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Chemoenzymatic Dynamic Kinetic Resolution of Alcohols and Amines

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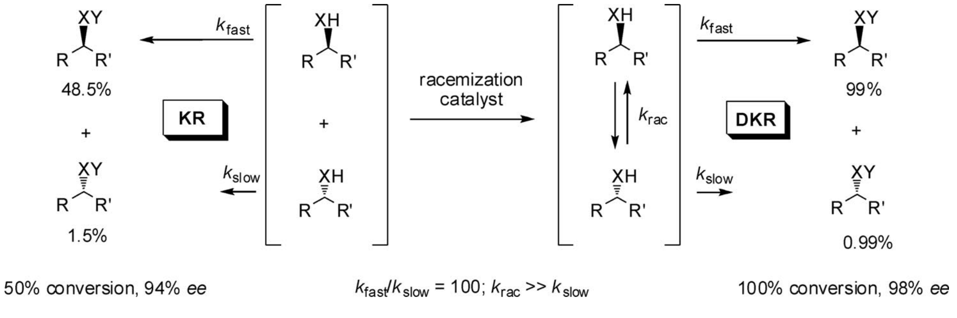
Dynamic kinetic resolution (DKR) is an attractive process for the transformation of racemic mixtures into optically active compounds. For successful DKR, efficient racemization is required while the kinetic resolution is proceeding. This Microreview mainly summarizes the recent developments in the DKR of alcohols and amines, based on metal-catalyzed racemization and enzymatic acylation in a single reaction vessel. Related reactions involving precursors of alcohols and amines such as ketones, enol acetates, and ketoximes are also described. Reaction conditions are arranged according to racemization catalysts, and substrates employed in the DKR are tabulated. Suggested mechanisms for metal-catalyzed racemizations are also summarized.

1. Introduction

Synthetic methods for optically active compounds are important for the preparation of pharmaceuticals, agricultural chemicals, and specialty materials for electronics and optics.[1] Of the conventional methods, enzymatic kinetic resolution (KR) of racemic mixtures is still the most practical for the preparation of desired enantiomers.[2] However, the critical drawback of KR is the maximum theoretical yield, which is limited to 50%. An attractive strategy for overcoming this limitation is the combination of kinetic resolution and the racemization of the slowly reacting enantiomer in a one-pot system, known as dynamic kinetic resolution (DKR).[3]

If the kinetic resolution is selective and the racemization fast enough, DKR can dramatically improve the synthetic efficiency for the desired enantiomer. If, for example, k_{rac} is much faster than k_{slow} and $k_{fast}/k_{slow} = 100$, the optical purity of the product of DKR will be 98% *ee* in 100% conversion yield, whereas that of KR will be 94% *ee* in 50% conversion yield (Scheme 1). This Microreview covers the chemoenzymatic DKR (consisting of enzymatic KR and metal-catalyzed racemization) of alcohols and amines. The key factor in chemoenzymatic DKR is compatibility between the enzyme and the metal catalyst. The first chemoenzymatic DKR was accomplished with 1-phenylethanol, with use of a lipase for the acyl-transfer reaction and a rhodium complex for the racemization (Scheme 2).[4] Acetophenone was employed as a hydrogen mediator for the racemization through hydrogen-transfer reactions, and the racemization of (*S*)-1-phenylethanol in the presence of the Rh catalyst (3 mol-%), potassium hydroxide, and *o*-phenanthroline was complete in 72 h. However, under conditions involving PFL (*Pseudomonas fluorescens* lipase) and vinyl



Scheme 1. Kinetic resolution and dynamic kinetic resolution.

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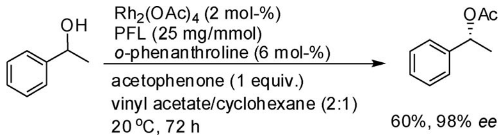
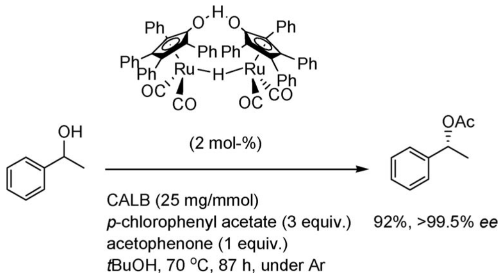
acetate in the absence of potassium hydroxide, only 60% of the substrate had been converted even after 72 h and the product was formed with 98% *ee* (Scheme 2).



Scheme 2. DKR of alcohols with the aid of $Rh_2(OAc)_4$ and PFL.

In 1997, Bäckvall and coworkers reported a notable catalyst system for DKR of 1-phenylethanol and indan-1-ol to give the corresponding (*R*)-acetates in more than 90% yields and with almost perfect optical purities (Scheme 3).[5] The success is based on the combination of Shvo's complex as a racemization catalyst and CALB (*Candida antarctica* lipase B immobilized on polyacrylamide; trade name Novozym 435^{TM}) as a transacylation catalyst. Shvo's complex showed a reasonable activity over 70 °C, so the thermostable CALB was a suitable counterpart for the racemization catalyst. Another essential factor for the success was the use of *p*-chlorophenyl acetate (PCPA) as an acylating reagent. The *p*-chlorophenol formed in the acylation step did not interfere in the DKR, whereas use of vinyl acetate (or isopropenyl acetate), from which acetaldehyde (or acetone) was formed in the acylation step, led to the oxidation of the substrate alcohol in significant amount. Although this catalyst system for DKR of alcohols showed remarkable potential, it has several problems: 1) the high reaction temperature limits the option for enzymes, 2) addition of a ketone as a hydrogen mediator is required for efficient racemization, 3) anaerobic conditions are required during the DKR to protect the ruthenium species, which is unstable toward oxygen, and 4) excess PCPA used in the DKR causes difficulties in the purification step.



Scheme 3. DKR of alcohols with Shvo's complex.

Meanwhile, in 1996 Reetz and Schimossek had reported the DKR of 1-phenylethylamine with palladium on carbon as the racemization catalyst and CALB for KR (Scheme 4).[6] Although the optical purity of the product amide was excellent, the yield was only 64% even after 8 days at 50–55 °C, due to side reactions. These early DKR procedures suffered mainly from the poor performances of the racemization catalysts and the very harsh reaction con-

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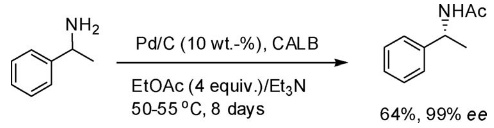
ditions for the enzymes. Most studies since then have therefore focused on the development of more efficient racemization catalysts.



Scheme 4. DKR of 1-phenylethylamine with palladium on carbon.

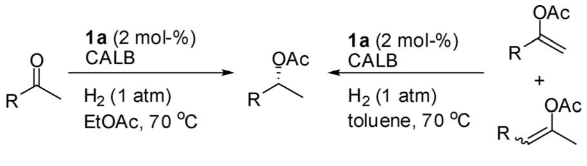
This Microreview summarizes the chemoenzymatic DKR of alcohols and amines, with the focus on the features of the racemization catalysts and on the substrate scope. The racemization catalysts used in the DKR are summarized in Figure 1 and Figure 2, below.

2. DKR of Alcohols

2.1. Racemization Catalysts and Reaction Conditions for DKR of Alcohols

Although there are far more catalysts active for alcohol racemization than those summarized in Figure 1,[7] many catalysts are not compatible with the conditions for enzymatic acylation. Strong bases cannot be employed for fast racemization, because the activity and stability of the enzyme would be affected seriously. Spontaneous chemical acylation, which lowers the optical purities of the product acetates, is also a problem caused by bases. Acyl donors and their products formed from the enzymatic acylation may interfere with the activities of racemization catalysts. Reaction temperature is another essential factor for the activities of racemization catalysts and for the stabilities of enzymes. In general, anaerobic conditions are needed during DKR to protect metal species that are unstable toward air. Additives are often required to optimize the efficiency of DKR. Reaction conditions according to racemization catalysts are summarized in Table 1.

When the DKR with Shvo's catalyst (**1a**) was performed without addition of ketones, the yields of the product esters were at most 80%, with formation of the corresponding ketones as side products.[5] Park and coworkers circumvented the "ketone" problem by employing ketones as the precursors of alcohols in the presence of hydrogen donors (Scheme 5).[8a] Hydrogen gas in a rubber balloon was a suitable hydrogen source, and ethyl acetate was used as the acyl donor and solvent. 2,6-Dimethylheptan-4-ol, which is not a substrate of CALB, can also be used as a hydrogen donor.[8b]



Scheme 5. Asymmetric transformation of ketones and enol acetates.

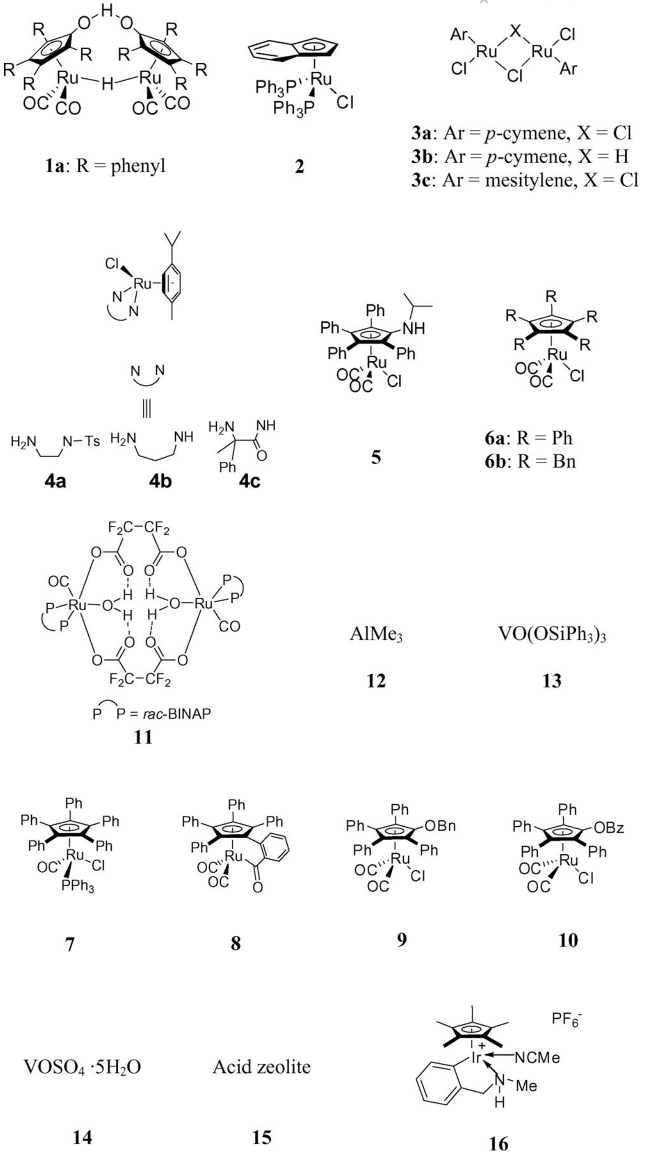
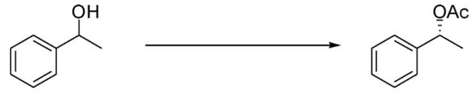


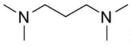
Figure 1. Racemization catalysts for DKR of alcohols.

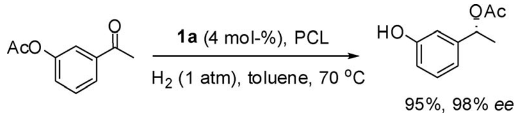
The use of enol acetates as substrates was introduced as another way to circumvent the "ketone" problem. The enol acetates serve not only as the precursors of ketones but also as the acyl donors. Acetoxyaryl ketones have also been used as substrates under the conditions for enol acetates. As an example, 3′-acetoxyacetophenone was transformed into (*R*)-1-(3-hydroxyphenyl)ethyl acetate in the presence of **1a** and a lipase under H_2 (1 atm) in 95% yield (Scheme 6).[9] The overall reaction appears to be a simple asymmetric reductive internal acyl migration. In fact, however, it is the result of nine catalytic steps: two ruthenium-catalyzed reductions, two ruthenium-catalyzed epimerizations, three lipase-catalyzed deacylations, and two lipase-catalyzed acylations. This process was applicable to a wide range of acyloxyaryl ketones.

Racemization of alcohols in the presence of the indenyl ruthenium complex **2** (Scheme 7) was fast in the absence of ketones. However, a strong base was needed; the racemiza-

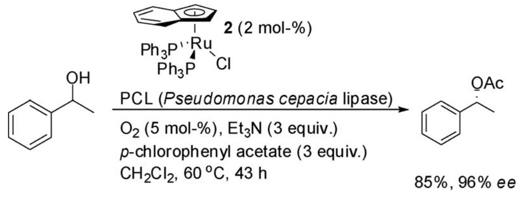
Table 1. Racemization catalysts and reaction conditions for DKR of 1-phenylethanol.



Entry	Catalyst (mol-%)	Acyl donor[a]	Enzyme[b]	Solvent	Atmos-phere	Temp. (°C)	Additives	Time (h)	Yield (%)
1[5]	**1a** (2)	PCPA	CALB	toluene	Ar	70	acetophenone (1 equiv.)	46	>99
2[10]	**2** (5)	PCPA	PCL	CH_2Cl_2	Ar	60	O_2 (1.5 mol-%), Et_3N (1.0 equiv.)	43	96
3[13]	**3a** (3)	TFEA	LPS-TN	[BMIm]PF_6	Ar	80	Et_3N (1.0 equiv)	45	80
4[16]	**3a** (3)	PCPA	CALB	toluene	Ar	80	 (30 mol-%) acetophenone (50 mol-%)	45	80
5[15]	**4a** (1.5)	PCPA	CALB	toluene	N_2	70	TEMPO (4.5 mol-%)	48	91
6[19]	**5** (4)	IPA	CALB	toluene	Ar	25	KO*t*Bu (5 mol-%), Na_2CO_3 (1.0 equiv.)	30	97
7[21b]	**6a** (5)	IPA	CALB	toluene	Ar	25	KO*t*Bu (5 mol-%), Na_2CO_3 (1.0 equiv.)	3	98
8[24]	**6b** (4)	IPA	CALB	toluene	Ar	25	KO*t*Bu (5 mol-%), Na_2CO_3 (3.0 equiv.)	24	94
9[25]	**7** (4)	IPA	CALB	toluene	Ar	25	Ag_2O (1.0 equiv.)	6	98
10[26]	**8** (5)	IPA	CALB	toluene	Ar	25	K_3PO_4 (1.0 equiv.), molecular sieves	10	97
11[27]	**9** (4)	IPA	CALB	toluene	air	25	K_3PO_4 (1.0 equiv.)	20	99
12[28]	**10** (4)	IPA	CALB	toluene	air	25	K_3PO_4 (1.0 equiv.)	20	99
13[29a]	**11** (0.1)	IPB	CALB	toluene	Ar	70	K_2CO_3 (0.42 equiv), acetophenone (0.2 equiv.) under reduced pressure (ca. 200 mbar)	10	98
14[30]	**12** (10)	PVA	CALB	toluene	Ar	25	*rac*-Binol (10 mol-%)	3	96
15[32]	**14** (62)	VO	CALB	octane	N_2	80		3.5	93
16[33]	**15**	OA	CALB	water/octane	air	60		22	78



Scheme 6. Asymmetric transformation of acyloxyaryl ketones.

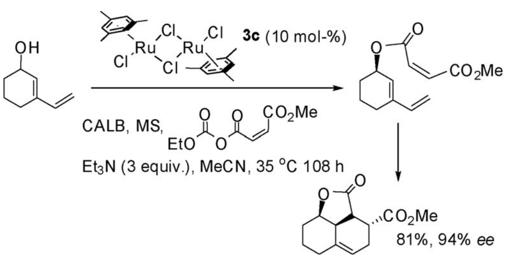


Scheme 7. DKR in the absence of hydrogen mediators.

tion of (*S*)-1-phenylethanol was complete within 20 min even at room temperature in the presence of KOH (5 mol-%) and **2** (1 mol-%).[7a] DKR of alcohols, however, was not possible, because chemical acylation and enzyme degradation occurred with use of KOH. Later, Park and coworkers found conditions, including the use of molecular oxygen, that were suitable for DKR. A catalytic amount of O_2 activated **2** through oxidization and consequent detachment of a phosphane ligand, and 1-phenylethanol was racemized in the presence of triethylamine.[10] The combination of an immobilized PCL (immobilized *Pseudomonas cepacia* lipase; Lipase PS-C^{TM}) and **2** at 60 °C in the presence of molecular oxygen and triethylamine was effective for DKR of alcohols.

The cymene ruthenium complex **3a** (Figure 1) was also active for racemization of alcohols at 40 °C in the presence of triethylamine. However, ketone was produced in twice the molar ratio of **3a** during the racemization. At the initial stage, the hydride-bridged complex **3b**, which can be obtained in quantitative yield from a 1:1 mixture of **3a** and 1-phenylethanol, was produced. When **3b** was used as the racemization catalyst, the amount of ketones formed during the racemization was half that obtained in the racemization with **3a**. Both **3a** and **3b** were effective for DKR both of aliphatic alcohols and of benzylic ones without addition of ketones. A noticeable feature of **3a** and **3b** was their high activities toward allylic alcohols; DKR was possible even at room temperature.[11] Kita and coworkers used the analogous mesitylene ruthenium complex **3c** (Scheme 8) for the interesting domino transformation consisting of DKR of 3-vinylcyclohex-2-en-1-ol and the Diels–Alder reaction of the resulting ester in one-pot fashion.[12]

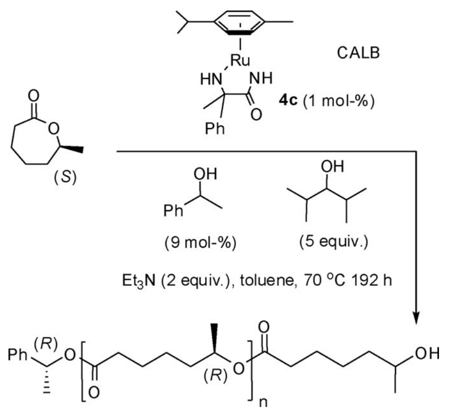
Another feature of **3a** and **3b** was their good activities for racemization of alcohols in ionic liquids such as [EMIm]-BF_4 and [BMIm]PF_6 ([EMIm] = 1-ethyl-3-methylimidazolium, [BMIm] = 1-butyl-3-methylimidazolium). DKR in the ionic liquids was possible at room temperature, and the ruthenium catalysts and the enzyme in the ionic liquid layer were reusable after extraction of the products with ether.[13] Chiral ruthenium complexes formed from **3a** and chiral bidentate nitrogen ligands have been extensively studied as catalysts for the asymmetric transfer hydrogenation of prochiral ketones.[14] Sheldon and coworkers prepared the achi-



Scheme 8. One-pot domino reaction consisting of DKR and a Diels–Alder reaction.

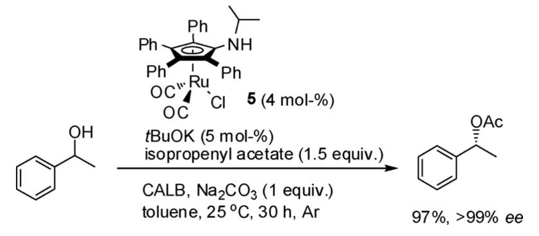
ral analogue **4a** (Figure 1) and tested it for DKR of alcohols. TEMPO was required as a co-catalyst.[15] (*R*)-1-Phenylethyl acetate (>99% *ee*) was obtained from 1-phenylethanol in 76% yield after 48 h with formation of acetophenone (15%). Trauthwein and coworkers tested the ruthenium catalyst **4b** generated from **3a** and propane-1,3-diamine, which was active without base, for racemization of alcohols. However, DKR with this catalyst system required a high reaction temperature (80 °C).[16]

Recently, Mijer and coworkers used **4c**, prepared from **3a** and 2-phenyl-2-aminopropionamide in the presence of K_2CO_3, in an iterative DKR to produce enantioenriched oligoesters (Scheme 9).[17] The enzymatic ring-opening of 6-methyl-ε-caprolactone was combined with the ruthenium-catalyzed racemization of the resulting alcohol to produce optically active oligomers of 6-methyl-ε-caprolactone. 2,4-Dimethylpentan-3-ol, a sterically hindered hydrogen donor that will not initiate enzymatic ring-opening nor take part in chemical transesterification, was used as an additive. Triethylamine was also added as a base to neutralize any hydroxyacid formed by ester hydrolysis. The same catalyst system was also applied to the condensation of racemic α,α′-dimethylbenzene-1,4-dimethanol and dimethyl adipate. Optically active polyesters (M_w = 3400 g mol^{-1}; M_n = 2100 g mol^{-1}) were obtained.[18]



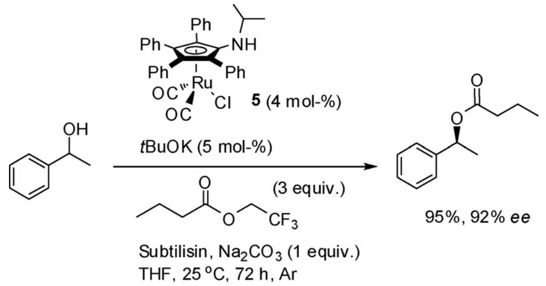
Scheme 9. Iterative DKR producing enantioenriched oligoesters.

CALB, a thermostable lipase, has extended the potential of chemoenzymatic DKR by allowing the use of racemization catalysts that are active at high temperatures. For the use of normal enzymes in DKR, however, racemization catalysts that are highly active under ambient conditions are desirable. Park and coworkers reported the synthesis of the novel aminocyclopentadienyl ruthenium chloride complex **5** (Scheme 10) and success in generating an active catalyst for the racemization of alcohols at room temperature by treating **5** with potassium *tert*-butoxide.[19] DKR both of aliphatic alcohols and of benzylic ones was possible with isopropenyl acetate as the acyl donor. The use of isopropenyl acetate improved DKR of alcohols remarkably in relation to PCPA; isopropenyl acetate is commercially available, easily separable from the product mixture, and more active than PCPA. A stoichiometric amount of sodium carbonate was needed to neutralize acetic acid formed by the hydrolysis of the acyl species. Use of molecular sieves in place of Na_2CO_3 was also effective for DKR.



Scheme 10. DKR of alcohols at room temperature.

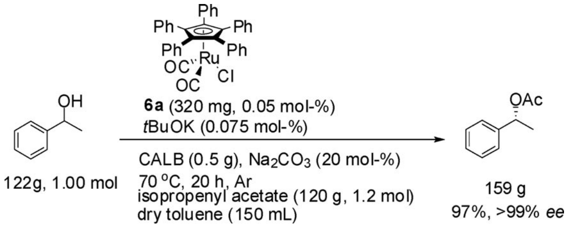
The complex **5** enabled the use of subtilisin, a protease that is unstable at high temperature but shows *S* selectivity for the acylation of alcohols. Kim and coworkers succeeded in optimizing its activity and stability by treating commercial subtilisin with a surfactant prior to use in DKR.[20] Trifluoroethyl butanoate proved to be an acylating agent suitable for DKR of a wide range of benzylic and aliphatic alcohols to give the corresponding (*S*)-esters (Scheme 11).



Scheme 11. *S*-Selective DKR with subtilisin.

Soon after the reports of **5**, Bäckvall and coworkers found that the known ruthenium complex **6a** (Scheme 12), which does not have an amino group such as in **5**, is also a precursor to a catalyst that is active for racemization of alcohols at room temperature.[7b] The racemization of 1-phenylethanol was complete within 10 min in the presence of **6** (0.5 mol-%) and potassium *tert*-butoxide. They succeeded in DKR of alcohols with **6a**, CALB, and isopropenyl acetate at room temperature.[21] Under optimized conditions, the DKR of benzylic alcohols was about one order of magnitude faster than that achieved with **5**. The synthesis of (*S*)-esters was performed with a combination of **6a** and subtilisin treated with surfactants.[22] Bäckvall and coworkers have recently demonstrated a large-scale DKR.

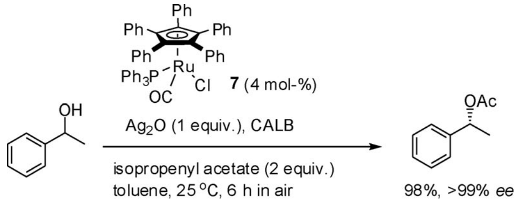
Under optimized conditions, (*R*)-1-phenylethyl acetate (159 g, 97%, >99% *ee*) was obtained from 1-phenylethanol (122 g, 1.00 mol) in the presence of **6a** (0.05 mol-%) and sodium carbonate (20 mol-%) at 70 °C for 20 h.[23]



Scheme 12. Large-scale DKR of 1-phenylethanol.

Leino and coworkers synthesized **6b**, a benzyl analogue of **6a**. In racemization and DKR of alcohols, **6b** showed a catalyst performance comparable to that of **6a**.[24] The results imply that the phenyl substituents on the Cp ring of **6a** are not essential for the catalytic activity. However, it is known that the parent ruthenium complex – CpRuCl(CO)$_2$ – is much less active for racemization of alcohols under similar conditions.[7b]

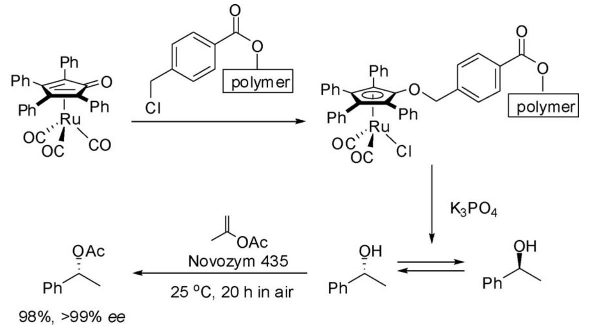
One of the two carbonyl ligands of **6a** can easily be replaced with triphenylphosphane with the aid of trimethylamine *N*-oxide to give the complex **7** (Scheme 13). Interestingly, **7** catalyzed the racemization of alcohols at room temperature in the presence of a catalytic amount of silver oxide. The catalytic species formed from **7** were stable in air and reusable at least ten times for the racemization. DKR of alcohols with **7** proceeded under ambient conditions, although stoichiometric amounts of Ag$_2$O were required.[25]



Scheme 13. DKR of alcohols under ambient conditions.

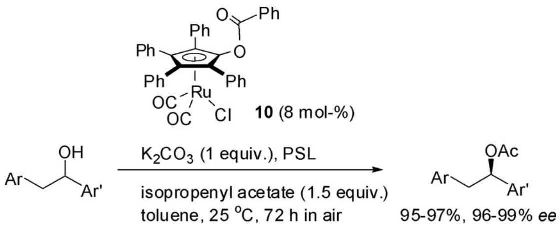
The unexpected ruthenium complex **8** (Figure 1) was obtained in 41% yield on treatment of pentaphenylcyclopenta-2,4-dien-1-ol with Ru$_3$(CO)$_{12}$.[26] This complex showed an activity comparable to that of **6a** in DKR of alcohols in the presence of K$_3$PO$_4$. Molecular sieves were required to capture water molecules in the reaction mixture.

Park and coworkers synthesized the complex **9** (Figure 1) through a one-step reaction between [Ph$_4$(η^4-C$_4$CO)]-Ru(CO)$_3$ and benzyl chloride. Unlike catalysts previously used for racemization of alcohols, **9** was stable toward oxygen during DKR,[27] so DKR of alcohols under ambient conditions was possible with **9**, which was also reusable. The synthetic method for **9** was also applied to the preparation of a polymer-bound derivative (Scheme 14); hydroxymethyl polystyrene was treated with 4-(chloromethyl)-benzoyl chloride to attach the chlorobenzyl group. Heating of a mixture of the resulting polymer and [Ph$_4$(η^4-C$_4$CO)]-Ru(CO)$_3$ gave the polymer-bound derivative, which showed an activity almost the same as that of **9** and was recycled five times for DKR.



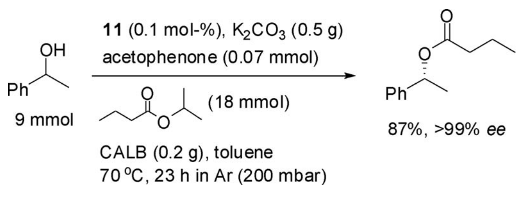
Scheme 14. Air-stable and reusable racemization catalyst.

The synthetic method used for complex **10** (Scheme 15) was similar to that employed for **9**, but the efficiency was much better. Complex **10** was obtained in 95% yield on treatment of [Ph$_4$(η^4-C$_4$CO)]Ru(CO)$_3$ with benzoyl chloride in toluene at 80 °C for 6 h,[28] whereas **9** was obtained only in 65% yield under conditions requiring a higher reaction temperature (110 °C) and a much longer reaction time (120 h).[27] Kim and coworkers used **10** as the racemization catalyst with PSL (*Pseudomonas stutzeri* lipase) for DKR of various 1,2-diarylethanols.[28]



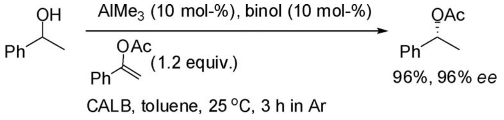
Scheme 15. DKR of 1,2-diarylethanols.

Hulshof and coworkers applied the diruthenium complex **11** (Figure 1) for DKR of alcohols;[29a] it had also been used as an catalyst for dehydrogenation of alcohols.[29b] DKRs of alcohols were performed on large scales (9 mmol) in the presence of **11** (0.1 mol-%), CALB, isopropyl butyrate as the acyl donor, potassium carbonate, and the corresponding ketones (about 20 mol-%) at 70 °C (Scheme 16). Propan-2-ol produced by acyl transfer was removed at a reduced pressure (200 mbar) during the DKR.



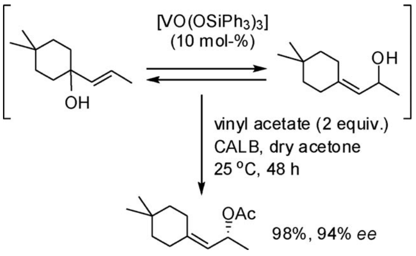
Scheme 16. DKR of alcohols with a (tetrafluorosuccinato)ruthenium complex.

Trimethylaluminium (**12**) is a rare catalyst for racemization of alcohols. Berkessel and coworkers envisioned that $AlMe_3$ should be an alcohol racemization catalyst on the basis of the known activity of aluminium alkoxides in the Meerwein–Ponndorf–Verley–Oppenauer (MPVO) reaction.[30] Aluminium complexes generated in situ from $AlMe_3$ and bidentate ligands were active for racemization of alcohols at room temperature. DKR of alcohols was performed with $AlMe_3$ (10 mol-%), binol (or 2,2′-biphenol), and CALB at room temperature (Scheme 17). Specific acyl donors, the enol esters derived from the corresponding ketones, were required for DKR with these systems.



Scheme 17. DKR of alcohols with aluminium catalyst.

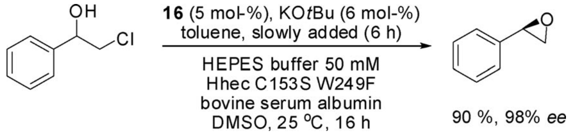
$VO(OSiPh_3)_3$ (**13**) is a catalyst for racemization of allylic alcohols,[31a] but its racemization mechanism is different from those of the previous ruthenium catalysts. Its discovery by Akai and coworkers was based on the known activity of oxovanadium(V) complexes – $VO(OR)_3$ – for the rearrangement of allylic alcohols through the formation of allyl vanadate intermediates.[31b] DKR of allylic alcohols was performed with **13** and an immobilized lipase (CALB, AK, or PS-D) at room temperature. Noticeably, vinyl acetate was the efficient acyl donor in this catalyst system (Scheme 18).



Scheme 18. DKR with vanadium catalyst.

Jacobs and coworkers surveyed vanadium salts to find catalysts for racemization of alcohols. $VOSO_4$ (**14**) and V_2O_4 showed activities for the racemization of benzylic alcohols[32] but were not active for aliphatic ones, because their activities are based on their acidic properties for the generation of carbenium intermediates. They were active in the absence of additives such as bases and hydrogen mediators in *n*-octane, but at 80 °C. The DKR of 1-phenylethanol was tested with **14**, CALB, and vinyl octanoate, giving the corresponding (*R*)-ester in 93% yield (99% *ee*) under optimized conditions. The formation of carbenium ion intermediates was suggested because of the results of ^{18}O-labeling experiments. Acid zeolites (**15**) were also tested for racemization of alcohols under biphasic conditions by Jacobs and coworkers.[33] Their scope, however, was also limited to benzylic alcohols, and electron-rich benzylic alcohols were not suitable substrates because of the formation of dimers. Under optimized conditions with H-Beta zeolite, CALB, and excess vinyl octanoate at 60 °C, (*R*)-1-phenylethyl octanoate (>99% *ee*) was obtained in 90% yield from 1-phenylethanol. Lozano and coworkers performed the DKR of 1-phenylethanol in the presence of acidic zeolite catalysts in IL/scCO_2 with a continuous reaction system.[34]

Recently, de Vries and coworkers succeeded in the DKR of β-halo alcohols to give the corresponding epoxides in single-step fashion (Scheme 19). They used an iridium complex (**16**) that was compatible with water as the racemization catalyst and a mutant haloalcohol dehalogenase as the resolving enzyme.[35]



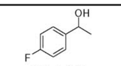
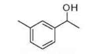
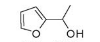
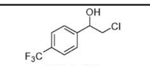
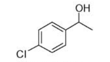
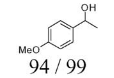
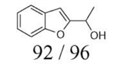
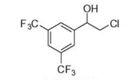
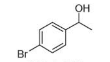
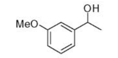
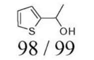
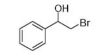
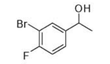
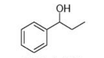
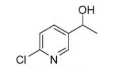
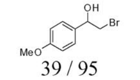
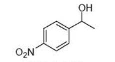
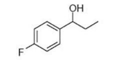
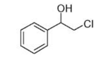
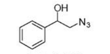
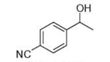
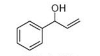
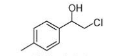
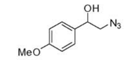
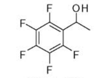
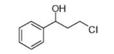
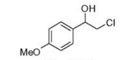
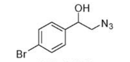
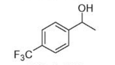
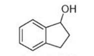
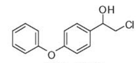
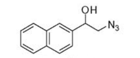
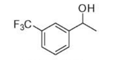
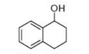
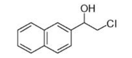
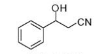
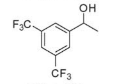
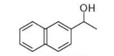
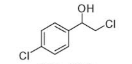
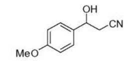
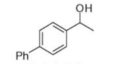
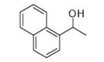
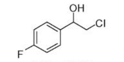
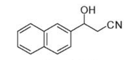
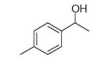
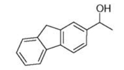
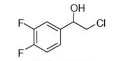
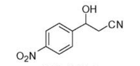
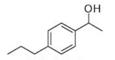
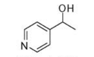
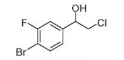
Scheme 19. DKR of β-haloalcohols.

2.2. Substrate Alcohols in Chemoenzymatic DKR

The scope of chemoenzymatic DKR of alcohols depends both on the enzymes and on the racemization catalysts. Common lipases used in the DKR have *R* selectivity, whereas a protease – subtilisin – has *S* selectivity for secondary alcohols. The alcohols employed in chemoenzymatic DKR are summarized in Tables 2, 3, 4, 5, 6, 7, and 8 according to their structural features.

Table 2 shows benzylic alcohols with the yields and the optical purities of the corresponding esters that have been reported as the best results. The electronic properties of the substituents on aromatic rings seem to exert little effect on the efficiency of DKR. In general, however, DKRs of those bearing electron-withdrawing substituents were faster than in the cases of those with electron-donating ones. There are several unsuccessful cases: Entries 19, 20, 22, 42, and 43. 1-Phenylpropanone was formed as a side product in 38% yield in the case of 1-phenylprop-2-en-1-ol (Entry 19). Slow enzymatic acylation was the problem in the DKR of 3-chloro-1-phenylpropanol (Entry 20), whereas 1-phenylpropanol and 1-(4-fluorophenyl)propanol are good substrates (Entries 17–18). The DKR of indan-1-ol was successful (Entry 21), but that of 1,2,3,4-tetrahydro-1-naphthol gave the corresponding (*R*)-acetate only in 65% yield (Entry 22). Large secondary alcohols such as naphthyl-, fluorenyl-, and biphenyl-substituted ones were acceptable, but required longer reaction times (Entries 23–25). Chemoenzymatic DKR was also effective for heteroaromatic substrates (Entries 26–30), β-functionalized benzylic alcohols such as chlorohydrins (Entries 31–41), azido alcohols (Entries 44–47), and cyano alcohols (Entries 48–51). However, the DKR of bromohydrins was less selective and slower than that of chlorohydrins (Entries 42–43).

Table 2. Benzylic alcohols.

Entry	Substrate Yield (%) / *ee* (%)	Entry	Substrate Yield (%) / *ee* (%)	Entry	Substrate Yield (%) / *ee* (%)	Entry	Substrate Yield (%) / *ee* (%)
1[26]	 90 / 99	14[13]	 87 / 98	27[21b]	 93 / 96	30[41]	 99 / 99
2[21b]	 91 / 99	15[21b]	 94 / 99	28[21b]	 92 / 96	41[41]	 99 / 98
3[10]	 98 / 99	16[39]	 91 / 99	29[21b]	 98 / 99	42[37]	 63 / 97
4[38]	 99 / 98	17[21b]	 90 / 99	30[40]	 96 / 99	43[37]	 39 / 95
5[21b]	 97 / 99	18[38]	 97 / 99	31[41]	 95 / 99	44[42]	 86 / 99
6[21b]	 95 / 99	19[19b]	 62 / 81	32[41]	 90 / 99	45[42]	 84 / 99
7[21b]	 97 / 99	20[19b]	 31 / 99	33[41]	 99 / 99	46[42]	 87 / 99
8[21b]	 98 / 99	21[27]	 91 / 88	34[41]	 87 / 99	47[42]	 85 / 99
9[38]	 98 / 99	22[5b]	 65 / 99	35[41]	 93 / 99	48[21b]	 85 / 97
10[38]	 98 / 99	23[21b]	 93 / 99	36[41]	 89 / 99	49[43]	 86 / 97
11[21b]	 96 / 99	24[21b]	 97 / 99	37[41]	 99 / 99	50[43]	 82 / 91
12[27]	 98 / 99	25[21b]	 97 / 99	38[41]	 86 / 98	51[43]	 80 / 94
13[21b]	 95 / 99	26[21b]	 96 / 99	39[41]	 99 / 98		

Unlike CALB and other common lipases, PSL (*Pseudomonas stutzeri* lipase) was highly enantioselective toward 1,2-diarylethanols. Table 3 shows the excellent results obtained in the DKR of 1,2-diarylethanols[28] and benzoins.[36]

Chemoenzymatic DKR is possible not only for simple aliphatic alcohols but also for those containing additional functional groups, such as alkenols, ethers, chlorohydrins, azido alcohols, amino alcohols, hydroxy esters, hydroxy phosphates, hydroxy sulfonates, and hydroxy amides (Table 4). In some cases, more than two functional groups were compatible with the conditions for DKR. A γ-hydroxy-δ-chloroamide, for example, was transformed highly selectively into the corresponding chiral acetate in a reasonable yield.

In contrast with the case of 1-phenylprop-2-en-1-ol (Table 2, Entry 19), isomerization into ketones under the DKR conditions was not significant for the allylic alcohols shown in Table 5. The tertiary alcohol of Entry 18 isomerized during DKR and was transformed into the chiral acetate identical to the product of Entry 17. A noticeable substrate is the cyclic allylic alcohol with an alkynyl group (Entry 20).

Symmetrical secondary diols were transformed into enantiomerically pure (*R*,*R*)-diacetates (Table 6), efficient use of all the diol being made with CALB and **6a** (Entries 1–5). (*E*)-Hex-3-ene-2,5-diol was a poor substrate, giving the corresponding (*R*,*R*)-diacetate in low yield (Entry 6). In the case of cyclohexene-1,3-diol in the presence of PS-C (Entry 7), the corresponding *cis*-(*R*,*S*)-diacetate (*cis*/*trans* 97:3) was obtained from a racemic *cis*/*trans* mixture in high yield (95%) and with high optical purity (92% *ee*). Various 1,5-diols were efficiently resolved into the corresponding enantiopure 1,5-diacetates in high yields and with good dia-

Table 3. 1,2-Diarylethanols and benzoins.

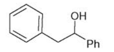
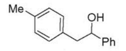
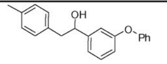
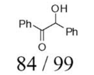
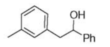
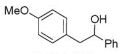
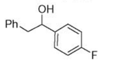
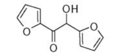
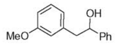
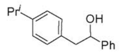
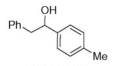
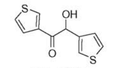
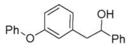
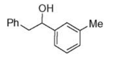
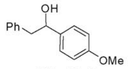
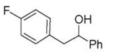
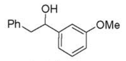
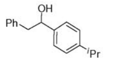
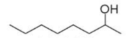
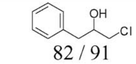
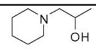
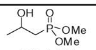
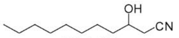
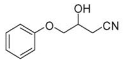
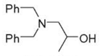
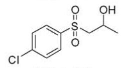
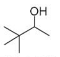
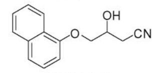
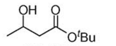
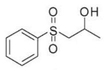
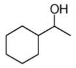
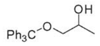
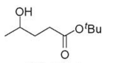
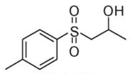
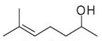
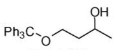
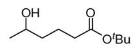
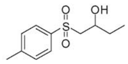
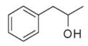
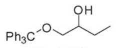
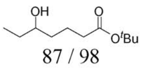
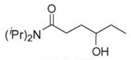
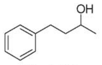
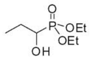
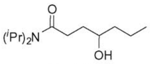
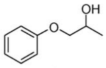
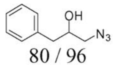
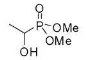
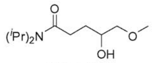
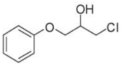
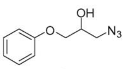
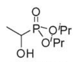
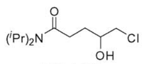
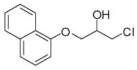
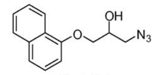
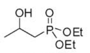
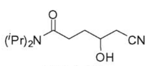
Entry	Substrate Yield (%) / *ee* (%)	Entry	Substrate Yield (%) / *ee* (%)	Entry	Substrate Yield (%) / *ee* (%)	Entry	Substrate Yield (%) / *ee* (%)
1[28]	 98 / 98	6[28]	 97 / 97	11[28]	 99 / 99	16[36]	 84 / 99
2[28]	 96 / 98	7[28]	 96 / 99	12[28]	 96 / 98	17[36]	 78 / 99
3[28]	 97 / 97	8[28]	 95 / 99	13[28]	 98 / 98	18[36]	 76 / 99
4[28]	 99 / 96	9[28]	 95 / 98	14[28]	 95 / 96		
5[28]	 98 / 97	10[28]	 96 / 98	15[28]	 97 / 99		

Table 4. Aliphatic alcohols.

Entry	Substrate Yield (%) / *ee* (%)	Entry	Substrate Yield (%) / *ee* (%)	Entry	Substrate Yield (%) / *ee* (%)	Entry	Substrate Yield (%) / *ee* (%)
1[30]	 95 / 92	11[37]	 82 / 91	21[21b]	 99 / 99	31[46]	 62 / 99
2[43]	 93 / 92	12[43]	 73 / 74	22[21b]	 97 / 97	32[26]	 94 / 94
3[44]	 75 / 97	13[43]	 95 / 44	23[26]	 99 / 97	33[48]	 70 / 99
4[30]	 98 / 99	14[19b]	 97 / 99	24[45]	 70 / 94	34[48]	 79 / 99
5[21b]	 90 / 98	15[19b]	 94 / 99	25[45b]	 92 / 98	35[48]	 42 / 99
6[21b]	 99 / 91	16[19b]	 91 / 99	26[45b]	 87 / 98	36[49]	 65 / 98
7[21b]	 91 / 96	17[47]	 93 / 95% *de*	27[46]	 73 / 99	37[49]	 59 / 92
8[21b]	 96 / 92	18[42]	 80 / 96	28[46]	 74 / 99	38[49]	 85 / 91
9[41]	 84 / 92	19[42]	 70 / 85	29[26]	 88 / 95	39[49]	 70 / 95
10[37]	 98 / 87	20[42]	 71 / 86	30[26]	 80 / 92	40[49]	 90 / 80

stereoselectivity in the presence of **6a** and CALB (or PS-C II) (Entries 8–16). An exceptional case was dimethyl 2,6-dihydroxyheptanedioate, for which both enantioselectivity and diastereoselectivity were poor (Entry 13).

Unsymmetrical 1,2- and 1,3-diols in which one of the two hydroxy groups cannot be acylated by enzyme directly were transformed into the corresponding *syn*-diacetates in one-pot reactions by combinations of enzymatic transesteri-

Table 5. Allylic alcohols.

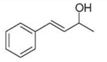
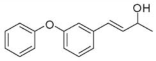
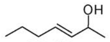
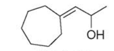
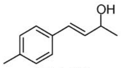
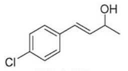
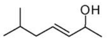
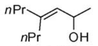
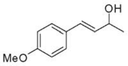
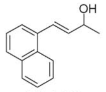
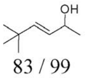
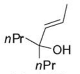
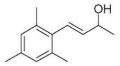
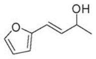
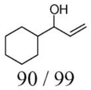
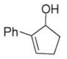
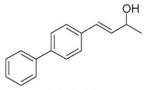
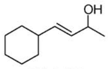
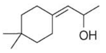
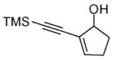
Entry	Substrate Yield (%) / *ee* (%)	Entry	Substrate Yield (%) / *ee* (%)	Entry	Substrate Yield (%) / *ee* (%)	Entry	Substrate Yield (%) / *ee* (%)
1[26]	 92 / 92	6[19b]	 93 / 99	11[11]	 83 / 95	16[31a]	 88 / 97
2[19b]	 92 / 99	7[19b]	 92 / 99	12[11]	 84 / 99	17[31a]	 91 / 99
3[19b]	 83 / 99	8[19b]	 90 / 99	13[11]	 83 / 99	18[31a]	 93 / 98
4[19b]	 94 / 99	9[11]	 86 / 99	14[19b]	 90 / 99	19[31a]	 96 / 99
5[19b]	 90 / 99	10[11]	 84 / 95	15[31a]	 94 / 98	20[31a]	 81 / 91

Table 6. Diols to *anti*-diacetates.

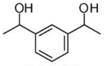
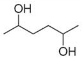
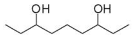
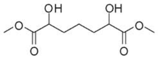
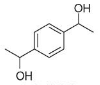
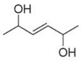
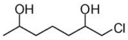
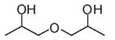
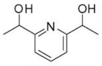
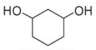
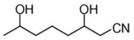
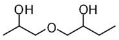
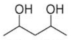
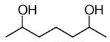
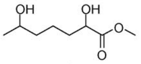
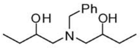
Entry	Substrate Yield (%) / *ee* (%) *anti*:*syn*	Entry	Substrate Yield (%) / *ee* (%) *anti*:*syn*	Entry	Substrate Yield (%) / *ee* (%) *anti*:*syn*	Entry	Substrate Yield (%) / *ee* (%) *anti*:*syn*
1[13]	 86 / 99 99:1	5[51]	 99 / 99 94:6	9[53], [54]	 89 / 99 96:4	13[53], [54]	 77 / 37 55:45
2[21b]	 90 / 99 99:1	6[50]	 43 / 99 74:26	10[53]	 78 / 95 76:24	14[53], [54]	 81 / 99 95:5
3[50]	 78 / 99 100:0	7[52]	 95 / 92 3:97	11[53], [54]	 61 / 99 94:6	15[53]	 49 / 99 94:6
4[51]	 96 / 99 97:3	8[53], [54]	 80 / 99 96:4	12[53], [54]	 71 / 98 80:20	16[53], [54]	 83 / 99 99:1

Table 7. Diols to *syn*-diacetates.

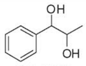
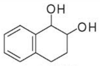
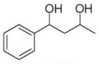
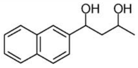
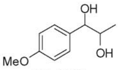
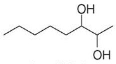
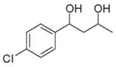
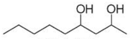
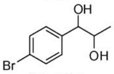
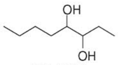
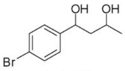
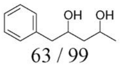
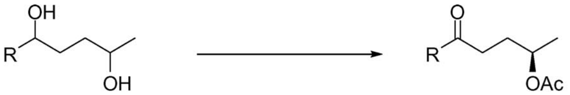
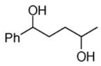
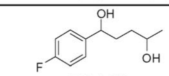
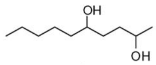
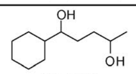
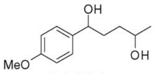
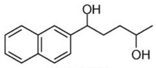
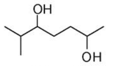
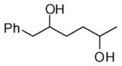
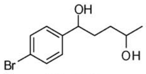
Entry	Substrate Yield (%) / *ee* (%) *anti*:*syn*	Entry	Substrate Yield (%) / *ee* (%) *anti*:*syn*	Entry	Substrate Yield (%) / *ee* (%) *anti*:*syn*	Entry	Substrate Yield (%) / *ee* (%) *anti*:*syn*
1[55]	 95 / 98 1:2	4[55]	 24 / 99 5:7	7[56]	 73 / 99 7:93	10[56]	 53 / 99 4:96
2[55]	 77 / 98 1:2	5[55]	 95 / 96 1:2	8[56]	 59 / 99 8:92	11[56]	 69 / 99 14:86
3[55]	 61 / 90 1:2	6[55]	 87 / 99 1:8	9[56]	 62 / 99 8:92	12[56]	 63 / 99 12:88

Table 8. Diols to ketoacetates.



Entry	Substrate Yield (%) / *ee* (%)	Entry	Substrate Yield (%) / *ee* (%)	Entry	Substrate Yield (%) / *ee* (%)	Entry	Substrate Yield (%) / *ee* (%)
1[57]	 69 / 84	4[57]	 72 / 86	6[57]	 77 / 48	8[57]	 73 / 90
2[57]	 96 / 21	5[57]	 82 / 79	7[57]	 89 / 86	9[57]	 70 / 74
3[57]	 81 / 88						

fication, ruthenium-catalyzed epimerization of a secondary alcohol into a diol or diol monoacetate, and intramolecular acyl migration to form a *syn*-diol monoacetate. The yields and enantioselectivities were moderate to excellent and the diastereoselectivities were moderate to good (Table 7).

Table 8 shows the results of the transformations of unsymmetrical 1,4-diols into γ-acetoxy ketones under the conditions of enzymatic acylation and Ru-catalyzed isomerization. Generally, enantioselectivity was not satisfactory. In particular, the methoxyphenyl-substituted diol was the worst case, giving the corresponding γ-acetoxy ketone in only 21% *ee* (Entry 2). Oxidation of the inner alcohol before the enzymatic acylation, producing the γ-hydroxy ketone, was suggested as a main reason for the poor enantioselectivity.

3. DKR of Amines

3.1. Racemization Catalysts and Reaction Conditions for DKR of Amines

In general, the racemization of amines is more difficult than that of alcohols and requires harsh conditions, because amines can act as strong ligands for active metal intermediates. In addition, amine C–N bonds can be cleaved by transition metal catalysts and the imine intermediates are sensitive toward moisture. Efficient catalysts for the racemization of amines (Figure 2) are thus rarer than those for the racemization of alcohols. Since Reetz and Schimossek[6] reported the use of palladium on charcoal (**17**) for DKR of amines, several heterogeneous catalysts on varying supporting materials have been introduced for racemization of amines (Table 9).[58–62] The Shvo-type ruthenium complexes **1**[63,64] and the iridium complex **21**[65,66] are unusual examples of homogeneous ones.

Kim and coworkers used **17** under modified conditions based on those of Reetz and Schimossek to transform ketoximes into chiral amides by DKR of intermediate amines (Scheme 20).[67] They envisioned that the use of low concentrations of the substrate amine should suppress the side reactions due to the palladium species. Indeed, the yield of (*R*)-*N*-(1-phenylethyl)acetamide was significantly increased in the indirect amine DKR in which 1-phenylethylamine was generated slowly from the corresponding ketoxime by catalytic hydrogenation.

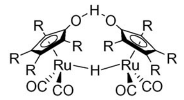
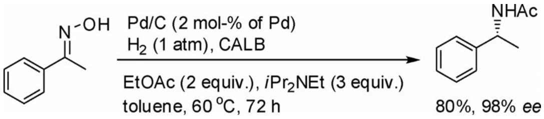
	Pd/C	Pd/BaSO$_4$	Pd/AlO(OH)	Raney Ni	[Cp*IrI$_2$]$_2$
1b: R = anisyl	**17**	**18**	**19**	**20**	**21**

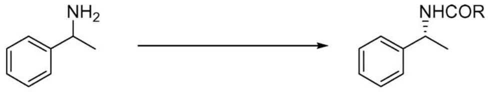
Figure 2. Racemization catalysts for DKR of amines.



Scheme 20. Asymmetric transformation of ketoximes.

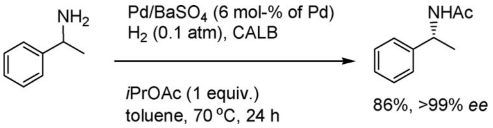
Jacobs and coworkers investigated the matrix effect of heterogeneous palladium catalysts. They found that palladium particles dispersed on alkaline earth salts such as BaSO$_4$, CaCO$_3$, and SrCO$_3$ are active for the racemization of benzylic amines.[58] They suggested that the racemization proceeds through dehydrogenation and hydrogenation, and that the main role of the basic supports is suppression of the condensation of the substrate amine and the intermediate imine. Pd/BaSO$_4$ (**18**) was the best for the DKR of 1-phenylethylamine. The H$_2$ pressure had a subtle influence on the DKR: H$_2$ directly participates in the racemization, but excessively high pressures might increase hydrogenolysis, producing ethylbenzene. They optimized the conditions with Pd/BaSO$_4$ (5%, 6 mol-% of Pd) under 0.1 bar of H$_2$ (Scheme 21). Later, they found that microwave irradiation was better than classical heating for the efficiency of the DKR.[61] However, the scope was still limited to benzylic amines.

Table 9. Racemization catalysts and reaction conditions for DKR of 1-phenylethylamine.



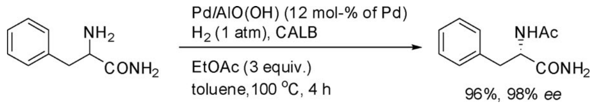
Entry	Catalyst (mol-%)	Acyl donor[a]	Enzyme[b]	Solvent	Atmos-phere	Temp. (°C)	Additives	Time (h)	Yield (%)
1[6]	**17** (0.9)	EA	CALB	Et_3N	Ar	55		192	64
2[67]	**17** (1.6)	EA	CALB	toluene	H_2	60	1 atm H_2, diisopropylethylamine (2.2 equiv.)	120	80
3[58]	**18** (6)	IPA	CALB	toluene	N_2	70	0.01 MPa H_2	24	86
4[61]	**18** (6)	EMA	CALB	toluene	N_2	100	0.005 MPa H_2 (under microwave)	50 min	89
5[61]	**18** (6)	EMA	CALB	toluene	N_2	100	0.005 MPa H_2	50 min	75
6[60]	**19** (1)	EA	CALB	toluene	Ar	70		72	97
7[60]	**19** (1)	EMA	CALB	toluene	Ar	70		72	98
8[69]	**20**	MD	CALB	toluene	N_2	80	0.01 MPa H_2	120	61
9[64]	**1b** (4)	IPA	CALB	toluene	Ar	90	Na_2CO_3 (40 mol-%)	72	90
10[70]	**1b** (4)	DBC	CALB	toluene	Ar	90	Na_2CO_3 (40 mol-%)	72	90
11[59]	**1b** (4)	IMA	CALB	toluene	Ar	90	Na_2CO_3 (40 mol-%), 1,2-dimethyl-3-pentanol (8 equiv.)	26	68

[a] EA = ethyl acetate; IPA = isopropyl acetate; EMA = ethyl 2-methoxyacetate; MD = methyl decanoate; DBC = dibenzyl carbonate; IMA = isopropyl 2-methoxyacetate. [b] CALB = *Candida antarctica* lipase B.



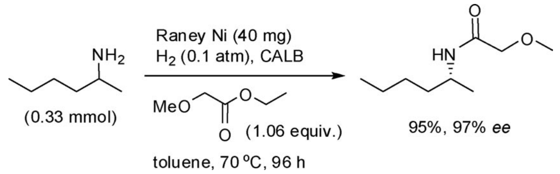
Scheme 21. Palladium on alkaline earth salts as a racemization catalyst.

Park and coworkers developed a simple one-pot method for the synthesis of highly active and recyclable catalysts through the generation of metal nanoparticles in a solution of inorganic alkoxides in alcohols and subsequent gelation by treatment with water.[68] The resulting gels showed high catalytic activities in the hydrogenation of alkenes and arenes,[68b–68d] in aerobic oxidation of alcohols,[68b,68e] in alcohol dehydrogenation,[68f] and in carbon–carbon cross-coupling reactions.[68a,68e,68g] Kim and coworkers used the palladium catalyst **19** for DKR of amines.[60] The DKR of benzylic amines was carried out at 70 °C with Pd (1 mol-%) and CALB. However, more catalyst (12 mol-% of Pd) and molecular hydrogen (1 atm) and a higher temperature (100 °C) were needed for the DKR of aliphatic amines. Under these conditions they also succeeded in the DKR of the amino acid derivative phenylalanine amide (Scheme 22). The palladium catalyst and CALB were recovered and reused at least 10 times without significant activity loss.



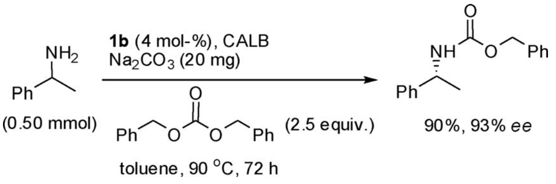
Scheme 22. DKR of phenylalanine amide.

Raney metals were studied as heterogeneous catalysts for racemization of amines by De Vos and coworkers.[69] Both Raney nickel (**20**) and Raney cobalt were effective for the racemization of amines. However, Raney cobalt with CALB showed little activity in the DKR of 1-phenylethylamine and was completely inactive in DKR of aliphatic amines. Raney nickel was better, but only moderate results were obtained in DKR of benzylic amines. In the case of simple aliphatic amines such as 2-hexylamine and 2-heptylamine (Scheme 23), reasonable results were obtained with **20**, CALB, and ethyl methoxyacetate under H_2 (0.01 MPa).



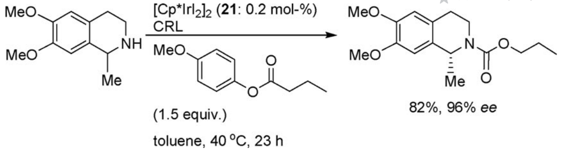
Scheme 23. DKR of amines with Raney nickel.

Bäckvall and coworkers tested Shvo's complex **1a** as a catalyst for racemization of amines.[63] The complex **1a** racemized amines at 110 °C in toluene, but side products were formed in significant amounts. Bäckvall and coworkers found that use of a hydrogen donor such as 2,4-dimethylpentan-3-ol inhibits the formation of side products. Various benzylic amines, including secondary amines, were racemized successfully under the conditions with **1a** and 2,4-dimethylpentan-3-ol at 110 °C. Although the DKR of amines with **1a** was possible, selectivity was not so satisfactory. It was found that the electron-rich derivative **1b** (Figure 2) shows a much better activity for DKR with CALB, isopropyl acetate, and sodium carbonate.[64] Sodium carbonate was an essential additive to trap acids generated variously from the polyacrylate support, the acyl donor, or the enzyme itself. Bäckvall and coworkers recently developed a practical procedure for the amine DKR with dibenzyl carbonate as the acyl donor; it produced the corresponding carbamates, which can easily be transformed into free amines by hydrogenolysis (Scheme 24).[70,64b]



Scheme 24. DKR of amines with a homogeneous Ru catalyst.

Page and coworkers reported the novel iridium-based amine racemization catalyst **21** (Figure 2).[65,66] Noticeably, the iridium complex – $[IrCp^*I_2]_2$ – was active for the racemization of secondary amines under conditions significantly milder than those described previously. Using **21** with CRL (*Candida rugosa* lipase), they succeeded in the DKR of an isoquinoline derivative (Scheme 25). The reaction was performed at 40 °C on a 3 g scale in the presence of 3-methoxyphenylpropyl carbonate as the acyl donor.



Scheme 25. DKR of amines with a homogenous Ir complex.

3.2. Substrate Amines in Chemoenzymatic DKR

Chemoenzymatic DKR has been performed both for aliphatic amines and for benzylic amines. In general, aliphatic amines were more difficult to racemize than benzylic ones. Several functional substituents on aromatic rings, including fluorine, bromine, ether, nitrile, nitro, trifluoromethyl, and selenoether, were compatible with the conditions for DKR (Table 10). Thiophenyl and naphthyl groups were also amenable to chemoenzymatic DKR. CALB was applicable to sterically somewhat hindered substrates (Entries 2, 8, 20–22, and 24).

Table 10. Benzylic amines.

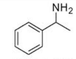
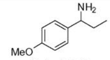
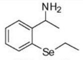
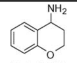
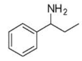
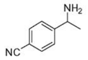
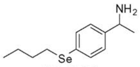
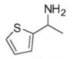
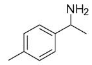
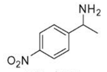
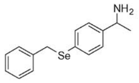
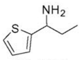
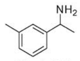
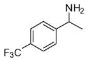
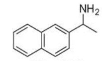
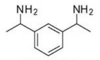
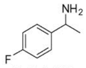
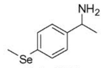
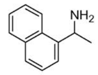
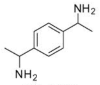
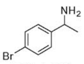
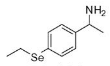
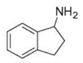
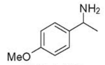
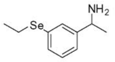
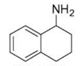
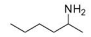
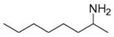
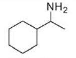
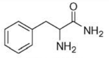
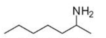
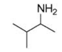
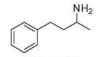
Entry	Substrate Yield (%) / *ee* (%)	Entry	Substrate Yield (%) / *ee* (%)	Entry	Substrate Yield (%) / *ee* (%)	Entry	Substrate Yield (%) / *ee* (%)
1[58b]	 86 / 99	8[64b]	 84 / 99	15[62]	 30 / 99	22[60]	 94 / 98
2[60]	 96 / 99	9[64b]	 73 / 99	16[62]	 77 / 99	23[64b]	 85 / 99
3[61]	 88 / 98	10[64b]	 70 / 99	17[62]	 72 / 99	24[64b]	 88 / 99
4[64]	 69 / 98	11[60]	 99%. 99	18[64b]	 80 / 99	25[59]	 70 / 86
5[64b]	 84 / 98	12[62]	 76 / 99	19[59]	 56 / 99	26[59]	 55 / 99
6[64]	 78 / 99	13[62]	 74 / 99	20[64b]	 92 / 95		
7[64]	 95 / 99	14[62]	 87 / 99	21[60]	 86 / 97		

Table 11. Aliphatic amines.

Entry	Substrate Yield (%) / *ee* (%)	Entry	Substrate Yield (%) / *ee* (%)	Entry	Substrate Yield (%) / *ee* (%)	Entry	Substrate Yield (%) / *ee* (%)
1[69]	 95 / 97	3[60]	 92 / 98	5[64b]	 92 / 96	7[60]	 96 / 98
2[59]	 83 / 94	4[64b],[70]	 60 / 99	6[58b]	 89 / 99		

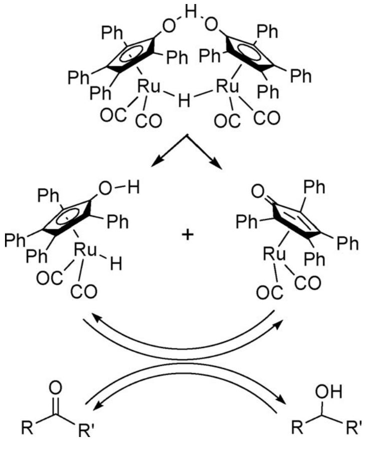
Diamines were also tested for DKR (Entries 25–26). In the case of a *p*-diamine the corresponding (*R*,*R*)-diamide was obtained in a high optical purity (99% *ee*) and the diastereoselectivity was also high (chiral/*meso* = 1:0.09).

Linear aliphatic amines worked well in chemoenzymatic DKR to give the corresponding amides or carbamates (Table 11; Entries 1–3). However, 3-methylbutan-2-amine was not a good substrate for CALB (Entry 4), whereas 1-cyclohexylamine was transformed as efficiently as the linear aliphatic amines (Entry 5). The DKR of an amino acid derivative – 2-amino-3-phenylpropanamide – demonstrated the potential of this methodology, although it is a rare example of DKR of a functionalized aliphatic amine.

4. Mechanisms of Racemization

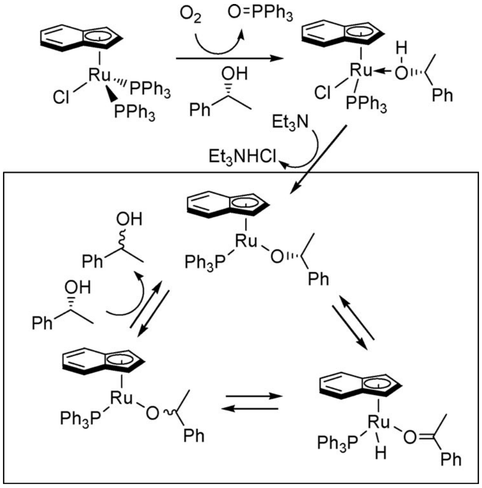
4.1. Racemization of Alcohols

Racemization catalysts are essential for the efficiency of chemoenzymatic DKR, and understanding of the mechanism of racemization should be the first step to improving the efficiency. With the exception of the formation of carbenium ions by acid catalysts, the most typical pathways for transition-metal-catalyzed alcohol racemization are reversible hydrogen-transfer reactions.[70–72] Shvo's complex **1a**, for example, generates two species, one of which is active for hydrogenation and another for dehydrogenation (Scheme 26).[72,73] Hydrogen mediators such as ketones are needed for racemization through hydrogen-transfer reactions. In Figure 1, complexes **1**, **3a**–**c**, **4a**–**c**, **11**, and **12** are known to follow this mechanism. In the case of **12**, addition of ketones is not required for DKR, but the corresponding enol acetates, which provide ketones through acyl-transfer reactions, act as acyl donors.[30]

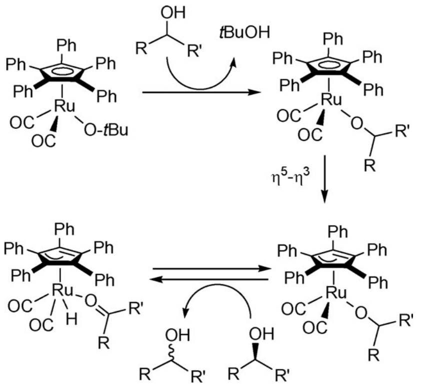


Scheme 26. Catalytic racemization with the aid of hydrogen mediators.

DKR with the complex **2** was the first case to be performed successfully without addition of ketones as hydrogen mediators. An inner-sphere racemization was suggested (Scheme 27).[7a] Intermediate ketones formed through β-hydride elimination do not leave the metal hydride intermediate. The step of ligand dissociation should be advanced before the β-hydride elimination to give a free coordination site. In the case of **2**, phosphane dissociation and HCl abstraction provide a coordinatively unsaturated 16-electron species. The racemization with complex **7** would follow a similar pathway.[25] Intensive mechanistic studies have been carried out for the racemization in the presence of complex **6a**.[71] In early studies, Bäckvall and coworkers observed a ruthenium *tert*-butoxide intermediate in the reaction between **6a** and potassium *tert*-butoxide, and suggested η^5–η^3 ring-slippage to give a coordinatively unsaturated intermediate (Scheme 28).[21b,71,74]

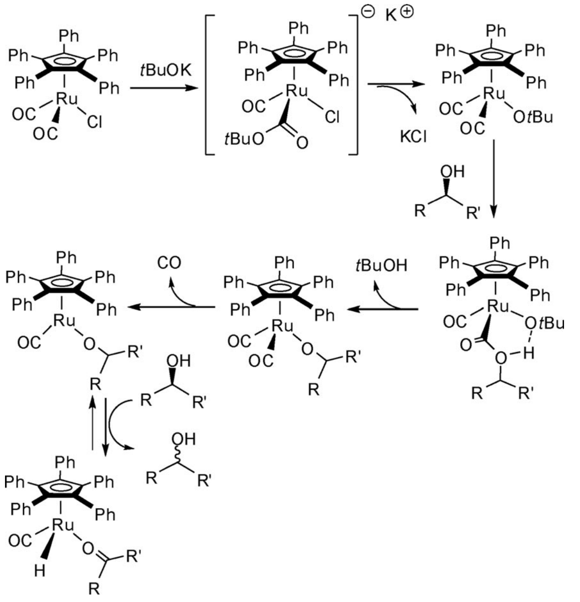


Scheme 27. Catalytic racemization without hydrogen mediator.



Scheme 28. Racemization through ring-slippage.

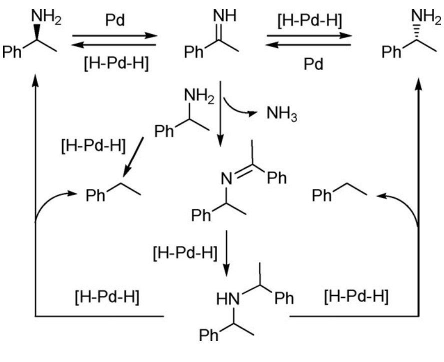
Recently, however, Bäckvall and coworkers observed an acyl intermediate by FT-IR and NMR spectroscopy, which implies that the CO ligand participates in the exchange of chloride for *tert*-butoxide. Two possible inner-sphere racemization pathways involving the ruthenium *tert*-butoxide intermediate were investigated by means of density functional calculations: an η^5–η^3 ring slippage or dissociation of a CO ligand to create a catalytically active 16-electron intermediate.[75–76] The η^5–η^3 ring-slip pathway was found to have a much higher energy barrier than the CO dissociation pathway (Scheme 29).



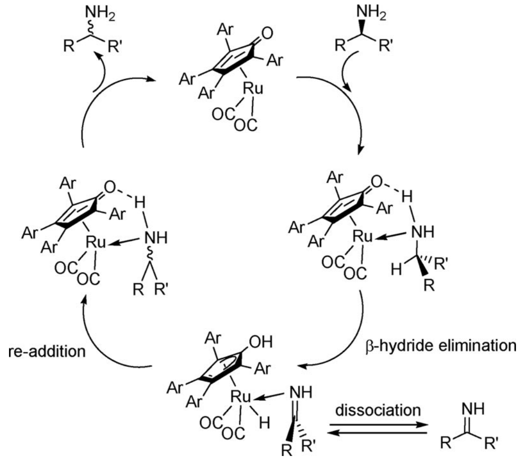
Scheme 29. Racemization mechanism involving CO dissociation.

4.2. Racemization of Amines

In view of the side products, such as ethylbenzene and bis(1-phenylethyl)amine, obtained in the racemization of 1-phenylethylamine in the presence of palladium catalysts, pathways for racemization in the presence of heterogeneous palladium catalysts as shown in Scheme 30 were proposed.[58b] The racemization occurs through dehydrogenation of amine and hydrogenation of the resulting imine. Bis(1-phenylethyl)amine is formed from the imine and the substrate amine through condensation followed by hydrogenation, and ethylbenzene is the product of hydrogenolysis breaking C–N bonds. The racemization of amines by Shvo-type complexes also produces the same condensation products as observed in racemization by palladium catalysts, so Bäckvall and coworkers proposed pathways similar to those in Scheme 30, involving β-hydride elimination and readdition within the coordination sphere (Scheme 31).[64b] The condensation products are formed from the dissociated imine and the substrate amine. The electronic properties of the racemization catalyst affected the condensation reaction: an electron-deficient derivative (Ar = *p*-fluorophenyl) produced more condensation products than an electron-rich one (Ar = *p*-methoxyphenyl), due to faster β-hydride elimination and slower re-addition, extending the lifetime of the free imine.



Scheme 30. Pd-catalyzed reactions of benzylic amines.



Scheme 31. Amine racemization in the presence of ruthenium catalysts.

5. Conclusion

It has been shown that the combination of metal-catalyzed racemization and enzymatic kinetic resolution is an attractive method for the synthesis of optically active compounds from racemic alcohols and amines. There are many metal complexes active for racemization, but the conditions for enzymatic acylation often limit the application of the metal complexes to DKR. For DKR of alcohols, complimentary catalyst systems are now available for the synthesis of both (*R*)- and (*S*)-esters: (*R*)-esters can be obtained by the combination of an *R*-selective lipase (CALB or LPS) and a racemization catalyst, whereas the use of an *S*-selective protease (subtilisin) at room temperature provides (*S*)-esters. Reusable catalyst systems that are stable under ambient conditions during DKR are also available. Palladium nanoparticles embedded on various supports are common catalysts for amine racemization, although there are some other catalysts such as Raney nickel and Shvo-type ruthenium complexes. Amine DKR is possible for aliphatic amines as well as for benzylic ones. DKR of amino acid derivatives is also possible. DKR of amines requires harsher conditions than DKR of alcohols, however, which hinders the use of normal enzymes.

An industrial company (DSM) has filed patents for the chemoenzymatic DKR of alcohols.[77] However, the efficiencies of racemization catalysts need to be enhanced substantially to compete with conventional processes for producing optically active compounds. In particular, the catalysts for the racemization of amines need to be improved to enable DKR to proceed under ambient conditions. Besides catalytic activity, recyclability is another essential factor for future catalysts. Simple reaction conditions that do not require restricted atmosphere and additives such as bases and hydrogen mediators should be also considered. With further improvements in these factors, chemoenzymatic DKR processes should find use in the industrial synthesis of optically active compounds in the near future.

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