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Stereoselective One-Pot Synthesis of β-Lactams by Lewis Acid Promoted Condensation of Silylketene Thioacetals with Imines

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Abstract: A series of silylketene thioacetals derived from 2-pyridylthioesters have been prepared and the (E)/(Z) configuration of some of them has been determined by NMR spectroscopy. In the presence of Lewis acids these compounds stereoselectively react with imines to afford β-lactams in a convenient one-pot procedure. An enantioselective β-lactam synthesis promoted by a chiral Lewis acid is also described.

2-Pyridylthioesters have proved to be valuable reagents for the one-pot synthesis of β-lactams by the condensation of their titanium,[1,2] tin,[3] and boron[4] enolates with imines.[5,6] Very recently, a limited number of silylketene thioacetals (SKTA) derived from 2-pyridylthioesters have become available by the work of Hirai *et al.*;[7] they also communicated on their $ZnCl_2$ promoted reactions with aldehydes[8a,b] and imines.[8a]

As a part of our project aimed to the development of new stereoselective one-pot procedures for the synthesis of β-lactams,[1,3,4,6] we decided to prepare a variety of these SKTA and to study their Lewis acid (LA) promoted Mukaiyama-type addition[9] to imines.[8a,10] This manuscript describes some of our results in this field.

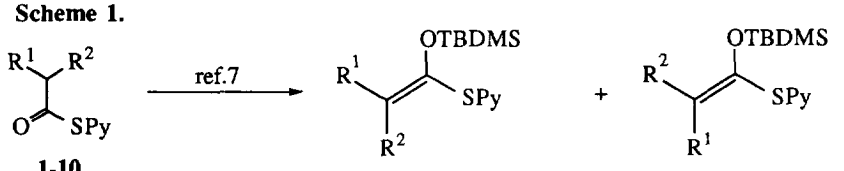
Starting from thioesters **1-10** the corresponding SKTA **11-20** have been prepared[7] (Scheme 1). With the only exception of the very unstable compound **11**, the products were obtained in good yields. The (E)/(Z) isomer ratios of SKTA **13-20** were easily determined by ^1H NMR analysis of the crude reaction products, and are reported in Table 1.

While alkyl substituted SKTA **13-16** were configurationally stable, heterosubstituted derivatives **17-20** were shown to isomerize upon standing in $CDCl_3$ solution at room temperature. The isomerization was slower at 0°C and was accelerated by exposure to light.

2D-NOESY experiments indicate the (E) configuration (CIP rules) for the only isomer observed for compounds **14** and **15**, and for the major isomer of derivative **16**.[11,12,13] The same experiments allowed the assignment of the configuration to the benzyloxy substituted SKTA **17**, to its silyloxy analogue **18**, and to the dibenzylamino derivative **20**. The isomerization of these compounds however, led to different results. Indeed, SKTA **17** and **20** isomerize to the (E) isomer, while compound **18** is converted into the (Z) one. The repulsive interaction between two large *cis* silyloxy residues in (E)-**18** can be invoked to account for this observation. The configurational assignment to SKTA **19** indicated in Table 1 is only tentative, and is based on the observed trend of the chemical shift value of the vinyl proton.

The condensation of SKTA **13** with imine **21** in CH_2Cl_2 solution in the presence of various LA to afford β-lactams **22t,c** was then investigated as a model reaction (Table 2). The best conditions and reactant molar ratio were established using $TiCl_4$ as LA (entries 1-6). These conditions involved exposure of **13** to 1.0 mol. equiv.

Scheme 1.



1-10 **11,12, (E) 13-20** **(Z) 13-20**

1, 11 $R^1 = R^2 = H$ **6, 16** R^1 = (R)-Me-CH(OTBDMS), $R^2 = H$
2, 12 $R^1 = R^2$ = Me **7, 17** R^1 = BnO, $R^2 = H$
3, 13 R^1 = Me, $R^2 = H$ **8, 18** R^1 = TBDPSO, $R^2 = H$
4, 14 R^1 = Et, $R^2 = H$ **9, 19** R^1 = PhS, $R^2 = H$
5, 15 R^1 = Pr-i, $R^2 = H$ **10, 20** $R^1 = Bn_2N$, $R^2 = H$

Abbreviations: TBDMS = t-BuMe_2Si; Bn = $PhCH_2$; TBDPS = t-BuPh_2Si.

Table 1. Synthesis of Silylketene Thioacetals **11-20** from 2-Pyridylthioesters **1-10**.

Thioester	SKTA	Yield %[a]	(E)/(Z) ratio[b]	(E)/(Z) ratio[c]
1	**11**	14	-	-
2	**12**	85	-	-
3	**13**	79	> 98/2	> 98/2
4	**14**	56	> 98/2	> 98/2
5	**15**	55	> 98/2	> 98/2
6	**16**	54	91/9	91/9
7	**17**	80	40/60	>98/2
8	**18**	82	93/7	<2/98
9	**19**	47	50/50	>98/2
10	**20**	67	12/88	>98/2

[a] Isolated yields after flash chromatography. [b] As determined by ^1H NMR analysis of the crude products.

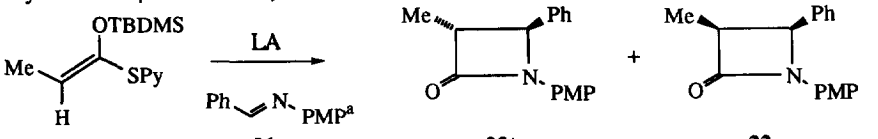
[c] Equilibrium ratio after 1 week standing in $CDCl_3$ solution at room temperature and in the light.

of $TiCl_4$ for 3 h at 0°C, followed by addition of 2.0 mol. equiv. of imine, and subsequent reaction at room temperature for 15 h (entry 5). However, when $TiCl_4$ (1.0 mol. equiv.) was added to a 1.0 : 2.0 mixture of SKTA **13** and imine **21** at room temperature, and the reaction was continued for 15 h , an increase in both yield and stereoselectivity[14] was observed (entry 7). In the conditions of entries 5 and 7 other LA were tested and were found to be effective promoters for this reaction (entries 8-18). They include $BF_3{\cdot}OEt_2$, $EtAlCl_2$,[15] $ZnCl_2$,[8a] t-butyldimethylsilyltriflate (TBDMSOTf), and $Yb(OTf)_3$.[10q-s] It is interesting to note that the synthesis of **22t,c** by $TiCl_4$ promoted addition of **13** to **21** can be favourably compared to that *via* trichlorotitanium enolate[1] in term of *trans* stereoselectivity (**t : c** ratio = 96 : 4 *vs* 70 : 30).

The reaction of other SKTA with imine **21** in the presence of selected LA was then studied (Table 3).Only the reaction of compound **14, 15, 17**, and **18** resulted in the formation of the corresponding β-lactams **23-26** as mixtures of *trans* and *cis* isomers. Independently of the LA used, SKTA **12, 16**, and **19** were found to be non-

reactive, while **20** afforded decomposition products.

Table 2. Synthesis of β-Lactam **22t,c** from SKTA **13** and Imine **21** in the Presence of LA.



13 **21** **22t** **22c**

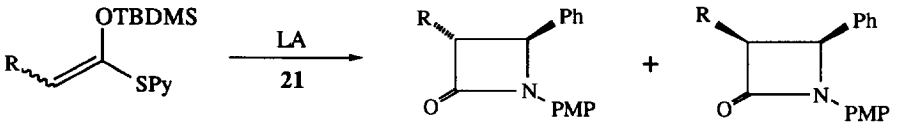
Entry	LA (mol.equiv.)	t (h)[b]	mol.equiv. of **21**	Yield %[c]	**22t : 22c**[d]
1	$TiCl_4$ (1.0)	4.5	0.5	66	79 : 21
2	$TiCl_4$ (1.0)	3.0	0.5	68	92 : 8
3	$TiCl_4$ (1.0)	1.5	0.5	19	>98 : 2
4	$TiCl_4$ (1.0)	3.0	1.0	72	91 : 9
5	$TiCl_4$ (1.0)	3.0	2.0	78	87 : 13
6	$TiCl_4$ (2.0)	3.0	1.0	30	93 : 7
7	$TiCl_4$ (1.0)	-[e]	2.0	81	96 : 4
8	$BF_3{\cdot}OEt_2$(1.0)	3.0	2.0	65	81 : 19
9	$BF_3{\cdot}OEt_2$(1.0)	-[e]	2.0	68	83 : 17
10	$EtAlCl_2$ (1.0)	3.0	2.0	73	70 : 30
11	$EtAlCl_2$ (2.0)	3.0	2.0	75	91 : 9
12	$EtAlCl_2$ (2.0)	-[e]	2.0	96	90 : 10
13	$ZnCl_2$ (1.0)	3.0	2.0	56	93 : 7
14	$ZnCl_2$ (1.0)	-[e]	2.0	44	90 : 10
15	TBDMSOTf (1.0)	3.0	2.0	43	84 : 16
16	TBDMSOTf (1.0)	-[e]	2.0	88	90 : 10
17	$Yb(OTf)_3$ (1.0)	3.0	2.0	39	83 : 17
18	$Yb(OTf)_3$ (1.0)	-[e]	2.0	68	78 : 22

[a] PMP is 4-MeOPh. [b] SKTA + LA reaction time at 0°C. [c] Isolated yields after flash chromatography. [d] As determined on the crude products. [e] A mixture of **13**, **21**, and LA was stirred at room temperature for 15 h.

In the case of the (E) configurated alkyl substituted SKTA the *trans* stereoselectivity of the $TiCl_4$ promoted reaction increases with increasing size of the R residue, the **t** : **c** ratios passing from 87 :13 when R = Me (entry 5, Table 1) to 94 : 6 when R = Et, and becoming >98 : 2 when R = i-Pr. In the case of the oxygen substituted SKTA **17** and **18**, the reactions of differently enriched (E)/(Z) isomeric mixtures were studied.[16] In both cases one of the two SKTA was found to be slightly less reactive than the other, namely the (E) isomer of **17** and the (Z) isomer of **18**.[17] The **t** : **c** ratio of β-lactams **25t,c** and **26t,c** do not correlate to the stereoisomeric composition of the starting SKTA, stereorandom reactions being observed with both (E) and (Z) derivatives.[17]

The reaction of SKTA **13** with other imines was also studied in order to establish scope and limitation of the process (Table 4). As can be seen from the reported data only aromatic and heteroaromatic imines **27-29** reacted with **13** in the presence of $TiCl_4$ or $EtAlCl_2$, the corresponding β-lactams **31-33** being obtained in moderate to good yields and low to fair stereoselectivities. Other LA were less effective. While the use of cinnamaldehyde and α-methylcinnamaldehyde derived imines was totally unsuccessful with a variety of different LA, the aliphatic

Table 3. Synthesis of β-Lactams **23t,c-26t,c** by Reaction of SKTA **14**, **15**, **17**, and **18** with Imine **21**.[a]



14, 15, 17, 18 **23t - 26t** **23c - 26c**

SKTA	R	(E)/(Z) ratio[b]	LA	Product	Yield%[c]	t : c ratio[d]
14	Et	>98/ 2	$TiCl_4$	**23t,c**	63	94 : 6
14	Et	>98/ 2	$TiCl_4$[e]	**23t,c**	13	>98 : 2
14	Et	>98/ 2	$BF_3{\cdot}OEt_2$	**23t,c**	41	88 : 12
14	Et	>98/ 2	$EtAlCl_2$[f]	**23t,c**	65	96 : 4
15	i-Pr	>98/ 2	$TiCl_4$	**24t,c**	80	>98 : 2
15	i-Pr	>98/ 2	$TiCl_4$[e]	**24t,c**	27	>98 : 2
17	BnO	90/10	$TiCl_4$[e]	**25t,c**	66	79 : 21
17	BnO	40/60	$BF_3{\cdot}OEt_2$	**25t,c**	90	55 : 45
17	BnO	40/60	$EtAlCl_2$[f]	**25t,c**	55	47 : 53
17	BnO	40/60	TBDMSOTf[g]	**25t,c**	55	55 : 45
17	BnO	>98/ 2	TBDMSOTf[g]	**25t,c**	47	50 : 50
18	TBDPSO	96/ 4	$BF_3{\cdot}OEt_2$	**26t,c**	46	50 : 50
18	TBDPSO	96/ 4	$EtAlCl_2$[f]	**26t,c**	32	50 : 50
18	TBDPSO	<2/98	$EtAlCl_2$[f]	**26t,c**	20	38 : 62

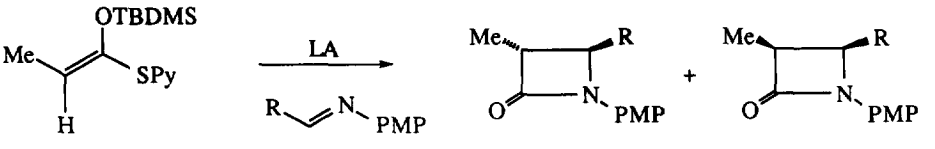
[a] In the conditions of entry 5, Table 2, unless otherwise stated. [b] Of SKTA at the beginning of the reaction. [c] Isolated yields after flash chromatography. [d] Of the crude products. [e] In the conditions of entry 7, Table 2. [f] In the conditions of entry 11, Table 2. [g] In the conditions of entry 16, Table 2.

imine **30** reacted with **13** in the presence of TBDMSOTf to afford a low excess of *cis* β-lactam **34c** over its *trans* isomer **34t**, in good yield. The use of $TiCl_4$ or $EtAlCl_2$ to promote the reaction of **30** resulted in extensive imine decomposition and in the formation of N-(4-methoxyphenyl)propionamide.

Many factors must be taken into account when attempting a rationalization of the stereochemical outcome of these reactions. First of all, a distinction should be made between configurationally stable SKTA **13-15**, that were obtained exclusively in the (E) configuration, and SKTA **17** and **18**, that are available as (E) and (Z) isomers. Another important factor is the chelating or non-chelating[18] nature of the LA employed.

In the case of the condensation of (E)-SKTA **13-15** with (E)-imines[19] in the presence of non-chelating $BF_3{\cdot}OEt_2$ and TBDMSOTf, antiperiplanar[20] models **A** and **B** can be used to explain the formation of*trans* and*cis* products, respectively (Figure 1).[21] In both models the SKTA are depicted in the "pin-wheel" conformation suggested by 2D-NOESY experiments.[12] Although the reason of the *trans* stereoselection does not clearly emerge from a comparison of **A** and **B**, it seems likely that the Ar/SPy steric interaction present in **B** is more destabilizing than the Ar/OTBDMS one featured by **A**.

Table 4. Synthesis of β-Lactams **31t,c-34t,c** from SKTA **13** and Imines **27-30**.[a]



13 **27-30** **31t -34t** **31c -34c**

Imine	R	LA	β-Lactam	Yield %[b]	t : c ratio[c]
27	4-MeOPh	$TiCl_4$	**31t,c**	38	70 : 30
27	4-MeOPh	$EtAlCl_2$	**31t,c**	64	83 : 17
28	2-Furyl	$TiCl_4$	**32t,c**	78	78 : 22
28	2-Furyl	$EtAlCl_2$	**32t,c**	49	83 : 17
29	2-Thienyl	$TiCl_4$	**33t,c**	29	67 : 33
29	2-Thienyl	$EtAlCl_2$	**33t,c**	88	78 : 22
30	c-C_6H_{11}	TBDMSOTf	**34t,c**	73	30 : 70

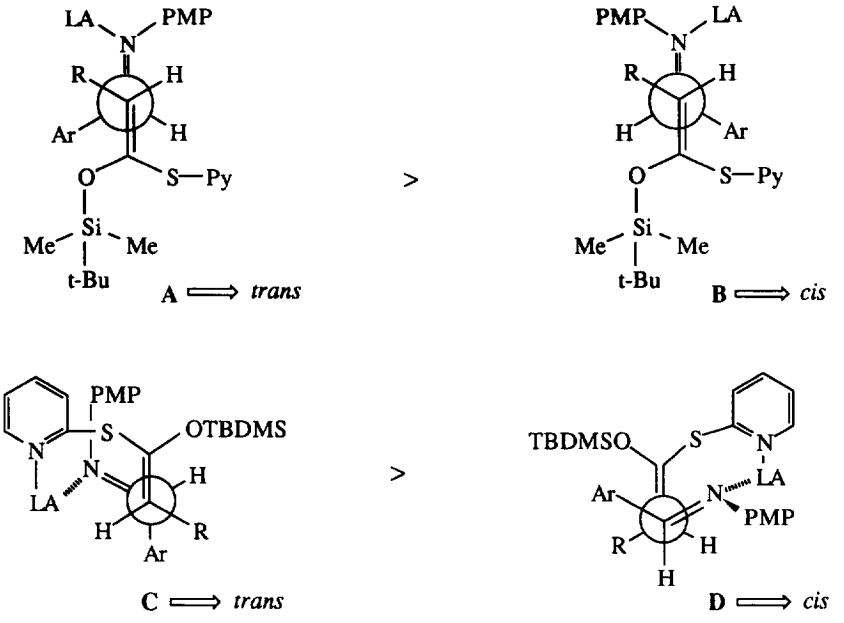
[a] Reaction conditions: $TiCl_4$, entry 5 of Table 2; $EtAlCl_2$, entry 11 of Table 2; TBDMSOTf, entry 16 of Table 2.
[b] Isolated yields after flash chromatography. [c] Determined on the crude products.

When chelating $TiCl_4$ and $EtAlCl_2$ were employed, co-ordination of the LA to the pyridine nitrogen can occur. This was indicated by 300 MHz ^1H NMR analysis of a CD_2Cl_2 solution of equimolar amounts of SKTA **13** and $TiCl_4$ cooled at 0°C.[22] Therefore, models of stereoselection in this case must involve LA co-ordination to both the imine and the pyridine nitrogens, as in **C** and **D** (Figure 1). Model **C**, that leads to the *trans* β-lactam, seems favored over model **D** since it can accommodate the imine Ar residue in a sterically less demanding position. The preferential formation of *trans* products and the increase of stereoselection observed with increasing size of the SKTA residue R can be nicely explained by these models.

The proposal of models of stereoslection for the reactions of SKTA **17** and **18** was not attempted since these compounds can react both as (E) and (Z) isomers. In addition to that, the oxygenated substituent at can provide another site of chelation for the LA, thus giving rise other reacting conformations. However, when non-chelating LA were employed, models **A** and **B**, or their analogues in which (Z)-SKTA are involved, can be used to explain the steric course of the reaction.

Finally, the adduct obtained by reaction of $BCl_3{\cdot}Me_2S$ with (1R,2S)-N-methylephedrine, that has been recently employed in an enantioselective β-lactam synthesis,[4] was tested as a chiral Lewis acid. Reaction of thisadduct with **13** for 3 h at 0°C, followed by addition of imine **21** afforded β-lactam **22t,c** in a satisfactory 86% yield, but with poor control of both relative and absolute stereochemistry. Indeed, the product was obtained as a 58 : 42 mixture of (-)-(3R,4S)-**22t** and (-)-(3S,4S)-**22c** isomers, having 50 and 24% e.e., respectively.[4,23] Unfortunately, the use of the same chiral LA in the reactions of other SKTA was disappointing; for this purpose new chiral promoters for this condensation are under active investigation in our laboratories.

Figure 1. Models of Stereoselection for the Synthesis of β-Lactams from (E)-SKTA 13-15 and (E)-Aromatic Imines.



Experimental.

^{1}H NMR spectra were obtained at 80 and 300 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. CH_2Cl_2 and DMF were distilled from CaH_2; THF and Et_2O from $LiAlH_4$; Et_3N from KOH. $TiCl_4$ was used as 1M solution in CH_2Cl_2; $EtAlCl_2$ as a 1M solution in hexanes; BF_3·OEt_2 was used neat.

The imines were prepared by stirring a CH_2Cl_2 solution of freshly distilled aldehyde and 4-methoxyaniline at rt (2 - 12 h) in the presence of $MgSO_4$. Filtration and evaporation of the solvent at rt gave the crude products that were used as such, with the exception of the products derived from benzaldehyde and 2-thienylcarbaldehyde that were crystallized before use.[19]

Thioesters **1-9** are known compounds.[1a,1b,1f] **S-2-Pyridyl (N,N-diphenylmethylamino)thio acetate 10** was prepared as follows.[24] A mixture of N,N-dibenzylglycine (2 mmol, 510 mg), PPh_3 (2.6 mmol, 681 mg), and dipyridyldisulfide (2.4 mmol, 528 mg) in CH_2Cl_2 (10 mL) were stirred overnight at rt in the presence of 1 g of pulverized 4A molecular sieves. The reaction mixture was filtered through celite, and the filtrate was washed with a sat. aqueous solution of Na_2CO_3, and then with water. The organic phase was dried, concentrated *in vacuo*, and the residue was purified by flash chromatography with a 60 : 40 hexanes : Et_2O mixture as eluant, to afford compound **10** (613 mg, 88% yield) as a yellow thick oil. IR: 3030, 2805, 1710, 1575, 1450, 1420, 1080 cm^{-1}. ^{1}H NMR: δ 7.20-8.60 (m, 14H); 3.78 (s, 4H); 3.45 (s, 2H). Anal Calcd for: $C_{21}H_{20}N_2OS$: C, 72.38; H, 5.78; N, 8.04. Found: C, 72.49; H, 5.69; N, 8.00.

Silylketene thioacetals **11-20** were prepared following the described procedure[7] in the yields and diastereoisomeric ratios reported in Table 1. Compounds **11**,[8a] **13**,[7] **14**,[8a,b] and **15**[8b] are known, but only

selected ^1H NMR data of **13-15** have been reported. All SKTA were oils that were purified by flash chromatography on a short column of silica gel with the hexanes : Et_2O eluting mixtures indicated in parentheses after the name of the compound. With the exception of **11**, the products were chemically stable enough to be stored for several weeks at -15°C in the dark. The infrared data and elemental analyses here reported refer to diastereoisomeric mixtures. Selected ^1H NMR data ($CDCl_3$) are in ppm downfield from Me_4Si, and are listed in this order: HC-3 of the pyridine ring, HC-2, relevant proton(s) of the substituent at C-2.

2-[[1-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-ethenyl]thio]pyridine 11 (70:30). IR: 2920, 1610, 1575, 1455, 1250, 1185 cm^{-1}. ^1H NMR: δ 7.30 (d, J=7.0 Hz); 4.83 (d, 2H, J=31.5 Hz). This compound was very unstable and the elemental analysis was not obtained.

2-[[1-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-2-methylpropenyl]thio]pyridine 12 (70:30). IR: 2930, 1650, 1560, 1460, 1420, 1260, 1175 cm^{-1}. ^1H NMR: δ 7.33 (d, J=7.0 Hz); 1.90 and 1.85 (2s, 3H each, Me_2-C). Anal Calcd for $C_{15}H_{25}NOSSi$: C, 60.96; H, 8.53; N, 4.74. Found: C, 61.01; H, 8.54; N, 4.69.

(E)-2-[[1-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-but-1-enyl]thio]pyridine 14 (70:30). IR: 2930, 1630, 1575, 1450, 1420, 1260, 1175 cm^{-1}. ^1H NMR: δ 7.33 (d, J=7.0 Hz); 5.39 (t, J=7.0 Hz); 2.20 (dq, 2H, J=7.0, 6.5 Hz, *CH*$_2$-Me). Anal Calcd for $C_{15}H_{25}NOSSi$: C, 60.96; H, 8.52; N, 4.74. Found: C, 61.11; H, 8.64; N, 4.65.

(E)-2-[[1-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-3-methylbut-1-enyl]thio]pyridine 15 (70:30). IR: 2960, 1625, 1575, 1460, 1260 cm^{-1}. ^1H NMR: δ 7.30 (d, J=7.0 Hz); 5.25 (d, J=9.0 Hz); 2.75 (m, 1H, J=9.0, 6.5 Hz, *CH*-Me_2). Anal Calcd for $C_{16}H_{27}NOSSi$: C, 62.08; H, 8.78; N, 4.52. Found: C, 62.16; H, 8.88; N, 4.46.

(R),(E)- and (R),(Z)-2-[[1-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-3-[[(1,1-dimethylethyl)dimethylsilyl]oxy]methylbut-1-enyl]thio]pyridine 16 (75:25). IR: 2930, 1630, 1575, 1450, 1420, 1255 cm^{-1}. ^1H NMR of the (E) isomer: δ 7.30 (d, J=7.0 Hz); 5.47 (d, J=8.0 Hz); 4.83 (dq, 1H, J=8.0, 6.6 Hz, *CH*-Me); of the (Z) isomer: δ 7.31 (d, J=7.0 Hz); 5.43 (d, J=8.5 Hz); 4.83 (dq, 1H, J=8.5, 6.6 Hz, *CH*-Me). Anal Calcd for $C_{21}H_{39}NO_2SSi_2$: C, 59.24; H, 9.23; N, 3.29. Found: C, 59.11; H, 9.11; N, 3.33. The 91 : 9 mixture of (E) and (Z) isomers had $[\alpha]_D^{23}$-28.4 (c 1.0, $CHCl_3$).

(E)- and (Z)-2-[[1-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-2-phenylmethoxyethenyl]thio] pyridine 17 (70:30). IR: 2930, 1650, 1575, 1450, 1420, 1255, 1150 cm^{-1}. ^1H NMR of the (E) isomer: δ 7.33 (d, J=7.0 Hz); 6.53 (s); 4.86 (s, 2H, O*CH*$_2$-Ph); of the (Z) isomer: δ 7.33 (d, J=7.0 Hz); 6.16 (s); 4.83 (s, 2H, O*CH*$_2$-Ph). Anal Calcd for $C_{20}H_{27}NO_2SSi$: C, 64.30; H, 7.28; N, 3.75. Found: C, 64.16; H, 7.33; N, 3.81.

(E)- and (Z)-2-[[1-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-2-[[(1,1-dimethylethyl)diphenylsilyl]oxy]ethenyl]thio]pyridine 18 (60:40). IR: 2960, 1655, 1575, 1475, 1430, 1265, 1205 cm^{-1}. ^1H NMR of the (E) isomer: δ 7.30 (d, J=7.0 Hz); 6.65 (s); of the (Z) isomer: δ 7.31 (d, J=7.0 Hz); 6.33 (d, J=8.5 Hz). Anal Calcd for $C_{29}H_{39}NO_2SSi_2$: C, 66.74; H, 7.53; N, 2.68. Found: C, 66.66; H, 7.44; N, 2.60.

(E)- and (Z)-2-[[1-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-2-phenylthioethenyl]thio]pyridine 19 (60:40). IR: 2930, 1650, 1575, 1450, 1420, 1255, 1125 cm^{-1}. ^1H NMR of the (E) isomer: δ 7.33 (d, J=7.0 Hz); 6.20 (s); of the (Z) isomer: δ 7.33 (d, J=7.0 Hz); 5.96 (s). Anal Calcd for $C_{19}H_{25}NOS_2Si$: C, 60.75; H, 6.71; N, 3.73. Found: C, 60.55; H, 6.85; N, 3.75.

(E)- and(Z)-2-[[1-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-2-(*N*,*N*-diphenylmethylamino) ethenyl]thio]pyridine 20 (70:30). IR: 2930, 1635, 1575, 1450, 1415, 1255, 1075 cm^{-1}. ^1H NMR of the (E) isomer: δ 7.33 (d, J=7.0 Hz); 6.06 (s); 4.34 (s, 4H, N*CH*$_2$-Ph); of the (Z) isomer: δ 7.33 (d, J=7.0 Hz);

6.00 (s); 4.03 (s, 4H, NCH_2-Ph). Anal Calcd for $C_{27}H_{34}N_2OSSi$: C, 70.08; H, 7.41; N, 6.05. Found: C, 70.14; H, 7.50; N, 6.13.

General Procedure for the Synthesis of β-Lactams. To a stirred 0.1 M solution of SKTA (1 mmol) in dry CH_2Cl_2 (10 mL) cooled at 0°C, the LA (1 mmol) was added dropwise. The solution was stirred at 0°C for 3 h, and then a 0.5 M solution of an imine (2 mmol) in dry CH_2Cl_2 (4 mL) was added *via* a cannula.The reaction was allowed to warm-up to room temperature and stirred overnight. Work-up involved addition of a sat. aqueous solution of $NaHCO_3$ (10 mL), filtration through celite, extraction of the aqueous phase with 3x20 mL portions of CH_2Cl_2, drying of the organic phase over sodium sulphate, filtration, and concentration *in vacuo*, to give the crude product. ^1H NMR analysis of the residue was then performed to evaluate the *trans/cis* ratio. The product was then isolated by flash chromatography with hexanes : Et_2O mixtures as eluant. Yields and diastereoisomeric ratios are reported in Tables 2-4. **22**,[1e] **23**,[1e] **24**,[1e] **25**,[3] **32**,[8] and **33**[8] are known.

3-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]-1-(4-methoxyphenyl)-4-phenylazetidin-2-one 26 was purified with a 80 : 20 hexanes : Et_2O mixture as eluant. The *trans* : *cis* mixture was a thick oil. IR: 1755 cm^{-1}. Selected ^1H NMR data of **26t**: δ 4.80 (d, 1H, J = 2.0 Hz); 4.67 (d, 1H, J = 2.0 Hz). Of **26c**: δ 5.10 (d, 1H, J = 5.5 Hz); 4.93 (d, 1H, J = 5.5 Hz). Anal Calcd for $C_{32}H_{33}NO_3Si$: C, 75.71; H, 6.54; N, 2.76. Found: C, 75.58; H, 6.51; N, 2.84.

1,4-Di-(4-methoxyphenyl)-3-methylazetidin-2-one 31 was purified with a 60 : 40 hexanes : Et_2O mixture as eluant. The *trans* : *cis* mixture was a low melting material. IR: 1755 cm^{-1}. Selected ^1H NMR data of **31t**: δ 4.48 (d, 1H, J = 2.0 Hz); 3.76 and 3.70 (2s, 3H each); 3.05 (dq, 1H, J = 2.0, 7.0 Hz); 1.40 (d, 3H, J = 7.0 Hz). Of **31c**: δ 5.08 (d, 1H, J = 5.5 Hz); 3.84 and 3.79 (2s, 3H each); 3.50 (dq, 1H, J = 5.5, 7.0 Hz); 0.85 (d, 3H, J = 7.0 Hz). Anal Calcd for $C_{18}H_{19}NO_3$: C, 72.71; H, 6.44; N, 4.71. Found: C, 72.53; H, 6.37; N, 4.80.

4-Cyclohexyl-1-(4-methoxyphenyl)-3-methylazetidin-2-one 34 was purified with a 60 : 40 hexanes : Et_2O mixture as eluant. The *trans* : *cis* mixture was a thick oil. IR: 1755 cm^{-1}. Selected ^1H NMR data of **34t**: δ 3.77 (s, 3H); 3.57 (dd, 1H, J = 2.2, 5.2 Hz); 3.05 (dq, 1H, J = 2.2, 7.5 Hz). Of **34c**: δ 3.90 (dd, 1H, J = 5.0, 6.0 Hz); 3.76 (s, 3H); 3.38 (dq, 1H, J = 5.0, 7.5 Hz). Anal Calcd for $C_{17}H_{23}NO_2$: C, 74.69; H, 8.48; N, 5.12. Found: C, 74.83; H, 8.37; N, 5.18.

Enantioselective Synthesis of 22t,c. To a stirred solution of SKTA **13** (0.8 mmol, 224 mg) in dry CH_2Cl_2 (4 mL) cooled at 0°C the BCl_3/N-methylephedrine adduct (0.8 mmol)[4] in CH_2Cl_2 (1 mL) was added. After 3 h stirring at 0°C, imine **21** (0.4 mmol, 85 mmol) in CH_2Cl_2 (1 mL) was added, and the reaction was allowed to warm up to room temperature overnight. The above described work-up followed by flash chromatography afforded 183 mg (86% yield) of a 58 : 42 mixture of **22t** and **22c**. The separated products were subjected to ^1H NMR analysis in the presence of Eu(hfc)$_3$ in conditions pre-established on racemic samples. (3R,4S)-**22t** , $[\alpha]_D^{23}$ -26.3 (c 1, $CHCl_3$), m.p. 97°C, had e.e. 50%; (3S,4S)-**22c** , $[\alpha]_D^{23}$ -44.3 (c 0.5, $CHCl_3$), m.p. 112°C, had e.e. 24%.

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13. By analogy with **14-16** the (E) configuration was assigned also to compound **13**. This assignment is in agreement with that of Hirai, *et al.* (ref.7), that used the (Z) descriptor for (E) **13** .
14. *Trans* : *cis* ratios were determined by 300 MHz ^{1}H NMR analysis of the crude reaction mixtures. The assignment resided on the value of the β-lactam HC-3/HC-4 coupling constant (J *trans* = 2.0-2.5 Hz; J *cis* = 5.0-6.0 Hz).
15. In this case the use of 2.0 mol. equiv. of LA gave better results (see entries 10-12, Table 2).
16. SKTA **17** and **18** were shown to be configurationally stable at 0°C in the dark in the presence of TBDMSOTf, thus showing that the LA does not promote (E)/(Z) isomerization.
17. For an anologous observation on the different reactivity of related SKTA see: Kobayashi, S.; Horibe, M.; Hachiya, I. *Tetrahedron Lett.* **1995**, *36*, 3173; and references cited therein.
18. For leading references to the concept of chelation see: Reetz, M.T. *Acc. Chem. Res.* **1993**, *26*, 462.
19. Imines of aromatic aldehydes are known to exist and react in the (E) configuration, while those of aliphatic aldehydes generally exist as mixtures of (E) and (Z) isomers. For a review see: McCarty, C.G. in: *"The Chemistry of the C-N Double Bond"*, Patai, S.; Ed.; Interscience, New York, 1970; chapter 9, pp 363-464. Aromatic imines such as **21** and **28** were shown not to isomerize even in the presence of strong LA (see ref. 1 and 4).
20. Antiperiplanar transition states have been found to be preferred over their synclinal counterparts in a intramolecular LA catalyzed aldol condensation: Denmark, S.E.; Lee, W. *J. Org. Chem.* **1994**, *59*, 707.
21. Models analogous to **A** and **B** are generally used to explain the simple *anti* stereoselectivity of Mukaiyama aldol condensations (see ref.9). For instance, they have been recently propose to rationalize the LA promoted addition of SKTA **13** to benzaldehyde (see ref.8b).
22. $TiCl_4$ is known to co-ordinate the pyridine nitrogen of 2-pyridylthioesters (see ref.1). When $TiCl_4$ was added to SKTA **13** the signals of the pyridine hydrogens were shifted downfield as follows: HC-3 from 7.23 to 7.86 ppm; HC-4 from 7.54 to 8.22 ppm; HC-5 from 6.98 to 7.72 ppm; HC-6 from 8.41 to 8.80 ppm. The Me and vinyl proton signals remained unchanged, as did the spectrum of the mixture after 3 h at 0°C. Thus, in these conditions neither a titanium enolate (ref. 1) is formed, nor SKTA **13** isomerizes.
23. These e.e. are slightly higher than those observed in the synthesis of **22t,c** by condensation of the enolate of 2-pyridylthiopropionate **3** with imine **21** in the presence of the BCl_3/N-methylephedrine adduct. The configuration of optically active **22t** and **22c** has been determined as described in ref. 4b.
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