Pergamon

Tetrahedron Letters 43 (2002) 3209–3212

TETRAHEDRON LETTERS

# Stereoselective nucleophilic addition of chiral lithium enolates to (*N*-tosyl)imines: enantioselective synthesis of β-aryl-β-amino acid derivatives

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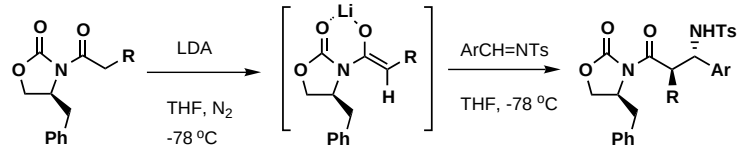
Received 7 January 2002; revised 28 February 2002; accepted 7 March 2002

**Abstract**—Nucleophilic addition of the chiral lithium enolates of (*S*)-(−)-4-benzyl-2-oxazolidinone acetamide with *N*-tosyl arylaldehyde imines gives β-aryl-β-amino acid derivatives in good yields and excellent diastereoselectivity. 

β-Amino acids and their derivatives have attracted considerable attention in recent years due to their occurrence in biologically active natural products.[1] β-Amino acids also serve as precursors in the synthesis of β-lactams,[2] piperidines,[3] indolizidines,[4] and therapeutically enhanced peptides.[5] Moreover, peptides consisting of β-amino acids, the so-called β-peptides, have been extensively studied recently.[6] Given their importance in various fields, considerable efforts have been directed to the stereoselective preparation of β-amino acids and their derivatives.[7]

Among the various methodologies, the reactions of imines with ester enolates or ketenes are powerful approaches for the synthesis of β-amino acids and β-lactams, and they have been extensively explored in the past decades.[8] *N*-Sulfonylimines have attracted considerable attention in recent years, since these highly electrophilic species are capable of undergoing some unique transformations, including nucleophilic additions and cycloadditions.[9] They are also readily available. Evans' chiral oxazolidinones have been widely employed in asymmetric synthesis, in particular, the aldol reactions of aldehydes with lithium or boron enolates have been found to give high diastereoselectivities in the presence of oxazolidinone as the chiral auxiliary.[10] The analogous reaction of *N*-sulfonylimines with chiral lithium enolates would be expected to give β-amino acid derivatives with high diastereocontrol (Scheme 1). Despite the apparent advantages of this approach, there is no report in the literature of the investigation of this reaction so far.[11] In this communication, we report our study on the reactions of *N*-tosyl arylaldehyde imines with chiral lithium enolates derived from (*S*)-4-benzyl-2-oxazolidinone amides. The results indicate that the reaction is highly efficient and stereoselective, thus constituting a practical procedure for the synthesis of enantiomerically pure β-aryl β-amino acids.

Thus, the (*S*)-4-benzyl-2-oxazolidinone acetamide **1a** was deprotonated with 1.1 equivalents of lithium diiso-




**1a, R = H**
**1b, R = Me**

**2a, R = H**
**2b, R = Me**

**3a, R = H**
**3b, R = Me**

**Scheme 1.**

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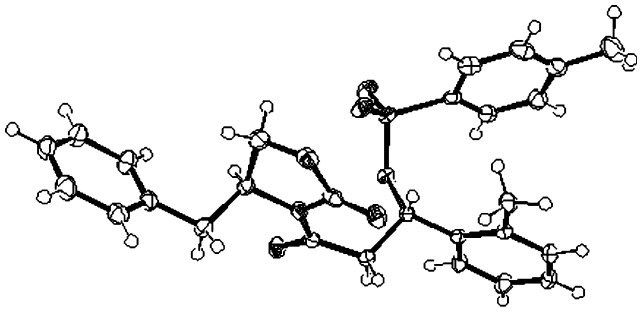
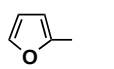
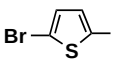
0040-4039/02/$ - see front matter 
PII: S0040-4039(02)00498-7

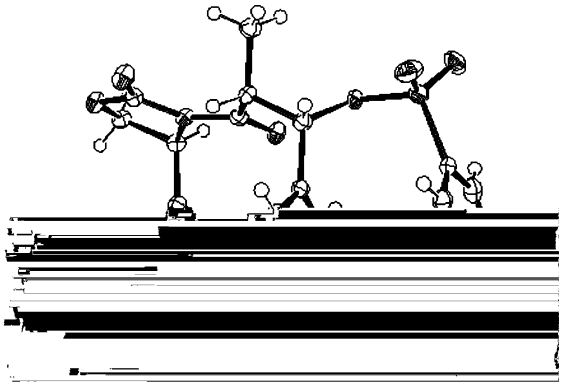
propylamide (LDA) at −78°C, followed by the addition of *N*-tosyl benzaldimine.[12] $^1$H NMR analysis of the crude reaction mixture indicated that the nucleophilic addition product was a single isomer. Reactions with other *N*-tosyl arylaldehyde imines all gave single addition products, except when the aryl group was *o*-methylphenyl, in which case an 89:11 mixture of two diastereoisomers was obtained (entry 6, Table 1). It is worth noting that this reaction works equally well with *N*-tosyl 2-furaldehyde imine, *N*-tosyl 5-bromo-2-thiophenecarboxaldehyde imine and *trans*-cinnamaldehyde imine (entries 7, 8, 9). In all these cases, excellent diastereoselectivities were achieved. The stereochemistry of the newly generated chiral center was confirmed as *S* from the X-ray structure of the addition product **3a** (Ar = *o*-$MeC_6H_4$) (Fig. 1).[13]

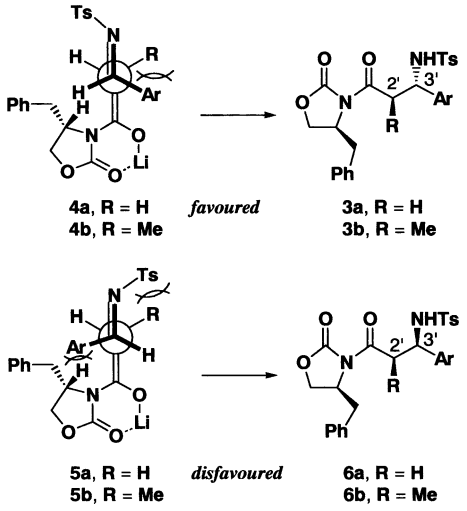


Encouraged by the success of the stereocontrol in the above reaction, we proceeded to extend the investigation using the lithium enolate derived from (*S*)-(+)-4-benzyl-3-propionyl-2-oxazolidinone. In this case, two chiral centers will be generated in the nucleophilic addition step, thus giving four possible diastereoisomers. Under similar reaction conditions to those mentioned above, the reaction of the lithium enolate **2b** with *N*-tosyl benzaldimine gave a mixture of addition products in moderately high yield. Inspection of the $^1$H NMR spectra (400 MHz) of the crude product indicated that there were only two diastereoisomers. The








**Scheme 2.**

## References


1. (a) Drey, C. N. C. In *Chemistry and Biochemistry of the Amino Acids*; Barrett, G. C., Ed.; Chapman and Hall: New York, 1985, Chapter 3; (b) Griffith, O. W. *Annu. Rev. Biochem.* **1986**, *55*, 855; (c) Cardillo, G.; Tomasini, C. *Chem. Soc. Rev.* **1996**, *25*, 117.
2. Juaristi, E.; Quintana, D.; Escalante, J. *Aldrichim. Acta* **1994**, *27*, 3.
3. For example, see: Jefford, C. W.; Wang, J. B. *Tetrahedron Lett.* **1993**, *34*, 2911.
4. For example, see: Jefford, C. W.; Wang, J. B. *Tetrahedron Lett.* **1993**, *34*, 3119.
5. Spatola, A. F. In *Chemistry and Biochemistry of Amino Acids, Peptides and Proteins*; Weinstein, B., Ed.; Marcel Dekker: New York, 1983; Vol. 7, pp. 331–333 and references cited therein.
6. For reviews on β-peptides, see: (a) Gellman, S. H. *Acc. Chem. Res.* **1998**, *31*, 173; (b) Seebach, D.; Abele, S.; Gademann, K.; Jaun, B. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 1596.
7. For reviews, see: (a) Cole, D. C. *Tetrahedron* **1994**, *50*, 9517; (b) *Enantioselective Synthesis of β-Amino Acids*; Juaristi, E., Ed; Wiley-VCH: New York, 1997; (c) Juaristi, E.; Lopez-Ruiz, H. *Curr. Med. Chem.* **1999**, *6*, 983; (d) Abele, S.; Seebach, D. *Eur. J. Org. Chem.* **2000**, 1.
8. For reviews, see: (a) Hart, D. J.; Ha, D.-C. *Chem. Rev.* **1989**, *89*, 1447; (b) Bloch, R. *Chem. Rev.* **1998**, *98*, 1407; (c) Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069.
9. For a review, see: Weinreb, S. M. *Top. Curr. Chem.* **1997**, *190*, 131; For a recent example, see: Jiang, N.; Qu, Z.; Wang, J. *Org. Lett.* **2001**, *3*, 2989.
10. (a) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127; (b) For a recent application in β–amino acid synthesis, see: Evans, D. A.; Wu, L. D.; Wiener, J. J. M.; Johnson, J. S.; Ripin, D. H. B.; Tedrow, J. S. *J. Org. Chem.* **1999**, *64*, 6411.
11. Several papers on the reaction of imines with chiral enolates in β-amino acid synthesis have appeared recently, see: (a) Kawakami, T.; Ohtake, H.; Arakawa, H.; Okachi, T.; Imada, Y.; Murahashi, S.-I. *Org. Lett.* **1999**, *1*, 107; (b) Pilli, R. A.; Alves, C. de F.; Bockelmann, M. A.; Mascarrenhas, Y. P.; Nery, J. G.; Vencato, I. *Tetrahedron Lett.* **1999**, *40*, 2891; (c) Ohtake, H.; Imada, Y.; Murahashi, S.-I. *J. Org. Chem.* **1999**, *64*, 3790; (d) Kawakami, T.; Ohtake, H.; Arakawa, H.; Okachi, T.; Imada, Y.; Murahashi, S.-I. *Chem. Lett.* **1999**, 795. (e) Kise, N.; Ueda, N. *Org. Lett.* **1999**, *1*, 1803; (f) Kise, N.; Ueda, N. *J. Org. Chem.* **1999**, *64*, 7511; (g) Vicario, J. L.; Badia, D.; Carrillo, L. *Org. Lett.* **2001**, *3*, 773.

aqueous $NH_4Cl$ solution at the same temperature, and the mixture was extracted with $CH_2Cl_2$. The combined organic layers were dried over anhydrous $Na_2SO_4$. The usual work-up gave a crude product which was analyzed by $^1H$ NMR for determining the diastereoisomeric ratio. Purification by column chromatography with silica gel and recrystallization gave a pure sample for characterization. Data for (4*S*)-benzyl-3-[(3′*S*)-(*N*-tosyl)amino-3′-(2-methyl)phenylpropionyl]-2-oxazolidinone (**3a**, R = H, Ar = *o*-$MeC_6H_4$): mp 128–130°C; $[\alpha]_D^{20}$ +3.85 (*c* 0.93, $CHCl_3$); IR (KBr) 3245, 1786, 1682 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 2.17 (s, 3H), 2.23 (s, 3H), 2.70 (dd, $J = 13.6$, 9.6 Hz, 1H), 3.23 (dd, $J = 13.6$, 2.5 Hz, 1H), 3.34 (dd, $J = 15.4$, 5.7 Hz, 1H), 3.51 (dd, $J = 15.5$, 8.4 Hz, 1H), 4.12–4.20 (m, 2H), 4.57–4.63 (m, 1H), 5.13–5.29 (m, 1H), 5.76 (d, $J = 8.2$ Hz, 1H), 7.01–7.53 (m, 13 H); $^{13}C$ NMR (50 MHz, $CDCl_3$) $\delta$ 18.94, 21.34, 37.68, 41.96, 50.86, 55.36, 66.36, 125.91, 126.35, 126.95, 127.30, 127.55, 128.93, 129.23, 129.38, 130.50, 135.11, 135.17, 137.55, 137.91, 143.03, 153.67, 170.11; EI–MS (*m*/*z*