the formation of the unwanted ketones.

[11] The absolute configuration of the acetylated products is assigned on the basis of the stereospecificity of PCL (Kazlauskas, R. J.; Weissfloch, A. N. E.; Rappaport, A. T.; Cuccia, L. A. *J. Org. Chem.* **1991**, *56*, 2656) and has been confirmed by comparing the optical rotation of deacetylated **9a** with the literature value. See ref 12.

[12] For example, the hydrolysis of (*R*)-**9a** (213 mg, 1.12 mmol, >99% ee) with K_2CO_3 in MeOH−water (4: 1) followed by standard workup provided (*R*)-**5a** (165 mg, 1.11 mmol, 99%, >99% ee) with the same optical purity: $[\alpha]^{23}_D$ +30.5° (*c* 1.0, $CHCl_3$) (lit.[4b] $[\alpha]^{23}_D$ −29.2° (*c* 1.0, $CHCl_3$), for (S)-enantiomer (>95% ee).