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# Stereoselective Formation of α-Quaternary Stereocenters in the Mannich Reaction

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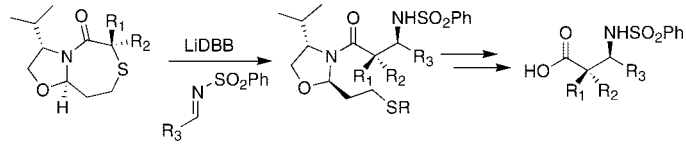
## ABSTRACT




**Condensation of α,α-disubstituted lithium enolates derived from bicyclic thioglycolate lactams with benzenesulfonyl imines affords Mannich addition products with excellent diastereoselectivity. Cleavage of the auxiliary under hydrolytic or reducing conditions affords *β*-amino acids and alcohols, respectively.**

The Mannich reaction is a fundamental process for the synthesis of the *β*-amino carbonyl motif found in *β*-amino acids and *β*-lactams and used as a precursor to *β*-amino alcohols.[1] There is a great deal of precedent for stereoselective formation of *β*-amino carbonyl compounds that are either unsubstituted or contain a single alkyl group at the α-position. This includes methods based on chiral auxiliaries,[2] Brønsted and Lewis acid activation of the imine,[3,4] and organocatalytic activation of a ketone or aldehyde.[5] In contrast, methods for the preparation of α,α-dialkyl-substituted Mannich products are much less common, particularly in cases where the two α-substituents are nonequivalent.[5e,6,7] In such instances, limited control over enolate *E*/*Z* stereochemistry often results in variable *syn*/*anti* selectivity. In this paper, we describe a stereoselective Mannich addition using a bicyclic lactam auxiliary that affords differentially α,α-disubstituted *β*-aminocarbonyl products in high yields and with excellent stereoselectivity.

We recently described a practical method for stereocontrolled formation of α,α-disubstituted enolates based on the reductive enolization of chiral thioglycolate lactams.[8] Pre-

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(2) For selected examples of a chiral auxiliary in Mannich reaction, see: (a) Tang, T. P.; Ellman, J. A. *J. Org. Chem.* **2002**, *67*, 7819. (b) Kawakami, T.; Ohtake, H.; Arakawa, H.; Okachi, T.; Imada, Y.; Murahashi, S. I. *Org. Lett.* **1999**, *1*, 107. (c) Palomo, C.; Oiarbide, M.; Landa, A.; González-Rego, M. C.; Garcia, J. M.; González, A.; Odriozola, J. M.; Martin-Pastor, M.; Linden, A. *J. Am. Chem. Soc.* **2002**, *124*, 8637. (d) Muller, R.; Goesmann, H.; Waldmann, H. *Angew. Chem., Int. Ed.* **1999**, *38*, 184.

(3) For selected examples of Lewis acid catalyzed Mannich reactions, see: (a) Saruhashi, K.; Kobayashi, S. *J. Am. Chem. Soc.* **2006**, *128*, 11232. (b) Juhl, K.; Gathergood, N.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 2995. (c) Trost, B. M.; Jaratjaroonphong, J.; Reutrakul, V. *J. Am. Chem. Soc.* **2006**, *128*, 2778. (d) Yamaguchi, A.; Matsunaga, S.; Shibasaki, M. *Tetrahedron Lett.* **2006**, *47*, 3985.

(4) For selected examples of Brønsted acid catalyzed Mannich reactions, see: (a) Wenzel, A. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 12964. (b) Yamanaka, M.; Itoh, J.; Fuchibe, K.; Akiyama, T. *J. Am. Chem. Soc.* **2007**, *129*, 6756. (c) Uraguchi, D.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 5356. (d) Hasegawa, A.; Naganawa, Y.; Fushimi, M.; Ishihara, K.; Yamamoto, H. *Org. Lett.* **2006**, *8*, 3175. (e) Tillman, A. L.; Dixon, D. J. *Org Biomol. Chem.* **2007**, *5*, 606.

(5) For selected examples of organocatalytic Mannich reactions, see: (a) List, B.; Pojarliev, P.; Biller, W. T.; Martin, H. J. *J. Am. Chem. Soc.* **2002**, *124*, 827. (b) Chowdari, N. S.; Ahmad, M.; Albertshofer, K.; Tanaka, F.; Barbas, C. F., III. *Org. Lett.* **2006**, *8*, 2839. (c) Ibrahem, I.; Zou, W.; Engqvist, M.; Xu, Y.; Córdova, A. *Chem.−Eur. J.* **2005**, *11*, 7024. (d) Cobb, A. J. A.; Shaw, D. M.; Longbottom, D. A.; Gold, J. B.; Ley, S. V. *Org. Biomol. Chem.* **2005**, *3*, 84. (e) Chowdari, N. S.; Suri, J. T.; Barbas, C. F., III. *Org. Lett.* **2004**, *6*, 2507.

(6) Lee, E. C.; Hodous, B. L.; Bergin, E.; Shih, C.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 11586.

(7) In the formation of cyclic α-quaternary centers, *E*/*Z* control is not an issue. For examples of formation of cyclic α-quaternary centers, see: (a) Ting, A.; Lou, S.; Schaus, S. E. *Org. Lett.* **2006**, *8*, 2003. (b) Tillman, A. L.; Ye, J.; Dixon, D. J. *Chem. Commun.* **2006**, 1191.

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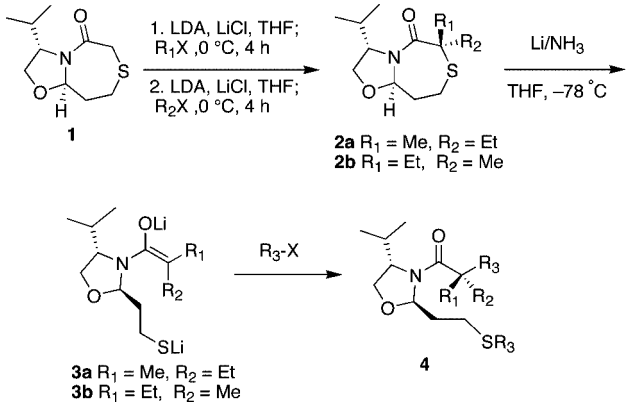
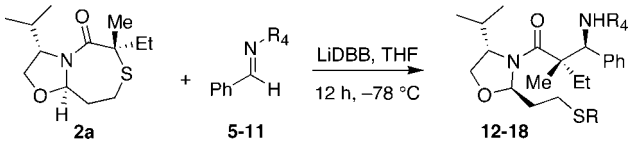
liminary studies showed that enolates formed from proline-derived bicyclic lactams underwent highly selective alkylation and aldol additions, the latter after transmetalation of the lithium enolate to boron in order to achieve high diastereoselectivity.[9] Subsequently, we developed chiral auxiliary **1**, which may be prepared on large scale in three short steps from commercially available materials and which proved to be highly effective in alkylation reactions through both *E*- and *Z*-enolates (Scheme 1).[10]

**Scheme 1.** α,α-Disubstituted Enolate Formation and Alkylation




To examine the application of our bicyclic lactams to Mannich additions, amide **2a** was prepared, as a single diastereomer, by sequential alkylation of **1**. Addition of *E*-enolate **3a**, formed by reductive enolization of **2a** with lithium di-*tert*-butylbiphenylide (LiDBB), to a series of N-protected benzaldimines was examined.[11] Although simple imines such as *N*-benzyl and *N*-phenyl were unreactive at −78 °C, imines bearing either electron-withdrawing or metal-chelating groups afforded addition products in moderate to excellent yields (Table 1). The best compromise between

**Table 1.** Imine Protecting Group Optimization

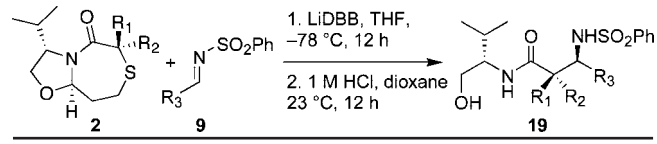



| entry | imine | $R_4$ | product | yield (%) |
|---|---|---|---|---|
| 1 | **5** | Bn | **12** | N.R. |
| 2 | **6** | Ph | **13** | N.R. |
| 3 | **7** | *o*-MeO-$C_6H_4$ | **14** | 44 |
| 4 | **8** | $SO_2PhMe$ | **15** | N.R. |
| 5 | **9** | $SO_2Ph$ | **16** | 83 |
| 6 | **10** | $P(O)Ph_2$ | **17** | 33 |
| 7 | **11** | Bz | **18** | 100 |

yield and ease of protecting group removal was the benzene sulfonyl group (entry 5).

Direct analysis of amides of form **16** is difficult due to the presence of amide rotamers in the $^1H$ NMR and their instability at high temperatures, which precludes high-temperature NMR and GC as analysis methods. To facilitate HPLC analysis of the diastereoselectivity, **16** was partially hydrolyzed using 1 M HCl in dioxane over a period of 12 h at room temperature to provide the stable valinol amide **19a** (Table 2). An authentic standard of all four diastereomers

**Table 2.** Scope of the Mannich Reaction

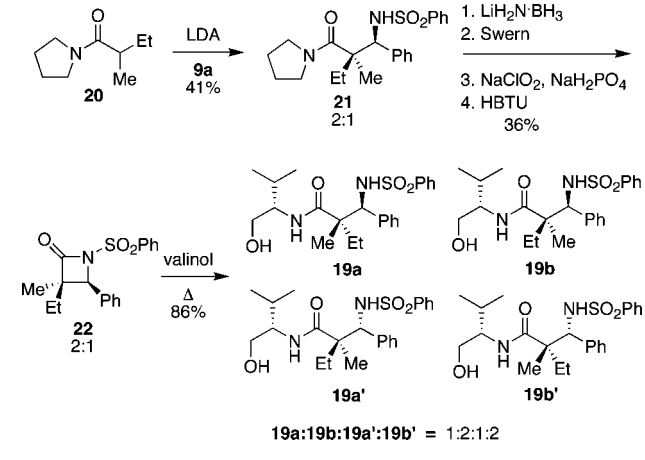



| lactam | $R_1$ | $R_2$ | imine | $R_3$ | product | yield (%) | ds |
|---|---|---|---|---|---|---|---|
| **2a** | Me | Et | **9a** | Ph | **19a** | 83 | 92:4:3:1 |
| **2b** | Et | Me | **9a** | Ph | **19b** | 83[a] | 97:1:1:1 |
| **2c** | Me | Pr | **9a** | Ph | **19c** | 100 | 87:10:2:1 |
| **2d** | Pr | Me | **9a** | Ph | **19d** | 100 | 95:3:2:0 |
| **2e** | Me | Bn | **9a** | Ph | **19e** | 72 | 98:1:1:0 |
| **2f** | Bn | Me | **9a** | Ph | **19f** | 76 | 93:5:2:0 |
| **2g** | Me | allyl | **9a** | Ph | **19g** | 86 | 94:4:2:0 |
| **2h** | allyl | Me | **9a** | Ph | **19h** | 98 | 93:5:2:0 |
| **2b** | Et | Me | **9b** | Ph(*p*-OMe) | **19i** | 93[a] | 99:1:0:0 |
| **2b** | Et | Me | **9c** | Ph(*p*-Br) | **19j** | 80 | 97:2:1:0 |
| **2b** | Et | Me | **9d** | CH=CHPh | **19k** | 76 | 85:12:2:1 |
| **2b** | Et | Me | **9e** | 2-furyl | **19l** | 86[a] | 92:5:2:1 |

[a] Reaction completed in 6 h.

of **19** was prepared via a Mannich reaction of a pyrrolidinyl amide (Scheme 2). Thus, deprotonation of pyrrolidine amide

**Scheme 2.** Synthesis of Authentic Standards




**20** with LDA at 0 °C, followed by addition to benzaldimine **9a**, gives the Mannich adduct **21** in 41% yield in a 2:1 diastereomeric ratio, a reflection of the low enolization stereoselectivity. Reduction of the amide to the primary alcohol using lithium amidoborohydride followed by reoxidation and treatment with HBTU affords β-lactam **22**, again

as a 2:1 mixture, in 36% yield over four steps. Treatment of the lactam with valinol in THF at reflux provides an authentic mixture of all four diastereomers of **19** in 86% yield and in a 1:2:1:2 ratio. Analysis of the Mannich addition product from **2a** by normal phase HPLC indicated that the addition had proceeded with high diastereoselectivity (92:4:3:1). This stereoselectivity was excellent given that no transmetalation of the lithium enolate was necessary. Moreover, reductive enolization of lactam **2b** to form *Z*-enolate **3b** and subsequent addition to imine **9a** afforded **19b**, again with excellent diastereoselectivity (Table 2).

The stereochemistry of both **19a** and **19b** could be determined explicitly by X-ray crystallography (Figure 1).

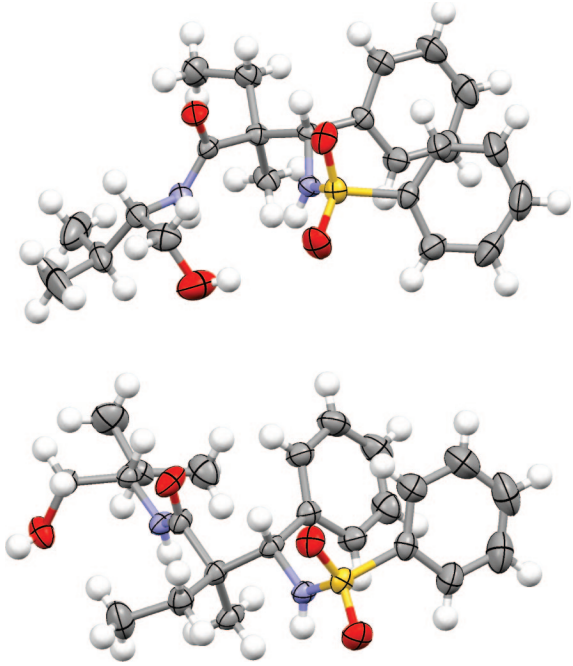


**Figure 1.** X-ray crystal structures of **19a** (top) and **19b** (bottom).

In both instances, the products are consistent with a Zimmerman−Traxler transition state with approach of the imine from the back face of the enolate (as drawn in Scheme 1). This sense of facial selectivity is consistent with that observed in reactions of **3a/b** with alkyl halides.[10] A plausible transition state for reaction of enolate **3a** with **9a** is shown in Figure 2. The enolate nitrogen is undoubtedly pyramidalized, and the enolate presumably twists to relieve A-1,3 interactions between the α-substituents and the ring and *syn*-pentane interactions between the α-substituents and R/R′ groups; the imine then approaches from the more accessible face.[12,13] By comparison of the HPLC traces of the authentic standard with the condensation products of **2a** and **2b** with **9a**, it was possible to determine that the minor isomers formed in 4% and 3% yield from **2a** arise from a small proportion of the *Z*-enolate and opposite facial approach of the imine on the *E*-enolate, respectively.

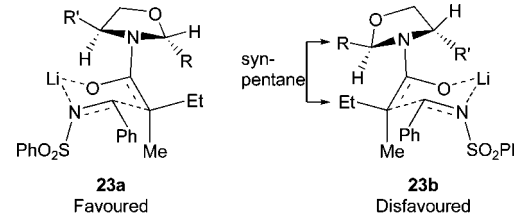
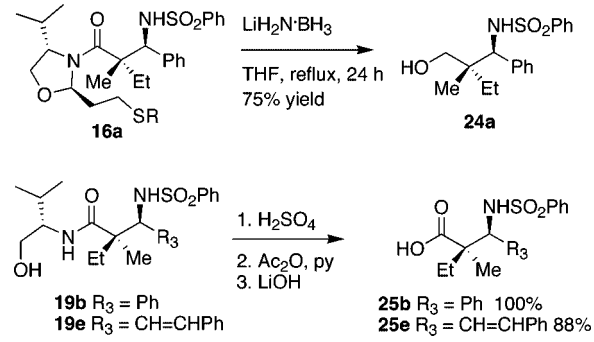



**Figure 2.** Proposed transition states.

A survey revealed that the reaction displays high diastereoselectivity and yields with a variety of amide and imine substrates (Table 2). A variety of α-substituents are well tolerated (propyl, benzyl, allyl), each affording good to excellent diastereoselectivity with both *E*- and *Z*-enolates. The reaction also works well with a series of electron-poor, electron-rich, heteroaromatic, and α,*β*-unsaturated imines.[14]

The chiral auxiliary could be removed cleanly under two sets of conditions. The Mannich addition product **16a** could be cleaved directly under reductive conditions using lithium amidoborohydride to afford protected *β*-amino alcohols in 75% yield (Scheme 3).[15,16] Alternatively, the N-protected *β*-amino acid may be revealed using a three-step hydrolytic sequence involving acid-catalyzed N → O acyl transfer, nitrogen acetylation, and saponification of the resultant amido

**Scheme 3.** Chiral Auxiliary Removal




(8) (a) Manthorpe, J. M.; Gleason, J. L. *J. Am. Chem. Soc.* **2001**, *123*, 2091. For recent non-reductive alternative approaches, see: (b) Qin, Y.-C.; Stivala, C. E.; Zakarian, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 7466. (c) Kummer, D. A.; Chain, W. J.; Morales, M. R.; Quiroga, O.; Myers, A. G. *J. Am. Chem. Soc.* **2008**, *130*, 13231.

(9) (a) Manthorpe, J. M.; Gleason, J. L. *Angew. Chem., Int. Ed.* **2002**, *41*, 2338. (b) Burke, E. D.; Gleason, J. L. *Org. Lett.* **2004**, *6*, 405.

(10) Arpin, A.; Manthorpe, J. M.; Gleason, J. L. *Org. Lett.* **2006**, *8*, 1359.

(11) In contrast to our alkylation studies, use of $Li/NH_3$ as reducing medium did not produce any imine addition products.

(12) Pugh, J. K.; Streitwieser, A. *J. Org. Chem.* **2001**, *66*, 1334–1338.

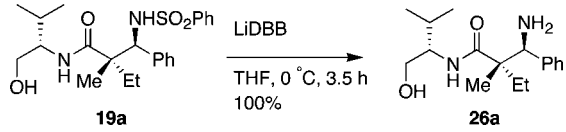
(13) Due to the pseudo-$C_2$-symmetric nature of the enolate auxiliary, rotation about the enolate C−N bond would produce transition states with a similar energy difference as those shown in Figure 2.

(14) Addition of the disubstituted enolates to aliphatic imines gave no identifiable Mannich products.

(15) Myers, A. G.; Yang, B. H.; Kopecky, D. J. *Tetrahedron Lett.* **1996**, *37*, 3623.

ester.[17] Finally, N-deprotection may carried out by titration with LiDBB to give the free amine quantitatively (Scheme 4).

**Scheme 4.** Removal of the Sulfonamide Protecting Group




In conclusion, we have developed a highly diastereoselective method for the formation of quaternary carbon centers via the Mannich reaction. The method is tolerant of a variety of groups on both the enolate and imine functional groups, and the products can be cleaved to afford $\beta$-amino acid and $\beta$-amino alcohol products in high yield.

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**Supporting Information Available:** Experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) Reduction does not proceed efficiently on the partially hydrolyzed prolinol amides **19**.

(17) Attempted direct hydrolysis to the carboxylic acid resulted only in decomposition.