

SYNLETT Spotlight 359

(S)-(+)-1-(2-Pyrrolidinylmethyl)-pyrrolidine

Compiled by Raghunath Chowdhury



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

Raghunath Chowdhury was born in Jhantipahari, West Bengal, India. He pursued his B.Sc. (honors) (2003) and M.Sc. (2005) in chemistry from the University of Burdwan. He then joined the Training School of Bhabha Atomic Research Centre, Mumbai and in 2006 the Bio-Organic Division of Bhabha Atomic Research Centre. Currently he is working towards his Ph.D. thesis under the supervision of Prof. Sunil K. Ghosh in the same institute. His research interests are focused on the diversity-oriented synthesis of small organic molecules using organocatalysts and sulphur ylides.

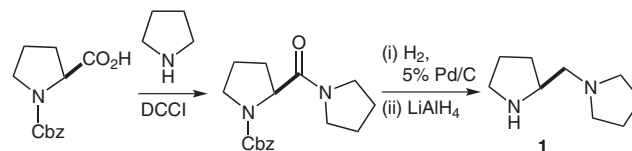
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Introduction

Last decade witnessed an explosive growth in asymmetric organocatalysis. A large number of organocatalysts have been developed by different research groups. (S)-(+)-1-(2-Pyrrolidinylmethyl)pyrrolidine (CAS: 51207-66-0) is a versatile organocatalyst, which is commercially available or can be easily prepared from commercially available Cbz-(L)-proline (Scheme 1).¹ It is known to catalyze many organic reactions, for example, the asymmetric

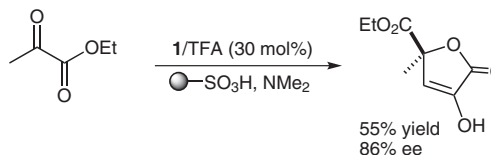
aldol reaction,^{2,3} Michael reaction,⁴⁻⁷ Mannich reaction,⁸ and the domino reaction.⁹ It is also used as a chiral ligand/additive in metal-mediated stereoselective organic syntheses.^{10,11}



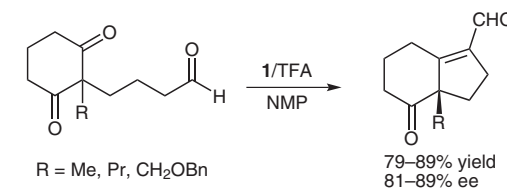
Scheme 1

Abstracts

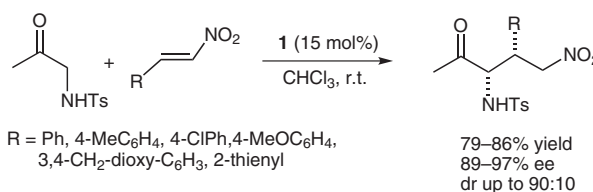
(A) The direct homoaldol reaction of ethyl pyruvate was reported to be catalyzed by (S)-(+)-1-(2-pyrrolidinylmethyl)pyrrolidine (**1**) and trifluoroacetic acid. The use of the polymer-supported acid facilitated the removal of **1**. The base allowed the lactonization of the aldol adduct and the isolation of the isotetronic acid derivative in its hydroxyl-free form.^{2c}



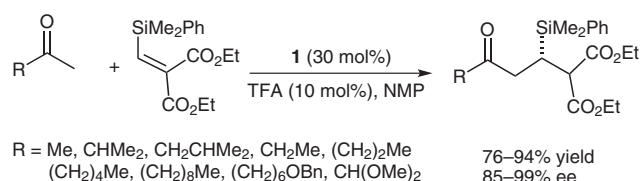
(B) The trifluoroacetic acid salt of **1**³ catalyzed the intramolecular aldol reaction of a series of tricarbonyl compounds wherein the keto group acted as an electrophile. This resulting bicyclo[4.3.0]nonene derivatives were formed in high yield and enantioselectivity (81–89% ee).



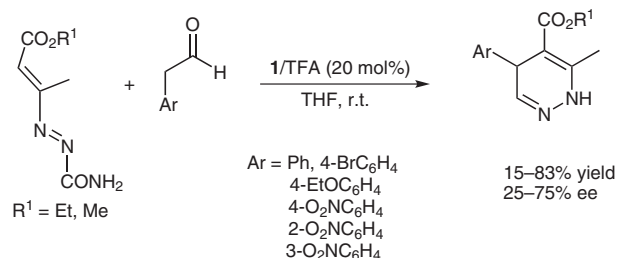
(C) The direct conjugate addition of an α -amino ketone to nitroolefins was reported to be catalyzed by **1**.⁵ The adducts are formed in high yield and ee's (89–97%). One of such addition product was converted into a pyrrolidine skeleton.



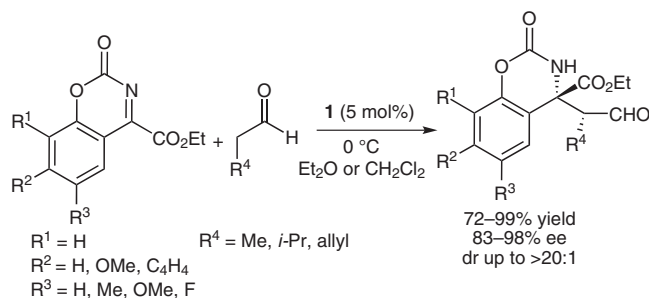
(D) The catalyst **1**/TFA (3:1) combination catalyzed the direct addition of alkyl methyl ketones to β -dimethyl(phenyl)silylmethylene malonate exclusively via the COME terminus. The adducts are formed in high yield and excellent enantioselectivity (99.6% ee).⁶ These addition products thus obtained can easily undergo deethoxy-carbonylation to give β -silylated keto esters with excellent synthetic potential.



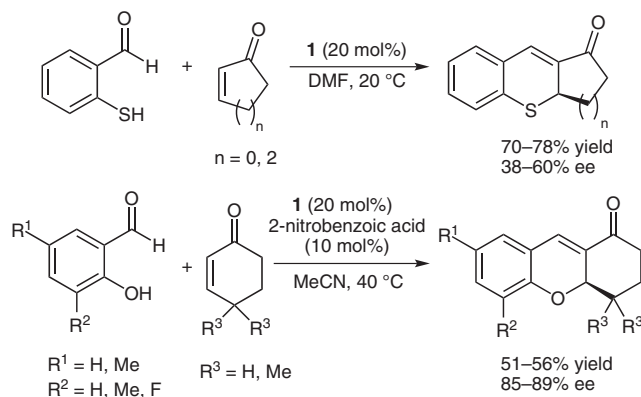
(E) The catalyst **1**/TFA combination is used for the synthesis of chiral 1,4-dihydropyridazines from 1,2-diaza-1,3-dienes and arylacetaldehydes. The ee values ranged from 25% to 75%.⁷



(F) The first organocatalytic enantioselective Mannich reaction of ketimines and unmodified aldehydes was investigated using **1**.^{8a} The reaction leads to the generation of a chiral quaternary center. The α,α -disubstituted amino acid derivatives were produced in good yield and very high optical purities (83–98% ee). The reaction was also catalyzed by L-proline, but produced the opposite diastereoisomer of the Mannich product. Quantum mechanical calculations provided a good explanation for the opposite diastereoselectivities of catalyst **1** and L-proline.^{8b}



(G) The domino reaction between 2-mercaptobenzaldehyde or salicylaldehyde derivatives and α,β -unsaturated cyclic ketones were catalyzed by **1** with excellent chemoselectivity to give the corresponding tetrahydrothioxanthenones or tetrahydroxanthenones with high enantioselectivity.^{9a,b}



References

- (1) Asami, M. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 721.
- (2) (a) Saito, S.; Yamamoto, H. *Acc. Chem. Res.* **2004**, *37*, 570. (b) Mase, N.; Tanaka, F.; Barbas, C. F. III *Angew. Chem. Int. Ed.* **2004**, *43*, 2420. (c) Dambruoso, P.; Massi, A.; Dondoni, A. *Org. Lett.* **2005**, *7*, 4657.
- (3) Hayashi, Y.; Sekizawa, H.; Yamaguchi, J.; Gotoh, H. *J. Org. Chem.* **2007**, *72*, 6493.
- (4) Mase, N.; Thayumanavan, R.; Tanaka, F.; Barbas, C. F. III *Org. Lett.* **2004**, *6*, 2527.
- (5) Belot, S.; Sulzer-Mosse, S.; Kehrl, S.; Alexakis, A. *Chem. Commun.* **2008**, 4694.
- (6) (a) Chowdhury, R.; Ghosh, S. K. *Org. Lett.* **2009**, *11*, 3270. (b) Chowdhury, R.; Ghosh, S. K. *Synthesis* **2011**, 1936.
- (7) Pitacco, G.; Attanasi, O. A.; Crescentini, L. D.; Favi, G.; Felluga, F.; Forzato, C.; Mantellini, F.; Nitti, P.; Valentin, E.; Zangrando, E. *Tetrahedron: Asymmetry* **2010**, *21*, 617.
- (8) (a) Zhuang, W.; Saaby, S.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2004**, *43*, 4476. (b) Li, H.; Fu, A.; Shi, H. *J. Mol. Catal. A: Chem.* **2009**, *303*, 1.
- (9) (a) Rios, R.; Sundén, H.; Ibrahim, I.; Zhao, G.-L.; Córdova, A. *Tetrahedron Lett.* **2006**, *47*, 8679. (b) Rios, R.; Sundén, H.; Ibrahim, I.; Córdova, A. *Tetrahedron Lett.* **2007**, *48*, 2181.
- (10) Sharma, A. K.; Maheshwary, Y.; Singh, P.; Singh, K. N. *ARKIVOC* **2010**, (ix), 54.
- (11) Raja, R.; Thomas, J. M.; Jones, M. D.; Johnson, B. F. G.; Vaughan, D. E. W. *J. Am. Chem. Soc.* **2003**, *125*, 14982.