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Asymmetric Reductive Amination

Chao Wang and Jianliang Xiao

Abstract Asymmetric reductive amination (ARA) affords synthetically valuable chiral amines straightforwardly. This chapter reviews the recent advances made in the area, focusing on ARA by hydrogenation, transfer hydrogenation, organocatalytic reduction, and biocatalytic reduction.

Keywords Asymmetric catalysis · Reductive amination · Hydrogenation · Transfer hydrogenation · Organocatalysis

Contents

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1 Introduction

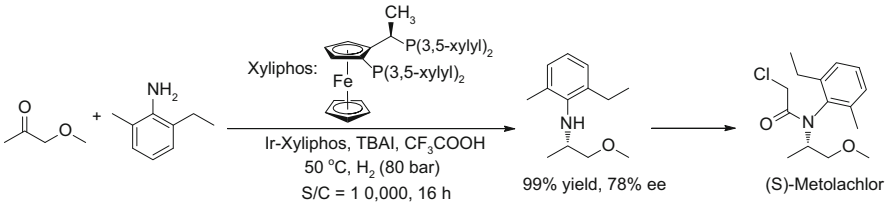
Amines are widely found in natural products, agrochemicals, and pharmaceuticals. As a result, a great deal of attention has been drawn to the development of efficient and economic methods for producing chiral amines [1–24]. One effective method is the reduction of imino C=N bonds, which are most conveniently obtained from the condensation of carbonyl compounds with amines [17, 20, 23–25]. However, imines are not always easy to synthesize and have limited stability. Reductive amination (RA) exploits imines generated in situ from carbonyl compounds and amines, alleviating the problematic imine isolation. Tremendous efforts have been made to develop efficient and selective RA reactions. The progress is rather slow, however, probably due to the following issues. (1) The carbonyl group used in RA is reducible itself, giving rise to an issue of chemoselectivity. (2) The reaction of the carbonyl with the amine results in an equilibrium, which usually disfavors the imine product, unless water is removed. (3) Various reducible intermediates, such as hemiaminals, aminals, enamines, and iminium ions, may appear during the RA reaction, complicating the reaction. (4) The amine substrate, imine intermediate, and amine product may poison the catalyst, particularly metal complex catalysts. (5) The acyclic imine intermediate has *E*/*Z* isomers, which makes stereoselective reduction difficult. Indeed, successful RA systems are sparse and asymmetric versions are even fewer. In this chapter, recent advances of ARA from areas of organometallic catalysis, organocatalysis, and biocatalysis are described, aiming to show the state-of-the-art ARA reactions. Stoichiometric reduction using borohydrides is not discussed [26, 27].

2 Organometallic Catalysis

Organometallic catalysis is the major driving force in the general area of asymmetric catalysis. This is also seen in ARA, where organometallic catalysts dominate the scene.

2.1 Metal Catalyzed Hydrogenation

Metal catalyzed hydrogenation is one of the most successful asymmetric catalytic reactions [28]. Using hydrogen gas as hydrogen source is desirable both economically and environmentally, owning to the 100% atom efficiency for the reduction and the low cost of H_2. Ruthenium, rhodium, and iridium complexes are the most widely used catalysts for hydrogenation [17, 20, 23, 24]. The key to controlling the stereoselectivity rests on the ligands, which are mostly phosphines. New concepts, such as cooperative catalysis, have also been explored in ARA.



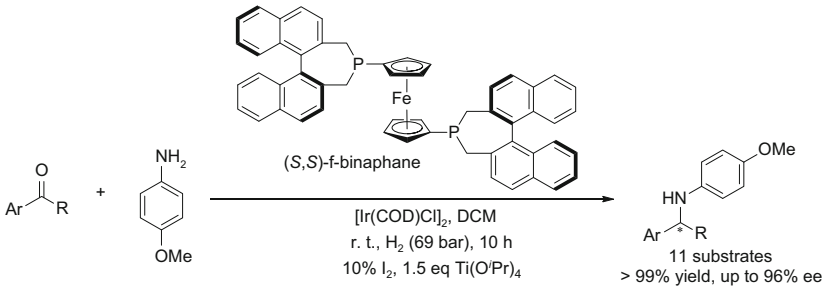
Scheme 1 First example of ARA of a ketone

The first ARA reaction by hydrogenation was reported by Blaser and co-workers [29]. In the production of the grass herbicide Metolachlor, a highly efficient imine reduction process was developed using a catalyst generated in situ from [Ir(COD)Cl]$_2$ (COD = cycloocta-1,5-diene) and the ferrocenyldiphosphine ligand Xyliphos (Scheme 1). Approximately 80% enantioselectivity was obtained at a substrate to catalyst ratio (S/C) of >1,000,000, with initial TOF up to 1,800,000 h^{-1}. A one-pot process, without the isolation of the unstable imine intermediate, was attempted. It turned out that the one-pot procedure can provide a similar *ee* (78%), but with much slower reaction rate. The best activity was observed at an S/C of 10,000 for 14 h, and the addition of iodide ions and acid was necessary. It should be noted that the ketone substrate used is an aliphatic one, which is a difficult class of substrates for obtaining high *ee*s by RA.

Despite the success of the Blaser system, highly enantioselective and active catalysts with broad substrate scope were lacking. In 2001, Zhang and co-workers reported a novel ligand, f-binaphane, which demonstrates good activity and enantioselectivity in iridium-catalyzed hydrogenation of imines derived from aryl-alkyl ketones and aromatic amines [30]. The one-pot ARA with this ligand was also studied (Scheme 2) [31]. Since the imine-formation step was found to be the rate-limiting step, various acids were used to accelerate the imine formations. The Lewis acid Ti(O*i*Pr)$_4$ was found to be an effective additive. Further, the addition of 10% of I_2 was vital for the reaction to proceed; no reaction was detected without it. With 1 mol% of the in situ formed catalyst from [Ir(COD)Cl]$_2$ and (*S*,*S*)-f-binaphane, various aryl-alkyl ketones reacted with *p*-anisidine, affording amines with excellent yields and *ee*s.

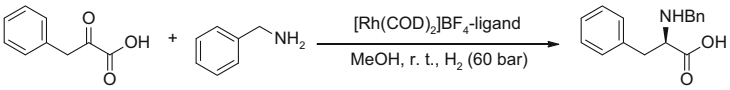
In 2000, Borner and co-workers reported that cationic Rh(I) complexes [Rh(dppb)(COD)]BF_4 [dppb = 1,4-bis(diphenylphosphino)butane and [Rh(dpoe)(COD)]BF_4 [dpoe = 1,2-bis(diphenylphosphinito)ethane] catalyzed hydrogenative RA of aldehydes and ketones [32]. Various aldehydes were aminated to afford amines at S/C of 500, although the selectivity between amine and alcohol products was not satisfactory. When the achiral ligands dppb and dpoe were replaced with a chiral ligand **1**, the RA between an α-keto acid and benzylamine afforded 59% yield and 38% *ee* (Table 1).

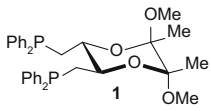
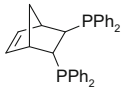
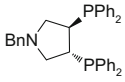
Subsequently in 2003, the same group disclosed their search for chiral hydrogenation catalysts aimed at ARA [33]. High throughput screening technology was deployed in their research. After screening 96 chiral ligands with [Rh(COD)$_2$]BF_4 and [Rh(COD)Cl]$_2$, respectively, Norphos and Deguphos were identified as



Scheme 2 ARA catalyzed by an Ir-f-binaphane catalyst

Table 1 Reductive amination catalyzed by chiral Rh-diphosphine catalysts

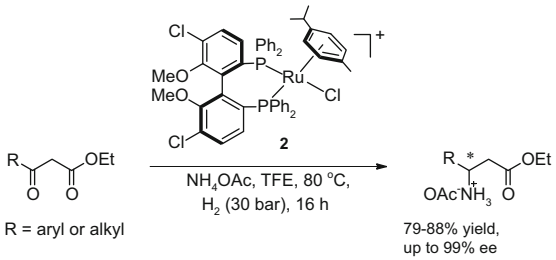


Entry	Ligand	Yield (%)	*ee* (%)
1	 **1**	59[a]	38
2	 (*R*,*R*)-Norphos	99	95
3	 (*R*,*R*)-Deguphos	98 (99)[b]	92 (98)[b]

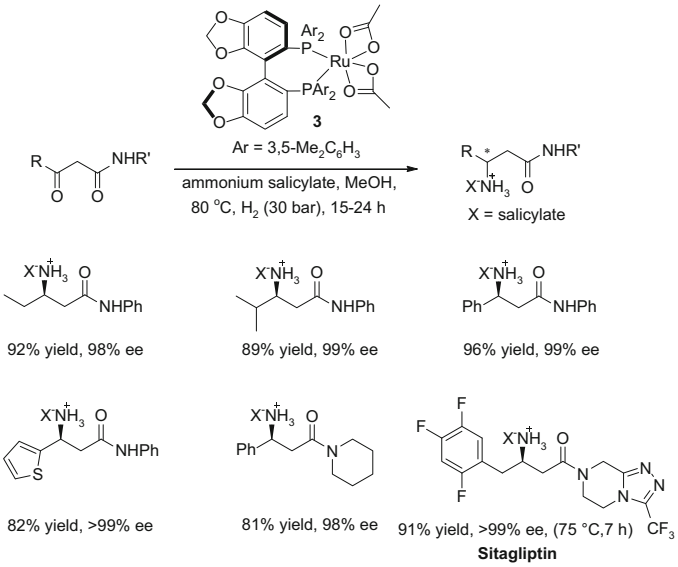
[a]50 bar H_2 pressure
[b]Isolated {Rh[(*R*,*R*)-Deguphos](COD)}BF_4 was used as catalyst for results in brackets

good ligands for the ARA of phenylpyruvic acid with benzylamine (Table 1). Using 1 mol% of in situ formed catalyst, *ee*s over 90% were observed with both Norphos and Deguphos. Up to 99% of yield and 98% of *ee* were obtained for phenylanaline by using isolated {Rh[(*R*,*R*)-Deguphos](COD)}BF_4 catalyst. However, only three substrates gave over 80% *ee* with this catalytic system.

Inspired by the work of Hsiao and co-workers on Rh catalyzed asymmetric hydrogenation of unprotected β-enamine esters and amides [34], Bunlaksananusorn and co-worker reported a Ru-catalyzed RA of β-keto esters with NH_4OAc to produce chiral β-amino esters in 2005 [35]. Using 1 mol% of Ru complex **2** as catalyst and trifluoroethanol (TFE) as solvent, both aryl and alkyl β-keto esters could be aminated into chiral β-amino esters with excellent chemo- and enantio-selectivities at 30 bar H_2 and 80 °C (Scheme 3). For example, when R = Me, the desired product could be obtained in 80% yield and 96% *ee*.



Scheme 3 Ru catalyzed ARA of β-keto esters



Scheme 4 Ru-catalyzed ARA of β-keto amides

Recently, research groups from Merck and Takasago reported RA of β-keto amides catalyzed by Ru-diphosphine complexes [36]. In this case, ammonium salicylate was used as the amine source and MeOH turned out to be the best solvent screened (Scheme 4). Excellent yields and *ee*s were obtained for all the substrates reported. Impressively, this method was applied to the synthesis of Sitagliptin, a potent DPP-IV inhibitor for the treatment of type II diabetes. With 1 mol% of catalyst **3**, Sitagliptin was obtained in 91% yield and >99% *ee* from its corresponding ketone. For the RA of β-keto esters and amides, imines were believed to be the intermediate that was reduced, although enamines are the more stable intermediate.

Since the first reported hydrogenative RA reaction, attention has been focused on the discovery of new diphosphine ligands. Development of phosphine-free catalytic systems with broad substrate scope and high enantioselectivities is still a challenge. In 2009, Xiao and co-workers reported a novel iridium catalyst for

Scheme 5 Hydrogenation of imines via cooperative catalysis

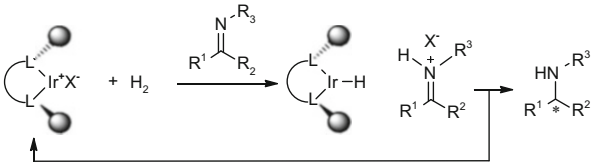
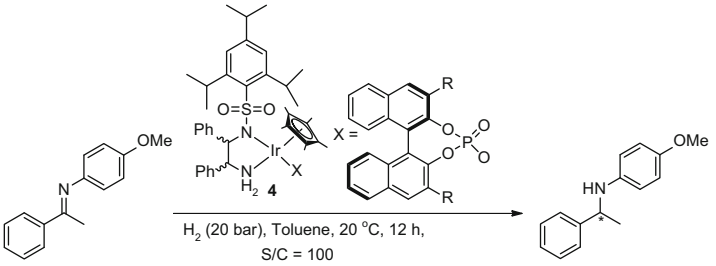


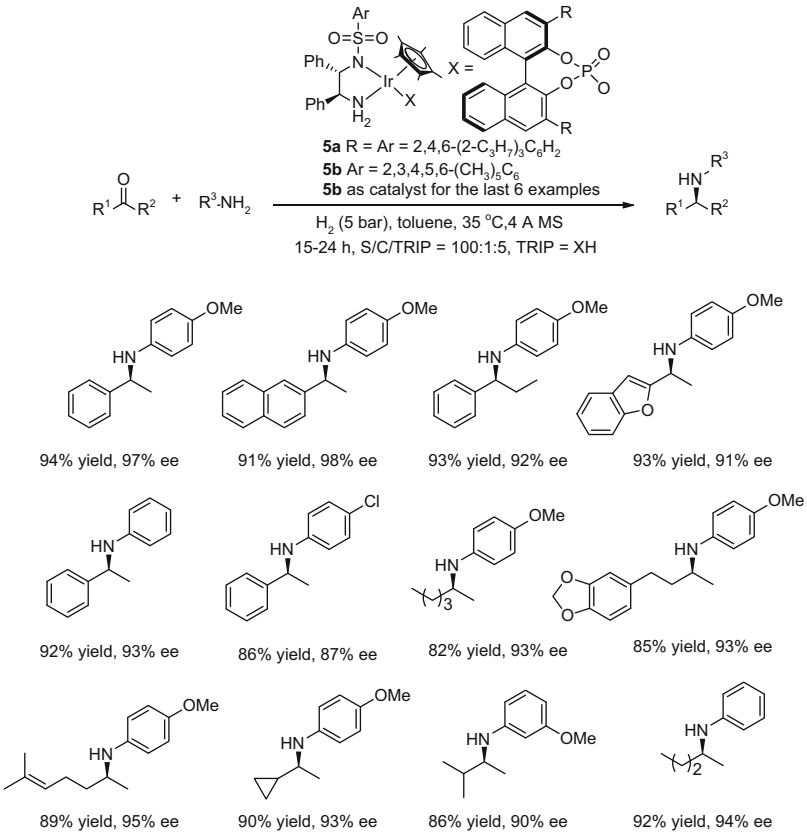
Table 2 Match/mismatch and anion structure effect on cooperative catalysis



Entry	Configuration	*R*	Conversion (%)	*ee* (%)
1	(*R*,*R*)	2,4,6-(2-C_3H_7)$_3C_6H_2$	47	38 (*R*)
2	(*S*,*S*)	2,4,6-(2-C_3H_7)$_3C_6H_2$	60	97 (*S*)
3	(*S*,*S*)	H	53	17 (*R*)
4	(*S*,*S*)	Ph	57	26 (*R*)
5	(*S*,*S*)	3,5-$(CF_3)_2C_6H_3$	40	20 (*S*)
6	(*S*,*S*)	1-Naphthyl	43	38 (*S*)

asymmetric hydrogenation of acyclic imines, which is a departure from the usual catalyst development paradigm [37]. This catalyst uses a chiral diamine ligand instead of the commonly used diphosphine ligand and bears a chiral anion, which has a significant influence on the stereo outcome of the hydrogenation. Drawing inspiration from studies in organocatalytic imino reduction with Hantzsch esters, a chiral iridium catalyst with a chiral phosphate was devised. The latter was expected to ion-pair with the iminium cation resulting from deprotonation of the Ir-H_2 intermediate and thereby affects the stereoselectivity of the Ir-H hydride (Scheme 5) [38].

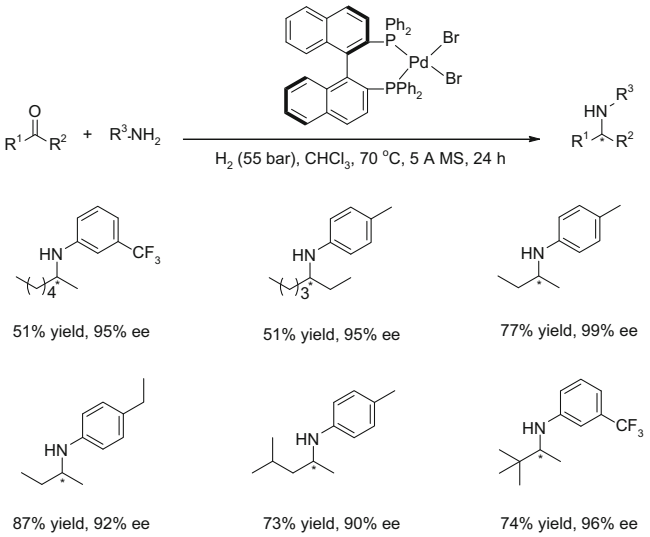
The strategy turned out to be successful. Good enantioselectivities required a match in chirality between the metal cation and its counteranion, however. The enantioselectivity increased from 38 (*R*) to 97% (*S*), when the configuration of the diamine ligand changed from *R*, *R* to *S*, *S* (Table 2, entry 1 vs 2). The substituents at the 3 and 3′ position of the phosphate also play an important role in the enantioselection. Without substitution or with a simple phenyl ring at the 3 and 3′ positions, poor *ee*s were obtained. Surprisingly, increasing the bulkiness of the substituent affords a product of not only higher *ee* but also opposite configuration (Table 2, entries 3 and 4 vs 2, 5, and 6). These results suggest that both the metal cation and its counteranion are involved in the enantioselectivity determining step [38].



Scheme 6 ARA of aryl and aliphatic ketones via cooperative catalysis

This catalytic system was very stereoselective in the hydrogenation of various imines at S/C of 100. A one-pot ARA was later developed based on this system with an even broader substrate scope, thanks to the obviation of isolation of imine intermediates [39]. With 1 mol% of catalyst **5a** and 5 mol% of the phosphoric acid, various ketones could be aminated with aromatic amines to afford chiral amines under 5 bar of hydrogen pressure at 35 °C (Scheme 6). Impressively, aliphatic ketones reacted well to give amines with high yields and enantioselectivities with **5b** as catalyst. This is the first ARA system to have such a broad substrate scope.

The metals used in asymmetric hydrogenative RA are usually ruthenium, rhodium, and iridium. In 2009, Rubio-Pérez and co-workers reported that a chiral palladium diphosphine complex catalyzes hydrogenative ARA [40]. Interestingly, the Pd-BINAP catalyst gave better results for aliphatic ketones than for aromatic ones. While less than 50% of *ee* was obtained for aromatic ketones, over 90% *ee* was observed for aliphatic ketones. The optimal results were obtained with 2.5% of catalyst under 55 bar hydrogen pressure at 70 °C in $CHCl_3$ in the presence of 5-Å molecular sieves (Scheme 7).



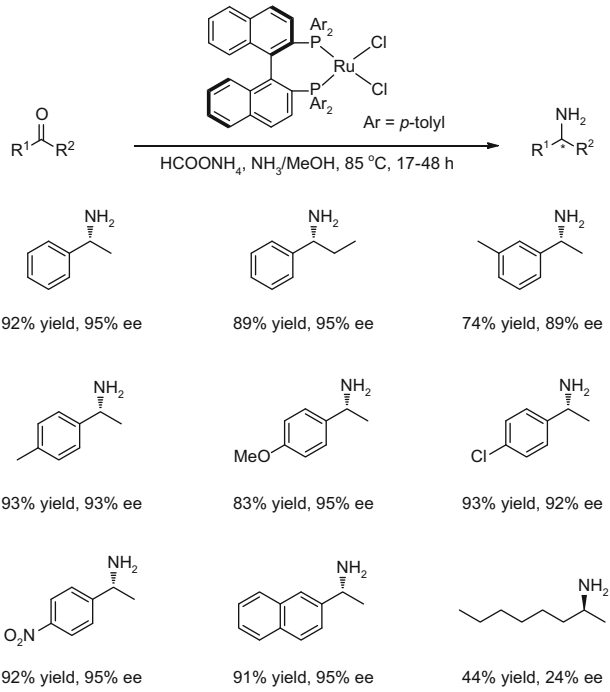
Scheme 7 Pd-BINAP complex catalyzed ARA

2.2 Metal Catalyzed Transfer Hydrogenation

Transfer hydrogenation, which uses hydrogen sources other than hydrogen gas, is an alternative way of reducing unsaturated bonds. The use of small organic molecules, such as alcohols, HCOOH, etc., as hydrogen sources avoids the use of hazardous hydrogen gas and high pressure apparatus. Due to its operational simplicity and versatility, metal catalyzed transfer hydrogen has attracted a great deal of attention and made substantial progress in recent years, particularly in the reduction of carbonyl groups [41–53]. However, the development of metal catalyzed transfer hydrogenation systems for reduction of C=N bonds lags behind that for carbonyl groups, and transfer hydrogenative RA reactions are even rarer. Only three examples of asymmetric transfer hydrogenative RA have been reported to date.

The first and only example of intermolecular asymmetric transfer hydrogenative RA was reported in 2003 by Kadyrov and co-workers [54]. After screening a series of Ru, Rh, and Ir catalysts, Ru catalysts with BINAP or tol-BINAP ligand gave the best enantioselectivities for the RA of acetophenone with ammonium formate in MeOH (Scheme 8). Addition of 15–20% of ammonia accelerated the reaction but decreased the enantioselectivity. A range of aromatic ketones could be aminated, affording excellent enantioselectivities. However, the reaction gave a mixture of free amine and its *N*-formylated product even under optimized conditions, although the free amine could be obtained by acidic hydrolysis of the reaction mixture. The catalyst was not good for aliphatic ketones, giving poor yields and enantioselectivities.

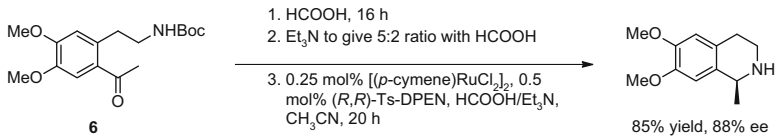
In the same year, Wills and co-workers reported the first intramolecular transfer hydrogenative ARA [55]. They applied the Noyori transfer hydrogenation system



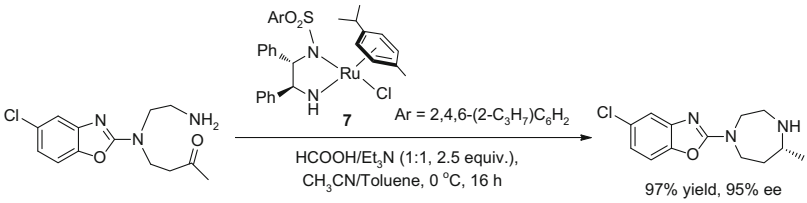
Scheme 8 Ru-tol-BINAP catalyzed transfer hydrogenative ARA

[56], which is highly effective for cyclic imine reduction, to the RA of substrates containing both a carbonyl and amino group, with the latter being Boc-protected. To perform the Ru catalyzed transfer hydrogenative RA, the Boc group had to be removed in pure formic acid first, and the reaction mixture was adjusted to be less acidic with Et_3N. Although many substrates afforded good conversions, enantioselectivity was observed only for one substrate. Compound **6** was converted to a chiral tetrahydroisoquinoline compound in 85% yield and 88% *ee* (Scheme 9). The authors believe that the configuration of the imine intermediate is crucial for the enantioselective step.

Strotman and co-workers carried out a detailed study of the Noyori's transfer hydrogenation system for the intramolecular RA of dialkyl ketones [57]. By using a sterically bulky ligand derived from DPEN, they achieved the first highly enantioselective intramolecular RA of dialkyl ketones. The carbon dioxide produced during decarboxylation of HCOOH was found to be detrimental to the reaction, decreasing the reaction rate by affecting the Ru hydride and Ru formate equilibrium and lowering the yield by forming carbamate with the product. Purging of the carbon dioxide in the system led to improved rate and isolated yield. Under optimized conditions, Suvorexant, a potent dual orexin antagonist, could be obtained with 97% yield and 95% *ee* (Scheme 10).



Scheme 9 Intramolecular transfer hydrogenative ARA



Scheme 10 Intramolecular transfer hydrogenative ARA of dialkyl ketone

3 Organocatalysis

Since 2000, organocatalysis has emerged as a powerful alternative to metal catalysis. Various organocatalytic asymmetric reduction systems have been developed, particularly for imine reduction. There are excellent reviews, which summarize the development of organocatalytic transfer hydrogenation reactions [19, 58]. In the following sections, ARA catalyzed by organocatalysts will be discussed.

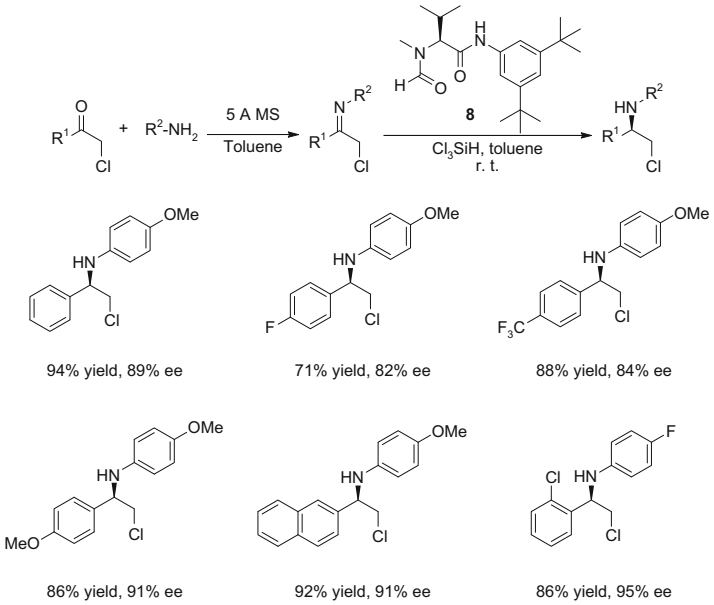
The hydrogen sources used in organocatalytic ARA are usually hydrosilanes or Hantzsch esters, which require Lewis base and phosphoric acid catalysts to activate them, respectively. Reactions with hydrosilanes as hydrogen source are presented first, followed by those using Hantzsch esters.

3.1 Hydrosilanes as Hydrogen Source

In organocatalytic ARA using hydrosilanes, the catalysts normally possess Lewis basic centers and hydrogen bond donors, with the former activating the silane reagents and the latter interacting with the imine intermediate.

The asymmetric reduction of isolated imines is simpler than ARA so the reduction of imines was studied earlier than that of ARA. In 2001, Matsumura and co-workers reported the first example of imine reduction with trichlorosilane. Using an *N*-formylpyrrolidine catalyst, good yields and moderate enantioselectivities were achieved [59]. Further development of this type of system for asymmetric imine reduction was undertaken by Malkov and Kočovský [60–62], Sun [63], Jones [64] and their co-workers.

In 2007, the first ARA with hydrosilanes catalyzed by chiral Lewis base catalysts was reported by Malkov, Kočovský, and co-workers [65]. α-Chloroketones were



Scheme 11 ARA of α-chloroketones

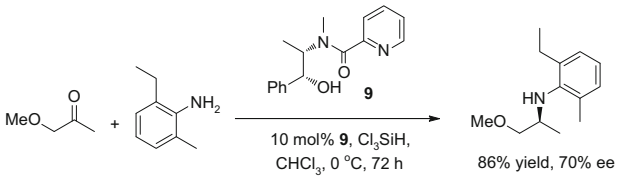
condensed with amines to form imines at RT for 24 h, which were subsequently reduced without isolation at 0 °C. With 5 mol% of **8**, a range of chiral α-chloroamines could be obtained in high enantioselectivities and yields, which could be further transformed into chiral aziridines (Scheme 11).

In more recent studies, Benaglia and co-workers screened a series of organocatalysts derived from chiral amino alcohols for imine reduction [66]. After identifying the best catalyst, one-pot RA was also examined and shown to work well. For example, methoxylacetone could react with an aromatic amine to form the key intermediate for Metolachlor in 86% yield and 70% *ee* (Scheme 12).

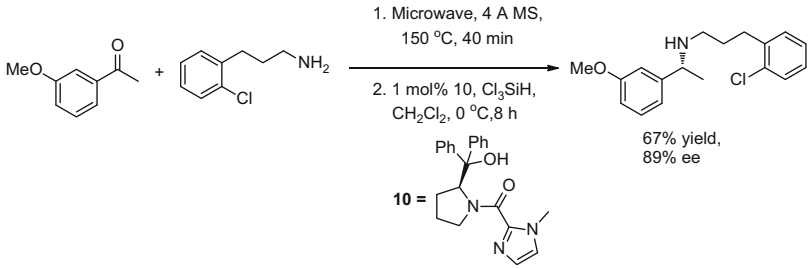
Further development along this line was made by Jones and co-workers. An imidazole-based organocatalyst **10** was found to catalyze the reduction of imines as well as ARA [67]. In the ARA reaction, yields were moderate and low in some cases, due to the slow formation of imine intermediates. Using a two-step-one-pot procedure, the imine formation was accelerated by microwave heating, leading to improved amine yields. The system was applied to the synthesis of a calcimimetic (*R*)-(+)-NPS R-568, affording it in 67% yield and 89% *ee* (Scheme 13).

3.2 Hantzsch Esters as Hydrogen Source

ARA with Hantzsch esters as hydrogen sources and chiral phosphoric acids as catalysts constitutes an important class of RA reactions. Hantzsch esters are mimics of nature's reducing agent – NADH, the hydride source used by enzymes for



Scheme 12 Organocatalytic ARA of an aliphatic ketone

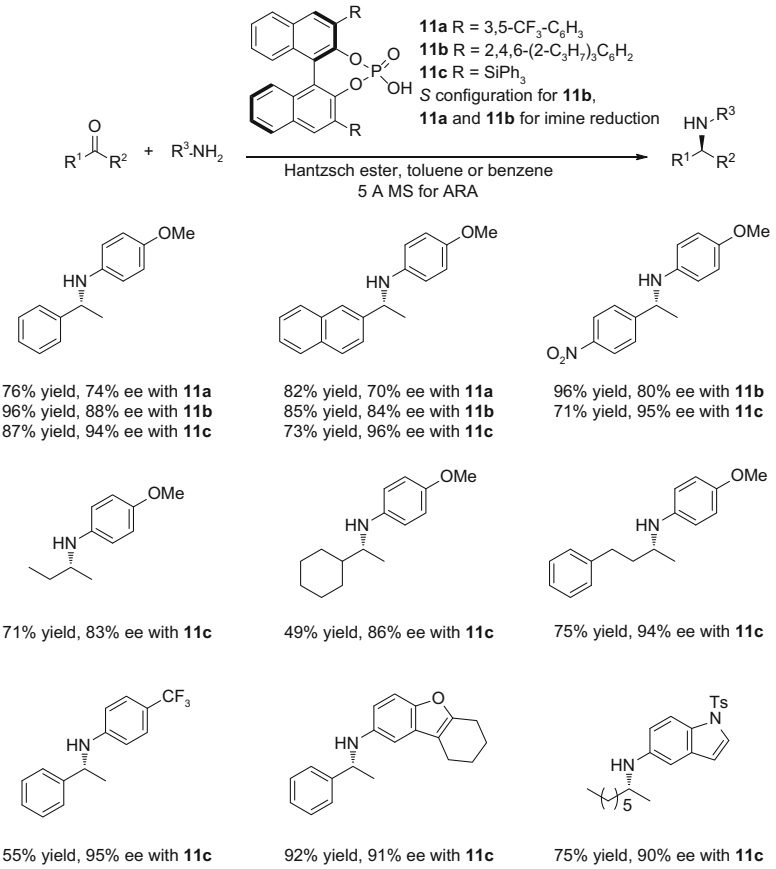


Scheme 13 Synthesis of (*R*)-(+)-NPS R-568

reduction reactions. In organocatalytic ARA with the chiral phosphoric acid/Hantzsch ester system, it is believed that the acid activates the imine intermediate through hydrogen bonding or protonation by the proton from the OH group. The Hantzsch ester is also activated through hydrogen bonding between its NH unit and the P=O group of the phosphoric acid. This model of activation is somewhat similar to the aforementioned chiral Lewis base/hydrosilane system.

Again, asymmetric imine reduction was first explored. Early in 1989, the first asymmetric organocatalytic reduction of imines using Hantzsch ester was reported [68]. However, no further development of this protocol was reported until 2005. Probably inspired by the emergence of the concept of organocatalysis, several papers on organocatalytic imine reduction and ARA with Hantzsch esters were reported nearly simultaneously from the groups of Rueping [69], List [70], and Macmillan [71].

Almost in parallel, Rueping [69] and List [70] and their co-workers reported the reduction of imines derived from aromatic ketones and aromatic amines. Chiral phosphoric acids, introduced into asymmetric reactions by Akiyama [72] and Terada [73], were used as catalysts with Hantzsch ester as the hydrogen source. In the List paper an example of one-pot RA was presented [70]. A comprehensive study by MacMillan and co-workers was then followed, disclosing the ARA of aromatic ketones with aromatic amines [71]. Interestingly, all three groups used similar chiral phosphoric acid (**11a**–**11c**) and the same hydrogen source (Scheme 14). From these three studies it is evident that increasing the bulkiness of the substituents on 3 and 3′ positions of the phosphoric acid improves the enantioselectivity. **11a** and **11b** were used for imine reduction, while **11c** was employed for ARA. The catalyst loading was 10 mol% for **11b** and **11c** and 20 mol% for **11a**, with the reduction run at 35, 60,

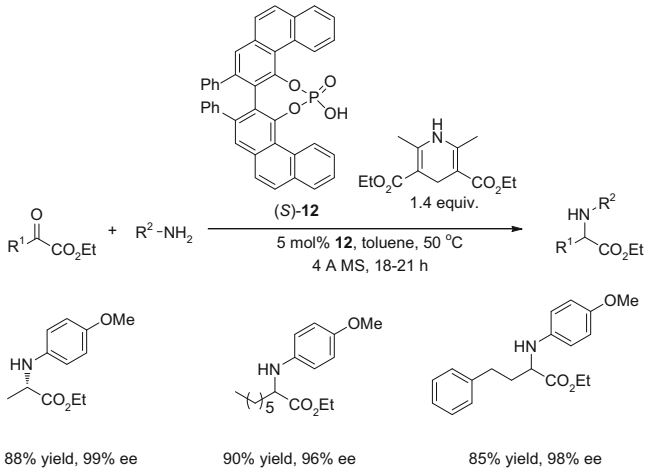


Scheme 14 Chiral phosphoric acids catalyzed imine reduction and ARA with Hantzsch ester as hydrogen source

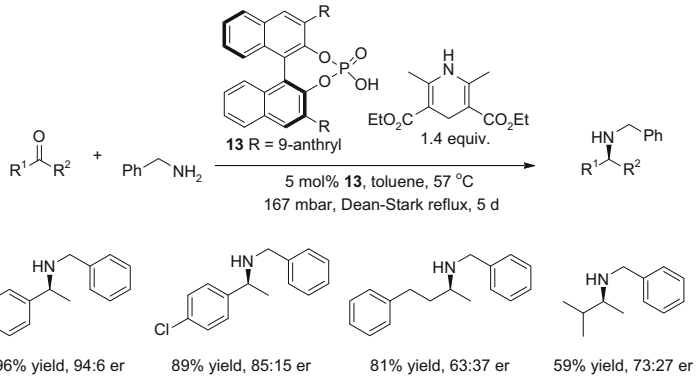
and 40 °C using **11a**, **11b**, and **11c**, respectively [69–71]. In the ARA catalyzed by **11c**, 5-Å molecular sieves were used to promote imine formation. A broad substrate scope was observed in the ARA catalyzed by **11c**, including aliphatic ketones and aromatic amines with different substituents. Examples are shown in Scheme 14 [69–71]. A single crystal X-ray structure of **11c**-bound aryl imine was obtained, shedding light on the origin of the enantioselectivity observed [71].

The scope of the ketone partner for the organocatalytic ARA was extended to α-keto esters. Antilla and co-workers reported the asymmetric reduction of imines derived from α-keto esters as well as their ARA using catalyst **12** [74]. The yields of ARA were generally 10–20% lower than imine reduction, but the *ee*s were identical. Scheme 15 shows examples of ARA.

The amine partners in the organocatalytic examples above are all aromatic ones. Aliphatic amines seem to be challenging substrates for ARA. Recently, List reported that benzylamine could be used for ARA reactions [75]. A low pressure



Scheme 15 Organocatalytic ARA of α-keto esters

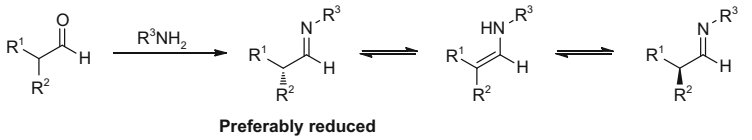


Scheme 16 Organocatalytic ARA of benzylamine

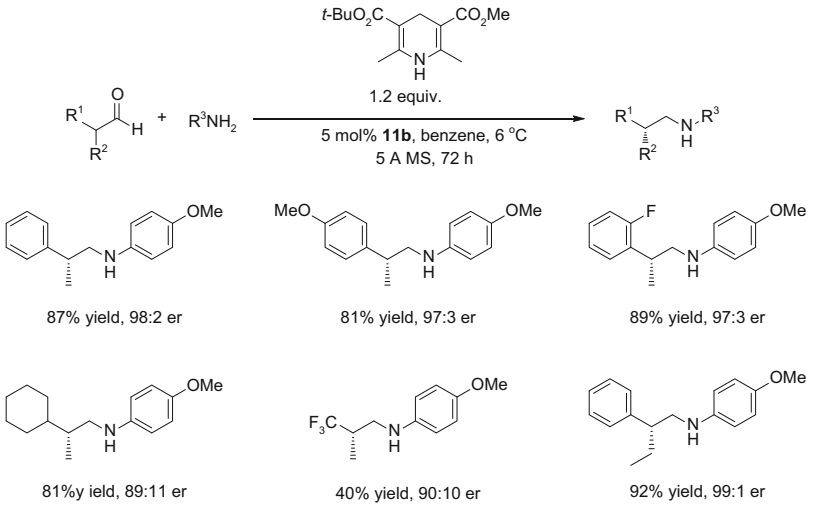
Dean-Stark trap was used to remove the water generated from the imine formation step. Aromatic ketones gave better *ee*s than aliphatic ones (Scheme 16).

Further application of the chiral phosphoric acid/Hantzsch ester system was explored by List and co-workers. α-Branched aldehydes were reductively aminated to afford chiral β-branched chiral amines via a dynamic kinetic resolution process (Scheme 17) [76]. In this case, **11b** turned out to be the best catalyst, and it was necessary to modify the structure of Hantzsch ester to ensure high enantioselectivity. Selected examples are presented in Scheme 18.

Another elegant application coming from the List group involves an aldolization-dehydration-conjugate reduction-reductive amination cascade process catalyzed by a single chiral phosphoric acid [77]. Starting from diketones, chiral cyclic amines could be obtained with good yields and high diastereo- and enantioselectivities



Scheme 17 ARA of α-branched aldehydes via dynamic kinetic resolution

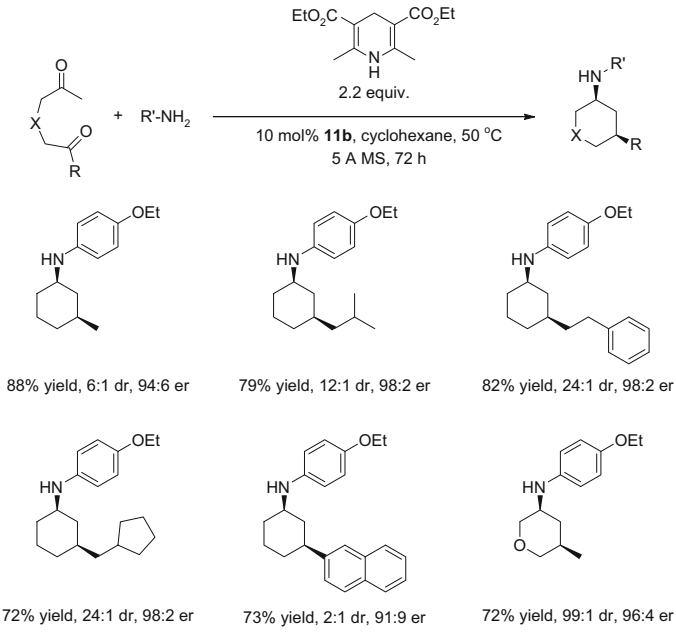


Scheme 18 Selected examples of ARA of α-branched aldehydes

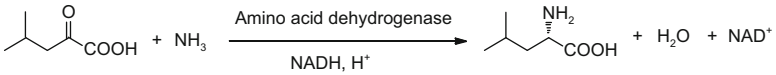
(Scheme 19). Their best catalyst **11b** (TRIP) was again employed. Other development of the chiral phosphoric acid-catalyzed imine reduction or ARA includes modification of the structure of chiral acids [78] or exploration of hydrogen sources of properties similar to Hantzsch esters [79].

4 Biocatalysis

Biocatalysis is an important complement to chemical catalysis for chiral amine synthesis, as it often gives products that are difficult to access by chemical means. Many reviews have appeared, summarizing the progress in biocatalytic reduction to access chiral amines [80–86]. In the following sections, selected examples of ARA from ketones and amines catalyzed by enzymes are presented. Reactions that involve kinetic resolution as well as dynamic kinetic resolution will not be covered here. There are two main types of enzymes that have been used to transform carbonyl groups into amino groups – amino acid dehydrogenases and transaminases.



Scheme 19 TRIP-catalyzed cascade amination

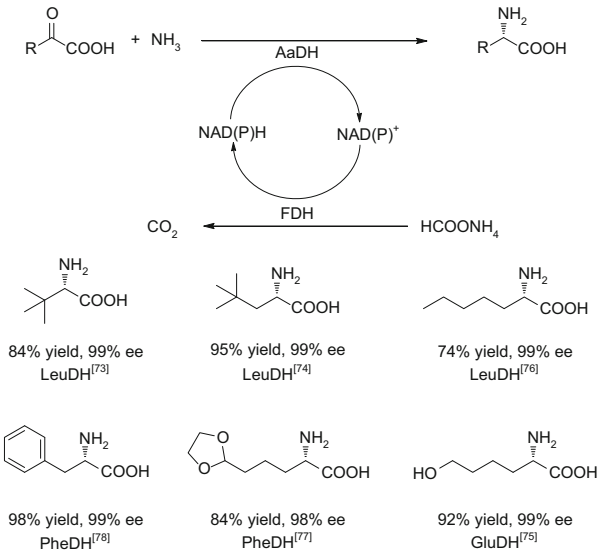


Scheme 20 Reductive amination catalyzed by amino acid dehydrogenase

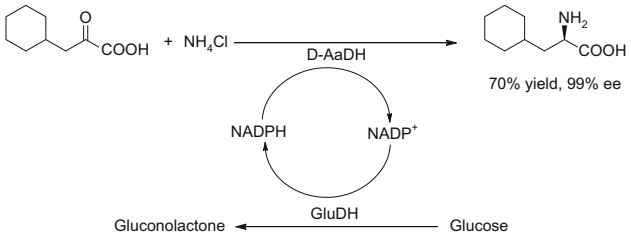
4.1 ARA with Amino Acid Dehydrogenases

Amino acid dehydrogenases can catalyze the amination of carbonyl compounds, usually α-keto acids/esters, with NADH as the hydrogen source. As early as in 1961, an example of RA catalyzed by an amino acid dehydrogenase (AaDH) to produce a chiral amino acid was reported (Scheme 20) [87].

The biocatalytic ARA with NAD(P)H as hydrogen source can be practically useful only if NAD(P)H is regenerated. The NAD(P)H regeneration system has thus been developed and used together with AaDH to effect ARA of keto acids with ammonium as amine source. The NAD(P)H regeneration system normally uses enzymes, e.g., formate dehydrogenase (FDH) or glucose dehydrogenase (GluDH), which convert $NAD(P)^+$ to NAD(P)H with small molecule hydrogen sources, e.g., ammonium formate or glucose. Large scale productions of amino acids have been possible with these systems. Some examples of biocatalytic ARA using AaDH coupled with FDH are found in Scheme 21 [88–93].



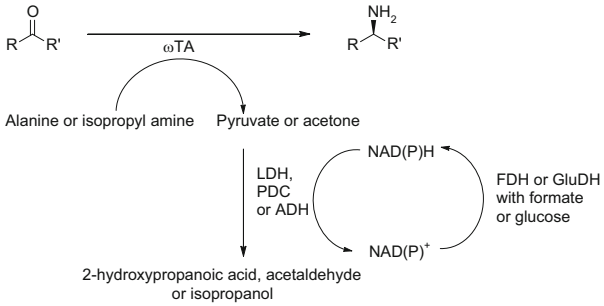
Scheme 21 Examples of biocatalytic ARA



Scheme 22 Production of D-amino acid with engineered enzyme on a gram scale

Most AaDHs are natural enzymes, which only selectively produce L-amino acids. In order to obtain D-enantiomers or unnatural amino acids, the enzymes have to be engineered. In 2006, Novick and co-workers reported the first D-amino acid dehydrogenase by directed evolution of an existing enzyme [94]. The engineered enzyme was capable of producing D-amino acids via ARA of keto acids with ammonia. For example, D-cyclohexylaniline was produced on a gram scale using the engineered enzyme coupled with a NADPH regeneration system (Scheme 22).

In the examples described above, isolated enzymes and NAD(P)H were employed. However, whole cell catalysts for ARA of α-keto acids are known [95], and further development in the direction has been reported [91, 96].



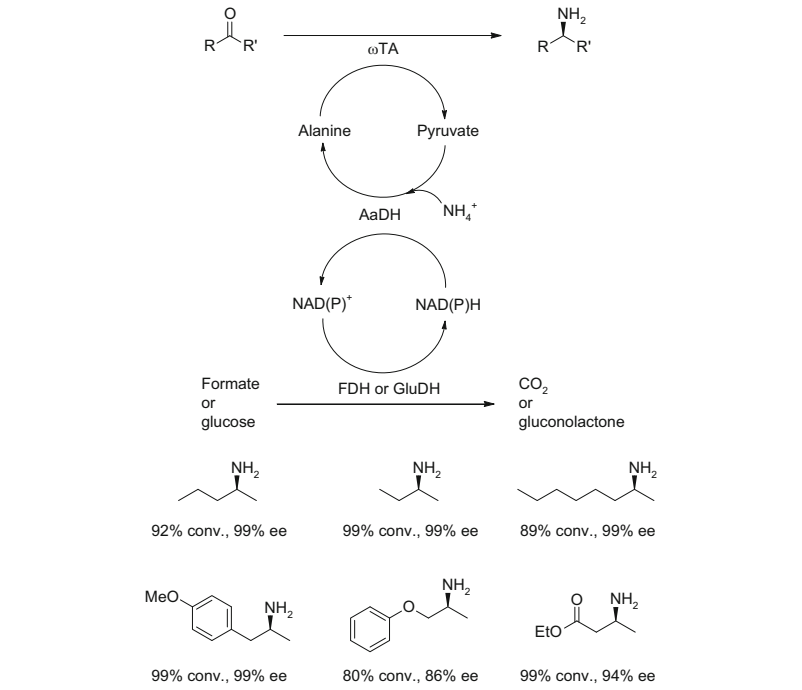
Scheme 23 ω-Transaminases catalyzed ARA

4.2 ARA with ω-Transaminases

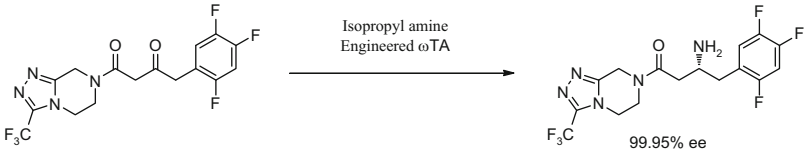
The major drawback of AaDHs is that they can only catalyse the ARA of α-keto acids to produce α-amino acids. This limitation was overcome by the use of ω-transaminases (ωTAs). ωTAs catalyze the transfer of amino group from cosubstrates to carbonyl compounds to form new chiral amines. A problem faced by ωTAs for practical applications is that new carbonyl compounds are generated after transferring amino groups from the amine source, and the newly formed carbonyl compounds would compete with the carbonyl substrates for transamination. It is thus crucial to remove the co-produced carbonyls in order for the desired reaction to go to completion. Alanine and isopropyl amine are the two most often used amine sources. The by-product from alanine is pyruvate, which could be removed from the system using pyruvate dehydrogenase or pyruvate decarboxylase (Scheme 23) [97, 98]. In addition, the acetone produced from isopropyl amine could be removed by distillation or selective alcohol dehydrogenase [99, 100]. During the by-product removal process, NAD(P)H is used as the co-factor for the enzymes, which can be recycled with the previously described regeneration systems using FDH or GluDH.

An elegant multiple enzymes cascade system was designed by Kroutil and co-workers in 2008 [101]. Rather than removing pyruvate generated from transamination of alanine, an amino acid dehydrogenase was employed to regenerate alanine from pyruvate via another RA using ammonia as the amine source. Thus, the true amine source is ammonia in this case. The strategy allows for a wide range of ketones to be transformed into chiral amines with high enantioselectivities (Scheme 24).

The substrate scope of ω-transaminases catalyzed ARA has been broadened by engineering the enzymes. For example, by a combination of in silico design and directed evolution of ω-transaminase, Savil, Janey, and co-workers developed an enzymatic system showing different substrate tolerance from natural enzymes. The utility of the enzyme has been demonstrated in the manufacture of the important pharmaceutical product, Sitagliptin, with high enantioselectivity (Scheme 25) [102, 103].



Scheme 24 Ammonia as amine source in ω-transaminases catalyzed ARA



Scheme 25 Manufacture of Sitagliptin with engineered ω-transaminase

5 Summary and Outlook

Recent progress in the area of ARA has been summarized. From the examples shown, we can see that apart from the traditional metal catalyzed ARA, organocatalytic and biocatalytic methods have emerged as powerful alternatives. In metal catalyzed ARA, transfer hydrogenation with isopropyl or formic acid as hydrogen source still lags behind hydrogenation with hydrogen gas in terms of substrate scope, catalyst activity, and productivity. New transfer hydrogenation systems may provide opportunities to enable more efficient transfer hydrogenative ARA. Organocatalytic ARA requires improvement in activity and productivity before practical use is possible. Large scale applications of ARA have been seen in biocatalysis. Its limitation in substrate scope may be tackled by enzyme engineering.

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