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ASYMMETRIC SYNTHESIS OF β-LACTAMS. I. THE REACTION OF DIMETHYLKETENE SILYL ACETAL WITH (S)-ALKYLIDENE(1-ARYLETHYL)AMINES PROMOTED BY TITANIUM TETRACHLORIDE

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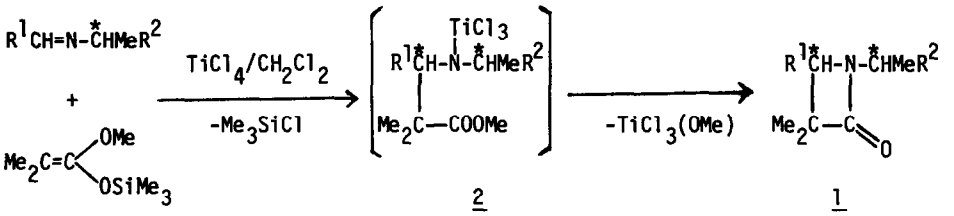
Summary: Asymmetric synthesis of β-lactams by means of the reaction of dimethylketene silyl acetal with (S)-alkylidene(1-arylethyl)amines in the presence of titanium tetrachloride was studied. The extent of the asymmetric induction was in the range of 44-78% (diastereomeric purity 72-89%) and the (S)-configuration was turned to be preferentially induced at the ^{4}C position of the resulting β-lactams.

Although a large number of methods for the synthesis of β-lactams have been developed in connection with the naturally occurring β-lactam antibiotics such as penicillins, cephalosporins and nocardicins,[1,2] there have been only a few reports on the application of these methods to the asymmetric synthesis,[3] e.g., recently, Furukawa et al.[3a] performed the asymmetric synthesis of β-lactams by means of the Reformatsky reaction with a chiral imine, and Kamiya et al.[3c] synthesized a nocardicin precursor by using the asymmetric ketene addition to the trimer of N-methylidene(4-benzyloxyphenyl)glycine methyl ester. As we found a new synthetic route to β-lactams using the reaction of ketene silyl acetals with imines promoted by titanium tetrachloride,[4] we have applied this reaction to the asymmetric synthesis of β-lactams. Herein, we wish to describe the effective asymmetric synthesis of β-lactams by the reaction of dimethylketene methyl trimethylsilyl acetal with (S)-alkylidene(1-arylethyl)amines in the presence of titanium tetrachloride.

In a typical run, a 1M solution of titanium tetrachloride in dichlorometh-



Scheme 1.

ane (10 ml) was added to the dichloromethane solution (10 ml) of (S)-isopentylidene(1-phenylethyl)amine (2.27 g, 12 mmol) at -78°C with stirring over a period of 10 min. Dimethylketene methyl trimethylsilyl acetal (1.74 g, 10 mmol) in dichloromethane (5 ml) was added dropwise to the resulting dark-brown solution and the stirring was continued for additional 30 min. Then, a dry ice - acetone bath was removed and the reaction mixture was allowed to warm up gradually to room temperature and stirred for 24 hr. The reaction mixture was hydrolyzed, extracted with dichloromethane, washed with aqueous solution of sodium chloride, dried over anhydrous magnesium sulfate, and submitted to a column chromatography on silica, which was carried out carefully to avoid the fractionation of the diastereomers. Then, 3,3-dimethyl-4-isobutyl-1-(1-phenylethyl)azetidin-2-one (1e, 1.83 g, 71%) was isolated as an oil. The extent of asymmetric induction at the ^{4}C position was determined to be 78% on the basis of 100 MHz spectrum using a shift reagent, Eu(fod)$_3$.[5]

Results on using a variety of Schiff bases are summarized in Table 1. As Table 1 shows, the attained asymmetric induction in the present reaction (44-78%) is considerably higher than that obtained in the corresponding Reformatsky reaction,[3a] and comparable to that realized in the nocardicin precursor synthesis.[3c] As is immediately seen from Table 1, the extent of asymmetric induction as well as the chemical yield is remarkably dependent upon the substituents of imines. For instance, a considerable decrease in stereoselectivity was observed on using isobutylidiene(1-phenylethyl)amine or isobutylidene[1-(1-naphthyl)ethyl]amine, and especially, in the case of isobutylidene(1-phenylethyl)amine, an inversion of the preferred configuration took place. These results imply that the bulkiness of the substituent(s) of imine plays a significant role in the asymmetric

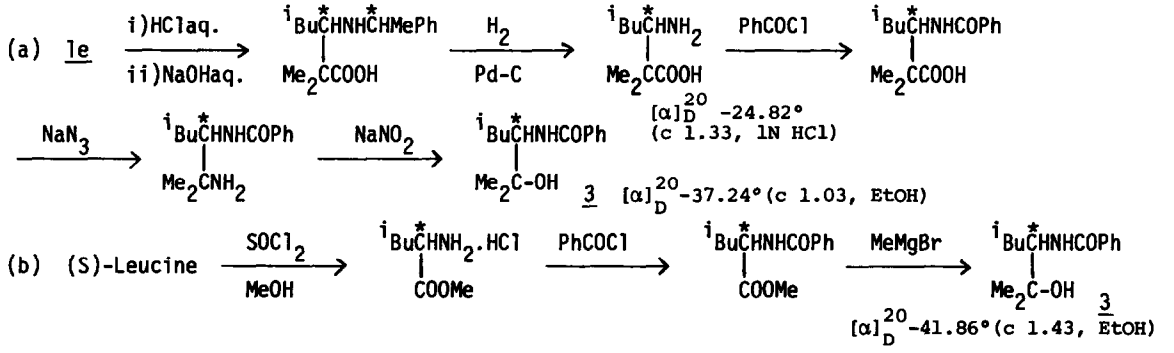
Table 1. Chiral β-lactams (1) obtained by the reaction of dimethylketene methyl trimethylsilyl acetal with (S)-alkylidene(1-arylethyl)amines in the presence of titanium tetrachloride

	R^1	R^2	Yield[a] (%)	NMR(δ ppm)[b] (S,R) NCHMeAr (S,S)		Asymmetric Induction (%)
a	Et	Ph	66	4.58 (23)	4.79 (77)	54
b	^{n}Pr	Ph	72	4.54 (17)	4.77 (83)	66
c	^{i}Pr	Ph	26[c]	4.42 (72)	4.81 (28)	44
d	^{n}Bu	Ph	73	4.56 (17)	4.78 (83)	66
e	^{i}Bu	Ph	71	4.52 (11)	4.77 (89)	78
f	Et	1-Np	69	5.45 (22)	5.63 (78)	56
g	^{n}Pr	1-Np	70	5.43 (19)	5.66 (81)	62
h	^{i}Pr	1-Np	10[c]	5.36 (24)	5.39 (76)	52
i	^{n}Bu	1-Np	69	5.45 (19)	5.65 (81)	62
j	^{i}Bu	1-Np	72	5.42 (15)	5.66 (85)	70

[a] Isolated yield based on the ketene silyl acetal. [b] Chemical shifts of the methine protons of two diastereomers. Values in the parentheses are the ratio of the integration of the methine protons. [c] (ketene silyl acetal)/(Schiff base)/($TiCl_4$) = 1:2:1.5.

induction in the present reaction, and the over-conjestion in the transition state may decrease the reactivity and the stereoselectivity.

In order to determine the preferred configuration at ^{4}C position of the resulting azetidin-2-ones (1), the stereochemical correlation of N-(1-hydroxy-1-methylethyl)isopentylbenzamide (3) derived from the obtained 4-isobutylazetidin-2-one (1e) was performed with the authentically prepared benzamide (3) from (S)-leucine (Scheme 2), and it turns out that the preferred configuration is S.



Scheme 2.

It is reasonable to assume that the titanium tetrachloride complex of an imine reacts with dimethylketene methyl trimethylsilyl acetal to form a titanium enolate complex as key intermediate, and the nucleophilic attack of the β-carbon of this enolate across the carbon-nitrogen double bond of Schiff base takes place from the less hindered side giving the N-metalated β-amino ester (2), which undergoes subsequent cyclization to give the corresponding azetidin-2-one (1). Figure 1 illustrates two possible transition states, A and B, for the asymmetric addition. CPK model inspection reveals that the transition state A is much more favorable than the transition state B by taking into account the steric repulsions between the substituents of imine, those of ketene silyl acetal and titanium moiety.

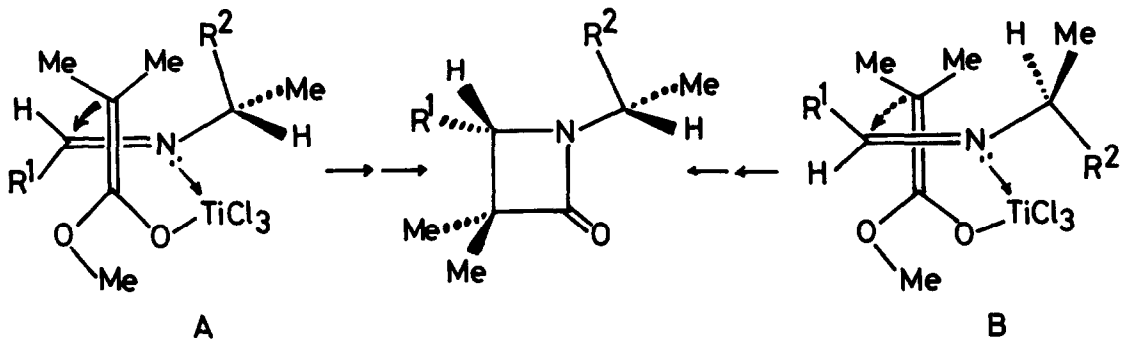


Figure 1.

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4. I. Ojima, S. Inaba and K. Yoshida, Tetrahedron Lett., 3643 (1977).
5. $Eu(fod)_3$ stands for tris[1,1,1,2,2,3,3,-heptafluoro-7,7-diemthyl-4,6-octadionato]europium (III). NMR spectra were measured with a Varian HA-100 or a Varian XL-100 spectrometer.

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