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Practical Ruthenium/Lipase-Catalyzed Asymmetric Transformations of Ketones and Enol Acetates to Chiral Acetates

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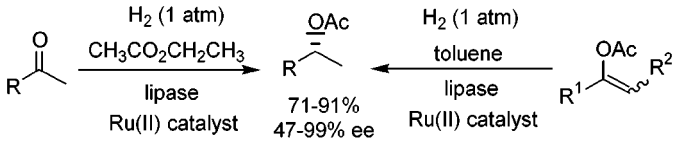
ABSTRACT

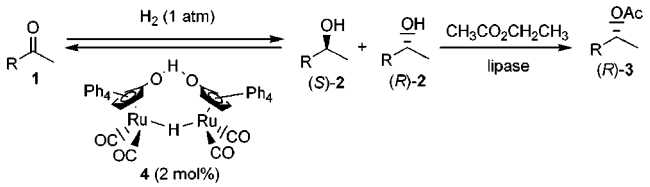


Ketones were asymmetrically transformed to chiral acetates by one-pot processes using a lipase and an achiral ruthenium complex under 1 atm of hydrogen gas in ethyl acetate. Molecular hydrogen was also effective for the transformation of enol acetates to chiral acetates without additional acyl donors with the same catalyst system.

A combination of enzymatic resolution and achiral metal catalysis has emerged as an attractive method for the preparation of enantiomerically enriched compounds.[1] A few examples with lipases and transition-metal catalysts were found by the dynamic kinetic resolution (DKR) of simple alcohols,[1b,d−g] α-hydroxy acid esters,[1i] allyl alcohols,[2] allyl acetates,[1a,h] and an amine.[1c] As novel extensions of the DKR of alcohols, we have demonstrated catalytic asymmetric transformation of enol acetates as well as ketones into chiral acetates by combining a lipase and a ruthenium complex.[3] For the transformation of ketones, 2,6-dimethylheptan-4-ol and 4-chlorophenyl acetate have been used as a hydrogen donor and an acyl donor, respectively.[4] Although the desired chiral acetates were produced in high yields and in high optical purities, practical applications of the processes were frequently hindered by separation problems caused by 2,6-dimethylheptan-4-one and unreacted 4-chlorophenyl acetate in product mixtures.[5] Herein we describe a significant advance to solve the separation problems by using molecular hydrogen or formic acid as a hydrogen donor and ethyl acetate as an acyl donor.

We focused on the known catalytic activity of ruthenium complex **4** for the reduction of ketones with formic acid or molecular hydrogen (Scheme 1).[6] Acetophenone was selected as a standard substrate and was subjected to various reaction conditions with using complex **4** and Novozym 435 (Table

Scheme 1. Transformation of Ketones to Chiral Acetates with H_2 and Ethyl Acetates



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(1) (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. (c) Reetz, M. T.; Schimossek, K. *Chimia* **1996**, *50*, 668. (d) Larsson, A. L. E.; Persson, B. A.; Bäckvall, J.-E. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 121. (e) Persson, B. A.; Larsson, A. L. E.; Ray, M. L.; Bäckvall, J.-E. *J. Am. Chem. Soc.* **1999**, *121*, 1645. (f) Persson, B. A.; Huerta, F. F.; Bäckvall, J.-E. *J. Org. Chem.* **1999**, *64*, 5237. (g) Koh, J. H.; Jung, H. M.; Kim, M.-J.; Park, J. *Tetrahedron Lett.* **1999**, *40*, 6281. (h) Choi, Y. K.; Suh, J. H.; Lee, D.; Lim, I. T.; Jung, J. Y.; Kim, M.-J. *J. Org. Chem.* **1999**, *64*, 8323. (i) Huerta, F. F.; Laxmi, Y. R. S.; Bäckvall, J.-E. *Org. Lett.* **2000**, *2*, 1037.

(2) Lee, D.; Huh, E.; Kim, M.-J.; Jung, H. M.; Koh, J. H.; Park, J. *Org. Lett.* In press.

(3) Jung, H. M.; Koh, J. H.; Kim, M.-J.; Park, J. *Org. Lett.* **2000**, *2*, 409.

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1).[7,8] Formic acid in toluene acted as a hydrogen donor compatible with 4-chlorophenyl acetate. However, 30% of the acetophenone remained after the reaction with 1 equiv of formic acid, while the use of more than 1 equiv made the lipase inactive. A significant improvement was achieved by employing triethylamine (entry 3): Only 6% of the acetophenone remained and optically pure 1-phenylethyl acetate (**3a**) was produced in a 94% yield in the reaction with 1 equiv of the 1:1 mixture of triethylamine and formic acid. Ethyl acetate also acted as an acyl donor, although more lipase and longer reaction times were needed for results comparable to those with 4-chlorophenyl acetate. As a hydrogen donor, molecular hydrogen showed apparent advantages over formic acid: Only 1 equiv of 4-chlorophenyl acetate is enough for a satisfactory result (entry 4), and the combination with ethyl acetate produces **3a** in much higher yield than that of formic acid and ethyl acetate (entry 6). Furthermore, in contrast to previous conditions for the reduction of ketones,[6a] 1 atm of H_2 was enough to provide 1-phenylethanol for the enzymatic resolution. In fact, more than 90% of the acetophenone was consumed within 24 h, and 1-phenylethanol was accumulated under 1 atm of H_2 at 70 °C (Figure 1). Another feature of the reaction profile in Figure 1 is that the transformation appears to stop at about 90% production of **3a** after 96 h. Noticeably, an apparent increase in the yield as well as in the optical purity of **3a** was achieved by periodic removal of ethanol and addition of fresh ethyl acetate during the transformation (entry 7). However, replacement of ethyl acetate with methyl propionate led to a rather poor result in both the yield and the optical purity of **3a**.[9]

Table 1. Transformation of Acetophenone to 1-Phenylethyl Acetate[a]

entry	H donor	acyl donor	time (h)	yield (%)[b]	% ee[c]
1	HCO_2H (1.0 equiv)	4-chlorophenyl acetate[d]	34	70	96
2	HCO_2H (1.2 equiv)	4-chlorophenyl acetate[d]	34	0[e]	
3	$HCO_2H{\cdot}NEt_3$ (1.0 equiv)	4-chlorophenyl acetate[d]	44	94	99
4	H_2 (1 atm)	4-chlorophenyl acetate[f]	44	95	99
5	$HCO_2H{\cdot}NEt_3$ (1.0 equiv)	ethyl acetate[g]	96	63	97
6	H_2 (1 atm)	ethyl acetate[g]	96	89	96
7[h]	H_2 (1 atm)	ethyl acetate[g]	96	95	>99
8[h]	H_2(1 atm)	methyl propionate[g]	96	75	82

[a] The reactions were carried out on a 0.25 mmol scale with 2 mol % of **4** and 7 mg of Novozym-435 at 70 °C. [b] The yield was determined by ^{1}H NMR. [c] The % ee was determined by HPLC using a chiral column ((R,R) Whelk-01, Merck). [d] 3.0 equiv. [e] 1-Phenylethanol was formed in 81%. [f] 1.1 equiv. [g] Novozym-435 (21 mg) was used in 0.8 mL of the acyl donor. [h] The reaction mixture was concentrated to one-third in volume every 24 h and the fresh acyl donor was added.

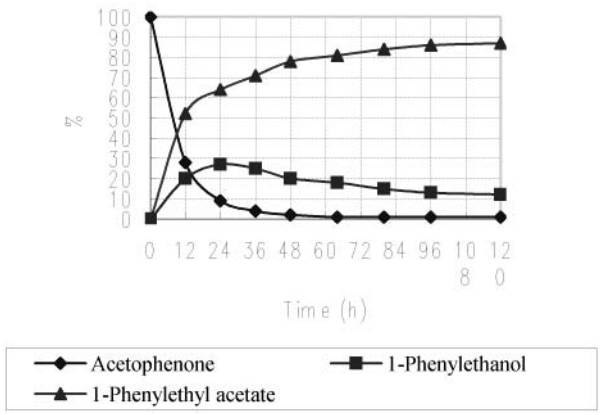


Figure 1. Reaction profile of acetophenone under a hydrogen atmosphere in ethyl acetate.

Various ketones, **1a**−**i**, were subjected to the reaction conditions of entry 6 in Table 1 to investigate the scope of this process for the preparation of chiral acetates **3a**−**i** (Table 2): In all cases, ketones **1** were consumed completely, and acetates **3** were easily isolated in good to high yields. In addition, the enantioselectivities for (*R*)-**3** were generally high and comparable to those given by the process using 2,6-heptan-4-ol and 4-chlorophenyl acetate in toluene.[10] However, 4-phenylbutan-2-one (**1h**) and 1-phenylacetone (**1i**) were exceptional substrates that transformed to acetates **3h** and **3i** with low optical purities, although the yields were comparable to others.

Enol acetates **5** were prepared from the corresponding ketones **1**[11] and were transformed to chiral acetates **3** under 1 atm of H_2 in toluene (Table 3). In comparison with the results from the previous processes using 2,6-dimethylheptan-4-ol as a hydrogen donor, the isolated yields of acetates **3** were higher, and their optical purities were nearly the same in most cases. However, enol acetates **5g**−**i** were transformed to the corresponding acetates **3g**−**i** with distinctly low enantioselectivities. Decreasing the amount of the lipase

(4) Bäckball and co-workers have selected 4-chlorophenyl acetate from a series of known acyl donors for enzymatic kinetic resolution of alcohols.[1d,e]

(5) Selective hydrolysis of unreacted 4-chlorophenyl acetate was needed before chromatographic separation of product acetates, and the separation of 2,6-dimethylheptan-4-one was difficult in the purification of aliphatic acetates.

(6) (a) Blum, Y.; Czarkie, D.; Rahamim, Y.; Shvo, Y. *Organometallics* **1985**, *4*, 1459. (b) Menashe, N.; Salant, E.; Shvo, Y. *J. Organomet. Chem.* **1996**, *514*, 97.

(7) The ruthenium complex is readily prepared from $Ru_3(CO)_{12}$ and tetraphenylcyclopentadienone: Shvo, Y.; Menashe, N. *Organometallics* **1991**, *10*, 3885.

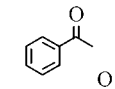
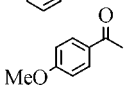
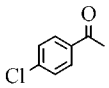
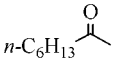
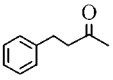
(8) The lipase from *Candida antarctica* is immobilized on acrylic resin (trade name: Novozym 435, Nordisk Korea).

(9) The inhibition of methanol liberated from dimethyl malonate has been noted in an enzymatic kinetic resolution: Fehr, C.; Galindo, J. *Angew. Chem., Int. Ed.* **2000**, *39*, 569.

(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. (b) Laumen, K.; Schneider, M. P. *J. Chem. Soc., Chem. Commun.* **1988**, 598.

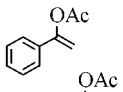
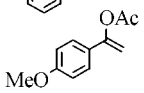
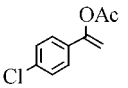
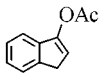
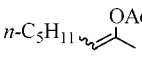
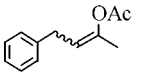
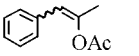
(11) For the synthesis of enol acetates, see: Larock, R. C. *Comprehensive Organic Transformations*; VCH: New York, 1989.

Table 2. Transformation of Ketones to Chral Acetates[a]

entry	substrate		time (h)	acetate (%)[b]	% ee[c]
1		**1a**	96	**3a** (81)	96
2		**1b**	76	**3b** (85)	99
3		**1c**	96	**3c** (72)	97
4		**1d**	76	**3d** (89)	99
5		**1e**	96	**3e** (87)	99[d]
6		**1f**	96	**3f** (87)	99[e]
7		**1g**	48	**3g** (87)	91[e]
8		**1h**	72	**3h** (83)	72[d]
9		**1i**	96	**3i** (71)	47[d]

[a] The reactions were carried out on a 1.00 mmol scale with 2 mol% of **4** and 84 mg of Novozym 435 in 3.0 mL of ethyl acetate under 1 atm of H_2 at 70 °C. [b] Isolated yield. [c] The % ee of acetates were determined by HPLC equipped with a chiral column ((R,R) Whelk-01, Merck). [d] The % ee was determined by HPLC equipped with a chiral column (Chiralcel OD) after hydrolysis to the corresponding alcohol. [e] The optical purity was determined by GC equipped with a chiral capillary column (Chiraldex B-PH, Alltech).

Table 3. Transformation of Enol Acetates to Chral Acetates[a]

entry	substrate		time (h)	acetate (%)[b]	% ee[c]
1		**5a**	50	**3a** (86)	96
2		**5b**	30	**3b** (74)	99
3		**5c**	36	**3c** (87)	98
4		**5d**	48	**3d** (87)	99
5		**5e**	42	**3e** (88)	99[d]
6		**5f**[e]	24	**3f** (90)	99[g]
7		**5g**[e]	68[f]	**3g** (91)	87[g]
8		**5h**[e]	34[f]	**3h** (85)	86[d]
9		**5i**[e]	154[f]	**3i** (84)	47[d]

[a] The reactions were carried out on a 1.00 mmol scale with 2 mol% of **4** and 30 mg of Novozym 435 in 3.0 mL of toluene under 1 atm of H_2 at 70 °C. [b] Isolated yield. [c] The % ee was determined by HPLC equipped with a chiral column ((R,R) Whelk-01, Merck). [d] The % ee was determined by HPLC equipped with a chiral column (Chiralcel OD) after hydrolysis to the corresponding alcohol. [e] Ratio of internal enol acetates to terminal enol acetate: **5f** (61:39), **5g** (52:48), **5h** (80:20), **5i** (86:14). [f] The amount of Novozym 435 was reduced to 8 mg. [g] The optical purity was determined by GC equipped with a chiral capillary column (Chiraldex B-PH, Alltech).

increased the optical purities of **3g**−**i** with extended reaction times, although **3i** was obtained only in 47% ee despite decreasing the amount to one-third of the standard condition.

Ruthenium complex **4** is a versatile redox catalyst that can be reduced not only by alcohols but also by formic acids or molecular hydrogen.[6] The reduced species is known to revert slowly to **4** with evolving molecular hydrogen.[6a] This unproductive consumption of reductants would be responsible for the incomplete reduction of acetophenone with 1 equiv of formic acid.[12] Interestingly, triethylamine appeared to prevent the unproductive reversion to **4**, and a significant improvement was achieved by the use of $HCO_2H{\cdot}NEt_3$ salt in combination with 4-chlorophenyl acetate. However, the salt was not suitable to ethyl acetate because of hydrolysis to produce acetic acid and ethanol, which can interfere in the acetylation step. The hydrolysis was not observed in the reaction with molecular hydrogen in ethyl acetate. Thus, only alcohols **2** were formed as side products in the transformation of ketones **1** under a hydrogen atmosphere in ethyl acetate.

A disadvantage in the use of ethyl acetate is a slow acyltransfer rate, which was supplemented by using three times more lipase for the results as compared to those with 4-chlorophenyl acetate. Another drawback is the generation of ethanol, which would interfere with the substrate alcohols in the catalytic reactions. However, fortunately, the effect was not serious under the conditions in Table 2. Furthermore, the interference can be readily minimized by periodic change of the reaction medium with fresh ethyl acetate. Meanwhile, the reduction of ketones **1** in ethyl acetate is fast enough to provide intermediate alcohols **2** even under 1 atm of H_2. In contrast to the previous reduction with 2,4-dimethylheptan-4-ol, the reduction with H_2 accompanies a decrease in the concentration of hydrogen mediators, making the racemization of intermediate alcohols **2** slow. This effect would deteriorate the enantioselectivity seriously when the acetylation proceeds with low specificity. Such a situation resulted in the distinctively low optical purities of **3h** and **3i**, which was observed again in the transformation of enol acetates **5i** with H_2. Generally, enol acetates **5** in toluene were transformed with faster rates than those of ketones **1** in ethyl

(12) There is a suggestion that a hydrogen-consuming process involving the employed enzyme is possible in the dynamic kinetic resolution of secondary alcohols.[1e]

acetate, possibly due to the difference in acylation rates. It is also notable that enol acetates **5** were intact under the same conditions as used in Table 3 but without the lipase while the hydrogenation of simple alkenes is much faster than that of ketones by the same catalyst (**4**) under 500 psi of H_2 at 145 °C.[6a] In comparison with 2,6-dimethylheptan-4-ol and formic acid, H_2 proved to be a better hydrogen donor in many aspects, including directly usable purity, cheaper price, and easier separation of product acetates **3** from the reaction mixtures.

In summary, we have developed highly practical one-pot processes for asymmetric transformations of ketones and enol acetates to chiral acetates. We found the conditions for employing ethyl acetate and molecular hydrogen as an acyl donor and a hydrogen donor, respectively, by combining catalytic activities of a ruthenium complex and a lipase. In particular, the transformations under 1 atm of H_2 demonstrated the widely applicable activity of the readily available ruthenium catalyst. The developed processes were suitable for the preparation of various chiral acetates except those for which the specificities of the lipase are low.

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Supporting Information Available: Typical experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org

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