CHEMISTRY LETTERS, pp. 293-296, 1987.

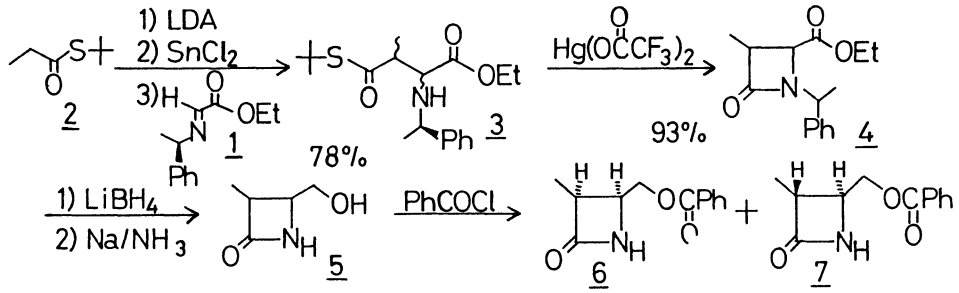
The Asymmetric Addition of the Sn(II) Enolates of Thioesters to α-Iminoesters. A Convenient Synthesis of Optically Active cis-Substituted β-Lactams.

Tohru YAMADA, Hiroshi SUZUKI, and Teruaki MUKAIYAMA
Department of Chemistry, Faculty of Science,
The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113

The asymmetric addition of the Sn(II) enolates derived from thioesters to α-iminoesters having the chiral auxiliary on the nitrogen atom proceeds smoothly to afford syn-β-aminoacid derivatives, which are in turn converted to optically active cis-substituted β-lactams.

In the previous paper,[1] we have described the diastereoselective addition of Sn(II) enolates of thioesters with α-iminoester giving syn-β-aminoacid derivatives in good yields. As β-aminoacid is one of the most important intermediates for the synthesis of β-lactam antibiotics, much attention has been paid for the preparation of these type of compounds as optically active forms. Recently, in the aldol-type reactions of metal enolates toward imino compounds, several examples of asymmetic induction using chiral enolates have been reported.[2] However, the effects of the chiral auxiliary on the nitrogen atom of imines have not yet been widely studied in these type reactions.[3] Now we wish to report an asymmetric induction in the addition reaction of Sn(II) enolates derived from thioesters to α-iminoesters having a chiral auxiliary on the nitrogen atom, and the conversion of the adducts thus prepared to the optically active β-lactams.

In the first place, the Sn(II) enolate of S-t-butylthiopropionate, formed by the metal exchange method,[1] was allowed to react with the chiral imine 1 prepared from (R)-α-methylbenzylamine[4] and the corresponding thioester of β-aminoacid



Scheme 1.

derivative 3 was obtained in 78% yield. The stereoselectivity was determined as follows: On treatment of the β-aminoacid derivative 3 with 2 equivalents of mercuric trifluoroacetate, the corresponding β-lactam 4 was obtained (93% yield). And the ethyl ester was reduced by $LiBH_4$ in THF into the corresponding alcohol,[6] followed by the removal of the chiral auxiliary under the Birch reduction condition. Then, the resulting alcohol 5 was benzoylated to give the mixture of cis-and trans-β-lactam (6 and 7), which was subjected to HPLC analysis. It was revealed that the ratio of cis- and trans-β-lactam is 91:9, that is, the diastereoselectivity of forming syn-adduct in the addition of Sn(II) enolate is up to 91:9. After the purification by TLC on silica gel, the optical purity of the cis-β-lactam 6 (J=5.4 Hz) was determined by the optically active column chromatography (Chiralcel OC(+) Daicel Co. Hexane:2-Propanol=9:1) to be 70% ee. The optical purity means that the asymmetric induction caused by the chiral auxiliary on the nitrogen atom of the imine is 85:15.

Several combinations of optically active imines and thioesters were screened, and the results are listed in Table 1. The addition reaction of Sn(II) enolate to the imine 8 prepared from (R)-α-methoxymethylbenzylamine[4] gave the corresponding β-aminoacid derivative 9 in good yield (entries 1,2). The β-lactams (6 and 7)

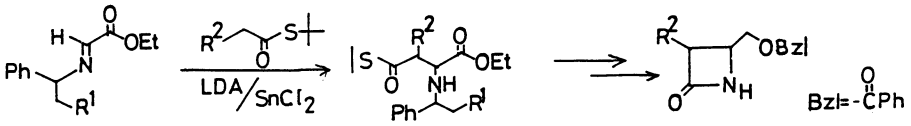
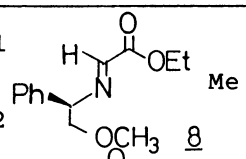
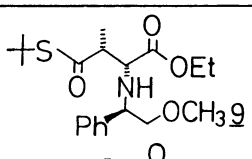
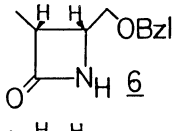
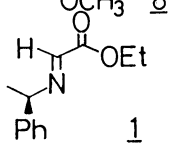
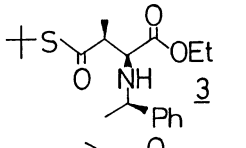
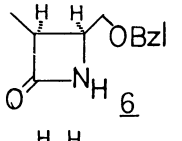
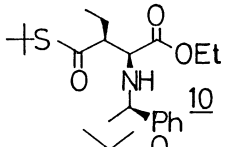
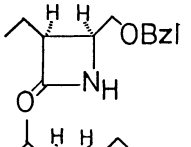
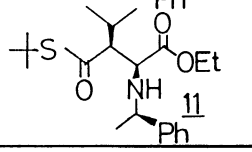
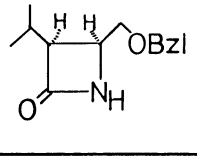
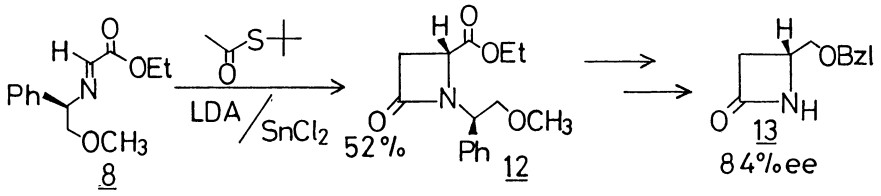


Table 1. Asymmetric addition of Sn(II) enolate of thioester to chiral imine[a]

Entry	Imine	R^2	Adduct(Yield/%)		SnX_2	β-Lactam	cis:trans[c]	e.e./%
1		Me		(85)	$SnCl_2$		75:25	77[d]
2				(81)	$Sn(OTf)_2$		67:33	84[d]
3		Me		(78)	$SnCl_2$		91: 9	70[d]
4	1	Et		(78)	$SnCl_2$		95: 5	72[d]
5	1	^{i}Pr		(79)	$SnCl_2$		95: 5	71[e]

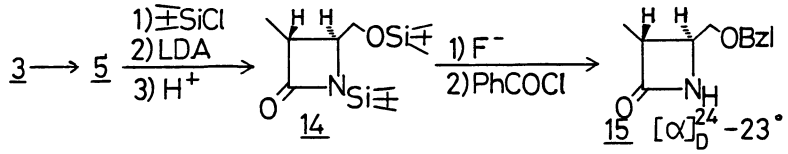
a) The reaction was carried out in Et_2O at -78 °C.[1]
b) All the products gave satisfactory ^{1}H-NMR and IR spectra.
c) Determined by HPLC analysis (Waters Resolve Silica, Hexane-AcOEt).
d) Determined by HPLC analysis (Daicel Co. Chiralcel OC(+), Hexane-2-Propanol).
e) Determined by HPLC analysis of the corresponding MTPA ester (Waters Resolve Silica, Hexane-AcOEt).



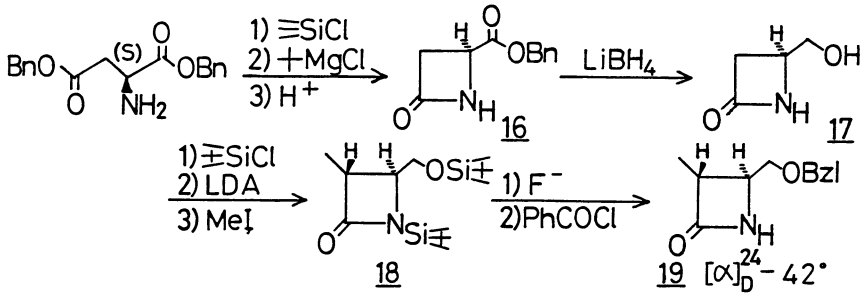
Scheme 2.

were obtained according to the similar procedure mentioned above. Although the optical purity of the cis-β-lactam 6 was higher than that derived from the imine 1, the diastereoselectivity (cis or trans) was decreased. It is noted that the addition of $Sn(OTf)_2$ instead of $SnCl_2$ enhanced the asymmetric induction (entry 2). The Sn(II) enolates of S-t-butylthiobutanoate and 3-methylbutanoate reacted with the imine 1 to afford the corresponding adducts 10 and 11 in good yields and in good stereoselectivities (entries 4,5). Further, it was observed that the Sn(II) enolate of S-t-butylthioacetate reacted with the imine 8 and simultaneously the β-lactamization occurred to give the β-lactam 12. After the same treatment described above, the benzoylate 13 was obtained, and its optical purity was found to be 84% ee. by the comparison of the optical rotation with the authentic sample prepared from dibenzyl (S)-aspartate.[7]

The absolute configuration of the β-lactam 6 was determined as follows: As shown in Scheme 3, the trans-β-lactam 15 (J=3.0 Hz) was obtained by the isomerization of the cis-β-lactam 5, derived from the syn-riched adduct 3. On the other hand, the authentic trans-β-lactam 19 was prepared starting from dibenzyl (S)-aspartate fundamentally according to Salzmann's procedure[8] (Scheme 4). It is confirmed that the cis-β-lactam 6 is obtained as the (3S, 4S)-enantiomer judged from the optical rotation.



Scheme 3.



Scheme 4.

The stereoselectivity of the present reaction can be explained by assuming the transition state shown in Fig. 1. It is known that the enolization of S-t-butylthioester by LDA in THF gives the (Z)-enolate predominantly,[9] and the (Z)-geometry of the enolate is kept during the metal exchange into the corresponding Sn(II) enolate. Further, as Sn(II) atom has considerably strong affinity toward the nitrogen atom,[10] it is reasonable to consider that the present reaction proceeds through the chair transition state[3] between the chiral imine and Sn(II) enolate of thioester.

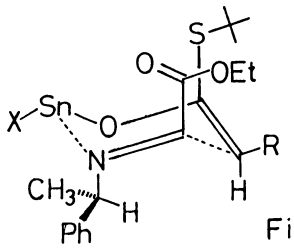


Fig.1.

Thus, it is noted that Sn(II) enolates of thioesters react with the imines having chiral auxiliary on the nitrogen atom to afford the corresponding syn-β-aminoacid derivatives in good diastereoselectivities, and the adducts thus prepared are converted into the optically active cis-β-lactams stereospecifically.

References

1) T. Mukaiyama, H. Suzuki, and T. Yamada, Chem. Lett., 1986, 915.
2) T. Iimori and M. Shibasaki, Tetrahedron Lett., 26, 1523 (1985); T. Chiba, M. Nagatsuma, and T. Nakai, Chem. Lett., 1984, 1927; D. J. Hart, C.-S. Lee, W. H. Pirkle, M. H. Hyon, and A. Tsipouras, J. Am. Chem. Soc., 108, 6054 (1986).
3) I. Ojima and S. Inaba, Tetrahedron Lett., 21, 2081 (1980); Y. Yamamoto, T. Komatsu, and K. Maruyama, J. Chem. Soc., Chem. Commun., 1985, 814; Y. Yamamoto, W. Ito, and K. Maruyama, ibid., 1985, 1131.
4) The imines were prepared from the reaction of ethyl glyoxylate and (R)-α-methylbenzylamine or (R)-α-methoxymethylbenzylamine,[5] and purified by vacuum distillation.
5) A. I. Meyers, G. S. Poindexter, and Z. Brich, J. Org. Chem., 43, 892 (1978).
6) W. F. Huffman, K. G. Holden, T. F. Buckley, III, J. G. Gleason, and L. Wu, J. Am. Chem. Soc., 99, 2352 (1977).
7) 13: $[\alpha]_D^{24}$ - 42.4° (c2.2, CH_2Cl_2). The authentic benzoylate ($[\alpha]_D^{26}$ + 50.5° (c2.1, CH_2Cl_2)) was prepared from the alcohol 17.[8]
8) T. N. Salzmann, R. Ratcliffe, B. G. Christensen, and F. A. Bouffard, J. Am. Chem. Soc., 102, 6161 (1980).
9) C. Gennari, A. Bernardi, S. Cardani, and C. Scolastico, Tetrahedron Lett., 26, 797 (1985).
10) T. Mukaiyama, N. Iwasawa, R. W. Stevens, and T. Haga, Tetrahedron, 40, 1381 (1984); N. Yamasaki, M. Murakami, and T. Mukaiyama, Chem. Lett., 1986, 1013.

(Received October 28, 1986)