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STEREOCONTROLLED CONSTRUCTION OF 3-SULFENYLAZETIDIN-2-ONES

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Abstract: Diastereoselective addition reaction of the enolate of α-sulfenylacetates to a chiral imine possessing a (4*S*,5*S*)-4,5-dimethoxymethyl-2-methyl-1,3-dioxolane ring as a chiral auxiliary could be regulated by the enolate metals and the substituents on the sulfur atom. Addition of the titanium enolates provided (3*R*,4*R*)-β-lactams exclusively, while the corresponding (3*R*,4*S*)-β-lactam was obtained predominantly by the condensation using the zinc enolate of *t*-butyl α-methylthioacetate with the chiral imine.

A number of compounds containing the β-lactam ring constitute an important class of antibiotics such as penams, cephams, carbapenams, and others. Recently a variety of synthetic methods for the construction of the β-lactam skeleton[1] have been developed including the ester enolate-imine condensation and the ketene-imine cycloaddition.[2] Especially, after the ester enolate-imine condensation reaction developed in the late 1970's, the enolate chemistry had become popular for β-lactam ring synthesis.[3] So far, the aldol type addition reaction of an α-sulfenyl ester enolate to an imine has been reported by two groups.[4] However, their papers deal with the synthesis of racemic 3-sulfenylazetidin-2-one from an achiral imine and an α-sulfenyl ester enolate. The 3-sulfenylazetidin-2-ones are useful precursors for the synthesis of *cis*-3,4-substituted β-lactams, which are not readily accessible. For example, Natsugari *et al.* reported[5] that the aldol reaction of 3-sulfenylazetidin-2-one with acetone followed by reductive removal of the sulfenyl group with trialkyltin hydride gave a 3,4-substituted *cis*-β-lactam, which was used as an intermediate for the synthesis of β-lactam antibiotics carpetimycin A. Moreover, sulfenyl groups are capable of being transformed into sulfoxides and sulfones, and can be used for further functional group manipulation.[6]

In our previous papers,[7] we reported the stereoselective construction of each of the stereoisomers of the 2-azetidinone ring from a single chiral imine by utilizing ester enolates with different metal cations. During these investigations, we found that the changeover of the diastereofacial selectivity in the addition to the chiral imine is highly influenced by the geometry of the enolate species. In the zinc enolate case, in particular, the use of the (*Z*)-enolate appears to be crucial for successful *re*-facial addition. Therefore the enolates derived from α-heteroatom substituted acetates intrigued us from the standpoint of fixation of the enolate geometry by coordination to the heteroatom. Among the ester enolates possessing α-heteroatoms, those of α-sulfenylacetates are of considerable interest due to the wide applicabilities (*vide supra*), and the enolate geometries should be dependent on the characteristics of the substituent at sulfur, *e. g.*, steric and electronic factors. In the generation of the (*Z*)-enolate from α-sulfenylacetate, a sterically less-demanding substituent at sulfur would be necessary for an efficient chelation between alkylthio and enolate metals, whereas a bulky group would facilitate the formation of the (*E*)-enolate. Herein we would like to report a successful example where the appropriate selection of α-sulfenyl groups of acetate and enolate metals results in the stereodivergent addition to the chiral imine leading to the selective synthesis of isomers of 3-sulfenyl-β-lactam from a single imine.

The starting chiral imine **1** was prepared from (2*S*,3*S*)-1,4-dimethoxy-2,3-butanediol in 3 steps.[7] In the previous study, the changeover of the diastereoselectivity was observed using a different metal enolate of bulky *t*-butyl acetate.[7] However, the enolates derived from *t*-butyl *t*-butylthioacetate and *t*-butyl phenylthioacetate did not effect the changeover of the diastereoselectivity, and instead, (3*R*,4*R*)-β-lactams[8,9] were exclusively obtained from the Ti enolates. In an effort to find a better enolate for stereodivergent synthesis of either isomer, a relatively small methylthio derivative was investigated. A solution of *t*-butyl methylthioacetate in dry THF was added dropwise to a solution of LDA in dry THF with stirring at -78°C for 15 min, and then a solution of $ClTi(O^iPr)_3$ in hexane was added in 15 min. A solution of chiral imine **1** in THF was added dropwise to the resulting enolate solution. After being stirred at -78°C to room temperature for 18 hrs, the reaction was quenched with brine. Purification by TLC on silica gel gave the directly cyclized azetidin-2-one in 77% yield. The diastereomeric ratio was determined by HPLC analysis, and only the (3*R*,4*R*) isomer[10] was obtained. The changeover of the diastereofacial selectivity at C-4 of the β-lactam was attained by using the Zn enolate. The zinc enolate, prepared in situ from the corresponding potassium enolate through deprotonation of the ester with potassium hexamethyldisilazide in THF at -78°C followed by transmetalation with $ZnCl_2$ at 0°C gave the uncyclized adduct, β-amino ester **5**, in a yield of 47%. The adduct **5** underwent hydrolysis followed by cyclization by a known method[11] to give the (3*R*,4*S*)-β-lactam[12] predominantly.

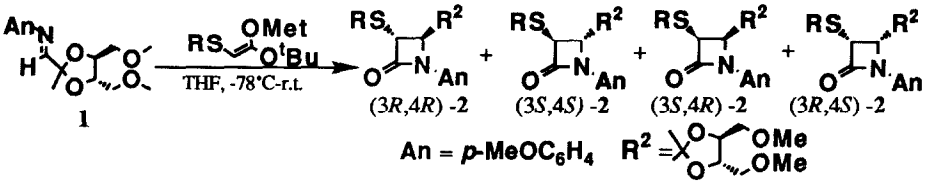


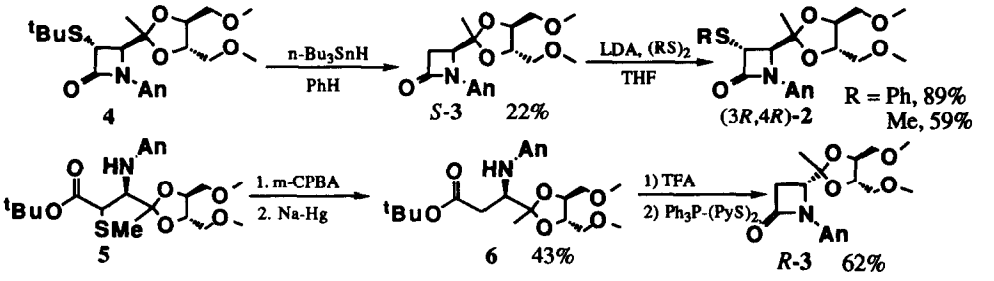
Table 1. Addition Reaction of Metal Enolates of *t*-Butyl Esters to the Chiral Imine 1

Entry	R	Metal	Enolate(eq)	Yield(%)[a]	(3*R*,4*R*) :	(3*S*,4*S*) :	(3*S*,4*R*) :	(3*R*,4*S*)[b]
1	Ph	Li	3	64	51 :	49 :	0 :	0
2	Ph	ZnCl	3	18	49 :	51 :	0 :	0
3	Ph	$Ti(O^iPr)_3$	3	90	100 :	0 :	0 :	0
4	^{t}Bu	Li	3	52	46 :	54 :	0 :	0
5	^{t}Bu	ZnCl	3	14	45 :	55 :	0 :	0
6	^{t}Bu	$Ti(O^iPr)_3$	3	65	100 :	0 :	0 :	0
7	Me	Li	3	47	78 :	22 :	0 :	0
8	Me	$Ti(O^iPr)_3$	3	77	100 :	0 :	0 :	0
9	Me	ZnCl	6	47[c]	5 :	16 :	4 :	75[d]

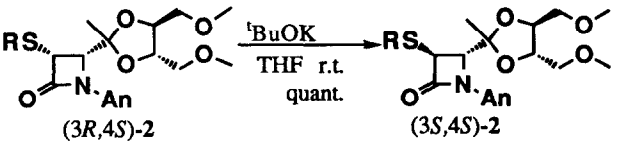
[a] Isolated yields. [b] The ratios were determined by capillary GLC (SE-30, 50m), and the assignment of 3,4-cis and trans stereochemistry was based on the coupling constant of the 270MHz NMR spectra. [c] Yield of adducts. [d] Ratio obtained after conversion into β-lactams.

The stereochemistry at C-4 in newly formed β-lactams was determined as follows. The β-lactam *S*-**3** without any substituents at the 3 position, prepared from the titanium enolate of ethyl acetate[7c], was transformed into the lithium enolate upon treatment with LDA at -78°C followed by sulfenylation with diphenyldisulfide, or dimethyldisulfide[5] to give **2**. Analyses of the products by ^1H NMR and HPLC established the stereochemistry

of C-4 of the β-lactams derived from the titanium enolate to be (3*R*,4*R*)-configuration. On the other hand, desulfenylation of **4** with n-Bu_3SnH[13] led to the β-lactam *S*-**3** to establish the structure to be (3*R*,4*R*). After oxidation of the α-methylthio-β-amino esters prepared from the zinc enolate of *t*-butyl methylthioacetate and a chiral imine **1** to the sulfoxide with m-CPBA, it was desulfonylated with Na-Hg to give the β-amino ester **6**, which underwent cyclization by a reported method[14] to determine the stereochemistry at C-3 of β-amino ester to be the *S* configuration.[7c]



β-Lactams having C-3,4-*cis*-configuration readily isomerized under the basic conditions. *cis*-β-Lactam (3*R*,4*S*)-**2** was epimerized with potassium *t*-butoxide in THF to give the corresponding *trans*-β-lactam (3*S*,4*S*)-**2** exclusively.



The reversal of the diastereoselectivity appears to be explained in terms of the different coordination ability of the enolate metals and the steric bulk of the sulfenyl group, *e. g.*, the characteristic coordination states of metals such as tetra- and hexa- coordinated intermediates involving different bond lengths of zinc and titanium in six-membered metalocycles and the enolate geometries influenced by the chelation between the enolate metal and the heteroatom as well as the stereospecificity of the transmetalation. In particular, the small substituent at sulfur is crucial for the changeover of the diastereoselectivity, indicating that unlike the α-methylthioacetate the more sterically demanding α-*t*-butylthio or phenylthio counterpart may fail to form the (*Z*)-enolate necessary for the reversal of the diastereoselectivity in the zinc enolate case.

In summary, we have developed a new method for the stereodivergent construction of β-lactams substituted at 3 and 4-positions from a single chiral imine by taking advantage of the different coordination states of the enolate metals. Noteworthy is that the addition of the titanium enolates of *t*-butyl phenylthio-, *t*-butylthio-, or methylthioacetate prepared via ready transmetalation of the Li or K enolates with $ClTi(O^iPr)_3$ in all cases provided (3*R*,4*R*)-β-lactams exclusively, whereas the addition of the zinc enolate of *t*-butyl methylthioacetate gave (3*R*,4*S*)-β-lactams with high selectivity. Removal of the chiral auxiliary was carried out under acidic conditions with aq. HCl in acetone to give the azetidin-2-one useful for the synthesis of β-lactam antibiotics. Moreover, since the sulfenyl group is capable of being transformed into other functional groups, the

diastereoselective synthesis of 3-sulfenylazetidin-2-ones provides both enantiomers of useful precursors for the synthesis of β-lactam antibiotics.

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(8) **2** (R = *t*-Bu): ^{1}H NMR (270MHz, $CDCl_3$) δ 1.36 (s, 3H), 3.28 (s, 3H), 3.30-3.38 (m, 8H), 3.76 (s, 3H), 4.02-4.05 (m, 2H), 4.27 (d, 1H, *J* = 2.31Hz), 6.66 (d, 2H, *J* = 9.24Hz), 7.25-7.39 (m, 5H), and 7.57 (d, 2H, *J* = 9.24Hz); IR (neat) 2925, 1755, 1640, 1515, 1440, 1380, 1245, 1140, 1080, 1030, 830, 740, and 690 cm^{-1}.

(9) **2** (R = Ph): ^{1}H NMR (270MHz, $CDCl_3$) δ 1.44 (s, 9H), 1.46 (s, 3H), 3.31 (s, 3H), 3.34-3.44 (m, 8H), 3.79 (s, 3H), 3.98 (d, 1H, *J* = 2.31Hz), 4.07-4.16 (m, 2H), 6.81 (d, 2H, *J* = 9.24Hz), and 7.49 (d, 2H, *J* = 9.24Hz); IR(neat) 3000, 1860, 1740, 1615, 1500, 1350, 1240, 1190, and 930cm^{-1}.

(10) **2** (R = Me): ^{1}H NMR (270MHz, $CDCl_3$) δ 1.45 (s, 3H), 2.19 (s, 3H), 3.32 (s, 3H), 3.34-3.51 (m, 6H), 3.79 (s, 3H), 4.03-4.08 (m, 2H), 4.09 (d, 1H, *J* = 2.31Hz), 6.83(d, 2H, *J* = 9.08Hz), and 7.50 (d, 2H, *J* = 9.08Hz); IR (neat) 2930, 1760, 1640, 1520, 1440, 1380, 1300, 1250, 1140, 1080 and 830 cm^{-1}.

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(12) **5** (R = Me):^{1}H NMR (270MHz, $CDCl_3$) δ 1.60 (s, 3H), 2.33 (s, 3H), 2.71 (dd, 1H, *J* = 6.93, 6.93Hz), 3.23 (s, 3H), 3.37 (s, 3H), 3.48-3.53 (m, 2H), 3.96-4.03 (m, 1H), 4.24 (d, 1H, *J* = 5.61Hz), 4.47 (d, 1H, *J* = 5.621Hz), 6.87 (d, 2H, *J* = 9.08Hz), and 7.47 (d, 2H, *J* = 9.08Hz) ; IR (neat) 2930, 1760, 1640, 1520, 1440, 1380, 1300, 1250, 1140, 1080, 1040, and 830 cm^{-1}.

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