Dynamic Kinetic Resolution of Acyclic Allylic Acetates Using Lipase and Palladium

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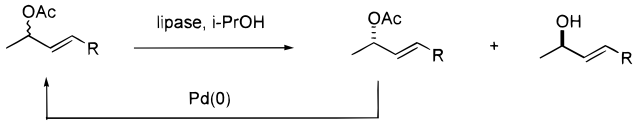
The complete transformation of a racemic mixture into a single enantiomer is one of the current challenging problems in asymmetric synthesis.[2] As a useful approach for such transformation, we have studied the dynamic kinetic resolution using enzymes and transition metal complexes.[3,4] In this manuscript, we report the first successful dynamic kinetic resolution of acyclic allylic acetates using a lipase and a palladium complex, leading to the synthesis of allylic alcohols with high optical purity.

The Williams group recently reported the first example for the dynamic kinetic resolution of allylic acetate using a lipase and a palladium complex.[4a] In this procedure, allylic acetate is resolved through the lipase-catalyzed hydrolysis, and the enzymatically unreactive enantiomer is racemized in situ through the palladium(II)-catalyzed rearrangement. The resolution is performed in phosphate buffer at 37−40 °C. The successful resolution was achieved only for a cyclic allylic acetate and required a long reaction time (19 days) due to the slow Pd-catalyzed step. The dynamic kinetic resolution would be more useful if it could be applicable to the resolution of acyclic allylic substrates which are readily available. For this goal, we explored a conceptually similar but chemically different approach: *the resolution through the lipase-catalyzed transesterification coupled with the Pd(0)-catalyzed racemization in organic solvent* (Scheme 1).

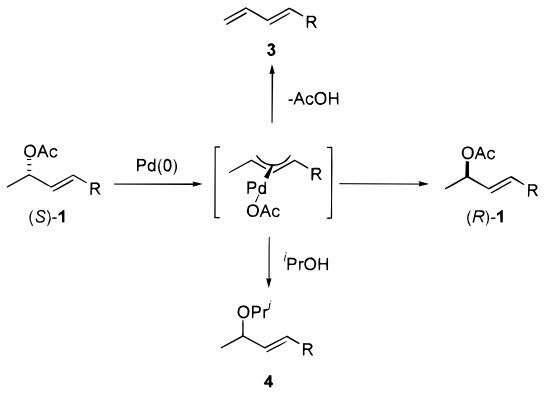
As the substrates to be resolved, 1,3-disubstituted allylic acetates **1a**−**e** with a methyl group at the 1-position and an aryl group at the 3-position were chosen. The lipases from *Pseudomonas cepacia* (PCL) and *Candida antarctica* (CAL), which are available in the immobilized forms,[5] were employed as the enzymes for the resolution. Both enzymes showed high enantioselectivity in the screening experiments: in the kinetic resolution of **1a**, the products of >99% ee were obtained at 45−48% conversion for both of them. As the acyl acceptor in the transesterification reaction, 2-propanol was chosen because it and its acetate can be readily removed after the reaction is complete. It was used in a 10-fold excess to shift the position of the equilibrium toward the resolved products. It was observed that, in the transesterification using only the enzymatically reactive enantiomer (*R*)-**1a** as the substrate, over 90% of the substrates was converted to the products in the presence of a 10-fold excess of 2-propanol. As the catalyst for the racemization of the enzymatically unreactive enantiomer,[6] tetrakis(triphenylphosphine)palladium(0) [$Pd(PPh_3)_4$] was used together with 1,1′-bis(diphenylphosphino)ferrocene (dppf).[7] The Pd-catalyzed racemization in the presence of 2-propanol in THF is accompanied by two side reactions, elimination and substitution, to yield **3** and **4**, respectively (Scheme 2). Accordingly, the unwanted reactions must be depressed without affecting the racemization for higher yield. This was achieved more effectively when the Pd complex was used together with 3 equiv of dppf.

In typical experiments, the reactions were carried out at room temperature under argon atmosphere on 0.5 mmol scale using substrate (0.1−0.3 M), 2-propanol (10 equiv), CAL (0.2−0.4 g/mmol substrate) or PCL (0.5−0.8 g/mmol substrate), $Pd(PPh_3)_4$ (5 mol %), and DPPF (15 mol %) in THF. The reactions started initially without

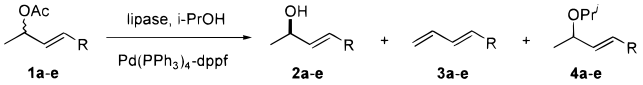
Scheme 1



Scheme 2



Scheme 3



a. R = Ph; **b**. R = *p*-Cl-Ph; **c**. R = *p*-Me-Ph; **d**. R^2 = 2-furyl; **e**. R = 1-naphthyl

(1) Undergraduate research participant.

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(3) Review on dynamic kinetic resolution: Ward, R. S. *Tetrahedron: Asymmetry* **1995**, *6*, 1475.

(4) Previous reports: (a) Allen, J. V.; Williams, J. M. J. *Tetrahedron Lett.* **1996**, *37*, 1859. (b) Dinh, P. M.; Howarth, J. A.; Hudnott, A. R.; Williams, J. M. J.; Harris, W. *Tetrahedron Lett.* **1996**, *37*, 7623−26. (c) Reetz, M. T.; Schimossek, K. *Chimia* **1996**, *50*, 668. (d) Persson, B. A.; Larsson, A. L. E.; Ray, M. L.; Bäckvall, J.-E. *J. Am. Chem. Soc.* **1999**, *121*, 1645.

(5) PCL immobilized on ceramic particles (trade name, Lipase PS−C (type II), Amano, Japan) and CAL immobilized on acrylic resin (trade name, Novozym 435, Novo Nordisk Korea) were used.

(6) Most likely this racemization proceeds via *cis*-migration of coordinated acetate in the intermediate (π-allyl)palladium complex (Trost. B. M.; Verhoeven, T. R.; Fortunak, J. M. *Tetrahedron Lett.* **1979**, 130. Bäckvall, J. E.; Nordberg, R. E.; Björkman, E. E.; Moberg, C. *J. Chem. Soc., Chem. Commun.* **1980**, 943. Bäckvall, J. E.; Nordberg, R. E.; Wilhelm, D. *J. Am. Chem. Soc.* **1985**, *107*, 6892). It may also proceed via a Pd-to-Pd displacement (Granberg, K. L.; Bäkvall, J. E. *J. Am. Chem. Soc.* **1992**, *114*, 6858).

(7) Dppf was the most effective among the diphosphine ligands, including dppf, 1,2-bis(diphenylphosphino)ethane (dppe), and 1,4-bis(diphenylphosphino)butane (dppb), that were screened for the racemization of (*S*)-**1a** by $Pd(PPh_3)_4$.

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Table 1. Dynamic Kinetic Resolution of Acyclic Allylic Acetates

entry	substrate	lipase[a]	time, d	conv, %[b]	yield, %[b]	ee, %[c]
1	**1a**	CAL	1.5	>99	83(71)	98
2	**1a**	PCL	3	92	81(72)	98
3	**1b**	CAL	3	>99	77(67)	97
4	**1c**	CAL	3	97	81(70)	98
5	**1c**	PCL	5	89	82(73)	98
6	**1d**	CAL	3	97	87(78)	>99
7	**1d**	PCL	6	86	78(67)	>99
8	**1e**	CAL	2.5	>99	70(61)	98

[a] CAL, *Candida antarctica* lipase; PCL, *Pseudomonas cepacia* lipase. [b] Based on the HPLC analysis. The isolated yields are given in parentheses. [c] Determined based on the HPLC analysis using a chiral column (Chiracel OD or Welko-O 1). Analytical conditions: **2a** and **2e**, Chiracel OD, hexane/2-propanol = 90/10, flow rate = 1.0 mL/min, UV 254 nm; **2b**−**d**, determined in the acetate form, Welko-O 1, hexane/2-proanol = 95/5, UV 254 nm for **2b**,**c** and 296 nm for **2d**.

$Pd(PPh_3)_4$ and dppf, to minimize the side reactions, both of which were then added at 45−50% conversion after 18−24 h (Scheme 2). The reactions were followed by chiral HPLC, and the products were isolated by flash chromatography.

The data given in Table 1 indicate that satisfactory resolution has been achieved in all the cases. In the resolutions using CAL (entries 1, 3, 4, 6, and 8), most of the substrate was consumed within 3 days, and the resolution was achieved in 70−87% yield with the enantiomeric excess (ee) of 97−99%. The isolation yield ranged from 61 to 78%. In the cases using PCL (entries 2, 5, and 7), approximately 90% of the substrate reacted in a period of 3−6 days, and approximately 90% of the reacted substrate was resolved to yield the product with 98−99% ee. In these cases, the longer reaction time was due to the lower activity of the enzyme. The isolation yield ranged from 67 to 73%. In most cases (entries 1−7), the elimination products (**3a**−**d**) were formed (usually 9−15%) together with a smaller amount (less than 6%) of the substitution products (**4a**−**d**). In the resolution of **1e** (entry 8), 70% of the substrate was converted to the wanted product (*R*)-**3e**, and the remaining 30% was transformed to the elimination product **3e** with no detectable **4e,** indicating that the substrate is more susceptible to the elimination compared to others. In all cases (entries 1−8), the side products were readily removed from the resolved products.

This work thus has demonstrated that acyclic allylic acetate in the racemic form can be efficiently transformed into a single enantiomeric product through the lipase-catalyzed transesterification coupled with the palladium-catalyzed racemization. This dynamic kinetic resolution procedure uses readily available enzymes and the transition metal complex as the catalysts and provides high optical purity and good yield. The reaction is carried out at lower temperature with relatively shorter time compared to the previous procedures.[4] We believe that this procedure is applicable in the resolution of a wider range of allylic acetates and thus provides a useful alternative to the chemical methods[8] for the synthesis of enantiomerically enriched allylic alcohols. Optically active allylic alcohols are versatile building blocks in the enantioselective synthesis of more complex molecules.[9] This procedure, however, needs to be further improved for higher yield. Further studies to overcome the problem of side reactions and broaden the scope are under progress in this laboratory.

Experimental Section

General Procedure for DKR. The DKR of **1a** using CAL as lipase is described as a representative procedure. A heterogeneous solution containing **1a** (100 mg, 0.53 mmol), CAL (0.2 g), and *i*-PrOH (0.4 mL) in dry THF (2 mL) was stirred at room temperature (16−18 °C) under argon atmosphere. After 24 h, $Pd(PPh_3)_4$ (29 mg, 0.025 mmol) and dppf (42 mg, 0.075 mmol) were added to the reaction mixture. The resulting solution was bubbled with argon for a few minutes and kept to be stirred at room temperature under argon atmosphere. As the reaction proceeded, some of $Pd(dppf)_2$ precipitated out as the yellowish solid due to the low solubility. After 2 days, the HPLC analysis indicated that >99% of the substrate was converted to the corresponding allylic alcohol, 1-phenyl-1,4-butadiene, and 1-phenyl-3-isopropyloxy-1-butene, respectively, in 83%, 15%, and 2% yield. The reaction was stopped by removing the enzymes, and the solution was concentrated and subjected to a flash chromatography to provide (*R*)-**2a** (55 mg, 0.371 mmol, 71%, 98% ee).

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