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Diastereoselective Addition of α-Sulfinyl Ester Enolate with Benzaldimines Possessing an Electron Withdrawing Group at the Nitrogen Atom

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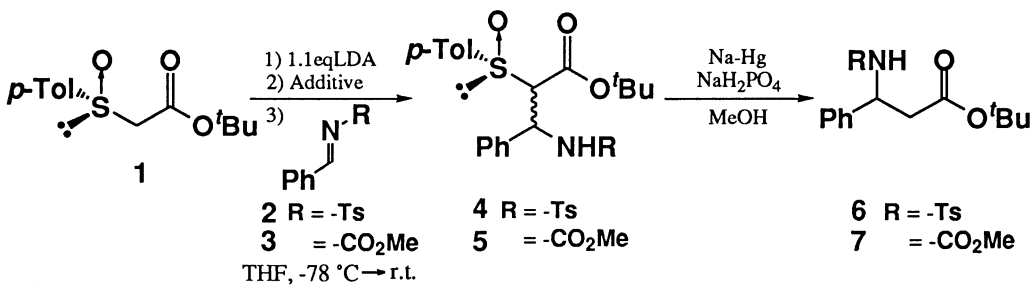
The reaction of optically pure α-sulfinyl ester enolate with benzaldimines possessing an electron withdrawing group at the nitrogen atom gave β-amino ester in both enantiomeric forms in satisfactory optical and chemical yields (up to 94%ee), in which the changeover of the diastereofacial selectivity was induced by suitable choice of the protecting group at the nitrogen and the use of additives.

The use of sulfoxides as chiral synthons in asymmetric synthesis is now a well-established and reliable strategy, and has been the subject of several excellent reviews.[1] The sulfinyl ester is easily available by the Andersen synthesis, but has not been used in the reaction of the imine-enolate condensation. The diastereoselective addition of ester enolates with imines has been applied to the preparation of chiral β-amino acid derivatives.[2] The chiral β-amino acid derivatives are varsatile synthons which can be transformed to a number of differently functionalized products. Among them non-proteinogenic β-amino esters are receiving increasing interest especially in connection with the synthesis of β-lactam antibiotics. It is extremely useful to synthesize both enantiomers from an identical starting chiral auxiliary, only by changing the reaction conditions without using the chiral auxiliary in both enantiomeric forms. In our recent works, we reported the synthesis of both enantiomers of β-lactams using an optically active imine or ester enolate possessing a chiral auxiliary at the alkoxy part.[3] In this paper we report diastereoselective addition of an optically active α-(*p*-toluene)sulfinyl ester enolate with benzaldimine possessing an electron withdrawing group at the nitrogen atom, in which β-phenyl-β-alanine derivatives were obtained in both enantiomeric forms in satisfactory optical and chemical yields after removal of the chiral sulfinyl group using sodium amalgam. These β-amino acid derivatives are useful chiral synthons for the synthesis of β-lactams and natural products.[4] We observed that the diastereoselectivity of asymmetric addition was influenced by the nature of enolate metal, the amount of additives and the protecting group at the nitrogen.



Scheme 1.

Table 1. Yields and Selectivities of Asymmetric Addition[a)]

Imine	Additive (eq)	Time/h	Yield of **4,5**/%[b)]	Yield of **6,7**/%[b)]	3*S* : 3*R*[c)]
2	None	6	30	82	87 : 13
	$ZnCl_2$ (1.0)	17	50	36	82 : 18
	$MgBr_2$·OEt_2 (3.0)	22	13	99	91 : 9
	$CeCl_3$ (1.0)	9	36	74	94 : 6
	Et_3B (3.0)	18	18	74	91 : 9
	Me_4Sn (1.0)	13	56	74	95 : 5
3	None	14	54	87	21 : 79
	None[d)]	4	44	41	3 : 97
	$MgBr_2$·OEt_2 (1.1)	16	78	73	35 : 65
	$MgBr_2$·OEt_2 (2.1)	15	62	78	42 : 58
	$MgBr_2$·OEt_2 (3.1)	17	60	83	45 : 55
	MgI_2 (1.1)	4	65	81	30 : 70
	MgI_2 (2.1)	16	67	67	64 : 36
	MgI_2 (3.1)	15	62	68	68 : 32

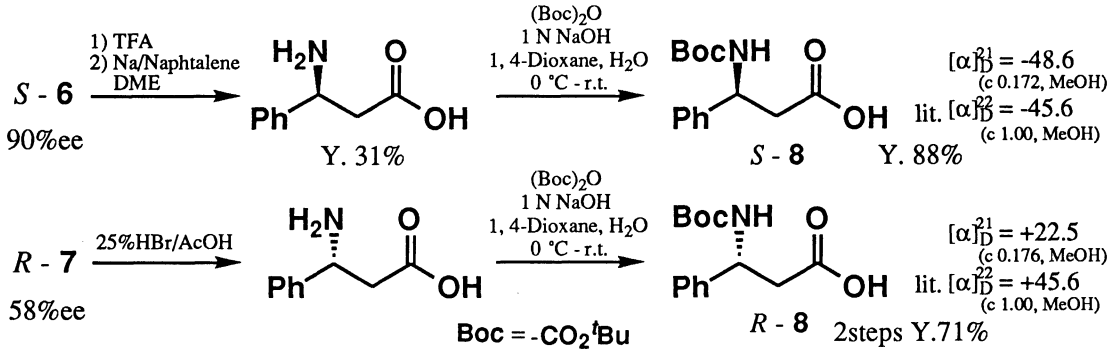
a) The reaction was carried out with the reactant ratio of enolate : imine = 1.1 : 1.0 at -78 °C. b) Isolated yield. c) Determined by HPLC using a chiral stationary column (Daicel OJ), and the determination of the absolute configuration, see text. d) Imine was added at -100 °C.

The starting α-sulfinyl ester[5)] and *N*-tosylimine[6)] were obtained by the known methods. The metal enolate of the enantiomeric pure α-sulfinyl ester **1** showed relatively low reactivity towards usual benzaldimines having such substituent as *N*-trimethylsilyl or *N*-(*p*-methoxyphenyl) group and so on, and no desirable addition products were obtained. *N*-Toluenesulfonyl benzaldimine **2** has a strong electron withdrawing group (EWG) at the nitrogen, and therefore exhibits high reactivity as an electrophile. Using this *N*-EWG substituted imine, the reaction of the ester enolate proceeded smoothly at low temperature in good yield. The enantiomeric excess of β-aminoester was determined by HPLC after removal of the chiral sulfinyl group with sodium amalgam.[7)]

The reaction was carried out by deprotonation of the ester with LDA, and to the resulting enolate was added the imine at -78 °C. In the cases where transmetallation or ate complex formation, additives were added to the lithium enolate, and the reaction was conducted as above. The resulting mixture was stirred for several hours at -78 °C to room temperature followed by an aqueous workup (quenched by phosphate buffer solution). The crude addition product was purified on preparative silica gel TLC. As shown in Table 1 addition products **4**[8)] was obtained in satisfactory yield and selectivity. Some cases where the addition products were obtained in low yields were mainly due to the recovery of the starting materials. Determination of the diastereomeric ratios of **4** was not trivial due to the high acidity of the proton α to the carbonyl, and therefore the removal of the sulfinyl group was carried out. The treatment of the addition products **4** with 10% sodium amalgam in the presence of anhydrous sodium dihydrogen phosphate in methanol gave β-phenyl-β-alanine derivatives **6**[9)] in satisfactory yield (Scheme 1). The optical purity of the amino ester was determined by HPLC using a chiral cel (Daicel OJ). The best result was obtained with the ate complex prepared from tetramethyl tin (90%ee, 3-*S*).

Although our initial target is changeover of the diastereofacial selectivity by changing the enolate metal or the equivalent of additives, these results are independent of the character and the amount of enolate metal, and

suggest that the lone pair of nitrogen atom of *N*-tosylimine would be sterically less demanding than those of usual imines, because of a strong electron withdrawing group, such as *p*-toluenesulfonyl group. To utilize the lone pair of the imine, *N*-methoxycarbonyl benzaldimine **3** easily prepared by a known method[10] was used. The reaction was carried out in a similar manner to the *N*-tosylimine cases, and the adduct **5**[11] thus obtained was reduced with sodium amalgam to **7**.[12] The optical purities were determined by HPLC using a chiral cel (Daicel OJ). Interestingly, the switchover of stereochemistry of the β-amino ester as compared with the case of *N*-tosylimine was observed. The best result was obtained with the lithium enolate (94%ee, 3-*R*, imine added at -100 °C). In the case of the bromomagnesium enolate, an increase of the amount of magnesium bromide results in the decrease of the diastereoselection. On the other hand, the changeover of the diastereofacial selectivity was observed in the iodomagnesium enolate, and the increasing the amount of magnesium iodide gave 3-*S* isomer as a major product. The absolute configurations of **6** and **7** were determined by converting them into the corresponding known *N*-protected β-amino acid **8**[13] after hydrolysis of the ester and deprotection of the amino group followed by protection of the amino group (Scheme 2).



Scheme 2.

The possible transition states of the present asymmetric addition[14] of ester enolate with *N*-EWG substituted imine are shown in Fig. 1. In the case of *N*-tosylimine, asymmetric addition would proceed through A or B via an anti-periplaner transition state regardless of the nature of the enolate metal in which B would be preferable one due to less sterically demanding open state. On the other hand, in the case of *N*-methoxycarbonyl imine, two transition states[15] may be involved, a chelation model C and a non-chelation model D. In the cases of the lithium and the bromomagnesium enolates, the reaction most probably proceeded through the chelation model C, whereas by using two equivalents magnesium iodide through the non-chelation model D. This difference originates in the difference of the Lewis acidity between magnesium bromide and magnesium iodide, and the difference of the bulkiness of the halogen atoms.

In conclusion, we demonstrated the aldol type condensation of an optically pure α-sulfinyl ester enolate

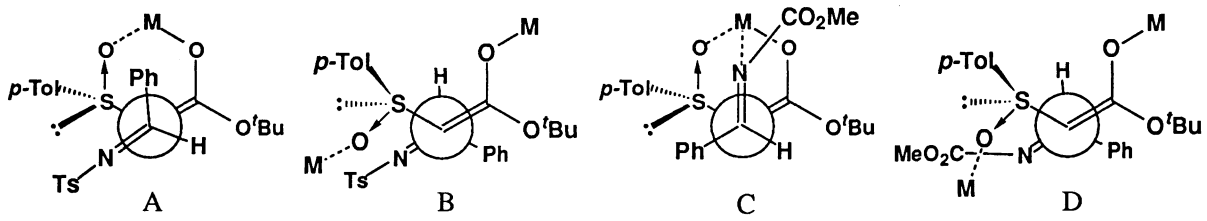


Fig. 1.

to *N*-EWG substituted imines, and succeeded in the switchover of the diastereofacial selectivity by changing of he enolate metal, the equivalent of the additives and the protecting group at the nitrogen. We obtained β-phenyl-β-alanine derivatives in both enantiomeric forms in satisfactory yields and in high enantiomeric excess.

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8) ^{1}H NMR (270 MHz, $CDCl_3$): δ = 0.75-1.28 (m, 9H), 2.37-2.43 (m, 3H), 3.60-3.91 (m, 1H), 4.76-5.38 (m, 1H), 6.37-7.85 (m, 13H); IR ($CHCl_3$) 3350, 1710, 1350, 1140, 1100, 900 cm^{-1}.
9) ^{1}H NMR (270 MHz, $CDCl_3$): δ = 1.30 (s, 9H), 2.37 (s, 3H), 2.59-2.75 (m, 2H), 4.65-4.72 (q, *J* = 6.3, 7.3 Hz, 1H), 5.75 (d, *J* = 1.0 Hz, 1H), 7.08-7.26 (m, 7H), 7.59 (d, *J* = 8.3 Hz, 2H); IR ($CHCl_3$) 3250, 2975, 1720, 1460, 1330, 1160 cm^{-1}.
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11) ^{1}H NMR (270 MHz, $CDCl_3$): δ = 0.84–0.96 (m, 9H), 2.41 (s, 3H), 3.72 (s, 3H), 5.02-5.66 (m, 1H), 6.49-6.92 (s, 1H), 7.13-7.64 (m, 9H); IR ($CHCl_3$) 3440, 1720, 1500, 1240, 1130, 1040 cm^{-1}.
12) ^{1}H NMR (270 MHz, $CDCl_3$): δ = 1.33 (s, 9H), 2.74–2.77 (bs, 2H), 3.67 (s, 3H), 5.09 (bs, 1H), 7.25-7.36 (m, 5H); IR ($CHCl_3$) 1720, 1500, 1370 cm^{-1}.
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