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Review

Racemization catalysts for the dynamic kinetic resolution of alcohols and amines

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Contents

Abstract

Metal–enzyme bicatalyses for the dynamic kinetic resolution (DKR) of alcohols and amines are summarized emphasizing the features of racemization catalysis. A metal complex catalyzes the racemization of alcohols and amines, and an enzyme catalyzes asymmetric acylation in the presence of acyl donor in organic solvent to produce the corresponding optically active acetates and amides, respectively. A few related reactions involving metal-catalyzed racemization, such as the transformations of ketones, enol acetates, ketoximes, and allylic acetates, are also described. The majority of racemization catalysts suitable for the DKR of alcohols are ruthenium complexes, while there are rhodium, palladium, aluminum, and vanadium catalysts effective for limited substrates. Some ruthenium catalysts are active even at room temperature and enable the use of thermally labile enzymes to give (*R*)-ester or (*S*)-esters from racemic alcohols. The DKR of amine is less developed than that of alcohols. Palladium on charcoal is the first example for the racemization catalyst in amine DKR. Improved activities are observed in the amine DKR using palladium on

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basic salts such as $CaCO_3$ and $BaCO_3$. Palladium nanoparticles dispersed in aluminum oxyhydroxide are effective for the DKR of aliphatic amines as well as for that of benzylic ones. The Shvo's complex is the sole example of homogeneous catalyst in the DKR of amines.

Keywords: Racemization catalyst; Enzyme; Dynamic kinetic resolution; Alcohol; Amine; Allyl acetate

1. Introduction

Though kinetic resolution (KR) is a useful method for the preparation of optically active compounds, it has a limitation in that the yield of one isomer cannot exceed 50%. In conventional methods to improve the yield, the undesired isomer should be isolated from the reaction mixture and recycled for the kinetic resolution. The dynamic kinetic resolution (DKR) [1] is a promising route to overcome the limitation of KR for the synthesis of optically pure compounds, especially alcohols and amines, from racemic mixtures without separating the undesired enantiomer after the reaction. For the successful and efficient DKR, continuous racemization of the less reactive enantiomer is required during the KR process (Scheme 1). The racemization can occur through various pathways [2], however, it should be possible for a wide range of substrates, compatible with resolving process, and not cause side reactions for successful DKR. These requirements have stimulated the development of transition metal catalysts active for the racemization of alcohols and amines [3].

The DKR of alcohols and amines by metal-catalyzed racemization combined with enzymatic kinetic resolution has attracted increasing interest [4], because the optically pure alcohols and amines are important chiral building blocks in fine chemical industries such as pharmaceutical, agrochemical, cosmetics, or food additive industry. Because the enzyme and the metal complex are in one vessel, the metal catalyst should be active under the conditions required for the enzymatic reactions.

For the last 10 years, significant advances have been made for the DKR by metal–enzyme bicatalysis. In this review, the transition metal complexes used as racemization catalysts for the DKR of alcohols, allyl acetates, and amines are summarized.

$$\begin{tikzcd}
(R)\text{-substrate} \arrow[r, "k_R"] \arrow[d, shift right] & (R)\text{-product} \\
(S)\text{-substrate} \arrow[r, "k_S"] \arrow[u, shift right] & (S)\text{-product}
\end{tikzcd}$$

$k_R >> k_S$ or vice versa

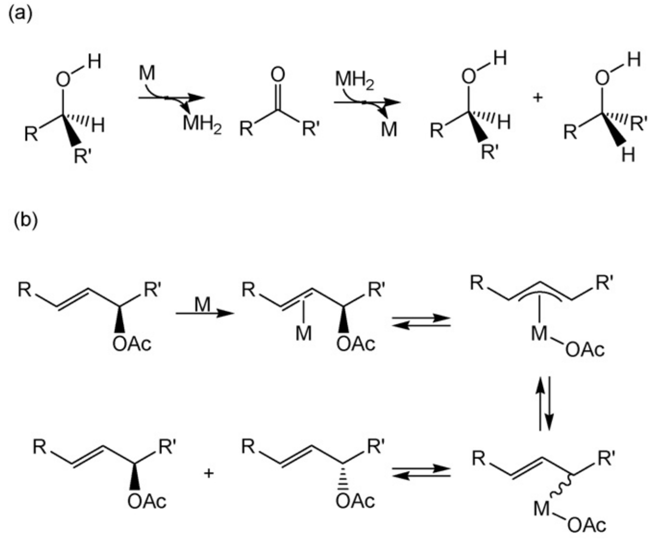
Scheme 1. Dynamic kinetic resolution.

2. Racemization catalysts for the DKR of alcohols and allyl acetates

Reversible hydrogen transfer reactions are typical pathways for alcohol racemization by transition metal catalysts [5] (Scheme 2). For allyl esters, rearrangement reactions are suggested for the racemization through reversible transformation between η^1- and η^3-allyl palladium complexes [6]. The allylic alcohol racemization catalyzed by $VO(OR)_3$ occurs through the formation of allyl vanadate intermediates [7]. In hydrogen transfer reactions, the α-hydrogen of secondary alcohol is transferred to the metal center of the racemization catalyst to give the corresponding ketone and metal hydride complex. Then, ketones are hydrogenated into a mixture of racemic alcohols by the metal hydride complex. In the rearrangement reactions, chiral allyl esters are coordinated to metal center to form η^2-ene complexes, which are transformed to η^3-allyl complexes. The η^3-allyl complexes are in equilibrium with the η^1-allyl complexes, from which the racemic mixture of allyl esters is given through reductive elimination.

2.1. Rhodium catalysts

In the first alcohol DKR by metal–enzyme bicatalysis, various rhodium, iridium, ruthenium, and aluminum complexes were tested [8]. Among the racemization catalysts, only $Rh_2(OAc)_4$ and $[Rh(cod)Cl]_2$ showed reasonable activity in the



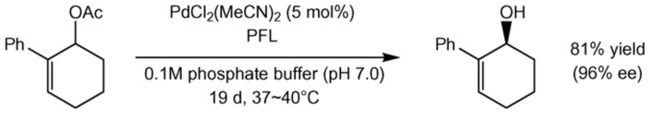
Scheme 2. Racemizations of alcohol and allyl acetates: (a) hydrogen transfer reaction and (b) π-allyl complex formation.

DKR of 1-phenylethanol. The racemization occurred through transfer-hydrogenation reactions and required stoichiometric amount of ketone as hydrogen acceptor. Potassium hydroxide was also needed presumably for the formation of metal alkoxide intermediates. Enzymatic reactions are not compatible with strong bases such as KOH, the DKR of 1-phenylethanol was performed in the absence of KOH by using $Rh_2(OAc)_4$ and PFL (*Pseudomonas fluorescens* lipase) to give (*S*)-1-phenylethyl acetate in 98% ee at 60% conversion after 72 h.

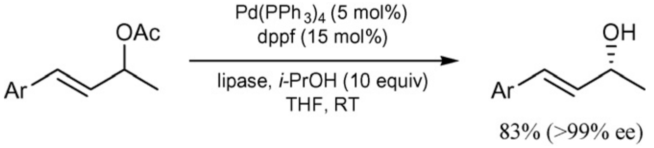
2.2. Palladium catalysts

A palladium complex, $PdCl_2(MeCN)_2$, was used as the catalyst precursor for the racemization of cyclic allyl acetates [6a]. The reaction of the palladium complex with allyl acetate forms the corresponding η^3-allyl palladium intermediate, which is in equilibrium with the both enantiomers of the allyl acetate (Scheme 2). Then, a lipase selectively hydrolyzes one enantiomer to optically active allyl alcohol. Because the racemization occurs through 1,3-shift, the η^3-allyl palladium intermediate should be symmetrical or the carbon–carbon double bond should be stabilized in one direction to avoid the formation of unwanted structural isomers. Thus, the successful example in the first report was a cyclic acetate, which was transformed to the corresponding (*S*)-alcohol in 81% yield and 96% ee through DKR for 19 days using $PdCl_2(MeCN)_2$ and a lipase in a phosphate buffer (Scheme 3).

Kim and co-workers significantly improved the DKR of linear allyl acetates using a palladium-dppf (dppf: 1,1′-bis(diphenylphosphino)ferrocene) complex as the racemization catalyst and 2-propanol as acyl acceptor [6b]. They suggested that the improvement comes from decreasing side reactions such as the elimination reaction to give conjugated dienes and the substitution reactions to give structural isomers. For example, (*R*)-4-phenylbut-3-en-2-ol was obtained in 83% yield and >99% ee within 36 h (Scheme 4).



Scheme 3. DKR of cyclic ally acetate.



Scheme 4. DKR of linear allylic acetate.

2.3. Ruthenium catalysts

Ruthenium complexes are the most popular catalysts for alcohol racemization [9]. However, only some of them are suitable for alcohol DKR by metal–enzyme bicatalysis (Fig. 1).

2.3.1. $\{[(\eta^5\text{-}Ph_4C_4CO)]_2H\}Ru_2(CO)_4(\mu\text{-}H)$ (**1**)

On the basis of known catalytic activity of the Shvo's complex, $\{[(\eta^5\text{-}Ph_4C_4CO)]_2H\}Ru_2(CO)_4(\mu\text{-}H)$ (**1**), in transfer-hydrogenation reactions [10], Bäckvall and co-workers first used it in alcohol DKR [11]. The complex **1** can be easily synthesized by heating a solution of $(\eta^4\text{-}Ph_4C_4CO)Ru(CO)_3$ in toluene [12]. However, **1** should be heated to generate active monoruthenium species **1a** and **1b** (Scheme 5) [13]. Ketone is hydrogenated

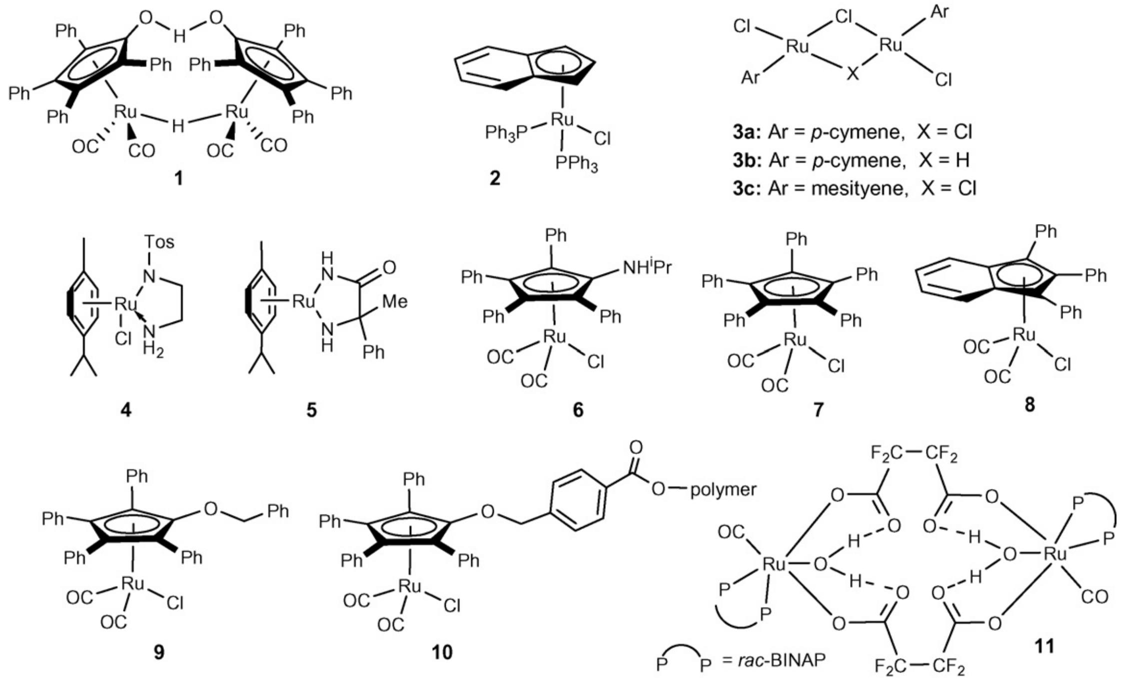
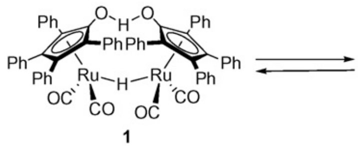
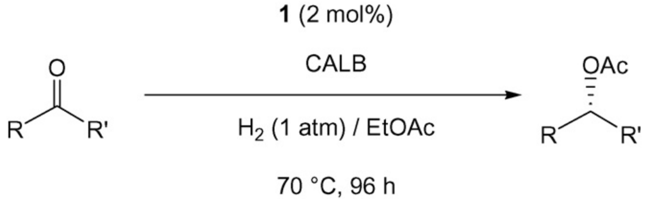


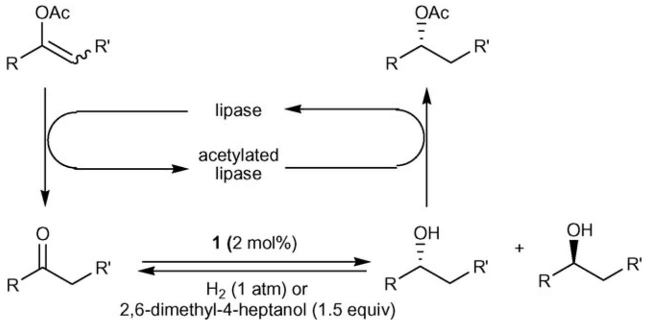
Fig. 1. Ruthenium catalysts for alcohol racemization.



Scheme 5. Dissociation of racemization catalyst **1**.



Scheme 7. Asymmetric reductive acylation of ketones.



Scheme 8. Asymmetric hydrogenation of enol acetate.

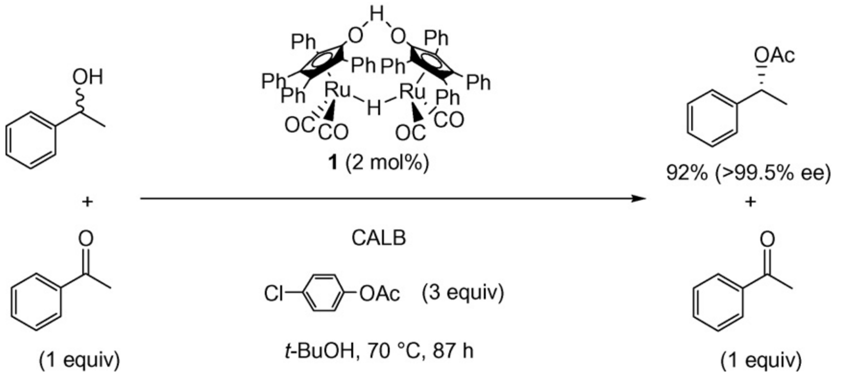
by **1a**, while alcohol is dehydrogenated by **1b**. In the racemization of 1-phenylethanol, acetophenone was formed in significant amount. Thus, for the DKR of 1-phenylethanol, one equivalent of acetophenone was added to the reaction mixture to increase the yield of 1-phenylethyl acetate in more than 80%.

Alcohol DKR was achieved by combining **1** and CALB (*Candida antarctica* lipase B, immobilized; Novozym 435^{TM}). Another key factor was the use of *p*-chlorophenyl acetate (PCPA) as acyl donor. When vinyl acetate was used as acyl donor in the DKR of 1-phenylethanol, acetophenone and 1-phenylethyl acetate were produced in 1:1 ratio. Under optimized conditions optically pure (*R*)-1-phenylethyl acetate was obtained in 92% yield (Scheme 6).

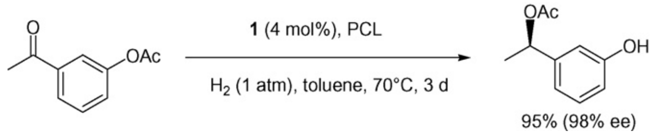
The catalysts system developed by Bäckvall and co-workers [14] were effective for the DKR of aliphatic alcohols as well as that of benzylic alcohols. Furthermore, the catalyst system was applied for the DKR of bifunctional alcohols, including diols, hydroxy acid esters [14b,15], hydroxyl aldehydes [14b], β-azido alcohols [16], β-hydroxyl nitriles [17], β-halo alcohols [18], and hydroxyalkanephosphonates [19]. These processes employed the DKR of aliphatic and benzylic secondary alcohols with simple alkyl esters such as isopropyl butyrate or methyl phenyl acetate at low catalyst loadings (0.5 mol%) [20]. The racemization with **1** is based on reversible transfer hydrogenation [13]. Meanwhile, molecular hydrogen liberation from the hydride intermediate **1a** causes the problem of ketone formation during the DKR of secondary alcohols. As a method to overcome the problem, Park and co-workers devised a novel asymmetric reductive acetylation of ketones. A key factor of this method was the selection of hydrogen donors compatible with the DKR conditions. 2,6-Dimethylheptan-4-ol, which cannot be acylated by lipases, was selected as a proper hydrogen donor in the transformation [21]. Asymmetric reductive acylation of ketones was also possible under 1 atm hydrogen in ethyl acetate, although a long reaction time (96 h) was required (Scheme 7). Ethanol formation did not cause critical problems, and various ketones were transformed successfully into the corresponding chiral acetates [21].

Based on the success in the asymmetric reductive acylation of ketones, enol acetates were used as acyl donors as well as precursors of ketones through deacylation and keto-enol tautomerization (Scheme 8). The overall reaction corresponds to the asymmetric reduction of enol acetate. For example, 1-phenylvinyl acetate was transformed to (*R*)-1-phenylethyl acetate by CALB and **1** in the presence of 2,6-dimethyl-4-heptanol in 89% yield (98% ee) [21a]. Molecular hydrogen (1 atm) was also effective for the transformation (86% yield, 96% ee) [21b]. A broad range of enol acetates was prepared from ketones and these were successfully transformed to the corresponding (*R*)-acetates under 1 atm H_2. From unsymmetrical aliphatic ketones, enol acetates were obtained as mixtures of regio- and geometrical isomers. Notably, however, the efficiency of the process was little affected by the isomeric composition of the enol acetates.

Asymmetric reductive acylation process was also applicable to acetoxyaryl ketones [22]. For example,



Scheme 6. DKR with racemization catalyst **1**.



Scheme 9. Asymmetric reductive acyl migration of acyloxyphenyl ketone.

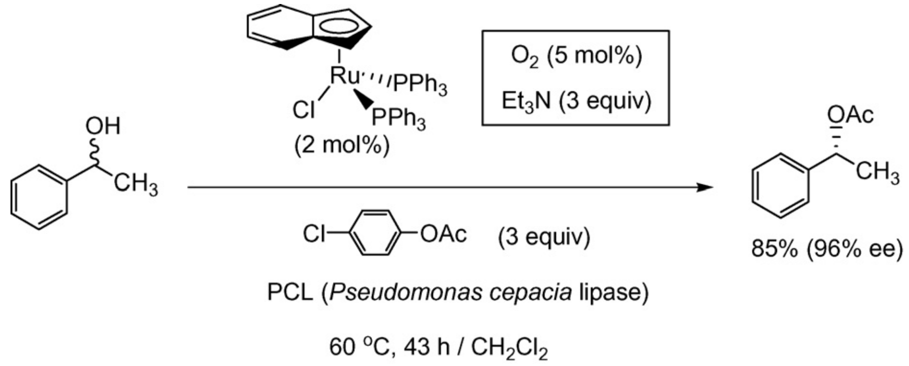
3′-acetoxyacetophenone was transformed to (*R*)-1-(3-hydroxyphenyl)ethyl acetate by **1** and PCL under 1 atm H_2 in 95% yield. The overall reaction seems to be a simple asymmetric reductive internal acyl migration. In fact, however, it is the result from nine catalytic steps: two ruthenium-catalyzed reductions, two ruthenium-catalyzed epimerizations, three lipase-catalyzed deacylations, and two lipase-catalyzed acylations (Scheme 9). This process was applicable to a wide range of acyloxyaryl ketones.

2.3.2. (η^5-Indenyl)RuCl(PPh_3)$_2$ (2)

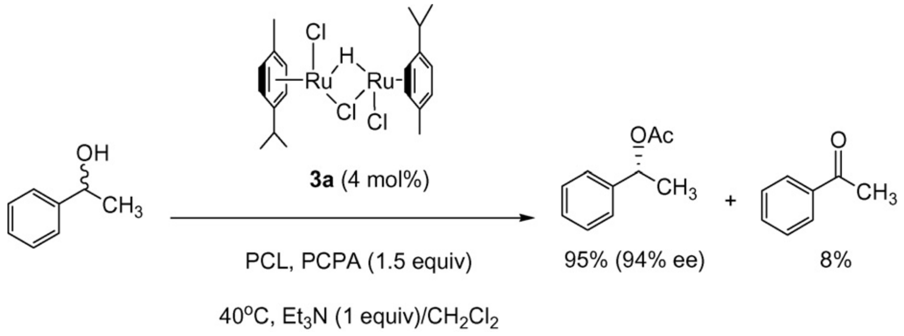
The indenyl ruthenium complex **2** was very active for the racemization of 1-phenylethanol in the presence of a strong base such as potassium hydroxide; the racemization was completed within 20 min at room temperature with 5 mol% of KOH and 1 mol% of **2** [9a]. Ketone production was negligible during the racemization. Interestingly, external ketones as hydrogen acceptors were not required for the racemization. Unfortunately, the racemization catalyst was not active without KOH that cannot be used in the DKR involving enzymatic acylation due to chemical acylation and enzyme degradation. Later, Park and co-workers found the conditions that do not require the use of strong base. Catalytic amount of molecular oxygen can activate **2**, and 1-phenylethanol was racemized by the resulting activated ruthenium species in the presence of triethylamine [23]. The combination of an immobilized PCL (*Pseudomonas cepacia* lipase, immobilized; Lipase PS-C^{TM}) and **2** at 60 °C was effective for the DKR of benzylic alcohols in the presence of molecular oxygen and triethylamine (Scheme 10). The catalyst system was less effective for the DKR of aliphatic alcohols than for that of benzylic alcohols.

2.3.3. Dimeric arene ruthenium complexes (3)

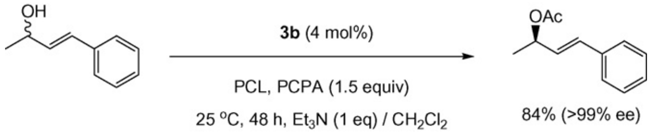
Cymene ruthenium complex **3a** was active for alcohol racemization in the presence of triethylamine at 40 °C (Scheme 11). Interestingly, ketone was produced in twice the molar ratio of **3a** during the racemization. At the initial stage, hydride-bridged complex **3b** was formed, which can be obtained in quantitative yield from a 1:1 mixture of **3a** and 1-phenylethanol. When **3b** was used as the racemization catalyst, the amount of ketone formed during the racemization was half of that in the racemization with **3a**. Both of **3a** and **3b** are effective for the DKR of aliphatic alcohols as well as that of benzylic alcohols without external ketone as hydrogen acceptor [24]. For example, (*R*)-2-octyl acetate of 85% ee was obtained in 93% yield by using **3b** and PCL. A noticeable feature of **3a** and **3b** was the high activity toward allylic alcohols so that the DKR was possible at room temperature [25] (Scheme 12). Another feature was its good activity in ionic liquids such as [EMIm]BF_4 and [BMIm]PF_6 ([EMIm] = 1-ethyl-3-methylimidazolium, [BMIm] = 1-butyl-3-methylimidazolium) [26]. The DKR in the ionic liquids was also possible at room temperature, and the ruthenium catalyst and enzyme in the ionic liquid layer were reusable after extract-



Scheme 10. DKR with racemization catalyst **2**.



Scheme 11. DKR with racemization catalyst **3a**.



Scheme 12. DKR of styryl carbinol with racemization catalyst **3b**.

ing the products with ether. Trauthwein and co-workers reported that **3a** and 1,3-propanediamine as chelating ligand racemizes alcohols within 5 h at 80 °C and applied this to DKR [27].

Kita and co-workers used another arene ruthenium complex **3c**, [1,3,5-trimethylbenzeneRuCl_2]$_2$, in the domino transformation which consists of the racemization of 3-vinyl-2-hexenol, the enzymatic acyation of the allylic alcohol, and the Diels-Alder reaction of the resulting ester in one pot (Scheme 13) [28].

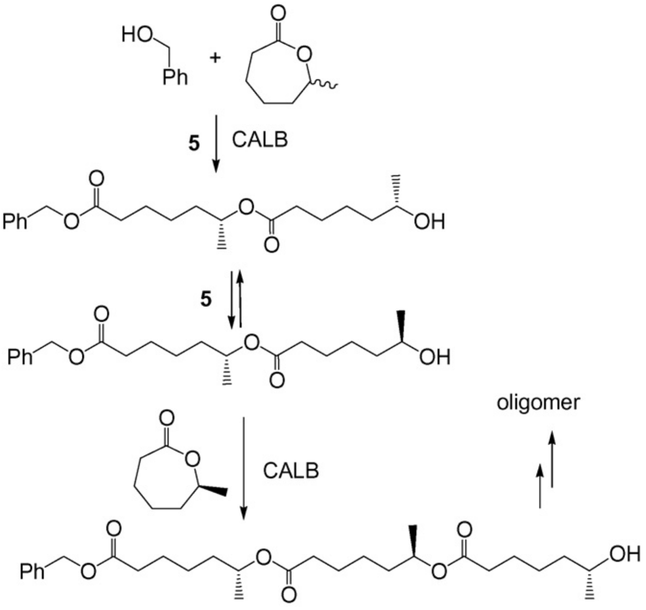
2.3.4. *(p-Cymene)RuCl [TosN(CH_2)$_2$$NH_2$] (**4**)*

Chiral ruthenium(II) complexes formed from [RuCl_2(*p*-cymene)]$_2$ and chiral bidentate nitrogen ligands are extensively studied as catalysts for the asymmetric transfer hydrogenation of prochiral ketones [29]. Sheldon and co-workers prepared **4** as an achiral analogue for alcohol racemization. A co-catalyst system of **4** and TEMPO racemized benzylic alcohols under the conditions for enzymatic acylation [30]. They suggested that a ruthenium hydride species generated from the mixture of **4**, TEMPO, and a benzylic alcohol is the active catalyst for racemization. (*R*)-1-Phenylethyl acetate (>99% ee) was obtained in 76% yield after 48 h with the production of acetophenone in 15%. However, aliphatic alcohols have not been tested with this catalyst system.

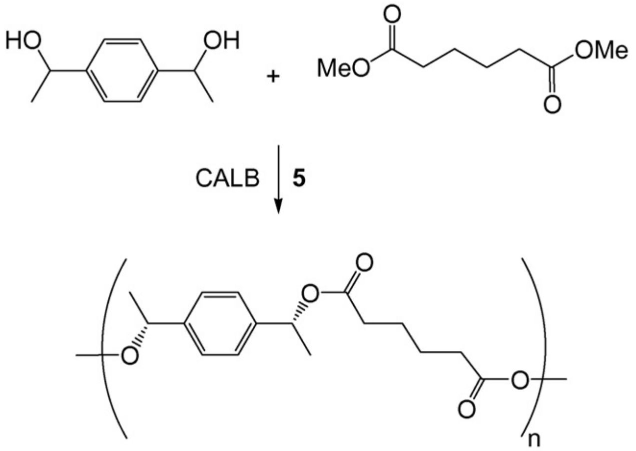
2.3.5. *(p-Cymene)RuCl [NHC(CH_3)(Ph)CONH] (**5**)*

Verzijl and co-workers [20a] prepared **5** by the reaction of [RuCl_2(*p*-cymene)]$_2$ and 2-phenyl-2-aminopropionamide in the presence of potassium carbonate and applied it to DKR as an alcohol racemization catalyst. Recently, Palmans, Mijer, and co-workers [31] used **5** in an iterative tandem catalysis. The enzymatic ring-opening of 6-methyl-*ε*-caprolactone was combined with ruthenium-catalyzed alcohol racemization to produce optically active oligomers of 6-methyl-*ε*-caprolactone (Scheme 14).

The same catalyst system was applied to the condensation of racemic α,α′-dimethyl-1,4-benzenedimethanol and dimethyl adipate. Optically active polyesters (M_w = 3400 g/mol; M_n = 2100 g/mol) were obtained [32] (Scheme 15).



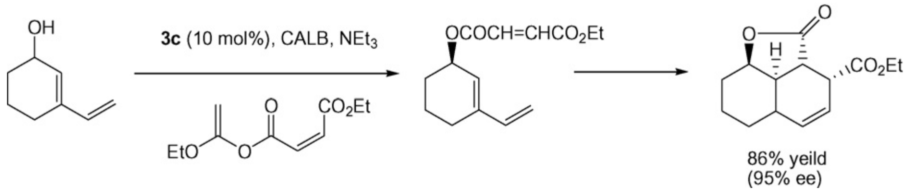
Scheme 14. Synthesis of optically active oligoesters by DKR.



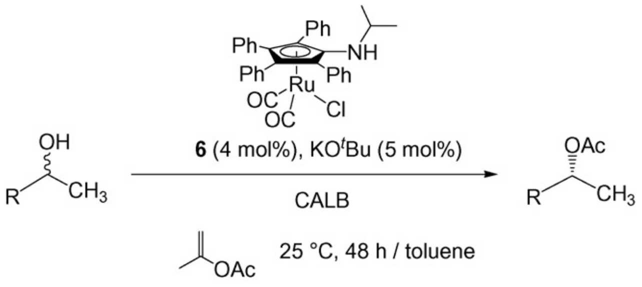
Scheme 15. Synthesis of optically active polyester by DKR.

2.3.6. *[2,3,4,5-Ph_4(η^5-C_4CNH^iPr)]Ru$(CO)_2$Cl (**6**)*

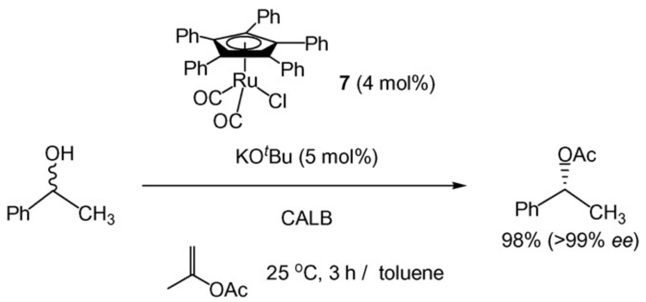
It is hard to find alcohol racemization catalysts, which are active at room temperature except for the arene ruthenium complexes **3** in the racemization of allylic alcohols. Kim, Park, and co-workers [33] synthesized the aminocyclopentadienyl ruthenium chloride complex **6**, and developed it as the alcohol racemization catalyst active at room temperature under DKR conditions. Fortunately, isopropenyl acetate was an efficient acyl donor in the alcohol DKR with **6**. Isopropenyl acetate is a much



Scheme 13. Domino transformation involving the racemization of allyl alcohol.



Scheme 16. DKR with racemization catalyst **6**.



Scheme 18. DKR with racemization catalyst **7**.

more convenient acylating reagent than PCPA; it is commercially available, easily separable from the product mixture, and more active than PCPA. Furthermore, the racemization with **6** did not require additional ketones as hydrogen acceptor. The catalyst **6** was effective for a wide range of benzylic alcohols and aliphatic ones; 2-octanol as well as 1-phenylethanol transform into the corresponding (*R*)-acetates in 89% (91% ee) and 95% (>99% ee), respectively, by using 4 mol% of **6** and CALB [34] (Scheme 16). Although the mechanism for the racemization with **6** is not clear yet, the amino group in **6** was suggested as a key factor for the racemization. However, Bäckvall and co-workers showed that a related ruthenium complex **7**, which does not have such an amino group, can also racemize alcohols at room temperature efficiently [9e,36].

The lipase-catalyzed alcohol DKR provides only (*R*)-products. Enzymes of (*S*)-stereoselectivity is needed to obtain (*S*)-products. The catalyst **6** active at room temperature enables the use of enzymes unstable at high temperature. Subtilisin was selected as a candidate, but its commercial form was not applicable to DKR due to its low enzymatic activity and instability in nonaqueous medium. Kim, Park, and co-workers succeeded in enhancing its activity and stability by treating it with a surfactant before use. Trifluoroethyl butanoate was a proper acylating agent for the DKR with **6** and subtilisin [36] (Scheme 17). This catalyst system was applicable to the DKR of a wide range of benzylic alcohols and aliphatic ones.

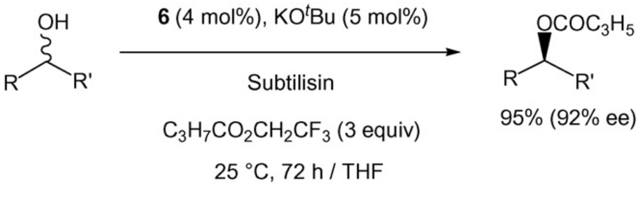
2.3.7. *(η^5-Ph$_5$C$_5$)Ru(CO)$_2$Cl (**7**) and (η^5-triphenylindenyl)Ru(CO)$_2$Cl (**8**)*

Bäckvall and co-workers found that **7** also catalyzes efficiently the racemization of alcohols at room temperature after being activated by potassium *t*-butoxide [9g]. The racemization of 1-phenylethanol was completed within 10 min by using 0.5 mol% of **7** at room temperature. Soon after, they succeeded in alcohol DKR by using **7**, CALB, and isopropenyl acetate as acyl donor at room temperature [33]. Under optimized conditions the DKR of benzylic alcohols was about one order of magnitude faster than the previous DKR with **6**. For example, the DKR of 1-phenylethanol was completed in 3 h (Scheme 18). This catalyst system was also effective for the DKR of aliphatic alcohols. The synthesis of (*S*)-esters was performed by combining **7** and subtilisin treated with surfactants [37].

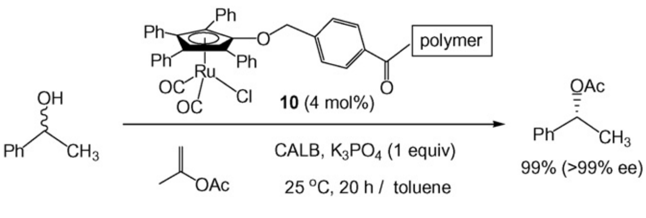
Recently, Zhang and co-workers synthesized (η^5-triphenylindenyl)Ru(CO)$_2$Cl (**8**) from 2,3-diphenylindenone in two steps [9j]. The complex **8** was tested in the racemization of 1-phenylethanol at room temperature after being activated by sodium hydride or *n*-butyllithium. Kinetic studies showed that the activation by sodium hydride is better than that by potassium *t*-butoxide ($t_{1/2} = 13.3$ min vs. $t_{1/2} = 31.3$ min). In the case of *n*-BuLi (0.5 mol%), $t_{1/2}$ was 15.5 min. Increasing the amount of *n*-BuLi (2.5 mol%) further accelerated the racemization ($t_{1/2} = 6.0$ min) so that (*S*)-1-phenylethanol was completely racemized within 30 min. By NMR experiments ruthenium hydride was suggested as a key intermediate in the catalytic cycle. However, the catalyst has not been tested in DKR.

2.3.8. *(η^5-Ph$_4$C$_4$OCH$_2$Ph)Ru(CO)$_2$Cl (**9**) and polymer-bounded Ru(CO)$_2$Cl (**10**)*

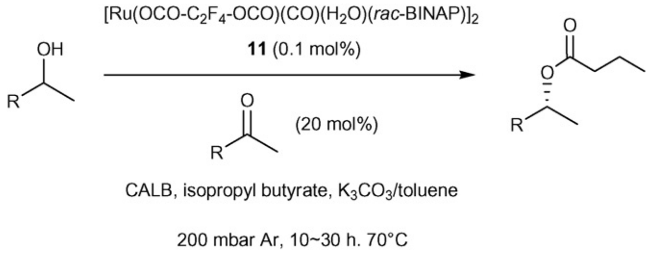
Kim, Park, and co-workers synthesized **9** by the one-step reaction of [Ph$_4$(η^4-C$_4$CO)]Ru(CO)$_3$ with benzyl chloride. In contrast to previous alcohol racemization catalysts, **9** was stable in the air during racemization [38]. The racemization was performed even under 1 atm of molecular oxygen. Thus, alcohol DKR was possible with **9** in the air at room temperature; (*R*)-1-phenylethyl acetate (99% yield, >99% ee) was obtained from 1-phenylethanol by using 4 mol% of **9**, CALB, and isopropenyl acetate in the presence of potassium phosphate. This catalyst system was effective for benzylic alcohols and aliphatic ones. The synthetic method for **9** was applied to the preparation of a polymer-bound derivative (**10**) (Scheme 19). Hydroxymethyl polystyrene was reacted with 4-(chloromethyl)benzoyl chloride



Scheme 17. DKR with racemization catalyst **6** and subtilisin.



Scheme 19. DKR with racemization catalyst **10**.



Scheme 20. DKR with racemization catalyst **11**.

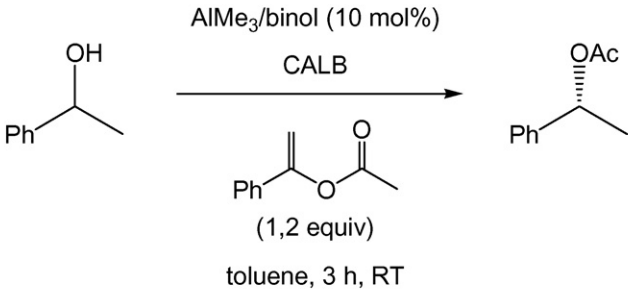
to attach chlorobenzyl groups. Heating a mixture of the resulting polymer and $[Ph_4(\eta^4\text{-}C_4CO)]Ru(CO)_3$ gave **10**, which was recycled for alcohol DKR.

2.3.9. *[Ru(μ–OCO–C$_2$F$_4$–OCO)(CO)(H$_2$O)(rac-BINAP)]$_2$ (**11**)*

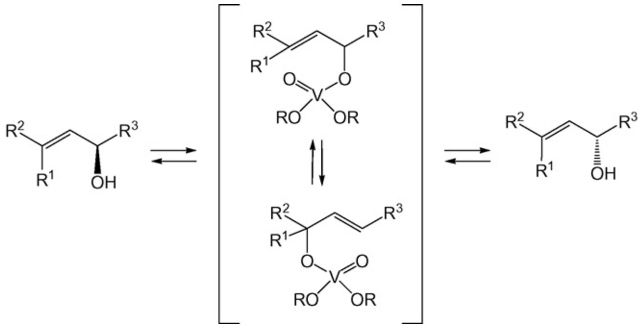
Hulshof and co-workers [39] introduced **11** as an alcohol racemization catalyst, which had showed the catalytic activity in the acceptorless dehydrogenation of alcohols. Alcohol DKR was performed with 0.1 mol% of **11**, CALB, isopropyl butyrate as the acyl donor, potassium carbonate, and about 20 mol% of the corresponding ketone at 70 °C (Scheme 20). Without the ketone, yield and optical purity of the product ester were decreased significantly. 2-Propanol produced by acyl transfer reaction was removed at reduced pressure during the DKR.

2.4. *Aluminum catalysts*

Based on the catalytic activity of aluminum alkoxides in Meerwein–Ponndorf–Verley–Oppenauer (MPVO) reaction, Berkessel et al. [40] envisioned that aluminum complexes can act as alcohol racemization catalysts. Aluminum alkoxide complexes generated from 1:1 mixture of $AlMe_3$ and a bidentate ligand such as binol or 2,2′-biphenol were effective catalysts for alcohol racemization. At room temperature, 10 mol% of the aluminum catalyst racemized 1-phenylethanol completely within 3 h in the presence of 0.5 equiv. of acetophenone. The aluminum catalysts were applicable for the DKR of various alcohols. However, specific acylating reagents were required, which are the enol esters derived from the corresponding ketones. For example, (*R*)-1-phenylethyl acetate (96% ee) was obtained in 96% yield from a mixture of 1-phenylethanol and 1-phenylvinyl acetate (1.2 equiv.) by using $AlMe_3$ (10 mol%), binol (10 mol%), and CALB at room temperature (Scheme 21).



Scheme 21. Aluminum-catalyzed DKR of 1-phenylethanol.



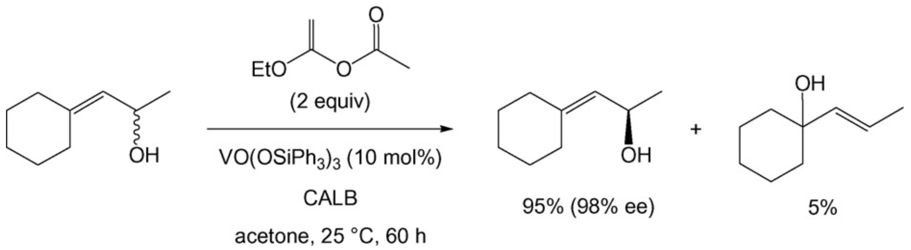
Scheme 22. Vanadium-catalyzed racemization of allylic alcohol.

2.5. *Vanadium catalysts*

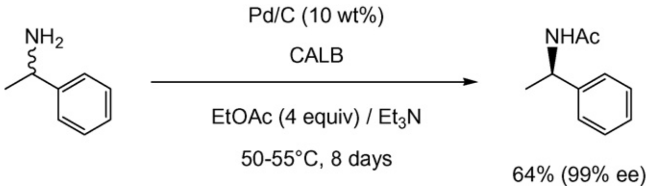
Oxovanadium(V) complexes, $VO(OR)_3$, have been known to catalyze the rearrangement of allylic alcohols through the formation of allyl vanadate intermediates [41] (Scheme 22). Akai et al. employed vanadium complexes for the DKR of allyic alcohols. They selected $VO(OSiPh_3)_3$, and optimized conditions for the DKR of 1-cyclohexylidenepropan-2-ol. (*R*)-1-Cyclohexylidenepropan-2-yl acetate (98% ee) was obtained in 95% yield by using 10 mol% of $VO(OSiPh_3)_3$, ethoxyvinyl acetate as acyl donor, CALB in acetone at room temperature for 60 h [7] (Scheme 23). (*E*)-1-(Prop-1-enyl)cyclohexanol was given as the by-product in 5%.

3. Racemization catalysts for DKR of amines

Generally, the racemization of amines is more difficult than that of alcohols and requires harsh conditions. Compared to alcohol racemization catalysts, efficient catalysts for amine racemization are rare. There are only two kinds of catalysts compatible with enzymes and applicable to the DKR of amines: palladium metals dispersed in porous supports and



Scheme 23. DKR of allylic alcohols with $VO(OSiPH_3)_3$.



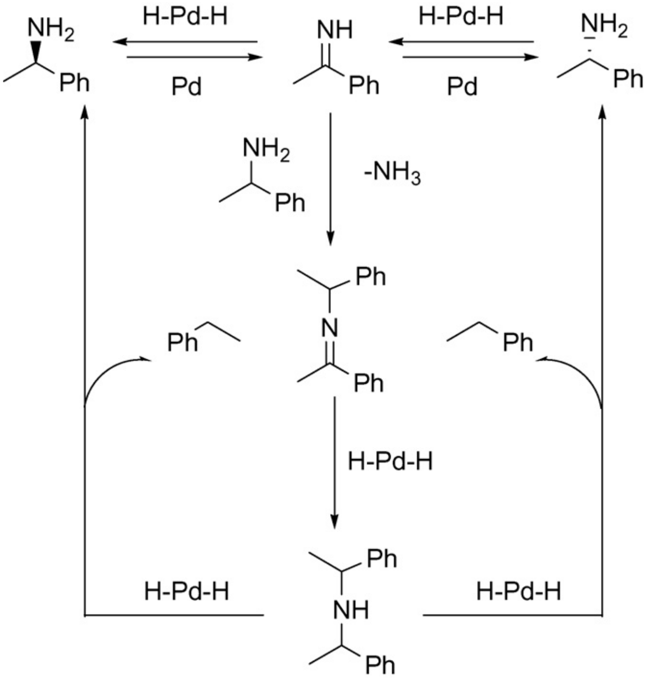
Scheme 24. DKR of 1-phenylethylamine with Pd/C.

the Shvo's complex **1** which is already described in alcohol DKR.

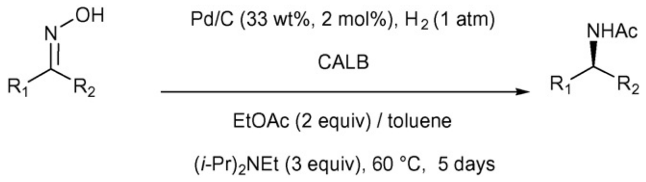
3.1. *Palladium catalysts*

Because many palladium complexes catalyze the elimination of hydrogen from primary or secondary amine and the hydrogenation of imines, palladium is naturally believed to have potential activity for the racemization of amines. Reetz and Schimossek [42] reported for the first time the DKR of 1-phenylethylamine by employing palladium on charcoal and CALB. The DKR required a very long reaction time (8 days) at 50–55 °C and provided (*R*)-*N*-(1-phenylethyl)acetamide (99% ee) only in 64% yield (Scheme 24). Ethyl acetate was used as acyl donor in triethylamine.

Based on the side products such as ethylbenzene and bis(1-phenylethyl)amine in the racemization of 1-phenylethylamine, pathways for the racemization and the side reactions were proposed as in Scheme 25 [43]. The racemization occurs through amine dehydrogenation and hydrogenation of the resulting imine. Because bis(1-phenylethyl)amine is formed from the condensation of amine and imine, the concentrations of amine and imine should be kept low and adequate imine hydrogenation rate maintained to suppress the secondary amine formation. In fact, the yield of (*R*)-*N*-(1-phenylethyl)acetamide increased significantly in an indirect amine DKR, in which 1-phenylethylamine was generated slowly from the corresponding ketoxime by hydrogenation [44]. The conversion of various prochiral ketoximes to the corresponding optically active acetamides (>98% ee) in 70–89% yield was achieved using a hydrogen balloon at 60 °C in the presence of Pd/C, CALB, ethyl acetate, and diisopropylethylamine in toluene (Scheme 26).



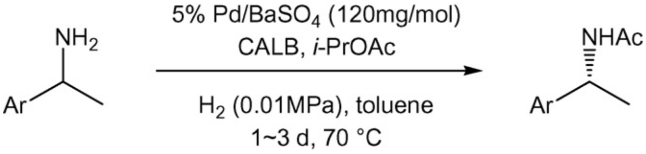
Scheme 25. Reactions of (*S*)-1-phenylethylamine with Pd Catalyst.



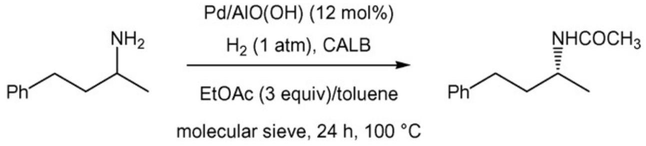
Scheme 26. Asymmetric transformation of keoximes.

Jacobs and co-workers paid attention to the effect of support of palladium catalysts. They found palladium particles immobilized on supports such as $BaSO_4$, $CaCO_3$ and $BaCO_3$ are efficient heterogeneous catalysts for the racemization of benzylic amines [41]. Kinetic studies revealed that the racemization is first-order in the amine substrate, and that the by-products arise via formation of a secondary amine and its subsequent hydrogenolysis. They suggested that the racemization proceeds via dehydrogenation and hydrogenation, and that the main role of a basic support is to suppress the condensation of the amine and the imine intermediate. The racemization with the palladium catalysts was combined with enzymatic kinetic resolution to provide enantiomerically pure amides from racemic amines. For example, (*R*)-*N*-(1-phenylethyl)acetamide (>99% ee) was obtained in 86% (94% selectivity at 91% conversion) by using isopropyl acetate as acyl donor, 5% $Pd/BaSO_4$, and CALB under 0.01 MPa H_2 at 70 °C (Scheme 27). The palladium catalyst and the immobilized enzyme could be recovered and reused several times without activity loss.

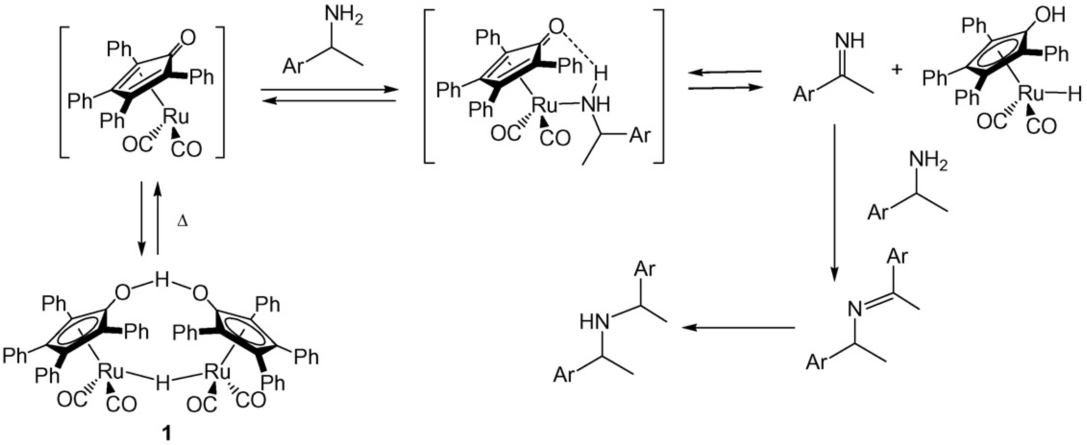
Park and co-workers [45] developed a simple one-pot method for the synthesis of highly reactive and recyclable catalysts through generation of metal nanoparticles in a solution of inorganic alkoxides in alcohols and subsequent gelation by treatment with water. The resulting gels showed the high catalytic activities in the hydrogenation of alkenes and arenas [43,46,47], in aerobic oxidation of alcohols [44], in alcohol dehydrogenation [48], and



Scheme 27. DKR of benzylic amines with $Pd/BaSO_4$.



Scheme 28. DKR of aliphatic amine with Pd/AlO(OH).

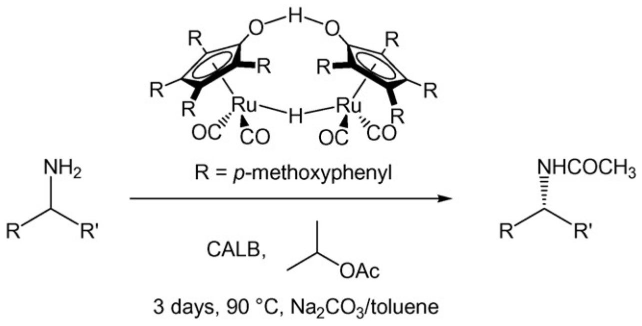


Scheme 29. Racemization of amines with **1**.

in carbon–carbon cross-coupling reactions [43,49]. Particularly, palladium in aluminum oxyhydroxide (Pd/AlO(OH)) showed excellent activity in amine racemization. Pd/AlO(OH) was effective not only for the DKR of benzylic amines and aliphatic amines but also for that of amino acid amide [50]. The DKR of aliphatic amines was performed at 100 °C with 12 mol% of Pd, while that of aromatic ones at 70 °C with 1 mol% of Pd. Even an amino acid amide, phenylalanine amide, was transformed successfully into (*S*)-2-acetamido-3-phenylpropanamide (98% ee) in 96% yield by using Pd/AlO(OH), CALB, and ethyl acetate at 100 °C (Scheme 28). The racemization catalyst was recovered and reused for the DKR without significant activity loss at least 10 times.

3.2. *Ruthenium catalysts*

The ruthenium catalyst **1** racemized amines at 110 °C in toluene, but the side products were formed in significant amount. Bäckvall and co-worker found that hydrogen donors such as 2,4-dimethyl-3-pentanol inhibits the formation of side products. Various benzylic amines, including secondary amines, were racemized successfully under the conditions using **1** and 2,4-dimethyl-3-penatanol at 110 °C [51] (Scheme 29). However, the conditions were too harsh to apply for the amine DKR with enzymes.



Scheme 30. DKR of amines with Shvo-type catalyst.

Bäckvall and co-worker synthesized derivatives of **1** by varying the substituents of cyclopentadienyl ring. The derivative having *p*-methoxyphenyl substituents showed the activity that is higher and more selective for the racemization of amines than that of **1**. This racemization catalyst was combined with CALB for the DKR of aliphatic amines and benzylic ones in the presence of isopropyl acetate as acyl donor and sodium carbonate as base trapping acids generated from either the polyacrylate support, the acyl donor, or the enzyme itself [52] (Scheme 30).

4. Conclusion

It has been shown that the combination of metal-catalyzed racemization and enzymatic kinetic resolution is an attractive method for the DKR of alcohols and amines. Various metal catalysts showed high catalytic activity in the racemization of alcohols and amines. Among them, those active under the conditions for enzymatic reactions in organic solvent have been developed for the DKR of alcohols and amines. For alcohols, a pair of complementary DKR procedures are now available for the synthesis of both (*R*)- and (*S*)-esters with the aid of racemization catalysts that are active at room temperature. Alcohol DKR can be performed not only for simple alcohols but also for those with additional functional groups. Alcohol DKR has also been used for the synthesis of chiral polymers and coupled to tandem reactions producing polycyclic compounds. Furthermore, robust racemization catalysts have been developed, which are stable even under aerobic conditions during DKR. Thus, catalyst recycling is now possible, although the efficiency is not good enough for industrial process. Compared to alcohol DKR, amine DKR requires harsh conditions and the catalysts for amine racemization are limited. Amine DKR is possible for aliphatic amines as well as for benzylic ones. There is also an example for the DKR of amino acid derivative. However, there is no racemization catalyst that is active enough to be coupled with thermally labile enzymes for amine DKR. Future racemization catalysts should be more active, selective, environmentally benign, cheap, and compatible with a broad range of enzymes under conditions suitable for industrial process.

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