NOVEL STRATEGIES FOR THE SYNTHESIS OF β-AMINO ACIDS AND THEIR DERIVATIVES

Reported by Samuel Albright February 14, 2023

INTRODUCTION

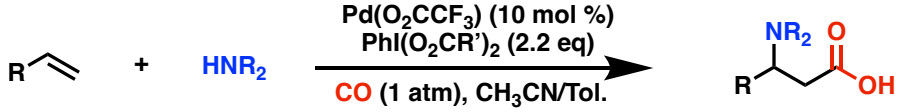
β-amino acids differ from their α counterparts via homologation of their carbon backbone by one methylene unit. These compounds have important applications in peptidomimetics, where substituting α-amino acid residues for β-amino acids can alter the biological properties of synthetic peptides by improving metabolic stability and target selectivity compared to the parent peptide.[1] Efficient synthetic access to β-amino acids is also desirable due to the prevalence of the moiety in natural products and drugs.[1]

Common synthetic strategies used to access β-amino acids include conjugate addition of amine nucleophiles to Michael acceptors, Mannich-type reactions, metal- catalyzed hydrogenation of β-amino linked acrylates, and homologations of α-amino acids like the Arndt-Eistert carboxylic acid homologation.[2] The downfall of these disconnection strategies is the required prefunctionalization of starting materials, multistep synthetic sequences, and, in some cases the use of hazardous reagents like diazomethane. Recent advances have allowed for more facile synthesis of β-amino acids necessitating fewer chemical transformations and utilizing simple building blocks like olefins and aziridines.

PALLADIUM-CATALYZED AMINOCARBONYLATION OF ALKENES

Liu and coworkers developed the first *intermolecular* aminocarbonylation of alkenes inspired by other aminopalladation methods such as the aza-Wacker reaction. This method utilizes hypervalent iodine to prevent nonproductive reduction of the palladium catalyst and is run under a carbon monoxide atmosphere to afford a suite of *N*-phthalimide or *N*-oxazolidine protected β-amino acid derivatives (**Scheme 1**).[3] Several mono-substituted styrenes and unactivated alkyl olefins are competent substrates for the method; however, electron-poor olefins suffer from reduced yields or complete nonreactivity.

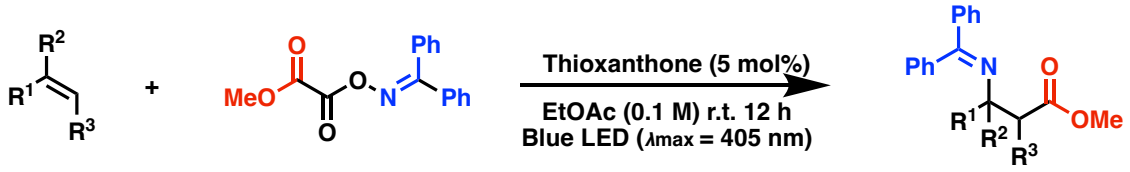
Scheme 1. Palladium catalyzed aminocarbonylation



PHOTOCHEMICAL AMINOCARBONYLATION OF ALKENES

Glorius and coworkers developed a one-step aminocarbonylation of alkenes and heteroarenes that relies on an energy transfer strategy via photocatalysis (**Scheme 2**).[4] This method takes advantage of a labile oxime oxalate ester that is cleaved under the reaction conditions to yield both ester and amino-centered radicals which add across the double bond in a regioselective fashion to afford N-protected, methyl esterified variants of β-amino acids.

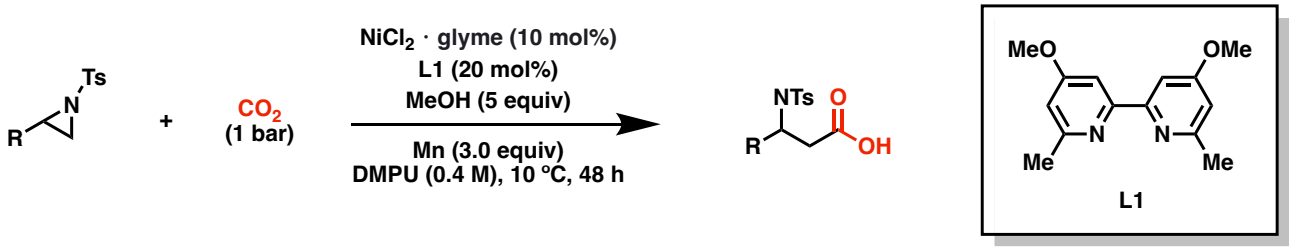
Scheme 2. Photocatalyzed aminocarbonylation



NICKEL CATALYZED CARBOXYLATION OF AZIRIDINES

Martin and coworkers developed a nickel-catalyzed carboxylation of aziridines that provides an alternate avenue to synthesize of β-amino acids (**Scheme 3).**[5] This reaction boasts a wide functional group tolerance, allowing access to mono-substituted β-amino acids, including some proteinogenic examples such as β-tyrosine, β-isoleucine, and β-tryptophan.

Scheme 3. Nickel catalyzed carboxylation of aziridines.



CONCLUSION AND OUTLOOK

Though these new methods represent a leap forward in synthetic accessibility to β-amino acid derivatives, there exist areas of potential improvement. Direct asymmetric synthesis of β-amino acids from olefins and aziridines remains elusive and access to β^2-substituted amino acids is not possible with this current set of methods.

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