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Synthesis of β-Lactams by Condensation of the Tin Enolates of 2-Pyridylthioesters with Imines. A Comparison between Titanium and Tin Enolates

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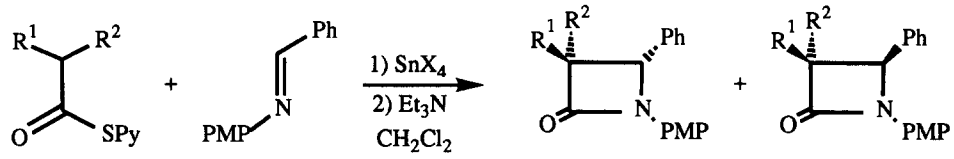
Abstract: Addition of triethylamine to a mixture of 2-pyridylthioesters and $SnCl_4$ or $SnBr_4$ affords the corresponding tin(IV) enolates that add to imines to give β-lactams in fair to good yields and with various degree of trans/cis stereoselectivity. Examples of highly diastereofacially selective reactions carried out on a chiral thioester and on a chiral imine are also reported. The results are compared with those obtained in the condensations promoted by $TiCl_4$ and $TiBr_4$.

In 1991 we reported[1] a convenient one-pot synthesis of β-lactams by condensation of the titanium enolates of 2-pyridylthioesters with imines.[2] This reaction, that tolerates a wide range of functional groups and can be efficiently stereocontrolled using chiral reagents,[3] owes its experimental simplicity to the easy generation of the titanium enolate, that is formed upon addition of triethylamine to a CH_2Cl_2 solution of 2-pyridylthioester and $TiCl_4$ at -78°C. We here report that also $SnCl_4$ and $SnBr_4$ can be used to perform this mild, one-pot synthesis of β-lactams,[5] and that in some cases the tin mediated reactions occur with a stereoselectivity that is higher than, or opposite to, that of the titanium promoted ones.

The reaction of non-heterosubstituted thioesters **1-4** with N-*para*-methoxyphenyl (PMP) benzaldimine **5** was studied first. The enolization was performed by adding triethylamine to a 1 : 1 mixture of thioester and SnX_4 in CH_2Cl_2 solution. After 30 min, the imine was added and the reaction mixture was stirred overnight at room temperature to afford β-lactams **6-9**. Compounds **6-8** were obtained as mixtures of trans (**t**) and cis (**c**) diastereoisomers. The isomer ratios were easily determined by 300 MHz ^1H NMR spectroscopy of the crude products. Trans and cis structures were assigned on the basis of the HC-3/HC-4 coupling constants values (J_{trans} *ca* = 2.0-3.0 Hz; J_{cis} *ca* = 5.0-6.0 Hz). The products were then isolated by flash chromatography. Yields and diastereoisomeric ratios are collected in Table 1.

As can be seen from the reported data, the use of $SnCl_4$ secures slightly better yields than that of $SnBr_4$. A low enolization temperature is also beneficial. As far as the diastereoselectivity is concerned, the observed trans : cis ratios are similar to, or higher than, those of the corresponding $TiCl_4$ mediated synthesis.[1,3]

Table 1. Synthesis of β-lactams **6t,c-8t,c** and **9** from thioesters **1-4** and imine **5** in the presence of $SnCl_4$ and $SnBr_4$.



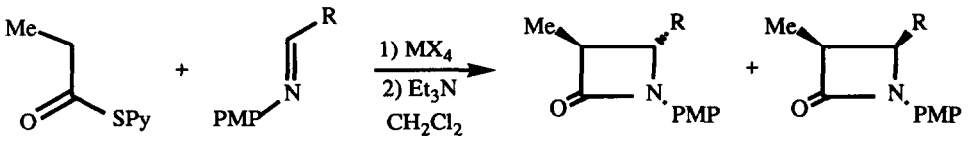
1-4 **5** **6t-8t, 9** **6c-8c**

Thioester[a]	R^1	R^2	X	T°C[b]	Product	Yield%[c]	t : c ratio[d]
1	Pr-i	H	Cl	-78	**6t,c**	80	92 : 8
1	Pr-i	H	Cl	-30	**6t,c**	79	92 : 8
1	Pr-i	H	Cl	0	**6t,c**	65	92 : 8
1	Pr-i	H	Cl	20	**6t,c**	12	-
1	Pr-i	H	Br	-78	**6t,c**	75	95 : 5
2	Et	H	Cl	-78	**7t,c**	67	90 :10
2	Et	H	Cl	-30	**7t,c**	32	91 : 9
2	Et	H	Br	-78	**7t,c**	65	92 : 8
3	Me	H	Cl	-78	**8t,c**	71	77 :23
3	Me	H	Br	-78	**8t,c**	61	92 : 8
4	Me	Me	Cl	-78	**9**	68	-
4	Me	Me	Br	-78	**9**	63	-
4	Me	Me	Br	-30	**9**	32	-

[a] Thioester : MX_4 : Et_3N : imine ratio is 1.0 : 1.0 : 1.0 : 0.5. [b] Complexation and enolization temperature; condensation temperature is from the enolization temperature to room temperature. [c] Isolated yields after flash chromatography. [d] As determined by 300 MHz ^{1}H NMR analysis.

In order to evaluate the influence of the Lewis acid (LA) activator on the outcome of the reaction, the condensations of thioester **3** with imine **5** and cinnamaldimine **10** to give β-lactams **8t,c** and **11t,c**, carried out at -78°C in the presence of $TiCl_4$, $TiBr_4$, $SnCl_4$, and $SnBr_4$, were studied and compared.[6] Isomer ratios and chemical yields, determined as mentioned before, are collected in Table 2. The results show that with $TiCl_4$ the yields are higher than those obtained with the other LA, and that an increase in the formation of trans β-lactams can be achieved not only on passing from Ti- to Sn-containing LA, but also from MCl_4 to MBr_4.[7]

Table 2. Synthesis of β-lactams **8t,c-11t,c** from thioester **3** and imines **5** and E-**10** in the presence of MX_4 at -78°C.



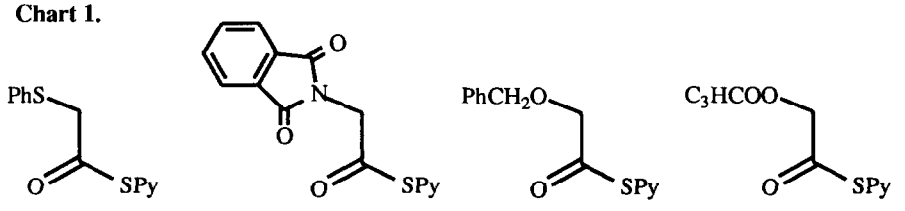
3 **5,10** **8t,11t** **8c,11c**

Imine[a]	R	MX_4	Product	Yield%[c]	t : c ratio[d]
5	Ph	$TiCl_4$	**8t,c**	99	70 : 30
5	Ph	$TiBr_4$	**8t,c**	90	91 : 9
5	Ph	$SnCl_4$	**8t,c**	71	77 : 23
5	Ph	$SnBr_4$	**8t,c**	61	92 : 8
10	Ph-CH=CH	$TiCl_4$	**11t,c**	99	60 : 40
10	Ph-CH=CH	$TiBr_4$	**11t,c**	55	80 : 20
10	Ph-CH=CH	$SnCl_4$	**11t,c**	85	70 : 30
10	Ph-CH=CH	$SnBr_4$	**11t,c**	32	91 : 9

[a] Thioester : MX_4 : Et_3N : imine ratio is 1.0 : 1.0 : 1.0 : 0.5. [b] Isolated yields after flash chromatography. [c] As determined by 300 MHz ^1H NMR analysis.

When the extension of the tin mediated reaction to α-heterosubstituted thioesters **12-15** (Chart 1) was attempted, it was found that compounds **12** and **13** did not react with imine **5** (enolization temperature from -78°C up to 20°C), while α-oxy substituted thioesters **14** and **15** afforded β-lactams **16t,c** and **17t,c** in low to good yields.

Chart 1.

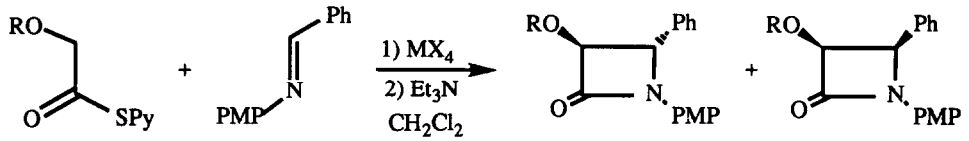


12 **13** **14** **15**

The results of these reactions are collected in Table 3, that includes also those of the corresponding $TiCl_4$ and $TiBr_4$ promoted condensations (see above for yields and diastereoselectivity determination).

The dependence of the trans : cis ratios of compound **16** on the nature of the LA halide is remarkable, an opposite stereoselectivity being observed on passing from MCl_4 to MBr_4. The good trans stereoselectivity in which compound **16t** is obtained with $SnBr_4$ as a promoter is unprecedented by other enolate/imine condensations, that generally lead to cis configurated 3-alkoxy substituted β-lactams.[2] In the case of azetidinone **17** a low predominance of the trans isomer is obtained only by the use of $SnBr_4$. Only very recently a highly stereosletive synthesis of compound **17t** has been reported by a modified Staudinger reaction,[8] en route to 2'-epitaxol.[9]

Table 3. Synthesis of β-lactams **16t,c** and **17t,c** from thioesters **14** and **15** and imine **5** in the presence of MX_4.



14,15 **5** **16t,17t** **16c,17c**

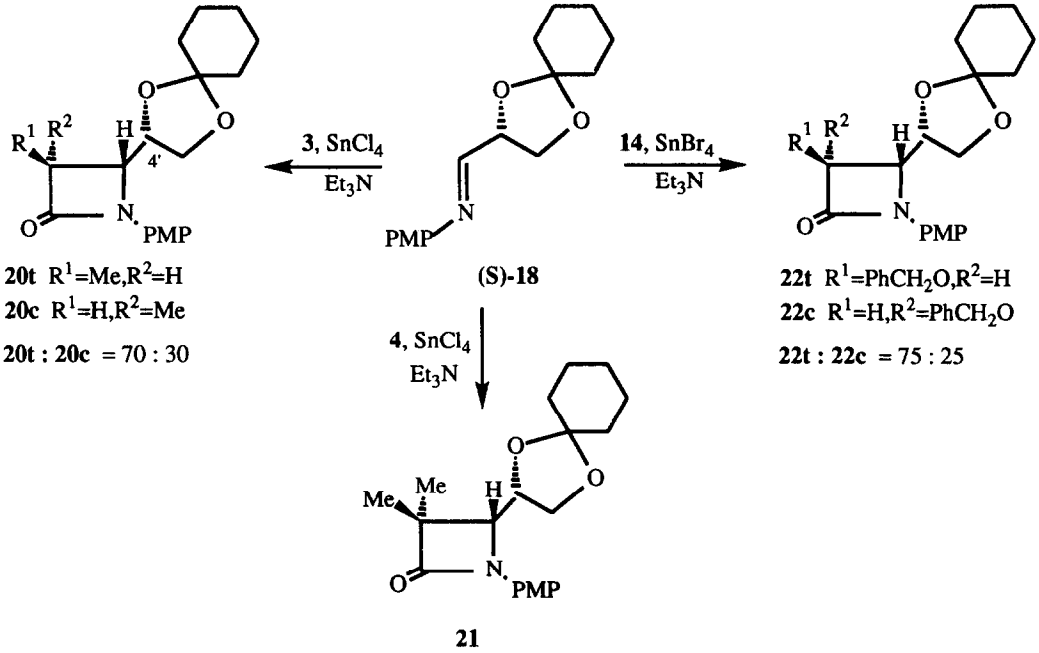
Thioester[a]	R	MX_4	T°C[b]	Product	Yield%[c]	t : c ratio[d]
14	$PhCH_2$	$TiCl_4$	-78	**16t,c**	74	39 : 61
14	$PhCH_2$	$TiBr_4$	-78	**16t,c**	56	73 : 27
14	$PhCH_2$	$SnCl_4$	-78	**16t,c**	18	10 : 90
14	$PhCH_2$	$SnBr_4$	-78	**16t,c**	92	87 :13
14	$PhCH_2$	$SnBr_4$	-30	**16t,c**	68	91 : 9
15	CH_3CO	$TiCl_4$	-78	**17t,c**	77	30 : 70
15	CH_3CO	$TiBr_4$	-78	**17t,c**	90	34 : 66
15	CH_3CO	$SnCl_4$	-78	**17t,c**	24	28 : 72
15	CH_3CO	$SnBr_4$	-78	**17t,c**	65	66 : 34

[a] Thioester : MX_4 : Et_3N : imine ratio is 1.0 : 1.0 : 1.0 : 0.5. [b] Complexation and enolization temperature; condensation temperature is from the enolization temperature to room temperature. [c] Isolated yields after flash chromatography. [d] As determined by 300 MHz ^1H NMR analysis.

The $SnCl_4$ and $SnBr_4$ mediated reactions of the chiral reagents (S)-**18** and (R)-**19** were then investigated (Chart 2). The condensation of imine (S)-**18** with thioesters **3** ($SnCl_4$, -78°C), **4** ($SnCl_4$, -78°C), and **14** ($SnBr_4$, -30°C) afforded β-lactams **20t,c**, **21**, and **22t,c** in 63, 75, and 37% yield,

respectively. As already observed for the corresponding $TiCl_4$ promoted reactions,[3a,3c] the imine diastereofacial selectivity was constantly excellent, and 4,4'-syn configurated products were exclusively obtained.[10] As for the trans : cis stereoselectivity, compounds **20t,c** and **22t,c** were obtained as 70 : 30 and 75 : 25 mixtures of trans and cis azetidinones, respectively. Thus, also in the case of imine (S)-**18**, the reaction with benzyloxythioester **14** in the presence of $SnBr_4$ leads to the preferential formation of a trans β-lactams.[11]

Chart 2.

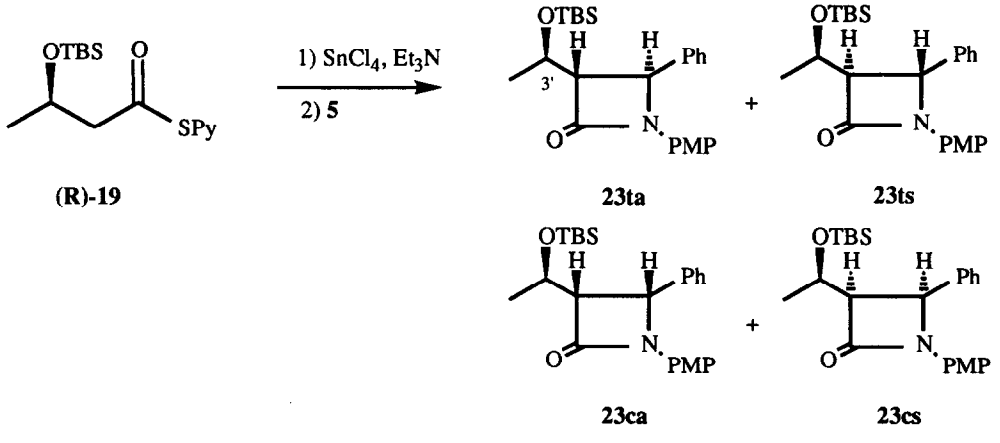


20t R^1=Me,R^2=H
20c R^1=H,R^2=Me
20t : 20c = 70 : 30

(S)-18

22t R^1=$PhCH_2O$,R^2=H
22c R^1=H,R^2=$PhCH_2O$
22t : 22c = 75 : 25

21



(R)-19

23ta **23ts**

23ca **23cs**

23ta : 23ts : 23ca : 23cs = 77 : 5 : 10 : 8

The reaction of the 3-hydroxybutanoic acid derivative (R)-**19** with imine **5** at -78°C in the presence of $SnCl_4$ gave the four possible diastereoisomers of compound **23** in 60% yield.[12] The (3,4-trans-3,3'-anti)-**23ta** : (3,4-trans-3,3'-syn)-**23ts** : (3,4-cis-3,3'-anti)-**23ca** : (3,4-cis-3,3'-syn)-**23cs** diastereoisomeric ratio was 77 : 5 : 10 : 8,[13], the major product having the correct configuration required by the carbapenem antibiotics of the thienamycin family. A comparison between the $TiCl_4$[3a] and the $SnCl_4$ mediated reactions shows that the former occurs in better yield (90 *vs* 60%), with higher trans stereoselectivity (97 : 3 *vs* 82 : 18), and slightly lower facial stereocontrol (11 : 1 *vs* 15.5 : 1) than the latter.[14]

In the absence of any reliable evidence on the nature of the enolate, the proposal of a model of stereoselection to account for the observed stereochemical outcome of the tin(IV) mediated reactions seems premature. It must be remembered that experimental work showed that tin(IV) enolates of ketones[15a] and thioesters[15b] exist as a C-Sn rather than as a O-Sn species. However, these compounds have been generated by transmetallation from the corresponding silyl enolethers (35°C) or silyl keteneacetals (-78°C) and not, as in the present work, by direct enolization carried out in the presence of a base, and therefore the nature of the tin derivative can be different. A multinuclear NMR investigation is currently underway in our laboratories with the aim of elucidating the enolate structure, and to evaluate the possibility that the pyridine nitrogen of the thioester can influence the co-ordination at the tin atom and the stereochemistry of the enolate.

Experimental.

NMR spectra were recorded at 80 or at 300 MHz using $CDCl_3$ as solvent. 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, and filtered before removal of the solvent. All reactions employing dry solvents were run under nitrogen. CH_2Cl_2 was distilled from CaH_2, Et_3N from KOH. MX_4 were used as commercially available 1M solution in CH_2Cl_2.

Thioesters **1-4**,[1] **12**,[3a] **13**,[1] **14**,[1] **15**, [3a] and **19**,[3a] imines **5**,[1] **10**,[1] and **18**,[3a] and β-lactams **6**,[3b] **7**,[3b] **8**,[1] **9**,[16] **11**,[1] **17**, [9] **22**,[3a] and **23**[3a] were known compounds. The titanium mediated reactions were carried out as previously described.[1,3]

Synthesis of β-lactams *via* tin enolates. General procedure: To a stirred 0.1 M solution of thioester in CH_2Cl_2 (see Tables for the enolization temperatures), a 1.0 M solution of SnX_4 (1 mol equiv) was added dropwise over a 1 min period. To the resulting yellow 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, after overnight stirring at room temperature, 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 room temperature (this hydrolysis was not performed in the case of the 3-acetoxy derivative **17**).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 : diethylether as eluant gave the purified products, generally as

mixtures of isomers. Yields and trans : cis ratios are reported in the Tables and in the text. For each new compound the hexanes : diethylether eluting mixture is reported in parenthesis after the name of the compound. Infrared spectra and analytical data were obtained on the diastereoisomeric mixtures.

1-(4-Methoxyphenyl)-3-phenylmethoxy-4-phenylazetidin-2-one 16 (50:50) . IR: 1755 cm^{-1}. Anal Calcd for $C_{23}H_{21}NO_3$: C, 76.86; H, 5.89; N, 3.90. Found: C, 76.97; H, 5.91; N, 3.84. Compound **16t** had mp 113-114°C. Selected ^1H NMR data of **16t**: δ 4.78 (d, 1H, HC-3, J = 2.0 Hz); 4.50 (d, 1H, HC-4); of **16c**: δ 5.12 (d, 1H, HC-3, J = 5.0 Hz); 4.95 (d, 1H, HC-4).

1-(4-Methoxyphenyl)-3-methyl-4-(1,4-dioxaspiro[4.5]dec-2-yl)azetidin-2-one 20 (40:60) . IR: 1755 cm^{-1}. Anal Calcd for $C_{19}H_{25}NO_4$: C, 68.86; H, 7.60; N, 4.23. Found: 68.79; H, 7.54; N, 4.18. Compound **20t** had mp 72-73°C, $[\alpha]_D^{23}$ +16.6 (c 0.5, $CHCl_3$). Selected ^1H NMR data: δ 2.83
(dq, 1H, HC-3, J = 2.8, 6.8 Hz); 3.71 (dd, 1H, HC-4, J = 2.8, 7.0 Hz); 4.35 (m, 1H, HC-4'). Compound **20c** had mp 82-83°C, $[\alpha]_D^{23}$ + 54.6 (c 0.3, $CHCl_3$). Selected ^1H NMR data: δ 3.40 (dq, 1H, HC-3, J = 6.5, 7.0 Hz); 3.67 (dd, 1H, HC-4, J = 6.5, 8.4 Hz); 4.30 (m, 1H, HC-4').

1-(4-Methoxyphenyl)-3,3-dimethyl-4(1,4-dioxaspiro[4.5]dec-2-yl)azetidin-2-one 21 (40:60) had mp 139-140°C, $[\alpha]_D^{23}$ +35.4 (c 0.8, $CHCl_3$). IR: 1755 cm^{-1}. Anal Calcd for $C_{20}H_{27}NO_4$: C, 69.54; H, 7.88; N, 4.05. Found: C, 69.71; H, 7.93; N, 3.99. Selected ^1H NMR data: δ 3.74 (d, 1H, HC-4, J = 9.0 Hz); 4.29 (m, 1H, HC-4').

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References and Notes

1. Cinquini, M.; Cozzi, F.; Cozzi, P.G.; Consolandi, E. *Tetrahedron* **1991**, *47*, 8767.
2. For reviews on the enolate-imine condensation route to β-lactams see: (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.
3. (a) Annunziata, R.; Cinquini, M.; Cozzi, F.; Cozzi, P.G. *J.Org.Chem.* **1992**, *57*, 4155. (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. *J.Org.Chem.* **1993**, *58*, 4746. (d) Annunziata, R.; Benaglia, M.; Cinquini, M.; Cozzi, F.; Raimondi, L. *Tetrahedron Lett.* **1993**, *34*, 6921. (e) Annunziata, R.; Benaglia, M.; Cinquini, M.; Cozzi, F.; Ponzini, F.; Raimondi, L. *Tetrahedron* **1994**, *50*, 2939.
4. For leading references to the preparation of titanium enolates by this method, 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.
5. $SnCl_4$ and $SnBr_4$ were the only efficient activators for 2-pyridylthioesters enolization that we identified among many LA tested. For an experimental evaluation of the relative strength of LA commonly employed in organic synthesis, see: Childs, R.F.; Mulholland, D.L.; Nixon, A. *Can. J. Chem.* **1982**, *60*, 801. The validity of the theoretical background of this evaluation has been

demonstrated: Laszlo, P.; Teston, M. *J. Am. Chem. Soc.* **1990**, *112*, 8750. From these studies $TiCl_4$ appears to be a stronger LA than $SnCl_4$, while the difference between MCl_4 and MBr_4 seems to be very small.

6. The reactions of the tin enolates of **3** with the imine derived from butyraldehyde and 4-methoxyaniline did not afford the expected azetidinones. The corresponding reactions of the titanium enolates were low yielding and poorly stereoselective (with $TiCl_4$: yield 48%, trans : cis ratio 33 : 67; with $TiBr_4$: yield 23%, trans : cis ratio 50 : 50).
7. In the case of titanium enolates this dependence of the stereoselectivity on the bulkiness of the halogen ligand is in agreement with the model of stereoselection that has been proposed to account for the stereochemical outcome of this β-lactam synthesis (see ref. 3e). A bulkier ligand at the metal should enhance the tendency toward Z-enolization and, as a consequence, the formation of trans product.
8. For a review, see: Georg, G.I.; Ravikumar, V.T. in *The Organic Chemistry of β-Lactams*; Georg, G.I., Ed.; Verlag Chemie, New York, 1993, pp 295-368. A standard Staudinger 2+2 α-alkoxyketene/imine cycloaddition affords cis 3-alkoxy substituted β-lactams in a highly stereoselective fashion.
9. Endo, M.; Droghini, R. *BioMed. Chem. Lett.* **1993**, *3*, 2483.
10. The absolute configuration of azetidinones **20-22** was easily assigned by comparison of NMR data with those of the same compound (**22**) or of β-lactams of closely related structure (Et instead of Me at C-3 in **20**; H instead of Me at C-3 in **21**) obtained by the $TiCl_4$ mediated reactions(see ref. 3a and 3c).
11. This tendency toward trans product formation was confirmed also by the reaction of **14** ($SnBr_4$, -30°C) with the imine derived from E Ph-CH=CMe-CHO and 4-methoxyaniline to give a 66 : 34 trans : cis mixture of 1-(4-methoxyphenyl)-3-phenylmethoxy-4-(E-1-phenyl-2-propenyl)azetidin-2-one in 55% yield.
12. For leading references to the preparation of β-lactams starting from the enolate of 3-hydroxybutanoic acid and its derivatives, see ref 2a, 2b, and: Georg, G.I.; Kant, J.; Gill, H.S. *J. Am. Chem. Soc.* **1987**, *109*, 1129.
13. The absolute configuration of **23ta** and **23ts** (77 and 5% of the mixture, respectively) was unambigously established by comparison of NMR data with those already reported (see ref 3a). The attribution of configuration to the two cis isomers **23ca** and **23cs** is tentative, and it is based on the reasonable assumption that the enolate facial selectivity should favor the formation of the 3,3'-anti configurated compound also in the case of the cis isomer.
14. The corresponding $TiBr_4$ promoted reaction performed only slightly better than the $TiCl_4$ promoted one, affording a 91 : 9 mixture of **23ta** and **23ts** in 91% yield; no traces of the cis isomers were observed.
15. (a) Kuwajima, I.; Nakamura, E. *Acc. Chem. Res.* **1985**, *18*, 181, and references therein.
    (b) Gennari, C.; Bernardi, A.; Poli, G.; Scolastico, C. *Tetrahedron Lett.* **1985**, *26*, 2373.
16. Gluchowski, C.; Cooper, L.; Bergbreiter, D.E.; Newcomb, M. *J. Org. Chem.* **1980**, *45*, 3413.

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