INTRODUCTION

The revolutionary discovery of solid phase peptide synthesis (SPPS) by Merrifield in 1963 made it possible for one to rapidly synthesize peptides of substantial length. However, despite many advances in the field of solution phase peptide synthesis and solid phase peptide synthesis, amide bond formation is still plagued by poor step and atom economy, which is inherent to the deprotection followed by coupling strategy, and is often limited to peptides under 50 amino acids in length due to aggregation, unwanted folding, or poor solubility caused by side chain protecting groups. With the demand of peptides and small proteins for the use as therapeutics and materials on the rise, the necessity for a method that does not produce a 10 to 45 fold excess of non-solvent waste is a necessity. Novel advances in amide bond formation have made increasing peptide lengths a possibility and atom economical amide bond formations have improved immensely and show promise in applications towards peptide synthesis.

RECENT ADVANCES IN AMIDE BOND FORMATION

As protected peptides increase in length, chances of side chain protecting group driven aggregation increases thus the synthesis of peptides greater than 50 amino acids is typically not feasible using classic methods. As most proteins are 100+ amino acids in length, methods for coupling unprotected peptide segments are required. Native chemical ligation (NCL) and α-ketoacid hydroxylamine (KAHA) coupling reactions have been developed for the synthesis of these larger peptide sequences through unprotected starting materials. NCL couples a thioester with a cysteine residue via reversible transthiostosterification followed by irreversible intramolecular amide bond formation (Figure 1). Unfortunately this method is limited to peptides which contain a thiol within the backbone. KAHA ligation developed by Bode and coworkers couples an α-ketoacid and a hydroxylamine, forming only CO$_2$ and water as the byproducts. The α-ketoacid fragment can be masked through SPPS and later revealed for coupling to make either cyclic or linear peptides (Figure 2).
Removing stoichiometric protecting groups and coupling reagents from amide bond formation has been the main goal for many groups in the past decade. In addition to KAHA coupling described by Bode, Movassaghi has developed an N-heterocyclic carbene (NHC) catalyzed ester amino alcohol coupling reaction (Figure 3)\textsuperscript{7}. This reaction has been shown to be amenable to the alcohol oxidation state of amino acids without appreciable epimerization and has a wide range of functional group tolerance. With only the alcohol from the ester as a byproduct of the reaction, this methodology could be a viable replacement for current peptide synthesis strategies.

Milstein has also shown that a PNN-Ru pincer complex is viable catalyst for oxidative alcohol amine coupling. These coupling reactions produce H\textsubscript{2} as their only byproduct (Figure 4)\textsuperscript{8}. This methodology has been shown to tolerate the alcohol oxidation state of amino acids and with low catalyst loadings and negligible reaction byproducts it has potential for future applications of atom economical peptide synthesis\textsuperscript{9}.

**SUMMARY**

Although it is a field that has been around for over a century, amide and peptide bond formation is still an ever growing area of research and there are many advances in both removal of stoichiometric additives and increasing the number of amino acid units for the synthesis of peptides.

**REFERENCES**


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