Pergamon

Tetrahedron Vol. 51, No. 32, pp. 8941-8952, 1995

0040-4020/95 $9.50+0.00

0040-4020(95)00503-X

Optically Active Aminoalcohol Promoted Addition of 2-Pyridylthioester Boron Enolates to Imines: Enantioselective One-pot Synthesis of β-Lactams

Rita Annunziata, Maurizio Benaglia, Mauro Cinquini,* Franco Cozzi,*

Valentina Molteni, and Laura Raimondi

Centro CNR and Dipartimento di Chimica Organica e Industriale, Universita' di Milano, via Golgi 19, 20133 Milano, Italy.

Abstract: The enolates derived from 2-pyridylthioesters by treatment with BCl_3-Me_2S and enantiomerically pure aminoalcohols react with aromatic and heteroaromatic imines to afford β-lactams in a convenient one-pot procedure and in up to 78% e.e. The aminoalcohol can be employed both as the metal ligand and as the base to generate the enolate. Among several aminoalcohols tested, N-methylephedrine turned out to be the more efficient in terms of stereoselectivity.

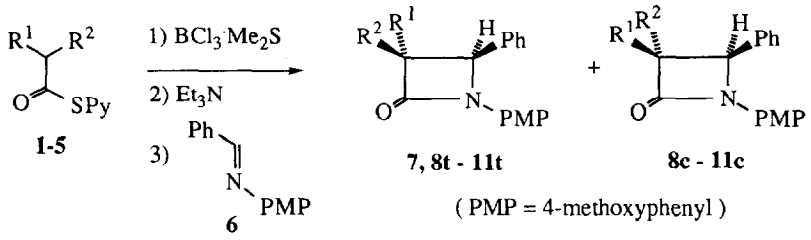
Optically active β-lactams are generally prepared by reaction of non-racemic reagents featuring covalently bound stereogenic groups capable of stereocontrolling the azetidinone nucleus formation. For instance, in an enolate/imine condensation[1] the stereogenic groups present in the reaction partners can either be maintained in the target molecule,[2] or can be removed from the reaction products, thus acting as chiral auxiliaries.[3]

Obviously, there is another and more appealing possibility to obtain enantiomerically enriched β-lactams, namely the use of an enantiomerically pure ligand for the metal of the enolate as the only element of stereocontrol. To the best of our knowledge, only two papers in the literature describe this kind of process. Corey and co-workers reported a synthesis of β-aminothioesters promoted by a chiral diazaborolidine that occurs in excellent diastereo- and enantioselectivity.[4] Yamamoto and his group prepared β-aminoesters by a highly selective chiral Lewis acid catalyzed addition of a silylketeneacetal to chiral imines.[5] Both of these methods, however, require β-aminoester ring closure to produce the desired azetidinone.

Over the last few years we have described a convenient one-pot synthesis of β-lactams by the condensation of the enolate of 2-pyridylthioesters with imines.[2h,2j,3j,6] The enolates are generated at low temperature in CH_2Cl_2 by addition of triethylamine to the 2-pyridylthioesters activated by a MX_4 Lewis acid (M = Ti, Sn; X = Cl, Br).[7] However, despite several attempts no appreciable stereoselection was observed when a variety of chiral metal ligands were used to control the absolute stereochemistry of this reaction. This is likely due to the multiple co-ordination modes of the octahedral Ti(IV) and Sn(IV) species, that cannot bind mono-dentate ligands[8] in a single and stereodetermining way. To solve this problem we turned our attention to the use of boron halides as the ester activators, on the assumption that these Lewis acids can co-ordinate a Lewis basic ligand exclusively in the tetrahedral geometry.[9,10]

The effectiveness of BCl_3 in promoting the reaction was easily demonstrated by the experiments collected in Table 1. Addition of triethylamine (1 mol equiv) to a cooled (-78°C) mixture of 2-pyridylthioesters **1-5** (1 mol equiv) and BCl_3·Me_2S (2 mol equiv) in CH_2Cl_2 resulted in the formation of the boron enolate, that condensed with imine **6** (0.5 mol equiv) to afford the corresponding β-lactams in fair to good yield and moderate *trans/cis* stereoselectivity.[11]

Table 1. Synthesis of β-Lactams **7** and **8t,c-11t,c** from Thioesters **1-5** and Imine **6** in the presence of BCl_3·Me_2S and Et_3N.



Thioester	R^1	R^2	Product	Yield %[a]	*trans* : *cis* ratio
1	Me	Me	**7**	57	-
2	Me	H	**8t,c**	43	75 : 25
3	Pr-i	H	**9t,c**	60	85 : 15
4	$PhCH_2O$	H	**10t,c**	63	70 : 30
5	CH_3COO	H	**11t,c**	37	70 : 30

[a] Isolated yields after flash chromatography.

With these results in hand, we were faced with the problem of selecting suitable chiral boron ligands for our reaction. To this end we first established that the boron species must feature two chlorine substituents to be sufficiently Lewis acidic to activate the pyridylthioesters toward enolization.[12] Prompted by a literature report[13] concerning the use of the boron reagent obtained from BBr_3 and (S)-*N*-methyl diphenylprolinol **12** as chiral catalyst for Diels-Alder cycloadditions, we tested this Lewis acid in the condensation of thioester **4** with imine **6**, using Et_3N as base. From this reaction β-lactam **10** was obtained in 50% yield as a 65 : 35 mixture of racemic *trans* (**t**) and *cis* (**c**) isomers. Similarly disappointing were the reactions carried out in the presence of compounds **13-15** reported in Chart 1, using the synthesis of β-lactam **7** as model reaction.[14]

A less discouraging result was obtained using (-)-(1R,2S)-*N*-methylephedrine **16** (NME). With the boron species derived from this aminoalcohol and BCl_3·Me_2S, azetidinone (-)-**7**, $[\alpha]_D^{23}$ - 34.0 (c 1, $CHCl_3$), m.p. 140-141°C, was obtained in 70% yield and 38% e.e.[15] It is interesting to note that the use of (1R,2S)-ephedrine **17** and of (1R,2S)-*N*,*O*-dimethylephedrine **18** afforded (-)-**7** in lower e.e. (< 3 and 28%, respectively), thus showing the importance of both the unprotected hydroxyl function and the tertiary amino group.[10]

The influence of different enolizing bases on the stereoselectivity of the synthesis of **7** carried out in the presence of the [BCl_3·Me_2S+(1R,2S)-**16**] adduct was then studied.The results are reported in Table 2. Although an improvement in the e.e. was observed with some achiral bases (entry 3, 4, and 6), only the use of (1R,2S)-**16** as the ligand and as the enolizing base led to a satisfactory level of stereoselection (entry 8-10). A variation of the conditions for preparing the [BCl_3·Me_2S+(1R,2S)-**16**] adduct gave (-)-**7** in best yield and e.e. (entry 10).

Chart 1.

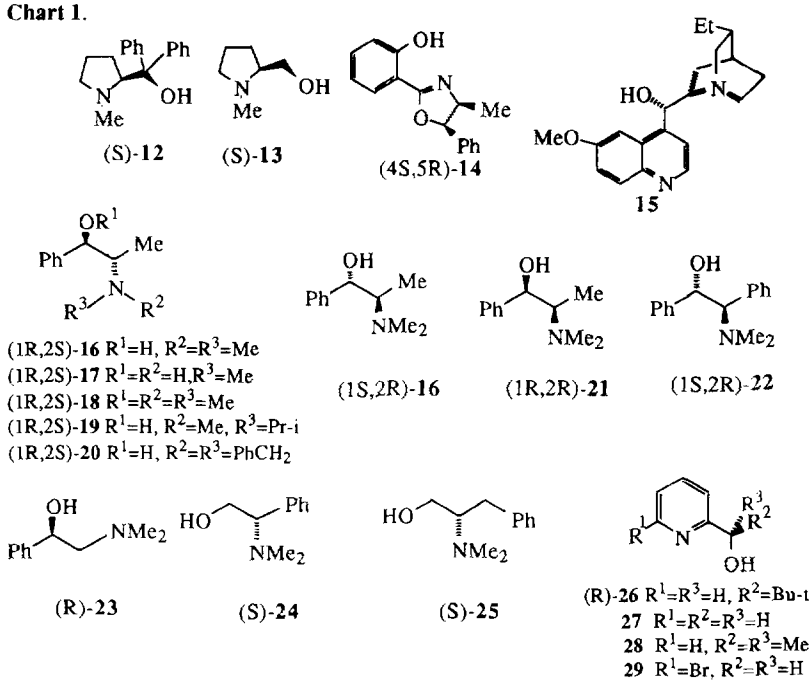
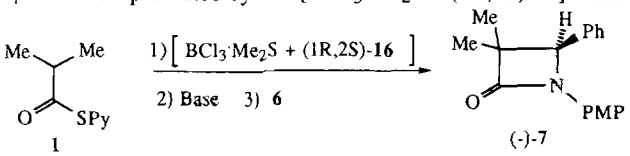


Table 2. Influence of Different Enolizing Bases and Reaction Conditions on the Stereoselectivity of the Synthesis of β-Lactam **7** promoted by the [$BCl_3.Me_2S$ + (1R,2S)-**16**] Adduct.[a,b]



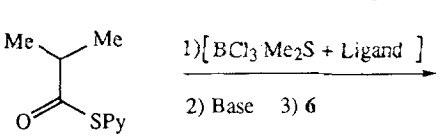
Entry	Base	Yield %	e.e. %
1	Et_3N	70	38
2	Quinuclidine	61	45
3	DABCO	37	65
4[c]	DABCO	60	65
5	DBU	37	40
6	Pyridine	32	57
7[d]	Et_3N	43	58
8	(1R,2S)-**16**	41	78
9[e]	(1R,2S)-**16**	72	72
10[f]	(1R,2S)-**16**	74	78
11[g]	(1R,2S)-**16**	55	75
12[h]	(1R,2S)-**16**	55	76
13[f]	(1S,2R)-**16**	70	<3

[a] 1 : [BCl_3·Me_2S + (1R,2S)-**16**] : Base : **6** molar ratio is 1 : [2+1] : 1 : 0.5 unless otherwise stated. [b] BCl_3·Me_2S + (1R,2S)-**16** reaction time is 1h in CH_2Cl_2 at room temperature; the solvent is evaporated before addition of **1**. [c] 0.5 mol equiv of base is used [d] 1 : [2+2] : 1 : 0.5 molar ratio. [e] BCl_3·Me_2S + (1R,2S)-**16** reaction time is 16h. [f] [BCl_3·Me_2S + (1R,2S)-**16** adduct was used without solvent evaporation. [g] 1 : [1+0] : 1 : 0.5 molar ratio. [h] 1 : [2+0] : 2 : 0.5 molar ratio.

In order to simplify the process, (1R,2S)-**16** was used only as the base to enolize the [BCl_3·Me_2S+**1**] adduct. In these conditions β-lactam (-)-**7** was obtained in lower yield, but, remarkably, still in good e.e. (entry 11 and 12). Finally, (1S,2R)-**16** was used as the base in combination with its enantiomer (1R,2S)-**16** as boron ligand (entry 13). From this reaction racemic 7 was obtained, thus indicating the possibility of an exchange between the aminoalcohol used as ligand and that used as base.[16]

Having established that NME-**16** is a suitable chiral promoter for our reaction, the influence exerted on the stereoselectivity of the synthesis of **7** by a modification of the structure of NME-**16** was examined.The amino-alcohols **19-29** employed in this study are reported in Chart 1, the results in Table 3.

Table 3. Stereoselective Synthesis of β-Lactam **7** in the presence of Aminoalcohols **16, 19-29**.[a]



1 **7**

Entry	Ligand	Base	Yield %	Configuration	e.e.%
1	(1R,2S)-**19**	(1R,2S)-**19**	44	(R)	72
2[b]	none	(1R,2S)-**19**	44	(R)	62
3[c]	(1R,2S)-**20**	Et_3N	36	(R)	28
4	(1R,2S)-**20**	(1R,2S)-**20**	32	(R)	57
5[b]	none	(1R,2S)-**20**	50	(R)	64
6[d]	(1R,2S)-**20**	(1R,2S)-**16**	59	(R)	67
7	(1R,2R)-**21**	(1R,2R)-**21**	45	(S)	20
8[b]	none	(1R,2R)-**21**	31	(S)	22
9[b]	none	(1S,2R)-**21**	28	(S)	16
10	(R)-**23**	(R)-**23**	48	-	<3
11	(S)-**24**	(S)-**24**	16	-	<3
12	(S)-**25**	(S)-**25**	32	(R)	15
13	(R)-**26**	(R)-**26**		no reaction	
14[c]	(R)-**26**	Et_3N	48	-	<3
15[d]	(R)-**26**	(1R,2S)-**16**	62	(R)	69
16[d]	(R)-**26**	(1S,2R)-**16**	60	(S)	63
17[d]	**27**	(1R,2S)-**16**	61	(R)	77
18[d]	**28**	(1R,2S)-**16**	52	(R)	66
19[d]	**29**	(1R,2S)-**16**	41	(R)	61

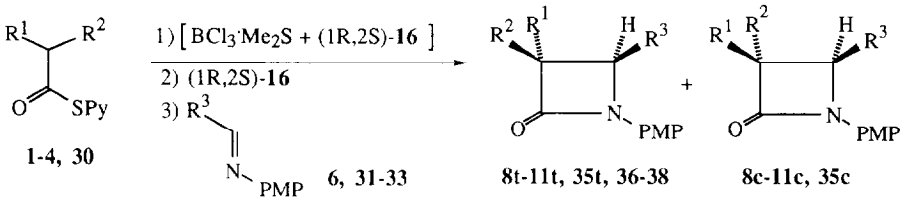
[a] Conditions of entry 8, Table 2, unless otherwise stated. [b] Conditions of entry 11, Table 2. [c] Conditions of entry 1, Table 2. [d] Conditions of entry 10, Table 2.

The data indicate that no improvement in stereoselection is achieved either by increasing the size of the nitrogen substituents (entry 1-6), or by changing the relative configuration at the stereocenters (entry 7, 8). Removal of one of these is detrimental (entry 10-12), as it is the use of a "bulkier" aminoalcohol like **22** (entry 9). Stimulated by the result of entry 6 of Table 2, pyridine derived alcohol (R)-**26** was tested. This however turned out to be too weak as a base (entry 13), and unable to improve the stereoselectivity of the reaction when

used as boron ligand, either in combination with Et_3N or with (1R,2S)- and (1S,2R)-**16** as bases (entry 14-16). The condensations carried out with achiral 2-pyridinemethanols **27-29** as ligands (entry 17-19) confirmed the limited influence of this class of compounds on the stereoselection.

The extension of this methodology to other thioesters and imines was then studied. The results are collected in Table 4. *Trans* : *cis* diastereoisomeric ratios and e.e. were determined as described above.[11,15]

Table 4. Stereoselective Synthesis of β-Lactams **8t,c-10t,c**, **35t,c** and **36-38** from Thioesters **1-4** and **30** and Imines **6** and **31-33** in the presence of (1R,2S)-NME-**16**.[a]



1-4, 30 **6, 31-33** **8t-11t, 35t, 36-38** **8c-11c, 35c**

Thioester	R^1	R^2	Imine	R^3	Yield %[b]	Product	t : c ratio[c]	e.e.% (t)	e.e.% (c)
2	Me	H	**6**	Ph	60	**8t,c**	75 : 25	38	20
30	Et	H	**6**	Ph	55	**35t,c**	77 : 23	64	45
3	Pr-i	H	**6**	Ph	25	**9t,c**	65 : 35	15	51
4	$PhCH_2O$	H	**6**	Ph	50	**10t,c**	75 : 25	74	14
1	Me	Me	**31**	4-MeOPh	42	**36**	-	62	
1	Me	Me	**32**	2-Furyl	52	**37**	-	51	
1	Me	Me	**33**	2-Thienyl	39	**38**	-	68	

[a] Reaction conditions of entry 10, Table 2. [b] Isolated yields after flash chromatography. [c] As determined on the crude products.

The reactions of thioesters **2-4** and **30** with imine **6** afford β-lactams **8t,c-10t,c** and **35t,c** with moderate *trans* selectivity that does not depend on the nature or on the bulkiness of the C-2 substituent of the thioester.[17] The e.e. do not exceed that observed in the reaction of **1** with imine **6** carried out in the same conditions. With the exception of β-lactam **9c**, the *cis* isomers are obtained in lower e.e. with respect to the *trans* ones. Other thioesters such as *S*-2-pyridylthioacetate, *S*-2-pyridylthio-α-phenylthioacetate, and *N*-acetyl- *S*-2-pyridylthio-glycinate were also tested without success.

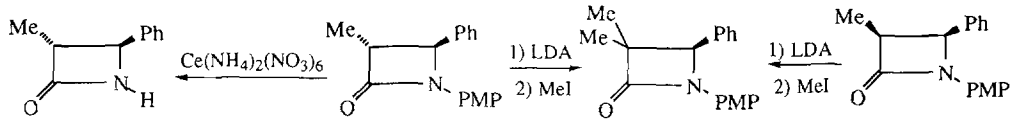
The possible variations of imine structure were rather limited. Indeed, only aromatic and heteroaromatic imines such as **31-33** could be successfully employed in the reaction with **1**. The use of imines derived from cinnamaldehyde, α-methylcinnamaldehyde, n-butanal, and cyclohexanecarbaldehyde mainly resulted in imine decomposition. In the case of β-lactams **36-38**, the e.e.were lower than the best observed for compound **7**.

The absolute configuration of some of the products was established by comparison of their sign of optical rotation with that of known compounds, and by the correlation experiments described in Scheme 1.

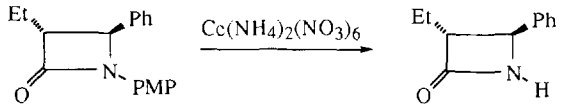
Compound (-)-(3R,4S)-**8t**, $[\alpha]_D^{23}$ -20.0 (c 1, $CHCl_3$), m.p. 97°C, e.e. 38%, was converted into the known [18] compound (-)-(3R,4S)-**39**, $[\alpha]_D^{23}$ -17.9 (c 1, $CHCl_3$), m.p. 117-118°C, {Lit.:[18] $[\alpha]_D^{22}$ -39.0 (c 1,

$CHCl_3$), m.p. 118-120°C, for a sample of e.e. >95%} by reaction with $Ce(NH_4)_2(NO_3)_6$.[19] C-3 Methylation of (-)-(3R,4S)-**8t** gave (-)-(R)-**7**, $[\alpha]_D^{23}$ -37.0 (c 0.3, $CHCl_3$), m.p. 140-142°C, e.e. 40%. (-)-(R)-**7**, $[\alpha]_D^{23}$ -29.2 (c 1.3, $CHCl_3$), m.p. 139-141°C, e.e. 25%, was also obtained by methylation of (-)-(3S,4S)-**8c**, $[\alpha]_D^{23}$ -43.0 (c 0.5, $CHCl_3$), m.p. 112°C, e.e. 23%. This series of experiments demonstrate that (-)-**8t**, (-)-**8c**, and (-)-**7** share the same ligand disposition at C-4.[20] The (3R,4S) configuration was also assigned to compound (-)-**35t** on the basis of its transformation into compound (-)-(3S,4R)-**40** of known absolute configuration.[21] On the basis of the reasonable assumption that the sense of imine enantioface discrimination is maintained in the reactions of thioesters **1-4** and **30** with imines **6** and **31-33** carried out in the presence of (1R,2S)-NME-**16**, the absolute configurations indicated in Table 4 was assigned to β-lactams **9**, **10** and **36-38**.

Scheme 1.



(-)-(3R,4S)-**39** (-)-(3R,4S)-**8t** (-)-(4R)-**7** (-)-(3S,4S)-**8c**



(-)-(3R,4S)-**35t** (-)-(3R,4S)-**40**

Several factors must be taken into account in attempting a rationalization of this β-lactam synthesis. These include: i) the activation of the thioester by the boron species; ii) the structure of the [BCl_3·Me_2S + NME-**16**] adduct; iii) the role played by the enolizing base; iv) the stereoselectivity of the enolate formation; v) the geometry of the transition state; and vi) the origin of the imine enantioface discrimination. A 300 MHz ^1H NMR study was undertaken to clarify some of these factors (Table 5).

A marked downfield shift is observed for the pyridine and the aliphatic protons of thioester **1** upon addition of 1 mol equiv of BCl_3·Me_2S. Since the boron atom cannot co-ordinate simoultaneously two Lewis basic sites,[9] the adduct seems to be the result of a rapid exchange between the two species **41** and **42** (Scheme 2) in which BCl_3 co-ordinates the carbonyl oxygen or the pyridine nitrogen. This phenomenon also occurs in the presence of a two fold excess of BCl_3·Me_2S.

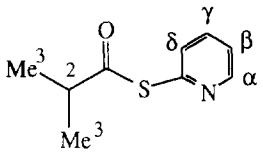
The spectrum of the boron reagent obtained by reaction of BCl_3·Me_2S with NME-**16** shows the presence of a broad signal at δ 9.70 ppm, likely due to a proton bound to a quaternary nitrogen.[13] This suggests **43** as a possible structure for this adduct.

The spectrum of the species obtained by mixing thioester **1** with the [BCl_3·Me_2S + NME-**16**] reagent is very complicated. However, co-ordination of the boron species to **1** is evident from the observed chemical shift values reported in Table 5 (also in this case an equilibrium between two or more species is possible). It is important to note that in this adduct the proton bound to the quaternary nitrogen resonates at δ 10.5 ppm, thus further downfield with respect to **43**, as if interacting with the lone pair of a heteroatom on the thioester (either the carbonyl oxygen or the pyridine nitrogen).

No enolate signals can be detected in the ^1H or in the 75.4 MHz ^{13}C NMR spectrum of the [**1**+BCl_3] adduct

upon addition of different bases. In this case, the signals of two species were observed in the ratio of 66 : 34 (Et_3N), 85 : 15 (DABCO), and 89 : 11 (pyridine). The major one is likely to be a new boron complex of **1** (from its ^1H NMR); the minor one features signals very similar to those of the starting [**1**+BCl_3] adduct.

Table 5. ^1H NMR Chemical Shift Values of Thioester **1** and of its Boron Adducts (CD_2Cl_2, -78°C).



Species	HC-2	HC-3	Hα	Hβ	Hγ	Hδ	
1	2.87	1.25	8.60	7.28	7.59	7.74	
[**1**+ BCl_3]	3.26	1.49	9.95	8.06	8.55	8.06	
1+ [BCl_3 + **16**]	3.26	1.50	9.15	8.30	8.76	8.30	
[**1**+ BCl_3] + base	3.10	1.43	8.84	7.60	8.05	7.80	major
	3.25	1.48	9.95	8.08	8.56	8.15	minor
[**1**+ BCl_3] + **16**	-[a]	1.42	8.80	7.40	8.06	7.80	major
	-[a]	1.48	9.95	-[a]	8.55	8.20	minor

[a] Undetermined because of peak overlap.

When NME-**16** was used as base to enolize the [**1**+BCl_3] complex, two adducts were obatined in a 60 : 40 ratio. They have thioester derived signals almost identical to those of the two [**1**+BCl_3]+achiral base species. Also the signals of NME were similar to those of the [BCl_3+NME] adduct, with the only remarkable difference of the proton bound to the quaternary nitrogen that is shifted way downfield at 11.35 ppm.

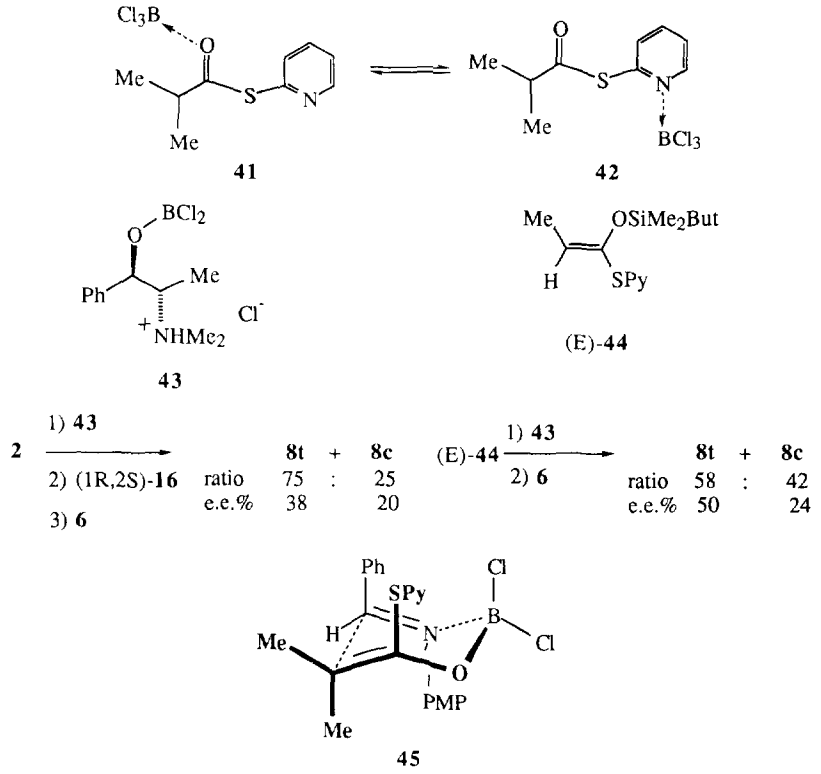
The spectrum of the mixture obtained by addition of Et_3N to the **1** + [BCl_3 + NME] adduct was less informative, since the intense signals of Et_3N overlap with those of the aliphatic protons of **1** and of NME. Inspection of the downfield region of the spectrum indicates a situation analogous to that of the [**1**+BCl_3] + NME mixture.[22]

Because of the impossibility to observe any enolate signal, NMR spectroscopy does not provide information about the geometry of the enolates derived from thioesters such as **2-5** and **30**, that can exist as (E) and (Z) isomers. The scarce *trans/cis* stereoselectivity observed in the synthesis of β-lactams **8-11** and **35** suggests either a poorly stereoselective enolization, or the existence of stereodivergent transition states.[23] In an attempt to clarify this point, thioester **2** was transformed into silylketene acetal (E)-**44** [(E) : (Z) ratio > 20 : 1].[24] Reaction of (E)-**44** with [BCl_3 + (1R,2S)-**16**] for 3h at 0°C, followed by addition of imine **6**, gave (86% yield) a 58 : 42 mixture of β-lactams **8t** and **8c**, in 50 and 24% e.e., respectively.[25] Thus, this reaction occurs with the same sense and a slightly different extent of relative and absolute stereochemistry control with respect to that of **2** with **6** carried out in the presence of [BCl_3 + (1R,2S)-**16**] as activator and of (1R,2S)-**16** as base. Although the mechanism of the two processes can be different,[26] it seems reasonable to propose that the enolate of **2** (and hence of **3-5** and **30**) can react with imine **6** *via* different and stereodivergent transition states.

As the result of this complex situation, we tentatively propose a model of stereoselection only for the BCl_3

promoted reaction of imine **6** with thioester **1**, that can occur *via* a single enolate. To this end, cyclic models were considered, in agreement with the reported rationalizations of the addition of thioester boron enolate to imines.[3e,4,27] On the basis of others' [5a] and ours observations,[28] we think that the transition state involves an (E) configurated imine, that does not isomerize in the course of the reaction. The presence of two methyls at C-2 of the enolate should strongly destabilize a boat-like transition state, thus leading to a chair-like one as **45**.[29] Substitution of either one of the two chlorine atoms with the NME residue should provide the element of imine enantioface discrimination.[30] However, the proposal of a model that rationalizes the stereoselectivity dependence

Scheme 2.



on the structure of the aminoalcohols described in Table 3 is presently beyond our efforts. Indeed, although the results of Table 3 seem to indicate that the sense of the stereoselectivity of the reaction is determined by the configuration of the nitrogen bearing stereocenter of the aminoalcohol,[31] we feel that many different competing effects combine to produce the observed stereochemical results, and they require much more experimental work to be fully elucidated.

Experimental.

^{1}H NMR spectra were obtained at 300 MHz, and ^{13}C NMR spectra at 75.4 MHz. Silica gel was used for analytical and flash chromatography. Organic extracts were dried over Na_2SO_4 and filtered before removal of the solvent. All the reactions employing dry solvents were run under nitrogen. CH_2Cl_2 was distilled from CaH_2;

THF and Et_2O from $LiAlH_4$; Et_3N from KOH. BCl_3·Me_2S was used as commercially available 2M solution in CH_2Cl_2.

Thioesters **1-5** and **30** were known compounds.[2b] The imines were prepared by stirring a CH_2Cl_2 solution of freshly distilled aldehyde and 4-methoxyaniline at rt for 12h in the presence of $MgSO_4$. Filtration and evaporation of the solvent at rt gave the crude products that were used as such. β-Lactams **7**,[6d] **8**,[6c] **9**,[6c] **35**,[6c] **10**,[6d] **11**,[6d] **39**,[18] and **40**,[21] were known compounds. Aminoalcohols **15-17** and **27** were commercial products; compounds (S)-**12**, $[\alpha]_D^{23}$+56.8 (c 1.0, $CHCl_3$), {Lit.: [32] $[\alpha]_D^{23}$+57.0 (c 1.0, $CHCl_3$)}; (S)-**13**, $[\alpha]_D^{23}$-50.6 (c 0.9, EtOH), {Lit.: [33] $[\alpha]_D^{28}$-50.7 (c 1.021, EtOH)}; (4S,5R)-**14**, $[\alpha]_D^{23}$-351.5 (c 3.0, $CHCl_3$), {Lit.: [34] $[\alpha]_D^{25}$-354.0 (c 2.98, $CHCl_3$)}; (1R,2S)-**18**, $[\alpha]_D^{23}$-71.5 (c 2.0, $CHCl_3$), {Lit.: [35] $[\alpha]_D^{25}$ -74.5 (c 2.5, $CHCl_3$)}; (1R,2S)-**19**, $[\alpha]_D^{23}$-2.4 (c 1.0, $CHCl_3$), {Lit.: [36] $[\alpha]_D^{20}$-2.1 (c 6.0, $CHCl_3$)}; (1R,2R)-**21**, $[\alpha]_D^{23}$-38.0 (c 3.0, MeOH), {Lit.: [37] $[\alpha]_D^{20}$+38.7 (c 6.65, MeOH) for the (1S,2S)-enantiomer}; (R)-**23**, $[\alpha]_D^{23}$-72.0 (c 1.0, $CHCl_3$), {Lit.: [37] $[\alpha]_D^{20}$+74.1 (c 1.3, $CHCl_3$) for the (S)-enantiomer}; (S)-**24**·HCl, $[\alpha]_D^{23}$+30.6 (c 0.8, H_2O), {Lit.: [38] $[\alpha]_D^{25}$-30.8 (c 0.85, H_2O) for the (R)-enantiomer}; (S)-**25**·HCl, $[\alpha]_D^{23}$+11.7 (c 2.5, H_2O), {Lit.: [38] $[\alpha]_D^{22}$ +11.9 (c 4.0, H_2O)}; and (R)-**26**, $[\alpha]_D^{23}$+40.0 (c 0.3, EtOH), {Lit.: [39] $[\alpha]_D^{23}$ +32.5 (c 1.2, EtOH) for a sample of 90% e.e.}, were prepared as described, as were achiral derivatives **28**[40] and **29**[41]. **(1R,2S)-2-Dibenzylamino-1-phenylpropanol 20** was obtained in 63% yield by treatment of commercially available (1R,2S)-*nor*-ephedrine in refluxing EtOH with 2 mol equiv of benzyl bromide in the presence of 3 mol equiv of anhydrous K_2CO_3. The product was purified by flash chromatography with a 70 : 30 hexanes : Et_2O mixture as eluant. Compound **20** was a thick oil, $[\alpha]_D^{23}$-38.0 (c 1.0, $CHCl_3$). IR : 3425, 3030, 2800, 1480, 1450, 1050, 740 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.19-7.38 (m, 15H); 4.75 (d, 1H, J = 6.4 Hz); 3.74 (A part of an AB system, 2H, J = 13.9 Hz); 3.51 (B part of an AB system, 2H, J = 13.9 Hz); 3.09-3.13 (m, 1H); 1.18 (d, 3H, J = 6.7 Hz). Anal. Calcd for: $C_{23}H_{25}NO$: C: 83.34; H, 7.60; N, 4.23. Found: C, 83.10; H, 7.84; N, 4.51. **(1S,2R)-2-Dimethylamino-1,2-diphenylethanol 22** was obtained in 92% yield by treatment of the corresponding commercially available *N*-unsubstituted aminoalcohol with an excess of 35% aqueous HCHO and 90% aqueous HCOOH 15h at reflux. It was a solid, m.p.88°C (Lit.:[42]m.p.88-89°C for a racemic sample),$[\alpha]_D^{23}$+106.8 (c 1.0, $CHCl_3$). IR (nujol): 3435, 3030,1475,1450, 1050, 740 cm^{-1}. ^1H NMR ($CDCl_3$): δ 6.75-7.25 (m, 10H); 5.27 (d, 1H, J = 4.7 Hz); 3.20 (d, 1H, J = 4.7 Hz); 2.33 (s, 6H). Anal. Calcd for: $C_{16}H_{19}NO$: C, 79.63; H, 7.94; N, 5.80. Found: C,79.90;H, 8.04; N, 5.71.

General Procedure for the Synthesis of β-Lactams. To a stirred 0.1 M solution of thioester (1 mol equiv) and of the boron reagent (2 mol equiv, see footnotes of Table 2 for its preparation) in dry CH_2Cl_2 cooled at -78°C, the tertiary amine (1 mol equiv) was added either as such (Et_3N, pyridine), or dissolved in CH_2Cl_2 (for all other bases). After 30 min stirring at -78°C, the imine (0.5 mol equiv) was added dissolved in CH_2Cl_2. The reaction was allowed to warm-up to rt, and then kept at that temperature overnight. The reaction was quenched by addition of a sat. aqueous solution of $NaHCO_3$, and the resulting mixture was filtered through celite. The organic phase was separated, washed with water, dried, and concentrated to give the crude product. This was dissolved in THF and treated with a two fold excess of 1N aqueous KOH to hydrolize the unreacted thioester (1-5h; this procedure was not followed in the case of compound **11**). Et_2O was then added, and the organic phase was separated, washed with brine, dried, and concentrated. ^1H NMR analysis of the residue was then performed to evaluate the *trans/cis* ratio if necessary. The product was then isolated by flash chromatography with a 70 : 30 hexanes : Et_2O mixture as eluant. The e.e. were determined generally exploiting the signals of the MeO or of the

gem-dimethyl group. Compound **35t** had m.p. 101°C, $[\alpha]_D^{23}$-35.2 (c 0.8, $CHCl_3$); compound **10t** had m.p. 124-125°C, $[\alpha]_D^{23}$-20.2 (c 0.6, $CHCl_3$); β-lactams **35c**, **9t**, **9c**, and **10c** were obtained only as isomeric mixtures; for compounds **7**, **8t**, and **8c** optical rotations and m.p. are reported in the text.

3,3-Dimethyl-1,4-di-(4-methoxyphenyl)azetidin-2-one 36, had m.p. 97°C, $[\alpha]_D^{23}$-52.0 (c 1.0, $CHCl_3$). IR (nujol): 1750 cm^{-1}.^{1}H NMR ($CDCl_3$): δ 6.80-7.25 (m, 8H); 4.72 (s, 1H, HC-4); 3.74 (s, 6H, 2 MeO); 1.48 and 0.83 (2s, 6H, 2 Me at C-3). Anal. Calcd for: $C_{19}H_{21}NO_3$: C, 73.29; H, 6.80; N, 4.50. Found: C, 73.12; H, 6.88; N,4.51.

3,3-Dimethyl-4-(2-furyl)-1-(4-methoxyphenyl)azetidin-2-one 37, had m.p. 130°C (dec.), $[\alpha]_D^{23}$-44.5 (c 0.8, $CHCl_3$). IR (nujol): 1750 cm^{-1}.^{1}H NMR ($CDCl_3$): δ 6.24-7.40 (m, 7H); 4.37 (s, 1H, HC-4); 3.75 (s, 3H, MeO); 1.48 and 1.07 (2s, 6H, 2 Me at C-3). Anal. Calcd for: $C_{16}H_{17}NO_3$: C, 70.83; H, 6.32; N, 5.16. Found: C, 70.66; H, 6.29; N, 5.27.

3,3-Dimethyl-1-(4-methoxyphenyl)-4-(2-thienyl)azetidin-2-one 38, was a low melting material, $[\alpha]_D^{23}$-41.0 (c 0.5, $CHCl_3$). IR (nujol): 1750 cm^{-1}.^{1}H NMR ($CDCl_3$): δ 6.80-7.26 (m, 7H); 4.96 (s, 1H, HC-4); 3.75 (s, 3H, MeO); 1.48 and 1.01 (2s, 6H, 2 Me at C-3). Anal. Calcd for: $C_{16}H_{17}NO_2S$: C, 66.87; H, 5.96; N, 4.87. Found: C, 66.71; H, 6.04; N, 4.82.

Chemical Correlations. β-Lactams **39** and **40** were obtained from compounds **8t** and **8c**, respectively, by $Ce(NH_4)_2(NO_3)_6$ promoted degradation of the 4-methoxyphenyl group. This was accomplished following precisely the procedure described by Georg, et al.[19] Compound **39** (75% yield) had m.p. 117-118°C, $[\alpha]_D^{23}$-17.9 (c 1.0, $CHCl_3$); compound **40** (82% yield) had m.p. 72-73°C, $[\alpha]_D^{23}$-35.8 (c 0.4, $CHCl_3$). Both products were purified by flash chrmatography with a 50 : 50 hexanes : Et_2O eluting mixture. β-Lactams **8t** and **8c** were converted into compound (-)-**7** by the following procedure. To a stirred 0.1 M solution of **8t** or **8c** (0.5 mmol, 0.133 g), in anhydrous THF (5 ml) cooled at -78°C, a 0.1 M solution of LDA (0.55 mmol) in THF was added *via* a cannula. The solution was allowed to warm-up to -40°C, and was kept at that temperature for 30 min. MeI (1 mmol, 0.062 ml) was then added, and the reaction was stirred overnight at rt. A sat. aqueous solution of NH_4Cl was then added, the organic phase was separated, dried, and concentrated. The residue was purified with a 80 : 20 hexanes : Et_2O eluting mixture to afford (-)-**7** in 72% (from **8c**) and 20% (from **8t**) yield, respectively. From the methylation of **8t**, the starting material was recovered in 75% yield.

Acknowledgements. Partial financial support by CNR-Progetto Strategico Tecnologie Chimiche Innovative is gratefully acknowledged.

References and Notes.

1. Reviews: (a) Hart, D.J.; Ha, D.-C. *Chem. Rev.* **1989**, *89*, 1447. b) Brown, M.J. *Heterocycles* **1989**, *29*, 2225. c) van der Steen, F.H.; van Koten, G. *Tetrahedron* **1991**, *47*, 7503.
2. For recent examples of the use of chiral enolates or imines not included in ref. 1 see: Enolates: a) Hatanaka, M.; Park, O.-S.; Ueda, I. *Tetrahedron Lett.* **1990**, *31*, 7631. b) Annunziata, R.; Cinquini, M.; Cozzi, F.; Cozzi, P.G. *J. Org. Chem.* **1992**, *57*, 4155. Imines: c) Andreoli, P.; Billi, L.; Cainelli, G.; Panunzio, M.; Bandini, E.; Martelli, G.; Spunta, G. *Tetrahedron* **1991**, *47*, 9061. d) Andreoli, P.; Cainelli, G.; Panunzio, M.; Bandini, E.; Martelli, G.; Spunta, G. *J. Org. Chem.* **1991**, *56*, 5984. e) Fujisawa, T.; Ukaji, Y.; Noro, T.; Date, K.; Shimizu, M. *Tetrahedron* **1992**, *48*, 5629. f) Fujisawa, T.; Hayakawa, R.; Shimizu, M. *Tetrahedron Lett.* **1992**, *33*, 7903. g) Fujisawa, T.; Iguchi, K.; Shimizu, M. *SYNLETT* **1993**, 59. h) Fujisawa, T.; Ukaji, Y.; Shimizu, M. *Tetrahedron Lett.* **1993**, *34*, 1307. i) Bandini, E.; Cainelli, G.; Martelli, G.; Panunzio, M.; Spunta, G. *Gazz. Chim. Ital.* **1993**, *123*, 509. j) Annunziata, R.; Benaglia, M.; Cinquini, M.; Cozzi, F.; Ponzini, F. *J. Org. Chem.* **1993**, *58*, 4746. k) Shimizu, M.; Ishida, T.; Fujisawa, T. *Chemistry Lett.* **1994**, 1403.
3. For recent examples of the use of enolates or imines made chiral by the presence of a chiral auxiliary not reported in ref. 1 see: Enolates: a) Ojima, I.; Habus, I.*Tetrahedron Lett.* **1990**, *31*, 4289. b) Ojima, I.; Habus, I.; Zhao, M.; Georg, G. I.; Jaysinghe, L.R. *J. Org. Chem.* **1991**, *56*, 1681. c) Ojima, I.; Park,

Y.H.; Sun, C.M.; Brigaud, T.; Zhao, M.*Tetrahedron Lett.* **1992**, *33*, 5737. d) Shimizu, M.; Teramoto, Y.; Fujisawa, T. *Tetrahedron Lett.* **1995**, *36*, 729. Imines: e) Mori, M.; Kagechika, K.; Sasai, H.; Shibasaki, M.*Tetrahedron* **1991**, *47*, 531. f) Brown, M.J.; Overman, L.E.*J. Org. Chem.* **1991**, *56*, 1933. g) van der Steen, F.H.; Kleijn, H.; Britovsek, G.J.P.; Jastrzebski, J.T.B.H.; van Koten, G. *J. Org. Chem.* **1992**, *57*, 3906. h) van Maanen, H.L.; Kleijn, H.; Jastrzebski, J.T.B.H.; Lakin, M.T.; Spek, A.L.; van Koten, G. *J. Org. Chem.* **1994**, *59*, 7839. j) Annunziata, R.; Benaglia, M.; Cinquini, M.; Cozzi, F.; Raimondi, L. *Tetrahedron* **1994**, *50*, 9471. k) Baldoli, C.; Del Buttero, P. *J. Chem. Soc. Chem. Commun.* **1991**, 983.

4. Corey, E.J.; Decicco, C.P.; Newbold, R.C. *Tetrahedron Lett.* **1991**, *32*, 5287.
5. a) Hattori, K.; Miyata, M.; Yamamoto, H. *J. Am. Chem. Soc.* **1993**, *115*, 1151. b) Hattori, K.; Yamamoto, H. *Tetrahedron* **1994**, *50*, 2785.
6. a) Cinquini, M.; Cozzi, F.; Cozzi, P.G.; Consolandi, E.*Tetrahedron* **1991**, *47*, 8767. b) Annunziata, R.; Cinquini, M.; Cozzi, F.; Lombardi Borgia, A. *Gazz. Chim. Ital.* **1993**, *123*, 181. c) Annunziata, R.; Benaglia, M.; Cinquini, M.; Cozzi, F.; Ponzini, F.; Raimondi, L. *Tetrahedron* **1994**, *50*, 2939. d) Annunziata, R.; Benaglia, M.; Cinquini, M.; Cozzi, F.; Raimondi, L. *Tetrahedron* **1994**, *50*, 5821.
7. For leading references to this method of preparation of titanium enolates see: Evans, D.A.; Bilodeau, M. T.; Somers, T.C.; Clardy, J.; Cherry, D.; Kato, Y. *J. Org. Chem.* **1991**, *56*, 5750, and references therein. $ZrCl_4$, $AlBr_3$, and $EtAlCl_2$ were also found to be effective thioester activators (unpublished results from these laboratories).
8. Bidentate ligands such as diols, binaphthols, and bis-sulfonamides depress the Lewis acidity of the Ti or Sn species, that become unable to promote the enolization process.
9. a) Masamune, S.; Ellingboe, J.W.; Choy, W. *J. Am. Chem. Soc.* **1982**, *104*, 5526. b) Martin, S.F.; Lee, W.C. *Tetrahedron Lett.* **1993**, *34* , 2711. c) Evans, D.A.; Duffy, J.L.; Dent, M.J. *Tetrahedron Lett.* **1994**, *35* , 8537. Resonance stabilized hypervalent boron species have been prepared: d) Lee, D. Y.; Martin, J.C. *J. Am. Chem. Soc.* **1984**, *106*, 5745.
10. For a preliminary account of part of this work see: Annunziata, R.; Benaglia, M.; Cinquini, M.; Cozzi, F. *Tetrahedron Lett.* **1995**, *36* , 613; the (-)-(1R,2S) enantiomer of *N*-methylephedrine was used instead of the (+)-(1S,2R) erroneously indicated in this paper.
11. Lower yields were obtained with BBr_3, while BI_3 and $BF_3{\cdot}Et_2O$ were not effective. Different thioester : $BCl_3{\cdot}Me_2S$: base : imine ratios (1 : 1 : 1 : 0.5; 1 : 2 : 1 : 1) and higher enolization temperatures (-30, 0, and 20°C) resulted in lower yields and similar diastereoselections. *Trans /cis* ratios were easily determined by 300 MHz ^1H NMR analysis of the crude reaction products exploiting the HC-3/HC-4 coupling constant values (J_{trans}: 2.0-2.5 Hz; J_{cis}: 5.0-6.0 Hz). It must be noted that *S*-t-butylthio- and *S*-phenylthiopropionate do not react with imines in these conditions.
12. Dialkyl- and dialkoxyboron halides were totally uneffective as thioester activators as was Corey's diazaborolidine (see ref. 4).
13. Kobayashi, S.; Murakami, M.; Harada, T.; Mukaiama, T. *Chem. Lett.* **1991**, 1341. See also: Aggarwal, V.K.; Anderson, E.; Giles, R.; Zaparucha, A. *Tetrahedron: Asymmetry*, **1995**, 1301. We thank Professor Aggarwal for a preprint of this work (private communication to F.C.).
14. The use of R^*OBCl_2 species, obtained by reaction of $BCl_3{\cdot}Me_2S$ with menthol, isoborneol, and (S)-1-phenylethanol, resulted in good yields of racemic β-lactam **7**.
15. The e.e. was determined by 300 MHz ^1H NMR analysis carried out in the presence of $Eu(hfc)_3$ in conditions pre-established on racemic **7**. Since moderate enantiomeric enrichment by flash chromatography was observed for compound **35t** (see below), the e.e. was always determined on a sample of the whole product, and not on single chromatographic fractions. This method for e.e. determination was found to be more reliable than the use of optical purity. The maximum rotation reported for enantiomerically pure **7** is $[\alpha]_D^{23}$ 88.0 (c 0.64, $CHCl_3$), see ref. 3d.
16. (-)-Sparteine and *O*-4-chlorobenzoyl protected dihydroquinine and dihydroquinidine were less efficient chiral bases than NME in terms of both yield and stereoselection.
17. A dependence of the β-lactam *trans /cis* ratios on the nature of the thioester activator and of the enolizing base can be observed by comparing the results reported for compounds **8-10** (Table 1,4).
18. Davies, S.G.; Walters, A.S. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1129. See also: Abrahams, I.; Motevalli, M.; Robinson, A.J.; Wyatt, P.B. *Tetrahedron* **1994**, *50*, 12755.
19. Georg, G.I.; Kant, J.; Gill, H.S. *J. Am. Chem. Soc.* **1987**, *109*, 1129.
20. The C-4 stereodescriptor, however, changes on passing from **8t** and **8c** to **7**.
21. Pirkle, W.H.; Tsipouras, A.; Hyon, M.H.; Hart, D.J.; Lee, C.-S. *J. Chromatogr.* **1986**, *358*, 377. See also: Hart, D.J.; Lee, C.-S.; Pirkle, W.H.; Hyon, M.H.; Tsipouras, A. *J. Am. Chem. Soc.* **1986**, *108*, 6054.
22. It is also important to note that the deprotonation of thioester **1** activated by the [BCl_3+NME] adduct can occur intramolecularly. Indeed, if the added base deprotonates the Me_2NH^+ group of [BCl_3+NME], then the dimethylamino moiety can act as base and enolize the thioester.

23. *S*-t-Butylthio- and *S*-phenylthiopropionate are known to enolize in the (Z) configuration (CIP rules) under kinetic control (THF, -78°C). For a discussion of the stereochemistry of the boron enolates of thioesters see: a) Evans, D.A.; Nelson, J.V.; Vogel, E.; Taber, T.R. *J. Am. Chem. Soc.* **1981**, 103, 3099. b) Gennari, C.; Bernardi, A.; Cardani, S.; Scolastico, C. *Tetrahedron* **1984**, *40*, 4059. The [BCl_3+NME] adduct does not activate *S*-t-butylthio- and *S*-phenylthiopropionate for Et_3N or NME enolization and reaction with imine **6**.
24. Hirai, K.; Iwano, Y.; Mikoshiba, I.; Koyama, H.; Nishi, T. *Heterocycles* **1994**, *38*, 277.
25. This experiment represents the first enantioselective one-pot synthesis of a β-lactam by a chiral Lewis acid promoted addition of a silylketene acetal to an imine to be reported in the literature. This reaction is currently under active investigation in our laboratories.
26. (E)-**44** can react with imine **6** *via* the acyclic transition states generally accepted for the Mukaiyama aldol condensation. For leading discussions of the mechanism of this reactions see: a) Gennari, C. in *Comprehensive Organic Synthesis*; Heatcock, C. Ed.; Pergamon: Oxford, U.K. **1991**; vol.2, p.629. b) Reetz, M.T.; Raguse, B.; Marth, C.F.; Hugel, H.M.; Bach, T.; Fox, D.N.A. *Tetrahedron* **1992**, 48, 5731 c) Cozzi, P.G.; Floriani, C.; Chiesi-Villa, A.; Rizzoli, C. *Organometallics* **1994**, *13*, 2131. Denmark, S.E.; Lee, W. *J. Org. Chem.* **1994**, *59*, 707, and references therein.
27. a) Shibasaki, M.; Ishida, Y.; Iwasaki, G.; Iimori, T. *J. Org. Chem.* **1987**, *52*, 3498. b) Iimori, T.; Ishida, Y.; Shibasaki, M. *Tetrahedron Lett.* **1986**, *27*, 2153.
28. Imine **6** was obtained in the (E) configuration and was shown to be complexed but did not isomerize in the presence of different amounts of BCl_3 by ^1H and ^{13}C NMR experiments. For a similar observation see ref. 5a.
29. Li, Y.; Paddon-Row, N.; Houk, K.N. *J. Org. Chem.* **1990**, *55*, 481.
30. It is important to note that the NME residue must feature a positively charged nitrogen atom as in **43** for the reaction to take place. Indeed, the neutral adduct obtained by reaction of BCl_3·Me_2S with the sodium salt of NME is not able to promote the condensation of thioester **1** with imine **6**. Also on the basis of the NMR data, it can be proposed that the proton of the Me_2NH^+ group of **43** facilitates the enolization of **1** by co-ordination to the carbonyl oxygen. If maintained in the transition state, this co-ordination can result in a conformationally more rigid disposition of the NME residue, that can be important in determining the stereoselectivity of the reaction. For a related example of carbonyl reactivity enhancement by Me_2NH^+ group/carbonyl oxygen interaction see ref. 13.
31. (R)- and (S)-**7** are obatined from **1** and **6** in the presence of aminoalcohols featuring (S) and (R) configurated nitrogen bearing stereocenters, respectively. Surprisingly, however, the use of the aminoalcohol (S)-**24** results in a non stereoselective reaction. The oxygen bearing stereocenter seems to exert a negligeable effect, since the use of (1R,2S)-**16** and (1R,2R)-**21** led to the formation of (R)- and (S)-**7**, respectively, and with (R)-**23** no stereoselection is observed.
32. Soai, K.; Ookawa, A.; Kabe, T.; Ogawa, K. *J. Am. Chem. Soc.* **1987**, *109*, 7111.
33. Mukaiyama, T.; Soai, T.; Sato, T.; Shimizu, H.; Suzuki, K. *J. Am. Chem. Soc.* **1979**, *101*, 1455.
34. Bolm, C.; Weickardt, K.; Zehnder, M.; Ranff, T. *Chem. Ber.* **1991**, *124*, 1173.
35. Coote, S.J.; Davies, S.G.; Goodfellow, C.L.; Sutton, K.H. *Tetrahedron : Asymmetry* **1990**, *1*, 817. See also: Elsevier, C.J.; Mooiweer, H.H. *J. Org. Chem.* **1987**, *52*, 1536.
36. Fehr, C.; Galindo, J. *J. Am. Chem. Soc.* **1988**, *110*, 6909. See also: Saavedra, J.E. *J. Org. Chem.* **1985**, *50*, 2271.
37. Gennari, C.; Molinari, F.; Cozzi, P.G.; Oliva, A. *Tetrahedron Lett.* **1989**, *30*, 5163.
38. Hayashi, T.; Konishi, M.; Fukushima, M.; Kanahira, K.; Hioki, T.; Kumada, M. *J. Org. Chem.* **1983**, *48*, 2195.
39. Bolm, C.; Ewald, M.; Felder, M.; Schlingloff, G. *Chem. Ber.* **1992**, *125*, 1169.
40. Curtis, N.J.; Brown, R.S. *Can. J. Chem.* **1981**, *59*, 65.
41. Ashimori, A.; Ono, T.; Uchida, T.; Ohtaki, Y.; Fukaya, C.; Watanabe, M.; Yokoama, K. *Chem. Pharm. Bull.* **1990**, *38*, 2446.
42. Puterbaugh, W.H.; Hauser, C.R. *J. Org. Chem.* **1963**, *28*, 3465.

(*Received in UK* 5 *May* 1995; *revised* 15 *June* 1995; *accepted* 23 *June* 1995)