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Concerted Catalytic Reactions for Conversion of Ketones or Enol Acetates to Chiral Acetates

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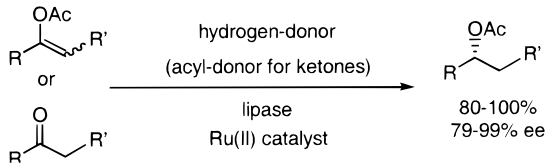
ABSTRACT

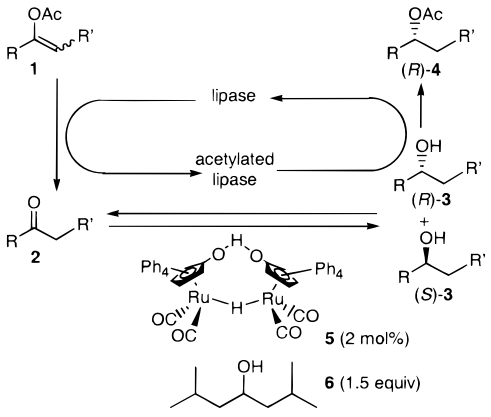


Enol acetates or ketones asymmetrically transformed to chiral acetates in high yields with high optical purities through multistep reactions catalyzed by a lipase and a ruthenium complex. 2,6-Dimethylheptan-4-ol was chosen as a suitable hydrogen donor, and 4-chlorophenyl acetate was used as an acyl donor for the conversion of ketones.

Asymmetric catalysis is one of the most fascinating topics in synthetic chemistry.[1] Many asymmetric transformations have been developed by employing either enzymatic reactions or chiral metal complex catalyzed reactions. However, the combined uses of enzyme and achiral metal catalyst have rarely been reported for asymmetric transformations.[2−4] A few examples with lipases and transition-metal catalysts were found by dynamic kinetic resolution (DKR) of alcohols, allyl acetates, and an amine.[5] Herein we report novel and versatile processes that convert achiral enol acetates **1** or ketones **2** asymmetrically to chiral acetates **4** through concerted reactions consisting of lipase-catalyzed steps and ruthenium-catalyzed ones.

The conversion of enol acetate **1** to chiral acetate **4** proceeds through a five-step process, as shown in Scheme 1: deacetylation of enol acetate **1** to give the corresponding

Scheme 1. Concerted Catalytic Reactions for the Conversion of Enol Acetates to Chiral Acetates



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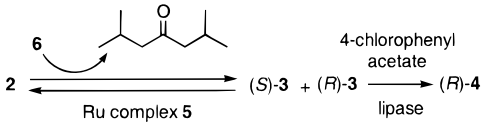
enol and the acetylated lipase, keto−enol tautomerization for the formation of ketone **2**, reduction of ketone **2** to the racemic mixture of alcohols (*R*)-**3** and (*S*)-**3**, enantioselective acetylation of (*R*)-**3** with the acetylated lipase to produce chiral acetate (*R*)-**4**, and reversible transformation between (*S*)-**3** and (*R*)-**3**. The ruthenium-catalyzed steps, reduction of ketone **2** and reversible transformation between (*S*)-**3** and (*R*)-**3**, are common to the ketone-conversion process, which requires independent acyl donors (Scheme 2). The common

Scheme 2. Concerted Catalytic Reactions for the Conversion of Ketones to Chiral Acetates

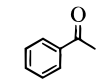
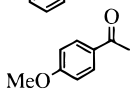
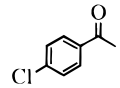
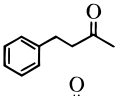
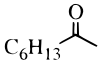


steps constitute a catalytic transfer-hydrogenation reaction of ketone, with alcohol acting as a hydrogen donor.[6] Therefore, both processes need a proper catalyst for the transfer-hydrogenation reaction and a hydrogen donor compatible with lipase-catalyzed acyl-transfer reactions.

We surveyed many transition-metal complexes used in transfer-hydrogenation reactions and found complex **5** as an excellent procatalyst for our processes. In fact complex **5** has been used in many catalytic reactions, including transfer-hydrogenation reactions and DKR of alcohols.[2b−d,7] For a hydrogen donor compatible with the lipase-catalyzed acyl-transfer reactions, 2,6-dimethylheptan-4-ol (**6**) was chosen, since it is a poor substrate against lipases and is commercially available.

The scope of the ketone-conversion process was investigated with ketones **2a**−**h** by using complex **5**, an immobilized lipase,[8] hydrogen donor **6**, and 4-chlorophenyl acetate as an acyl donor in toluene at 70 °C (Table 1).[9] Chiral

Table 1. Conversion of Ketones to Chiral Acetates[a]

entry	substrate		alcohol (%)[b]	acetate (%)[b]	% ee[c]
1		**2a**	0	97	98
2		**2b**	0	94	99
3		**2c**	0	97	99
4		**2d**	0	94	99
5		**2e**	13	82	90
6		**2f**	0	100	99
7		**2g**	0[d]	98[d]	99[d]
8		**2h**	0[d]	95[d]	95[d]

[a] The reactions were carried out on a 0.25 mmol scale with 2 mol % of **5**, 7.5 mg of Novozym 435, 1.5 equiv of 2,6-dimethylheptan-4-ol, and 3 equiv of 4-chlorophenyl acetate in 0.8 mL of toluene at 70 °C for 44 h under an argon atmosphere. [b] The yields were estimated by ^{1}H NMR. [c] The % ee values of acetates were determined by HPLC carried out with a chiral column ((R,R) Whelk-01, Merck). [d] The yields and optical purities were determined by GC carried out with a chiral capillary column (Chiraldex B-PH, Altech).

acetates (*R*)-**4** were produced in high yields (94−100%) with high enantioselectivities (95−99% ee) not only from aromatic ketones but also from aliphatic ones.[10] In all cases ketones **2** were left only in less than a 5% amount, regardless of their oxidation potentials.[11] Moreover, intermediate alcohols **3** were not detected in all but the reaction of **2e**, in which a considerable amount of **3e** (13% yield) remained, and chiral acetate **4e** was formed in a lower yield (82%) with a lower optical purity (90% ee).

Enol acetates **1a**−**h**, corresponding to ketones **2a**−**h**, were prepared and tested for the conversion to chiral acetates **4** under the same reaction conditions as in Table 1 but without 4-chlorophenyl acetate.[12] Initial results were not satisfactory, due to the production of ketones **2** and alcohols **3** in large amounts. However, we found that the purity of hydrogen

(3) (a) Allen, J. V.; Williams, J. M. J. *Tetrahedron Lett*. **1996**, *37*, 1859. (b) Choi, C. K.; Suh, J. H.; Lee, D.; Lim, I. T.; Jung, J. Y.; Kim, M.-J. *J. Org. Chem*. **1999**, *64*, 8423

(4) Reetz, M. T.; Schimossek, K. *Chimia* **1996**, *50*, 668.

(5) Reviews for DKR: (a) Ward, R. S. *Tetrahedron: Asymmetry* **1995**, *6*, 1475. (b) Noyori, R.; Tokunaga, M.; Kitamura, M. *Bull. Chem. Soc. Jpn*. **1995**, *68*, 36. (c) Caddick, S.; Jenkins, K. *Chem. Soc. Rev*. **1996**, 447. (d) Stürmer, R. *Angew. Chem.* **1997**, *109*, 1221; *Angew. Chem., Int. Ed. Engl*. **1997**, *36*, 1173. (e) Strecher, H.; Faber, K. *Synthesis* **1997**, 1. (f) Ebbers, E. J.; Ariaans, G. J. A.; Houbiers, J. P. M.; Bruggink, A.; Zwanenburg, B. *Tetrahedron* **1997**, *53*, 9417. (g) Strauss, U. T.; Felfer, U.; Faber, K. *Tetrahedron: Asymmetry* **1999**, *10*, 107. (h) Gihani, M. T. E.; Williams, J. M. J. *Curr. Opin. Chem. Biol*. **1999**, *3*, 11.

(6) Recent reviews: (a) Zassinovich, G.; Mestroni, G.; Gladiali, S. *Chem. Rev*. **1992**, *92*, 1501. (b) de Graauw, C. F.; Peters, J. A.; van Bekkum, H.; Huskens, J. *Synthesis* **1994**, 1007. (c) Noyori, R.; Hashiguchi, S. *Acc. Chem. Res*. **1997**, *30*, 97.

(7) (a) Blum, Y.; Czarkie, D.; Rahamim, Y.; Shvo, Y. *Organometallics* **1985**, *4*, 1459. (b) Shvo, Y.; Czarkie, D.; Rahamim, Y. *J. Am. Chem. Soc*. **1986**, *108*, 7400. (c) Shvo, Y.; Czarkie, D. *J. Organomet. Chem*. **1986**, *315*, C25. (d) Menashe, N.; Shvo, Y. *Organometallics* **1991**, *10*, 3885. (e) Menashe, N.; Salant, E.; Shvo, Y. *J. Organomet. Chem*. **1996**, *514*, 97. (f) Almeida, M. L. S.; Beller, M.; Wang, G.-Z.; Bäckvall, J.-E. *Chem. Eur. J*. **1996**, *2*, 1533 and references therein. (g) Shvo, Y.; Goldberg, I.; Czerkie, D.; Reshef, D.; Stein, Z. *Organometallics* **1997**, *16*, 133.

(8) The lipase from *Candida antarctica* is immobilized on acrylic resin (trade name: Novozym 435, Nordisk Korea).

(9) Bäckvall and co-workers selected 4-chlorophenyl acetate as a suitable acyl donor after surveying various alkenyl acetates and activated esters. However, the separation of the product from unreacted 4-chlorophenyl acetate is difficult in some cases.[2c]

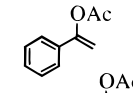
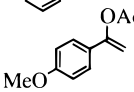
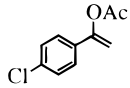
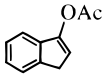
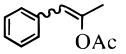
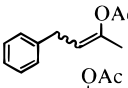
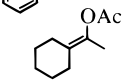
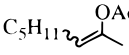
(10) The absolute configuration of the acetates was determined by comparing their optical rotations with known data. See: (a) Naemura, K.; Murata, M.; Tanaka, R.; Yano, M.; Hirose, K.; Tobe, Y. *Tetrahedron: Asymmetry* **1996**, *7*, 3285−3294. (b) Laumen, K.; Schneider, M. P. *J. Chem. Soc., Chem. Commun*. **1988**, 598−600.

(11) Adkins, H.; Elofson, R. M.; Rossow, A. G.; Robinson, C. C. *J. Am. Chem. Soc*. **1949**, *71*, 3622.

(12) For the synthesis of enol acetates, see: Larock, R. C. *Comprehensive Organic Transformations*; VCH: New York, 1989.

donor **6** is crucial to increase the yields of chiral acetates **4** (Table 2).[13] With the same amount of lipase as in Table 1, reactions of enol acetates **1** were completed within 2 days, although those of **1e**−**h** were carried out with a smaller amount of lipase for longer times to increase enantioselectivity. Ketones **2** (1−16%) and alcohols **3** (1−9%) were formed in various amounts by competitive acyl-transfer reactions, possibly involving the impurities of hydrogen donor **6** and water contained in lipase. The low oxidation potential of ketone is an apparent factor for the production of ketones **2b** (16%) and **2d** (13%) in large amounts.[11] In general, high enantioselectivities (91−99% ee) were observed in reactions of aliphatic enol acetates as well as in those of aromatic ones. It is notable that the results of entries 5−8 were obtained from mixtures of terminal enol acetate and geometric isomers of internal enol acetate.[12] Meanwhile, the reaction of **1e** was much less enantioselective (79% ee), due to the slow racemization of the corresponding alcohol (**3e**) and low specificity of the employed lipase for **3e**.[14]

Table 2. Conversion of Enol Acetaes to Chiral Acetates[a]

entry	substrate	time (h)	ketone (%)[b]	alcohol (%)[b]	acetate (%)[b,c]	% ee[d]
1	 **1a**	42	10	1	89 (85)	98
2	 **1b**	42	16	4	80 (70)	98
3	 **1c**	42	5	4	91 (84)	97
4	 **1d**	72	13	0	87 (85)	99
5	 **1e**[e]	110[f]	1	9	90 (89)	79[g]
6	 **1f**[e]	48[f]	3	5	92 (89)	94[g]
7	 **1g**[e]	38	4[h]	3[h]	94[h] (90)	99[h]
8	 **1h**[e]	68[f]	2[h]	3[h]	95[h] (89)[i]	91[h]

[a] The reactions were carried out on a 0.25 mmol scale with 2 mol% of **5**, 7 mg of Novozym 435, and 1.5 equiv of 2,6-dimethylheptan-4-ol in 0.8 mL of toluene at 70 °C under an argon atmosphere. [b] The yields were estimated by ^{1}H NMR. [c] The values in parentheses are the isolated yields from 1.0 mmol scale reactions. [d] The % ee values of acetates were determined by HPLC carried out with a chiral column ((R,R) Whelk-01, Merck). [e] Ratios of internal enol acetates to terminal enol acetate: **1e**, 61:39; **1f**, 52:48; **1g**, 80:20; **1h**, 86:14. [f] The amount of Novozym 435 was reduced to 2 mg. [g] The % ee values were determined by HPLC carried out with a chiral column (Chiralcel OD) after hydrolysis to alcohols. [h] Yields and optical purities were determined by GC carried out with a chiral capillary column (Chiraldex B-PH, Altech). [i] Acetate **4h** was contaminated with 2,6-dimethylheptan-4-one, and the yield was estimated by GC.

In general, high enantioselectivities (91−99% ee) were observed in reactions of aliphatic enol acetates as well as in those of aromatic ones. It is notable that the results of entries 5−8 were obtained from mixtures of terminal enol acetate and geometric isomers of internal enol acetate.[12] Meanwhile, the reaction of **1e** was much less enantioselective (79% ee), due to the slow racemization of the corresponding alcohol (**3e**) and low specificity of the employed lipase for **3e**.[14]

The ketone conversion process is an efficient way around the undesirable ketone production in the DKR of racemic alcohols.[2c] It takes advantage of ketone involvement in the racemization of alcohols, which is necessary but deteriorates the yields of chiral acetates in the DKR of alcohols.[15] Thus, the ketone-conversion process produces chiral acetates (*R*)-**4** in much higher yields with comparable enantioselectivities in comparison with the DKR of alcohols. In the meantime, the enol acetate conversion process demonstrates a highly atom-economical transformation that is a practical alternative to the processes using independent acyl donors. Furthermore, more optically pure chiral acetates can be obtained from enol acetates by this process than by asymmetric catalytic hydrogenation reactions,[16] particularly from acyclic enol acetates and simple species without secondary donor groups. Competitive acyl-transfer reactions are, however, obvious weak points of our process. To overcome the side reactions, an investigation into other hydrogen donors and catalysts is now in progress.

In summary, we have developed new and highly efficient one-pot processes for asymmetric transformations of ketones or enol acetates to chiral acetates. A lipase and an achiral transition-metal complex catalyze the asymmetric transformations proceeding through at least four different reactions concerted in one reaction vessel.

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Supporting Information Available: Spectroscopic data and experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) The purity of commercial 2,6-dimethylheptan-4-ol is about 90%; it was further purified through enzymatic acetylation of the impurity and fractional distillation.

(14) Acetate **4e** was obtained in 92% yield with 35% ee after 42 h under the same reaction conditions as for the conversion of **1a**.

(15) Recently we have reported ruthenium-catalyzed racemizations of alcohols without ketones.[2e,f]

(16) (a) Jiang, Q.; Xiao, D.; Zhang, A.; Cao, P.; Zhang, X. *Angew. Chem., Int. Ed.* **1999**, *38*, 516 and references therein. (b) Burk, M. J. *J. Am. Chem. Soc.* **1991**, *113*, 8518. (c) Burk, M. J.; Kalberg, C. S.; Pizzano, A. *J. Am. Chem. Soc.* **1998**, *120*, 4345.