Account

Dynamic Kinetic Resolutions and Asymmetric Transformations by Enzyme-Metal Combo Catalysis

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Enzyme-metal combo catalysis is described as a useful methodology for the synthesis of optically active compounds. The key point of the method is the use of enzyme and metal in combination as the catalysts for the complete transformation of racemic substrates to single enantiomeric products through dynamic kinetic resolution (DKR). In this approach, enzyme acts as an enantioselective resolving catalyst and metal does as a racemizing catalyst for the efficient DKR. Three kinds of enzyme-metal combinations - lipase-ruthenium, subtilisin-ruthenium, and lipase-palladium – have been developed as the catalysts for the DKRs of racemic alcohols, esters, and amines. The scope of the combination catalysts can be extended to the asymmetric transformations of ketones, enol acetates, and ketoximes via the DKRs. In most cases studied, enzyme-metal combo catalysis provided enantiomerically-enriched products in high yields.

Key Words : Catalytic racemization, Dynamic kinetic resolution, Asymmetric transformation, Enzyme-metal combo catalysis, Chirotechnology

Introduction

The methods for the synthesis of optically pure compounds are of great importance in pharmaceutical, agrochemical, and other fine chemical industries.[1] One of the popular methods is the kinetic resolution (KR) of racemic mixtures by enzymes such as lipases and esterases.[2,3] The methodology has been widely used for the preparation of optically pure alcohols, acids, and their esters. However, KR has an intrinsic limitation; the yield cannot exceed 50% for a single enantiomer. Thus, the conventional KR usually is accompanied by additional processes; separation, racemization, and recycling of unwanted enantiomers. The limitation, however, can be overcome if the kinetic resolution could be transformed to the dynamic kinetic resolution (DKR) by being coupled with a racemization reaction for the in situ conversion of unwanted enantiomers to products.[4]

Recently, several groups have reported the use of a metal complex as the racemizing catalyst with an enzyme for the DKR.[5] Williams *et al.* reported a lipase-palladium combination for the DKR of allyl acetates[6] and a lipase-rhodium combination for the DKR of secondary alcohols.[7] In the same year, Reetz *et al.* reported the DKR of 1-phenylethylamine by a lipase-palladium combination.[8] Soon after, we and the Bäckvall group reported substantially improved DKRs of secondary alcohols. In particular, we developed a new racemizing catalyst for the efficient DKRs of alcohols, which displayed high activity at room temperature.[9] The room-temperature DKRs were successfully done with both lipase and subtilisin to provides (*R*)- and (*S*)-products, respectively. The DKRs by enzyme-metal combinations have been extended to the asymmetric transformations of ketones, enol esters, and ketoximes.

This account covers the DKRs and asymmetric transformations by enzyme-metal comninations since the first report from the Williams group in 1996.

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DKR by Enzyme-Metal Combo Catalysis

DKR by Lipase-Ruthenium Combination

DKR of Secondary Alcohols. The first DKR of secondary alcohols, described by the Williams group in 1996,[6] was performed with rhodium complexes as the racemizing catalysts. In the DKR of 1-phenylethanol using vinyl acetate as an acyl donor, the optical purity of the acetylated product was only 80% ee even at 76% conversion.

One year later, Bäckvall *et al.* reported a significantly improved procedure using a diruthenium complex (**1**) and an immobilized and thermally stable lipase (*Candida antarctica* lipase B (CALB); trade name, Novozym-435) at 70 ºC.[10] *p*-Chlorophenyl acetate (PCPA) was a noticeable acyl donor that is compatible with the racemization catalyst. DKR of 1-phenylethanol by the procedure gave optically pure (*R*)-α-phenylethyl acetate (> 99.5% ee) in a high yield (100% conversion, 92% isolated yield) (Table 1). However, the DKR required a stoichiometric amount of acetophenone acting as hydrogen acceptors for racemization, otherwise a large amount (> 20%) of acetophenone formed with decreasing the yield of (*R*)-α-phenylethyl acetate.[10b]

Meanwhile, we found that an indenylruthenium complex (**2**) racemized secondary alcohols without the aid of ketones during DKR.[11] The DKR with **2**, however, required a catalytic amount of triethylamine and molecular oxygen to activate **2**. The combination of an immobilized *Pseudomonas cepacia* lipase (PCL, trade name, Lipase PS-C®) and **2** at 60 ºC was effective for the DKR of benzylic alcohols, but was somewhat less effective for that of aliphatic alcohols (Table 2).

Then, we found a cymene-ruthenium complex (**3**) and its activated hydride form (**4**) effective as the racemizing catalysts. The activated complex **4**, in particular, displayed satisfactory performances in the DKRs of aliphatic alcohols as well as benzylic alcohols (Table 3). A noticeable feature of the catalyst is the high racemizing activity toward allylic alcohols[12] so that their DKRs can be done at room temperature to provide high yields with excellent optical purities (Table 4). Another feature is its good activity in ionic liquids such as [EMIm]BF_4 and [BMIm]PF_6 ([EMIm]

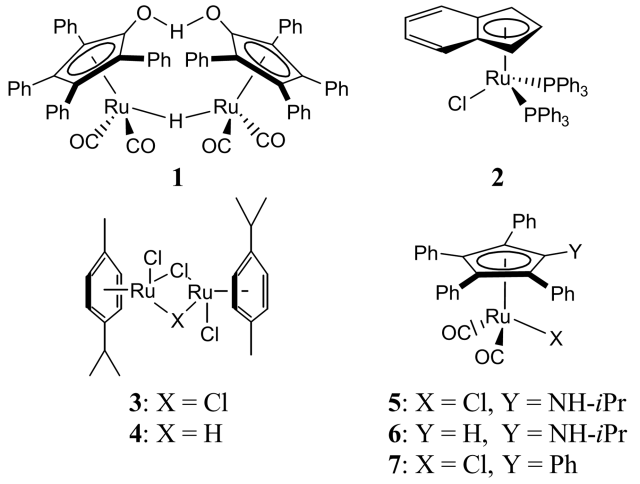
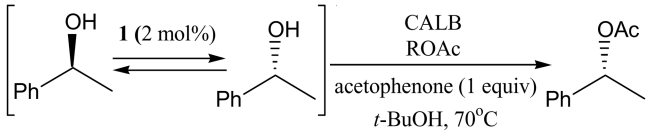


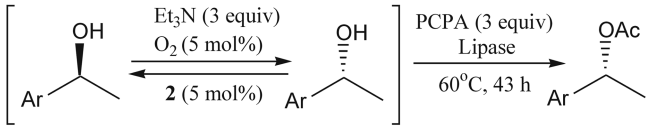
Figure 1. Ruthenium complexes employed as the racemization catalysts for the DKR of secondary alcohols.

Table 1. DKR of 1-phenylethanol with diruthenium complex **1**



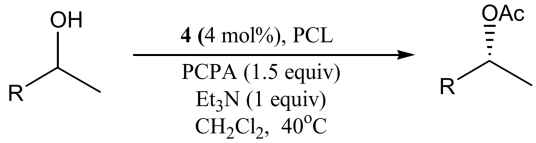
R	yield (%)	ee (%)
vinyl	50	> 99
isopropenyl	72	> 99
4-chlorophenyl	100	> 99

Table 2. DKR of secondary alcohols with indenyl ruthenium complex **2**



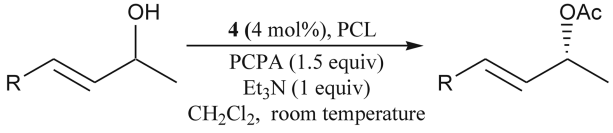
$ArCH(OH)CH_3$	yield (%)	ee (%)
1-phenylethanol	86	96
1-(4-methoxyphenyl)ethanol	82	99
1-(4-bromophenyl)ethanol	98	99
1-indanol	88	82
1-phenyl-2-propanol	60	97

Table 3. DKR of alcohols with cymene-ruthenium catalyst **4**



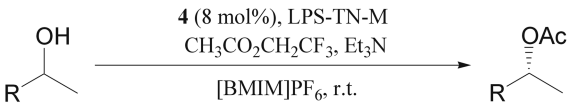
R	yield (%)	ee (%)
phenyl	95	94
p-chlorophenyl	93	99
p-methoxyphenyl	93	99
benzyl	85	> 99

Table 4. DKR of allylic alcohols with cymene-ruthenium catalyst **4**



R	yield (%)	ee (%)
phenyl	84	> 99
p-chlorophenyl	91	99
p-methoxyphenyl	85	99
2-furyl	92	99
cyclohexyl	90	95
t-butyl	85	> 99

Table 5. DKR of alcohols with cymene-ruthenium catalyst **4** in $[BMIm]PF_6$



$RCH(OH)CH_3$	yield (%)	ee (%)
1-phenyl-2-propanol	85	99
1-phenyl-3-butanol	85	99
1-(3-methylphenyl)ethanol	87	98
1-(4-methylphenyl)ethanol	87	99
1-(4-methoxyphenyl)ethanol	85	99
1-(4-chlorophenyl)ethanol	87	99
1-(4-bromophenyl)ethanol	92	99
1-indanol	85	99
1-[4-(1-hydroxyethyl)phenyl]ethanol	87	99 (de 99%)
1-[3-(1-hydroxyethyl)phenyl]ethanol	86	99 (de 97%)

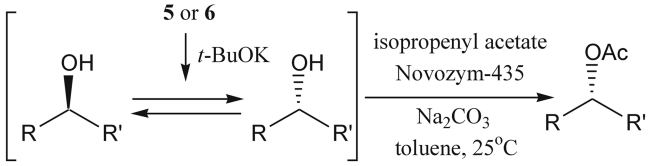
= 1-ethyl-3-methylimidazolium, [BMIm] = 1-butyl-3-methyl-imidazolium).[13] The DKRs in the ionic liquids were also possible at room temperature, and the racemizing catalyst and enzyme in the ionic liquid layer were reusable after extracting the products with ether (Table 5).[14]

In efforts to develop racemizing catalysts active at room temperature under DKR conditions, we synthesized a novel aminocyclopentadienyl ruthenium chloride complex (**5**), and found that it transforms to the corresponding hydride complex (**6**) by treatment with potassium *t*-butoxide in the presence of alcohols.[9] The hydride species **6** was active without the aid of base in the DKRs of aliphatic alcohols as well as in those of aromatic alcohols at room temperature (Table 6). Interestingly, isopropenyl acetate was usable as an efficient acyl donor in the DKRs. Isopropenyl acetate is a much better acylating reagent than *p*-chlorophenyl acetate (PCPA) used in the previous DKRs: It is readily available, easily separable from the DKR products, and more active than PCPA.[15] Although the mechanism for the catalytic racemization is not clear yet, according to our mechanistic studies, the amino group in **5** or **6** seems to be crucial for the racemization, while the recent report by the Bäckvall group suggests a different pathway.[16] The Bäckvall group used a modified complex **7** as the efficient racemizing catalyst, which is similar to **5** but has no amino group.

A new catalyst system of $[TosN(CH_2)_2NH_2]RuCl$(*p*-cymene) and 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) was reported by Sheldon *et al.* for the DKR of alcohols.[17] However, it was tested only for 1-phenylethanol to get 1-phenylethyl acetate in 76% yield.

DKR of Functionalized Alcohols. The DKRs of functionalized alcohols such as diols, hydroxy esters, hydroxy

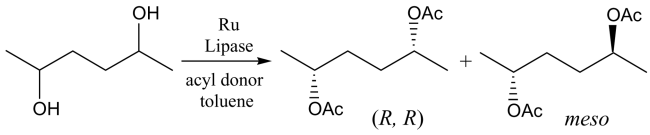
Table 6. DKR of alcohols with aminocyclopentadienyl ruthenium complex



R	R'	catalyst	yield (%)	ee (%)
phenyl	methyl	**5**	95	> 99
phenyl	methyl	**6**	92	> 99
4-chlorophenyl	methyl	**5**	94	> 99
4-chlorophenyl	methyl	**6**	91	> 99
4-methoxyphenyl	methyl	**5**	90	> 99
4-methoxyphenyl	methyl	**6**	94	> 99
1-indanyl		**5**	89	95
cyclohexyl	methyl	**5**	86	> 99
cyclohexyl	methyl	**6**	98[a]	> 99
4-nitrophenyl	methyl	**6**	97	> 99
4-cyanophenyl	methyl	**6**	95	> 99
phenyl	ethyl	**6**	90	> 99
n-hexyl	methyl	**5**	89	91
2-phenylethenyl	methyl	**5**	93	98
phenyl	vinyl	**5**	62	81
cyclohexyl	vinyl	**5**	90	> 99
trityloxymethyl	methyl	**5**	97	99

[a]Yield based on NMR data

Table 7. DKR of diols with diruthenium complex **1**



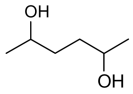
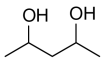
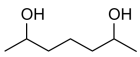
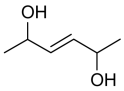
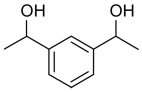
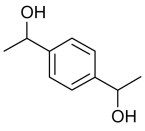
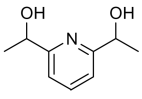
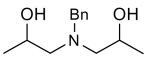
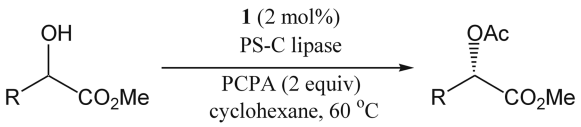
substrate	catalyst	yield (%)	(*R*,*R*)/*meso*	ee (%)
	**1**	63	86/14	> 99
	**1**	90	38/62	> 99
	**1**	63	90/10	> 97
	**1**	43	74/26	> 99
	**1**	76	98/2	> 99
	5	95	99/1	> 99
	**1**	77	98/2	> 99
	5	94	98/2	> 99
	6	90	99/1	> 99
	**1**	78	100/0	> 99
	**1**	64	89/11	> 96

Table 8. DKR of α-hydroxy esters



R	yield (%)	ee (%)
phenyl	80	94
4-methoxyphenyl	76	94
4-bromophenyl	69	98
cyclohexyl	80	98
2-phenylethyl	62	30
butyl	60	80

aldehydes, azido alcohols, and hydroxy nitriles were well performed by lipase-ruthenium bicatalysis. The DKR of diols was achieved with diruthenium catalyst **1** and CALB in the presence of PCPA to give the corresponding diacetates of (*R,R*)-configuration from the mixture of *dl*- and *meso*-isomers (Table 7).[18] The DKRs of rigid benzylic diols with **1** gave better results in terms of *de* compared to those of more flexible aliphatic diols, reflecting that lipase displays higher stereoselectivity toward benzylic diols than aliphatic diols.

The DKRs of α-, β-, γ-, and δ-hydroxy esters were also accomplished with PCL and **1** at 60-70 ºC.[19] In the DKRs, the enantioselectivities were good in most cases, but the yields were moderate. The use of H_2 was necessary in the DKRs of γ- and δ-hydroxy esters to suppress the formation of ketones (Table 8, 9, and Figure 2).

The DKRs of small functionalized alcohols such as 2-hydroxybutanoic acid, 2-hydroxypropanal, and 1,2-propanediol were carried out after the protection of the terminal groups with a bulky group (Table 10 and Figure 3) since the bulky protecting groups enhanced the enantioselectivity of enzyme in the DKR.[20] In the DKR of hydroxy acids, *t*-butyl group was the best as the protecting group of the carboxylic acid functionality. The trityl group was a proper choice for the protection of primary alcohols in diols such as 1,2-propanediol, 1,2-butanediol, and 1,3-butanediol.[20] 1,2-Benzenedimethanol was used for protecting the formyl groups of α- and β-hydroxy aldehydes.[20] High enantiomeric excesses (95 % and higher) were obtained in the DKRs of the protected diols and hydroxy aldehydes. 2,6-Dimethyl-4-heptanol was used as a hydrogen source to suppress the formation of the oxidized side products.

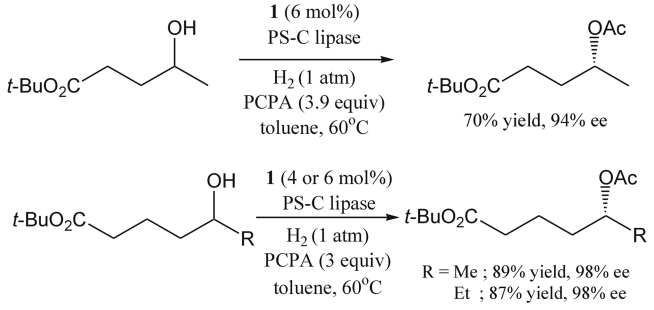
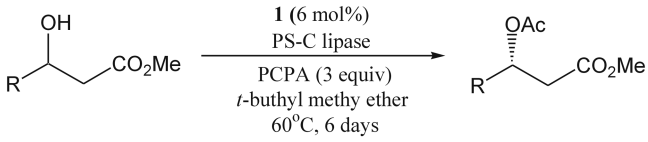


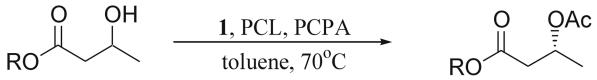
Figure 2. DKR of γ- and δ-hydroxy esters.

Table 9. DKR of β-hydroxy esters



R	yield (%)	ee (%)
phenyl	76	95
4-methoxyphenyl	74	99
benzyl	80	96
cyclohexyl	82	70

Table 10. DKR of hydroxy acids, diols, and hydroxy aldehydes



R	yield (%)	ee (%)
benzyl	88	86
4-methoxybenzyl	91	93
4-biphenyl	92	94
t-butyl	88	> 99

The DKRs of β-azidoalcohols[19d] and β-hydroxynitriles[21a] were also accomplished by employing **1** and CALB with PCPA as the acyl donor. The DKRs of β-azidoalcohols were performed at 60 ºC while those of β-hydroxynitriles required a higher temperature (100 ºC) to increase the racemization rate. The optical purities of products were satisfactory in all cases. In the cases of β-hydroxynitriles, dehydrogenation lowered the yield.

DKR by Subtilisin-Ruthenium Combination

DKR of Secondary Alcohols. The lipase-catalyzed DKRs provide only (*R*)-products. To obtain (*S*)-products, we need an enzyme with a complementary (*S*)-stereoselectivity. We surveyed (*S*)-selective enzymes usable in DKR at room temeparature with the racemizing catalyst **5**. Subtilisin was a candidate, but its commercial form was not applicable to DKR due to its low enzymatic activity and instability in nonaqueous medium. However, we succeeded in enhancing its activity and stability by treating it with a surfactant before use. At room temperature DKR with subtilisin, trifluoroethyl butanoate was employed as an acylating agent and the (*S*)-products were obtained in good yields with high optical purities (Table 11).[22]

The (*S*)-selective DKR of alcohols with subtilisin was also possible in ionic liquid at room temperature (Table 12).[14] In this case, the cymene-ruthenium complex **3** was used as the racemization catalyst. In general, the optical purities of (*S*)-esters were lower than those of (*R*)-esters described in Table 5.

DKR by Lipase-Palladium Combination

DKR of Allylic Acetates. The DKR of allylic acetates

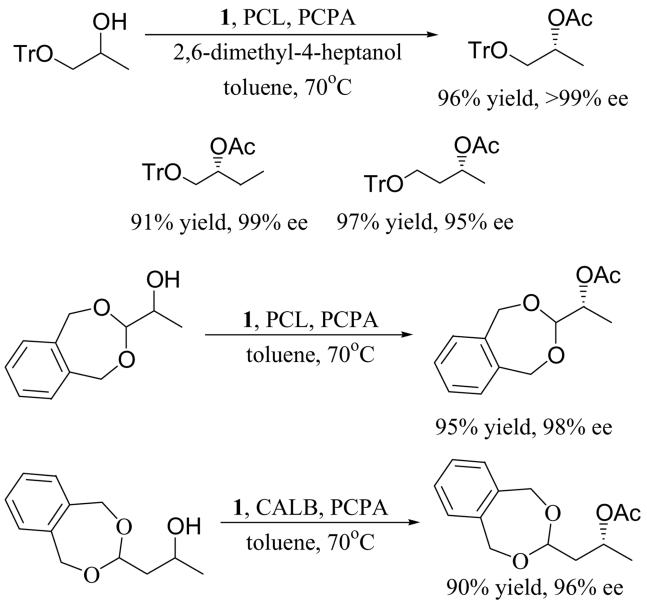
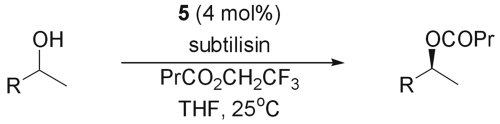


Figure 3. DKR of protected diols and hydroxy aldehydes by lipase-ruthenium combination.

Table 11. DKR of secondary alcohols by subtilisin-ruthenium bicatalysis

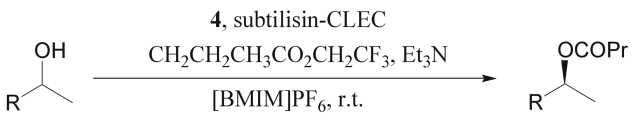


R	yield (%)	ee (%)
phenyl	95	92
4-chlorophenyl	92	99
4-methoxyphenyl	93	94
benzyl	89	92
2-phenylethyl	80	98
cyclohexyl	80	98
n-hexyl	77	98
2-phenylethynyl	90	95

was accomplished through coupling Pd-catalyzed racemization and enzymatic hydrolysis of allylic acetates in buffer solution.[6] However, the DKR under these conditions was limited to cyclohexenyl acetates to give symmetrical palladium-allyl intermediates. Among them, 2-phenyl-2-cyclohexenyl acetate was the only substrate to have been resolved with good results (96% conversion, 81% yield, 96% ee) (Figure 4).

We improved the DKR of allylic acetates significantly by replacing the enzymatic hydrolytic reaction with the enzymatic transesterification reaction and employing $Pd(PPh_3)_4$, and 1,1'-bis(diphenylphosphino)ferrocene (dppf) as the racemizing catalyst system in tetrahydrofuran (THF).[23] 2-Propanol was used as an acyl acceptor. The use of the chelating ligand (dppf) decreased the formation of by-products (1,3-dienes) during the DKR. Various acyclic allylic acetates were transformed to their corresponding

Table 12. DKR by subtilisin-ruthenium bicatalysis in $[BMIm]PF_6$



$RCH(OH)CH_3$	yield (%)	ee (%)
1-phenyl-2-propanol	89	97
1-phenyl-3-butanol	90	97
1-(3-methylphenyl)ethanol	90	85
1-(4-methylphenyl)ethanol	90	85
1-(4-methoxyphenyl)ethanol	80	99
1-(4-chlorophenyl)ethanol	92	87
1-(4-bromophenyl)ethanol	91	82
1-indanol	84	86
1-[4-(1-hydroxyethyl)phenyl]ethanol	78	86 (de 52%)
1-[3-(1-hydroxyethyl)phenyl]ethanol	83	96 (de 63%)

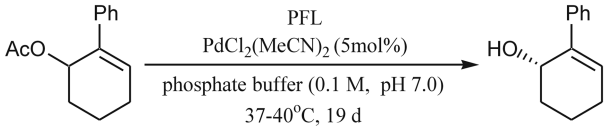
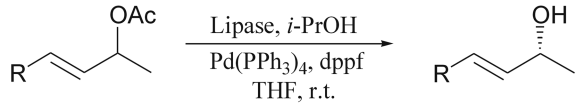


Figure 4. DKR of 2-phenyl-2-cyclohexenyl acetate by lipase-palladium bicatalysis.

Table 13. DKR of allylic acetates by lipase-palladium bicatalysis



R	yield (%)	ee (%)
phenyl	83	98
4-chlorophenyl	77	97
4-methylphenyl	82	98
2-furyl	87	> 99
1-naphthyl	70	98

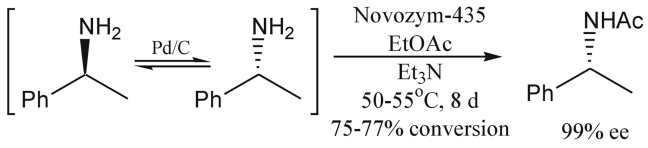
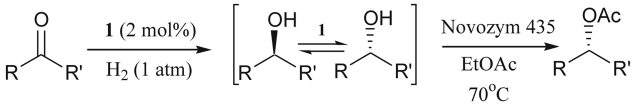


Figure 5. DKR of 1-phenylethylamine by lipase-palladium bicatalysis.

allylic alcohols at room temperature in good yields and excellent enantioselectivities (Table 13).

DKR of Amines. Reetz *et al.* reported for the first time the DKR of 1-phenylethylamine by employing palladium on carbon and CALB.[8] However, the DKR required a very long reaction time (8 days) at 50-55 ºC and provided a poor isolated yield (60%) (Figure 5). Recently, Bäckvall *et al.* reported that diruthenium complex **1** racemizes aromatic amines at 110 ºC in toluene, but the racemization conditions

Table 14. Asymmetric reductive acetylation of ketones



RCOR'	yield (%)	ee (%)
acetophenone	81	96
4-methoxyacetophenone	85	99
4-chloroacetophenone	72	97
1-indanone	89	99
α-tetralone	87	99
acetylcyclohexane	87	90
2-octanone	87	91
4-phenyl-2-butanone	83	72

were not applicable to the DKR involving enzymes.[24]

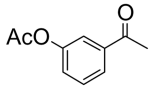
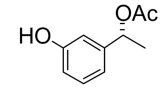
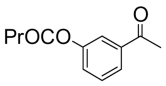
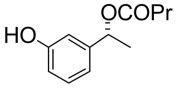
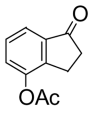
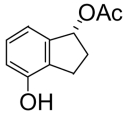
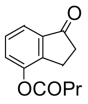
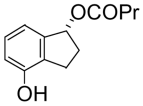
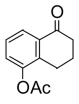
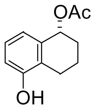
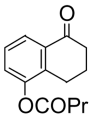
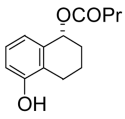
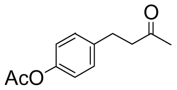
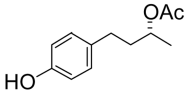
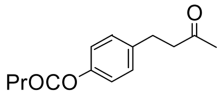
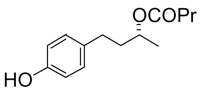
Asymmetric Transformations by Enzyme-Metal Combo Catalysis

Asymmetric Transformation by Lipase-Ruthenium Combination

Asymmetric Reductive Acetylation of Ketones. The catalytic alcohol racemization with diruthenium catalyst **1** is based on the reversible transfer hydrogenation mechanism. Meanwhile the problem of ketone formation in the DKR of secondary alcohols with **1** is caused by molecular hydrogen liberation. Then we envisioned a novel asymmetric reductive acetylation of ketones to circumvent the problem of ketone formation. A key factor of this process was the selection of hydrogen donors compatible with the DKR conditions. 2,6-Dimethylheptan-4-ol, which can not be acylated by lipases, acted as a proper hydrogen donor in the DKR of alcohols with PCPA.[25] Asymmetric reductive acetylation of ketones was also possible under 1 atm hydrogen in ethyl acetate, although a long reaction time (96 h) was required. Ethanol formation did not cause critical problem, and various ketones were transformed successfully into the corresponding chiral acetates (Table 14).[25b]

Asymmetric reductive acetylation process was also applicable to acetoxyaryl ketones.[26] For example, 3'-acetoxyacetophenone was transformed to (*R*)-1-(3-hydroxyphenyl)-ethyl acetate under 1 atm H_2 in 95% yield. The overall reaction seems to be a simple asymmetric reductive internal acyl migration. In fact, however, it is the result from nine catalytic steps: two ruthenium-catalyzed reductions, two ruthenium-catalyzed epimerizations, three lipase-catalyzed deacylations, and two lipase-catalyzed acylations (Figure 6). This process was applicable to a wide range of acyloxy-

Table 15. Asymmetric transformations of acyloxyphenyl ketones

substrate	product	yield (%)	ee (%)
		95	98
		96	98
		94	93
		93	96
		88	89
		88	98
		92	96
		89	98

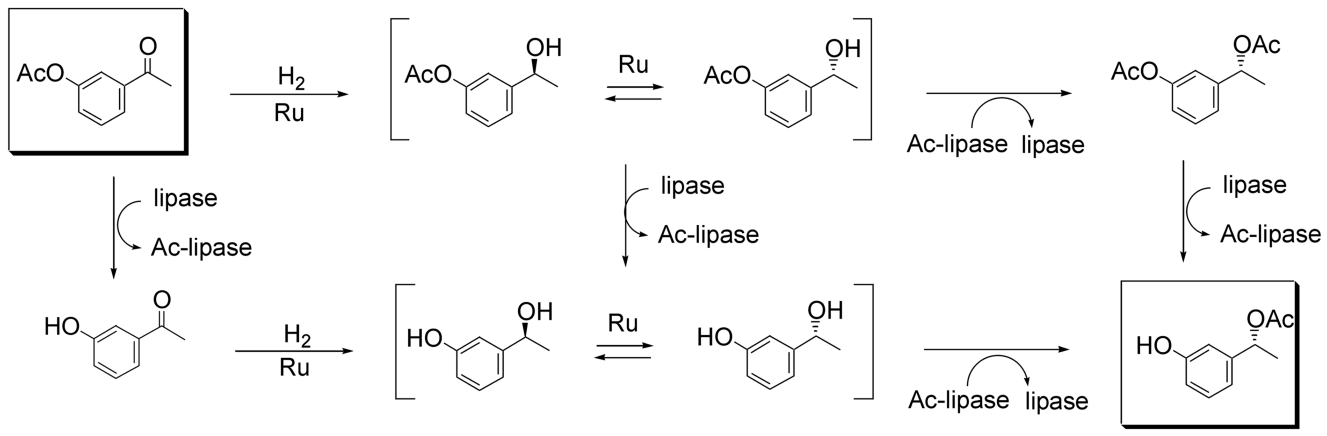


Figure 6. Reaction Pathway for the Asymmetric Transformation of 3'-Acetoxyacetophenone.

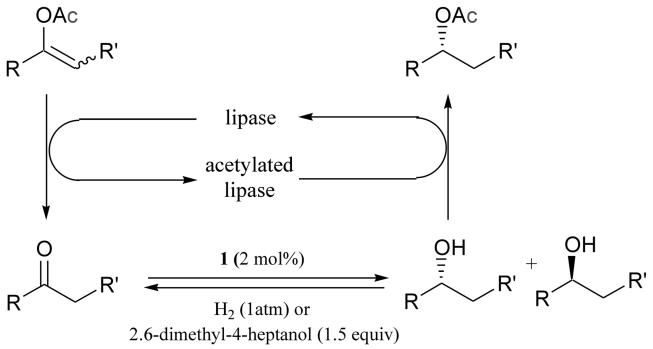


Figure 7. Asymmetric hydrogenation of enol acetates.

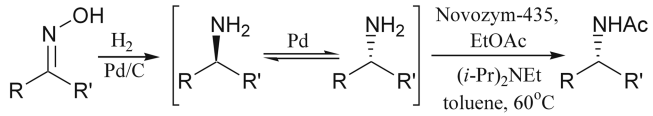
Table 16. Asymmetric hydrogenation of enol acetates

R	R'	yield (%)	ee (%)
phenyl	H	89	98
4-methoxyphenyl	H	80	98
4-chlorophenyl	H	91	97
1-indenyl		87	99
benzyl	H	90	79
2-phenylethyl	H	92	94
cyclohexyl	H	94	99
n-hexyl	H	95	91

phenyl ketones (Table 15).

Asymmetric Hydrogenation of Enol Acetates. After succeeding in the asymmetric reductive acylation of ketones, we studied to see if enol acetates can be used as acyl donors and precursors of ketones at the same time through deacylation and keto-enol tautomerization (Figure 7). The overall reaction thus corresponds to the asymmetric reduction of enol acetate. For example, 1-phenylvinyl acetate was transformed to (*R*)-1-phenylethyl acetate by CALB and diruthenium complex **1** in the presence of 2,6-dimethyl-4-heptanol in 89% yield (98% ee).[25a] Molecular hydrogen (1 atm) was almost equally effective for the transformation (86% yield, 96% ee).[25b] A broad range of enol acetates were prepared from ketones and were successfully transformed to the corresponding (*R*)-acetates under 1 atm H_2 (Table 16). From unsymmetrical aliphatic ketones, enol acetates were obtained as the mixtures of regio- and geometrical isomers. Notably, however, the efficiency of the process was little affected by the isomeric composition of the enol acetates.

Table 17. Asymmetric reductive acetylation of ketoximes



R	R'	yield (%)	ee (%)
phenyl	methyl	80	98
4-methylphenyl	methyl	84	97
3-methylphenyl	methyl	81	94
4-methoxylpheny	methyl	82	96
phenyl	ethyl	76	98
1-indanyl		84	95
α-tetralyl		70	97
4-chromayl		89	99

Asymmetric Transformation by Lipase-Palladium Combination

Asymmetric Reductive Acetylation of Ketoximes. The strategy for the asymmetric reductive acylation of ketones was extended to ketoximes by coupling the reduction of ketoximes to the DKR of amines. The asymmetric reactions of ketoximes were performed with CALB and Pd/C in the presence of hydrogen, diisopropylethylamine, and ethyl acetate in toluene at 60 °C for 5 days (Table 17).[27] In comparison to the direct DKR of amines, the yields of chiral amides increased significantly. Diisopropylethylamine was a factor for the increase. However, the major factor would be the slow generation of amines, which maintains the amine concentration low enough to suppress side reactions including the reductive deamination. Disappointingly, this process is limited to benzylic amines. Low turnover frequencies also need to be overcome.

Conclusion

This account describes that enzyme-metal combo-catalysis provides a novel approach for the conversion of racemic substrates to single enantiomeric products. It has been demonstrated that the racemic alcohols, esters, and amines can be efficiently converted to the corresponding enantiomeric products through the enzyme-metal catalyzed DKR. The key feature of this methodology is the combination of metal-catalyzed racemization and enzymatic resolution in a single reaction flask. For the DKR of alcohols, a pair of complementary procedures are now available for the synthesis of both (*R*)- and (*S*)-esters. The DKR can be done at room temperature with commercially available enzymes and racemizing catalyst in good yields and high optical purities in most cases. However, the DKR of amines is limited to benzylic amines and require high temperature. Accordingly, for the efficient DKR of amines, further efforts will be directed toward developing practical racemizing catalysts with high reactivity and broad specificity at room temperature.[28]

Acknowledgement. We acknowledge the financial supports from the Ministry of Science and Technology through KISTEP (the NRL program) and KOSEF (the SRC program, CIMS), and the Ministry of Education and Human Resources through KRF (the BK21 program).

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Klibanov, A. M. *Enzymatic Reactions in Organic Media*; Blackie Academic & Professional: Glasgow, Scotland, 1996. (c) Faber, K. *Biotransformations in Organic Chemistry*, 3rd ed.; Springer: Berlin, Germany, 1997. (d) Bornscheuer, U. T.; Kazlauskas, R. J. *Hydrolases in Organic Synthesis*; Wiley-VCH: Weiheim, Germany, 1999. (e) Drauz, K.; Waldmann, H. *Enzyme Catalysis in Organic Synthesis: A Comprehensive Handbook*, 2nd ed.; Wiley-VCH: Weinheim, Germany, 2002; Vols. I-III.

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