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Synthesis of β-Lactams by Condensation of Titanium Enolates of 2-Pyridylthioesters with Imines. Influence of the Imine Structure on the trans/cis Stereoselectivity

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Abstract: The condensation of the titanium enolates of C-2 alkyl substituted 2-pyridylthioesters with imines affords β-lactams in trans/cis ratios that largely depend on the structure of the C-imine residue. Bulky and non-chelating heteroatom-containing groups lead to the formation of trans β-lactams, while sterically non-requiring or chelating groups favour the formation of the cis-products. On the basis of NMR evidences a rationale is proposed to account for the observed stereoselectivity.

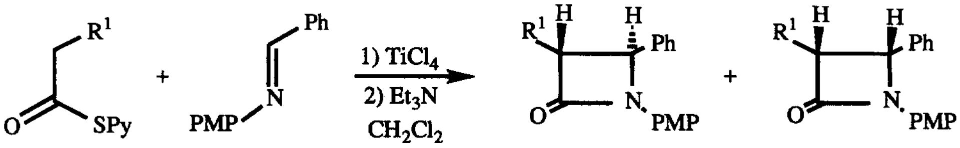
We recently reported[1] a convenient one-pot synthesis of β-lactams by the condensation of the titanium enolates[2] of 2-pyridylthioesters with imines.[3] This reaction, that features a remarkable diastereofacial selectivity when extended to chiral thioesters[4a] or imines,[4a,b,c] generally experiences variable levels of trans/cis stereoselectivity at C-3/C-4 of the azetidinone ring.

By studying the condensation of thioesters **1a-i** with benzaldehyde derived imine **2** as a model reaction (Scheme 1), the following trends of trans/cis selectivity as a function of the thioester structure were observed:[1,4a,4d] trans β-lactams **3** predominated with thioesters featuring bulky alkyl or non-chelating heteroatom containing substituents at C-2 (**1a-f, i**); cis products were selectively formed when R^1 is an oxygen-containing and chelating residue as in **1g** and **1h**.[5]

However, when the reaction was extended to imines other than **2**, these trends did not always hold true. Indeed, while benzyloxy- or acetoxy-2-pyridylthioacetate **1g** and **1h** constantly gave cis products in a highly selective fashion,[4a,4b] alkyl substituted thioesters **1a-d** displayed a more scattered behaviour.[1,4] A systematic study was therefore undertaken to elucidate the dependence of the trans/cis selectivity of the reactions of **1a-d** on the imine structure, and to better understand the origin of the stereoselectivity of the process. The results are here reported.

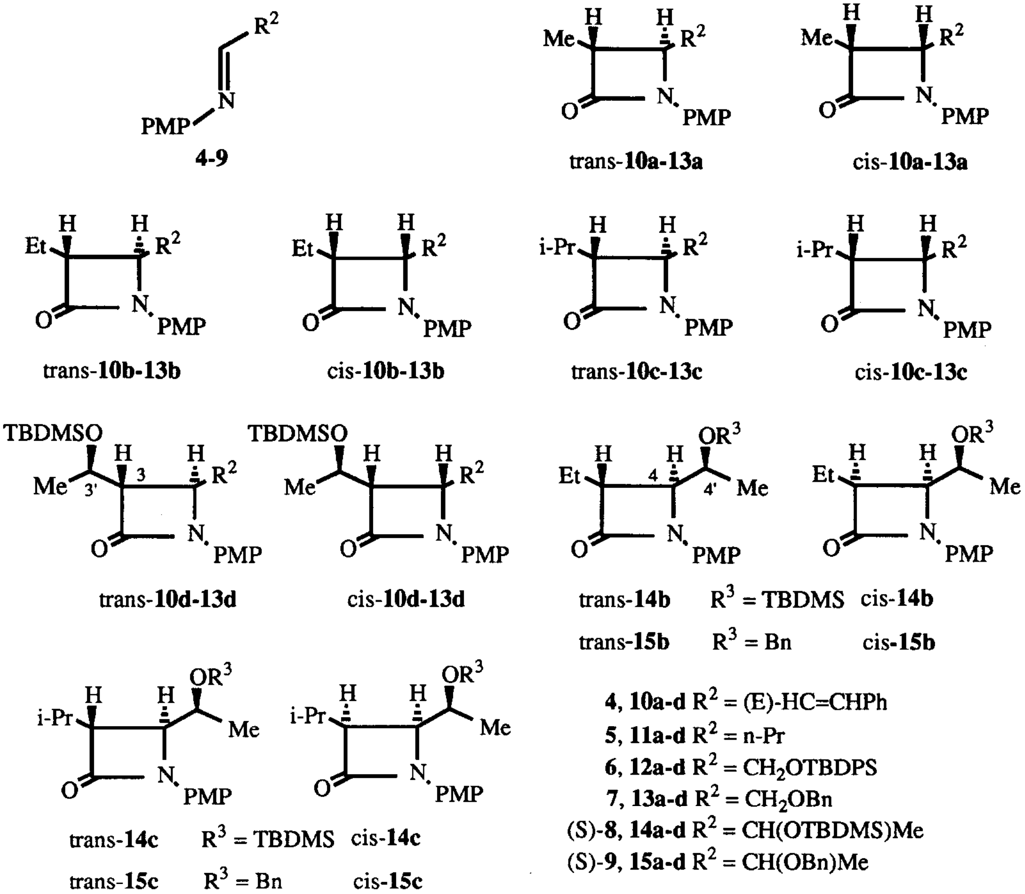
The imines **4-9** that were used are depicted in Scheme 1. The R^2 substituents were selected in order to represent the different imines that are generally employed to prepare synthetically useful β-lactams.[6] In the case of α-alkoxy imines, compounds featuring chelation allowing[7] (as in **7** and **9**) and chelation preventing[7]

Scheme 1



1a-i **2** trans-**3a-i** cis-**3a-i**

1a-i, **3a-i**: R^1 : **a** = Me; **b** = Et; **c** = Pr-i; **d** = Me(OTBDMS)CH;
e = TIPSO; **f** = TBDPSO; **g** = BnO; **h** = AcO; **i** =MeS



4, 10a-d R^2 = (E)-HC=CHPh
5, 11a-d R^2 = n-Pr
6, 12a-d R^2 = $CH_2OTBDPS$
7, 13a-d R^2 = CH_2OBn
(S)-**8, 14a-d** R^2 = CH(OTBDMS)Me
(S)-**9, 15a-d** R^2 = CH(OBn)Me

Abbreviations: TBDMS = t-$BuMe_2Si$; TIPS = i-Pr_3Si; TBDPS = t-$BuPh_2Si$;
Bn = $PhCH_2$; Ac = MeCO; PMP = 4-$MeOC_6H_4$.
Only one enantiomer is shown in every case for simplicity

(as in **6** and **8**) oxygen protecting groups have been included. The results of the condensation reactions of **1a-d** with **2** and **4-9** are collected in Table 1. Trans/cis configurations were easily assigned by 300 MHz ^{1}H NMR analysis of the crude reaction mixture on the basis of the values of the HC-3/HC-4 coupling constant: for trans isomers, $J_{3,4}$ = 1.5-2.4 Hz; for cis isomers, $J_{3,4}$ = 5.0-6.4 Hz. Diastereoisomeric ratios were also determined by ^{1}H NMR spectroscopy on the crude products, and confirmed on the materials purified by flash chromatography. When the chiral substrates **1d**, **8**, and **9** were employed, the reported trans/cis ratios refer to the overall product distribution. In these cases the configuration of the products (reported in Scheme 1) has been established by chemical correlation, or by comparison of ^{1}H and ^{13}C NMR data.[4a]

One can look at the reported data from two different perspectives: the influence of the thioester structure and that of the imine. By considering the thioester structure variation, it is evident that the trans/cis ratio increases with increasing bulkiness of the alkyl group along the series **1a** < **1b** < **1c** < **1d**. This is clearly true for non α-heterosubstituted imines **2**, **4**, **5**, and also in the case of non chelating α-alkoxy imines **6** and **8**. In the case of chelating imines **7** and **9** the reaction seems to constantly display a moderate level of cis selectivity, the formation of virtually a single cis isomer of **13d** from **1d** and **7** being an exception in the extent but not in the sense of the stereocontrol.[4a]

On the other hand, for each thioester, the imine structure variation induces analogous changes in the stereoselectivity. Trans/cis ratio generally decreases along the series R^2 = aryl > alkenyl > alkyl. The importance not only of the bulkiness of the R^2 group of the imine, but also of its chelating ability, it is suggested by a comparison between the reactions of imines **6** and **8** with those of **7** and **9**.

The organization of all these data in a single framework appears very difficult, since many different factors can concur in determining the observed stereochemical results. Among these, enolate and imine structure seems the most important.

The problem of the structure of the enolates derived from thioesters **1a-d** has been addressed before by a low temperature ^{1}H NMR study of the thioester/$TiCl_4$ complexation and of the enolization.[1, 4a, 8] It was found that: 1) Six membered chelates involving the carbonyl oxygen, the octahedrally hexacoordinated titanium atom, and the pyridine nitrogen are formed upon addition of $TiCl_4$ to the thioesters. 2) The enolate isomer ratio increases with the bulkiness of the R^1 substituent of the thioester (80 : 20 for **1a**, R = Me; 89 : 11 for **1b**, R = Et; 95 : 5 for **1c**, R = Pr-i).[9] 3) The enolates do not equilibrate in a temperature range from -70° to -10°C. We rationalize these observations by proposing the formation of a (Z) enolate (CIP rules) as the result of proton abstraction from conformation **A** of the thioester/$TiCl_4$ adduct (Figure 1). This conformation should be more favored and therefore more abundant than **B** on steric grounds.[10] It is also worth pointing out the correlation existing between the stereoselectivity of the enolate formation and the trans/cis ratios of the β-lactams obtained from **1a-d** (see Table 1).[4a]

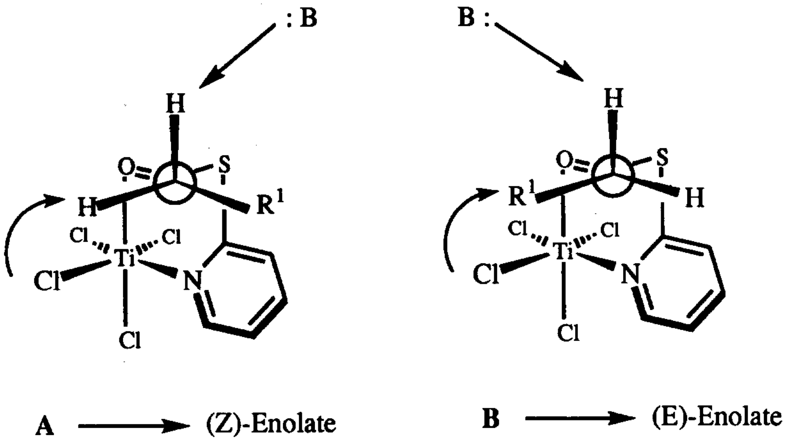
As for the imines, the (E) configuration of compounds **2** and **4** was easily established by simple n. O. e. experiments.[11] We could also demonstrate by ^{1}H NMR spectroscopy that (E)-N-benzylideneaniline (**2**, phenyl instead of 4-methoxyphenyl at nitrogen) in CD_2Cl_2 solution co-ordinates $TiCl_4$ and does not show any tendency to isomerize in the temperature range from -70° to -10°C.[12] We think therefore that the (E)-imines react in this configuration. On the other hand, C-alkyl or -alkoxyalkyl substituted imines were found to exist as scarcely unbalanced mixtures of (E) and (Z) isomers. In the presence of $TiCl_4$ they were rather unstable, and gave rise to complex mixtures of products. This prevented to reach any conclusion either on

Table 1. Stereoselective Synthesis of β-Lactams **3**, **10-15**.

Thioester	R^1	Imine	R^2	Product	Yield %	trans/cis ratio
1a	Me	**2**	Ph	**3a**	99	70/30[a]
1b	Et	**2**	Ph	**3b**	90	80/20[b]
1c	i-Pr	**2**	Ph	**3c**	91	85/15
1d	CH(OTBDMS)Me	**2**	Ph	**3d**	90	97/ 3[c]
1a	Me	**4**	HC=CHPh	**10a**	99	60/40[a]
1b	Et	**4**	HC=CHPh	**10b**	76	70/30[b]
1c	i-Pr	**4**	HC=CHPh	**10c**	52	75/25[a]
1d	CH(OTBDMS)Me	**4**	HC=CHPh	**10d**	42	98/2[c]
1a	Me	**5**	n-Pr	**11a**	48	37/63
1b	Et	**5**	n-Pr	**11b**	40	47/53
1c	i-Pr	**5**	n-Pr	**11c**	45	83/17
1d	CH(OTBDMS)Me	**5**	n-Pr	**11d**	72	90/10[c]
1a	Me	**6**	$CH_2OTBDPS$	**12a**	40	46/54
1b	Et	**6**	$CH_2OTBDPS$	**12b**	52	63/37[b]
1c	i-Pr	**6**	$CH_2OTBDPS$	**12c**	46	61/39
1d	CH(OTBDMS)Me	**6**	$CH_2OTBDPS$	**12d**	63	70/30[c]
1a	Me	**7**	CH_2OBn	**13a**	40	23/77
1b	Et	**7**	CH_2OBn	**13b**	43	24/76
1c	i-Pr	**7**	CH_2OBn	**13c**	48	33/67
1d	CH(OTBDMS)Me	**7**	CH_2OBn	**13d**	50	2/98[c]
1b	Et	**8**	CH(OTBDMS)Me	**14b**	59	67/33[c]
1c	i-Pr	**8**	CH(OTBDMS)Me	**14c**	70	98/2[c]
1b	Et	**9**	CH(OBn)Me	**15b**	77	37/63
1c	i-Pr	**9**	CH(OBn)Me	**15c**	61	36/64

[a] Ref.1 [b] Ref. 4d [c] Ref.4a

Figure 1. Enolization of the thioester/$TiCl_4$ adduct.



their configurational stability or on their reactive conformation.[13] The problem of reactive conformation is particularly relevant in the case of α-alkoxy imines, that can react as a five membered chelate, involving the imine nitrogen, the titanium atom, and the alkoxy oxygen.[14] It must be noted, however, that chelation can be possible only for (E) configurated imines that feature a chelation-allowing oxygen protecting group as **7** or **9**.[14]

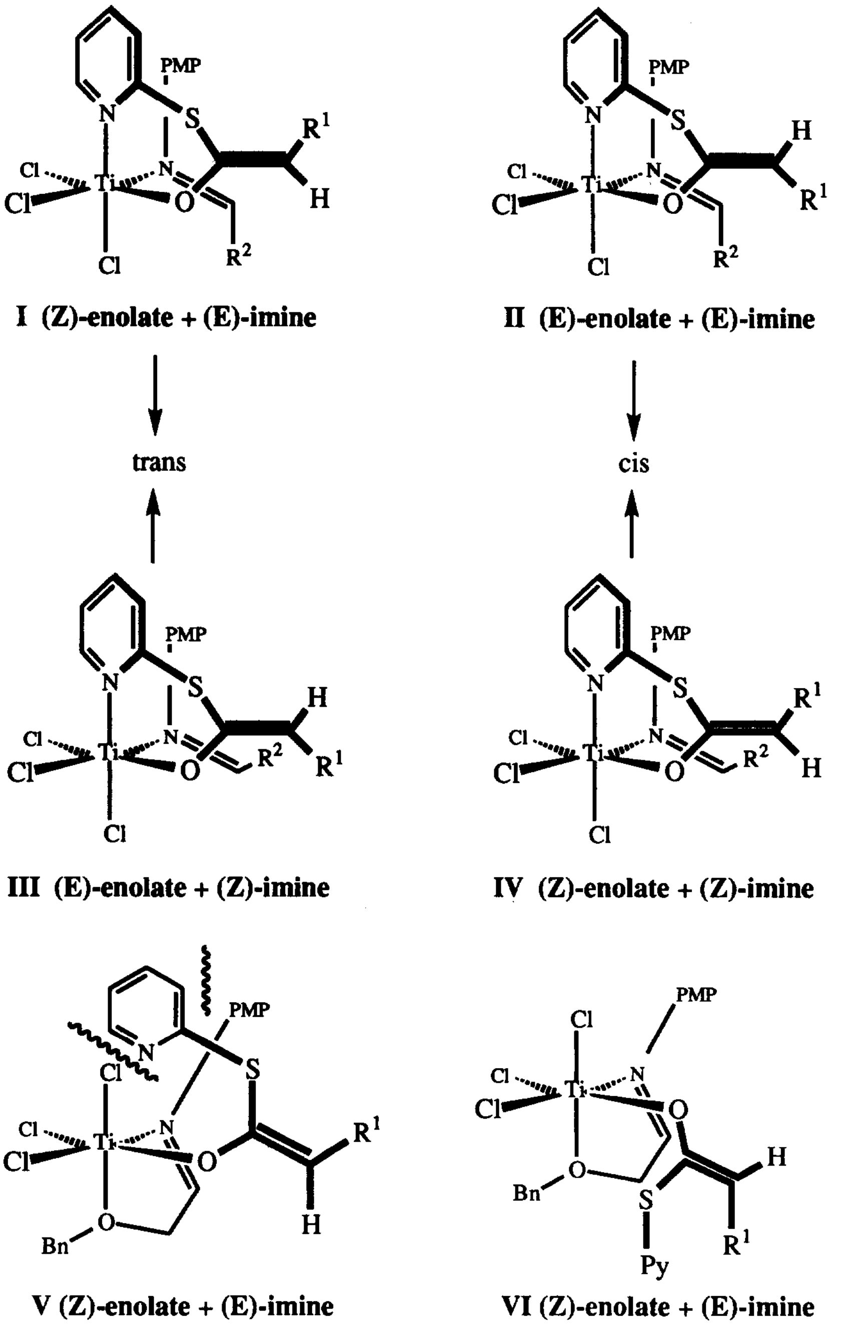
In proposing models of stereoselection, we think that cyclic rather than open transition states should be taken into account, since in a poorly co-ordinating solvent as dichloromethane the imine nitrogen should definitely be co-ordinated to a good Lewis acid as the titanium enolate. Support to this hypothesis was found in the following NMR experiment. Addition of N-benzylidene aniline to the **1c**/$TiCl_4$ adduct[15] in CD_2Cl_2 solution at -70°C resulted in the co-ordination of the imine nitrogen to the titanium atom and in the displacement[16] of the pyridine moiety of the thioester from titanium. This ligand exchange was clearly indicated by the disappearance of the downfield shifted proton signals of the pyridine in the thioester/$TiCl_4$ adduct (see above), and can be rationalized by the more basic nature of the imine nitrogen with respect to the pyridine one.[15] It is worth mentioning, however, that addition of the imine to the enolate does not require pyridine displacement, since in this case titanium can tolerate six ligands in a octahedral co-ordination.[8]

The four possible combinations of enolate and imine geometries are depicted in Figure 2.

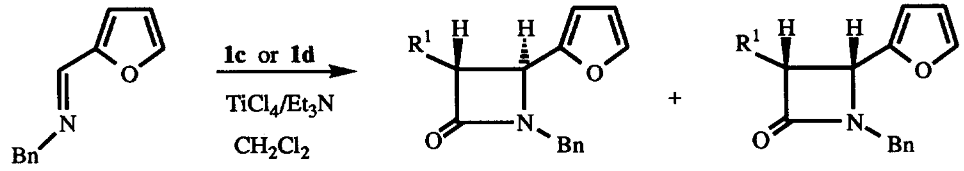
We think that trans products should be formed *via* model **I** that features the reagents in their preferred configuration. This model should be particularly favoured when R^1 and R^2 are both bulky residues, as in the case of the thioesters **1c** and **1d**, and of imine **2**, that is indeed the situation when maximum trans selectivity is observed. The contribution of model **III** to the generation of the trans isomer should be negligible, since in **III** both reagents are in their less abundant configuration.

To rationalize the formation of cis products one can use either model **II** or **IV**. The former should be at work with thioesters as **1a** and **1b**, that feature small R^1 residues and in some degree exist as (E) enolates; the latter should be the model by which the partly (Z) configurated aliphatic imines react with the predominant isomer of the enolates.

Figure 2. Possible models of stereoselection for the reactions of **1a-d** with **2,4-7**.



Scheme 2



16 trans-17 R^1 = i-Pr cis-17

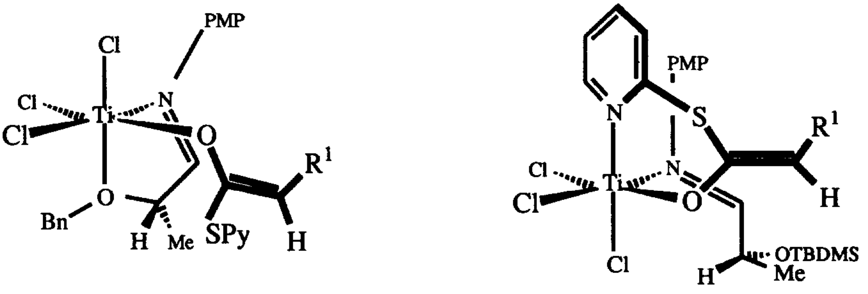
trans-18 R^1 = CH(OTBDMS)Me cis-18

α-Alkoxy substituted imines deserve a particular comment. Non-chelating imines **6** and **8** behave like alkyl substituted compound **5**, and give poorly stereoselective reactions. Chelating derivatives **7** and **9** gave constantly a predominance of cis products that cannot be accounted for simply by invoking the intervention of the minor (E) enolates as in **II**, or of (Z) imines as in **IV**. As mentioned above these imines can chelate the titanium atom when they are in the (E) configuration. If a chelated imine is involved in the cyclic model however, the insertion of an additional ligand at titanium (the alkoxy group) should lead as before to the displacement of pyridine. As a consequence of the ligand exchange, the pyridine ring turns out to be in a very sterically unfavoured situation as indicated in model **V** of Fig.2 (only (Z) enolates are considered for simplicity). To relief this steric congestion, we believe that rotation around the titanium/enolate oxygen bond occurs to give model **VI**, in which the enolate (that maintains its configuration) attacks the (E) imine using the face of the double bond opposite to that involved in model **I**, thus leading to cis compounds. A model analogous to **VI** involving (E) enolate can account for the formation of trans compounds.

The influence on the stereoselectivity exerted by an α-oxygen on the imine was further shown by the reactions described in Scheme 2. For these experiments 2-furylimine **16** was selected since it can be considered an analogue of an α-alkoxy imine, can give chelation, and exists exclusively in the (E) configuration as shown by n.O.e. experiments. Furthermore NMR studies strongly suggested that, in the presence of $TiCl_4$ and in CD_2Cl_2 solution, **16** gives a five membered chelate[17] that is stable from -70° to -10°C. By reacting **16** with **1c** and **1d** (two thioesters that showed high trans selectivity in their reactions with aromatic imines)[18] β-lactams **17** and **18** were obtained as 66/34 and 67/33 mixtures of trans/cis isomers in 51% and 59% yield, respectively. Thus, also in this case, the presence of a chelating α-oxygen on the imine brings about the partial formation of cis β-lactams. The poorly co-ordinating nature of the furan oxygen of **16** with respect to the alkoxy oxygen of **7** and **9** can account for the observed lower cis selectivity.

The role played by an α-oxygen on the imine is particularly relevant in the case of chiral compounds (S)-**8** and (S)-**9**. In their reactions with **1b** and **1c**, 4/4' syn configurated compounds **14** and **15** were exclusively obtained (Table 1), but with imine **8** the trans products predominated, while with imine **9** partial formation of the cis isomers was observed. On the basis of the results of the present work, the diastereofacial selectivity of these reactions can be tentatively rationalized as follows. Imine **9** reacts in a chelated conformation as described in model **VII** (Figure 3). Non-chelating imine **8** should adopt the conformation of model **VIII** (derived from model **I**), that features the small substituent at the stereocenter in the more

Figure 3. Possible models of stereoselection for chiral imines (S)-**8** and (S)-**9**.



VII (Z)-enolate + (E)-imine → 3,4-cis-4,4'-syn-**15**

VIII (Z)-enolate + (E)-imine → 3,4-trans-4,4'-syn-**14**

sterically demanding position, and undergoes attack on the same diastereoface as **9**. The higher trans selectivity observed with (S)-**8** with respect to **6** can simply be due to the presence in the former of a larger R^2 group.

Experimental.

NMR spectra were recorded at 80 or at 300 MHz using $CDCl_3$ as solvent. Low temperature spectra were obtained at 300 MHz in CD_2Cl_2 solutions. Chemical shifts are in ppm downfield from TMS; coupling constants are in Hz. Silica gel was used for analytical and flash chromatography. Organic extracts were dried over sodium sulphate. All reactions employing dry solvents were run under nitrogen. CH_2Cl_2 was distilled from CaH_2, THF from LAH, Et_3N from KOH. $TiCl_4$ was used as commercially available 1M solution in CH_2Cl_2.

Thioesters **1a-d** were known compounds.[1,4a] Imines **2**, **4-9**, and **16** were prepared from the corresponding aldehyde by reaction with the amine (1 mol equiv) in CH_2Cl_2 solution (2-12 h, RT) in the presence of anhydrous magnesium sulphate. With the only exception of **2** and **4**, they were used as crude products. β-Lactams **3a**,[1] **3b**,[4d] **3c**,[4d] **3d**,[4a] **10a**,[1] **10b**,[4d] **10c**,[1] **10d**,[4a] **11b**,[4d] **11d**,[4a] **12b**,[4d] **13d**,[4a] **14b**,[4a] **14c**,[4a] were known compounds.

Synthesis of β-lactams. General procedure: To a stirred 0.1 M solution of thioester in CH_2Cl_2 cooled at -78°C, a 1.0 M solution of $TiCl_4$ (1 mol equiv) was added dropwise over a 1 min period. To the resulting purple solution, Et_3N (1 mol equiv) was added dropwise and stirring was continued at -78°C for 30 min. To this mixture a solution of the imine (0.5 mol equiv) in CH_2Cl_2 was added over a 2 min period, and the dry ice/methanol bath was replaced by an ice bath. After 4-12 h stirring at 0°C the reaction was quenched by the addition of a saturated aqueous solution of sodium bicarbonate, and the resulting mixture was filtered through a celite cake. The organic phase was separated, washed with water, dried, and evaporated. The unreacted thioester was removed by stirring a THF solution of the crude product in the presence of a 5 fold mol excess of 1N aqueous KOH solution for 2-12 h at RT. The mixture was extracted with Et_2O, and the organic phase was dried, and evaporated to give the crude product, that was analyzed by ^1H NMR. Flash chromatography with hexanes : Et_2O as eluant gave the purified product generally as mixtures of isomes. Yields and trans/cis ratios are collected in Table 1. For each new compound the eluting mixture is reported in parenthesis after the name of the compound. Selected ^1H NMR data are given in this order: δ HC-3; δ HC-4; $J_{3,4}$ of trans and cis isomer, respectively. Infrared spectra and analytical data were obtained on the diastereoisomeric mixtures.

1-(4-Methoxyphenyl)-3-methyl-4-(1-propyl)azetidin-2-one 11a (70:30) was an oil.IR: 1755 cm^{-1}. Anal Calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 71.94; H, 8.28; N, 5.94. ^1H NMR: 2.89, 3.60, 2.5; 3.39, 4.05, 5.4.

1-(4-Methoxyphenyl)-3-(1-methylethyl)-4-(1-propyl)azetidin-2-one 11c (70:30) was an oil. IR: 1755 cm^{-1}. Anal Calcd for $C_{16}H_{23}NO_2$: C, 73.53; H, 8.87; N, 5.36. Found: 73.33; H, 8.95; N, 5.28. ^1H NMR: 2.67, 3.74, 2.1; 3.00, 4.08, 5.6.

4-[(1,1-Dimethylethyl)diphenylsilyl]oxymethyl-1-(4-methoxyphenyl)-3-methylazetidin-2-one 12a (85:15) was an oil. IR: 1750 cm^{-1}. Anal Calcd for $C_{28}H_{33}NO_3Si$: C, 73.16; H, 7.24; N, 3.05. Found: C, 73.01; H, 7.15; N, 3.00. ^1H NMR: 3.19, 3.72, 2.1; 3.45, 4.11, 5.6.

4-[(1,1-Dimethylethyl)diphenylsilyl]oxymethyl-1-(4-methoxyphenyl)-3-(1-methylethyl) azetidin-2-one 12c (85:15) was an oil. IR: 1750 cm^{-1}. Anal Calcd for $C_{30}H_{37}NO_3Si$: C, 73.88; H, 7.65; N, 2.87. Found: C, 73.69; H, 7.61; N, 2.78. ^1H NMR: 2.93, 3.84, 1.6; 3.03, 4.13, 5.0.

3-[1-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]ethyl]-4-[(1,1-dimethylethyl)diphenyl silyl] oxymethyl-1-(4-methoxyphenyl)azetidin-2-one 12d (90:10) was a low melting material. IR: 1755 cm^{-1}. Anal Calcd for $C_{35}H_{49}NO_4Si_2$: C, 69.61; H, 8.18; N, 2.32. Found: C, 69.89; H, 8.20; N, 2.38. ^1H NMR: 3.13, 4.20, 2.0; 3.29, 4.30, 6.4.

1-(4-Methoxyphenyl)-3-methyl-4-phenylmethoxymethylazetidin-2-one 13a (70:30) was an oil. IR: 1755 cm^{-1}. Anal Calcd for $C_{19}H_{21}NO_2$: C, 73.29; H, 6.80; N, 4.50. Found: C, 73.20; H, 6.71; N, 4.44. ^1H NMR: 3.09, 3.82, 2.0; 3.46, 4.23, 5.6.

3-Ethyl-1-(4-methoxyphenyl)-4-phenylmethoxymethylazetidin-2one 13b (70:30) was an oil. IR: 1755 cm^{-1}. Anal Calcd for $C_{20}H_{23}NO_3$: C, 73.82; H, 7.12; N, 4.30. Found: C, 73.66; H, 7.19; N, 4.26. ^1H NMR: 3.00, 3.90, 2.3; 3.27, 4.28, 5.5.

1-(4-Methoxyphenyl)-3-(1-methylethyl)-4-phenylmethoxymethylazetidin-2-one 13c (70:30) was an oil. IR: 1755 cm^{-1}. Anal Calcd for $C_{21}H_{25}NO_3$: C, 74.31; H, 7.42; N, 4.13. Found: C, 74.18; H, 7.50; N, 4.08. ^1H NMR: 2.85, 3.95, 2.4; 3.06, 4.27, 5.5.

3-Ethyl-1-(4-methoxyphenyl)-4-[1-(phenylmethoxy)ethyl]azetidin-2-one 15b (60:40) was an oil. IR: 1750 cm^{-1}. Anal Calcd for $C_{21}H_{25}NO_3$: C, 74.31; H, 7.42; N, 4.13. Found: 74.22; H, 7.51; N, 4.18. ^1H NMR: 2.91, 3.83, 1.5; 320, 4.12, 5.8.

1-(4-Methoxyphenyl)-3-(1-methylethyl)-4-[1-(phenylmethoxy)ethyl]azetidin-2-one 15c (60:40) was an oil. IR: 1750 cm^{-1}. Anal Calcd for $C_{22}H_{27}NO_3$: C, 74,76; H, 7.70; N, 3.96. Found: C, 74.59; H, 7.77; N, 3.94. ^1H NMR: 2.79, 3.90, 2.0; 3.10, 4.17, 6.0.

4-(2-Furyl)-3-(1-methylethyl)-1-phenylmethylazetidin-2-one 17 (70:30) was a waxeous material. IR: 1750 cm^{-1}. Anal Calcd for $C_{17}H_{19}NO_2$: C, 75.81; H, 7.11; N, 5.20. Found: C, 75.65; H, 7.01; N, 5.27. ^1H NMR: 3.17, 4.14, 2.3; 3.03, 4.55, 5.2.

3-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-4-(2-furyl)-1-phenylmethylazetidin-2-one 18

(80:20) was a low melting material. IR: 1755 cm^{-1}. Anal Calcd for $C_{22}H_{31}NO_3Si$: C, 68.53; H, 8.10; N, 3.63. Found: C, 68.71; H, 8.10; N, 3.70. ^1H NMR: 3.35, 4.57, 2.3; 3.42, 4.58, 5.0.

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5. N-Boc or N-phthaloyl 2-pyridylthioglycinate gave good trans selectivity in the condensation with the N-benzylimine of benzaldehyde (see ref. 1).
6. (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.
7. Reetz, M.T. *Acc.Chem.Res.* **1993**, *26*, 462, and references therein.
8. The enolate structure is not only a stereochemical problem. The possibility that these enolates are ate-complexes has been pointed out by Evans, et.al. (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 (Reetz, M.T. *Organotitanium Reagents in Organic Synthesis*; Springer, Berlin, **1986**). Therefore the models of stereoselection that we propose are simple working hypotheses.
9. The enolate of **1d** was shown to be a 65 : 35 mixture of two species. However, since the enolization process has been studied on racemic **1d**, the possibility exists that the two observed species are two diastereoisomeric dinuclear titanium complexes formed in one case by homomers and in the other by enantiomers of a same enolate. The high stereoselectivity displayed by the reactions of **1d** is in agreement with this possibility.
10. For leading references to the stereochemical problems involved in the enolization 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, and references therein. It must be noted that on passing from $TiCl_4$ to bulkier $TiBr_4$ more stereoselective reactions were observed, in agreement with the proposed rationale for (Z) enolate formation (unpublished results from this laboratory). In the case of thioesters **1g** and **1h**, where chelation involves the carbonyl and the benzyloxy or acetoxy oxygens, (E) enolates are formed exclusively (see ref. 4a).
11. These compounds are crystalline solids and stable enough to be stored indefinitely at room temperature. Alkyl substituted imines are much less stable, and were used as crude products.
12. N-benzylidene aniline was selected for these experiments instead of **2** in order to provide a single possible site of chelation to $TiCl_4$.
13. For an example of imine configuration that is affected by co-ordination to $TiCl_4$ see: Ojima, I.; Inobe, S. *Tetrahedron Lett.* **1980**, *21*, 2081. For an example of an (E) imine that is postulated to react in the (Z) configuration see: Corey, E.J.; Decicco, C.P.; Newbold, R.C. *Tetrahedron Lett.* **1991**, *32*, 5287.
14. For leading references to the higher reactivity of a chelated species with respect to a non-chelated one, and 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.
15. Obviously this experiment can not be carried out on the enolate because reaction takes place. In the course of the experiment we found that the imine nitrogen is basic enough to generate the titanium enolate of the thioester, although at a very limited extent, as indicated by the appearance of the signals of the β-lactam.
16. Ligand displacement at an octahedrally co-ordinated titanium atom is believed to occurr via a Berry pseudorotation mechanism (Berry, R.S. *J.Chem.Phys.* **1960**, *32*, 923). Theoretical calculations are in agreement with this hypothesis (Branchadell, V.; Oliva, A. *J.Am.C hem.Soc.* **1992**, *114*, 4357).
17. Addition of $TiCl_4$ to a solution of **16** resulted in the following downfield shifts for the indicated protons: CH_2-N, 0.60 ppm; H-3, 0.40 ppm; H-4, 0.33 ppm; H-5, 0.13 ppm; H-C=N, 0.06 ppm.
18. The influence of the arylimine N-substituent on the stereoselectivity of the reactions was very limited. For instance, in the condensation of **1c** and **1d** with N-benzyl benzaldimine trans/cis ratios of 92/8 and 98/2 were observed, respectively. The β-lactams obtained from **1d** and **16** were shown to be >95/5 diastereisomerically pure materials, likely featuring the 3/3' anti configuration (see ref.4a for an analogous behaviour of **1d** in the condensation with other imines).

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