Notes

Yb(OTf)$_3$-Catalyzed One-Pot Synthesis of β-Lactams from Silyl Ketene Thioacetals by a Two- or a Three-Component Reaction†

Rita Annunziata, Mauro Cinquini,* Franco Cozzi,* Valentina Molteni, and Olaf Schupp

Centro C.N.R. and Dipartimento di Chimica Organica e Industriale, via Golgi 19, 20133 Milano, Italy

Received May 7, 1996

The Lewis acid (LA)-catalyzed addition of silyl ketene acetals to imines is reported to afford β-amino esters.[1] When this approach is used *en route* to β-lactams, a two-step procedure involving condensation and 2-azetidinone ring closure is therefore required.[1c,h,k]

We[2] and others[3] recently described an one-pot synthesis of β-lactams by condensation of silyl ketene thioacetals (SKTA) derived from 2-pyridyl thioesters with imines[4] carried out in the presence of stoichiometric amounts of LA. We now report that a 10% molar amount of Yb(OTf)$_3$ (OTf = OSO_2CF_3)[1j−m] is able to promote the addition of SKTA to imines in a reaction that represents the first *catalytic* one-step synthesis of β-lactams. An extremely simple three-component version of this process that allows the 2-azetidinone ring formation from a mixture of an aldehyde, an amine, and a SKTA has also been realized.

SKTA **1**−**5**[2] were reacted with 2.0 mol equiv of imines **6**−**10** in the presence of 0.1 mol equiv of Yb(OTf)$_3$[5] to afford mixtures of *trans* (**t**) and *cis* (**c**) β-lactams **11t,c**−**19t,c** (Scheme 1).[6]

Reaction conditions were established studying the condensation of SKTA **1** with imines **6** and **7**. The results, collected in Table 1, show that acetonitrile as solvent secured the best stereoselectivity (Table 1, entries 2 and 7). A better yield can be obtained by either extending the reaction time (Table 1, entry 8) or increasing the temperature (Table 1, entry 9). However, the latter change is detrimental for the stereoselection. Remarkably, Yb(OTf)$_3$ can be recovered from the aqueous phase during reaction workup and can be recycled to afford the product virtually in the same yield and stereoselection (Table 1, entry 3).[7] A switch from acetonitrile to nitromethane positively influences the yield but negatively affects the stereocontrol (Table 1, entries 4 and 10). The use of a 50:50 mixture of these solvents leaves the yield unchanged and depresses the **t**:**c** ratio (Table 1, entry 5).[8] The reaction could also be performed in dichloromethane (Table 1, entry 1) and in methanol (Table 1, entry 6).

The condensations of SKTA **1** with imines **8**−**10** and of SKTA **2**−**5** with imine **6** to give β-lactams **13t,c**−**19t,c** were then studied to establish the scope and limitations of this process. The data, collected in Table 2, show that the reaction can be extended to imines derived from heteroaromatic and aliphatic aldehydes as well as to other alkyl-substituted and oxygen-substituted SKTA. The chemical yields range from moderate to good and become low in the case of the sterically demanding SKTA **3** and of the silyloxy derivative **5**. With the oxygenated SKTA **4** and **5**, a dependence of the yield on the isomeric composition of SKTA was also observed.[9] The diastereoselectivity is high for the reactions involving alkyl-substituted (*E*)-SKTA **1**−**3**[2] with (*E*)-imines **6**−**8**[10] and is poor when configurationally unstable SKTA **4** and **5**[2] or aliphatic imines were employed (see Figure 1).[10,11]

It was recently demonstrated[15] that the Mukaiyama-type condensation catalyzed by metal triflates can actually be promoted by an *in situ* generated R_3SiOTf species. This could also be the case in our reaction, since the condensation of SKTA **1** with imine **6** in the presence of

† Dedicated to Professor Paolo Grünanger on the occasion of his 70th birthday.

(1) (a) Ikeda, K.; Achiwa, K.; Sekiya, M. *Tetrahedron Lett.* **1983**, *24*, 913 and 4707. (b) Morimoto, T.; Sekiya, M. *Chem. Lett.* **1985**, 1371. (c) Guanti, G.; Narisano, E.; Banfi, L. *Tetrahedron Lett.* **1987**, *28*, 4331 and 4335. (d) Mukaiyama, T.; Kashiwagi, K.; Matsui, S. *Chem. Lett.* **1989**, 1397. (e) Mukaiyama, T.; Akamatsu, H.; Han, J. S. *Chem. Lett.* **1990**, 889. (f) Soga, T.; Takenoshita, H.; Yamada, M.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 3122. (g) Mladenova, M.; Bellassoued, M. *Synth. Commun.* **1993**, *23*, 725. (h) Onaka, M.; Ohno, R.; Yanagiya, N.; Izumi, Y. *Synlett* **1993**, 141. (i) Ishiara, K.; Funahashi, M.; Hanaki, N.; Miyata, M.; Yamamoto, H. *Synlett* **1994**, 963. (j) Kobayashi, S.; Araki, M.; Ishitani, H.; Nagayama, S.; Hachiya, I. *Synlett* **1995**, 233. (k) Kobayashi, S.; Araki, M.; Yasuda, M. *Tetrahedron Lett.* **1995**, *36*, 5773. (l) Makioka, Y.; Shindo, T.; Taniguchi, Y.; Takaki, K.; Fujiwara, Y. *Synthesis* **1995**, 801. For examples of Yb(OTf)$_3$ catalyzed allylation of imines see: (m) Bellucci, C.; Cozzi, P. G.; Umani-Ronchi, A. *Tetrahedron Lett.* **1995**, *36*, 7289. (n) Cozzi, P. G.; Di Simone, B.; Umani-Ronchi, A. *Tetrahedron Lett.* **1996**, *37*, 1691.

(2) Annunziata, R.; Cinquini, M.; Cozzi, F.; Molteni, V.; Schupp, O. *Tetrahedron* **1996**, *52*, 2573.

(3) (a) Hirai, K.; Iwano, Y.; Mikoshiba, I.; Koyama, H.; Nishi, T. *Heterocycles* **1994**, *38*, 277. (b) Hirai, K.; Homma, H.; Mikoshiba, I. *Heterocycles* **1994**, *38*, 281.

(4) The reaction of various metal enolates of 2-pyridyl thioesters with imines affords β-lactams in an one-pot process. (a) Titanium enolates: Annunziata, R.; Benaglia, M.; Chiovato, A.; Cinquini, M.; Cozzi, F. *Tetrahedron* **1995**, *51*, 10025 and references therein. (b) Tin enolates: Annunziata, R.; Benaglia, M.; Cinquini, M.; Cozzi, F.; Raimondi, L. *Tetrahedron* **1994**, *50*, 5821 and references therein. (c) Boron enolates: Annunziata, R.; Benaglia, M.; Cinquini, M.; Cozzi, F.; Molteni, V.*Tetrahedron* **1995**, *51*, 8941 and references therein. (d) Aluminum enolates: Annunziata, R.; Benaglia, M.; Cinquini, M.; Cozzi, F.; Molteni, V. *Tetrahedron* **1996**, *52*, 2583. In a control experiment it was found that Yb(OTf)$_3$ does not promote the reaction between 2-pyridyl thioesters and imines.

(5) Two different samples of commercially available (Aldrich) Yb(OTf)$_3$ were employed and used without the need of any further purification. When purchased, the first sample contained ca. 1.5 mol and the second one ca. 2.3 mol of water/mole of Yb(OTf)$_3$. However, they behave identically. Since Yb(OTf)$_3$ is hygroscopic, its water content can increase.

(6) *Trans*:*cis* ratios were determined by 300 MHz ^{1}H NMR analysis of the crude products (J_{trans} = 2.0−2.5 Hz; J_{cis} = 5.0−6.0 Hz).

(7) Kobayashi, S. *Synlett* **1994**, 689.

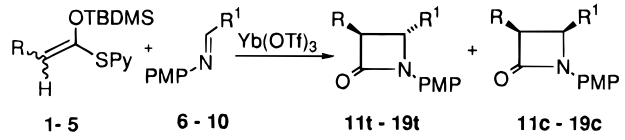
(8) When SKTA **1** was exposed to a catalytic amount of Yb(OTf)$_3$ in acetonitrile-d_3 or nitromethane-d_3, slow formation of the corresponding 2-pyridyl thioester occurred. The proton required by this conversion should derive either from traces of water present in the solvent or from the water associated with Yb(OTf)$_3$ (see ref 5).

(9) For a similar observation on the different reactivity of (*E*) and (*Z*) isomers of oxygenated SKTA see: Kobayashi, S.; Horibe, M.; Achiya, I. *Tetrahedron Lett.* **1995**, *36*, 3173 and references therein.

(10) 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 **6** were shown not to isomerize even in the presence of strong LA (see ref 4).

S0022-3263(96)00844-4 CCC: $12.00 © 1996 American Chemical Society

Scheme 1[a]



1- 5 **6 - 10** **11t - 19t** **11c - 19c**

(E) - **1** R = Me
(E) - **2** R = Et
(E) - **3** R = Pr - i
(E/Z) - **4** R = BnO
(E/Z) - **5** R = TBDPSO

6 R^1 = Ph
7 R^1 = Ph-CH=CH
8 R^1 = 2-Thienyl
9 R^1 = C_6H_{11}-c
10 R^1 = i-Bu

11t,c R = Me; R^1 = Ph
12t,c R = Me; R^1 = Ph-CH=CH
13t,c R = Me; R^1 = 2-Thienyl
14t,c R = Me; R^1 = C_6H_{11}-c
15t,c R = Me; R^1 = i-Bu
16t,c R = Et; R^1 = Ph
17t,c R = Pr-i; R^1 = Ph
18t,c R = BnO; R^1 = Ph
19t,c R = TBDPSO; R^1 = Ph

[a] Abbreviations: TBDMS, *t*-$BuMe_2Si$; Py, 2-pyridyl; PMP, 4-MeOPh; Bn, $PhCH_2$; TBDPS, *t*-$BuPh_2Si$.

Table 1. Synthesis of β-Lactams 11t,c and 12t,c from SKTA (*E*)-1 and imines 6 and 7[a]

entry	imine	solvent	product	yield[b] (%)	**t**:**c** ratio[c]
1	**6**	CH_2Cl_2	**11t,c**	77	66:34
2	**6**	CH_3CN	**11t,c**	63	97:3
3	**6**	CH_3CN	**11t,c**	62[d]	95:5
4	**6**	CH_3NO_2	**11t,c**	99	89:11
5	**6**	CH_3NO_2/CH_3CN	**11t,c**	65	93:7
6	**6**	CH_3OH	**11t,c**	58	77:23
7	**7**	CH_3CN	**12t,c**	27	98:2
8	**7**	CH_3CN	**12t,c**	42[e]	98:2
9	**7**	CH_3CN	**12t,c**	64[f]	84:16
10	**7**	CH_3NO_2	**12t,c**	90	60:40

[a] SKTA:Yb(OTf)$_3$:imine ratio 1.0:0.1:2.0; reaction temperature 20 °C; reaction time 15 h, unless otherwise stated. [b] Isolated yield after flash chromatography. [c] As determined by 300 MHz ^{1}H NMR spectroscopy on the crude products. [d] This reaction was performed with a sample of catalyst that was recovered from a previous reaction (entry 2) and recycled. [e] Reaction time 72 h. [f] Reaction temperature 60 °C.

Table 2. Synthesis of β-Lactams 13t,c−19t,c from SKTA 1−5 and imines 6 and 8−10

SKTA[a]	imine	solvent[b]	product	yield[c] (%)	**t**:**c** ratio[d]
1	**8**	CH_3CN	**13t,c**	29	96:4
1	**8**	CH_3NO_2	**13t,c**	57	87:13
1	**9**	CH_3CN	**14t,c**	89	37:63
1	**10**	CH_3NO_2	**15t,c**	36	63:37
2	**6**	CH_3CN	**16t,c**	62	95:5
3	**6**	CH_3NO_2	**17t,c**	16	98:2
4[e]	**6**	CH_3CN	**18t,c**	49	60:40
5[f]	**6**	CH_3CN	**19t,c**	21	40:60

[a] (*E*)/(*Z*) ratio >98:2 unless otherwise stated. [b] In CH_3CN: reaction conditions of entry 2, Table 1. In CH_3NO_2: reaction conditions of entry 4, Table 1. [c] Isolated yield after flash chromatography. [d] As determined by 300 MHz ^{1}H NMR spectroscopy on the crude products. [e] (*E*)/(*Z*) ratio of starting SKTA = 40:60. With a (*E*)/(*Z*) ratio = 90:10, 20% yield, **t**:**c** ratio 50:50. With a (*E*)/(*Z*) ratio = 60:40 in CH_3NO_2, 36% yield, **t**:**c** ratio 60:40. [f] (*E*)/(*Z*) ratio of starting SKTA = 92:8. With (*E*)/(*Z*) ratio = 4:96 no reaction was observed.

0.1 mol equiv of TBDMSOTf afforded β-lactam **11** in 76% yield as a 95:5 **t**:**c** mixture in acetonitrile and in 86% yield as an 89:11 **t**:**c** mixture in nitromethane, respectively (cf. entries 3 and 4, Table 1). In the latter solvent, however, the product was contaminated by the compound derived from addition of nitromethane to imine **6**, which was not formed in the Yb(OTf)$_3$-catalyzed reaction.

Trying to make this simple β-lactam synthesis even more simple, and keeping in mind the great ability of Yb(OTf)$_3$ to activate imines toward nucleophilic attack,[1j−m,16] a three-component reaction was attempted

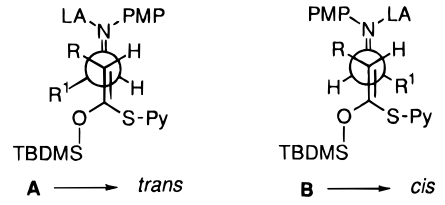


Figure 1.

in which the imine was generated *in situ*.[1k] We were pleased to find that when a mixture of Yb(OTf)$_3$ (0.1 mol equiv), an aldehyde (2.0 mol equiv), 4-methoxyaniline (2.0 mol equiv), and SKTA **1**, **2**, or **4** (1.0 mol equiv) in nitromethane was stirred at room temperature for 15 h, β-lactams **11t**,**c**−**14t**,**c**, **16t**,**c**, and **18t**,**c** were obtained as mixtures of *trans* and *cis* isomers in fair to high isolated yield (Table 3).[17]

Remarkably, no dehydrating agent was required, the addition of $MgSO_4$[1k] leading to identical yields and isomeric ratios. It is also worth mentioning that when TBDMSOTf was used as catalyst in the three-component reaction both yields and stereoselectivity decreased (Table 3, entry 2 *vs* 1).[18,19]

The use of enantiomerically pure reagents was also investigated to achieve control of the absolute configuration of the newly formed stereocenters (Scheme 2).

(11) The *trans* steroeselectivity observed in the synthesis of β-lactams **11**−**13**, **16**, and **17** can be explained by antiperiplanar model **A**[12,13] (Figure 1), which features an (*E*)-SKTA in the so called "pin-wheel" conformation[14] and an (*E*)-imine activated by the LA. If it is assumed that the R/R^1 steric interaction in **A** is similar to the R/PMP one present in **B**, model **A** appears to be favored over model **B**, that leads to *cis* products, because the R^1/OTBDMS interaction present in **A** should be less sterically demanding than the R^1/SPy one present in **B** (Figure 1).[2,12]

(12) Antiperiplanar transition states have been found to be preferred over their synclinal counterparts in an intramolecular LA-catalyzed aldol condensation: Denmark, S. E.; Lee, W. *J. Org. Chem.* **1994**, *59*, 707. Models analogous to **A** and **B** have been used to explain the stereoselectivity of Mukaiyama aldol condensation in general and of the aldol reaction of SKTA **1** in particular: Suh, K.-H.; Choo, D.-J. *Tetrahedron Lett.* **1995**, *36*, 6109. For a review see: Gennari, C. In *Comprehensive Organic Synthesis*; Trost, B., Fleming, I., Heathcock, C. H., Eds.; Pergamon Press: Oxford, 1991; Paart 2, Vol. 2, pp 629−660.

(13) NMR experiments showed that Yb(OTf)$_3$ coordinates the imine but not the pyridine nitrogen. Therefore, a seven-membered cyclic transition state as that proposed for the $TiCl_4$ addition of SKTA **1**−**3** to imines (see ref 2) should be ruled out.

(14) NMR experiments (see ref 2) showed that (*E*)-SKTA **1**−**3** adopt this conformation in solution. For similar observations see: Wilcox, C. S.; Babston, R. E. *J. Org. Chem.* **1984**, *49*, 1451. Babston, R. E.; Lynch, V.; Wilcox, C. S. *Tetrahedron Lett.* **1989**, *30*, 447.

(15) Hollis, T. K.; Bosnich, B. *J. Am. Chem. Soc.* **1995**, *117*, 4570. For a recent example of imine activation by Me_3SiCl see: Wang, D.-E.; Dai, X.-L.; Hou, X.-L. *Tetrahedron Lett.* **1995**, *36*, 8649.

(16) (a) Kobayashi, S.; Ishitani, H.; Nagayama, S. *Chem. Lett.* **1995**, 423. (b) Kobayashi, S.; Ishitani, H.; Nagayama, S. *Synthesis* **1995**, 1195. (c) Ishitani, H.; Nagayama, S. Kobayashi, S. *J. Org. Chem.* **1996**, *61*, 1902.

(17) The three-component reaction can be explained either by a SKTA addition to imine that is faster than that to the aldehyde or by an extremely fast imine formation that *de facto* prevents any addition of SKTA to the aldehyde. Two experimental observations seem to support the first hypothesis. First, in ancillary NMR experiments carried out in acetonitrile-d_3, it was shown that Yb(OTf)$_3$ strongly coordinates the imine **6** nitrogen and poorly coordinates the benzaldehyde oxygen (the −CH=N− proton of imine **6** and of the **6** + Yb(OTf)$_3$ adduct resonates at 8.57 and at 9.00 ppm, respectively; the −CH=O proton of benzaldehyde and of the benzaldehyde + Yb(OTf)$_3$ adduct resonates at 10.0 and at 9.85 ppm, respectively). Second, in the presence of Yb(OTf)$_3$ the formation of imine **6** requires 3 h to occur at 60% yield at rt. As suggest by one of the reviewers, other possible scenarios involve imine fast formation *and* higher reactivity or a reversible SKTA additon to aldehydes and an irreversible one to imines.

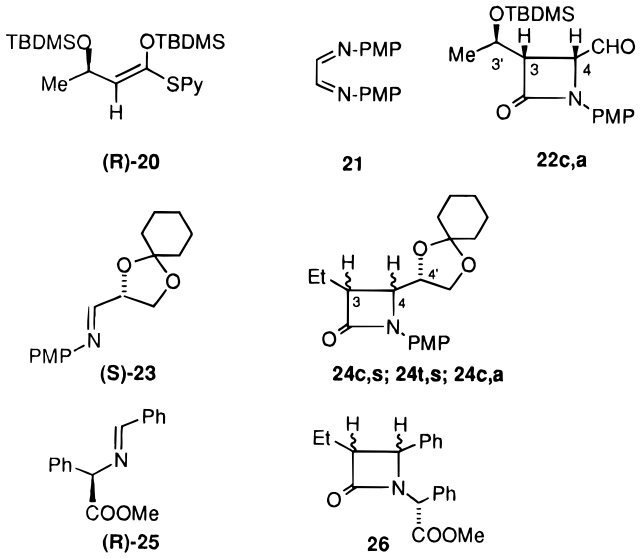
(18) In this synthesis of **11** the adduct derived from the condensation of nitromethane with imine **6** was obtained in 40% yield.

Table 3. Three-Component Synthesis of β-Lactams 11t,c−14t,c, 16t,c, and 18t,c from SKTA 1, 2, and 4 and in Situ Generated Imines 6−9 in CH_3NO_2[a]

entry	SKTA[b]	imine	product	yield[c] (%)	**t:c** ratio[d]
1[e]	**1**	**6**	**11t,c**	82	90:10
2	**1**[f]	**6**	**11t,c**	56	82:18
3	**1**	**7**	**12t,c**	69	60:40
4	**1**	**8**	**13t,c**	54	87:13
5	**1**	**9**	**14t,c**	90	40:60
6	**2**	**6**	**16t,c**	78	95:5
7	**4**	**6**	**18t,c**	59	69:31

[a] SKTA:Yb(OTf)$_3$:aldehyde:amine ratio 1.0:0.1:2.0:2.0; reaction temperature 20 °C; reaction time 15 h, unless otherwise stated. [b] (*E*)/(*Z*) ratios: for **1** and **2**, >98:2; for **4**, 40:60. [c] Isolated yield after flash chromatography. [d] As determined by 300 MHz ^{1}H NMR spectroscopy on the crude products. [e] In CH_3CN this reaction gave **11t,c** in 48% yield and a 96:4 **t:c** ratio. [f] With TBDMSOTf as catalyst.

Scheme 2[a]



[a] Abbreviations: see Scheme 1.

Reaction of SKTA (*R*)-**20**,[2] derived from (*R*)-methyl 3-hydroxybutyrate *via* the corresponding *O*-silyl-protected 2-pyridyl-thioester,[20] with bis-imine **21**[21,22] in nitromethane afforded, after acidic workup,[22] β-lactam **22c,a** as a single *cis* isomer in a poor 24% overall yield. The configuration of this product was determined as 3,4-*cis*-3,3′-*anti* (**c,a**) by checking that its ^{1}H NMR spectrum was consistent with the proposed structure and different from those of its 3,4-*trans*-3,3′-*anti*, 3,4-*trans*-3,3′-*syn*, and 3,4-*cis*-3,3′-*syn* isomers reported in the literature[23] (see Scheme 2 for numbering).

Condensation of SKTA **2** with imine (*S*)-**23**[20] in nitromethane gave in 86% yield a 54:36:10 mixture of β-lactams **24**[20] having the 3,4-*cis*-4,4′-*syn* (**c,s**), 3,4-*trans*-4,4′-*syn* (**t,s**), and 3,4-*cis*-4,4′-*anti* (**c,a**) configurations, respectively, as assigned by comparison of ^{1}H NMR data.[20,24,25]

Finally, when SKTA **2** was reacted with imine (*R*)-**25** in nitromethane a 46:39:15 mixture of two *trans* and one *cis* isomers of β-lactam **26** was obtained in 72% yield.[26]

Therefore, the reactions with chiral reagents occurred either with good stereocontrol but in poor yield (as for β-lactam **22**) or with scarce stereoselectivity but in high yield (as for **24** and **26**). As a consequence, this catalytic β-lactam synthesis does not appear to be the method of choice for the preparation of enantiomerically pure compounds starting from chiral substrates.[27]

The reaction of SKTA **1** with imine **6** catalyzed by two recently described[28,29] chirally modified Yb reagents was also studied, but this approach gave disappointing results. Indeed, in the presence of the reagent prepared from Yb(OTf)$_3$, (*R*)-binaphthol, and a tertiary amine[28] the reaction did not occur; on the other hand, when the bistriflamide of (1*S*,2*S*)-1,2-diphenylethylendiamine was used as Yb ligand,[29] β-lactam **11** was obtained in 36% yield as a 86:14 mixture of virtually racemic *trans* and *cis* isomers.

In conclusion, the first catalytic one-pot synthesis of β-lactams has been realized by a two- or a three-component reaction in which Yb(OTf)$_3$ catalyzes the addition of various SKTA to pre-formed imines (two-component reaction) or to imines generated in situ from aldehydes and 4-methoxyaniline (three-component reaction). The products were formed in fair to high yields and with variable degrees of *trans*/*cis* stereoselectivity, which depend on the SKTA and the imine structures. Extension of the reaction to enantiomerically pure reagents had a limited success, as had the use of chirally modified Yb species. Work is underway in our laboratories to apply this method to a solid-phase synthesis of β-lactams and to exploit the three-component reaction in the field of combinatorial chemistry.[30]

(19) β-Lactam **11t,c** can be obtained from SKTA **1** and imine **6** in nitromethane also in the absence of the catalyst (two-component reaction: 22% yield; three-component reaction: 8% yield). An uncatalyzed Mukaiyama−Michael addition of a silyl ketene acetal to an unsaturated ketone in nitromethane has been previously reported: RajanBabu, V. T. *J. Org. Chem.* **1984**, *49*, 2083. The reaction of benzaldehyde with nitromethane rather than with a silyl ketene acetal in a Rh-catalyzed aldol process has been recently described: Kiyooka, S.-I.; Tsutui, T.; Maeda, H.; Kaneko, Y.; Isobe, K. *Tetrahedron Lett.* **1995**, *36*, 6531.

(20) Annunziata, R.; Cinquini, M.; Cozzi, F.; Cozzi, P. G. *J. Org. Chem.* **1992**, *57*, 4155.

(21) Kliegman, J. M.; Barnes, R. K. *J. Org. Chem.* **1970**, *35*, 3140.

(22) For an example of the use of imine **21** in the synthesis of 4-formyl-substituted β-lactams see: Alcaide, B.; Martin-Cantalejo, Y.; Perez-Castells, J.; Rodriguez-Lopez, J.; Sierra, M. A.; Monge, A.; Perez-Garcia, V. *J. Org. Chem.* **1992**, *57*, 5921.

(23) Georg, G. I.; Kant, J.; Gill, H. S. *J. Am. Chem. Soc.* **1987**, *109*, 1129 and references cited therein. It must be noted that β-lactam **22c,a** features the 3,3′-*anti* configuration and the functional groups required for the synthesis of the carbapenem antibiotics of the thienamycin family.

(24) When this reaction was carried out in dichloromethane the yield was 64% and the **c,s:t,s:c,a:t,a** isomer ratio was 17:21:27:35. In acetonitrile, the yield was 46% and the isomer ratio 55:30:5:10.

(25) The reactions of SKTA **2** with the *N*-4-(methoxyphenyl)imines derived from (*S*)-2-(benzyloxy)- and (*S*)-2-[(*tert*-butyldimethylsilyl)oxy]-propanal occurred in low yields (28 and 18%, respectively) and poor stereocontrol.

(26) For recent examples of β-lactam synthesis by enolate additon to imines bearing chiral auxiliaries, see ref 4a and references cited therein. For the use of imine (*R*)-**25**, see: Annunziata, R.; Benaglia, M.; Cinquini, M.; Cozzi, F.; Raimondi, L. *Tetrahedron* **1994**, *50*, 9471. In that work, other imines were employed that gave better results than (R)-**25**. These, however, did not give any satisfactory results in the Yb(OTf)$_3$-catalyzed reaction described here.

(27) For instance, the use of imines such as **23** or of the 2-pyridyl thioester precursor of **20** in the $TiCl_4$-promoted stereoselective synthesis of β-lactams gave much more satisfactory results: see ref 20.

(28) (a) Kobayashi, S.; Ishitani, H. *J. Am. Chem. Soc.* **1994**, *116*, 4083. (b) Kobayashi, S.; Ishitani, H.; Hachiya, I.; Araki, M. *Tetrahedron* **1994**, *50*, 11637.

(29) Uotsu, K.; Sasai, H.; Shibasaki, M. *Tetrahedron: Asymmetry* **1995**, *6*, 71.

(30) The first example of solid-phase combinatorial β-lactam synthesis has just been published: Ruhland, B.; Bhandari, A.; Gordon, E. M.; Gallop, M. A. *J. Am. Chem. Soc.* **1996**, *118*, 253. This method relies on a simple synthesis of imines immobilized on a polymeric matrix: Look, G. C.; Murphy, M. M.; Campbell, D. A.; Gallop, M. A. *Tetrahedron Lett.* **1995**, *36*, 2937.

Experimental Section

SKTA **1**−**5** and **20** were known compounds.[2] Imines **6**−**10**, **21**,[21] **23**,[20] and **25**[26] were prepared by stirring equimolar amounts of aldehyde and the required amine in dichloromethane in the presence of $MgSO_4$ at rt for 2−12 h; filtration and removal of the solvent in vacuum gave the crude imines that were used as such.[10]

General Procedure for the Yb(OTf)$_3$-Catalyzed Two-Component *β*-Lactam Synthesis. The preparation of 1-(4′-methoxyphenyl)-3-methyl-4-phenylazetidin-2-one (**11t,c**) in CH_3CN is illustrative of the procedure. To a stirred solution of $Yb(OTf)_3$ (0.031 g, 0.05 mmol) in anhydrous CH_3CN (2 mL) kept at rt under nitrogen was added SKTA **1** (0.141 g, 0.5 mmol) in CH_3CN (2 mL) *via* a cannula, immediately followed by imine **6** (0.211 g, 1 mmol) in CH_3CN (2 mL). The mixture was stirred at rt for 15 h. Et_2O (10 mL) and water (5 mL) were then added, and the two phases were separated. The aqueous phase was extracted with Et_2O, and the combined organic phase was dried over sodium sulfate, filtered, and evaporated in vacuum. The residue was analyzed by ^1H NMR spectroscopy for the **t:c** ratio determination and was purified by flash chromatography with a 30:70 Et_2O:hexanes mixture as eluant to afford *β*-lactam **11t,c** (0.079 g, 0.315 mmol, 63% yield) as a 97:3 mixture of **t** and **c** isomers. Evaporation to dryness of the aqueous phase of several reactions allowed recovery of $Yb(OTf)_3$ that can be recycled (see text and Table 1, entry 3).

General Procedure for the Yb(OTf)$_3$-Catalyzed Three-Component *β*-Lactam Synthesis. The preparation of 1-(4′-methoxyphenyl)-3-methyl-4-(2-phenylethenyl)azetidin-2-one (**12t,c**) in CH_3NO_2 is illustrative of the procedure. To a stirred solution of $Yb(OTf)_3$ (0.031 g, 0.05 mmol) in CH_3NO_2 (2 mL) kept at rt under nitrogen were added cinnamaldehyde (0.132 g, 1 mmol) in CH_3NO_2 (2mL) and 4-methoxyaniline (0.123 g, 1 mmol) in CH_3NO_2 (2mL). After 10 min of stirring at rt, SKTA **1** (0.141 g, 0.5 mmol) in CH_3NO_2 (2mL) was added *via* a cannula. The mixture was stirred at rt for 15 h. After addition of Et_2O and water the reaction was worked up as described above to afford, after flash chromatographic purification, *β*-lactam **12t,c** (0.096 g, 0.345 mmol, 69% yield) as a 60:40 mixture of **t** and **c** isomers.

β-Lactams **11**,[2] **12**,[4b] **13**,[2] **14**,[2] **16**−**19**,[2] **24c,s**,[20] and **24t,s**[20] were known compounds and had physical properties and spectral data in agreement with those reported in the literature. The relevant ^1H NMR data of the two unknown isomers of **24** were as follows. **24c,a** ($CDCl_3$): δ 4.30 (1H, dt, J = 6.0, 7.7 Hz); 4.10 (1H, t, J = 5.8 Hz); 3.31 (1H, m). Of **24t,a** ($CDCl_3$): δ 4.41 (1H, dt, J = 3.8, 6.8 Hz); 3.87 (1H, dd, J = 2.2, 3.8 Hz); 3.04 (1H, dt, J = 2.2, 6.1 Hz).

1-(4′-Methoxyphenyl)-3-methyl-4-(2-methylpropyl)azetidin-2-one (15t,c). The 63:37 *trans*:*cis* diastereoisomeric mixture was an oil. IR: 1740 cm^{-1}. Anal. Calcd for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 5.66. Found: C, 72.69; H, 8.63; N, 5.70. Selected ^1H NMR data of **15t** ($CDCl_3$): δ 3.63 (1H, m); 2.88 (1H, dq, J = 2.1, 6.7 Hz); 2.00 and 1.37 (2H, AB system, J = 5.0, 11.0 Hz).1.37, (3H, d, J = 6.7 Hz). ^{13}C NMR data of **15t** ($CDCl_3$): δ 167.6, 156.0, 131.0, 118.7, 114.4, 58.8, 55.5, 50.7, 41.0, 25.8, 23.3, 22.4, 13.4. Selected ^1H NMR data of **15c** ($CDCl_3$): δ 4.10 (1H, m); 3.40 (1H, dq, J = 5.4, 7.0 Hz); 1.73 and 1.50 (2H, AB system, J = 3.0, 7.0 Hz).1.27, (3H, d, J = 7.0 Hz). ^{13}C NMR data of **15c** ($CDCl_3$): δ 168.0, 156.0, 130.9, 118.9, 114.4, 55.5, 53.5, 46.6, 36.1, 29.6, 23.3, 22.2, 9.1

(3*S*,3′*R*,4*R*) 3-[1[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-ethyl]-4-formyl-1-(4′-methoxyphenyl)azetidin-2-one (22c,a). This compound was a light yellow oil that had $[\alpha]^{22}_D$ 47.8 (*c* 0.56 in $CHCl_3$). IR: 1740, 1720 cm^{-1}. Anal. Calcd for $C_{19}H_{29}NO_4Si$: C, 62.78; H, 8.04; N, 3.85. Found: C, 62.69; H, 8.08; N, 3.77. Selected ^1H NMR data ($CDCl_3$): δ 10.00 (1H, d, J = 3.6 Hz); 4.45 (1H, dd, J = 3.6, 5.9 Hz); 4.44 (1H, dq, J = 2.5, 6.7 Hz); 3.77, (3H, s); 3.67 (1H, dd, J = 2.5, 5.9 Hz); 1.21 (3H, d, J = 6.7 Hz). ^{13}C NMR data: δ 200.1, 164.2, 156.5, 117.0, 114.0, 65.2, 63.9, 59.8, 55.5, 25.6, 21.8, 17.8, −4.5, −5.0.

(α*R*)-Methyl α,2-Diphenyl-3-ethyl-4-oxo-1-azetidineacetate (26). The mixture of three isomers was a thick oil. IR: 1755, 1740 cm^{-1}. Anal. Calcd for $C_{20}H_{21}NO_3$: C, 74.28; H, 6.54; N, 4.33. Found: C, 74.38; H, 6.63; N, 4.19. Selected ^1H NMR data ($CDCl_3$) of the major *trans* isomer: δ 5.28 (1H, s); 4.09 (1H, d, J = 2.4 Hz); 3.00 (1H, dt, J = 2.4, 8.0 Hz). Selected ^{13}C NMR data ($CDCl_3$) of the major *trans* isomer: δ 172.0, 168.5, 61.9, 61.5, 59.9, 52.5, 21.4, 11.2. Selected ^1H NMR data of the minor *trans* isomer: δ 5.45 (1H, s); 4.60 (1H, d, J = 2.2 Hz); 2.94 (1H, dt, J = 2.2, 7.0 Hz). Selected ^{13}C NMR data of the minor *trans* isomer: δ 172.2, 170.0, 62.1, 61.5, 58.4, 52.3, 21.6, 11.4. Selected ^1H NMR data of the *cis* isomer: δ 5.22 (1H, s); 4.78 (1H, d, J = 5.7 Hz); 3.30 (1H, dt, J = 5.7, 7.3 Hz). Selected ^{13}C NMR data of the *cis* isomer: δ 172.0, 168.7, 60.5, 59.9, 56.5, 52.4, 18.8, 12.0.

Acknowledgment. Partial financial support by MURST and CNR—Piano Strategico Tecnologie Chimiche Innovative is gratefully acknowledged. O.S. thanks the Deutsche Forschungsgemeinschaft for a postdoctoral fellowship.

JO960844U