SYNLETT Spotlight 424

This feature focuses on a reagent chosen by a postgraduate, highlighting the uses and preparation of the reagent in current research.

α-Amido Sulfones as Imine Precursors in Enantioselective Nucleophilic Additions

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Introduction

α-Amido sulfones have emerged as valuable precursors of imines in enantioselective nucleophilic addition reactions because their use offers several advantages.1 Imines are generated in situ from α-amido sulfones by the elimination of the sulfone group under basic or acid conditions. The in situ formation avoids the competitive enolization process that often occurs when using imines and which hinders an effective nucleophilic addition. Moreover, unlike imines, α-amido sulfones are stable solids which can be easily synthesized and stored for a long period of time.

Preparation

Various methodologies have been described for the synthesis of diverse α-amido sulfones.2 The most extended preparation method consists of a three-component coupling of aldehyde, carbamate (or a proper nitrogenated compound, such as an amide) and sodium p-toluene sulfinate.

Abstracts

(A) Mannich Reaction

α-Amido sulfones are used as aliphatic imine precursors in the catalytic asymmetric Mannich reaction with glycine derivative 5. Linear, branched or cyclic substrates give the corresponding products in excellent diastereo- and enantioselectivities. Noteworthy are the use of formaldehyde-derived α-amido sulfone for α-aminomethylation of glycine derivatives and the selective orthogonal N-deprotection of the obtained β-alkyl-α,β-diamino acid derivatives 6.3

(B) Hydrophosphonylation

Enantioenriched α-amino phosphoric acid derivatives 8 can be synthesized by the asymmetric hydrophosphonylation of aliphatic N-Cbz and N-Boc α-amido sulfones 3 using a phase-transfer catalyst. High yields and enantioselectivities are afforded.4

(C) Cycloaddition

Propionyl chloride 9 and α-amido sulfones as precursors of N-thiocarbonylaziridines undergo catalytic asymmetric [4+2] cycloadditions with excellent enanto- and diastereoselectivities. The in situ formation of the imine is crucial to overcome its tautomerization to the enamine. The final enantioenriched thiazinone adducts 10 behave as activated ester surrogates.5
(D) Alkylation
The catalytic enantioselective addition of organometallic reagents to α-amido sulfones was developed by Feringa and co-workers. Dialky zinc reagents are utilized for the addition of ethyl, isopropyl and n-butyl nucleophiles. However, the introduction of the methyl group is achieved with Me3Al. High enantioselectivities are obtained with para- and meta-substituted substrates, whereas ortho-substituted and aliphatic α-amido sulfones lead to a low enantiomeric excess.

(E) Strecker Reaction
Differently N-protected aromatic α-amido sulfones have also been reported. The aza-Henry reaction of aromatic α-amido sulfones has also been successfully applied to the asymmetric addition of nitroalkanes to α-amido sulfones. Several N-Cbz protected propargylic amines are prepared by the catalytic enantioselective addition of aromatic alkynes in situ formed from aromatic α-amido sulfones using Et3Zn and a BINOL-type ligand. Further transformations of the alkynylation products were successfully achieved.

(G) Aza-Henry Reaction
The asymmetric addition of nitroalkanes to N-Boc imines, in situ formed from α-amido sulfones, is performed in the presence of a novel rosin-derived thiourea catalyst and a base. The reaction proceeds in a doubly stereocontrolled manner with high enantioselectivities and moderate diastereoselectivities. Catalytic phase transfer conditions have also been successfully applied to the asymmetric aza-Henry reaction of α-amido sulfones.

(H) Aza-Morita–Baylis–Hillman Reaction
N-Boc α-amido sulfones are demonstrated to be suitable imine precursors in the asymmetric addition of vinyl methyl ketone catalyzed by a BINOL-derived catalyst. Moderate to high yields and enantioselectivities are afforded. The enantioselective aza-Morita–Hillman-type reaction with αβ-unsaturated aldehydes and α-amido sulfones has also been reported.

References