Catalytic Asymmetric Synthesis of Cα-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].

Cα-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 for the treatment of facial hirsutism and sleeping sickness [6]. 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].

The catalytic asymmetric addition of nucleophiles to ketimines I 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 electrophiles such as halides, aldehydes, imines and electro-deficient olefins is a versatile method to synthesize Cα-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 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 NCCO2Et. 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 on oxindole based ketimines and α-difluoromethyl or trifluoromethyl ketimines was recently disclosed by our group [12,13].

![Figure 1: Catalytic asymmetric strategies to Cα-tetrasubstituted α-amino acids.](image)

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