1.2.3. Chemical Biology Applications

The recent literature by the top scientists, such as Jeffrey Daye and Jason Chin at the Centre of Chemical & Synthetic Biology at the University of Cambridge in the example cited point to the sensitive fact that the utilization of unnatural amino acids as biologic therapy is growing17. This condition enables protein structure and action to be researched in a more exact way than ever before. Photoactivatable amino acids allow the spatiotemporal control of protein activity whereas clickable amino acids allow the post-synthetic incorporation of fluorescent probes or other functional groups. The synthesis of artificial amino acids possessing specific spectroscopic properties has also earned it a formidable contribution toward exploring protein folding, enzyme activity and cellular signaling, in real-time process.

1.3. Existing Methods for Preparing Artificial Amino Acids

Artificial amino acid synthesis has been a topic of research development over the past decades and currently, there is a multitude of methodologies that can be used to acquire valuable amino acids. Unnatural amino acids are currently synthesized predominantly through asymmetric catalysis, and many such methods involve several steps, although a few direct and simple routes have been developed.[31] Recently, there has been a drive towards developing solutions to the issues surrounding α,α-disubstituted α-amino acids where synergistic enantioselective catalysis, visible-light-mediated photocatalysis, metal-free

methodologies and CO_2 fixation offer new possibilities towards the development of this challenging class of synthetic products.[18]

1.3.1. Classical and Asymmetric Catalytic Approaches

The Strecker Synthesis and Modern Adaptations Strecker synthesis pioneered in 1850 remains one of the most popular methods of amino acid synthesis. This three-component reaction involves condensation of an aldehyde, ammonia, and hydrogen cyanide to produce an α-aminonitrile which is then hydrolyzed to produce the amino acid. Simple and easily prepared chiral amido-thiourea catalysts with high stereoselectivity have been used to control the addition step in scaleable catalytic asymmetric Strecker syntheses of unnatural α-amino acids, with low catalyst loading rates and broad functional group compatibility.[16]

Fig 1.9 The Strecker Synthesis of Amino acids from Aldehyde.16

Alkylation-Based Strategies Alkylation of glycine analogs provides another strategy where nucleophilic species are formulated as derivatized glycine systems. Myers auxiliary method has been especially useful in preparation of α,α-disubstituted amino acids involving the use of glycine equivalent derived by use of pseudoephedrine. Bis-alkylation methods have become effective for quaternary amino acids through sequential alkylation of a glycine equivalent with well-controlled reaction conditions.

Transition Metal-Catalyzed Approaches The development of asymmetric catalysis has transformed amino acid synthesis, enabling enantiomerically pure products with greater efficiency and selectivity.[10] Enantioconvergent nickel-catalyzed cross-coupling has emerged as an important method for synthesis of unprotected unnatural α-amino acids, offering applications in bioactive compound development.[13] Palladium-catalyzed C(sp^3)-H functionalization methodologies have also been developed significantly for overall synthetic peptides and unnatural amino acids.[30]

1.3.2. Photochemical and Photoredox Approaches

Visible-light photoredox catalysis has emerged as an effective method in organic synthesis, offering mild reaction conditions and high functional group compatibility.[22] Ruthenium and iridium-based photocatalysts enable efficient room temperature synthesis of unnatural chiral α-amino acids using readily available starting materials.[33] Photoredox-mediated C-O bond activation protocols using chiral glyoxylate-derived N-sulfinyl imines have demonstrated efficient synthesis of unnatural α-amino acids.[6] Synergistic photoredox-biocatalysis approaches have created enzymatic reactions amenable to synthetically relevant scaled production.[29]

Fig 1.10 Photoredox-catalyzed radical cross-coupling protocol for the synthesis of beta amino acid derivatives.41

1.3.3. Enzymatic and Biocatalytic Methods

The selectivity and environmentally friendly conditions of enzymatic methods have attracted attention, ω-transaminases have demonstrated utility in the synthesis of non-canonical amino acids with readily available ketone and aldehyde precursors in high stereoselectivity.[15] Cascade reactions between aldolases and transaminases have been employed to accomplish complex amino acid synthesis using biocatalysts, preferably developed by directed evolution.[9]

1.3.4. Metallar-free and Green Chemistry Methods.

Synthetic processes where metals are not used have been of concern because of environmental concerns and avoiding heavy metals contamination in drugs. Organocatalysis is a viable alternative to high levels of stereoselectivity in transition metal catalysis. Hydrogen-bonding catalysts that utilize thiourea and chiral amine catalysts have been developed to engage in the synthesis of amino acids in high enantioselectivity. Continuous production of amino acids has been made safer, easier to scale and more efficient by flow chemistry. The microreactor systems offer superior control in thermal and mass transfer whereas the integrated flow system offers multi-step synthesis with minimum manipulation of the intermediates. Solvents that are solvent-free and solvents that are water-based have been developed as green chemistry methods to minimize the environmental impact. An excellent example is the organocatalytic Asymmetric strecker synthesis of amino acids that has already been shown above.

1.4. Synthetic Organic Electrochemistry and Kolbe Electrolysis

Over the past decade, electrochemical synthesis has seen a renewal since organic chemists have sought to adopt green and effective ways of bond construction. Carbon-carbon bonds are produced by the Kolbe reaction, which uses electrochemical decarboxylative coupling. Even after over 100 years of research, the reaction has not been utilized extensively due to poor chemoselectivity and the requirement of precious metal electrodes.[27]

Newer studies have shown additional, improved methods of non-Kolbe electrolysis of N-protected-α-amino acids using modern ElectraSyn 2.0 systems to enable electrochemical decarboxylative methoxylation under mild conditions.[28] This can be regarded as significant progress in the practical utilization of electrochemical procedures in amino acid chemistry.

In electrochemical synthesis of amino acids, special possibilities are given for simple access to complex structures that can hardly be prepared by classical methods. The capacity to form reactive radical intermediates under controlled conditions allows the production of quaternary carbon centers that are

difficult to produce using other methods

The Kolbe electrolysis is a radical process, proceeding in two steps: electrochemical decarboxylation to give a radical intermediate, which then dimerizes during a radical reaction.[36]

The equation below illustrates the general mechanism of Kolbe electrolysis. At the anode, the carboxylate ion undergoes oxidative decarboxylation, releasing carbon dioxide and generating an alkyl radical. These radical intermediates subsequently recombine to form a new carbon–carbon bond, typically yielding symmetrical hydrocarbons. This transformation is a classical example of electrochemical radical chemistry and demonstrates the ability of electrolysis to construct simple hydrocarbons directly from carboxylic acid salts.

Kolbe synthesis reaction can be generalized by the following equation:

$2RCO2^- \rightarrow R{-}R + 2CO2 + 2e^-$

In this reaction, R is a hydrocarbon functional group, e.g. an alkyl or aryl group, and CO_2 is carbon dioxide. In a carboxylate salt (either sodium acetate or potassium benzoate) aqueous solution containing a cathode and an anode, the reaction occurs in an electrolytic cell.

Water is reduced at the cathode to form hydrogen gas and hydroxide ions:

$2H_2O + 2e^- \rightarrow H_2 + 2OH^-$

The carboxylate ions at the anode are oxidized to reactive radicals:

$RCO_2^- \rightarrow R\bullet + CO_2 + e^-$

These radicals then react with water and the result is the hydrocarbons:

$R\bullet + H_2O \rightarrow R{-}H + OH\bullet$

The Kolbe reaction normally forms hydrocarbons with relatively high molecular weight, which may not be easily isolated and purified. The reaction is also restricted to acids which are stable in the condition of the reaction used and mostly it demands high temperatures and large current densities.

Mechanistic Steps:

1. Radical Formation: The electron is removed by the carboxylate ion at the anode to produce a radical:

$RCO_2^- \rightarrow RCO_2\bullet + e^-$

2. Dimerization: The radical dimerizes with another carboxylate ion to obtain a dimer:

$RCO_2\bullet + RCO_2^- \rightarrow RCO_2RCO_2^-$

3. Fragmentation: The