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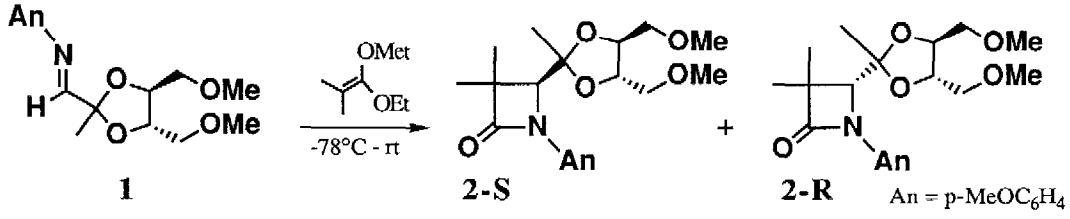
A STEREODIVERGENT CONSTRUCTION OF β-LACTAM SKELETONS VIA CONDENSATION OF ESTER ENOLATES AND A CHIRAL IMINE

Tamotsu FUJISAWA,* Yutaka UKAJI, Tomohiro NORO, Kengo DATE, and Makoto SHIMIZU
Department of Chemistry for Materials, Mie University, Tsu, Mie 514, Japan

SUMMARY: Diastereofacial selectivity in an addition reaction of ester enolates to a chiral imine with 1,3-dioxolane, derived from (*S*,*S*)-1,4-dimethoxy-2,3-butanediol as a chiral auxiliary, could be fully regulated by the appropriate selection of metal enolates used. Addition of the lithium enolates provided (4*S*)-β-lactams, while the corresponding (4*R*)-β-lactams were obtained by the condensation of titanium enolates with the chiral imine.

Since optically active 2-azetidinones are useful intermediates for the synthesis of many naturally occurring and synthetic β-lactam antibiotics such as penicillins, cephalosporins, monobactams, thienamycin, etc., much effort has been spent on the development of short selective procedures for their preparation. In recent years condensation reactions of imines with metal enolates and silyl ketene acetals have been shown to be useful for the construction of the 2-azetidinone ring.[1] Although asymmetric version of such reactions offers the chiral 2-azetidinone ring, availability of chiral auxiliary from naturally occurring compounds such as amino acids results in the production of one of the two enantiomers. Preparation of either enantiomer of 2-azetidinone from a same starting material has been still requited from biochemical and biological standpoints. For the addition reaction to ketones, ester enolate has been reported to attack different sides of diastereoface by selecting the metal species.[2,3] Being concerned with imino group, we have been studying diastereodifferentiating reaction of chiral imino function to afford either diastereomer selectively depending on the different coordination effects of metal used.[4] We would like to report here the stereoselective construction of both stereoisomers of 2-azetidinone ring from the same chiral imine by utilizing different metal species of ester enolates.

Chiral imine **1** was prepared from (*S*,*S*)-1,4-dimethoxy-2,3-butanediol[5] in 3 steps.[6] First, using lithium enolate generated from ethyl isobutyrate, the addition reaction to the chiral imine was investigated. A solution of the ester 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 imine **1** in dry THF was added dropwise. After being stirred at -78 °C to room temperature for 12 hours, the mixture was quenched with brine. After purification by TLC on silica gel, the directly cyclized 2-azetidinone was obtained in 78% yield. The diastereomeric ratio of (4*S*)-isomer (**2-*S***)[7] to (4*R*)-isomer (**2-*R***)[8] was determined by capillary GLC analysis to be 93 : 7. The reaction of the lithium enolate



1 **2-S** **2-R** An = p-$MeOC_6H_4$

Table 1. Addition Reaction of Metal Enolates of Ethyl isobutyrate to the Chiral Imine 1[a]

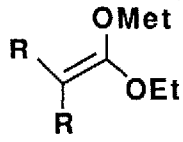
Entry	Met	Solvent	Yield/%[b]	2-*S* : 2-*R*[c]
1	Li	THF	78	93 : 7
2	Li	Et_2O	81	93 : 7
3	Li	DME	96	99 : 1
4	Li	$PhCH_3$	79	84 : 16
5	Na	THF	10	95 : 5[d]
6	ZnCl	THF	84	85 : 15
7	$Ti(O^iPr)_3$	THF	80	8 : 92
8	$Ti(O^iPr)_3$	Et_2O	94	4 : 96
9	$Ti(O^iPr)_3$	DME	91	7 : 93
10	$Ti(O^iPr)_3$	$PhCH_3$	96	11 : 89

[a] All reactions were performed on 0.2 mmol scale with the same procedure as described in the text. [b] Isolated yields. [c] The ratios were determined by capillary GLC (SE-30, 50m). [d] The Ratio after cyclization of uncyclized adduct to 2-azetidinone with lithium diisopropyl amide in THF.

in various solvents was examined, and satisfactory yields were obtained when 6 equivalents of the enolate were used in THF, Et_2O, and $PhCH_3$, whereas in DME excellent yield and selectivity were obtained with 3 equivalents of the enolate as shown in Table 1. Sodium enolate of ethyl isobutyrate prepared using sodium hexamethyldisilazide gave only 10 % yield of expected azetidinone along with uncyclized adduct in a yield of 61 %, in which the ratio of the two diastereomers was 95 : 5. As another metal enolate prepared *in situ* from the corresponding lithium enolate via transmetallation with one equivalent of metal salts, zinc enolate[9] was used for the addition to the imine **1** to give **2** in good yield with an isomeric ratio being 85 : 15. Next, in order to synthesize the other isomer (**2-*R***), the reaction with ester enolate using other metals was examined.[10] Among the various metals, titanium enolate[11a] derived from $ClTi(O^iPr)_3$ realized the reversal of diastereoselection to furnish the corresponding (*R*)-isomer selectivity. In the case of titanium enolate, Et_2O was the best solvent for the reaction from *re*-face of the imine **1**. For increasing the product yields to a satisfactory level, it was necessary to use 6 equivalents of the enolate especially in the titanium case.

These standard procedures were applied to the preparation of a series of β-lactams (**4a~d**). As shown in the Table 2, reversal of diastereoselection occurred using the enolates of ethyl cyclohexanecarboxylate (**3a**), ethyl 2-ethylbutyrate (**3b**) and ethyl diethoxyacetate (**3c**) with excellent selectivity. Yields were affected by the bulkiness of the enolates especially in the reaction of titanium enolate. Interestingly, in the case of ethyl acetate (**3d**), possessing no α-substituent, the changeover of diastereoselection could not be observed between lithium and titanium enolates.

The stereochemistry at C-4 in newly formed β-lactams was determined as depicted in Scheme 1. The β-lactam **4d** without any substituents at 3 position prepared from titanium enolate of ethyl acetate was converted



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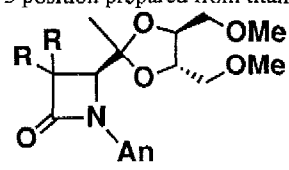
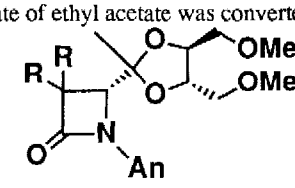


4-S



4-R

a: R, R =-$(CH_2)_5$-; b: R = Et; c: R = OEt; d: R = H

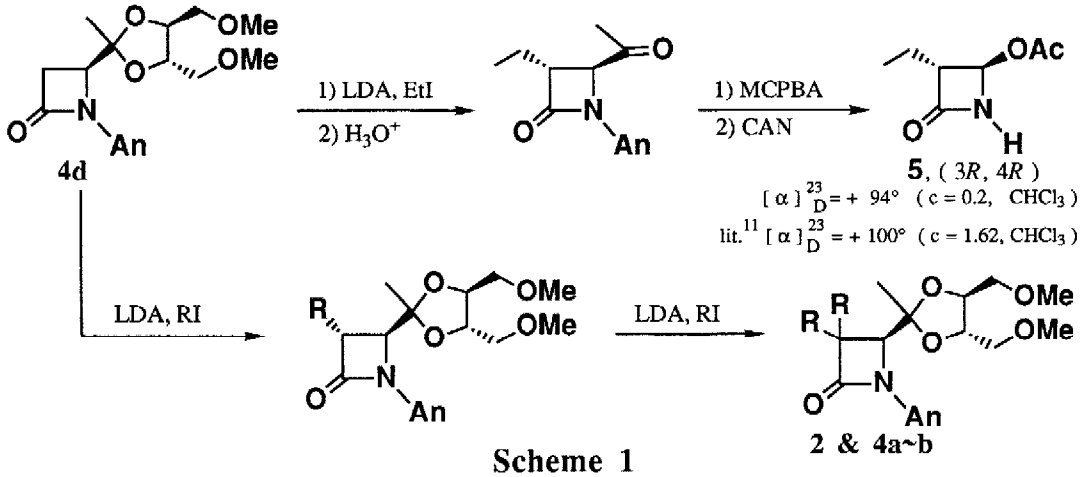
An = p-$MeOC_6H_4$

Table 2. Addition Reaction of Various Ester Enolate to the Chiral Imine 1[a]

Entry	Enolate	Met	Solvent	Yield/%[b]	4-*S* : 4-*R*
11	**3a**	Li	DME	85[c]	98 : 2[f]
12	**3a**	$Ti(O^iPr)_3$	Et_2O	82[d]	8 : 92[f]
13	**3b**	Li	DME	72[d]	98 : 2[g]
14	**3b**	$Ti(O^iPr)_3$	Et_2O	76[e]	5 : 95[g]
15	**3c**	Li	DME	55[d]	85 : 15[g]
16	**3c**	$Ti(O^iPr)_3$	Et_2O	19[d]	9 : 91[g]
17	**3d**	Li	DME	42[c]	87 : 13[g]
18	**3d**	$Ti(O^iPr)_3$	Et_2O	85[d]	99 : 1[g]

[a] All reactions were performed on 0.2 mmol scale with the same procedure as described in the text. [b] Isolated yields. [c] Three equivalents of ester enolate were used. [d] Six equivalents of ester enolate were used. [e] Fifteen equivalents of ester enolate were used. [f] The ratios were determined by HPLC (n-Hexane : Ethyl Acetate = 3 : 1). [g] The ratios were determined by capillary GLC (SE-30, 50m).

to the known 2-azetidinone **5**[11] by stereoselective alkylation,[13] removal of chiral auxiliary,[14] the Baeyer-Villiger oxidation, and oxidative cleavage of methoxyphenyl group,[15] whereas di-alkylation reaction[13] afforded β-lactams **2** & **4a~b**, which analyzed by ^1H NMR and chromatographies to establish the stereochemistry.



Scheme 1

Thus the present method provides a useful entry into the preparation of both epimers of optically active β-lactams from the same starting material by the choice of the appropriate metals of ester enolates.

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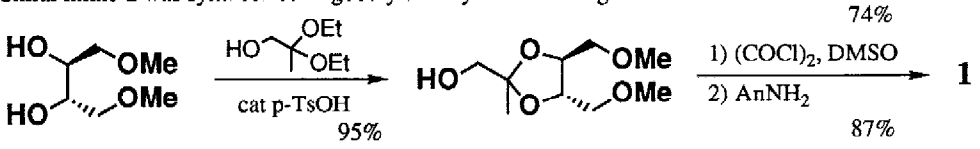
6. Chiral imine **1** was synthesized in good yields by the following Scheme.



7. ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.39 (s, 3H), 1.42 (s, 3H), 1.43 (s, 3H), 3.16-3.24 (m, 1H), 3.29-3.41 (m, 10H, including two singlets at 3.31 and 3.33 ppm), 3.78 (s, 3H), 3.98 (s, 1H), 4.01~4.82 (m, 1H), 6.84 (d, 2H, J = 9.2 Hz) and 7.51 (d, 2H, J = 9.2 Hz); IR (neat) 2890, 1750, 1520, 1470, 1400, 1380, 1300, 1250, 1150, and 1100 cm^{-1}.
8. ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.40 (s, 3H), 1.42 (s, 3H), 1.43 (s, 3H), 3.07~3.12 (m, 1H), 3.24 (s, 3H), 3.33~3.39 (m, 4H, including a singlet at 3.36 ppm), 3.47-3.48 (m, 2H), 3.59-3.64 (m, 1H), 3.78 (s, 3H), 3.91-3.98 (m, 2H, including a singlet at 3.95 ppm), 6.85 (d, 2H, J = 9.2 Hz), and 7.46 (d, 2H, J = 9.2 Hz); IR (neat) 2925, 1750, 1515, 1460, 1390, 1380, 1245, 1140, and 1080 cm^{-1}.
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