**Progress in Asymmetric Biomimetic Transamination of Carbonyl Compounds**

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Progress in Asymmetric Biomimetic Transamination of Carbonyl Compounds

Ying Xie, Hongjie Pan, Mao Liu, Xiao Xiao and Yian Shi

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Transamination of α-keto acids with transaminases and pyridoxamine phosphate is an important process to form optically active α-amino acids in biological systems. Various biomimetic transamination systems have been developed for carbonyl compounds including α-keto acid derivatives, fluoroalkyl ketones, and unactivated ketones with chiral vitamin B\textsubscript{6} analogues, artificial transaminase mimics, chiral nitrogen sources, and chiral catalysts. This review describes a brief summary in this area.

Key learning points
(1) Introduction of biological transamination of α-keto acids.
(2) Design of chiral pyridoxamine analogues and artificial transaminase mimics.
(3) Development of catalytic asymmetric transamination of carbonyl compounds.

1. Introduction
Optically active amino acids and their derivatives play a very important role in biological systems and chemical synthesis. Transamination of α-keto acids is an important biological process to generate α-amino acids (Scheme 1).

Pyridoxamine 5’-phosphate (PMP) and pyridoxal 5’-phosphate (PLP) belong to the vitamin B\textsubscript{6} family (Scheme 2) and function as co-enzymes for the transamination in biological systems. A variety of chiral pyridoxamine analogues have been synthesized and investigated for the asymmetric biomimetic transamination.

2. Vitamin B\textsubscript{6} Analogues
Pyridoxamine 5’-phosphate (PMP) and pyridoxal 5’-phosphate (PLP) belong to the vitamin B\textsubscript{6} family (Scheme 2) and function as co-enzymes for the transamination in biological systems. A variety of chiral pyridoxamine analogues have been synthesized and investigated for the asymmetric biomimetic transamination.
Scheme 2. Members of the vitamin B₆ family

For example, in 1978, Kuzuhara and coworkers reported their studies on transamination of α-keto acids with chiral “ansa chain” based pyridoxamine analogue 10 (Scheme 3). Phenylalanine was obtained in 55-83% yield and 6-26% ee when the sodium salt of phenylpyruvic acid was treated with 10 in the presence of Zn²⁺ at room temperature. Further studies showed that higher ee was obtained with 11 than 10. The molar ratio of Zn²⁺/10 or 11 was important for the enantioselectivity. A number of amino acids were obtained in 60-96% ee when the reactions were carried out with sodium salts of α-keto acids (2 equiv), pyridoxamine analogue 11 (1 equiv), and Zn(ClO₄)₂·6H₂O (0.5 equiv) in MeOH at room temperature. In all cases, the corresponding aldehyde of 11 can be isolated in 75-85% yield.

Scheme 3. Transamination of α-keto acids

Breslow and coworkers investigated a series of chiral pyridoxamine analogues containing basic side chains such as 12, 13, 14, 15, and 16 for the transamination of α-keto acids (Scheme 4). Up to 92% ee was obtained for α-amino acids when the reaction was carried out with α-keto acids and bicyclic compound 13 in the presence of Zn(OAc)₂ in MeOH (pH = 4.0) at 30 °C. The high enantioselectivity obtained with 13 can be attributed to the rigidity of the basic side arm, which allows the proton transfer to occur predominately from one face (Scheme 5). Significant rate acceleration was also observed for the transamination as compared to pyridoxamine analogue without the basic group in the side chain. 13-15

Scheme 4. Chiral pyridoxamine analogues with basic side chains

Scheme 5. Enantioselective deprotonation and protonation

3. Artificial Transaminase Mimics

Transamination with a pyridoxamine linked to β-cyclodextrin (18) was reported by Breslow and coworkers in 1980 (Scheme 6). A 200-fold rate acceleration was observed with 18 as compared to pyridoxamine itself for the conversion of indolepyruvic acid to tryptophan. A 5:1 ratio of L-Phe to D-Phe was obtained for the transamination of phenylpyruvic acid with 18. In 1985, Tabushi and coworkers showed that β-cyclodextrin-pyridoxamine-ethylenediamine 19 was highly effective for the transamination, giving L-phenylalanine, L-tryptophan, and L-phenylglycine in 90-96% ee (Scheme 6). 19,20

Scheme 6. β-Cyclodextrin-pyridoxamines

Breslow and coworkers also investigated the asymmetric transamination with pyridoxamine analogues bound to chiral dendrimers 21,22 and polymers (Scheme 7). For example, up to 66% ee was obtained for L-Val at the initial stage of the reaction with pyridoxamine 20 bound to chiral PEI 21 via hydrophobic interactions in 40% aqueous methanol at pH 7.3-7.8. Racemization of the amino acid was observed under the reaction conditions. With covalently bound chiral polymer-pyridoxamine 22, L-phenylalanine was obtained in 58% ee from phenylpyruvic acid. Little racemization of the amino acid occurred with this system. In 2004, Nicholls and coworkers reported that a transition state analogue-imprinted polymer could act as a transaminase mimic, giving phenylalanine in 32% ee. 24
Murakami and coworkers reported the asymmetric transamination with supramolecular bilayer membrane based artificial aminotransferase. For example, up to 92% ee was obtained for D-alanine when the reaction was carried out with pyruvate (5 equiv), L-Phe (5 equiv), peptide lipid (1 equiv), hydrophobic pyridoxal analogue (0.05 equiv), and Cu(ClO$_4$)$_2$ (0.05 equiv) in aqueous 2-(2-hydroxyethyl)ethanesulfonic acid (HEPES) buffer (pH 7.0) at 30 °C (Scheme 8). L-Phenylalanine not only acted as the nitrogen source for the conversion of pyruvate to D-alanine, but also played an important role in the enantioselectivity as a chiral ligand for the Cu(II) complex (Scheme 9). Distefano and coworkers illustrated that high enantioselectivity (up to 94% ee) can be achieved for the transamination with protein pyridoxamine conjugates linked via disulfide bond.

In 2002, Berg and coworkers showed that ketimines derived from α-keto esters and 9-aminothioxanthene 10,10-dioxide, were efficiently isomerized to ketimines in up to 45% ee with 5 mol% chiral guanidine catalyst (Scheme 11). Studies suggest that the reaction may proceed via a stepwise, bifunctional mechanism, which provides valuable insight for the development of more effective systems.

In 2003, Jørgensen and coworkers reported that asymmetric transamination was realized with chiral Lewis acids via in situ formation of the ketimine. Methyl-3-indole pyruvate (31) was converted into amino ester in 37% and 46% ee, respectively, with catalysts 34 and 35 using 4-picolylamine (32) as amine donor (Scheme 12). The pyridine of 32 was found to be important for the reactivity as benzylamine was shown to be ineffective for the reaction. The solvent had significant impact on the enantioselectivity, with MeNO$_2$ being the best.

4. Catalytic Asymmetric Transamination

In 1983, Bernauer and coworkers reported that optically active phenylalanine was formed from phenylpyruvic acid with pyridoxamine and a chiral Cu(II) catalyst (Scheme 10). The Cu(II) catalyst promoted the ketimine-aldimine isomerization and induced the chirality for the reaction. It was found that the enantioselectivity decreased as the reaction proceeded likely due to in situ racemization of aldimine complex 27. The ee was estimated to be 80% ee at the beginning of the reaction.
In 2011, Shi and coworkers reported an effective chiral base-catalyzed transamination of α-keto esters. Various chiral bases were examined with ethyl 2-oxo-4-phenylbutanoate (36) as substrate and o-CIPhCH$_2$NH$_2$ (37) as nitrogen source (Scheme 13). Up to 69% ee was obtained with quinine derived catalyst 45. Studies showed that the enantioselectivity was increased with a bigger ester group. For example, 92% ee was obtained with α-keto ester 47 using o-CIPhCH$_2$NH$_2$ (37) (Scheme 14). The enantioselectivity was found to be highly dependant on the structures of amine donors, with o-CIPhCH$_2$NH$_2$ (37) being the best in terms of both reactivity and enantioselectivity (Scheme 14). The transamination reaction with 45 and 37 was extended to a wide variety of α-keto esters, giving the corresponding α-amino esters in 88-92% ee (Scheme 15).

The 6′-OH in catalyst 45 played a very important role in the transamination for both reactivity and enantioselectivity, likely via a H-bond with the imine to facilitate the reaction and influence the enantioselectivity. To further understand the effect of the H-bonding, catalysts with different H-bond donors at the 6′ position were investigated for the transamination. A quinine derivative containing 2,4,6-triethylbenzenesulfonamide (61) was found to be a highly effective catalyst (Scheme 16). A wide variety of α-amino esters were obtained from more readily available t-Bu keto esters in 61-93% yield and 90-94% ee with 61 and 37 in benzene at 50 °C. The transamination was amenable to gram scale. With a related catalyst 64, various β-branched α-keto esters were transaminated to the corresponding amino esters in 50-96% yield and 87-95% ee with 4-CNPbCH$_2$NH$_2$ (53) as nitrogen source (Scheme 17). The 4-CN group of the benzylamine likely enhanced the acidity of the ketimine and facilitated the proton transfer.
Scheme 16. Asymmetric transamination of α-keto esters

Scheme 17. Asymmetric transamination of β-branched α-keto esters

The ketimine can adopt two possible (trans and cis) configurations for the base catalyzed proton shift (Scheme 18). The relative content of the trans and cis configurations is likely dependant on the relative size of the side chain and the ester group of the keto ester. Two possible transition states for each configuration are outlined in Scheme 19. The (R)-amino ester is formed predominately via transition state A and/or C. The (S)-enantiomer is disfavored likely due to the steric interaction between the ester group of the substrate and the catalyst in transition state B and D. The enantioselectivity appears to be more influenced by the size of the ester group than the side chain, thus providing a broad scope for the keto ester substrate (Schemes 15-17).

Scheme 18. The trans and cis configurations of the ketimine

Scheme 19. Proposed transition state model for transamination

The extent of the involvement for each transition state likely depends on the structure of the keto ester. To further probe this issue, the transamination of keto ester 47 was carried out with catalyst 61 and optically active deuterated α-chlorobenzylamine (Scheme 20). It appears that the proton shift from the ketimine to the aldime predominately proceeded via transition state A in this case, based on the yield and ee of the amino ester (48a & 48b) as well as the deuterium content of the amino ester and α-chlorobenzaldehyde.

Scheme 20. Transamination with optically active deuterated benzylamines

5. Transamination of Fluoroalkyl Ketones

Optically active fluoroalkyl amines are very important...
functional moieties in various biologically and medicinally important molecules. Efforts have been made in the synthesis of fluoroalkyl amines from fluoroalkyl ketones via transamination using either chiral amine sources or chiral catalysts. In 1997, Soloshonok and coworkers showed that ketimines 65, prepared by the direct condensation of the corresponding fluoroalkyl ketones and (S)-α-phenylethylamine, were stereoselectively isomerized to ketimines 66 in up to 97% ee with DBU (Scheme 21). The use of DBU as both base and solvent was found to be crucial for the reaction. The isomerization process was used for the synthesis of optically active β-fluoroalkyl-β-amino acids. For example, 96% ee was obtained for aldimine 69 from the isomerization of 68 with DBU (Scheme 22). Yuan and coworkers reported that 1-amino-2,2,2-trifluoroethanephosphonic acid was synthesized from ketimine 71 via a base-catalyzed transamination and subsequent hydrolysis (Scheme 23).

In 1994, Soloshonok and coworkers reported that β-fluoroalkyl-β-amino acids were obtained with up to 36% ee via chiral base-catalyzed isomerization of enamines under solvent-free conditions (Scheme 24). In 2007, Plaquevent and coworkers showed that trifluoromethyl enamines such as 78 were isomerized to the corresponding aldimines in up to 71% ee with dimeric cinchona alkaloid (DHQ)2PHAL (Scheme 25).

In 2012, Deng and coworkers reported the asymmetric isomerization of trifluoromethyl ketimines (85) derived from trifluoromethyl ketone and 4-NO2PhCH2NH2 (Scheme 27). The corresponding trifluoromethyl aldimines containing aryl or alkyl groups were obtained in up to 94% ee with cinchona alkaloid derivative 87 as catalyst, and they were hydrolyzed to trifluoromethyl amines in high yields.
In their studies, Shi and coworkers showed that trifluoromethyl ketimines \(^{88}\) were readily converted to aldmines \(^{89}\) with catalyst \(^{90}\) in up to 99% yield and up to 94% ee (Scheme 28).\(^{46}\) As illustrated in Scheme 29, trifluoromethyl amine \(^{93}\) was prepared from the corresponding ketone \(^{91}\) in 81% overall yield via condensation of \(^{91}\) with 2-Cl-4-CNPhCH\(_2\)NH\(_2\) \(^{92}\), asymmetric proton shift, and subsequent hydrolysis. The Pd-catalyzed cyclization of amine \(^{93}\) gave optically active tetrahydroquinoline \(^{94}\) in 91% yield. The asymmetric isomerization of ketimine \(^{88}\) to aldmine \(^{89}\) was proposed to predominately proceeded via transition state E, favoring the (R)-enantiomer (Scheme 30).

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\text{Scheme 27. Chiral base-catalyzed isomerization of trifluoromethyl ketimines}
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\[
\text{Scheme 28. Chiral base-catalyzed isomerization of trifluoromethyl ketimines}
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\text{Scheme 29. Asymmetric transamination of trifluoromethyl ketone and cyclization}
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\text{Scheme 30. The proposed transition state model for transamination}
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\text{6. Transamination of Unactivated Ketones}
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Significant progress has been made for the asymmetric transamination of \(\alpha\)-keto esters and fluoroalkyl ketones. In these ketones, the electron-withdrawing ester and fluoroalkyl groups greatly facilitate the reactions. The transamination for ketones without these electron-withdrawing groups still remains challenging. Efforts have also been made in this area.

In 1995, Zwanenburg and coworkers reported the chiral base-catalyzed isomerization of ketimines to the corresponding aldmines.\(^{47}\) With aminoalcohol derived chiral base \(^{98}\), aldmine \(^{96}\) was obtained from ketimine \(^{95}\) in up to 44% ee (Scheme 31).

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\text{Scheme 31. Chiral base-catalyzed isomerization of ketimine}
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\text{In 2012, Shi and coworkers showed that aromatic ketones \(^{99}\) can be transaminated to the corresponding amines \(^{101}\) in 70-85% ee with quinine-derived base \(^{102}\) as catalyst and \(\alpha\)-HOPhCH\(_2\)NH\(_2\) \(^{100}\) as nitrogen source in toluene at 110 °C (Scheme 32).\(^{48}\) Under similar reaction conditions, \(\alpha\)-amino acetals were obtained from \(\alpha\)-keto acetals in 82-86% ee (Scheme 33).\(^{49}\) \(\alpha\)-HOPhCH\(_2\)NH\(_2\) was found to be crucial for the reaction. The \(\alpha\)-OH group of the benzylamine likely formed a H-bond with the imine and facilitated the transamination.\(^{48,50}\)}

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\text{Scheme 32. Asymmetric transamination of aromatic ketone}
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\text{Scheme 33. Asymmetric transamination of \(\alpha\)-keto acetal}
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particularly useful if a simple ketone can be efficiently transaminated to an optically active amine under mild conditions. We hope that this review would stimulate new ideas in this area.

Conclusions

Optically active α-amino acids can be efficiently generated from α-keto acids via transamination with vitamin B₆ dependant transaminases in biological systems. Biomimetic asymmetric transamination of carbonyl compounds provides an attractive approach to optically active amine derivatives and has received considerable attention. Great progress has been made in the last few decades. Earlier studies focused on the development of chiral vitamin B₆ analogues and artificial transaminase mimics. High enantioselectivity has been achieved in some cases. In recent years, highly enantioselective transamination processes have been developed for α-keto acid derivatives and fluoroalkyl ketones with chiral catalysts particularly chiral bases. Some mechanistic understanding of the enantioselectivity has also been gained. Asymmetric transamination for ketones without electron-withdrawing ester or fluoroalkyl groups has also been shown to be feasible. It can be expected that more effective transamination systems will emerge with further understanding of the reaction mechanism and development of new catalysts. It would be particularly useful if a simple ketone can be efficiently transaminated to an optically active amine under mild conditions. We hope that this review would stimulate new ideas in this area.

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Notes and references

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