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Solvent-Free, One-Pot Synthesis of β-Lactams by the $Sc(OTf)_3$-Catalyzed Reaction of Silyl Ketene Thiocetals with Imines

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Dedicated to Professor Donato Pocar on the occasion of his 70th birthday

Keywords: Synthetic methods / Lactams / Scandium triflate / Solvent-free conditions / Catalysis

A solvent-free, catalytic, one-pot synthesis of β-lactams is described. The reaction involves the reaction between silyl ketene thioacetals derived from 2-pyridyl thioesters and imines at room temperature in the presence of catalytic amounts of $Sc(OTf)_3$ and in the absence of solvent. Extension of this procedure to the synthesis of an enantiomerically pure azetidinone, a precursor of industrially relevant bioactive β-lactams, is also reported.

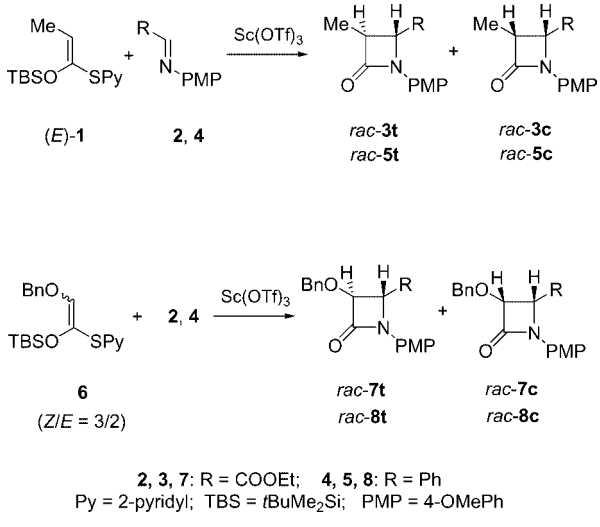
Introduction

It has recently been demonstrated that the global cost of a reaction mostly depends on the total mass of chemicals employed in the transformation.[1] Among the strategies envisaged to cut reaction costs, the elimination of solvent and the switch from stoichiometric to catalytic processes have been recognized as very promising. Therefore, the identification of catalytic procedures that can be run under solvent-free conditions is particularly attractive for the development of environmentally friendly and economically advantageous chemical processes.

Herein we report an example of a one-pot synthesis of a class of compounds as important as the β-lactams[2] carried out in the presence of catalytic amounts of scandium(III) triflate and in the absence of solvent. An application of this protocol to the stereoselective synthesis of a precursor of the biologically active and industrially relevant azetidinones of the thienamycin family is also described.

Results and Discussion

The reaction between 2.0 mol-equiv. of silyl ketene thioacetal (SKTA) **1**, readily obtained as a single (*E*) isomer from 2-pyridyl thiopropanoate,[3] and the *N*-(4-methoxyphenyl) imine of ethyl glyoxylate **2** carried out in the presence of $Sc(OTf)_3$[4] (0.1 mol-equiv.) for 20 h at room temperature in the absence of solvent afforded a 50:50 mixture of *trans*-β-lactam **3t** and its *cis* diastereoisomer **3c**, as determined by 300-MHz ^{1}H-NMR analysis of the crude reaction mixture (Scheme 1).[5] In addition to the products, the ^{1}H-NMR spectrum showed the presence of unreacted SKTA **1** and of the β-amino thioester precursors of the azetidinones. No traces of the imine could be detected indicating that the reaction proceeded with a high conversion. Flash chromatographic purification of the reaction mixture diluted in dichloromethane (1 mL/g of the crude material) and not otherwise worked-up allowed β-lactams **3t** and **3c** to be isolated in 71% combined yield.[6]



Scheme 1. Synthesis of β-lactams **3**, **5**, **7** and **8**.

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With the goal of eliminating the need for chromatographic purification of the products, which are oily materials and therefore cannot be isolated by crystallization, reduction of the amount of SKTA **1** employed in the reaction was attempted. However, the use of 1.0 and 1.5 mol-equiv. of **1** resulted in lower chemical yields of **3t**,**c** (40 and 55%, respectively) and flash chromatography was still needed to obtain product samples >95% pure by ^{1}H NMR spectroscopy.[7] Therefore a 2:1 molar ratio of the SKTA and the imine was employed in subsequent experiments when the reaction was extended to the benzaldehyde-derived imine **4** and the benzyloxy-substituted SKTA **6** (Scheme 1).

The combination of SKTA **1** and imine **4** afforded the corresponding β-lactams **5t** and **5c** in 70% isolated yield as a 70:30 mixture of *trans*/*cis* isomers which were separated by flash chromatography. Reaction of SKTA **6**[3] with imine **2** allowed β-lactams **7t** and **7c** to be obtained in 45% yield. The ratio of the separable *trans*/*cis* isomers was 50:50. Finally, compounds **8t** and **8c** were synthesized as a 67:33 separable mixture of *trans*/*cis* isomers by reaction of SKTA **6** with imine **4** in 48% yield.

The different diastereoselectivities in which the β-lactams were obtained deserves some comment. A few assumptions were made in proposing models of stereoselection to account for the observed diastereoisomeric ratios of the products **3** and **5**.[8] First, the reaction was considered to proceed through an antiperiplanar transition structure which was experimentally found to be preferred over its synclinal counterpart in the mechanistically related Lewis acid catalyzed addition of silyl ketene acetals to aldehydes.[9] Secondly, SKTA **1** has been depicted in the so-called "pinwheel" conformation, which was experimentally demonstrated to be adopted both in solution and in the crystalline state by very similar SKTAs.[3,10] Furthermore, in the case of the reaction leading to compound **3**, it seems reasonable that imine **2** should react in a chelated conformation with $Sc(OTf)_3$ with coordination through the imine nitrogen and the carbonyl oxygen atoms.[4]

As can be seen by inspection of models **A** and **B** reported in Figure 1, each transition structure features a different pair of steric interactions: Model **A**, leading to **3c**, involves a Me/PMP and a COOEt/SPy interaction; model **B**, leading to **3t**, involves a Me/COOEt and a COOEt/OTBS interaction. It seems possible that, as a whole, each pair destabilizes these transition structures to the same extent and thus a nonstereoselective reaction is observed. Comparison of models **A** and **B** also seems to suggest that replacement of the methyl group of SKTA **1** with a much bulkier R residue should steer the reaction towards the formation of a *cis*-configured product because the interaction of a larger R group with the proximal COOEt group would destabilize model **B** much more than the interaction between R and the relatively remote PMP residue would destabilize model **A**. (Indeed, this turned out to be the case, see below.) The moderate *trans* selectivity observed in the reaction involving SKTA **1** and imine **4** can be explained by a comparison between models **C** and **D** (Figure 1), leading to *cis* and *trans* isomers, respectively. If it is assumed that the Me/PMP interaction in **C** is similar to the Me/Ph one in **D**, the latter appears to be favored because of the pin-wheel conformation of the SKTA which should make the Ph/OTBS interaction in **D** less sterically demanding than the Ph/SPy one present in **C**.

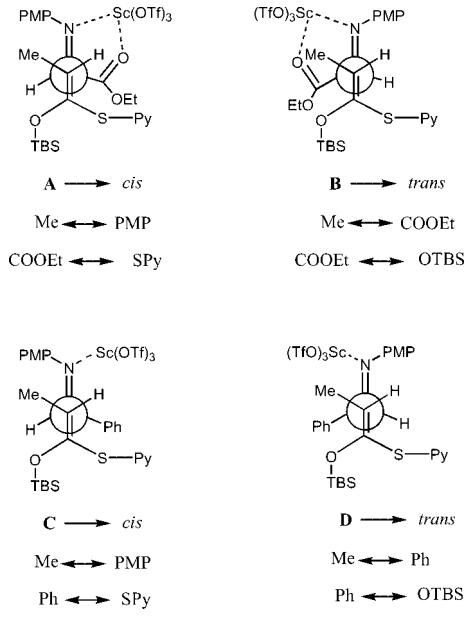


Figure 1. Stereoselective model accounting for the stereoselectivity observed in the generation of products **3** and **5**.

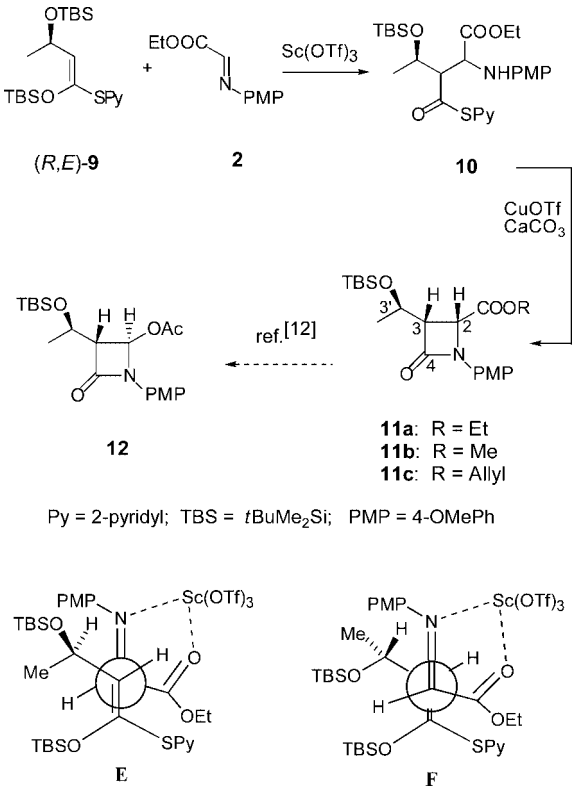
Further improvement to this catalytic, solvent-free protocol was envisaged by the possibility of recycling the Lewis acidic catalyst. However, the use of a commercially available polystyrene-supported scandium(III) triflate in the reaction of SKTA **1** with imine **2** only resulted in very low yields of products **3t**,**c** and of their uncyclized β-amino thioester precursors.[11]

Suspecting that any attempt to separate the catalyst from the reaction mixture would result in its inactivation,[12] it was decided to formally "recycle" the catalyst in situ by adding fresh reagents to the reaction vessel without isolating the products, thus mimicking a continuous flow process. At the end of the first reaction of SKTA **1** with imine **2** in the presence of 10 mol-% $Sc(OTf)_3$, the same amounts of reagents were added and a second reaction was allowed to proceed for the usual 20 h. After three further iterations of this procedure (for a total five reaction cycles and 100 h reaction time) products **3t**,**c** were isolated in 65% yield as a 60:40 mixture of *trans*- and *cis*-β-lactams. Note that the overall yield of these five subsequent reactions was very similar to that observed in a single reaction. The flash chromatographic purification of the product also allowed the isolation of **3t**,**c** contaminated with uncyclized β-amino thioesters in another roughly estimated 25% combined yield of these products.

This in situ recycling procedure can also be regarded as a formal decrease of the amount of catalyst from 10 to 2 mol-%. However, note that when such a low catalyst loading was used to promote the reaction of SKTA **1** and imine **2**, it was discovered that under these conditions imine disap-

pearance and formation of the intermediate β-amino thioesters were fast, but ring closure of the latter to the azetidinones **3t**,**c** was very slow, even after a reaction time of 48 h. Thus, in this β-lactam synthesis the scandium(III) catalyst seems to play a dual role, activating the imine towards attack of the carbon nucleophile[4] and promoting the ring-closing step.[13] However, the latter activity can be exerted only if the catalyst's concentration is sufficiently high.

Finally, application of this protocol to the stereoselective synthesis of a precursor of the biologically active and industrially relevant β-lactams of the thienamycin family was attempted (Scheme 2). In this context, it is important to remember that these compounds must feature the (3*S*,3′*R*) configuration in order to display biological activity (see Scheme 2 for numbering). Although the control of the stereochemistry at C-3′ can be easily secured by selecting a derivative of the inexpensive (*R*)-3-hydroxybutanoic acid as the precursor of the SKTA, it is important that the reaction with the imine proceeds highly stereoselectively to afford a product with the *anti* relative configuration at C-3 and C-3′.



Scheme 2. Stereoselective synthesis of β-lactam **11a**.

Reaction of 1.5 mol-equiv. of (*R*,*E*)-SKTA **9** derived from ethyl (*R*)-3-hydroxybutanoate[3] with imine **2** in the presence of 0.1 mol-equiv. of $Sc(OTf)_3$ for 20 h at room temperature in the absence of solvent afforded β-amino thioester **10** and very minor amounts of the corresponding β-lactam **11a**, as determined by NMR analysis of the crude reaction product obtained after aqueous work up of the reaction. Attempts to promote the ring-closure step by increasing the amount of catalyst employed to up to 0.3 mol-equiv. of $Sc(OTf)_3$ or by prolonging the reaction times to up to 96 h were unsuccessful; the use of higher reaction temperatures led to extensive product decomposition. Also note that the reaction did not proceed beyond the β-amino thioester stage when it was run in dichloromethane as solvent. In this case, however, the NMR yield of **10** was slightly higher than that observed for the reaction carried out in the absence of solvent.

Transformation of crude **10** into β-lactam **11a** was accomplished by reaction with CuOTf and $CaCO_3$ (refluxing toluene, 2 h) according to a previously reported procedure.[14] The overall yield for the two-step synthesis was 72%. β-Lactam **11a** was obtained as a >95% diastereoisomerically pure isomer, as determined by NMR analysis of the crude product of the ring-closure reaction. This analysis did not show the presence of unreacted **10** along with **11a**, thus ruling out diastereoisomeric enrichment in the ring-closure step. By comparison of the ^1H and ^{13}C NMR spectroscopic data of **11a** with those of virtually identical compounds **11b** (R = methyl) and **11c** (R = allyl) and of some of their stereoisomers, 2,3-*cis*-3,3′-*anti* stereochemistry was assigned to **11a**.[15] Note that the transformation of compound **11c** into 2-acetoxyazetidinone **12** (Scheme 2) has already been accomplished.[15] As **12** is the commonly employed building block for the preparation of many biologically active β-lactams, and most notably for the preparation of the thienamycin family,[2] compound **11a** can be considered a precursor of these industrially relevant derivatives.

A tentative explanation of the stereoselectivity observed in the reaction of SKTA **9** with imine **2** is presented in Scheme 2. On the basis of the exclusive formation of a *cis* product, only transition structures that lead to β-amino ester precursors of 2,3-*cis*-configured β-lactams (that is, transition structures similar to model **A** of Figure 1) were considered. In proposing a model of stereoselection, it seems reasonable to assume that the imine should approach the SKTA from the side of the double bond shielded by the small hydrogen atom at the SKTA's stereocentre, as in models **E** and **F**. As the COOEt/SPy and PMP/H interacting pairs are present in both models, these could be differentiated by considering that the OTBS/OTBS interaction, with both a steric and an electronic component, should destabilize model **F** much more than the purely steric Me/OTBS one should destabilize model **E**, leading to the observed (3*R*,3′*R*)-configured compound.

Conclusions

In conclusion, β-lactams have been obtained by a new protocol involving a catalytic, one-pot reaction carried out in the absence of solvent. The $Sc(OTf)_3$-catalyzed condensation between silyl ketene thioacetals derived from 2-pyridyl thioesters and imines carried out at room temperature led to the formation of azetidinones in fair-to-good yields (45–71%). The procedure was extended to the highly stereo-

selective synthesis of an enantiomerically pure azetidinone precursor of bioactive β-lactams, which was obtained in a two-step procedure.

Experimental Section

General: ^{1}H NMR spectra were recorded at 300 MHz in [D]chloroform ($CDCl_3$) unless otherwise stated and chemical shifts are referenced to tetramethylsilane (TMS, δ = 0.00 ppm). ^{13}C NMR spectra were recorded at 75 MHz and chemical shifts are referenced to $CDCl_3$. (δ = 77.0 ppm). Optical rotations were obtained with a Perkin–Elmer 241 polarimeter at 589 nm. IR spectra were obtained with a Jasco FTIR 4100 type A instrument. Reagents and solvents were used as purchased. SKTA **1**, **6**, and **9** were prepared as described previously.[3] β-Lactams **5**,[3] **7**,[16] and **8**[1] gave NMR spectroscopic data in agreement with those reported in the literature.

General Procedure for the Synthesis of the β-Lactams: The synthesis of ethyl 1-(4-methoxyphenyl)-3-methyl-4-oxoazetidine-2-carboxylate (**3**) is representative of the procedure used in the preparation of the β-lactams. $Sc(OTf)_3$ (0.015 g, 0.03 mmol), imine **2** (0.062 g, 0.3 mmol), and SKTA **1** (0.169 g, 0.6 mmol) were added in this order to a 2 mL glass vial and the resulting dark mixture was stirred for 20 h at room temperature. Dichloromethane (0.25 mL) was then added and the resulting suspension was purified by flash chromatography with a 10:90 AcOEt/hexanes mixture as eluent. The *trans* product **3t** (0.028 g, 35.5% yield) was eluted first as a thick pale yellow oil followed by the *cis* product **3c** (0.028 g, 35.5% yield) which was also a thick pale yellow oil. IR (neat): $\tilde{\nu}$ = 3053, 2986, 1751, 1633, 1513, 1265, 737 cm^{-1}. ^{1}H NMR ($CDCl_3$) for **3t**: δ = 1.30 (t, J = 6.7 Hz, 3 H, Me of ethyl group), 1.50 (d, J = 7.0 Hz, 3 H, 3-Me), 3.35 (dq, J = 2.0, 7.0 Hz, 1 H, 3-H), 3.80 (s, 3 H, MeO), 4.10 (d, J = 2.0 Hz, 1 H, 2-H), 4.25 (q, J = 6.7 Hz, 2 H, CH_2 of ethyl group), 6.85 (B part of AB system, J = 9.0 Hz, 2 H, aromatic protons), 7.24 (A part of AB system, J = 9.0 Hz, 2 H, aromatic protons) ppm. ^{13}C NMR ($CDCl_3$): δ = 13.3, 14.1, 50.3, 55.5, 58.5, 61.8, 114.4, 117.8, 131.2, 156.3, 166.2, 169.9 ppm. ^{1}H NMR ($CDCl_3$) for **3c**: δ = 1.30 (m, 6 H, 3-Me and Me of ethyl group), 3.65 (dq, J = 5.8, 7.0 Hz, 1 H, 3-H), 3.77 (s, 3 H, MeO), 4.25–4.35 (m, 2 H, CH_2 of ethyl group), 4.55 (8 d, J = 5.8 Hz, 1 H, 4-H), 6.85 (B part of AB system, J = 9.0 Hz, 2 H, aromatic protons), 7.24 (A part of AB system, J = 9.0 Hz, 2 H, aromatic protons) ppm. ^{13}C NMR ($CDCl_3$): δ = 10.0, 14.2, 47.8, 55.4, 55.8, 61.6, 114.3, 117.9, 131.1, 156.3, 166.0, 168.8 ppm. $C_{14}H_{17}NO_4$ (263.12): calcd. C 63.86, H 6.51, N 5.32; found C 63.74, H 6.55, N 5.46.

Formal Procedure for "Recycling" of the Catalyst in the Synthesis of β-Lactam 3: $Sc(OTf)_3$ (0.015 g, 0.03 mmol), imine **2** (0.062 g, 0.3 mmol), and SKTA **1** (0.169 g, 0.6 mmol) were added in this order to a 5 mL round-bottomed flask and the resulting dark mixture was stirred for 20 h at room temperature. After ^{1}H NMR analysis of a sample of the crude product showed complete conversion of the imine, imine **2** (0.062 g, 0.3 mmol) and SKTA **1** (0.169 g, 0.6 mmol) were again added in this order. This procedure was iterated four times. After a total reaction time of 100 h, dichloromethane (1.25 mL) was then added and the resulting suspension was purified by flash chromatography with a 10:90 AcOEt/hexanes mixture as eluent. Products **3t**,**c** were isolated in 65% yield as a 60:40 mixture of *trans*- and *cis*-β-lactams.

Ethyl (3′*R*,3*S*,2*R*)-3-{1-[(*tert*-Butyl)dimethylsilyloxy]ethyl}-1-(4-methoxyphenyl)-4-oxoazetidine-2-carboxylate (11a): $Sc(OTf)_3$ (0.016 g, 0.033 mmol), imine **2** (0.068 g, 0.33 mmol), and SKTA **9** (0.212 g, 0.5 mmol) were added in this order to a 2 mL glass vial and the resulting dark mixture was stirred for 20 h at room temperature. Dichloromethane (2.0 mL) was then added and the resulting suspension was extracted twice with water (2 × 1 mL). The separated organic layer was dried with Na_2SO_4, filtered, and concentrated under vacuum to afford the crude β-amino thioester **10**. A suspension of Cu^{I}OTf–½ toluene complex (0.186 g, 0.36 mmol) in dry toluene (3 mL) was slowly added over a period of 1 h to a refluxing suspension of the latter and $CaCO_3$ (0.060 g, 0.6 mmol) in dry toluene (2 mL) under nitrogen. The reaction was stirred for 60 min, cooled to room temperature, and quenched by the addition of phosphate buffer (pH 7, 3 mL). AcOEt (2 mL) was added and the organic layer was separated. The aqueous phase was extracted once again with EtOAc (3 mL) and the combined organic phases were dried with Na_2SO_4, filtered, and concentrated under vacuum to afford the crude product. This was purified by flash chromatography with a 20:80 EtOAc/hexanes mixture as eluent to afford the product **11a** as a thick pale yellow oil in 72% overall yield (0.134 g). IR (neat): $\tilde{\nu}$ = 3019, 1753, 1514, 1215, 759 cm^{-1}. $[\alpha]_D^{23}$ = 30.9 (c = 0.36, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 0.04 (s, 3 H, Me of TBS group), 0.07 (s, 3 H, Me of TBS group), 0.85 (s, 9 H, *t*Bu of TBS group), 1.25 (t, J = 7.0 Hz, 3 H, Me of ethyl group), 1.38 (d, J = 7.0 Hz, 3 H, 3′-Me), 3.55 (t, J = 6.0, Hz, 1 H, 3-H), 3.77 (s, 3 H, MeO), 4.22 (q, J = 7.0 Hz, 2 H, CH_2 of ethyl group), 4.45 (quint, J = 6.0 Hz, 1 H, 3′-H), 4.58 (d, J = 2.0 Hz, 1 H, 2-H), 6.85 (B part of AB system, J = 9.0 Hz, 2 H, aromatic protons), 7.24 (A part of AB system, J = 9.0 Hz, 2 H, aromatic protons) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.0, 18.0, 22.1, 25.7, 29.7, 54.3, 55.5, 61.3, 65.0, 114.3, 118.2, 131.1, 156.3, 164.0, 168.4 ppm. $C_{21}H_{33}NO_5Si$ (407.56): calcd. C 61.88, H 8.16, N 3.44; found C 62.01, H 8.27, N 3.39.

Acknowledgments

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[1] M. Eissen, J. O. Metzeger, *Chem. Eur. J.* **2002**, *8*, 3580–3588.
[2] For a review on the antibiotic activity of β-lactams, see: a) R. B. Morin, R. Gorman (Eds.), *Chemistry and Biology of β-Lactam Antibiotics*, Academic Press, New York, **1982**, vols. 1–3. β-Lactam chemistry has witnessed a recent resurgence of interest since the discovery that some of these compounds have a strong activity as enzymatic inhibitors. For a collection of papers on this subject, see: b) *Recent Aspects of the Chemistry of β-Lactams, Part II*, in *Tetrahedron (Symposium-in-Print No. 80)*, **2000**, *56*, issue 31.
[3] For the synthesis of these silyl ketene 2-pyridyl thioacetals and their use in the synthesis of β-lactams promoted by stoichiometric amounts of Lewis acids ($TiCl_4$, BF_3·OEt_2, $EtAlCl_2$, $ZnCl_2$, *t*$BuMe_2SiOTf$), see: a) R. Annunziata, M. Cinquini, F. Cozzi, V. Molteni, O. Schupp, *Tetrahedron* **1996**, *52*, 2573–2582. These Lewis acids did not promote the reaction when applied in catalytic amounts. Only the use of $YbOTf_3$ allowed the amount of Lewis acid to be reduced to 0.1 mol-equiv.; b) R. Annunziata, M. Cinquini, F. Cozzi, V. Molteni, O. Schupp, *J. Org. Chem.* **1996**, *61*, 8293–8296. However, $YbOTf_3$ was less effective than $Sc(OTf)_3$ as a catalyst in the solvent-free procedure.
[4] For reviews, see: a) S. Kobayashi, *Synlett* **1994**, 689–701, and references therein; b) S. Kobayashi, H. Ishitani, *Chem. Rev.* **1999**, *99*, 1069–1094, and references therein.

[5] *trans*/*cis* configurations were assigned on the basis of the 2-H/3-H coupling constants values (J_{trans} = 2.0–2.7 Hz; J_{cis} = 5.0–6.0 Hz).
[6] The yield was actually higher because β-lactams contaminated by β-amino thioesters were also obtained. Interestingly, NMR analysis of the crude product of the reaction carried out in dichloromethane showed the same β-lactams/β-amino thioester ratio as observed in the solvent-free process. The yield of isolated β-lactams was 72%.
[7] When hydrolysis of the unreacted SKTA **1** was attempted to avoid chromatographic purification of the product, some β-lactam decomposition was also observed.
[8] Models were proposed only for the reactions involving SKTA **1**, known to exist and react exclusively in the (*E*) configuration (see ref.[3]). The fact that SKTA **6** is a mixture of (*E*) and (*Z*) isomers, likely equilibrating in the presence of the Lewis acidic catalyst (see ref.[3,4]), makes any attempts to rationalize its stereochemical behavior highly speculative.
[9] S. E. Denmark, W. Lee, *J. Org. Chem.* **1994**, *59*, 707–709.
[10] a) C. S. Wilcox, R. E. Babston, *J. Org. Chem.* **1984**, *49*, 1451–1453; b) R. E. Babston, V. Lynch, C. S. Wilcox, *Tetrahedron Lett.* **1989**, *30*, 447–450.
[11] a) S. Kobayashi, S. Nagayama, *J. Org. Chem.* **1996**, *61*, 2256–2257; for a recent application of this catalyst to C–C bond forming reactions, see: b) S. Iimura, K. Manabe, S. Kobayashi, *Tetrahedron* **2004**, *60*, 7673–7678. This supported catalyst also proved to be poorly active when the reaction was run for longer times (up to 96 h) or with a catalyst sample preswelled in organic solvents (dichloromethane, toluene). A more active, but commercially unavailable, supported scandium(III) catalyst has also been reported by professor Kobayashi: c) S. Kobayashi, S. Nagayama, *J. Am. Chem. Soc.* **1996**, *118*, 8977–8978.
[12] Adsorption of $Sc(OTf)_3$ on silica gel or Celite to facilitate catalyst recycling was attempted without success. The possibility of recycling an aqueous solution containing different scandium(III) salts is currently under investigation.
[13] It can be hypothesized that the Lewis acidic catalyst promotes the ring-closing step by coordinating the nitrogen atom of the 2-pyridylthiol residue of the thioester, making it a better leaving group. In agreement with this hypothesis is the observation that, when noncoordinating TMSOTf and TfOH were used to catalyze the reaction of **1** with **2**, the β-amino ester precursors of **3t**,**c** were isolated as the largely predominant products.
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[15] F. Cozzi, R. Annunziata, M. Cinquini, L. Poletti, A. Perboni, B. Tamburini, *Chirality* **1998**, *10*, 91–94. For instance the ^{1}H NMR chemical shift values for the diagnostic protons of **11a**–**11c** are 4.58, 4.58, 4.60 ppm for 2-H, 4.45, 4.43, 4.45 for 3′-H, and 3.55, 3.54, 3.55 ppm for 3-H; the *J* values (in Hz) are 6.0, 6.0, 5.8 Hz for 2-H/3-H and 6.0, 5.0, 5.8 Hz for 3-H/3′-H. Typical $J_{3,3'}$ values for the 2,3-*cis*-3,3′-*syn* products range from 8.0 to 8.5 Hz.
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