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Switchover of Diastereofacial Selectivity in the Condensation Reaction of Optically Active *N*-Sulfinimine with Ester Enolate

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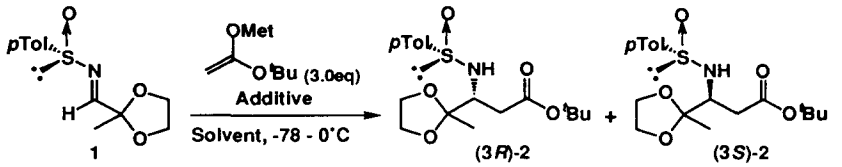
Abstract: Both diastereomers of β-aminoester can be obtained diastereoselectively in the reaction of optically active *N*-sulfinimine possessing 2-methyl-1,3-dioxolanyl group with ester enolate simply by changing the enolate metal species, additives, and solvents. The β-aminoester can be converted into the corresponding 3-unsubstituted β-lactam. Copyright © 1996 Elsevier Science Ltd

β-Lactams are four-membered cyclic amides derived from 3-amino-propanoic acids. The first member of this class of compounds was synthesized by Staudinger.[1] The importance of β-lactam antibiotics, however, was not recognized until the discovery of penicillin by Fleming in 1929.[2] 3-Unsubstituted β-lactams are useful precursors which are able to be converted into antibiotics such as clavulanic acid, and other necessary substituents can be introduced into 3-position.[3] In our recent works, we reported the synthesis of both enantiomers of β-lactams using an optically active imine or ester enolates possessing a chiral auxiliary at the alkoxy part.[4,5] 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.[6] *N*-Sulfinimines are easily available by the reaction of the corresponding aldehydes with lithium hexamethyldisilazide (LHMDS), (*S*)-(-)menthyl sulfinate,[7] and CsF.[8] Generally the diastereomers possessing an optically active sulfinyl group are separable, and S-N bond is to be easily cleaved.[9] A careful examination of the current literatures has revealed that the reaction of *N*-sulfinimine with ester enolate is scarce and of limited scope,[10] and there has been no precedent for the selective synthesis of each diastereomers from a single chiral *N*-sulfinimine. In this paper we wish to report the diastereoselective addition of ester enolate to optically active *N*-sulfinimine **1**, in which 3-unsubstituted β-lactam derivative could be obtained in both enantiomeric forms in good chemical and excellent optical yields after removal of the chiral sulfinyl group, hydrolysis of the ester part, and cyclization. The changeover of the diastereofacial selectivity was observed simply by changing the enolate metal species, additives and solvents.[11]



The starting material of the optically active *N*-sulfinimine **1** was prepared by the reaction of the corresponding aldehyde **8** with LHMDS, (*S*)-(-)menthyl-*p*-toluene sulfinate, and CsF in 5 steps.[12] The

asymmetric addition was carried out in the following manner: deprotonation of *t*-butyl acetate with LDA was followed by addition of *N*-sulfinimine **1** at -78°C. In the cases of transmetallation, additives such as $ClTi(O^iPr)_3$, $ClAlEt_2$ were added to the lithium enolate, and the resulting enolate was stirred for 30 min followed by addition of *N*-sulfinimine **1**. The resulting mixture was stirred for several hrs at -78°C to 0°C and quenched by a phosphate buffer solution. The crude addition product was purified on preparative silica gel TLC which was pretreated with phosphate buffer.

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

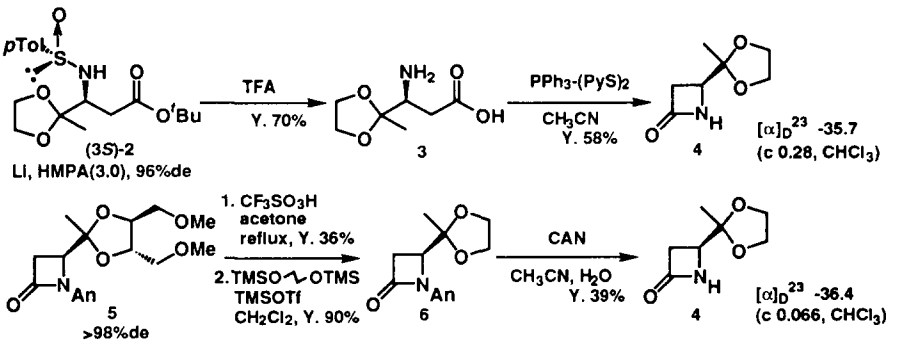
Metal	Additive (eq)	Solvent	Time/h	Yield/%[b)]	3*R* : 3*S* [c)]
Li	-	THF	11	65	14 : 86
	HMPA (3.0)	THF	8	68	2 : 98
	HMPA (4.5)	THF	7	71	4 : 96
	-	Et_2O	7	75	82 : 18
$Ti(O^iPr)_3$	-	THF	5	89	96 : 4
$AlEt_2$	-	THF	19	39	84 : 16
AlEtCl	-	THF	5	79	77 : 23
K	18-Crown-6 (3.0)	THF	12	51	6 : 94

a) The reaction was carried out with the reactant ratio of enolate : imine = 3.0 : 1.0 at -78 °C. b) Isolated yield. c) Determined by HPLC analysis (Hibar Column), and for the determination of the absolute configuration, see text.

As shown in Table 1, addition products **2**[13] were obtained in good yield and with excellent selectivity. The case of aluminum enolate where the addition products were obtained in only 39% yield was mainly due to the recovery of the starting chiral imine. The diastereomeric ratio of the β-amino ester was determined by HPLC analysis using a pre-packed column (Merck Hibar). The best result was obtained with the lithium enolate in the presence of 3 eq of HMPA in THF (68% yield, 3*R* : 3*S* = 2 : 98). Switchover of diastereofacial selectivity was accomplished by changing the enolate metal, and it was also effected by changing the solvent in the case of the Li enolate. The titanium enolate prepared by transmetallation with $ClTi(O^iPr)_3$ afforded the best result (89% yield, 3*R* : 3*S* = 96 : 4). In order to gain an insight into the transition state, the reaction was carried out with the potassium enolate prepared by deprotonation with potassium hexamethyldisilazide (KHMDS) in the presence of 18-crown-6-ether. The reaction proceeded most probably through a non-chelation pathway to afford the addition product which had the same stereochemistry as in the case of the lithium enolate in the presence of 3 eq of HMPA in THF. The diastereomers (3*R*)- and (3*S*)-**2** could also be separated on silica gel TLC.

Determination of the absolute configurations of the amino esters **2** and synthesis of 3-unsubstituted β-lactam were carried out in the following manner: removal of the chiral sulfinyl group[9] and concomitant hydrolysis of the *t*-butyl ester of **2** were effected with TFA to give amino acid **3** in 70% yield. Cyclization of β-amino acid **3** using PPh_3-$(PyS)_2$[14] in acetonitrile gave 3-unsubstituted β-lactam **4**[15] in 58% yield. The β-lactam **5** already reported[4c] was converted into the same β-lactam **4** by removal of the chiral auxiliary and ketalization to the dioxolane ring,[16a] followed by deprotection on nitrogen atom.[16b] Comparison of the spectral data and the optical rotation of **4** established the absolute stereochemistry.

Possible transition states of the present asymmetric addition of ester enolate with *N*-sulfinimine are shown in Fig. 1. The sense of diastereoselectivity is predictable by non-chelation and chelation-control models.



In the cases of the lithium enolate in THF and the potassium enolate with 18-crown-6-ether in THF, asymmetric addition would proceed through a non-chelation transition state to give the *S*-adduct. In the presence of HMPA, the diastereomeric ratio was improved due to the solvation of the lithium cation with HMPA. On the other hand, in the case of the titanium enolate, a six-membered chair-like transition state containing a four-membered metallocycle,[9a] and/or a seven-membered counterpart may be involved, which is responsible for the formation of *R*-isomer. In each case, the ester enolate approaches from the direction opposite to the sterically congested *p*-tolyl group, forming the carbon-carbon bond with high diastereoselectivity.

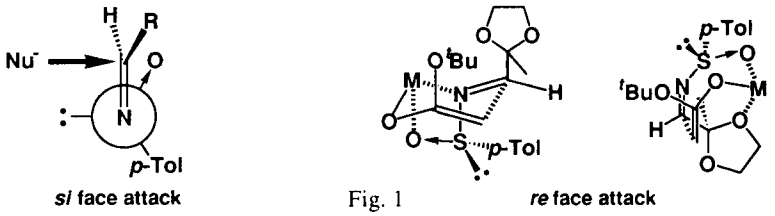


Fig. 1

In conclusion, we demonstrated the aldol type condensation of the ester enolate with optically active *N*-sulfinimine, and succeeded in the switchover of the diastereofacial selectivity by changing the enolate metal, additive, and solvent. The β-amino acid derivatives were obtained in both enantiomeric forms in good yield and with excellent enantiomeric purity. These β-amino acid derivatives are useful chiral synthons for 3-unsubstituted β-lactams and other natural compounds.[17]

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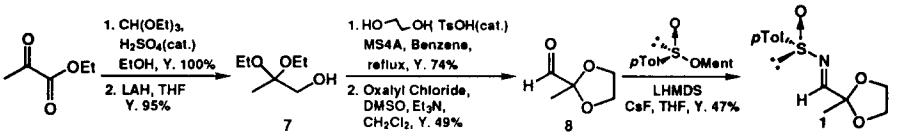
12. The starting material of optically active *N*-sulfinimine was prepared in the following manner. Ethyl pyruvate was treated with 2.2 eq of triethyl orthoformate in EtOH in the presence of a catalytic amount of sulfuric acid to give diethyl acetal in 100% yield. Reduction of the diethyl acetal was conducted with 1.2 eq of lithium aluminum hydride in tetrahydrofuran (THF) to afford alcohol **7** in 95% yield. To build the 2-methyl-1,3-dioxolanyl group, alcohol **7** was treated with 1.1eq of ethylene glycol in benzene in the presence of a catalytic amount of *p*-TsOH at 80°C to afford 2-methyl-1,3-dioxolanyl derivative in 74% yield. Aldehyde **8** was obtained by the Swern oxidation in 49% yield, and the subsequent treatment with LHMDS and (*S*)-(-)-menthyl sulfinate in the presence of CsF afforded the optically active *N*-sulfinimine **1** in 47% yield. ^{1}H-NMR (270MHz, $CDCl_3$): δ 1.55 (s, 3H), 2.40 (s, 3H), 3.92-4.07 (m, 4H), 7.29 (d, 2H, *J* = 8.1Hz), 7.55 (d, 2H, *J* = 8.1Hz), 8.02 (s, 1H); IR (neat): 2900, 1630, 1180, 1100, 1040, 860, 810 cm^{-1}; $[\alpha]_D^{23}$ +286.3 (c 0.50, $CHCl_3$).



13. ^{1}H-NMR (3*S*, 270MHz, $CDCl_3$): δ 1.26 (s, 3H), 1.46 (s, 9H), 2.40 (s, 3H), 2.53 (dd, 1H, *J* = 7.0Hz, 15.0Hz), 2.65 (dd, 1H, *J* = 5.5, 15.5Hz), 3.81-3.99 (m, 5H), 4.63 (d, 1H, *J* = 9.5Hz), 7.28 (d, 2H, *J* = 9.5Hz), 7.61 (d, 2H, *J* = 8.5Hz); ^{1}H-NMR (3*R*, 270MHz, $CDCl_3$): δ 1.41 (s, 3H), 1.43 (s, 9H), 2.40 (s, 3H), 2.53 (d, 2H, *J* = 6.3Hz), 3.90-3.98 (m, 5H), 4.64 (d, 1H, *J* = 8.9Hz), 7.29 (d, 2H, *J* = 8.1Hz), 7.62 (d, 2H, *J* = 8.1Hz); IR (neat): 3900, 2975, 1730, 1360, 1140, 1080 cm^{-1}.
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15. ^{1}H-NMR (270MHz, $CDCl_3$): δ 1.32 (s, 3H), 2.82-3.01 (m, 2H), 3.71-3.73 (m, 1H), 3.92-4.06 (m, 4H); IR ($CHCl_3$): 3400, 1760, 1350, 950 cm^{-1}; $[\alpha]_D^{23}$ -35.7 (c 0.28, $CHCl_3$).
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