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

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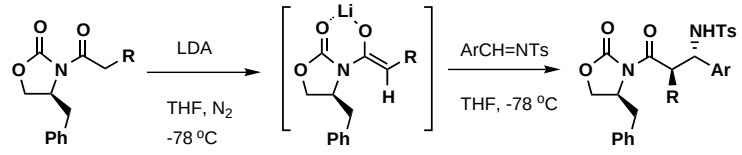
Abstract—Nucleophilic addition of the chiral lithium enolates of (*S*)-(−)-4-benzyl-2-oxazolidinone acetamide with *N*-tosyl arylaldehyde imines gives β-aryl-β-amino acid derivatives in good yields and excellent diastereoselectivity.

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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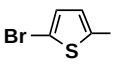
propylamide (LDA) at −78°C, followed by the addition of *N*-tosyl benzaldimine.[12] ^{1}H NMR analysis of the crude reaction mixture indicated that the nucleophilic addition product was a single isomer. Reactions with other *N*-tosyl arylaldehyde imines all gave single addition products, except when 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 diastereoselectivity of the two isomers was only moderate (dr = 77:23) (Table 2, entry 1). Addition of lithium chloride (5 equivalents) to the reaction did not improve the stereoselectivity. For two other *N*-tosyl imine substrates, similar results were obtained (entries 3 and 4). On the other hand, when the enolate was generated by $TiCl_4/Et_3N$,[14] the nucleophilic addition gave diminished distereoselectivity (entry 5).

The stereochemistry of the two newly generated chiral centers for the major product was established as (2′*R*, 3′*S*) from the X-ray structure of **3b** (Ar = C_6H_5) (Fig. 2).[13] Although the stereochemistry of the minor isomer was not experimentally confirmed, it is postulated to be (2′*R*, 3′*R*), based on the analysis of the transition state of the reaction (vide infra).

Table 1. Reaction of chiral enolate **2a** with *N*-tosyl imines

Entry	*N*-Tosyl imines Ar =	Diastereoisomeric ratio[a]	Yield (%)[b]
1	C_6H_5	>95:5	87
2	*m*-$CF_3C_6H_4$	>95:5	91
3	*p*-FC_6H_4	>95:5	81
4	*p*-ClC_6H_4	>95:5	92
5	*p*-$MeOC_6H_4$	>95:5	83
6	*o*-MeC_6H_4	89:11	89
7		>95:5	78
8		>95:5	77
9	*trans*-PhCH=CH	>95:5	74

[a] Product ratio was determined by ^{1}H NMR (400 or 200 MHz).
[b] Yields after chromatographic purification on silica gel.

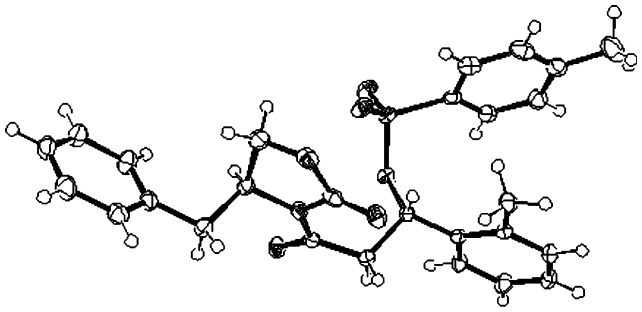


Figure 1. ORTEP view of the addition product **3a** (Ar = *o*-MeC_6H_4).

Table 2. Reaction of chiral enolate **2b** with *N*-tosyl imines

Entry	*N*-Tosyl imine (Ar =)	Reaction conditions	Ratio[a]	Yield (%)[b]
1	C_6H_5	LDA	77:23	57
2	C_6H_5	LDA + LiCl	73:27	63
3	*m*-$CF_3C_6H_4$	LDA	76:24	90
4	*p*-FC_6H_4	LDA	67:33	78
5	*p*-FC_6H_4	$TiCl_4/Et_3N$	54:46	70

[a] Product ratio was determined by ^{1}H NMR (400 or 200 MHz).
[b] Yields after chromatographic purification on silica gel.

The stereochemical outcome can be rationalized by the transition state depicted in Scheme 2.[15] The absolute configuration at C-3′ is controlled by the enantiofacial selection of *N*-sulfonylimine, while the stereochemistry at C-2′ is due to the structure of the lithium enolate, which is predominantly the *Z*-enolate.

In contrast to the reaction of aldehydes with lithium or boron enolates, in which the oxygen of the aldehyde carbonyl group coordinates to the lithium or boron to form a six-membered ring transition state, the nitrogen of the *N*-sulfonylimine has little ability to coordinate to lithium because of the strongly electron-withdrawing

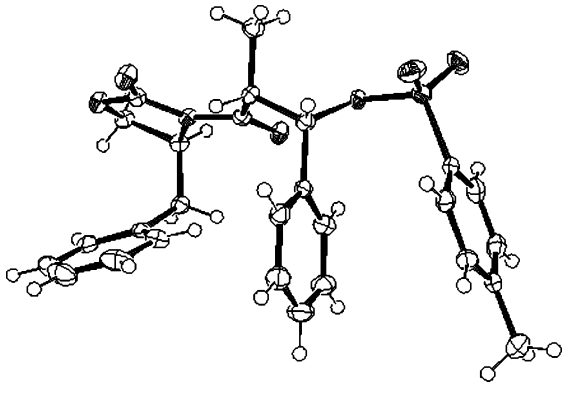
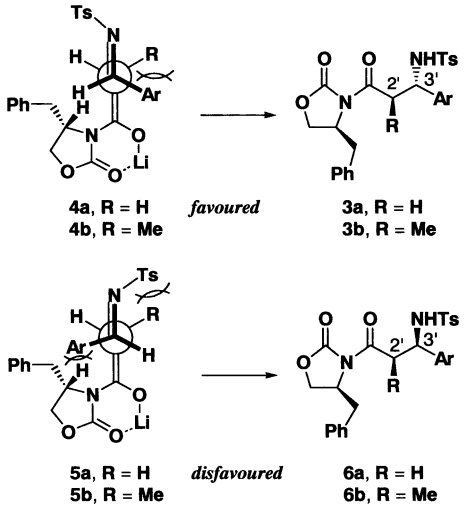


Figure 2. ORTEP view of the addition product **3b** (Ar = C_6H_5).



Scheme 2.

tosyl group attached. Consequently, the nucleophilic addition most likely proceeds through an open transition model **4a** in which the *N*-sulfonylimine orientates to avoid steric repulsion. On the other hand, when the R is a methyl group, the *gauche* interaction between the phenyl group and the methyl group raises the energy of the transition state **4b**, thus resulting in the low diastereoselectivity.

It is interesting to note that in the aldol reaction with Evans' oxazolidinone auxiliary, the enolate derived from acetamide gives poor selectivity at the C-3′ position, while the enolates derived from other amides in general give excellent diastereoselectivity. In the reaction with *N*-sulfonylimine, we have observed opposite results, the selectivity for **2a** is high, while that for **2b** is poor. These results can be rationally explained according to the transition state model shown in Scheme 2.

In summary, we have shown that the reaction of *N*-tosylimines with chiral lithium enolates derived from (*S*)-(−)-4-benzyl-2-oxazolidinone acetamide give high yields and excellent diastereoselectivity. The reaction is operationally simple and the *N*-tosylimines are readily available. Therefore, this is a highly efficient method for the synthesis of β-aryl β-amino acid derivatives, the stereoselective synthesis of which has been particularly challenging with only limited methods available.[16]

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12. A typical procedure. Butyllithium (1 mL, 1.1 M in hexane, 1.1 mmol) was added dropwise to diisopropylamine (1.2 mmol) in anhydrous THF (6 mL) at −78°C, under a nitrogen atmosphere. After the solution was stirred for about 15 min at the same temp., (*S*)-(−)-4-benzyl-2-oxazolidinone acetamide (**1a**, 1 mmol) in anhydrous THF (6 mL) was added dropwise. The solution was stirred for 30 min, then a solution of *N*-tosyl aldehydimine (1.1 mmol) in anhydrous THF (6 mL) was slowly added at −78°C. The mixture was stirred at this temperature until TLC indicated that no starting oxazolidinone remained (about 4 h). The reaction mixture was quenched with saturated

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, $CDCl_3$) δ 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, $CDCl_3$) δ 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*, relative intensity) 492 (M^+, 3), 321 (12), 303 (2), 274 (8), 219 (5), 171 (34), 145 (100), 118 (70), 91 (94), 65 (60), 43 (38); Anal. Calcd for $C_{27}H_{28}N_2O_5S$: C, 65.84; H, 5.73; N, 5.69. Found: C, 65.79; H, 5.73; N, 5.71.

13. The crystallographic measurement was made on a Rigaku R-AXIS RAPID image plate diffractometer with graphite monochromated Mo–Kα radiation (λ = 0.71073 Å). An absorption correction was applied by correction of symmetry-equivalent reflections using the ABSCOR program. The structure was solved by direct methods and successive difference maps (SHELXS 97) and refined by full-matrix least-squares on F^2 using all unique data (SHELXL 97). The non-hydrogen atoms were refined anisotropically. The hydrogen atoms were included in their calculated positions with geometrical constraints and refined in the riding model. Lists of refined coordinates have been deposited at the Cambridge Crystallographic Data Centre (deposition number **3a**, R = H, Ar = *o*-MeC_6H_4, CCDC 175691; **3b**, R = Me, Ar = C_6H_5, CCDC 176744). Copies of the available material can be obtained free of charge on application to the CCDC, 12, Union Rd., Cambridge CB2 1EZ, UK E-mail: deposit@ccdc.cam.ac.uk.
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