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Stereoselective Synthesis of β-Lactams by Condensation of Titanium Enolates of 2-Pyridyl Thioesters with Imines Bearing a Chiral Auxiliary

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Abstract: Several amines have been tested as chiral auxiliaries in the stereoselective synthesis of β-lactams by condensation of the titanium enolates of 2-pyridyl thioesters with chiral imines. The amines were selected among the following classes of compounds: benzylic amines, β-aminoalcohols, β-heterosubstituted α-aminoesters. Inexpensive and available in both enantiomeric forms α-methylbenzylamine was identified as the chiral auxiliary that generally combines good reactivity and satisfactory levels of stereocontrol. To illustrate the potential of the method a precursor of a component of a renin inhibitor was prepared. A tentative rationalization of the stereochemical results is presented.

Introduction.

The ester enolate/imine condensation route[1] to β-lactams[2] offers different possibilities to obtain enantiomerically enriched compounds. For the preparation of β-lactams that feature defined stereogenic substituents at C-3 and C-4 of the azetidin-2-one nucleus, the use of chiral reagents represent a very popular approach, as demonstrated by the reactions of the enolates of several 3-hydroxybutyric acid derivatives [1a,3] and of the imines obtained from chiral alkoxy aldehydes.[1,4]

An entry of wider applicability to the stereoselective synthesis of β-lactams is represented by those reactions in which chiral auxiliaries are inserted either on the enolate[1,5] or on the imine[1,6] to be exploited as elements of stereocontrol. Finally boron reagents featuring chiral ligands were also shown to promote highly stereoselective syntheses of β-aminoesters that were eventually converted into azetidin-2-ones.[7,8]

In extending our recently reported mild, one-pot synthesis of β-lactams[9] by condensation of titanium

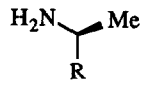
enolates[10] of 2-pyridyl thioesters with imines to the preparation of optically active compounds, we obtained satisfactory results using intrinsically chiral esters[11] and imines.[11,12] In order to widen the scope of our method, a study was undertaken to identify efficient chiral auxiliaries for both the esters and the imine components. The results obtained exploiting imines bearing a chiral auxiliary are here reported.[13]

Results and Discussion.

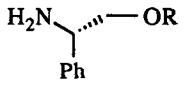
The necessity to remove the chiral auxiliary at the end of the reaction restricts the choice of the chiral amine to three main families of compounds: benzylic amines (stereocenter removed by hydrogenolysis),[6c,d,g,k] β-aminoalcohols and β-heterosubstituted α-aminoesters (stereocenter removed by oxidative degradation).[6h,m,n] The amines **1-13** that were selected for this study are indicated in Chart 1. They were reacted with benzaldehyde in the presence of magnesium sulfate[14] to afford the corresponding imines.[15,16] These were condensed with the non-stereogenic titanium enolate derived from 2-pyridylthioisobutyrate **14** to give β-lactams **15a,b-27a,b**, generally as mixtures of major (**a**) and minor (**b**) diastereoisomers (Table 1).[17] This condensation was chosen as a model reaction since it does not lead to mixtures of trans and cis β-lactams, and allows a simple evaluation of the imine diastereofacial selectivity.

Diastereoisomeric ratios were determined by 300 MHz ^{1}H NMR spectroscopy on the crude products, generally exploiting the HC-4 singlet. They were confirmed on the products purified by flash chromatography. The attribution of absolute configuration at C-4 resided on spectroscopic evidences and on chemical correlations. The (4S) configuration of compound **15a** was unambiguously established by comparison of ^{1}H NMR data with those reported in the literature by Belzecki, *et al.*[6j] Following an empirical rule proposed by Belzecki,[6j] that is based on the chemical shift value of the methine proton of the chiral auxiliary **1**,[18] the (4S) configuration was reasonably extended to the major isomer of azetidin-2-one **16**.

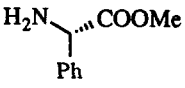
Chart 1



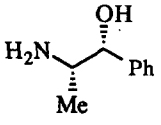
(S) - **1** R = Ph
(S) - **2** R = α-Naph



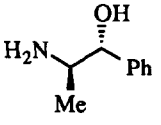
(S) - **3** R = H
(S) - **4** R = Bn
(S) - **5** R = *t*-BuPh$_2$Si



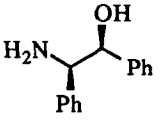
(R) - **6**



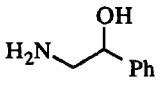
(1R, 2S) - **7**



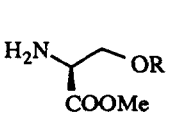
(1R, 2R) - **8**



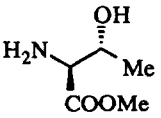
(1S, 2R) - **9**



rac - **10**

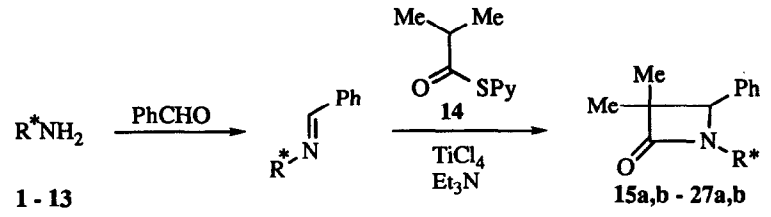


(S) - **11** R = H
(S) - **12** R = *t*-BuMe$_2$Si



(2S, 3R) - **13**

Table 1. Stereoselective synthesis of β-lactams **15-27** from thioester **14**.



1 - 13 **15a,b - 27a,b**

Amine	Product	Yield % [a]	Diastereisomer ratios [b]	C - 4 abs conf of major isomer
1	**15**	80	96: 4	S
2	**16**	79	95: 5	S
3	**17**	50	> 98: 2	R
4	**18**	33	80:20	R
5	**19**	13	74:26	R
6	**20**	54	75:25	S
7	**21**	25	> 98: 2	-- [c]
8	**22**	75	58:42	-- [c]
9	**23**	84	> 98: 2	-- [c]
10	**24**	15	50:50	--
11	**25**	30	> 98: 2	-- [c]
12	**26**	35	64:36	-- [c]
13	**27**	21	> 98: 2	-- [c]

[a] Isolated yields after flash chromatography

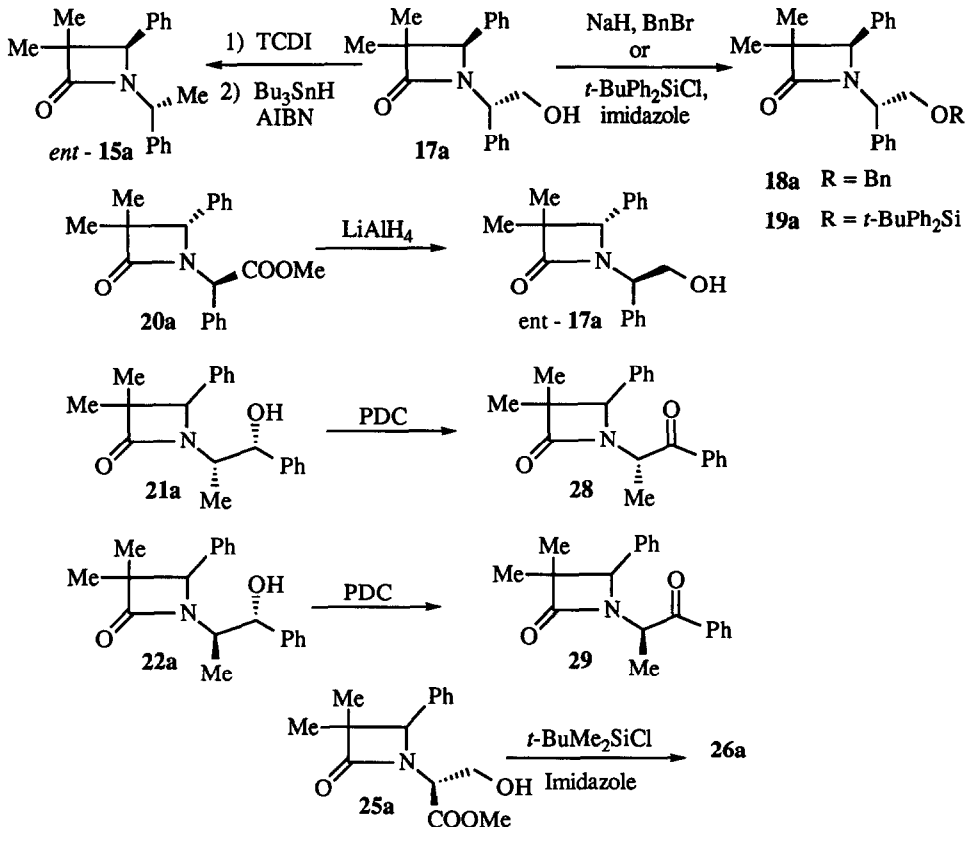
[b] As determined by 300 MHz ^{1}H NMR analysis of the crude products.

[c] Absolute configuration undertermined.

The C-4 absolute configuration of β-lactams **17a-20a** was established by chemical correlation (Scheme 1). The only detected isomer **17a** was transformed into the enantiomer of compound **15a** by standard deoxygenation procedure, and thus was shown to have the (4R) configuration. Benzylation and silylation of (4R)-**17a** afforded (4R)-**18a** and (4R)-**19a**, respectively. Finally, upon controlled $LiAlH_4$ reduction, the major isomer of **20** afforded the enantiomer of compound **17a**, thus showing that azetidin-2-one **20a** has the (4S) configuration.

Only internal correlations were performed between β-lactams **21/22**, and **25/26**, since these were obtained either in low yield or with poor stereocontrol (Scheme 1). By oxidation of the alcohol function of the chiral auxiliary the two major isomer **21a** and **22a** afforded two diastereoisomeric ketones **28** and **29**. Since

Scheme 1

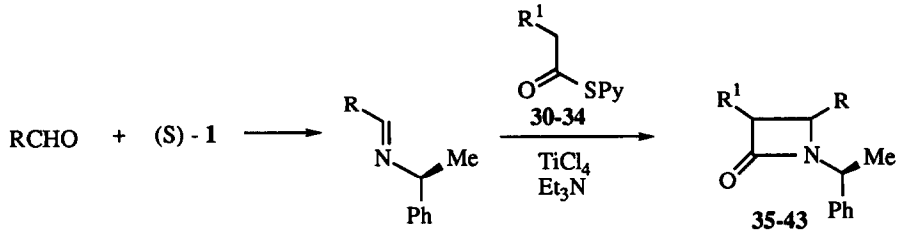


the two chiral auxiliaries **7** and **8** have opposite configuration at the nitrogen bearing stereocenter, the two ketones **28** and **29** must have the same stereochemistry at C-4. Finally, silylation of β-lactam **25a** gave **26a**.

In commenting on the results reported in Table 1, the following major conclusions can be drawn: 1) sterically well differentiated substituents at the nitrogen bearing stereocenter of the chiral auxiliary as in **1-3** and **9** generally promote good stereoselectivity (diastereoisomeric ratios > 95/5); 2) the stereocontrolling ability of the nitrogen bearing stereocenter can be enhanced by the presence of another stereocenter on the chiral auxiliary, but only if this is properly configurated (compare the synthesis of β-lactam **21** and **22**); 3) a single stereocenter in the β-position with respect to the amino group of the auxiliary as in **10** is not able to promote any stereocontrol; 4) the presence of an OH group on the chiral auxiliary is generally beneficial but does not secure *per se* high stereocontrol; 5) protection of the OH group of the auxiliary constantly depresses the stereoselectivity, but does not affect its sense, as demonstrated by the above mentioned chemical correlations of β-lactams **17a** with **18a** and **19a**, and of **25a** with **26a**. Furthermore, since glycinol derivatives **3-5** and aminoesters **11** and **12** feature OR groups of very different chelating ability,[19] addition of the enolate to a chelated conformation of the imines derived from these auxiliaries seems unlikely.

Considering several factors such as chemical yields and stereoselectivity of the β-lactam formation, and

Table 2. Stereoselective synthesis of β-lactams **35-43** from thioesters **30-34**.



R	Thioester	R^1	Product	Yield % [a]	trans/cis ratio [b]	diastereoisomer ratio [b] trans	cis
Ph	**30**	Me	**35**	86	93: 7	50:50	50:50
Ph	**31**	Et	**36**	79	93: 7	80:20	---- [c]
Ph	**32**	Pr-*i*	**37**	62	93: 7	91: 9	52:48
Ph	**33**	BnO	**38**	91	48:52	58:42	89:11
Ph	**34**	$(Pr\text{-}i)_3SiO$	**39**	90	62:38	90:10	84:16
PhCH=CH	**32**	Pr-*i*	**40**	20	96: 4	87:13	>98: 2
PhCH=CMe	**32**	Pr-*i*	**41**	35	>98: 2	91: 9	-----
$t\text{-}BuPh_2SiOCH_2$	**32**	Pr-*i*	**42**	42	80:20	89:11	88:12
C_6H_{11}-*c*	**32**	Pr-*i*	**43**	60	>98: 2	91: 9	-----

[a] Isolated yields after flash chromatography

[b] As determined by 300 MHz ^1H NMR analysis of the crude products.

[c] Undertermined.

the commercial availability and cost of both enantiomers of the amines under investigation, α-methylbenzylamine **1** was identified as the most convenient chiral auxiliary for this study. Amine (S)-**1** was therefore tested in the reactions of its benzaldimine with stereogenic thioesters **30-34**, and of the imines derived from other aldehydes with thioester **32**, to give β-lactams **35-43** (Table 2). Since these thioesters are stereogenic as many as four stereisomeric products can be obtained. Diastereiosomeric ratios were determined as before by 300 MHz ^1H NMR analysis of the crude products. Trans/cis structure were easily assigned exploiting the HC-3/HC-4 coupling constants values (J_{trans} : 1.5-2.5 Hz; J_{cis} : 5.5-6.5 Hz). Absolute configurations were assigned either by comparison of NMR data with those reported in the literature,[6j] or, exploiting Belzecki's empirical rule (see above).[6j,18] On these bases the (3S,4R), (3S,4R), and (3S,4S) configuration was assigned to the major trans isomers of azetidin-2-ones **36**, **37**, and **39**, respectively.[20,21]

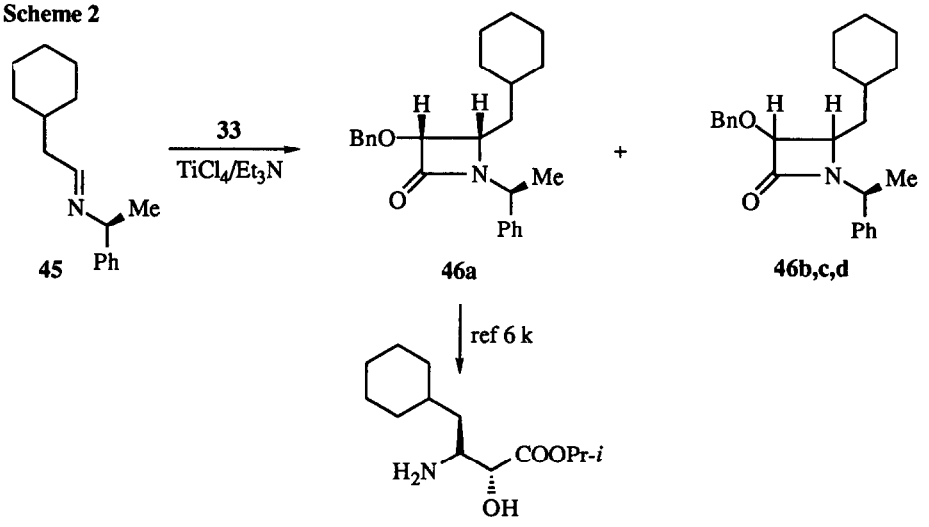
The results reported in Table 2 deserve a few comments. The reactions of the three alkyl substituted thioesters **30-32** showed a good level of trans/cis selectivity, but the imine diastereofacial selection was satisfactory only with sterically demanding R^1 groups (and only for the trans configurated β-lactams). α-Alkoxy substituted thioesters **33** and **34** gave lower trans/cis stereocontrol[22] and good imine diastereofacial

discrimination for the cis isomer of azetidin-2-one **38** and for both isomers of compound **39**.

The good stereoselectivity observed for the reaction of thioester **32** prompted us to examine the condensation of this compound with the other imines reported in Table 2, that are more synthetically useful.[1,2] As can be seen from the experimental data, β-lactams **40-43** were obtained only in low to fair yields, but generally with good trans and facial stereoselectivity (determined as before by ^{1}H NMR analysis). The absolute configuration of the major trans isomers of azetidin-2-ones **40-43** was tentatively assigned as (3S,4R) on the basis of the reasonable assumption that the sense of diastereofacial discrimination on the imine should be the same observed so far for the benzaldimine derived from (S)-**1**.[23]

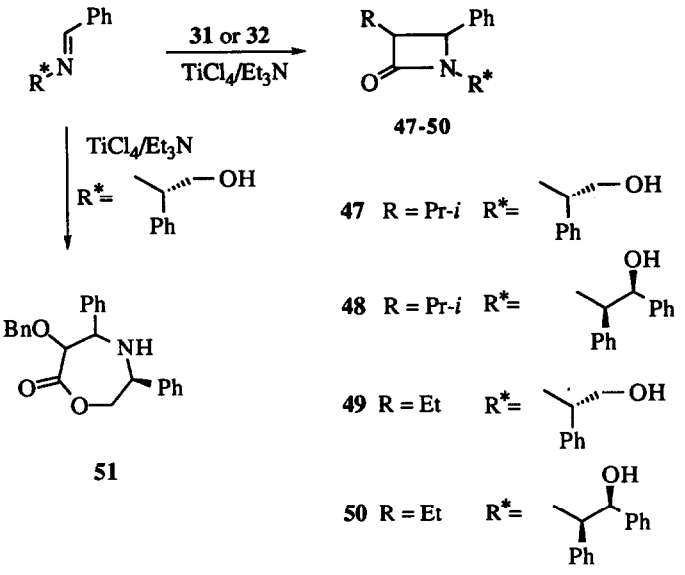
A possible application of this method to the stereoselective synthesis of an acyclic compound was envisaged in the preparation of a precursor of isopropyl (2R,3S)-3-amino-4-cyclohexyl-2-hydroxybutyrate **44**, a component of one of the renin inhibitors that exhibits remarkable antihypertensive activity[6k,12,24] (Scheme 2). Terashima *et al.*[6k] obtained α-hydroxy-β-amino ester **44** in 90% yield starting from β-lactam **46a**.

Scheme 2



This was produced[6k] as the major isomer of a 52 / 32 / 10 / 6 mixture by Staudinger reaction of benzyloxyacetyl chloride with imine **45** in the presence of triethylamine. We prepared azetidin-2-one **46a** by condensation of the titanium enolate of thioester **33** with imine **45**. This reaction gave **46a,b,c,d** in 66% yield as a 89/11 mixture of cis and trans product, both isomers being a 78/22 mixture of diastereoisomers. The overall **46a** (major cis) / **46b** (minor cis) / **46c** (major trans) / **46d** (minor trans) ratio was 69.4 / 19.6 / 8.6 / 2.4.[25] In a previous work[12] we prepared an analogue of **46a**, i.e. (3R,4S)-1-(4-methoxyphenyl)-3-[[tris-(1-methylethyl)silyl]oxy]-4-cyclohexylmethyl-azetidin-2-one[5e] (in formula **46a**: i-Pr$_3$Si instead of benzyl at oxygen, 4-methoxyphenyl instead of α-methylbenzyl at nitrogen) by a six step sequence carried out in 15% overall yield, starting from the completely stereoselective condensation of thioester **33** with an imine derived from (R)-glyceraldehyde. A comparison between the two approaches clearly indicates that the one that exploits the intrinsically chiral imine[12] is more stereoselective but longer and lower yielding than the one here reported, that is based on the use of a chiral auxiliary.

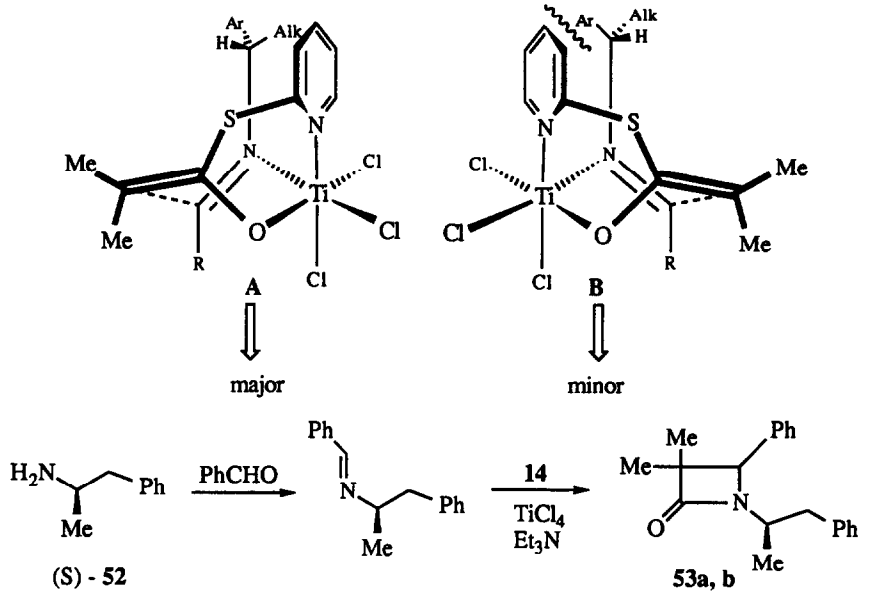
Scheme 3



The excellent diastereoselections promoted by aminoalcohols (S)-**3** and (1R,2S)-**9** led us to react their benzaldimines with thioesters other than **14** (Scheme 3). The condensations with compound **32** were very successful, and β-lactams **47** and **48** were obtained as single trans products (within the limit of ^{1}H and ^{13}C NMR spectroscopy) in 75 and 82% yield, respectively. The absolute configuration of these compounds was not established. However, when the reactions were repeated starting from thioester **31**, single trans azetidin-2-ones **49** and **50** were obtained, but in low yields (15 and 26%, respectively). The condensation of thioester **33** with the benzaldimine derived from (S)-**3** gave even worse results. In this case, no trace of the expected β-lactam was observed. To the only isolated product (26% yield) the oxazepinone structure **51** was tentatively assigned on the basis of spectroscopic and reactivity evidences.[26]

The proposal of a model of stereoselection to account for the observed stereochemical results can merely be an exercise in speculation, since the structure of these titanium enolates has not been firmly established.[27] However, on the basis of several experimental evidences that mainly rely on a ^{1}H NMR study of the enolization process of these thioesters,[9a,11] we propose models **A** and **B** as working hypothesis to rationalize the formation of major and minor products from the reaction of the enolate of thioester **14** with the (E) imines derived from the benzylic amines **1-5** (Scheme 4).We think that in both models, that feature the imine nitrogen coordinated to the titanium atom,[28] the small H substituent at the stereocenter is in the more sterically crowded position (i.e. close to the oncoming enolate). Then, model **A** should be more favored than **B** since in **A** the steric interactions between the alkyl group at the stereocenter and the pyridine ring is less destabilizing than the aryl group/pyridine one present in **B**. This rationale is in agreement with the experimental results. As predicted by the model: 1) small alkyl groups at the stereocenter such as Me or CH_2OH secures best stereoselections; accordingly, an increase of the size of the alkyl group depresses the stereoselection, as observed for the reactions involving chiral auxiliaries (S)-**4** and (S)-**5** compared to that involving (S)-**3** (Table 1); 2) only the presence of sterically well differentiated substituents at the stereocenter promotes good stereocontrol, as clearly shown by the synthesis of β-lactams **15-17** and **23**.

Scheme 4



Further support in favor of this observation was found in the condensation of thioester **14** with the benzaldimine derived from (S)-amphetamine **52**, that gave the corresponding azetidin-2-one **53a,b** as a 55 : 45 mixture of epimers at C-4 (Scheme 4) in 65% yield. 3) When the alkyl group at the stereocenter of the chiral auxiliary bears an oxygen atom this does not seem to be coordinated to titanium in the stereochemistry determining step of the condensation.

In conclusion, we have shown that the stereochemistry of the β-lactams obatined by reaction of the titanium enolates of 2-pyridyl thioesters with imines can be efficiently controlled by the presence of a chiral auxiliary located on the imine nitrogen.

Experimental Section.

^{1}H NMR spectra were obtained at 80 or at 300 MHz and ^{13}C NMR spectra were obtained 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 $LiAlH_4$; toluene from Na; Et_3N from KOH. $TiCl_4$ was used as commercially available 1M solution in CH_2Cl_2.

Amines **1-3**, **7-11**, **13**, and **52** were commercial products. Amines **4**,[29] **6**,[30] and **12**[6h] were prepared following literature procedures.

(S)-2[[(1,1-Dimethylethyl)diphenylsilyl]oxy]-1-phenylethanamine 5 was prepared by a modification of a published procedure.[31] To an oil free suspension of NaH (0.053 g, 2.2 mmol) in dry THF (25mL), (S)-**3** (0.274 g, 2 mmol) in dry THF (3 mL) was added dropwise at 0°C. After 1 h stirring at 0°C, t-$BuPh_2SiCl$ (0.604 g, 2.2 mmol) was added, the cooling bath was removed, and stirring was continued for 15 h. The reaction mixture was then poured into water, extracted with Et_2O, and the organic layer was dried and concentrated to give the crude product, that was purified by short path chromatography with Et_2O as eluant.

Amine (S)-**5** was obtained as an oil in 82% yield. IR: 3360, 3080, 2855, 1600, 750 cm^{-1}. Anal Calcd for $C_{24}H_{29}NOSi$: C, 76.75; H, 7.78; N, 3.73. Found: C, 76.89; H, 7.83; N, 3.66.^1H NMR: δ 7.85-7.10 (m, 15H); 4.10 (dd, 1H, J = 4.0, 7.0 Hz); 3.90-3.40 (m, 2H); 1.85 (bs, 2H); 1.05 (s, 9H).

Thioesters **14**, and **30-33** were known compounds.[9a]

2-Pyridylthio-[[tris(1-methylethyl)silyl]oxy]acetate 34 was prepared in three steps from methyl glycolate, without isolation of the intermediates, by standard silylation (1 mol equiv of i-Pr_3SiCl, DMF, imidazole rt, 5 h) and hydrolysis procedure (1N NaOH, EtOH, rt, 5 h) to afford the crude acid that was subjected to Mukaiyama's reaction with PPh_3 and dipyridyldisulfide.[32] Compound **35**, a thick, yellow oil was obtained in 73% overall yield after flash chromatography with a 70 : 30 hexanes Et_2O mixture as eluant. IR: 1695 cm^{-1}. Anal Calcd for $C_{16}H_{27}NO_2SSi$: C, 59.03; H, 8.36; N, 4.30. Found: C, 58.89; H, 8.44; N, 4.19. ^1H NMR: δ 8.60-7.10 (m, 4H); 4.45 (s, 2H); 1.30-0.90 (m, 21H).

The imines employed in this work were prepared immediately before use by stirring a CH_2Cl_2 solution of the corresponding aldehydes (1 mol equiv), amine (1 mol equiv), and $MgSO_4$ (2 mol equiv) at rt for 2-12 h. Filtration and evaporation of the solvent at rt gave the crude products, that were used as such. In the case of the benzaldimines obtained from amines **3**, **7-11**, and **13** the corresponding oxazolidines were also formed, generally as mixtures of diastereoisomers. The imine/oxazolidines ratios were: 90 : 6 : 4 for the imine obtained from amine **3**; 70 : 20 : 10 (from **7**); 30 : 60 : 10 (from **8**); 90 : 6 : 4 (from **9**); 80 : 10 : 10 (from **10**); 70 : 20 : 10 (from **11**); 30 : 35 : 35 (from **13**).

General Procedure for the Synthesis of β-Lactams. The preparation of compound **15** is illustrative of the procedure. To a stirred 0.1 M solution of thioester **14** (0.362 g, 2 mmol) in CH_2Cl2 (20 mL), cooled at -78°C, a 1 M solution of $TiCl_4$ in CH_2Cl_2 (2 mL, 2 mmol) was added dropwise. After 5 min stirring at -78°C, Et_3N (0.280 mL, 2 mmol) was added over a 1 min period. After 30 min stirring at -78°C, a CH_2Cl_2 (3 mL) solution of the benzaldimine derived from (S)-**1** (1 mmol) was added over a 5 min period, and the mixture was stirred while the temperature was allowed to raise to 0°C. After 5 h the reaction was quenched by addition of sat. $NaHCO_3$ and the mixture was filtered through celite. The organic phase was separated, washed with water, dried, and concentrated. The unreacted thioester was removed by 1N KOH hydrolysis in THF at rt for 2-12 h. This procedure was shown not to alter the diastereoisomeric ratio and greatly simplified the NMR analysis of the crude product. This was then purified by flash chromatography with a 60 : 40 hexanes : Et_2O mixture as eluant to give β-lactam **15** in the indicated yield and diastereoisomeric ratio.

For all the products yields and diastereoisomeric ratios are reported in Tables 1 and 2 or in the text. IR spectra and elemental analyses were generally obtained on the diastereoisomeric mixtures. Selected NMR data are collected in Tables 3 and 4. For each β-lactam the hexanes : Et_2O eluting mixture employed for their purification is reported in parenthesis after the name of the compound. The diastereisomeric mixtures have the following physical status: compounds **16**, **19**, **26**, **37**, **40**, **41**, and **42** are low melting materials; compounds **18**, **20**, **22**, **38**, **39**, **43**, **49**, and **53** are thick oils; compound **24** is a solid. For those products that were obtained as pure isomers physical properties and optical rotations are reported after the elemental analysis. β-Lactams **15**,[6j] **35**,[6j] **36**,[6j] and **46**[6k] were known compounds.

1-[(S)-(1-Naphthyl)ethyl]-3,3-dimethyl-4-phenylazetidi-2-one 16 (70 : 30). IR : 1750 cm^{-1}. Anal Calcd for $C_{23}H_{23}NO$: C, 83.85; H, 7.04; N, 4.25. Found: C, 83.73; H, 6.99; N, 4.30.

1-[(S)-(1-Phenyl-2-hydroxy)ethyl]-3,3-dimethyl-4-phenylazetidin-2-one 17 (20 : 80). IR: 3550, 1755 cm^{-1}. Anal Calcd for $C_{19}H_{21}NO_2$: C, 77.26; H, 7.17; N, 4.74. Found: C, 77.13; H, 7.23;

Table 3. Selected ^{1}H and ^{13}C NMR data for 3,3-dimethyl substituted β-lactams **16-29** and **53.**

Compound	HC-4	HC-1'	C-3	C-4	C-1'
16a	3.46	5.92	54.9	46.8	66.7
16b	-a	5.30	59.0	46.7	66.5
17a	4.31	4.46	54.5	69.3	64.2
18a	4.36	3.62	54.7	69.1	59.7
18b	4.19	3.85	-a	-a	-a
19a	4.44	3.71	54.9	68.3	61.7
19b	4.19	3.93	-a	-a	-a
20a	4.27	5.08	54.4	67.5	62.3
20b	3.70	4.71	54.6	68.5	60.8
21a	3.86	3.44	53.9	68.3	57.7
22a	4.27	3.39	53.3	65.7	58.2
22b	3.76	3.46	54.0	69.6	57.8
23a	3.70	4.03	53.7	69.9	68.2
24a	4.14	3.66/3.24	55.2	69.0	51.5
24b	4.25	3.52/3.20	55.5	68.0	51.6
25a	4.59	4.25	56.2	68.6	58.0
26a	4.72	4.50	56.8	68.6	61.2
26b	4.51	4.38	-a	-a	-a
27a	4.43	3.72	55.1	68.6	64.5
28	4.48	4.99	-a	-a	-a
29	4.25	5.05	-a	-a	-a
53a	4.21	3.49	54.7	68.0	51.9
53b	3.75	3.71	54.8	66.2	51.0

[a] Undetermined.

N, 4.75. **17a** had mp 155-156°C; $[\alpha]_D^{23}$ -120.9 (c 0.7, $CHCl_3$).

1-[(S)-(1-Phenyl-2-phenylmethoxy)ethyl]-3,3-dimethyl-4-phenylazetidin-2-one 18 (60 : 40). IR: 1750 cm^{-1}. Anal Calcd for $C_{26}H_{27}NO_2$: C, 81.01; H, 7.06; N, 3.63. Found: C, 80.91; H, 7.17; N, 3.66. **18a**, obtained pure by benzylation of **17a**, was an oil; $[\alpha]_D^{23}$ -100.8 (c 0.5, $CHCl_3$).

1-[(S)-1-Phenyl-2-[(1,1-dimethylethyl)diphenylsilyl]oxyethyl]-3,3-dimethyl-4-phenyl-azetidin-2-one 19 (70 : 30). IR: 1750 cm^{-1}. Anal Calcd for $C_{35}H_{39}NO_2Si$: C, 78.75; H, 7.36; N, 2.62. Found, C, 78.87; H, 7.47; N, 2.69. **19a** , obtained pure by silylation of **17a**, had mp 100-102°C; $[\alpha]_D^{23}$ -42.1 (c 0.5, $CHCl_3$).

(αR) Methyl (α,2-diphenyl-3,3-dimethyl-4-oxo)-1-azetidinacetate 20 (60 : 40). IR: 1755,1725 cm^{-1} Anal Calcd for $C_{20}H_{21}NO_3$: C, 74.28; H, 6.54; N, 4.33. Found: C, 74.13; H, 6.47; N,

4.39.

1-[(1R,2S)-1-Phenyl-1-hydroxyprop-2-yl]-3,3-dimethyl-4-phenylazetidin-2-one 21 (50 : 50). IR: 3550, 1755 cm^{-1}. Anal Calcd for $C_{20}H_{23}NO_2$: C, 77.64; H, 7.49; N, 4.53. Found: C, 77.49; H, 7.44; N, 4.61. **21a** was a low melting white solid; $[\alpha]_D^{23}$ -89.7 (c 0.3, $CHCl_3$).

1-[(1R,2R)-1-Phenyl-1-hydroxyprop-2-yl]-3,3-dimethyl-4-phenylazetidin-2-one 22 (40 : 60). IR: 3550, 1755 cm^{-1}. Anal Calcd for $C_{20}H_{23}NO_2$: C, 77.64; H, 7.49; N, 4.53. Found: C, 77.53; H, 7.51; N, 4.50. **22a** was an oil; $[\alpha]_D^{23}$ -113.0 (c 0.3, $CHCl_3$).

1-[(1R,2S)-1,2-Diphenyl-2-hydroxyethyl]-3,3-dimethyl-4-phenylazetidin-2-one 23 (60 : 40). IR: 3550, 1755 cm^{-1}. Anal Calcd for $C_{25}H_{25}NO_2$: C, 80.83; H, 6.78; N, 3.77. Found: C, 80.71; H, 6.81; N, 3.72. **23a** had mp 180°C; $[\alpha]_D^{23}$ +176.0 (c 1.3, $CHCl_3$).

1-[(2R,S)-2-Hydroxy-2-phenylethyl]-3,3-dimethyl-4-phenylazetidin-2-one 24 (20 : 80). IR: 3550, 1755 cm^{-1}. Anal Calcd for $C_{19}H_{21}NO_2$: C, 77.62; H, 7.17; N, 4.74. Found: C, 77.57; H, 7.07; N, 4.77. The diastereoisomeric mixture melted between 100 and 118°C.

(αS) Methyl (α-hydroxymethyl-2-phenyl-3,3-dimethyl-4-oxo)-1-azetidinacetate 25 (10 : 90). IR: 3550, 1755, 1720 cm^{-1}. Anal Calcd for $C_{15}H_{19}NO_4$: C, 64.96; H, 6.71; N, 5.05. Found: C, 65.03; H, 6.66; N, 5.00. **25a** had mp 89-90°C; $[\alpha]_D^{23}$ +49.0 (c 1.0, $CHCl_3$).

(αS) Methyl α-[[(1,1–dimethylethyl)dimethylsilyl]oxy]-2-phenyl-3,3-dimethyl-4-oxo)-1-azetidinacetate 26 (60 : 40). IR: 1755, 1720 cm^{-1}.Anal Calcd for $C_{21}H_{33}NO_4Si$: C, 64.41; H, 8.49; N, 3.58. Found: C, 64.29; H, 8.58; N, 3.61. **26a**, obtained by silylstion of **25a** had mp 72-74°C; $[\alpha]_D^{23}$ +52.3 (c 0.7, $CHCl_3$).

(αS) Methyl α-[[(1R)-1-hydroxyethyl]-2-phenyl-3,3-dimethyl-4-oxo]-1-azetidinacetate 27 (10 : 90). IR: 3550, 1755, 1720 cm^{-1}. Anal Calcd for $C_{16}H_{21}NO_4$: C, 65.96; H, 7.26; N, 4.81. Found: C, 66.03; H, 7.20; N, 4.90. **27a** had mp 110-112°C; $[\alpha]_D^{23}$ +76.8 (c 0.8, $CHCl_3$).

1-[(1S)-1-Phenylethyl]-3-(1-methylethyl)-4-phenylazetidin-2-one 37 (70 : 30). IR: 1750 cm^{-1}. Anal Calcd for $C_{20}H_{23}NO$: C, 81.87; H, 7.90; N, 4.77. Found: C, 81.80; H, 7.97; N, 4.83. The major trans isomer had mp 122-123°C; $[\alpha]_D^{23}$ +41.0 (c 1.0, $CHCl_3$).

1-[(1S)-1-Phenylethyl]-3-phenylmethoxy-4-phenylazetidin-2-one 38 (60 : 40). IR: 1750 cm^{-1}. Anal Calcd for $C_{24}H_{23}NO_2$: C, 80.64; H, 6.49; N, 3.92. Found: C, 8.49; H, 6.57; N, 3.96.

1-[(1S)-1-Phenylethyl]-3-[[tris-(1-methylethyl)silyl]oxy]-4-phenylazetidin-2-one 39 (90 : 10). IR: 1750 cm^{-1}. Anal Calcd for $C_{26}H_{37}NO_2Si$: C, 73.71; H, 8.80; N, 3.31. Found: C, 73.87; H, 8.88; N, 3.24.

1-[(1S)-1-Phenylethyl]-3-(1-methylethyl)-4-(E-2-phenylethenyl)-azetidin-2-one 40 (50 : 50). IR: 1750 cm^{-1}. Anal Calcd for $C_{22}H_{25}NO$: C, 82.72; H, 7.89; N, 4.38. Found: C, 82.82; H, 7.80; N, 4.44.

1-[(1S)-1-Phenylethyl]-3-(1-methylethyl)-4-[E-(1-methyl-2-phenyl)ethenyl]-azetidin-2-one 41 (50 : 50). IR: 1750 cm^{-1}. Anal Calcd for $C_{23}H_{27}NO$: C, 82.84; H, 8.16; N, 4.20. Found: C, 82.92; H, 8.10; N, 4.23.

1-[(1S)-1-Phenylethyl]-3-(1-methylethyl)-4-[(1,1-dimethyl)diphenyl)silyl]oxymethyl-azetidin-2-one 42 (70 : 30). IR: 1750 cm^{-1}. Anal Calcd for $C_{31}H_{39}NO_2Si$: C, 76.73; H, 8.09; N, 2.88. Found: C, 76.68; H, 8.10; N, 2.93.

Table 4. Selected ^{1}H and ^{13}C NMR data for β-lactams **37-43** and **47-50**.

Compound[a]	HC-3	HC-4	HC-1'	$J_{3,4}$	C-3	C-4	C-1'
37a	2.79	3.95	5.04	2.1	58.3	51.8	66.5
37b	2.79	4.03	4.44	2.1	58.2	54.6	66.5
37c	2.89	4.42	5.02	5.5	58.3	52.1	66.2
37d	2.95	4.47	4.25	5.5	58.0	54.5	62.1
38a	4.48	4.16	5.01	2.0	88.9	54.4	62.9
38b	4.43	4.21	4.23	2.0	89.0	52.2	63.0
38c	4.71	4.44	5.09	4.5	82.8	51.8	61.2
38d	4.77	4.51	4.35	4.5	82.3	54.3	61.2
39a	4.64	4.08	4.92	2.0	84.4	52.2	66.0
39b	4.61	4.17	4.26	2.0	84.3	54.5	65.9
39c	4.93	4.43	5.07	4.8	77.8	51.6	62.6
39d	4.99	4.48	4.31	4.8	77.3	54.0	62.8
40a	2.70	3.69	5.00	2.1	57.6	51.3	63.1
40b	2.68	3.46	4.60	2.1	57.1	52.9	63.3
40c	2.86	4.04	5.05	5.0	-[b]	-[b]	-[b]
41a	2.74	3.65	4.97	2.0	60.3	51.8	62.9
41b	2.72	3.77	4.51	2.0	60.3	53.5	60.8
42a	2.61	3.17	4.96	2.3	56.6	51.2	64.9
42b	2.67	3.24	4.57	2.3	55.5	53.3	64.0
42c	2.78	3.55	4.85	5.5	56.8	51.8	63.3
42d	2.79	3.54	4.53	5.5	55.4	53.4	62.0
43a	2.60	3.03	4.78	2.1	56.7	52.7	61.1
43b	2.60	3.05	4.54	2.1	57.0	53.5	59.4
47	2.86	4.12	4.55	2.2	60.5	65.4	64.1
48	2.61	3.73	4.10	2.4	61.8	65.3	67.7
49	3.01	4.07	4.53	2.6	59.9	62.5	62.6
50	2.73	3.58	4.05	2.3	60.3	63.6	62.8

[a] **a, b, c, d** indicate major trans, minor trans , major cis, and minor cis isomers, respectively.
[b] Undetermined.

1-[(1S)-1-Phenylethyl]-3-(1-methylethyl)-4-cyclohexylazetidin-2-one 43 (60 : 40). IR: 1750 cm^{-1}. Anal Calcd for $C_{20}H_{29}NO$: C, 80.22; H, 9.76; N, 4.68. Found: C, 80.11; H, 9.80; N, 4.75.

1-[(1S)-1-Phenyl-2-hydroxyethyl]-3-(1-methylethyl)-4-phenylazetidin-2-one 47 (20 : 80). IR: 3550, 1755 cm^{-1}. Anal Calcd for $C_{20}H_{23}NO_2$: C, 77.64; H, 7.49; N, 4.53. Found: C, 77.66; H, 7.58; N, 4.46. The product was an oil; $[\alpha]_D^{23}$ -47.1 (c 0.6, $CHCl_3$).

1-[(1R,2S)-1,2-Diphenyl-2-hydroxyethyl]-3-(1-methylethyl)-4-phenylazetidin-2-one 48 (60 : 40). IR: 3550, 1755 cm^{-1}. Anal Calcd for $C_{26}H_{27}NO_2$: C, 81.01; H, 7.06; N, 3.62. Found: C, 80.91; H, 7.11; N, 3.69. The product had mp 141-142°C; $[\alpha]_D^{23}$ +144.8 (c 0.7, $CHCl_3$).

1-[(1S)-1-Phenyl-2-hydroxyethyl]-3-ethyl-4-phenylazetidin-2-one 49 (30 : 70). IR: 3550, 1755 cm^{-1}. Anal Calcd for $C_{19}H_{21}NO_2$: C, 77.26; H, 7.17; N, 4.74. Found: C, 77.36; H, 7.22; N, 4.68. The product was an oil; $[\alpha]_D^{23}$ -44.4 (c 0.2 , $CHCl_3$).

1-[(1R,2S)-1,2-Diphenyl-2-hydroxyethyl]-3-ethyl-4-phenylazetidin-2-one 50 (70 : 30). IR: 3550, 1755 cm^{-1}. Anal Calcd for $C_{25}H_{25}NO_2$: C, 80.83; H, 6.78; N, 3.77. Found: C, 80.81; H, 6.75; N, 3.86. The product had mp 100-101°C; $[\alpha]_D^{23}$ +140.3 (c 0.3, $CHCl_3$).

1-[(1S)-1-methyl-2-phenylethyl]-3,3-dimethyl-4-phenylazetidin-2-one 53 (60 : 40). IR: 1755 cm^{-1}. Anal Calcd for $C_{20}H_{23}NO$: C, 81.87; H, 7.90; N, 4.77. Found: C, 81.99; H, 7.80; N, 4.81.

2,4-Diphenyl-6-phenylmethoxy-1,4-oxazepin-7-one 51 (50 : 50). IR: 3340, 1735 cm^{-1}. Anal Calcd for $C_{24}H_{23}NO_3$: C, 77.19; H, 6.21; N, 3.75. Found: C, 77.08; H, 6.14; N, 3.81. The product had mp 118-120°C; $[\alpha]_D^{23}$ -19.3 (c 0.6, $CHCl_3$). Selected ^1H NMR data: δ 5.22 (dd, 1H, J= 12.0, 8.0 Hz, one H of CH_2OCO); 4.38 (s, 1H, *H*C-OBn); 4.24 (m, 2H, two *CH*Ph); 4.16 (dd, 1H, J= 12.0, 1.0 Hz, one H of CH_2OCO). Selected ^{13}C NMR data: δ 172.0 (C=O); 85.3 (*C*H-OBn); 74.2 (CH_2OCO); 72.8 (PhCH_2O); 64.0 (CH_2-*C*-N); 61.7 (CH-*C*-N). The attribution resides on J_1 and J_n H/C heterocorrelate NMR experiments.

Chemical Correlations.

17a to *ent*-15a: Following a described procedure,[33] compound **17a** was converted into its imidazolyl thiocarbonate (mp 102°C, dec; $[\alpha]_D^{23}$ -95.0, c 0.6, $CHCl_3$; 91% yield), and deoxygenated with Bu_3SnH/AIBN in refluxing degassed toluene, to give *ent*-**15a**[6j] ($[\alpha]_D^{23}$ -95.1, c 0.5, $CHCl_3$) in 57% yield.

17a to 18a: Standard benzylation procedure (NaH, THF, $Bu_4N^+I^-$, benzylbromide, rt,15 h) of **17a** gave **18a** in 63% yield.

17a to 19a: Standard silylation procedure (t-BuPh_2SiCl, imidazole, DMF, rt, 24 h) of **17a** gave **19a** in 80% yield.

17a from 20: Compound **17a** was obtained upon reduction with 1 mol equiv of $LiAlH_4$ in Et_2O at 0°C in 32% yield. The starting material was recovered in 43% yield. Higher reaction temperatures or $LiAlH_4$/substrate ratios led to overreduction of **20**.[34]

21a to 28 and 22a,b to 29: These oxidations were carried out stirring a CH_2Cl_2 solution of the starting alcohols and pyridinium dichromate (2 mol equiv) ar rt for 15 h in the presence of pulverized 4A mol sieves.The mixtures were filtered through celite and purified by flash chromatography.

1-[(1R)-1-methyl-2-oxo-2-phenylethyl]-3,3-dimethyl-4-phenyl-azetidin-2-one 28 (30 : 70). IR: 1750, 1725 cm^{-1}. Anal Calcd for $C_{20}H_{21}NO_2$: C, 78.15; H, 6.87; N, 4.56. Found: C, 78.07; H, 6.93; N, 4.63. The product was a thick oil obtained in 91% yield; $[\alpha]_D^{23}$ -120.3 (c 0.2, $CHCl_3$).

1-[(1S)-1-methyl-2-oxo-2-phenylethyl]-3,3-dimethyl-4-phenyl-azetidin-2-one 29 (30:70). Compound **29** was obtained in 40% yield in mixture with the unreacted alcohol **22**.

25a to 26a: Standard silylation procedure (t-BuMe_2SiCl, imidazole, DMF, rt, 15 h) of **25a** gave **26a** in 90% yield.

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References and Notes.

1. For reviews on the enolate-imine condesation route to β-lactams see: (a) Hart, D.J.; Ha, D.-C. *Chem. Rev.* **1989**, *89*, 1447. (b) Brown, M.J. *Hetereocycles* **1989**, *29*, 2225. (c) Van der Steen, F.H.; van Koten, G. *Tetrahedron* **1991**, *47*, 7503.
2. (a) Perrone, E.; Franceschi, G. in *Recent Progress in the Chemical Synthesis of Antibiotics;* Lukacs, G.; Ohno, M. Eds.; Springer, New York, **1990**, pp 615-703. (b) Palomo, C. *ibid* pp 565-612. (c) Georg, G.I. in *Studies in Natural Product Chemistry*, Rahman, A.-U. Ed.; Elsevier, New York, **1989**, vol 4, p 431. (d) Nagahara, T.; Kametani, T. *Heterocycles* **1987**, *25*, 729. (e) Durckheimer, W.; Blumbach, J.; Lattrell, R.; Scheunemann, K.H. *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 180. (f) Cainelli , G.; Panunzio, M. *Farmaco*, **1991**, *46*, 177.
3. (a) Georg, G.I.; Kant, J.; Gill, H.S. *J.Am.Chem. Soc.* **1987**, *109*, 1129; and references therein. (b) Iimori, T.; Ishida, Y.; Shibasaki, M. *Tetrahedron Lett.* **1986**, *27*, 2153; and references therein. (c) Cainelli, G.; Panunzio, M.; Basile, T.; Bongini, A.; Giacomini, D.; Martelli, G. *J.Chem.Soc. Perkin Trans. 1* **1987**, 2637. (d) Hatanaka, M.; Park, O.-S.; Ueda, I. *Tetrahedron Lett.* **1990**, *31*, 7631.
4. (a) Andreoli, P.; Cainelli, G.; Panunzio, M.; Bandini, E.; Martelli, G.; Spunta, G. *J.Org.Chem.* **1991**, *56*, 5984. (b) Andreoli, P.; Billi, L.; Cainelli, G.; Panunzio, M.; Bandini, E.; Martelli, G.; Spunta, G. *Tetrahedron* **1991**, *47*, 9061. (c) Fujisawa, T.; Ukaji, Y.; Noro, T.; Date, K; Shimizu, M. *Tetrahedron Lett.* **1991**, *32*, 7563. (d) Fujisawa, T.; Ichikawa, M.; Ukaji, Y.; Shimizu, M. *Tetrahedron Lett.* **1993**, *34*, 1307. (e) Bandini, E.; Cainelli, G.; Martelli, G.; Panunzio, M.; Spunta, G. *Gazz. Chim. Ital.* **1993**, *123*, 509.
5. (a) Evans, D.A.; Sjogren, E.B. *Tetrahedron Lett.* **1985**, *26*, 3783. (b) Hart, D.J.; Lee, C.-S.; Pirkle, W.H.; Hyon, M.H.; Tsipouras, A. *J.Am.Chem.Soc* . **1986**, *108*, 6054. (c) Ojima, I.; Habus, I. *Tetrahedron Lett.* **1990**, *31*, 4289. (d) Ojima, I.; Habus, I.; Zhao, M.; Georg, G.I.; Jaysinghe, L.R. *J.Org.Chem.* **1991**, *56*, 1681. (e) Ojima, I.; Park, Y.H.; Sun, C.M.; Brigaud, T.; Zhao, M. *Tetrahedron Lett.* **1992**, *33*, 5737. (f) Jacobi, P.A.; Zhang, W. *Tetrahedron Lett.* **1993**, *34*, 2581, 2585.
6. For previous examples of β-lactam synthesis involving chiral auxiliary bearing imines see the following. For the enolate-imine condensation: (a) Ojima, I.; Inobe, S.I. *Tetrahedron Lett.* **1980**, *21*, 2077, 2081. (b) Overman, L.E.; Osawa, T. *J.Am.Chem.Soc.* **1985**, *107*, 1698. (c) Yamada, T.; Suzuki, H.; Mukaiyama, T. *Chem.Lett.* **1987**, 293. (d) Shibasaki, M.; Ishida, Y.; Iwasaki, G.; Iimori, T. *J.Org.Chem.* **1987**, *52*, 3498. (e) Brown, M.J.; Overman, L.E. *J.Org.Chem.* **1991**, *56*, 1933. (f) Kleijn, H.; van Maanen, H.L.; Jastrzebski, J.T.B.H.; van Koten, G. *Recl.Trav. Chim. Pays-Bas* **1992**, *111*, 497. (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. For the Staudinger reaction: (h) Just, G.; Liak, T.J. *Can.J.Chem.* **1978**, *56*, 211; (i) Tenneson, S.M.; Belleau, B. *Can.J.Chem.* **1980**, *58*, 1605. (j) Rogalska, E.; Belzecki, C. *J.Org.Chem.* **1984**, *49*, 1397. (k) Kobayashi, Y.; Takemoto, Y.; Kamijo,T.; Harada, H.; Ito, Y.; Terashima, S. *Tetrahedron* **1992**, *48*, 1853. (l) Georg, G.I.; Akgun, E.; Mashava, P.M.; Milstead, M.; Ping, H.; Wu, Z.J.; Vander Velde, D.

Tetrahedron Lett. **1992**, *33*, 2111. (m) Farina, V.; Hauck, S.I.; Walker, D.G. *SynLett* **1992**, 761. (n) Bose, A.K.; Manhas, M.S.; van der Veen, J.M.; Bari, S.S.; Wagle, D.R. *Tetrahedron* **1992**, *48*, 4831.

7. (a) Corey, E.J.; Decicco, C.P.; Newbold, R.C. *Tetrahedron Lett.* **1991**, *32*, 5287. (b) Hattori, K.; Miyata, M.; Yamamoto, Y. *J.Am.Chem.Soc.* **1993**, *115*, 1151. A combination of chiral boron ligand and of a chiral auxiliary containing imine was used in this work.
8. Recently we discovered that chiral BCl_2OR^* species promote enantioselective one-pot β-lactam synthesis from achiral 2-pyridyl thioesters and imines (unpublished results).
9. (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.
10. For leading references to the preparation of titanium enolates by the $TiCl_4/Et_3N$ method see: Evans, D.A.; Bilodeau, M.T.; Somers, T.C.; Clardy, J.; Cherry, D.; Kato, Y. *J.Org.Chem.* **1991**, *56*, 5750.
11. Annunziata, R.; Cinquini, M.; Cozzi, F.; Cozzi, P.G. *J.Org.Chem.* **1992**, *57*, 4155.
12. Annunziata, R.; Benaglia, M.; Cinquini, M.; Cozzi, F.; Ponzini, F. *J.Org.Chem.* **1993**, *58*, 4746.
13. For a preliminary account of part of this work, see: Annunziata, R.; Benaglia, M.; Cinquini, M.; Cozzi, F.; Raimondi, L. *Tetrahedron Lett.* **1993**, *34*, 6921.
14. In the case of amines **8**, **11**, and **13** that were used as their hydrochlorides, 1.1 mol equiv of Et_3N was added to the reaction mixture.
15. In the case of β-hydroxy substituted amines **3**, **7-11**, and **13** the imines were accompanied by variable amounts of the corresponding oxazolidines. The imine/oxazolidine ratios and the diastereoisomeric composition of the latter were determined by ^1H NMR spectroscopy and are reported in the Experimental Section. For recent studies on the ring/chain tautomerism of the imines derived from β-aminoalcohols, see: (a) Fulop, F.; Pihlaja, K.; Neuvonen, K.; Bernath, G.; Argay, G.; Kalman, A. *J.Org.Chem.* **1993**, *58*, 1967. (b) Miao, C.K.; Sorcek, R.; Jones, P.-M. *Tetrahedron Lett.* **1993**, *34*, 2259. (c) Higashiyama, K.; Inoue, H.; Takahashi, H. *Tetrahedron* **1994**, *50*, 1083.
16. The reaction of benzaldehyde with cysteine methylester gave the corresponding thiazolidine that did not react with the titanium enolate of thioester **14**.
17. The **a** and **b** notations do not have any structural meaning; in other word major **a** isomers can be either (R) or (S) configurated at C-4 (see Table 1).
18. This empirical rule is valid for 4-aryl substituted β-lactams featuring N-CH(Me)Ar residues such as in **15** and in **16**. It relies on the fact that the aryl group at the stereocenter lies in the mean plane of the azetidinone ring. The signal of the methine proton at the stereocenter then occurs at lower field if the methine proton and the C-4 aryl group are situated on the same side of the ring, and at higher field in the opposite case. By examining the NMR spectra reported in the literature for a variety of β-lactams of known configuration that feature this substitution pattern (aryl groups at C-4, N-substituents as in **15** or **16**) we always found that this empirical rule holds true.
19. For leading references to the influence of the oxygen protecting group on the extent of chelation, see: Chen, X.; Hortelano, E.R.; Eliel, E.L.; Frye, S.V. *J.Am.Chem.Soc.* **1992**, *114*, 1778; and references therein. For an example of a highly stereoselective enolate addition to a chelated imine derived from (S)-**4**, see reference 6e.

20. The change in configurational descriptors at C-4 for the major isomers of β-lactams **15**, trans-**36**, trans-**37**, and trans-**39** is only due to CIP priority rules.
21. NMR evidences (see reference 18) allowed also the following tentative assignments of configuration: (3R,4R) to the "major" cis isomer of **37**; (3S,4S) to the major trans isomer and (3R,4S) to the major cis isomer of **38**; (3R,4S) to the major cis isomer of **39**.
22. The poor trans/cis stereoselectivity of the reaction of benzyloxy substituted thioester **33** is particularly puzzling, since this compound always showed a strong preference to form cis β-lactams in the reactions with achiral (reference 9a) and chiral (reference 11 and 12) imines.
23. It must be noted that β-lactams similar to **40-42** have been exploited to prepare precursors of the carbapenem antibiotics PS-6 and 1β-methyl PS-6 (see reference 1 and 2). However, **40-42** have the opposite absolute configuration at C-3 and C-4 with respect to the required one. The correct stereochemistry can be simply obtained starting from (R)-**1**.
24. Iisuka, K.; Kamijo, T.; Harada, H.; Akahane, K.; Kubote, T.; Umeyama, H.; Ishida, T.; Kiso, Y. *J.Med.Chem.* **1990**, *33*, 2707, and references therein. For other syntheses of compound **44** see reference 6k.
25. A similar stereochemical result was observed when imine **45** was reacted with the titanium enolate of 2-pyridylthio acetoxyacetate. In this case a 70 / 20 / 8 / 2 mixture of isomers was obtained in 75% yield.
26. Compound **51** was isolated as a single diastereoisomer. The observed O=C-C*H*-C*H*-N coupling constant value (0 Hz) was not compatible with any β-lactam structure. Oxazepine **51** was recovered unchanged after reaction with t-BuPh_2SiCl. The formation of **51** can tentatively be explained by β-lactam ring opening by addition of the OH group on the carbonyl carbon. Coordination of a Lewis acidic titanium species between the carbonyl and the benzyloxy oxygen can favor this process. For a review on the mechanism of β-lactam ring opening, see: Page, M.I. *Acc.Chem.Res.* **1984**, *17*, 144.
27. The possibility that Ti enolates are "ate" complexes has been pointed out: Evans, D.A.; Urpi', F.; Somers, T.C.; Clark, J.S.; Bilodeau, M.T. *J.Am.Chem.Soc.* **1990**, *112*, 8215. The aggregation state of these titanium species is another major problem still to be solved. For leading references to this topic, see: Reetz, M.T. *Organotitanium Reagents in Organic Synthesis*; Springer, Berlin, **1986**.
28. NMR experiments carried out on achiral imines confirmed the strong tendency of the imine nitrogen to coordinate the titanium atom of $TiCl_4$ and of a $TiCl_4$/thioester adduct: Annunziata, R.; Benaglia, M.; Cinquini, M.; Cozzi, F.; Ponzini, F.; Raimondi, L. *Tetrahedron* **1994**, *50*, 2939.
29. Chang, Z.-Y.; Coates, R.M. *J.Org.Chem.* **1990**, *55*, 3475.
30. Duhamel, L.; Plaquevent, J.-C. *Bull.Soc.Chim.Fr.* **1982**, II-75. See also: Devine, P. N.; Reilly, M.; Oh, T. *Tetrahedron Lett.* **1993**, *34*, 5827.
31. Meyer, A.I.; Poindexter, G.S.; Brich, Z. *J.Org.Chem.* **1978**, *43*, 892.
32. Mukaiyama, T.; Matsueda, R.; Suzuki, M. *Tetrahedron Lett.* **1970**, *22*, 1901.
33. RajanBabu, T.V.; Fukunaga, T.; Reddy, G.S. *J.Am.Chem.Soc.* **1989**, *111*, 1759.
34. For leading references for the reduction of β-lactams, see: Ojima, I.; Zhao, M.; Yamata, T.; Nakahashi K.; Yamashita, M.; Abe, R. *J.Org.Chem.* **1991**, *56*, 5263.

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