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Towards a stereoselective synthesis of α,α-disubstituted proline analogues

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ABSTRACT

A mild organocatalytic protocol for the syntheses of α,α-disubstituted proline analogues has been developed. The 3-ketoproline scaffold was functionalised using various aromatic nitrostyrenes in the presence of a bifunctional organocatalyst. The resulting quaternary proline derivatives could easily be transformed into α-alkyl-β-hydroxyproline analogues. Furthermore, the methodology could also be applied to the synthesis of 3-ketoproline functionalized peptides with high selectivity and good yields.

Introduction

α,α-Disubstituted (quaternary) α-amino acids are a class of non-natural amino acids that have received considerable attention within biological and medicinal chemistry.[1-4] α,α-Disubstituted α-amino acids are inert toward racemization, and their restricted conformational freedom contributes to their significance as unnatural building blocks in peptide design;[5] i.e. the incorporation of such amino acids into the peptide backbone is an important tool to reduce the intrinsic flexibility of the peptide.[5, 6,7]

Similarly, proline – the only naturally occurring amino acid that forms a tertiary amide bond when incorporated in peptides and proteins, is crucial for the formation of secondary structures such as β-turns or polyproline helices.[7-9] The ability of proline to induce turns and reduce conformational flexibility in peptides can have a significant effect on its biological conformation, thereby influencing ligand binding and protein activity.[9, 10] Unsurprisingly, α,α-disubstituted proline analogues represent a class of artificial amino acid residues that has been heavily exploited in the design of peptides with well-defined backbone conformations.[9, 11, 12]

In addition to multiple biological applications,[13-15] the pyrrolidine motif of proline is a crucial element in many widely used organocatalysts.[16-18] Hence, there is a large interest in synthetic methodologies for the preparation of substituted prolines with inherent functional diversity from both the biomedical and asymmetric catalysis research communities.

Surprisingly, the catalytic asymmetric synthesis of α,α-disubstituted proline analogues have been rather neglected. Their synthesis generally relies on the use of stoichiometric amounts of external/internal chirality inducers.[19] Cao and Williams synthesized α,α-disubstituted proline analogues by the enzymatic resolution of racemic *N*-Boc protected 3-ketoproline followed by deprotonation using LDA and subsequent alkylation.[20] To our knowledge, only one report on the direct catalytic asymmetric transforamtion of 3-ketoproline derivatives has been reported. In this case, Maruoka and co-workers employed a phase transfer catalyst for functionalisation, which limited the range of electrophiles to benzylic bromides.[21]

Herein, we describe an organocatalytic methodology for the preparation of α,α-disubstituted proline analogues by the asymmetric α-substitution of the 3-ketoproline backbone. In addition, further synthetic transformations of the *N*-Boc protected 3-ketoproline core to enhance its functional diversity for the incorporation into peptides are also outlined.

Results and Discussion

It should be noted that 2-oxocyclopentanecarboxylate (cyclopentane analogue of 3-ketoproline) is amongst the most widely used substrate class in asymmetric catalysis due to its inherent keto-enol tautomerism, e.g. undergoing Michael addition under organocatalytic conditions.[22-24] Most commonly, these substrates have been activated with bifunctional organocatalysts;[25-30] hence we selected cinchonine and quinine derived organocatalysts **I** and **II**, respectively, for the benchmark Michael addition reaction of 3-ketoproline and nitrostyrene (Scheme 1).