

SYNLETT Spotlight 424

α -Amido Sulfones as Imine Precursors in Enantioselective Nucleophilic Additions

Compiled by Alicia Monleón



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

Alicia Monleón was born in Valencia, Spain, in 1985. She obtained her B.Sc. and M.Sc. degrees in Chemistry from the University of Valencia, where she is currently pursuing her Ph.D. under the supervision of Prof. José Ramón Pedro and Prof. Gonzalo Blay. She has carried out pre-doctoral stays at the University of Aachen, Germany, with Prof. C. Bolm and at the University of Strathclyde, UK, with Dr. E. Hevia.

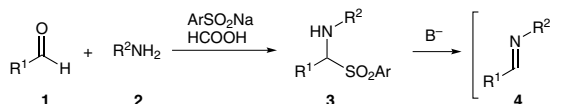
Departament de Química Orgànica, Facultat de Química, Universitat de València, C/ Dr. Moliner 50, 46100 Burjassot, Spain
E-mail: alicia.monleon@uv.es

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*-toluenesulfinate.

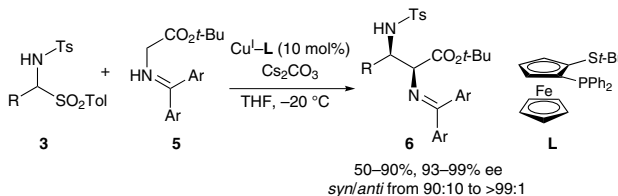


Scheme 1 Synthesis of α -amido sulfones and in situ generation of imines under basic conditions.

Abstracts

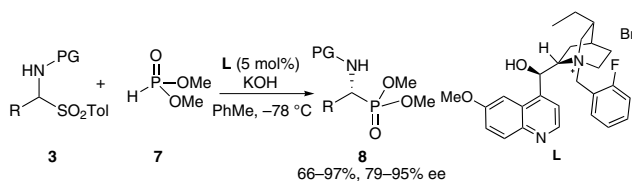
(A) Mannich Reaction

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



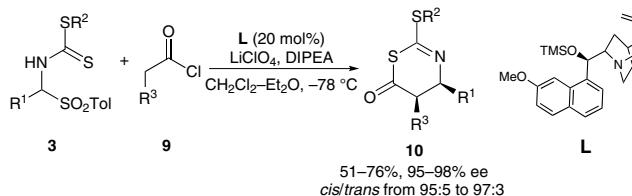
(B) Hydrophosphonylation

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



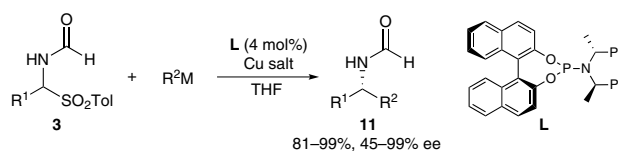
(C) Cycloaddition

Propionyl chloride **9** and α -amido sulfones as precursors of *N*-thioacylimines undergo catalytic asymmetric [4+2] cycloadditions with excellent enantio- 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



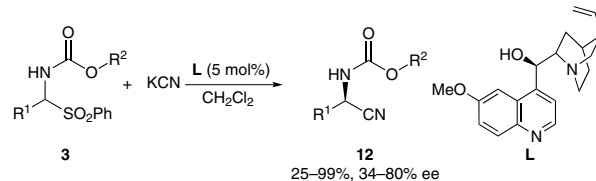
(D) Alkylation

The catalytic enantioselective addition of organometallic reagents to α -amido sulfones was developed by Feringa and co-workers. Dialkyl zinc reagents are utilized for the addition of ethyl, isopropyl and *n*-butyl nucleophiles. However, the introduction of the methyl group is achieved with Me_3Al . High enantioselectivities are obtained with *para*- and *meta*-substituted substrates, whereas *ortho*-substituted and aliphatic α -amido sulfones lead to a low enantiomeric excess.⁶



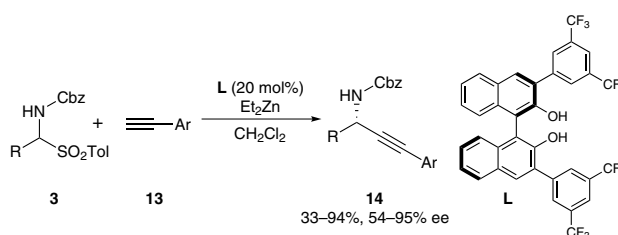
(E) Strecker Reaction

Differently N-protected aromatic α -amido sulfones undergo the organocatalytic enantioselective cyanation catalyzed by quinine. KCN is used as the cyanide source. The cyanated products **12** are obtained in good yields and enantioselectivities.^{7a} The asymmetric Strecker reaction with aliphatic α -amido sulfones has also been carried out.^{7b}



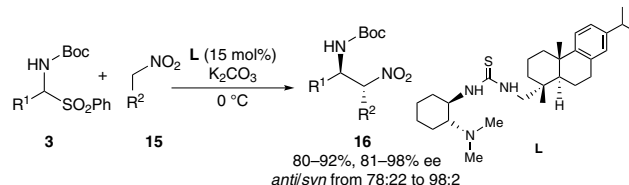
(F) Alkynylation

Several *N*-Cbz protected propargylic amines **14** are prepared by the catalytic enantioselective addition of aromatic alkynes **13** to imines in situ generated from aromatic α -amido sulfones using Et_2Zn and a BINOL-type ligand. Further transformations of the alkynylation products were successfully achieved.⁸



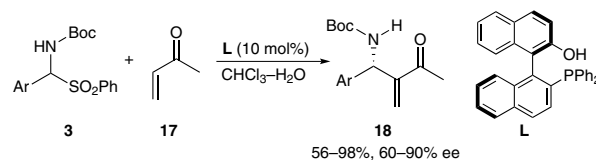
(G) Aza-Henry Reaction

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.^{9a} Catalytic phase transfer conditions have also been successfully applied to the asymmetric aza-Henry reaction of α -amido sulfones.^{9b}



(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.^{10a} The enantioselective aza-Baylis–Hillman-type reaction with α,β -unsaturated aldehydes and α -amido sulfones has also been reported.^{10b}



References

- (1) (a) Petrini, M. *Chem. Rev.* **2005**, *105*, 3949. (b) Yin, B.; Zhang, Y.; Xu, L.-W. *Synthesis* **2010**, 3583.
- (2) (a) Engberts, J. B. F. N.; Strating, J. *Rec. Trav. Chim. Pays-Bas* **1964**, *83*, 733. (b) Schöllkopf, U.; Blume, E. *Tetrahedron Lett.* **1973**, *14*, 629. (c) Matthies, D. *Synthesis* **1978**, 53. (d) Paik, S.; White, E. H. *Tetrahedron* **1996**, *52*, 5303. (e) Chemla, F.; Hebbe, V.; Normant, J.-F. *Synthesis* **2000**, 75. (f) Côté, A.; Boezio, A. A.; Charette, A. B. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5405.
- (3) Hernando, E.; Arrayás, R. G.; Carretero, J. C. *Chem. Commun.* **2012**, 48, 9622.
- (4) Fini, F.; Micheletti, G.; Bernardi, L.; Pettersen, D.; Fochi, M.; Ricci, A. *Chem. Commun.* **2008**, 4345.
- (5) Xu, X.; Wang, K.; Nelson, S. G. *J. Am. Chem. Soc.* **2007**, *129*, 11690.
- (6) Pizzuti, M. G.; Minnaard, A. J.; Feringa, B. L. *J. Org. Chem.* **2008**, *73*, 940.
- (7) (a) Reingruber, R.; Baumann, T.; Dahmen, S.; Bräse, S. *Adv. Synth. Catal.* **2009**, *351*, 1019. (b) Ooi, T.; Uematsu, Y.; Fujimoto, J.; Fukumoto, K.; Maruoka, K. *Tetrahedron Lett.* **2007**, *48*, 1337.
- (8) Blay, G.; Brines, A.; Monleón, A.; Pedro, J. R. *Chem.–Eur. J.* **2012**, *18*, 2440.
- (9) (a) Jiang, X.; Zhang, Y.; Wu, L.; Zhang, G.; Liu, X.; Zhang, H.; Fu, D.; Wang, R. *Adv. Synth. Catal.* **2009**, *351*, 2096. (b) Gomez-Bengoa, E.; Linden, A.; López, R.; Múgica-Mendoza, I.; Oiarbide, M.; Palomo, C. *J. Am. Chem. Soc.* **2008**, *130*, 7955.
- (10) (a) Guan, X.-Y.; Wei, Y.; Shi, M. *Eur. J. Org. Chem.* **2010**, 4098. (b) Číhalová, S.; Remeš, M.; Čísařová, I.; Veselý, J. *Eur. J. Org. Chem.* **2009**, 6277.