A New Method for the Synthesis of β-Amino Acid Derivatives and β-Lactams. Reaction of *N*-Alkoxycarbonyl-1-methoxyamines with Esters

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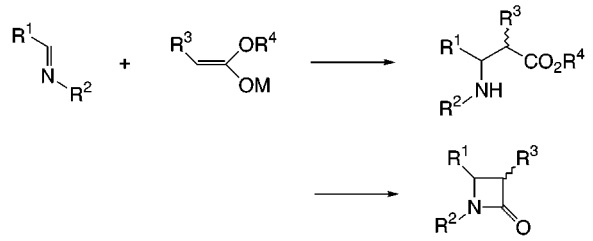
The reaction of *N*-alkoxycarbonyl-1-methoxyamines with esters is an alternative to the reaction of imines with esters for the synthesis of β-amino acid derivatives. In this reaction, *N*-alkoxycarbonyl-1-methoxyamines corresponding to unstable imines can also be employed. Although *anti* adducts were obtained preferentially in the absence of Ti complexes, the diastereoselectivity of this reaction was reversed by the addition of Ti(OPr-*i*)$_4$. The obtained adducts were transformed to the corresponding β-lactams.

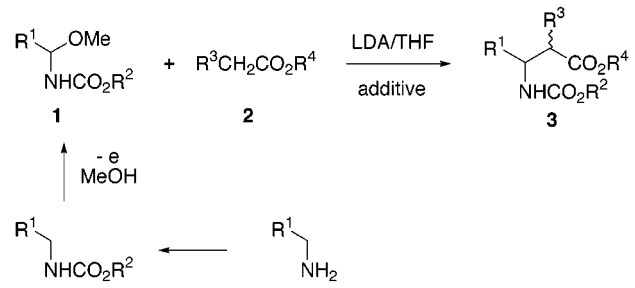
Introduction

Reaction of imines with ester enolates or ketene acetals is a potential method for the synthesis of β-amino acid derivatives, which are important precursors for β-lactam synthesis (Scheme 1).[1,2] However, readily enolizable imines (R^1 = benzyl, allyl) or imines susceptible to β-elimination (R^1 = β-alkoxyethyl)[3] cannot be employed for these reactions. We have reported a new synthetic method from *N*-alkoxycarbonyl-1-methoxyamines **1** and esters **2** to β-amino acid derivatives **3** (Scheme 2).[4] The key steps of this method are simultaneous in situ generation of an ester enolate and an *N*-alkoxycarbonylimine and subsequent addition of the former to the later. This method provides a novel route to β-amino acids starting from amines. Herein we report full details of our study on this reaction. It is noted that *N*-alkoxycarbonyl-1-methoxyamines corresponding to unstable imines (R^1 = benzyl, allyl, and β-alkoxyethyl) can be employed for this reaction. The diastereoselectivity of this reaction was also studied in the absence and the presence of Ti complexes. The reversal of the diastereoselectivity was observed by the addition of Ti(OPr-*i*)$_4$.

Scheme 1



Scheme 2



Results and Discussion

Reaction with Alkyl Acetates. *N*-Alkoxycarbonyl-1-methoxyamines **1** were prepared from *N*-alkoxycarbonyamines[5] or α-amino acids[6] by anodic oxidation in methanol. The reaction of **1a** (R^1 = Me) with acetate **2a** or **2b** (R^3 = H) was carried out by adding a THF solution of **1** and **2** to a solution of LDA at −70 °C and raising the temperature to 0 °C. The results are depicted in Table 1. Methyl acetate (**2a**) gave a poor result due to self-condensation of the acetate (run 1), while *tert*-butyl acetate (**2b**) gave a satisfactory result (run 2). When TiCl(OPr-*i*)$_3$ was added to the reaction mixture, the reaction proceeded at −70 °C and afforded a good result even with **2a** (run 3). In addition, **1b**−**e** (R^1 = allyl, benzyl, and β-alkoxyethyl) corresponding to unstable imines also gave the adducts **3c**−**g** in good yields (runs 4−8).

The reaction of **1f**,[7] prepared from L-threonine, with *tert*-butyl acetate (**2b**) afforded *anti* adduct preferentially (Scheme 3). The yield and stereoselectivity of **3h** slightly increased in the presence of TiCl(OPr-*i*)$_3$. The stereochemistry of the adduct **3h** was determined by ^{1}H NMR

(1) For reviews, 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.

(2) For recent reports, see: (a) Cainelli, G.; Panunzio, M.; Bandini, E.; Martelli, G.; Spunta, G. *Tetrahedron* **1996**, *52*, 1685. (b) Cozzi, P. G.; Simone, B. D.; Umani-Ronchi, A. *Tetrahedron Lett.* **1996**, *37*, 1691. (c) Annunziata, R.; Cinquini, M.; Cozzi, F.; Molteni, V.; Schupp, O. *Tetrahedron* **1996**, *52*, 2573; *J. Org. Chem.* **1996**, *61*, 8293. (d) Shankar, B. B.; Kirkup, M. P.; McCombie, S. W.; Clader, J. W.; Ganguly, A. K. *Tetrahedron Lett.* **1996**, *37*, 4095. (e) Baldoli, C.; Buttero, P. D.; Lincandro, E.; Papagni, A. *Tetrahedron* **1996**, *52*, 4849. (f) Cainelli, G.; Giacomini, D.; Galletti, P. *Synthesis* **1997**, 886.

(3) The reaction of imines derived from 3-benzyloxypropanal has been reported with boron enolates: Iimori, T.; Ishida, Y.; Shibasaki, M. *Tetrahedron Lett.* **1986**, *27*, 2153.

(4) Some parts of this study have been reported in preliminary communications: (a) Shono, T.; Kise, N.; Sanda, F.; Ohi, S.; Tsubata, K. *Tetrahedron Lett.* **1988**, *29*, 231. (b) Shono, T.; Kise, N.; Sanda, F.; Ohi, S.; Yoshioka, K. *Tetrahedron Lett.* **1989**, *30*, 1253.

(5) Shono, T.; Hamaguchi, H.; Matsumura, Y. *J. Am. Chem. Soc.* **1975**, *97*, 4264.

(6) Horikawa, H.; Iwasaki, T.; Matsumoto, K.; Miyoshi, M. *J. Org. Chem.* **1978**, *43*, 335.

(7) Renaud, P.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 843.

10.1021/jo990821q CCC: $18.00
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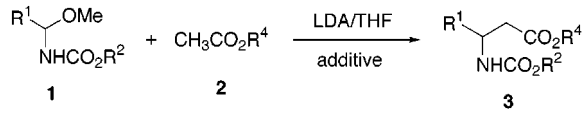
Table 1. Reactions of 1a−e with Alkyl Acetates 2a,b

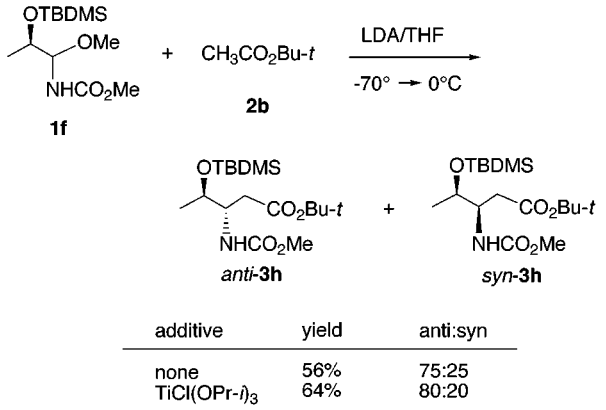


1 2 3

run	1	R^1	R^2	2	R^4	additive		% yield of **3a**
1	**1a**	Me	Me	**2a**	Me	none[b]	**3a**	<10
2	**1a**	Me	Me	**2b**	*t*-Bu	none[b]	**3b**	78
3	**1a**	Me	Me	**2a**	Me	$TiCl(OPr\text{-}i)_3$[c]	**3a**	84
4	**1b**	allyl	Me	**2a**	Me	$TiCl(OPr\text{-}i)_3$[c]	**3c**	74
5	**1c**	allyl	*t*-Bu	**2a**	Me	$TiCl(OPr\text{-}i)_3$[c]	**3d**	76
6	**1d**	benzyl	Me	**2b**	*t*-Bu	none[b]	**3e**	67
7	**1d**	benzyl	Me	**2a**	Me	$TiCl(OPr\text{-}i)_3$[c]	**3f**	72
8	**1e**	TBDMSO-CH_2CH_2	Me	**2a**	Me	$TiCl(OPr\text{-}i)_3$[c]	**3g**	79

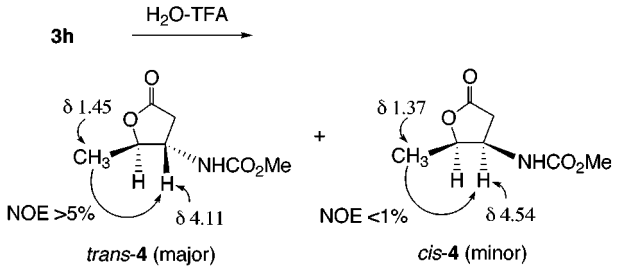
[a] Isolated yields. [b] −70 °C → 0 °C. [c] −70 °C.

Scheme 3



additive	yield	anti:syn
none	56%	75:25
$TiCl(OPr\text{-}i)_3$	64%	80:20

Scheme 4



spectral analysis of γ-lactone **4** derived from **3h** (Scheme 4). The isomer showing a larger NOE between 4-H and 5-CH_3 was assigned to be *trans*-**4**. The *anti* selectivity can be explained by nonchelation control (dipolar model or Felkin−Anh model)[8] in the addition of the ester enolate to the *N*-alkoxycarbonylimine generated from **1f** (Figure 1).

Reaction with Alkyl Butyrates and Methyl Isovalerate. Next, we examined the reactions of **1** with butyrates and isovalerates **2c**−**e** in the absence and presence of Ti complexes (Tables 2 and 3). The diastereoselectivities were determined by ^1H NMR analysis. The stereoconfigurations of the adducts were confirmed by their transformation to β-lactams (vide infra). In the absence of Ti complexes, the reactions of **1** with **2c**−**e** gave *anti* isomers of adducts **3** preferentially in all the cases (Table 2). The stereoselectivity was influenced by the R^1−R^4 groups in reactants **1** and **2**. According to runs 1, 4, and 6 in Table 2, the *anti* selectivity increased as

(8) For a review of the chelation and nonchelation control additions, see: Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 556.

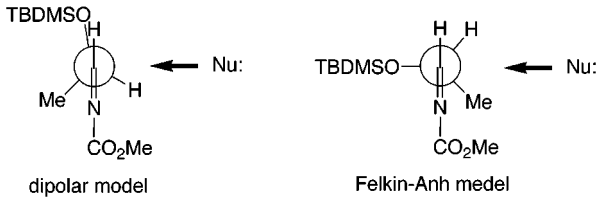


Figure 1. Nonchelation models.

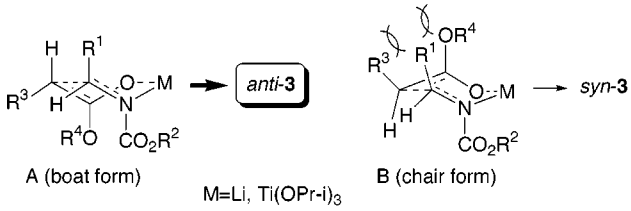


Figure 2. Closed transition states.

the size of R^1 increased (Me → *i*-Pr → *t*-Bu). Larger R^3 (Et → *i*-Pr) and R^4 (Me → *i*-Pr) also raised the *anti* selectivity (runs 8 and 10), while larger R^2 (Me → *t*-Bu) lowered the selectivity to some extent (run 16). Although the addition of $TiCl_4$ had little effect on the yield and diastereoselectivity of **3** (run 2), the addition of $TiCl(OPr\text{-}i)_3$ slightly increased the *anti* selectivity in most cases.

On the contrary, *syn* selectivity was observed in the presence of $Ti(OPr\text{-}i)_4$ (Table 3). As in the above results, increasing bulk of R^1 (Me → *i*-Pr → *t*-Bu) increased the *syn* selectivity (runs 1−3). However, larger R^2 (Me → *t*-Bu), R^3 (Et → *i*-Pr), and R^4 (Me → *i*-Pr) groups decreased the *syn* selectivity (runs 4, 5, and 8).

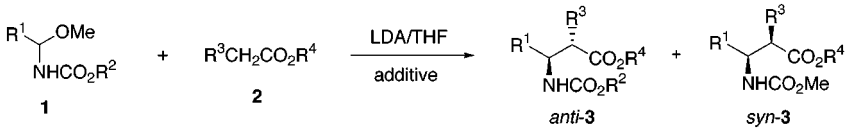
Transition State Hypotheses. The present reactions proceed through the nucleophilic addition of ester enolates to *N*-alkoxycarbonylimines. It is known that esters form lithiated *E*-enolates predominantly by treatment with LDA[9] and Li enolates are transformed to Ti enolates by the addition of $TiCl(OPr\text{-}i)_3$.[10] Although the geometry of the *N*-alkoxycarbonylimines could not be confirmed, it is likely that *E*-forms are more favorable than *Z*-forms. The *anti* selectivity can be explained by considering closed transition states (boat and chair forms) in which the nitrogen atom of the *N*-alkoxycarbonylimine coordinates the lithium or titanium metal of the enolate as shown in Figure 2. Boat form **A** is more favorable than chair form **B** due to the R^1−R^3 and R^1−OR^4 steric interactions in **B**. Therefore, large R^1, R^3, and R^4 groups increased the *anti* selectivity. On the other hand, it is reported that Ti ate complexes are formed from Li enolates and $Ti(OPr\text{-}i)_4$.[10] The *syn* selectivity in the presence of $Ti(OPr\text{-}i)_4$ might be elucidated by open transition states depicted in Figure 3, in which transition state **C** is more likely than **D** due to the steric repulsion between R^1 and R^3 groups in **D**. This hypothesis is consistent with the result that large R^1 groups increased the *syn* selectivity; however, it cannot explain the fact that large R^3 groups decreased the *syn* selectivity.

Transformation of Adducts to β-Lactams. The obtained adducts **3** were transformed to the correspond-

(9) (a) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868. (b) Heathcock, C. H. *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. III, pp 123−124.

(10) (a) Reetz, M. T.; Peter, R. *Tetrahedron Lett.* **1981**, *22*, 4691. (b) Reetz, M. T. *Organotitanium Reagents in Organic Synthesis*; Springer-Verlag: Berlin, 1986; pp 148−174.

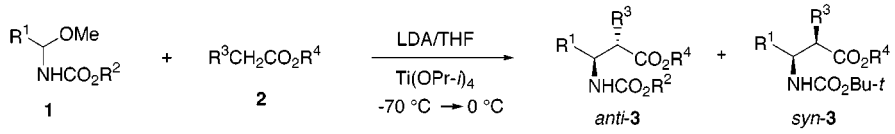
Table 2. Reactions of 1 with Alkyl Butyrate 2c,e and Methyl Isovalerate 2d



run	**1**	R^1	R^2	**2**	R^3	R^4	additive	% yield of **3**[a]		anti:syn[b]
1	**1g**	*i*-Pr	Me	**2c**	Et	Me	none[c]	**3i**	87	70:30
2	**1g**	*i*-Pr	Me	**2c**	Et	Me	$TiCl_4$[d]	**3i**	90	67:33
3	**1g**	*i*-Pr	Me	**2c**	Et	Me	$TiCl(OPr\text{-}i)_3$[d]	**3i**	88	75:25
4	**1a**	Me	Me	**2c**	Et	Me	none[c]	**3j**	78	67:33
5	**1a**	Me	Me	**2c**	Et	Me	$TiCl(OPr\text{-}i)_3$[d]	**3j**	74	70:30
6	**1h**	*t*-Bu	Me	**2c**	Et	Me	none[c]	**3k**	93	85:15
7	**1h**	*t*-Bu	Me	**2c**	Et	Me	$TiCl(OPr\text{-}i)_3$[d]	**3k**	80	55:45
8	**1g**	*i*-Pr	Me	**2d**	*i*-Pr	Me	none[c]	**3l**	92	78:22
9	**1g**	*i*-Pr	Me	**2d**	*i*-Pr	Me	$TiCl(OPr\text{-}i)_3$[d]	**3l**	84	72:28
10	**1g**	*i*-Pr	Me	**2e**	Et	*i*-Pr	none[c]	**3m**	92	80:20
11	**1g**	*i*-Pr	Me	**2e**	Et	*i*-Pr	$TiCl(OPr\text{-}i)_3$[d]	**3m**	83	80:20
12	**1d**	benzyl	Me	**2c**	Et	Me	none[c]	**3n**	57	67:33
13	**1d**	benzyl	Me	**2c**	Et	Me	$TiCl(OPr\text{-}i)_3$[d]	**3n**	84	75:25
14	**1e**	$TBDMSOCH_2CH_2$	Me	**2c**	Et	Me	none[c]	**3o**	86	70:30
15	**1e**	$TBDMSOCH_2CH_2$	Me	**2c**	Et	Me	$TiCl(OPr\text{-}i)_3$[d]	**3o**	88	75:25
16	**1i**	*i*-Pr	*t*-Bu	**2c**	Et	Me	none[c]	**3p**	95	65:35
17	**1c**	allyl	*t*-Bu	**2c**	Et	Me	none[c]	**3q**	72	60:40
18	**1j**	$TBDPSOCH_2CH_2$	*t*-Bu	**2c**	Et	Me	none[c]	**3r**	73	67:33
19	**1j**	$TBDPSOCH_2CH_2$	*t*-Bu	**2d**	*i*-Pr	Me	none[c]	**3s**	71	63:37[e]
20	**1j**	$TBDPSOCH_2CH_2$	*t*-Bu	**2e**	Et	*i*-Pr	none[c]	**3t**	74	75:25[e]

[a] Isolated yields. [b] Determined by ^1H NMR analysis. [c] −70 °C → 0 °C. [d] −70 °C. [e] Determined by ^1H NMR analysis of decarbamated amines.

Table 3. Reactions of 1 with 2 in the Presence of $Ti(OPr\text{-}i)_4$



run	**1**	R^1	R^2	**2**	R^3	R^4	%yield of **3**[a]		anti:syn[b]
1	**1g**	*i*-Pr	Me	**2c**	Et	Me	**3i**	90	8:92
2	**1a**	Me	Me	**2c**	Et	Me	**3j**	85	33:67
3	**1h**	*t*-Bu	Me	**2c**	Et	Me	**3k**	88	5:95
4	**1g**	*i*-Pr	Me	**2d**	*i*-Pr	Me	**3l**	85	33:67
5	**1g**	*i*-Pr	Me	**2e**	Et	*i*-Pr	**3m**	89	18:82
6	**1d**	benzyl	Me	**2c**	Et	Me	**3n**	90	35:65
7	**1e**	$TBDMSOCH_2CH_2$	Me	**2c**	Et	Me	**3o**	92	33:67
8	**1i**	*i*-Pr	*t*-Bu	**2c**	Et	Me	**3p**	85	33:67
9	**1c**	allyl	*t*-Bu	**2c**	Et	Me	**3q**	65	25:75
10	**1j**	$TBDPSOCH_2CH_2$	*t*-Bu	**2c**	Et	Me	**3r**	71	35:65
11	**1j**	$TBDPSOCH_2CH_2$	*t*-Bu	**2d**	*i*-Pr	Me	**3s**	68	40:60[c]
12	**1j**	$TBDPSOCH_2CH_2$	*t*-Bu	**2e**	Et	*i*-Pr	**3t**	64	40:60[c]

[a] Isolated yields. [b] Determined by ^1H NMR analysis. [c] Determined by ^1H NMR analysis of decarbamated amines.

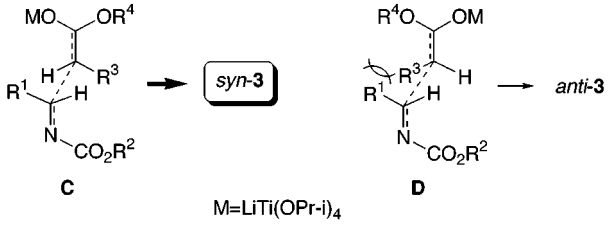


Figure 3. Open transition states.

ing β-lactams **5** by deprotection of carbamate group and subsequent cyclization (Table 4). The stereochemistry of each diastereomer of **3** was confirmed by ^1H NMR spectral analysis of β-lactam **5**. The coupling constants between 3-H and 4-H were 5−6 Hz for *cis*-**5** and 2−2.5 Hz for *trans*-**5**.[1,2c]

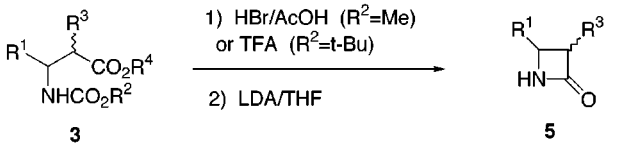
Conclusion

The reaction of *N*-alkoxycarbonyl-1-methoxyamines **1** with esters **2** is a useful method for the synthesis of β-amino acid derivatives and β-lactams. By this method, *N*-alkoxycarbonyl-1-methoxyamines corresponding to unstable imines (R^1 = benzyl, allyl, and β-alkoxyethyl) can also be employed. The reactions in the absence of Ti complexes or in the presence of $TiCl(OPr\text{-}i)_3$ gave *anti* adducts preferentially. On the other hand, *syn* selectivity was observed when the reaction was carried out in the presence of $Ti(OPr\text{-}i)_4$.

Experimental Section

General Methods. IR spectra were recorded with a Shimadzu FTIR-8100 infrared spectrometer. ^1H and ^{13}C NMR spectra were measured with a JEOL GX-270 spectrometer with tetramethylsilane (TMS) as an internal standard. Column

Table 4. Transformation of 3 to β-Lactams 5



3 5

run	3	R^1	R^2	R^3	%yield of 5[a]	
1	*anti*-**3i**	*i*-Pr	Me	Et	*trans*-**5a**	76
2	*syn*-**3i**	*i*-Pr	Me	Et	*cis*-**5a**	55
3	*anti*-**3j**	Me	Me	Et	*trans*-**5b**	68
4	*syn*-**3j**	Me	Me	Et	*cis*-**5b**	42
5	*anti*-**3k**	*t*-Bu	Me	Et	*trans*-**5c**	64
6	*syn*-**3k**	*t*-Bu	Me	Et	*cis*-**5c**	48
7	*anti*-**3l**	*i*-Pr	Me	*i*-Pr	*trans*-**5d**	84
8	*syn*-**3l**	*i*-Pr	Me	*i*-Pr	*cis*-**5d**	46
9	*anti*-**3n**	benzyl	Me	Et	*trans*-**5e**	67
10	*syn*-**3n**	benzyl	Me	Et	*cis*-**5e**	46
11	*anti*-**3q**	allyl	*t*-Bu	Et	*trans*-**5f**	61
12	*syn*-**3q**	allyl	*t*-Bu	Et	*cis*-**5f**	40
13	*anti*-**3r**	$TBDPSOCH_2CH_2$	*t*-Bu	Et	*trans*-**5g**	82
14	*syn*-**3r**	$TBDPSOCH_2CH_2$	*t*-Bu	Et	*cis*-**5g**	58
15	*anti*-**3s**	$TBDPSOCH_2CH_2$	*t*-Bu	*i*-Pr	*trans*-**5h**	84
16	*syn*-**3s**	$TBDPSOCH_2CH_2$	*t*-Bu	*i*-Pr	*cis*-**5h**	60

[a] Isolated yields.

chromatography was performed on silica gel 60 (Merck). Tetrahydrofuran was distilled from benzophenone ketyl.

***N*-Alkoxycarbonyl-1-methoxyamines 1** were prepared from the corresponding *N*-alkoxycarbonyamines by anodic oxidation in methanol[5] except for **1d** and **1f**[7] which were synthesized from *N*-methoxycarbonyl-α-amino acids.[6]

General Procedure for the Reaction of 1 and 2. A mixture of **1** (2 mmol) and ester **2** (2.2 mmol) in THF (3 mL) was added to a solution of LDA (4.5 mmol) in THF−hexane (6 mL) at −70 °C. After stirring for 15 min, an additive (2.2 mmol) was added to the mixture. The mixture was stirred for 1−6 h at the temperature described in Tables 1 and 2 until almost all of **1** was consumed (checked by TLC). The mixture was diluted with 1 M HCl (20 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The product **3** was isolated by column chromatography on silica gel (hexane−ethyl acetate).

Decarbamation of 3 was accomplished by usual methods, that is, the treatment with HBr/AcOH for methylcarbamates and with TFA for *tert*-butoxycarbamates. The obtained amines were subjected to cyclization without purification.

Preparation of β-Lactams 5. A solution of decarbamated **3** (1 mmol) in THF (3 mL) was added to a solution of LDA (1.5 mmol) in THF−hexane (5 mL) at 0 °C. The mixture was stirred for 2−8 h at this temperature until almost all of the starting β-amino ester was consumed (checked by TLC). The mixture was diluted with 1 M NH_4Cl (20 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The product **5** was isolated by column chromatography on silica gel (hexane−ethyl acetate).

Supporting Information Available: Compound characterrization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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