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Catalytic Asymmetric Synthesis of C$^{\alpha}$-tetrasubstituted α-Amino Acids

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The ever-increasing demand for better life requires the development of more effective drugs to cope with diseases and to prolong the life span. Today, the creation of new drugs is not only by high-throughput screenings, but also by rational design. It is now believed that the screening of synthetic libraries that derived from various types of privileged scaffolds, rather than commercial ones, is more promising to discover new small molecule drugs [1]. Therefore, in recent years, the need for efficient and diverse synthesis of optically active compounds with privileged scaffolds stimulated the catalytic asymmetric synthesis of 3,3-disubstituted oxindoles [2], trifluoromethylated compounds [3] and difluoroalkylated compounds [4].

C$^{\alpha}$-tetrasubstituted α-amino acids represent a type of privileged structural motifs widely occurred in drugs and pharmaceutically active compounds [5]. Some quaternary α-amino acids are drugs. For example, α-difluoromethylornithine (Eflornithine), is a drug for the treatment of facial hirsutism and sleeping sickness [6], and L-α-methyl-3,4-dihydroxyphenylalanine (Aldomet), is used as a sympatholytic or antihypertensive [7]. In addition, a variety of drugs such as AG-041R and LFA-1 antagonist contain C$^{\alpha}$-tetrasubstituted α-amino acid moieties [8,9]. In biomimetic research, the incorporation of conformational constrained C$^{\alpha}$-tetrasubstituted α-amino acids into peptides may bring about beneficial physiological effects, which has played an important role in the design of peptides with enhanced properties [10]. Accordingly, the catalytic asymmetric synthesis of quaternary α-amino acids constitutes a very active research in the modern asymmetric catalysis. The past decade have witnessed much progress in this field, with four effective strategies have been developed (Figure 1).

The first strategy is Strecker reaction (path a), namely the catalytic asymmetric addition of a cyanide to ketimine **I**, either by metal catalysis or by organocatalysis [11]. The widely used cyanide sources include trimethylsilyl cyanide (TMSCN), NaCN, KCN, MeCOCN and $NCCO_2Et$. Depending on the structure of the ketimines, this strategy is able to prepare acyclic or cyclic quaternary α-amino acids, together with those cyclic ones featuring the nitrogen atom in the cyclic system. The new trend is to employ this strategy to construct special type of quaternary α-amino acids integrating special structures of wide interests. For example, highly enantioselective Strecker reaction of oxindole based ketimines and α-difluoromethyl or trifluoromethyl ketimines was recently disclosed by our group [12,13].

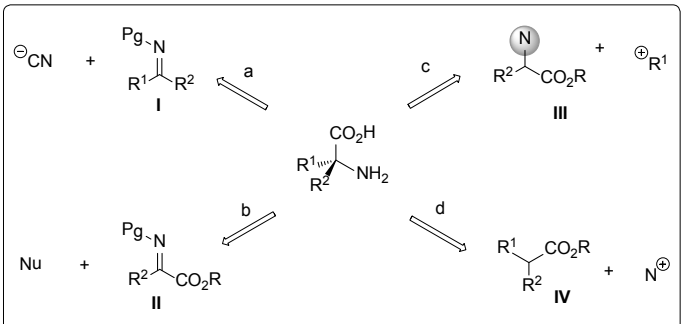

Figure 1: Catalytic asymmetric strategies to C$^{\alpha}$-tetrasubstituted α-amino acids.

The catalytic asymmetric addition of nucleophiles to ketimines **I** **II** derived from α-keto esters is an attractive strategy and potentially very useful (path b), although less explored as compared with the Strecker reaction, as the electron-withdrawing ester group increases the electrophilicity of the corresponding ketimines. This strategy is also viable for the synthesis of cyclic quaternary α-amino acids with the nitrogen atom embedded in the cyclic system. An excellent example to elucidate the usefulness of this strategy is the first highly enantioselective aza-Morita-Baylis-Hillman reaction using ketimines II achieved by Yao et al. [14].

The catalytic asymmetric allylation and arylation of α-nitrogen substituted esters by various types of electrophilies such as halides, aldehydes, imines and electro-deficient olefins is a versatile method to synthesize C$^{\alpha}$-tetrasubstituted α-amino acids, including acyclic or cyclic ones (path c). α-mono substituted glycine derivatives [15], oxazolones [16] and α-monosubstituted α-nitroacetates recently emerged as a useful synthon for reaction design. Our group reported the first catalytic asymmetric amination and hydroxylation of α-monosubstituted α-nitroacetates [17,18].

The direct catalytic enantioselective amination of α,α-disubstituted carbonyl compounds is also a powerful strategy worthwhile to explore (path d). The popular amination reagents include diazocarboxylates and nitrosobenzene. α,α-Disubstituted aldehydes and highly reactive α-alkyl or aryl α-cyanoacetates have been examined in this type of reactions [19,20].

With these four distinct strategies, a variety of enantioselective protocols for the catalytic synthesis of C$^{\alpha}$-tetrasubstituted α-amino acids have been developed in the past decade. However, due to the challenge in the construction of tetrasubstituted carbon stereogenic centers, there still have much room for further improvement in terms of substrate cope, catalyst loading, enantioselectivity and practicability. As the importance of enantiopure C$^{\alpha}$-tetrasubstituted α-amino acids is never overstated, one can expect that exciting results in this field will come out with the development of new synthetic methodologies and new powerful chiral catalyst systems, the use of cost-effective, environmental benign reagents and reaction conditions, together with the synthesis of C$^{\alpha}$-tetrasubstituted α-amino acids via tandem reactions in a biomimetic fashion from simple starting maters.

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