STEREOSELECTIVE SYNTHESIS OF OPTICALLY ACTIVE β-LACTAMS BY THE REACTION OF CHIRAL IMINES DERIVED FROM *ERYTHRO*-2-AMINO-1,2-DIPHENYLETHANOL WITH ESTER ENOLATES#

Yukihiko Hashimoto,*,† Tsuneo Ogasawara,† Minoru Hayashi,† and Kazuhiko Saigo*,‡

†Department of Chemistry and Biotechnology, Graduate School of Engineering, The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113-8656, Japan
‡Department of Integrated Biosciences, Graduate School of Frontier Sciences, The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113-8656, Japan

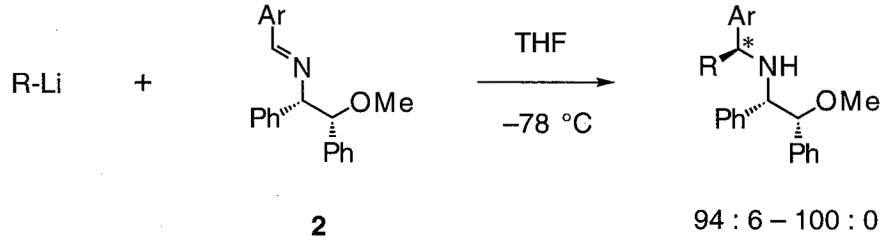
Abstract- Chiral imines, derived from (1*S*,2*R*)-2-methoxy-1,2-diphenylethylamine and aromatic aldehydes, reacted with ester enolates prepared from ketene silyl acetals and methyllithium to give β-lactams in good yields with high diastereoselectivity. This method provides a useful and simple route for the construction of optically active β-lactam skeletons.

Since β-lactams are one of the most important classes of antibiotics, much effort has been focused on the enantioselective construction of β-lactam rings.[1] Among them, the reaction of ester enolates with imines, derived from chiral amines, is one of the most attractive routes to optically active β-lactams or β-amino esters because of the simplicity of the approach and the easy availability of the starting materials.[2] For this category of reaction, several groups have recently reported the successful reactions of ketene silyl acetals with imines, derived from chiral amines, under Lewis acidic conditions.[3] β-Amino esters, however, are usually formed under the Lewis acidic conditions, therefore appropriate derivatizations are required in order to obtain β-lactams from the products of these reactions. In contrast, the reaction between metal ester enolates and imines under basic conditions commonly gives β-lactams in one step.[2] Although the asymmetric construction of β-lactams from chiral esters under basic conditions has given some successful results,[4] similar methods using chiral imines have been scarcely reported so far.

In the previous papers, we have reported the synthesis and resolution of a synthetic chiral compound, *erythro*-2-amino-1,2-diphenylethanol (**1**),[5] and its application in asymmetric reactions as a chiral auxiliary.[6,7] Among them, a nucleophilic alkylation reaction of chiral imine (**2**), derived from **1**, has showed extremely high stereoselectivity (Scheme 1).[6] On the basis of this result, it was postulated that β-lactams could be obtained with high selectivity by using ester enolates in the place of organolithiums.

Dedicated to Professor Teruaki Mukaiyama on the occasion of the celebration of his 73rd birthday.

Scheme 1

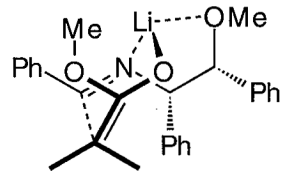


2 94 : 6 – 100 : 0

We herein report highly diastereoselective, one-step construction of β-lactam derivatives by the reaction of chiral imine (**2**) with lithium ester enolates.

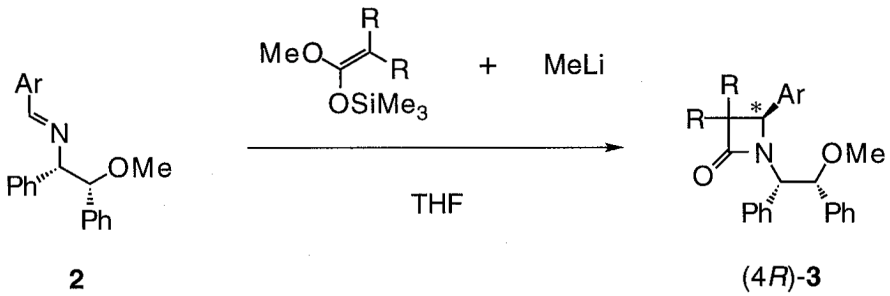
Throughout the examination of the reaction conditions for the reaction of a chiral imine with an ester enolate, (1*S*,2*R*)-*N*-benzylidene-2-methoxy-1,2-diphenylethylamine (**2a**),[6] which was easily prepared from amino alcohol (**1**) in two steps, was used. At first we tried the reaction of chiral imine (**2a**) with lithium enolate of methyl isobutyrate, which was prepared with LDA. In THF, the reaction smoothly proceeded at –78 °C to room temperature, and not only an addition to the carbon-nitrogen double bond but a cyclization occurred spontaneously to give the corresponding β-lactam derivative **3a** in 96% yield with 92:8 diastereoselectivity. The X-Ray crystallographic study on the major product of this reaction showed that it had an *R*-configuration at the 4-position in the azetidinone ring,[8] indicating that the nucleophilic attack of the enolate to the chiral imine (**2**) proceeded with the same diastereofacial selectivity as the alkylation reaction with organolithiums. An plausible transition state, leading to the 4*R*-diastereomer, is depicted in Figure 1.

Figure 1



Relatively high stereoselectivity and simplicity of the procedure for the β-lactam ring construction encouraged us to investigate thoroughly the reaction conditions. Upon screening the methods for the generation of the enolate, solvents and so on, the reaction of an amine-free lithium enolate, prepared from the ketene silyl acetal and methyllithium, in THF was found to give the best stereoselectivity (98:2). This result can be explained by considering the chelation in Figure 1, which would be weakened by an amine or another coordination species.

A typical procedure for the synthesis of β-lactam (**3**) is as follows: To a THF (3 mL) solution of 1-methoxy-2-methyl-1-trimethylsiloxypropene (244 mg, 1.4 mmol) was added an ethereal solution of methyllithium (0.90 mmol) at room temperature. The reaction mixture was stirred for 1 h and then cooled to 0 °C. To the mixture, a THF (2 mL) solution of (1*S*,2*R*)-*N*-benzylidene-2-methoxy-1,2-diphenylethylamine (**2a**, 98 mg, 0.31 mmol) was added, and the reaction mixture was stirred for 24 h at



2 (4*R*)-**3**

Table 1. The Reaction of Chiral Imine (**2**) with Lithium Ester Enolates.

Entry	Ar	R, R·	Conditions	Yield (%)	Diastereomer Ratio[a] (4*R*) : (4*S*)
1	Ph	Me, Me	0 °C, 24 h	81	98 : 2
2	*p*-$MeOC_6H_4$	Me, Me	rt, 24 h	76	99 : 1
3	*p*-ClC_6H_4	Me, Me	0 °C, 7 h	79	98 : 2
4	PhCH=CH	Me, Me	0 °C, 3 h	0[b]	–
5	Ph	-$(CH_2)_5$-	rt, 24 h	81	94 : 6

a) Determined by HPLC and/or ^{1}H-NMR.

b) The Michael type reaction occurred predominantly to give six membered lactams in 77% yield with a diastereomer ratio of 53:47.

the same temperature. The reaction was quenched by adding aqueous sodium hydrogencarbonate, and the products were extracted with dichloromethane. Combined extracts were dried over sodium sulfate and concentrated, and the crude material was purified by TLC to give the corresponding β-lactams (**3a**). Under the optimized conditions, the reactions were carried out for various combinations of ester enolates and chiral imines. The results are summarized in Table 1. As can be seen from Table 1, the reactions of aromatic aldimines proceeded with high stereoselectivity comparable to that of the alkylation reaction. Moreover, it is noted that the products thus obtained have high crystallinity due to the chiral auxiliary part and that simple recrystallization gives enantiomerically pure β-lactams.[9]

In summary, we have developed a method for the preparation of β-lactams by using a synthetic chiral auxiliary, *erythro*-2-amino-1,2-diphenylethanol (**1**). This method provides a useful and simple route for the construction of optically active β-lactam skeletons.

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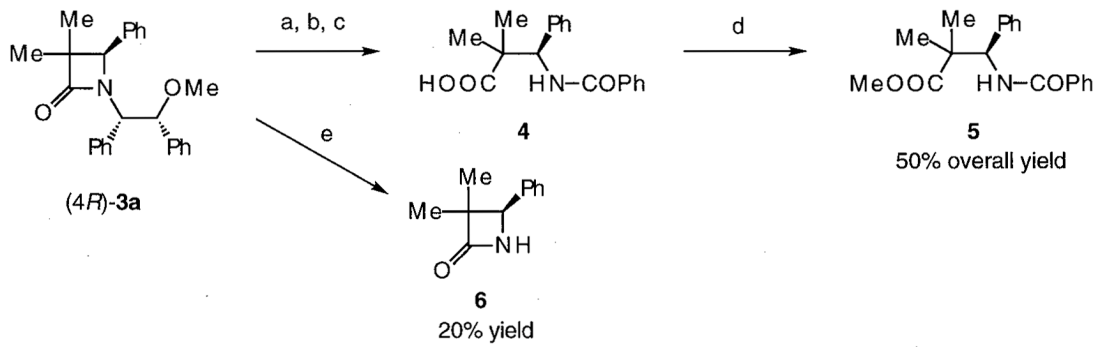
8. Crystal data for the major diastereomer of **3a**: $C_{26}H_{27}NO_2$, *Mw* = 385.51, orthorhombic, space group $P2_12_12_1$, *a* = 15.512(3) Å, *b* = 16.588(3) Å, *c* = 8.764(2) Å, *V* = 2255.2(7) Å^3, *Z* = 4, *Dc* = 1.135 gcm^{-3}, *R* = 0.051, *Rw* = 0.048, *S* = 1.018, reflection used = 1502.
9. Starting from (4*R*)-β-lactam (**3a**, Ar = Ph), *N*-benzoylated β-amino acid (**4**) , which was isolated as methyl ester (**5**), was obtained in 50% overall yield via oxidative degradation of the auxiliary. Also, unprotected β-lactam (**6**) was obtained directly by the reaction with $K_2S_2O_8$, although the yield was somewhat low.



a) *t*-BuOK, DMSO, rt, 30 min; b) mCPBA, CH_2Cl_2, rt, 5 h; c) $Ca(ClO)_2$, AcOH, MeCN/H_2O, 0 °C→rt, 16 h; d) $TMSCHN_2$, C_6H_6/MeOH, rt, 1h; e) $K_2S_2O_8$, AcOH/H_2O, 90 °C, 1.5 h.

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